

Use of Corticosteroids in Coronavirus Disease 2019 Pneumonia: A Systematic Review of the Literature

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30 **Keywords:** COVID-19; coronavirus; corticosteroids; methylprednisolone; pneumonia; ARDS; SARS-
31 Cov-2.

32 **Abstract**

33 The aim was to investigate the effectiveness of glucocorticoid therapy in patients with COVID-19. A
34 systematic search of the literature across 9 databases was conducted from inception until 15th March
35 2020, following the PRISMA guidelines. Patients with a validated diagnosis of COVID-19 and using
36 corticosteroids were included, considering all health outcomes. Four studies with 542 Chinese
37 participants were included. Two studies reported negative findings regarding the use of corticosteroids
38 in patients with COVID-19, i.e. corticosteroids had a detrimental impact on clinical outcomes; one
39 study reported no significant association between the use of corticosteroids and clinical outcomes. One
40 study, on the contrary, in 201 participants with different stages of pneumonia due to COVID-19, found
41 that in more severe forms, the administration of methylprednisolone significantly reduced the risk of
42 death by 62%. The literature to date does not fully support the routine use of corticosteroids in COVID-
43 19, but some findings suggest that methylprednisolone could lower mortality rate in more severe forms
44 of the condition.

45 **1 Introduction**

46 Coronaviruses are ribonucleic acid viruses. Importantly, in humans the viruses may infect the
47 respiratory, gastrointestinal, hepatic and central nervous systems [1]. Infection with four of the most
48 common coronaviruses strains (HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1) usually
49 lead to mild, self-limiting upper respiratory tract infections [2]. However, other coronaviruses, are
50 associated with severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory
51 syndrome (MERS-CoV).

52 In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global
53 pandemic. COVID-19 is caused by SARS-CoV-2, a variant of coronavirus. As of 10 April 2020, over
54 1,500,000 confirmed cases have been diagnosed in more than 130 countries and areas, resulting in
55 about 93,000 fatalities thus far [3]. Symptoms of infection are usually non-specific, and include fever,
56 cough, and myalgia, with diarrhoea, with or without the subsequent development of dyspnea [4].
57 Severe cases that include respiratory distress, sepsis, and septic shock have been increasingly reported
58 [5].

59 During the SARS-CoV epidemic of 2003, therapeutic systemic corticosteroids were administered in
60 patients who were infected and developed severe respiratory disease. In a meta-analysis of
61 corticosteroid use in patients with SARS, only four studies provided conclusive data, all indicating
62 higher mortality [6]. One recent systematic review and meta-analysis identified ten observational
63 studies investigating the administration of corticosteroids in 6,458 patients affected by influenza [7].
64 The review identified increased mortality in patients who were given corticosteroids. Moreover, the
65 length of stay in an intensive care unit was increased, as was the rate of secondary bacterial or fungal
66 infection. Corticosteroids have been investigated also for respiratory syncytial virus (RSV) in clinical
67 trials in children, with no conclusive evidence of benefit and are therefore not recommended [8].

68 Two recent commentaries published in the Lancet between February and March 2020 reported that
69 corticosteroids should not be used for the treatment of COVID-19 [9,10]. However, these assumptions
70 are mainly based on the findings of the meta-analyses cited above, on disease caused by similar viruses,
71 but not research on COVID-19 specifically.

72 Therefore, the clinical, therapeutic, and side effects of systemic glucocorticoid therapy in COVID-19
73 patients are currently unclear. Given this background, the present review investigates the effectiveness
74 of glucocorticoid therapy in patients with COVID-19, by applying a systematic review of the literature

75 currently available. The main objective is to investigate whether there is a clinical necessity, or
76 therapeutic justification, for the use of systemic corticosteroids in patients with COVID-19.

77 **2 Methods**

78 This systematic review followed the MOOSE and PRISMA guidelines [11,12].

79 **2.1 Data sources and literature search strategy**

80 Two investigators (NV and JD) independently conducted a literature search using Embase, PubMed,
81 Web of Science, CNKI, Medline, Cinahl, Toxline, SCOPUS. Specific research in Chinese database
82 Wan-Fang of published and unpublished literature was conducted by one author LY and checked by
83 another researcher (LZ). The database search was run from database inception until 15th March 2020.
84 All studies reporting information regarding the use of corticosteroids in COVID-19 were included. In
85 PubMed, the following search strategy was used: “(COVID-19 OR Novel Coronavirus–Infected
86 Pneumonia OR 2019 novel coronavirus OR 2019-nCoV OR SARS-CoV-2) AND (cortic* OR
87 “glucocorticoids” OR “steroids” OR “corticosteroids” OR “hydrocortisone” OR “prednisone” OR
88 “methylprednisolone” OR “dexamethasone” OR “prednisolone”). The strategy was then adapted for
89 the other databases. Conference abstracts and reference lists of included articles were hand-searched
90 to identify any potential additional relevant articles. Any inconsistencies were resolved by consensus
91 with a third author (LS).

92 **2.2 Study selection**

93 Following the PICO framework [13], we included: participants who had a validated diagnosis of
94 COVID-19, irrespective of stage or severity; intervention: use of corticosteroids (no a priori definition
95 of dosage or route was made); comparison: patients affected by COVID-19 not taking corticosteroids;
96 outcomes: all health outcomes were included, due to the anticipated scarcity of data. A priori, both
97 intervention and observational data were considered.

98 **2.3 Data extraction**

99 Two independent investigators (NV and JD) extracted key data from the included articles in a
100 standardized Excel database and a third independent investigator (LS) validated the data extraction.
101 For each article, we extracted data regarding authors, year of publication, country, city or region in
102 which the study was conducted, the period of observation, how the diagnosis of COVID-19 was
103 obtained, the stage of COVID-19 infection (asymptomatic forms, pneumonia, acute respiratory
104 distress syndrome (ARDS), requiring intensive care unit, ICU; convalescent), sample size included,
105 number of males and females, mean age and its standard deviation (or similar information such as
106 median and range), the percentage of people treated with corticosteroids in the sample as a whole, and,
107 if possible, the route of administration and type of corticosteroid considered. The dosage of
108 corticosteroids used in these studies was mainly unavailable.

109 **2.4 Data synthesis and statistical analysis**

110 Data are reported descriptively according to the best evidence synthesis. When possible, numerical
111 data, are reported.

112

113

114 3 Results

115 3.1 Search results

116 As shown in **Figure 1**, among 31 initially included studies (14 in English and 17 in Chinese), eight
117 were reviewed as full-text and four finally included [14-17]. Two studies were excluded since they
118 were commentaries [9,10], one excluded as it was a protocol [18] and one a letter to Editor [19].

119 3.2 Patients characteristics and main findings

120 **Table 1** shows the descriptive characteristics of the four included studies. Altogether, 542 Chinese
121 participants, mainly males (=55.7%) of a mean age of 52 years (range: 34-68) were included. All the
122 studies were conducted between the end of 2019 and February 2020. The diagnosis of COVID-19 was
123 made in all the studies using reverse transcriptase-polymerase chain reaction on throat swab samples.
124 Three among the four studies included pneumonia, at any stage, from mild to more complicated forms
125 and one convalescent people.

126 **Table 2** summarizes the findings of the studies included. The percentage of patients taking
127 corticosteroids ranged from 7.6 to 44.9% of the cohorts included. Two studies [14,15] reported negative
128 findings regarding the use of corticosteroids in patients with COVID-19 since Wang et al [15] showed
129 the group treated with corticosteroids experience a doubled risk of being admitted to an ICU; in Ling
130 et al [14], the duration of viral RNA for oropharyngeal swabs and faeces was almost doubled in
131 corticosteroids group than controls. Liu et al did not report any benefit of the use of intravenous
132 methylprednisolone (30–80 mg/day) on clinical outcomes (i.e. short-term disease progression) in 137
133 participants [17]. Finally, Wu et al carried out among 201 participants with different stages of
134 pneumonia due to COVID-19, found that in more severe forms (i.e. in subjects having ARDS due to
135 COVID-19), the administration of standard doses of methylprednisolone significantly reduced the risk
136 of death by 62% [16].

137 4 Discussion

138 In this systematic review including 542 Chinese patients, we have for the first time summarized the
139 ultimate available literature regarding the use of corticosteroids in the treatment of a recent viral
140 condition that is wide spreading on a global scale. Overall, two studies reported negative findings
141 regarding these medications, one reported no significant association between corticosteroids and
142 clinical outcomes and one concluded that methylprednisolone was associated with a significant
143 reduction of mortality in patients with COVID-19 pneumonia developing ARDS.

144 Since COVID-19 was first reported in December 2019, it has attracted global attention owing to its
145 similarity to SARS-CoV and MERS-CoV in causing fatal respiratory disease, and its potential for
146 causing large-scale human infection and economic disruption. When considering patients with SARS
147 and MERS, the use of corticosteroids therapy is still debated [20,21]. Corticosteroids therapy was used
148 in the treatment of severe SARS because early anecdotal experience supported it, and radiological
149 findings and histologic features of critically ill patients with SARS were similar to those of patients
150 with ARDS [22,23]. In March 2003, China summarized its experience in the management of SARS,
151 and suggested that high-dose glucocorticoids should be used if patients had fever persisting for more
152 than 3 days, or if radiologic findings were suggestive of persistent lung involvement or progressive
153 deterioration [24]. One systematic review of studies on patients with SARS-CoV, including 29 studies
154 documenting glucocorticoid use, found 25 studies that were inconclusive regarding the role of the
155 adjunctive use of glucocorticoids to standard therapy, and 4 studies demonstrated that the use of

156 systemic glucocorticoids in SARS patients may cause possible harm [6]. Moreover, a prospective,
157 randomized double-blinded, placebo-controlled trial compared early hydrocortisone treatment (before
158 day 7 of the illness) with placebo, and found that early hydrocortisone therapy was associated with a
159 higher subsequent plasma viral load [25].

160 Glucocorticoid therapy was also used for critically ill patients with MERS. In one study, hypoxemic
161 patients with MERS-CoV pneumonia who were not showing signs of improvement, were given
162 glucocorticoid therapy [20]. However, the study reported that there was no difference in 90-days
163 mortality, and these patients were associated with delayed MERS-CoV RNA clearance. This finding
164 is somewhat confirmed in our systematic review on COVID-19, since one study reported that the
165 duration of viral RNA for oropharyngeal swabs and faeces was almost doubled in corticosteroids group
166 compared to controls [14].

167 Among those infected with COVID-19, some develop mild symptoms, however, a significant
168 proportion progress to severe ARDS and thus require intensive care [26]. The use of corticosteroids in
169 patients presenting with ARDS of different aetiologies remains controversial owing to mixed results
170 in the existing literature, mainly derived from observational studies [27]. Globally, high-dose
171 glucocorticoids is among the most frequently used adjuncts in ARDS (17.9%) [28]. Systemic
172 corticosteroids have long been used among critically ill patients presenting with ARDS given their role
173 in lowering the circulating levels of proinflammatory mediators [29,30]. Moreover, adequate and
174 prolonged glucocorticoid supplementation have proved to mitigate the Critical Illness Related
175 Corticosteroid Insufficiency (CIRCI) thus enhancing resolution of lung and systemic inflammation
176 [31]. One systematic review conducted an analysis of individual patient data from randomized trials,
177 and found that, compared with the placebo group, prolonged glucocorticoid treatment improved
178 clinical outcomes [32]. A recent individual patient data meta-analysis combined four RCTs evaluating
179 prolonged methylprednisolone therapy for ARDS, reported a significant reduction in mortality, with
180 an increase in ventilator-free days (13 vs. 7, $p < 0.001$) [33].

181 Recent evidence suggests that a subset of patients with severe COVID-19 may have cytokine storm
182 syndrome [34], which is a condition frequently related to lung involvement (including ARDS) [35] and
183 multi-organ failure. In order to induce immunosuppression to antagonize virally driven
184 hyperinflammation, treatments with tocilizumab (IL-6 receptor blockade) are ongoing in patients in
185 which a hypercytokinemia laboratory pattern is identified. In these patients, a therapeutic role can also
186 be hypothesized for corticosteroids [36].

187 Animal experiments may also provide evidence during the acute phase of severe disease for the use of
188 glucocorticoids to (i) reduce inflammation, (ii) attenuate acute lung injury, and (iii) improve survival
189 [32]. However, other studies have failed to provide convincing evidence to prove the efficacy of
190 corticosteroids in decreasing the mortality of ARDS, thus suggesting that glucocorticoid therapy is not
191 necessary in this condition, and may even aggravate the clinical course of the disease. Challenging
192 analytic issues within these studies (including immortal time bias and indication bias from time-varying
193 confounding) make these results inconclusive and larger specifically designed clinical trials are needed
194 to clarify the favourable and unfavourable effects for corticosteroid therapy in ARDS patients.

195 The present review has summarized the current evidence of corticosteroids on clinical outcomes in
196 COVID-19 to inform clinicians and policymakers on the current state of the literature. Importantly,
197 one study identified in this review in patients with ARDS owing to COVID-19 infection showed that
198 methylprednisolone significantly decreased the risk of mortality. It should be noted that there is

199 currently one ongoing clinical trial that is directly addressing this research question and its results are
200 eagerly awaited [18].

201 The present review should be interpreted in light of its limitations. First, only four studies from China
202 were included and heterogeneous data were reported. More research on this topic is needed before
203 concrete recommendations can be made. Second, the type and dosage of corticosteroids varied between
204 studies and, except in the case of Wu et al. [16], corticosteroids were considered as only class whilst
205 they have different actions and properties. Third, the data are based only on retrospective findings and
206 cohort studies are now urgently needed. Finally, existing data comes only from China and,
207 consequently, it is not known if the genetic background of Chinese people may modify the results
208 found in the present work and in which direction.

209 **5 Conclusions**

210 In conclusion, the literature so far available does not fully encourage the routine use of corticosteroids
211 in COVID-19, but some findings suggest that methylprednisolone could lower mortality rate in more
212 severe forms of this condition, such as in ARDS. Findings from future clinical trials, that are ongoing,
213 are needed to better understand the role of corticosteroids in COVID-19.

214 **6 Conflict of Interest**

215 The authors declare that the research was conducted in the absence of any commercial or financial
216 relationships that could be construed as a potential conflict of interest.

217 **7 Author Contributions**

218 All authors listed have made a substantial, direct and intellectual contribution to the work, and
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222 **9 References**

- 223 1. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and
224 pathogenesis. *J. Med. Virol.*, 2020;92(4):418-423.
- 225 2. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen K-Y. Coronaviruses—drug discovery and
226 therapeutic options. *Nat. Rev. Drug Discov.*, 2016;15(5):327-347.
- 227 3. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report, 45. 2020.
228 <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports> Accessed
229 April,10 2020.
- 230 4. Chan JF-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019
231 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *The Lancet*,
232 2020;395(10223):514-523.
- 233 5. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health
234 concern. *The Lancet* 2020;395(10223):470-473.

- 235 6. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *Plos Med.*,
236 2006;3(9):e343.
- 237 7. Ni Y-N, Chen G, Sun J, Liang B-M, Liang Z-A. The effect of corticosteroids on mortality of
238 patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care*, 2019;23(1):99.
- 239 8. McGee S, Hirschmann J. Use of corticosteroids in treating infectious diseases. *Arch. Intern.*
240 *Med.*, 2008;168(10):1034-1046.
- 241 9. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment
242 for 2019-nCoV lung injury. *The Lancet*, 2020;395(10223):473-475.
- 243 10. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia.
244 *The Lancet*, 2020;395(10225):683-684.
- 245 11. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for a systematic review and
246 meta-analysis of individual participant data: the PRISMA-IPD statement. *Jama*, 2015;313(16):1657-
247 1665.
- 248 12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in
249 epidemiology: a proposal for reporting. *Jama*, 2000;283(15):2008-2012.
- 250 13. Santos CMdC, Pimenta CADM, Nobre MRC. The PICO strategy for the research question
251 construction and evidence search. *Rev Lat Am Enfermagem*, 2007;15(3):508-511.
- 252 14. Ling Y, Xu SB, Lin YX, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus
253 disease rehabilitation patients [published online February 28, 2020]. *Chin Med J*. doi:
254 10.1097/CM9.0000000000000774
- 255 15. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel
256 coronavirus-infected Pneumonia in Wuhan, China. *JAMA*, 2020;323(11):1061-1069.
- 257 16. Wu C, Chen X, Cai Y, et al. Risk Factors associated with acute respiratory distress syndrome
258 and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China [published online
259 March 13, 2020]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2020.0994
- 260 17. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary
261 hospitals in Hubei Province [published online February 7, 2020]. *Chin Med J*. doi:
262 10.1097/CM9.0000000000000744
- 263 18. Zhou YH, Qin YY, Lu YQ, et al. Effectiveness of glucocorticoid therapy in patients with severe
264 novel coronavirus pneumonia: protocol of a randomized controlled trial [published online March 5,
265 2020]. *Chin Med J*. doi: 10.1097/CM9.0000000000000791
- 266 19. Zhou W, Liu Y, Tian D, et al. Potential benefits of precise corticosteroids therapy for severe
267 2019-nCoV pneumonia. *Signal Transduct Tar*, 2020;5:18.
- 268 20. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients
269 with Middle East respiratory syndrome. *Am J Respir Crit Care Med*, 2018; 197(6): 757-767.

- 270 21. Yam LY-C, Lau AC-W, Lai FY-L, et al. Corticosteroid treatment of severe acute respiratory
271 syndrome in Hong Kong. *J. Infect.*, 2007;54(1):28-39.
- 272 22. So LK, Lau AC, Yam LY, et al. Development of a standard treatment protocol for severe acute
273 respiratory syndrome. *The Lancet*, 2003;361(9369):1615-1617.
- 274 23. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong
275 Kong. *N Engl J Med*, 2003;348(20):1986-1994.
- 276 24. Zhong NS, Zeng GQ. Our strategies for fighting severe acute respiratory syndrome (SARS).
277 *Am J Respir Crit Care Med*, 2003;168(1):7-9.
- 278 25. Lee N, Chan KA, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-
279 associated Coronavirus RNA concentrations in adult patients. *J Clin Virol*, 2004;31(4):304-309.
- 280 26. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus
281 in Wuhan, China. *The Lancet*, 2020;395(10223):497-506.
- 282 27. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nat*
283 *Rev Dis Primers*, 2019;5(1):1-22.
- 284 28. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients
285 with acute respiratory distress syndrome in intensive care units in 50 countries. *Jama*, 2016;315(8):788-
286 800.
- 287 29. Meduri GU, Tolley EA, Chrousos GP, Stentz F. Prolonged methylprednisolone treatment
288 suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome:
289 evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell
290 resistance to glucocorticoids. *Am J Respir Crit Care Med*, 2002;165(7):983-991.
- 291 30. Rocco PR, Souza AB, Faffe DS, et al. Effect of corticosteroid on lung parenchyma remodeling
292 at an early phase of acute lung injury. *Am J Respir Crit Care Med*, 2003;168(6):677-684.
- 293 31. Annane D, Pastores SM, Arlt W, et al. Critical illness-related corticosteroid insufficiency
294 (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine
295 (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Intensive Care Med*,
296 2017;43(12):1781-1792.
- 297 32. Meduri GU, Bridges L, Shih M-C, Marik PE, Siemieniuk RA, Kocak M. Prolonged
298 glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients'
299 data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care*
300 *Med*, 2016;42(5):829-840.
- 301 33. Meduri GU, Siemieniuk RA, Ness RA, Seyler SJ. Prolonged low-dose methylprednisolone
302 treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients
303 with ARDS. *J. Intensive Care*, 2018;6(1):1-7.
- 304 34. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus
305 in Wuhan, China. *Lancet*, 2020;395:497-506.

- 306 35. Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary involvement in patients
307 with hemophagocytic lymphohistiocytosis. *Chest*, 2016;149:1294-1301.
- 308 36. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine
309 vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review
310 of medical records. *Lancet*, 2020;395:809-815.

Table 1. Descriptive characteristics of the studies included

Author, year	City/region	Period of observation	COVID diagnosis	Stage of COVID	Sample size	Number of males	Mean/median age (SD or range)
Liu, 2020	Nine tertiary hospitals in Hubei province	December 30, 2019 to January 24, 2020	RT-PCR on Throat swab samples	Pneumonia	137	61	55 (16)
Wang, 2020	Zhongnan Hospital of Wuhan University	January 1 to January 28, 2020	RT-PCR on Throat swab samples	Pneumonia	138	75	56 (42-68)
Wu, 2020	Wuhan Jinyintan Hospital	December 25, 2019 to January 26, 2020	RT-PCR on Throat swab samples	Pneumonia	201	128	51 (43-60)
Ling, 2020	Shanghai Public Health Clinical Center	January 20, 2020 to February 10, 2020	RT-PCR on Throat swab samples	Convalescent	66	38	44 (34-62)

Abbreviations: COVID: coronavirus disease 2019; RT-PCR: Reverse transcriptase-polymerase chain reaction.

Table 2. Main findings of the studies included

Author, year	Percentage of people treated with corticosteroids	Findings regarding corticosteroids
Liu, 2020	29.2	Intravenous methylprednisolone (30–80 mg/day) did not show significant benefits. Not numerical data were reported
Wang, 2020	44.9	Glucocorticoid therapy was associated with a greater risk of ICU admission: 26 (72.2) vs. 36 (35.3), $p < 0.001$
Wu, 2020	30.8	Administration of methylprednisolone reduced the risk of death (hazard ratio, 0.38; 95% CI, 0.20-0.72; $P = 0.003$) in subjects having ARDS for COVID 19
Ling, 2020	7.6	The duration of viral RNA detection for oropharyngeal swabs and feces in the corticosteroid treatment group was longer than that in the non-corticosteroid treatment group, which were 15 days vs. 8.0 days ($P = 0.013$) and 20 days vs. 11 days ($P < 0.001$).

Abbreviations: ICU: intensive care unit; ARDS: Acute respiratory distress syndrome; COVID: coronavirus disease 2019.

Figure 1. PRISMA flow-chart

