

Expert Consensus Statements on the Use of Corticosteroids in Non-severe COVID-19

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ABSTRACT

Introduction: There is strong evidence for the use of corticosteroid in the management of severe coronavirus disease 2019 (COVID-19). However, there is still uncertainty about the timing of corticosteroids. We undertook a modified Delphi study to develop expert consensus statements on the early identification of a subset of patients from non-severe COVID-19 who may benefit from using corticosteroids.

Methods: A modified Delphi was conducted with two anonymous surveys between April 30, 2021, and May 3, 2021. An expert panel of 35 experts was selected and invited to participate through e-mail. The consensus was defined as >70% votes in multiple-choice questions (MCQ) on Likert-scale type statements, while strong consensus as >90% votes in MCQ or >50% votes for "very important" on Likert-scale questions in the final round.

Results: Twenty experts completed two rounds of the survey. There was strong consensus for the increased work of breathing (95%), a positive six-minute walk test (90%), thorax computed tomography severity score of >14/25 (85%), new-onset organ dysfunction (using clinical or biochemical criteria) (80%), and C-reactive protein >5 times the upper limit of normal (70%) as the criteria for patients' selection. The experts recommended using oral or intravenous (IV) low-dose corticosteroids (the equivalent of 6 mg/day dexamethasone) for 5 to 10 days and monitoring of oxygen saturation, body temperature, clinical scoring system, blood sugar, and inflammatory markers for any "red-flag" signs.

Conclusion: The experts recommended against indiscriminate use of corticosteroids in mild to moderate COVID-19 without the signs of clinical worsening. Oral or IV low-dose corticosteroids (the equivalent of 6 mg/day dexamethasone) for 5 to 10 days are recommended for patients with features of disease progression based on clinical, biochemical, or radiological criteria after 5 days from symptom onset under close monitoring.

Keywords: Corticosteroids in moderate COVID-19, Delphi study, Non-severe COVID-19, SARS-CoV-2.

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INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) continues to overwhelm healthcare resources worldwide. In a cohort of 72,314 symptomatic COVID-19 patients from China during the early days of the pandemic, 81% had mild disease and 14% had severe disease.¹ Patients with the mild disease usually do not require hospitalization or any specific treatment. World Health Organization (WHO) defined severe COVID-19 as tachypnea (respiratory rate ≥ 30 /minute), hypoxia [peripheral oxygen saturation (SpO₂) less than 90% or PaO₂/FiO₂ less than 300 mm Hg], and signs of respiratory distress, while critical COVID-19 is defined by the criteria of acute respiratory distress syndrome, sepsis, and septic shock.² Severe or critical COVID-19 patients may require hospitalization or intensive care unit (ICU) admission and have higher mortality.³

In the absence of any proven antiviral agent, immunomodulators like corticosteroids are the mainstay of therapy.⁴ The evidence from large randomized controlled trials (RCTs) strongly supports corticosteroid use in critically ill COVID-19 patients with reduced mortality and need for invasive mechanical ventilation.⁵ The RECOVERY trial found no mortality benefit of corticosteroids in patients without respiratory support.⁶ The questions on appropriate timing, type, duration, and dose of corticosteroids in COVID-19 are still unanswered. The WHO living guidance suggests (weak or conditional recommendation) against the use of corticosteroids for non-severe COVID-19 (absence of any criteria for severe or critical COVID-19).² However, it was acknowledged the areas of uncertainty

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due to the absence of blinding or survival benefit and suggests a shared decision-making to the treating physician on conditions like clinical signs of disease progression in moderate COVID-19 (pneumonia without hypoxemia).²

There is an urgent need for recommendations on early intervention for patients with clinical progression, which may reduce the disease burden with already overwhelmed resources currently observed in various regions of India. There is an argument that using a combination of clinical, biochemical, or radiological criteria to identify patients with disease progression among non-severe COVID-19 and timely use of corticosteroids along with adequate monitoring may improve the outcomes. We conducted this modified Delphi study to develop expert consensus statements on early identification of a subset of patients from non-severe COVID-19 who may benefit from corticosteroids and provide recommendations on an appropriate dose, duration, and monitoring along with warning (red-flag) signs.

MATERIAL AND METHODS

This modified Delphi was conceptualized by senior members of the Indian Society of Critical Care Medicine (ISCCM). A two-member nonvoting steering group (PN and RJ) was selected to conduct the anonymous Delphi rounds and manage the data. An expert panel group of clinicians was selected based on the predefined criteria: member of the hospital or state task force for COVID-19 and actively involved in the management of COVID-19 patients. An e-mail invitation was sent to all selected experts. The steering group did a thorough literature search from the PUBMED database, with

keywords like, “glucocorticoids OR inflammation OR inflammatory biomarkers OR C-reactive protein AND COVID-19.” After applying filters for the date range, age, species, and original articles, a total of 173 articles were selected for the review. The steering group and senior members reviewed the evidence and identified six key problem areas for the use of corticosteroids in non-severe COVID-19.

Due to the time-sensitive nature of the project, closing criteria were defined a priori as two rounds of anonymous voting and consensus on clinical statements using controlled feedback. The Delphi rounds survey was prepared in the form of a questionnaire on “Google Forms” software by Google LLC, USA. Each survey was circulated for 48 hours to generate responses from the experts. The survey consisted of two types of questions, namely multiple-option type and five-point Likert-scale statements. A consensus was defined as >70% votes in multiple-option type or Likert-scale type statements. A similar definition for consensus on percentage was used in previously published studies.⁷

The round two survey was modified based on the open comments received in round one, and options that did not generate consensus were either removed or modified. We used a semiquantitative method to grade the consensus as “strong consensus” if >90% votes in multiple-choice questions or >50% votes for “very important” on Likert-scale questions (the options which generate consensus >70%) in the final round.

Microsoft Excel software, MS Office 2019, Microsoft Corp, Washington, USA was used for descriptive statistical analysis. As this study used proprietary intellectual data only, the ethics committee approval was not taken. Study participants (experts) gave consent for using this data for publication at the start of the study.

RESULTS

Two rounds of the survey were completed between April 30, 2021, and May 3, 2021. Of 32 invited experts, 21(65.6%) agreed to participate in the study and 20 (95.2%) experts completed both round surveys. The majority of the experts were from private institutions (72.72%) and intensivists (77.27%) (Table 1). Out of six questions and 49 points to vote for consensus in the first round, three questions and 16 (45.7%) options generated consensus. After reviewing the responses and comments from round one, we modified, deleted, and added few options to achieve further consensus:

Table 1: Demographics of the participating experts

Hospital affiliation	Age distribution (in years)				Grand Total
	31–40	41–50	51–60	61–70	
Private hospital	1	13	1		15
Trust run charitable Institution			1		1
University affiliated hospital		3	1	1	5
Grand total	1	16	3	1	21
Working specialty					Count
Critical care medicine					16
Internal medicine					4
Pulmonary medicine					1
Grand Total					21

- Options that generated >70% consensus were selected for stability in round two.
- Options that received >50% were clubbed/modified to achieve better consensus.
- Options with less than 50% votes were removed for round two

Twenty-one options were deleted or modified from round one. Twenty-one (91.3%) out of 23 options and all six questions in the second round generated consensus. The detailed results of the round two survey are in Table 2.

At the end of two Delphi rounds, we found eight criteria where steroids could be considered in non-severe COVID-19 after 5 days of symptoms onset. There was strong consensus on the increased work of breathing (95%), a positive six-minute walk test (90%), thorax computed tomography severity score of >14/25 (85%), new-onset

organ dysfunction (using clinical or biochemical criteria) (80%), and C-reactive protein (CRP) >5 times the upper limit of normal (70%). A drop of 3 to 4 points in SpO₂ from the baseline got consensus (75%) as the criteria for deciding a positive six-minute walk test. Experts had a strong consensus (95%) on the dose of corticosteroids equivalent to 6 mg/day dexamethasone and consensus (80%) on the duration of 5 to 10 days in non-severe COVID-19 (Fig. 1). The simple clinical parameters like SpO₂ (100%) and body temperature (100%) generated strong consensus for monitoring patients on corticosteroids. There was strong consensus on SpO₂ <90% (100%), worsening of current symptoms (100%), persistent fever not responding to paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) (95%), new-onset organ dysfunction (95%), and development of new symptoms (95%) as "red-flag" signs for urgent reassessment (Table 1).

Table 2: Summary of the concluding round (round two)

<i>Likert-scale clinical statements</i>	<i>Neutral (%)</i>	<i>Agree (%)</i>	<i>Consensus level</i>
Q1. Corticosteroids may be considered in non-severe COVID-19 (after 5 days from the onset of symptoms)			
Increased work of breathing	5%	95%	Strong consensus
Six-minute walk test positive	10%	90%	Strong consensus
CTSI >14/25	15%	85%	Strong consensus
Persistent high-grade Fever (>38.3°C or 101°F)	20%	80%	Consensus
Resting respiratory rate > 20/minute	20%	80%	Consensus
New-onset organ dysfunction (by clinical or laboratory criteria)	20%	80%	Strong consensus
CRP more than five times than upper limit of normal	30%	70%	Strong consensus
Raised other inflammatory biomarkers (e.g., Ferritin >500 ng/mL or LDH >600 U/L)	30%	70%	Consensus
Resting heart rate >120/minute	35%	65%	
Lymphopenia <10%	40%	60%	
Q5. What should include in the monitoring of non-severe COVID-19 patients who are prescribed corticosteroids?			
Oxygen saturation (SpO ₂)	0%	100%	Strong consensus
Temperature	0%	100%	Strong consensus
Repeat inflammatory markers after at least 3 days	15%	85%	Consensus
Clinical scoring system (e.g., Modified Early Warning Score (MEWS), WHO ordinal scale)	15%	85%	Consensus
Q6. What are the red-flag signs while using corticosteroids in non-severe COVID-19?			
Oxygen saturation (SpO ₂) less than 90%	0%	100%	Strong consensus
Worsening of current symptoms	0%	100%	Strong consensus
Persistent fever not responding to paracetamol or NSAIDs	5%	95%	Strong consensus
New-onset organ dysfunction (e.g., altered mental status)	5%	95%	Strong consensus
Development of new symptoms	5%	95%	Strong consensus
Blood Sugar >300 mg% for two consecutive values at least 4 hours apart	15%	85%	Consensus
Multiple-choice questions			
Q2. For a six-minute walk test, how much drop of oxygen saturation can be considered significant?			
Drop of 3 to 4 points	75%		Consensus
Unable to complete due to breathlessness or respiratory distress	65%		
SpO ₂ drops to <94% after the walk	60%		
Q3. What daily dose of corticosteroids (dexamethasone) would you recommend for non-severe COVID-19?			
6 mg dexamethasone (equals to 8 mg of dexamethasone phosphate)	95%		Strong consensus
>6 mg dexamethasone (>8 mg of dexamethasone phosphate)	5		
Q4. What should be the recommended duration of corticosteroids in non-severe COVID-19?			
<5 days	20		Consensus
5–10 days	80		
Longer duration depending on the inflammatory markers	30		

Consensus >70% votes for a particular option (cumulative of important or very important) in Likert-scale question and multiple-choice questions (MCQ). Strong consensus if >80% votes on a particular option in MCQ or >50% votes for option 2 (only for consensus statement) in Likert-scale statements; CTSI, CT severity index for COVID-19; CRP, C-reactive protein; NSAIDs, Nonsteroidal anti-inflammatory drugs; SpO₂, Peripheral oxygen saturation; WHO, World Health Organization

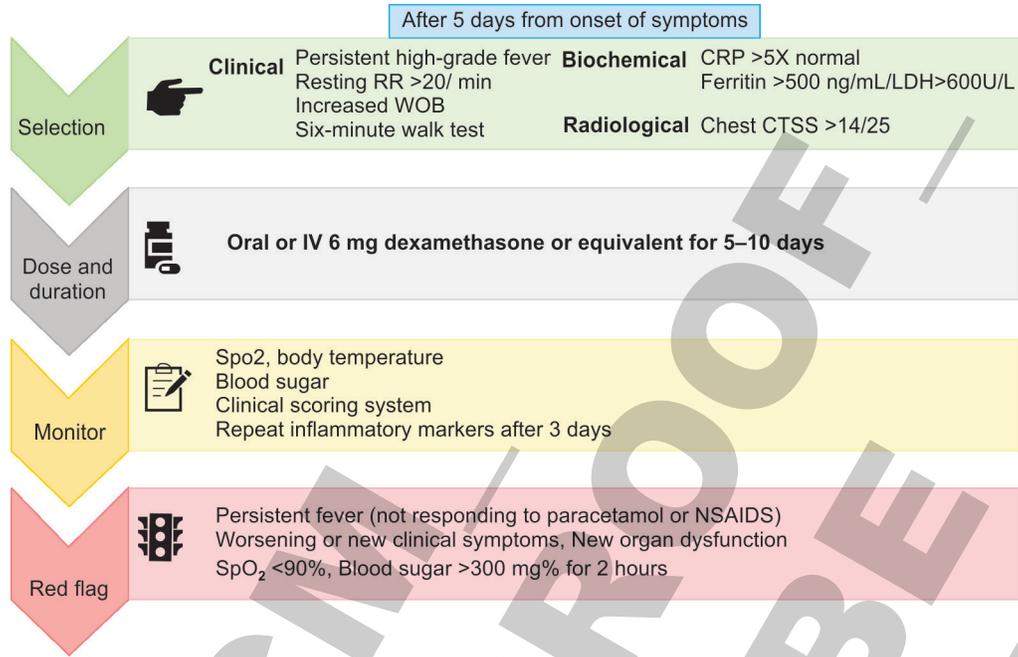


Fig. 1: Experts recommendation on the use of corticosteroids in non-severe COVID-19. COVID-19, Coronavirus disease 2019; RR, Respiratory rate; WOB, Work of breathing; CRP, C-reactive protein; CTSS, Computed Tomography severity score; SpO₂: Peripheral oxygen saturation

DISCUSSION

This modified Delphi study with 21 experts generated consensus statements on the use of low-dose corticosteroids in select monitored patients of non-severe COVID-19 after 5 days from the onset of symptoms and showing signs of disease progression. The experts recommended using oral or intravenous (IV) low-dose corticosteroids (the equivalent of 6 mg/day dexamethasone) for 5 to 10 days in patients identified for disease progression using a combination of clinical, biochemical, or radiological criteria (Fig. 1). The patients who are started on corticosteroids should be monitored for SpO₂, body temperature or a clinical scoring system [like Modified Early Warning Score (MEWS) or WHO ordinal scale], and for any “red-flag” signs.

The primary pathophysiology of severe COVID-19 involves a dysregulated host immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invasion into the host cells with a release of cytokines and other inflammatory markers like interleukin (IL)-1, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor- α , interferon (IFN)- λ , and IFN- β . The excessive release of cytokines and the chemoattraction of neutrophils and T-cells progress to hyperinflammation and cellular or organ injury.⁴ There were initial concerns about the use of corticosteroids in COVID-19.⁸ The immunomodulating effect of corticosteroids on the dysregulated immune response has to be balanced with concerns on delayed viral clearance, hyperglycemia, and secondary infections. Two meta-analyses of the studies, including seven RCTs, strongly supported the corticosteroid use in critically ill COVID-19 patients.^{5,9} There is conflicting evidence on delayed viral clearance and secondary infections in the studies published so far in COVID-19.^{9,10} A retrospective cohort study did not find a delay in SARS-CoV-2 clearance with the early use of corticosteroids moderate/severe COVID-19.¹⁰ There is a two-way relation between COVID-19 and diabetes mellitus (DM), whereby COVID-19 may worsen glycemic

control in DM. In a meta-analysis, patients with DM had a two-fold higher mortality due to COVID-19.¹¹ In a recently published cross-sectional survey, there was a considerable variation in the practice of corticosteroid use for COVID-19 among physicians of India.¹² The authors acknowledge the scope of improvement in the corticosteroid use for non-severe COVID-19.

The WHO living guidance gave a strong recommendation for the use of corticosteroids in severe and critical COVID-19.² The suggestion to avoid corticosteroid in non-severe COVID-19 is based on a weak or conditional recommendation. The recommendation is based on the RECOVERY trial subgroup analysis, showing a non-significant higher 28-day mortality in patients with COVID-19 without oxygen support.⁶ This low certainty evidence does not exclude a potential benefit in patients with clinical progression of non-severe COVID-19.² The theory of “one size does not fit all” stands true for corticosteroid use in COVID-19. Early identification of the progression of the disease from clinical signs like persistent fever or increased work of breathing is critical for the timely use of corticosteroids to halt the progression. The experts are against the indiscriminate use of steroids in the absence of clinical signs of worsening in mild or moderate COVID-19. The disease progression is usually seen between 4 and 8 days.¹² The median duration of progression of dyspnea to acute respiratory distress syndrome was found at 2.5 days.^{13,14} In a meta-analysis, the dyspnea, elevated CRP, and radiological findings have higher odds of severe disease and mortality.¹⁵

The six-minute walk test is a simple test to evaluate cardiopulmonary functional capacity using a graded aerobic exercise. The test can be used as a noninvasive bedside clinical test to unmask silent hypoxia, a marker of disease progression.¹⁶ The test needs to be done only when baseline SpO₂ is more than 94% and the patient is afebrile. The expert panel in our study had a strong consensus on a six-minute walk test for starting corticosteroids in non-severe

COVID-19, with a positive test defined as 3 to 4 points drop in SpO₂ from the baseline, an equivalent to dropping of more than 3%.¹⁷

The RECOVERY trial used 6 mg/day dexamethasone (equals 8 mg of dexamethasone phosphate) for 10 days.⁶ However, WHO living guidance suggests that corticosteroid choice is immaterial but supports a low dose of corticosteroid. Our expert panel also recommend 6 mg/day oral or IV dexamethasone or equivalent other corticosteroids for 5 to 10 days in non-severe COVID-19.⁵

Our experts recommended close monitoring of patients who are started on corticosteroids to identify any complications or progression of the disease. Data are still scarce on the risk associated with the use of corticosteroids and COVID-19, and hence recommendation based on the collective intelligence of experts is of value. The expert panel recommended clinical and biochemical monitoring parameters, including SpO₂, body temperature, and clinical scoring system. The hyperglycemia even with low-dose corticosteroids is an existent risk and needs periodical blood glucose monitoring. The experts acknowledged that corticosteroids might cause complications with masking of clinical signs even at a low dose. There was strong consensus on persistent fever (not responding to paracetamol or NSAIDs), worsening or new clinical symptoms, new organ dysfunction, SpO₂ <90%, and blood sugar >300 mg% (for two consecutive value, 4 hours apart) as “red-flag” for urgent reevaluation or escalation of care in patients started on corticosteroids (Table 2).

Strength and Limitation

This study used a modified Delphi process and has many strengths, such as timely completion of the survey with recommendations for clinicians on the use of corticosteroids using simple criteria in patients with disease progression. This study has recommendations on monitoring and warning signs for patients on corticosteroids. However, being a time-sensitive study, unintentional bias due to strong “belief perseverance” and the selection of experts cannot be excluded. The key elements of a Delphi study, like iterative rounds of the survey, could not be performed, and group stability was not checked. This study only depicts a collective opinion, and hence recommendations may become redundant after adequate evidence is available. However, apart from all strengths and limitations, this study highlights many areas for future research.

CONCLUSION

We provide expert consensus statements for using steroids in non-severe COVID-19 patients using the collective intelligence of 21 experts on a topic with scarce data. The experts recommend against the indiscriminate use of corticosteroids for non-severe disease in the absence of clinical worsening. Low-dose corticosteroids (the equivalent of 6 mg dexamethasone) for 5 to 10 days are recommended for patients identified for disease progression using clinical, biochemical or radiological criteria after 5 days from the onset of symptoms. A drop of 3 to 4 points on SpO₂ after a six-minute walk test may be used to identify such patients. In the absence of clear evidence and as the risk of worsening may still exist, the patients who are started on corticosteroids should be monitored for SpO₂, body temperature or clinical scoring system, and any “red-flag” signs.

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