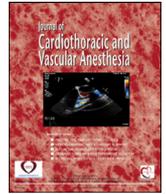




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Original Article

# Corticosteroids for Patients With Coronavirus Disease 2019 (COVID-19) With Different Disease Severity: A Meta-Analysis of Randomized Clinical Trials

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**Objectives:** Efficacy and safety of corticosteroids in patients with 2019-nCoV (novel coronavirus 2019) infection still are debated. Because large randomized clinical trials (RCTs) and a well-conducted meta-analysis on the use of corticosteroids, focused on patients with coronavirus disease (COVID-19) in intensive care units, recently were published, a meta-analysis of RCTs on corticosteroids therapy in patients with different disease severity was performed to evaluate the effect on survival.

**Design:** A meta-analysis of RCTs was performed.

**Setting:** Patients admitted to hospital.

**Participants:** Patients with coronavirus disease.

**Interventions:** Administration of corticosteroids.

**Measurements and Main Results:** A search was performed for RCTs of adult patients with acute hypoxemic failure related to 2019-nCoV infection who received corticosteroids versus any comparator. The primary endpoint was mortality rate. Five RCTs involving 7,692 patients were included. Overall mortality of patients treated with corticosteroids was slightly but significantly lower than mortality of controls (26% v 28%, relative risk {RR} = 0.89 [95% confidence interval {CI} 0.82-0.96],  $p = 0.003$ ). The same beneficial effect was found in the subgroup of patients requiring mechanical ventilation (RR = 0.85 [95% CI 0.72-1.00],  $p = 0.05$  number needed to treat {NNT} = 19). Remarkably, corticosteroids increased mortality in the subgroup of patients not requiring oxygen (17% v 13%, RR = 1.23 [95% CI 1.00-1.62],  $p = 0.05$  number needed to harm {NNH} = 29). Tests for comparison between mechanically ventilated subgroups and those not requiring oxygen confirmed that treatment with corticosteroids had a statistically significant different effect on survival. Patients treated with corticosteroids had a significantly lower risk of need for mechanical ventilation.

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**Conclusions:** Corticosteroids may be considered in severe critically ill patients with COVID-19 but must be discouraged in patients not requiring oxygen therapy. Urgently, further trials are warranted before implementing this treatment worldwide.

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**Key Words:** corticosteroids; mortality; COVID-19; 2019-nCoV; mechanical ventilation; meta-analyses

SINCE THE INFLUENZA OUTBREAK of 1918, the coronavirus disease 2019 (COVID-19) pandemic probably represents the biggest global crisis faced by public health worldwide. Different drugs previously used to treat other coronavirus infections, such as severe acute respiratory syndrome and Middle East respiratory syndrome, were considered as the first potential candidates to treat COVID-19. Among them, in addition to other therapeutics, corticosteroids were used widely during severe acute respiratory syndrome and Middle East respiratory syndrome outbreaks and recently were adopted in patients with 2019-nCoV (novel coronavirus 2019) infection.

It is well-known that acute respiratory distress syndrome is caused partly by host immune responses.<sup>1</sup> 2019-nCoV virus, once entered into humans, targets a key angiotensin-converting enzyme 2 (ACE2) receptor and replicates within cells causing cellular injury or death with release of pro-inflammatory alarmins.<sup>2</sup> Moreover, viral particles can stimulate innate immune response, leading to the activation of alveolar macrophages and the complement system. The resultant massive inflammatory response causes alveolar and vascular damage, microvascular thromboses, and a progressive worsening of ventilation–perfusion mismatch.<sup>3–5</sup> In the late stages of the disease, the systemic inflammatory reaction may involve other organs, causing multiorgan failure and death. Theoretically, corticosteroid treatment could have a role in suppressing lung inflammation and inhibiting immune responses and pathogen clearance. Nonetheless, a recent meta-analysis on pharmacologic agents for adults with acute respiratory distress syndrome found insufficient evidence to determine with certainty whether corticosteroids may reduce early all-cause mortality or the duration of mechanical ventilation.<sup>6</sup> Even less evidence exists in the literature to indicate whether corticosteroids are effective in treating coronavirus disease infection.<sup>7</sup>

A recent large randomized clinical trial (RCT) showed that the use of dexamethasone resulted in lower 28-day mortality among patients with COVID-19 who were receiving either random invasive mechanical ventilation or oxygen alone, but not among patients receiving no respiratory support.<sup>8</sup> This study had resonated worldwide because nowadays dexamethasone is the first strategy proven to reduce mortality in COVID-19 patients. The updated living World Health Organization guideline on drugs for COVID-19 suggests not to use corticosteroids in the treatment of patients with nonsevere COVID-19 but with a weak or conditional recommendation.<sup>9</sup>

Because other high-quality RCTs<sup>10–13</sup> and a well-performed meta-analysis on the effect of corticosteroids on patients in the intensive care unit (ICU) recently were published,<sup>14</sup> the authors decided to perform a meta-analysis of RCTs on

corticosteroid therapy to evaluate the effect on survival of subgroups of patients with COVID-19 who require different respiratory support.

## Methods

### Search Strategy

Pertinent studies were searched independently in BioMed Central, PubMed, Embase, medRxiv, bioRxiv and the Cochrane Central Register of Controlled Trials by two investigators (L.P., G.L.). The full PubMed search strategy aimed to include any RCTs ever performed with corticosteroids in patients with COVID-19 and is presented in the Supplementary Material. In addition, the authors employed backward snowballing (ie, scanning of references of retrieved articles and pertinent reviews) and contacted international experts for further studies. No language restriction was imposed.

### Study Selection

References first were examined independently at a title or abstract level by two investigators (L.P., G.L.), with divergences resolved by consensus and then, if potentially pertinent, retrieved as complete articles. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment (corticosteroids *v* any comparator with no restrictions on dose or time of administration) and studies involving patients with acute hypoxemic failure or pneumonia related to 2019-nCoV infection. The exclusion criteria were duplicate publications (in this case the authors referred to the first article published and retrieved data from the article with the longest follow-up available), nonadult patients, and lack of data on all outcomes of interest. Two investigators (L.P., G.L.) independently assessed compliance to selection criteria and selected studies for the final analysis, with divergences resolved by consensus.

### Data Abstraction and Study

Baseline, procedural, and outcome data were abstracted independently by two investigators (L.P., G.L.; Table 1). At least two separate attempts to contact original authors were made in cases of missing data. The primary endpoint of the present review was mortality rate at the longest available follow-up. Co-primary endpoints were mortality rate of mechanically ventilated patients and patients who did not receive oxygen therapy. The secondary endpoint was need for mechanical ventilation.

Table 1  
Description of the Studies Included in the Meta-analysis

First Author	Year	Setting	Inclusion Criteria	Primary Outcome	Corticosteroids Patients	Control Patients	Corticosteroid Type and Dosage	Duration of Study Treatment	Comparator	Antiviral Therapies	Reported Follow-up
Jeronimo CMP	2020	Ordinary ward	Clinical and/or radiological suspicion of COVID-19 (history of fever and any respiratory symptom (eg, cough or dyspnea and/or ground glass opacity or pulmonary consolidation on CT scan), aged 18 years or older with SpO <sub>2</sub> ≤ 94% at room air or in use of supplementary oxygen or under IMV	28-d mortality	209	207	Intravenous methylprednisolone (0.5 mg/kg) twice daily	5 d			Placebo + usual care
None	28 d										
RECOVERY Trial	2020	Ordinary ward	Clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial. hydroxychloroquine, lopinavir–ritonavir, or interleukin-6 antagonists. Remdesivir was administered to 3 patients in the dexamethasone group and 2 patients in the usual care group.	28-d mortality	2,104	4,321	Oral or intravenous dexamethasone 6 mg once daily	Up to 10 d (or until hospital discharge if sooner)	Usual care	0% to 3% of patients received	
REMAP-CAP Trial	2020	ICU	Adult patients with presumed or confirmed SARS-CoV-2 infection who were admitted to an ICU for provision of respiratory or cardiovascular organ support	Organ support-free days within 21 d	295	108	Intravenous hydrocortisone 50 mg, every 6 h; intravenous hydrocortisone, 50 mg, every 6 h while in shock	For 7 d or for up to 28 d while in shock	Usual care	Patients were eligible for randomized assignment to alternative	interventions
28 d											
CoDEX Trial	2020	ICU	Adult patients with confirmed or suspected COVID-19 infection, receiving MV within 48 h of meeting criteria for moderate to severe ARDS with PaO <sub>2</sub> :FIO <sub>2</sub> ratio of 200 or less	Ventilator-free days during the first 28 d	151	148	Intravenous Dexamethasone 20mg intravenously once daily for 5 d, followed by 10 mg IV once daily for additional 5 d or until ICU discharge	10 d or up to ICU discharge	Usual care	None	28 d
Dequin PF	2020	ICU	Adult ICU patients with biologically confirmed or suspected COVID-19 and severe acute respiratory syndrome	Treatment failure on day 21	76	73	Hydrocortisone 200mg/d until day 7 and then decreased to 100 mg/d for 4 d and 50 mg/d for 3 d	14 d or ICU discharge	Placebo	Adjunctive antiviral treatments could be	administered at the discretion of the patients' primary physicians
21 d											

Abbreviations: ARDS, Acute Respiratory Distress Syndrome, CoDEX, COVID Dexamethasone; COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; IMV, Invasive Mechanical Ventilation; RECOVERY, Randomised Evaluation of COVID-19 Therapy; REMAP-CAP, Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

### Internal Validity and Risk of Bias Assessment

The internal validity and risk of bias of included trials were appraised by two independent reviewers according to the latest version of the Risk of Bias Assessment Tool developed by The Cochrane collaboration,<sup>15</sup> and divergences were resolved by consensus. Publication bias was assessed by visually inspecting funnel plots.

### Data Analysis and Synthesis

Computations were performed with Review Manager (Rev-Man) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020. The hypothesis of statistical heterogeneity was tested by means of Cochran Q test, with statistical significance set at the two-tailed 0.10 level, whereas extent of statistical consistency was measured with  $I^2$ , defined as  $100\% \times (Q-df)/Q$ , where Q is Cochran's heterogeneity statistic and *df* the degrees of freedom.

Binary outcomes were analyzed to compute the individual and pooled risk ratio (RR) and pertinent 95% confidence interval (CI) by means of the same models as previously described. Binary outcomes from individual studies were analyzed to compute individual and pooled RR and pertinent 95% CI by means of inverse variance method, with a fixed-effect model in case of low statistical inconsistency ( $I^2 \leq 25\%$ ), or with random-effect model (which better accommodates clinical and statistical variations) in case of moderate or high statistical inconsistency ( $I^2 > 25\%$ ). Sensitivity analyses were performed by sequentially removing each study and reanalyzing the remaining dataset (producing a new analysis for each study removed) by analyzing only data from studies with low risk of bias and by analyzing, with a random effect analysis, studies

with low heterogeneity ( $I^2 \leq 25\%$ ). Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. Unadjusted p values were reported throughout. A prespecified trial sequential analysis was performed on mortality outcome. The authors estimated the required information size on the calculated minimal intervention effect considering a type I error of 5% and a power of 80%. This post hoc conservative approach allowed the authors to assess whether the data were convincing enough to prove the effect.

To compare different groups (mechanically ventilated patients and patients who did not require oxygen therapy), tests for subgroup differences were performed based on random-effects models. In case of p values = 0.05, the authors repeated sensitivity analyses with Review Manager and Stata.

This study was registered on PROSPERO (CRD 42020197509) and performed in compliance with The Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>16,17</sup>

## Results

### Study Characteristics

Database searches, snowballing, and contacts with experts yielded a total of 1,168 articles. Excluding 1,157 nonpertinent titles or abstracts, the authors retrieved (in complete form) and assessed 11 studies according to the selection criteria (Fig 1). Six studies were further excluded because of the prespecified exclusion criteria: five because they were not randomized,<sup>18-22</sup> and one because it did not report outcomes of randomized patients.<sup>23</sup>

The five RCTs finally included in the meta-analysis involved 7,692 patients (2,835 received corticosteroids and 4,837 received standard treatment<sup>8,10-13</sup>; Table 1).

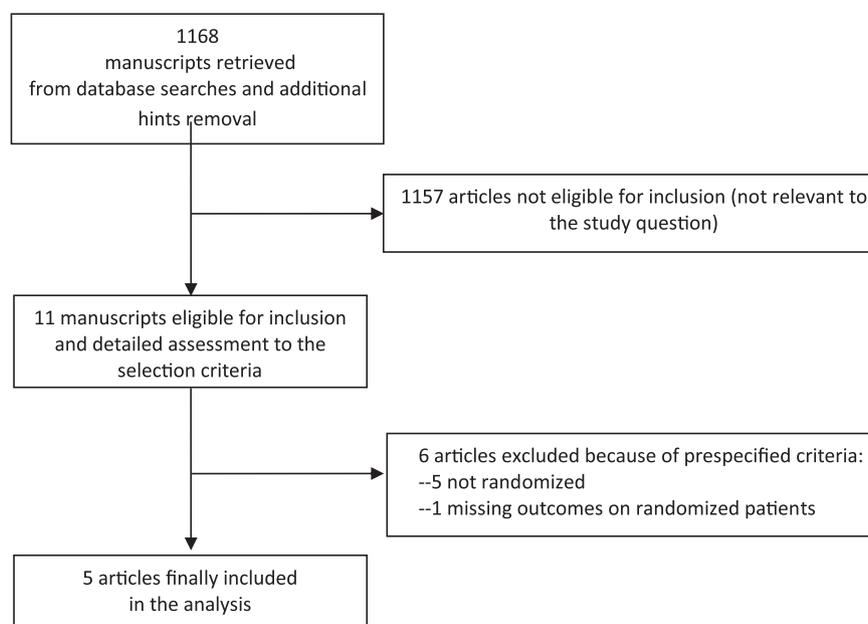


Fig 1. Flowchart of article selection.

Table 2  
Outcomes

Outcome	Number of Included Studies	Corticosteroids Patients	Control Patients	RR	95% CI	p for Effect	I <sup>2</sup> (%)
Overall studies		2,835	4,857				
Mortality	5	727 of 2,835 (26%)	1,336 of 4,857 (28%)	0.89	0.82-0.96	0.003	0
MV patients	3	224 of 529 (42%)	423 of 888 (48%)	0.85	0.72-1.00	0.05	58
Non-MV patients	2	403 of 1,876 (21%)	859 of 3,741 (23%)	0.95	0.86-1.06	0.35	0
Patients who did not require oxygen therapy	2*	90 of 531 (17%)	145 of 1,076 (13%)	1.28	1.00-1.62	0.05	0
Need for MV	3	126 of 2329 (5%)	311 of 4,544 (7%)	0.75	0.60-0.94	0.007	18

Abbreviations: RR, relative risk; CI, confidence interval; MV, mechanical ventilation

\* Additional data provided by corresponding author (Prado-Jeronimo)

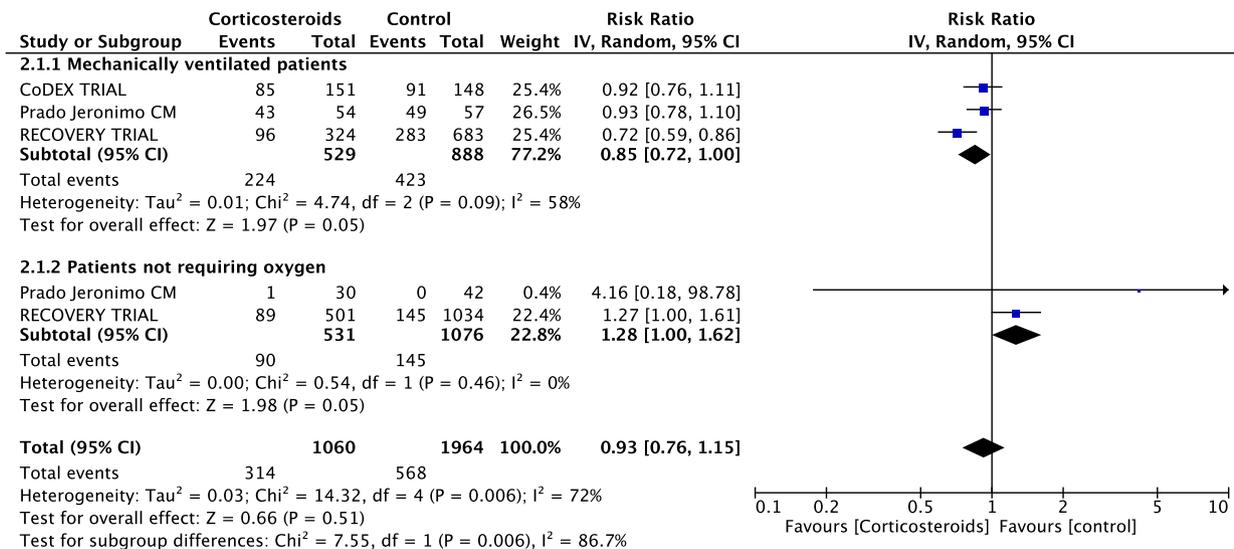


Fig 2. Tests for comparison between mechanically ventilated subgroups and those who did not require oxygen therapy based on random-effects models.

Characteristics of included studies are presented in Table 1. Clinical heterogeneity mostly was due to inclusion criteria, initiation of oxygen therapy or mechanical ventilation, type of corticosteroid, dosage and duration of administration, concomitant antiviral or anti-inflammatory drugs, and length of follow-up (Table 1). Overall risk of bias of the included studies was moderate (Supplementary Material).

### Quantitative Data Synthesis

Overall mortality of patients treated with corticosteroids was slightly but significantly lower than mortality of patients in the control group (727 of 2,835 [26%]; in the corticosteroids group v 1,336 of 4,857 [28%] in the control group, RR = 0.89 [95% CI 0.82-0.96], p for effect 0.003, I<sup>2</sup> = 0%, with five trials included; see Table 2 and Supplementary Material), with results confirmed at sensitivity analyses. Reduction in mortality also was observed in the subgroup of patients who required mechanical ventilation (224 of 529 [42%] in the corticosteroids group v 423 of 888 [48%] in the control group, RR = 0.85 [95% CI 0.72-1.00], p for effect 0.05, I<sup>2</sup> = 58%; see Table 2 and Supplementary Material). Notably, the use of corticosteroids increased mortality in the subgroup of patients not requiring oxygen (90 of 531 [17%] in the corticosteroids group v 145 of 1,076 [13%] in the control group, RR = 1.23 [95% CI

1.00-1.62], p for effect 0.05, I<sup>2</sup> = 0%; see Table 2 and Fig 2). No difference in mortality was found in the subgroups of patients who did not require intubation. (Table 2) All results were confirmed at sensitivity analyses. Trial sequential analysis suggested that additional trials are needed to confirm the findings (Supplementary Material).

Patients treated with corticosteroids had a significantly lower risk of need for mechanical ventilation than controls (126 of 2,329 [5%] in the corticosteroids group v 311 of 4,544 [7%] in the control group, RR = 0.74 [95% CI 0.59-0.92], p for effect = 0.007, I<sup>2</sup> = 18%, three trials included; see Table 2 and Supplementary Material). Nonetheless, this result was not confirmed at sensitivity analyses. Given the low number of included trials, funnel plots were not analyzed.

Tests for comparison between mechanically ventilated subgroups and those who did not require oxygen therapy, based on random-effects models, revealed that treatment with corticosteroids had a statistically significant different effect on survival in patients with COVID-19 with different disease severity:  $\chi^2 = 7.55$ , p for effect = 0.006; I<sup>2</sup> = 86.7% (Fig 2).

### Discussion

This was the first meta-analysis of RCTs that showed that the effect of corticosteroids on patient survival depended on

the disease severity. In fact, although a recent meta-analysis published in *JAMA* by the REACT (Real-time Assessment of Community Transmission) COVID group concluded that administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in patients admitted to ICU, the present study showed that the use of corticosteroids has detrimental effects on survival of patients not requiring oxygen, with a number needed to harm of 29, and that a significant difference existed between the two patients categories. Unlike analyzing the whole ICU population, as the REACT COVID group did, the authors focused the present study on different disease severity and achieved very informative results. This finding is of paramount importance because, fortunately, the majority of patients with COVID-19 experience a mild or moderate illness and do not require hospital admission. Only a small minority of patients with more severe illness are admitted to the hospital, where they often need oxygen therapy or respiratory mechanical support. Therefore, patients with COVID-19 who might benefit from corticosteroids therapy are a small minority. In addition, the authors found that spontaneously breathing patients treated with corticosteroids had less requirement for intubation and mechanical ventilation, but higher mortality rate than patients who did not receive corticosteroids. These important findings, although apparently incongruous, stress the hypothesis that the use of corticosteroids might improve respiratory function (in patients who are already on oxygen), while probably increasing the risk of death (in patients who are not yet requiring oxygen).

The efficacy and safety of corticosteroids in COVID-19 still is debated. A recent large randomized clinical trial showed that the use of dexamethasone resulted in reduced 28-day mortality among patients who were receiving either invasive MV or oxygen alone, but not among patients who were receiving no respiratory support.<sup>8</sup> Actually, this was the first strategy proven to reduce mortality in patients with COVID-19 and had a great scientific impact worldwide. Nonetheless, it showed a potential detrimental effect of dexamethasone in patients who were not receiving oxygen (17.8% mortality in dexamethasone group v 14.0% in placebo group) and who represent the majority of patients worldwide. On the contrary, Jeronimo et al. found a reduced mortality rate only in older patients (>60 years) treated with corticosteroids.<sup>10</sup>

Moreover, recently published systematic reviews on this topic showed contrasting results. Pei et al., in their study on the use of antiviral agents, glucocorticoids, antibiotics and immunoglobulin usage in patients with COVID-19, showed a probable survival benefit of antiviral agent usage and a harmful effect of glucocorticoids.<sup>24</sup> On the contrary, Hasan et al., in accordance with the results of the latest meta-analysis published on this topic,<sup>14</sup> found that low-dose corticosteroid therapy or pulse corticosteroid therapy appeared to have a beneficial role in the management of severely ill patients with COVID-19.<sup>25</sup> Similarly, corticosteroids have an overall beneficial effect in the majority of critically ill patients, including those with pulmonary disease, as suggested by a meta-analysis of RCTs.<sup>26</sup>

The authors acknowledge that the study presented some limitations. Although it included randomized clinical trials, the number of included studies was very low. Moreover, these trials did not reach the required sample size to verify the small difference in absolute mortality reduction found between groups (2%). This small effect probably already is reduced, as the observed in-hospital mortality appears to rapidly be decreasing.<sup>27</sup> Nonetheless, because there were millions of COVID-19 cases throughout the world, even an absolute mortality reduction of 6% in mechanically ventilated patients (number needed to treat=19) and an absolute mortality increase of 4% in patients not on oxygen (number needed to harm=29) can save thousands of lives, especially of patients not requiring oxygen, who are the vast majority of patients with COVID-19. In addition, initiation of oxygen therapy or mechanical ventilation, type of corticosteroid, dosage and duration of administration, and concomitant antiviral or anti-inflammatory drugs were significantly different between studies. Moreover, studies carried out both in ICUs and ordinary wards were included, which increased overall heterogeneity. Nonetheless, the aim of the present study was to investigate the effect of corticosteroids therapy on survival of subgroups of patients with COVID-19 who required different respiratory support. Therefore, it was necessary to include patients admitted to different clinical settings, as it is unlikely to find patients who do not require oxygen in the ICU. In addition, the role of confounding variables, such as age, severity of disease, presence of pulmonary disease, and so on, remains to be explored.

In conclusion, the present study clearly showed that the use of corticosteroids may be considered in severe critically ill patients with COVID-19 but must be discouraged in all patients who do not require oxygen support. Given the small effect on survival of critically ill patients, they must be compared with other anti-inflammatory drugs, as other therapies (eg, anakinra) with better safety profile recently were tested with success.<sup>28</sup> Larger, high-quality randomized clinical trials on this topic urgently are warranted before implementing this treatment worldwide, in particular in less critical, younger patients who do not require oxygen therapy or hospitalization.

### Conflict of Interest

None.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1053/j.jvca.2020.11.057](https://doi.org/10.1053/j.jvca.2020.11.057).

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