Review Article

Tailoring glucocorticoids in patients with severe COVID-19: a narrative review

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Objective: To discuss the pathogenesis of severe coronavirus disease 2019 (COVID-19) infection and the pharmacological effects of glucocorticoids (GCs) toward this infection. To review randomized controlled trials (RCTs) using GCs to treat patients with severe COVID-19, and investigate whether GC timing, dosage, or duration affect clinical outcomes. Finally. to discuss the use of biological markers, respiratory parameters, and radiological evidence to select patients for improved GC therapeutic precision.

Background: COVID-19 has become an unprecedented global challenge. As GCs have been used as key immunomodulators to treat inflammation-related diseases, they may play key roles in limiting disease progression by modulating immune responses, cytokine production, and endothelial function in patients with severe COVID-19, who often experience excessive cytokine production and endothelial and renin-angiotensin system (RAS) dysfunction. Current clinical trials have partially proven this efficacy, but GC timing, dosage, and duration vary greatly, with no unifying consensus, thereby creating confusion.

Methods: Publications through March 2021 were retrieved from the Web of Science and PubMed. Results from cited references in published articles were also included.

Conclusions: GCs play key roles in treating severe COVID-19 infections. Pharmacologically, GCs could modulate immune cells, reduce cytokine and chemokine, and improve endothelial functions in patients with severe COVID-19. Benefits of GCs have been observed in multiple clinical trials, but the timing, dosage and duration vary across studies. Tapering as an option is not widely accepted. However, early initiation of treatment, a tailored dosage with appropriate tapering may be of particular importance, but evidence is inconclusive and more investigations are needed. Biological markers, respiratory parameters, and radiological evidence could also help select patients for specific tailored treatments.

Keywords: Coronavirus disease 2019 (COVID-19); glucocorticoid (GC); cytokines; C-reactive protein (CRP); computed tomography

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Introduction

Coronavirus disease 2019 (COVID-19) has become an unprecedented worldwide challenge. To date, over 130 million people have been infected and almost three million have died (1). As cases surge, intensive care units (ICUs) in many countries are facing huge pressures to treat critically ill patients, concomitant with on-going governmental efforts to tackle the pandemic.

The first report from the RECOVERY group in July 2020 provided a potentially promising glucocorticoid (GC) treatment regimen for patients infected with COVID-19 (2). Dexamethasone resulted in a lower 28-day mortality among those receiving either invasive mechanical ventilation (IMV) or oxygen alone, suggesting GCs may be effective in some populations (2).

While controversy continues over whether GCs may be a definitive treatment, updated World Health Organization (WHO) guidelines now recommend using them in clinical practice (3). However, evidence gaps exist as there have been no prospective trials specifically reporting on GC timing, dosage, or duration. Thus, uncertainties around GCs must be clarified for prescribing physicians and patients.

In this review, we discuss the pathogenesis of severe COVID-19 infection and the pharmacological effects of GCs toward this infection. We review randomized controlled trials (RCTs) using GCs to treat patients with severe COVID-19, and investigate whether GC timing, dosage, or duration affect clinical outcomes. Finally, we discuss the use of biological markers, respiratory parameters, and radiological evidence to select patients for improved GC therapeutic precision.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/atm-21-1783).

Methods

PubMed and Web of Science were searched using the terms "glucocorticoid", "corticosteriod", "steriod" and "COVID-19" in English through March 2021. Articles in English and in Chinese were included. We also included results from cited references in published articles searched by using the method described above. The final reference list was generated on the basis of relevance and originality with regard to the topics covered in this review.

The pathogenesis of severe COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen causing COVID-19, initially binds to host cells expressing the surface receptor, angiotensin-converting enzyme 2 (ACE2) (4). Multiple subsequent reactions are involved in pathogenesis, producing a unique pathophysiological landscape contributing to COVID-19 infection (*Figure 1*).

Cytokine production

Cytokine production is an important element of immune response initiated in infected individuals. Upon binding to SARS-CoV-2, cells expressing ACE2, including alveolar epithelial cells, undergo pyroptosis and release damage associated molecular patterns (4) consistent with post-mortem histopathological findings characterized by diffuse alveolar damage (DAD) (5-7). This damage is recognized by monocytes and macrophages which trigger pro-inflammatory cytokine and chemokine cascades (4).

Elevated cytokine levels, particularly in severely ill patients, suggest that excessive cytokine production may contribute to COVID-19 pathogenesis (8,9). Increased interleukin (IL) levels, including IL-2, IL-6, IL-7, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) are observed during COVID-19 infection (10,11). The term "cytokine storm" has been used to describe this distinctive immune response (12). Among these cytokines, increased IL-6 levels are highly associated with shorter patient survival times (13). These observations suggest that balancing immune responses after infection are vital to successful treatment outcomes.

Endothelial dysfunction

As ACE2 receptors are primarily located on endothelial cells in the lungs, they are the main victims in SARS-CoV-2 infection. Numerous circulating markers of endothelial injury, such as coagulation factor VIII, von-Willebrand-factor, and angiopoietin 2 are increased in patients with COVID-19 (14). Similarly, autopsies have also revealed the formation of hyaline membranes and micro-thromboses as key pathological patterns besides DAD (5,7).

Endotheliopathy reflects micro-thrombosis in end-

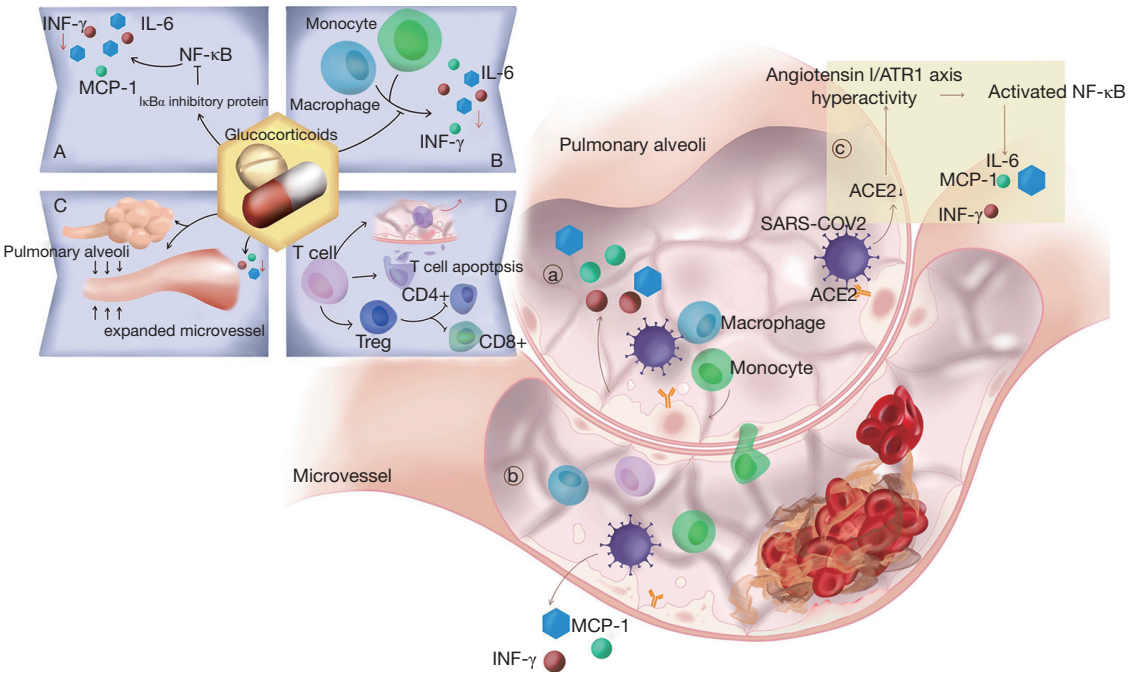

Figure 1 The pathogenesis of severe COVID-19 and the pharmacology of glucocorticoid (GC). Multiple reactions may be involved in the pathogenesis of COVID-19 and tend to coordinate with each other. GC can target these reactions pharmacologically. (a) Alveolar epithelial cells infected by SARS-CoV-2 undergo pyroptosis and release damage associated molecular patterns which are recognized by neighbouring monocytes and macrophages, triggering the generation of pro-inflammatory cytokines and chemokines. (b) Infected vascular endothelial cells threaten the integrity of vessels, leading to infiltration of leukocytes to lung tissue. Besides, numerous markers are released, facilitating the formation of thrombosis. Cytokines are also released because of damaged vascular endothelial cells. (c) ACE2 downregulation leads to a hyperactivity of the angiotensin II/ATR1 axis. resulting in the binding of angiotensin II to ATR1. Nuclear factor kappa B (NF-κB) is then activated, causing the release of cytokine. (A) GC inhibits the activation of NF-κB via induction of the IκBα inhibitory protein (B) GC reduces cytokine production among macrophages and monocytes by the genomic effect (C) GC restricts the extent of endotheliopathy through cytokine reduction, barrier enhancement and vascular modification. (D) GC exerts unique actions on T cells. First, GC decreases the number of circulating T cells by favoring their migration back to the bone marrow and secondary lymphoid tissues. It also induces apoptosis of T cells in peripheral lymphoid organs and down-regulates adhesion molecule. In addition, GCs increases the frequency of regulatory T cells (Treg), which inserts an immunosuppressive effect on the activation, proliferation and cytokine production of CD4+ T cells and CD8+ T cells.

organ damage, and mediates inflammatory cell infiltration particularly in T cells in the lungs (15). Complex interactions between coagulopathy, thrombocytopathy, and endotheliopathy contribute to COVID-19-associated thrombo-inflammation (16,17). Also, diffuse infiltration of alveolar walls by CD4+ and CD8+ T lymphocytes has been identified in patient autopsies (7,18). Local inflammation aggravation involving increased pro-inflammatory cytokine and chemokine secretion into patient blood attracts immune cells, notably T lymphocytes from the blood to infected sites, generating lymphopenia in the peripheral blood (4,11,19). Such coordinated activation of inflammatory and thrombotic responses is a major cause of morbidity and mortality (16). Thus, early identification of endotheliopathy and strategies to mitigate its progression may improve COVID-19 outcomes (20).

Renin-angiotensin system (RAS) dysfunction

SARS-CoV-2 enters respiratory epithelial cells via ACE2 interactions, causing receptor internalization and subsequent down-regulation (21). Reduced ACE2 levels, which have been shown to regulate RAS, could lead to RAS dysfunction, potentially enhancing inflammation and airway vascular permeability (22). ACE2 down-regulation reduces the transformation of angiotensin II to angiotensin-(1–7),

thus causing hyperactivity of the angiotensin II/angiotensin receptor 1 (ATR1) axis (23), resulting in angiotensin II binding to ATR1. This reaction activates nuclear factor-κB (NF-κB) (24), which is the most important checkpoint in COVID-19-related pro-inflammatory events, with potential roles in COVID-19-related cytokine storms (25,26). Activated NF-κB leads to the downstream production of several pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α (25,27,28), which potentially enhance inflammation and airway vascular permeability (22).

The pharmacological effects of GCs on severe COVID-19

Several signaling pathways are impacted by GCs that affect cellular activities, with most reactions mediated by glucocorticoid receptors (GRs) (29). In the absence of GCs, GRs reside in the cytoplasm and are complexed with chaperone molecules composed of heat shock proteins (HSP) 90, 70, and immunophilins (30). The GRα is of particular importance in critical illnesses thanks to its dominant effect on GC-mediated activities (31).

GCs enter cells as free molecules and produce biological effects via three pathways (genome, non-genome, and mitochondrial). In the classic genomic pathway, upon cytoplasmic entry, GCs bind to GRs, which induce conformational changes permitting GRs to dissociate from chaperone molecules and dimerize (32). These dimerized complexes are then actively transported to the nucleus where they bind to palindromic GC response elements (GRE) in gene promoters, permitting the subsequent recruitment of co-activators leading to chromatin remodeling and downstream transcription (32,33).

Immune cell modulation

Cytokine production inhibition by macrophages and monocytes is a major GC anti-inflammatory mechanism (34). Macrophages and monocytes are among the most effective producers of pro-inflammatory mediators. Through genomic effects, GCs inhibit IL-1β, IL-6, IL-12, and TNFα transcription and down-regulate chemokine expression, including IL-8 and MCP-1 (34) to limit overwhelming and sustained inflammation.

GCs also exert specific immunosuppressive actions on T cells (35). Circulating T cell numbers are decreased by GCs which promote their migration back to bone marrow and secondary lymphoid tissue. GCs also induce T cell apoptosis in peripheral lymphoid organs and down-regulate adhesion molecules (36-38). These effects potentially reduce T cell infiltration to inflamed areas, especially in the lungs of patients with COVID-19. Also, GC treatment increases regulatory T cell (Treg) frequency (39), in part by enhancing Treg cell numbers or activity, and promoting the development of IL-10-producing T cells (40). This exerts immunosuppressive effects on the activation, proliferation, and cytokine production of CD4+ T cells and CD8+ T cells (41).

Cytokine reduction and inhibition

GCs modulate cytokine expression via a combination of genomic mechanisms. The activated GR complex binds to and inactivates key pro-inflammatory transcription factors, such as AP-1, whereas it up-regulates the expression of cytokine inhibitory proteins via its GRE, and reduces the half-life and utility of cytokine mRNAs (42,43). Additionally, GCs are potent NF-κB activation inhibitors (44). This process is important in RAS dysfunction, and is mediated by induction of the inhibitor of nuclear factor-κB (IκBα) protein trapping activated NF-κB in inactive cytoplasmic complexes (45).

Improvements in endothelial function

Inflammatory cell infiltration and increases in vascular permeability and diameter are important characteristics in endotheliopathy (46), whereas GCs restrict the extent of endotheliopathy via cytokine reduction, barrier enhancement, and vascular modification.

As GCs modulate immune cellular activities and act on specific pathways to reduce inflammatory mediators, they inhibit the attraction and infiltration of immune cells to specific inflammation tissue sites by reducing cytokine and chemokine release (47). GC enhancement of barrier function at the lung endothelium is also required to suppress vascular leakage and infiltration of inflammatory cells into the lung (48,49). GCs preserve endothelial barrier integrity by up-regulating junctional proteins such as occludin (50) and down-regulating matrix metallopeptidase 9 (MMP-9) which is an enzyme involved in junctional protein cleavage (51-53). GCs also indirectly modify vascular diameter by inhibiting inflammatory mediators to reduce vessel swelling (54).

GCs and patients with severe COVID-19

GCs have long been considered potential immunomodulators

Table 1 RCTs regarding severe COVID-19 patients treated with GCs

Author	Size T/C	Type of GC	Timing median [IQR]	Dosage	Duration	Main Outcome
The RECOVERY Collaborative Group (2)	324/689	DX	8 [5–13]	6 mg qd	Up to 10 days	The incidence of death is lower among patients receiving IMV (29.3% *vs.* 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81)
Jeronimo *et al.* (66)	194/199	MP	13 [9–16]	0.5 mg/kg bid	5 days	The overall 28-day mortality was not significant between the placebo group and the MP group (P=0.629)
The Writing Committee for the REMAP-CAP Investigators (62)	283/101	HC	N/A	50 mg or 100 mg q6h or 50 mg q6h when shock was clinically evident	7 days	HC resulted in 93% probabilities of superiority, with regard to the odds of improvement in organ support-free days within 21 days
Dequin *et al.* (64)	76/73	HC	N/A	200 mg qd then 100 mg qd then 50 mg qd	7 days then 4 days then 3 days	There was no significant difference for Treatment failure on day 21 between HC group compared and the placebo group (P=0.29)
Tomazini *et al.* (67)	151/148	DX	9 [7–11]	20 mg qd then 10 mg qd for	5 days then 5 days or discharge	The mean number of days alive and free from mechanical ventilation during the first 28 days was significantly higher in the DX group (6.6 *vs.* 4.0; difference, 2.26, P=0.04)
Edalatifard *et al.* (65)	34/28	MP	N/A	250 mg qd	3 days	The mortality rate was lower in the MP group (5.9% versus 42.9%; P<0·001). Patients in the MP group also had a significantly increased survival time (P<0.001)
Corral-Gudino *et al.* (63)	56/29	MP	N/A	40 mg bid, then 20 mg bid	3 days then 3 days	The use of MP was associated with a reduced risk of the composite endpoint in the intention-to-treat, age-stratified analysis (P=0.024)

When different regimens were adopted in a study, the one that dominated is presented here. RCT, randomized clinical trial; DX, Dexamethasone; MP, Methylprednisolone; HC, Hydrocortisone; T, Testing group; C, Control group; GC, glucocorticoid; qd, quaque die; bid, bis in die; IMV, Invasive Mechanical Ventilation, IQR: interquartile range.

in many inflammatory diseases. But recommendations for systemic use of GC when treating severe infections, such as sepsis, are weak and are not well supported (55). In the previous SARS and Middle East respiratory syndrome (MERS) epidemics, while clinical evidence was inconclusive, GCs were still regarded as important treatment options (56-58). In this COVID-19 pandemic, the current evidence indicates that inflammation is a prominent pathophysiological process (59), with acute respiratory distress syndrome (ARDS) observed in over 70% of ICU patients and 90% of non-survivors (60). As GCs potentially improve patient outcomes in similar diseases such as ARDS (61), several studies have investigated its potential effects.

To date, seven RCTs (2,62-67) with substantially different GC administration timings, dosages, and durations have investigated whether GCs positively affect patients with severe COVID-19. Importantly, most have reported positive results, such as improved 28-day mortality (*Table 1*). A meta-analysis also concluded that GCs improved 28-day mortality (68). Based on these observations, clinical guidelines and protocols have been updated to recommend GCs for severely infected patients (69-71).

Timing of GC administration

The timing of GC administration is highly significant in affecting not only its pharmacological properties, but also disease course. Physiologically, early GC administration may be critical to decrease the acute and long-term negative impact on critically ill patients, as homeostatic correction could quickly turn into exhaustion (31,72). Early (<72 h) methylprednisolone (MP) administration when compared to late (≥7 days) was associated with faster disease resolution and ICU discharge in patients with ARDS (73). Recently,

the DEXA-ARDS trial concluded that early dexamethasone administration reduced the duration of mechanical ventilation (MV) and overall mortality (74).

In patients with severe COVID-19, when RCTs reported GC timings (2,66,67), the average time for treatment initiation was approximately 8–13 days from symptom onset, a relatively late GC treatment schedule. Mixed results concerning mortality and days free from ventilation were reported in these studies. As benefits of early initiation of treatment have been proved in ARDS, an earlier treatment initiation is worthy of investigation. According to a recently published clinical-therapeutic staging proposal, an early phase in COVID-19 is characterized by an incubation period with mild and non-specific symptoms (75). For the moment, clinicians should decide on a case-by-case basis as no clear evidence has indicated the best possible initiation time for treatment. However, this kind of research is difficult. Confirming a COVID-19 diagnosis takes time, and hospitals are under huge pressure with unpredictable patient surges. Therefore, trialing and treating patients in an orderly manner are highly challenging.

GC dosage

While the precise relationship between GC dose, cellular concentration, and clinical effects remain to be established, it is believed an adequate initial loading bolus is required, particularly when GCs are administered as a continuous infusion (76). Tapering is also another key factor. RCTs have reported that abrupt GC discontinuation was rapidly followed by rebound inflammatory responses with severe clinical relapses (77-79). Additional MV days and increased morality risk were also reported (80,81).

In most critical care studies, the daily MP equivalent of 80–100 mg (dexamethasone 15–18.8 mg) is used to separate low from moderate doses (31). Low-to-moderate GC doses (MP <2 mg/kg/day) significantly reduced the mortality rate of patients with ARDS, while high-GC doses (MP >2 mg/kg/day) provided no significant benefit toward mortality rate reduction (82). In the aforementioned DEXA-ARDS trial, patients in the dexamethasone group received a daily intravenous dose of 20 mg from day 1 to 5, which was reduced to 10 mg daily from day 6 to 10. Reduced duration of mechanical ventilation and higher overall mortality in patients with established moderate-to severe ARDS were observed (74).

Despite the importance of an initial loading bolus, different dosage regimens have been reported in patients with severe COVID-19 (2,62-67). One particular regimen comprised consistent GC doses throughout the treatment course. However, mixed results were reported for this approach (2,66). The administration of 6 mg dexamethasone for up to 10 days reduced the 28-day mortality in those receiving either IMV or oxygen alone (2), while MP at 0.5 mg/kg for 5 days did not reduce mortality (66). Another regimen comprised the administration of tapering dosages, but inconsistent results were reported (62-64,67). This dosage category did not reduce treatment failure in patients with COVID-19-related acute respiratory failure (64). However, it was associated with more ventilator-free days (67). Another regimen comprised the administration of pulse dosages for a short time period; an MP pulse (intravenous injection, 250 mg/day for 3 days) generated a significantly increased survival time in patients with severe COVID-19. But the impact of this study is limited as a very small number of participants (34 patients in each group) were included and that ARDS was considered an exclusion criterion, thus offering poor values when treating patients with severe COVID-19. (65). While direct comparisons between studies are questionable, as certain variables were not controlled, these results suggest more studies are required to investigate the impact of GC dosage. Thus, clinical decisions should be made without excluding all options.

GC duration

The duration of GC administration is a main determinant of treatment efficacy (31). A protocol for prolonged MP treatment in patients with early ARDS, featuring a 28-day tapering plan, was recommended in recently published guidelines (83).

Durations adopted in RCTs for GC treatment in patients with severe COVID-19 are related to the dosage regimen being used and whether tapering was included. The only trial with pulse dosage treatment lasted for 3 days, with positive results observed (65). A consistent dosage plan was provided for 5, 7, and up to 10 days in different trials (2,65,66), and tapering was included in three trials, lasting from 6–14 days. However, no consensus results were reached across categories.

These mixed timing, dosage and duration results were attributed to several reasons. Both inclusion criteria and patient baseline characteristics differed greatly between studies. Patient populations with different mean ages, different disease stages, and a wide range of diverse

commodities were investigated. These factors may have had a significant impact on treatment outcomes. In addition, positive conclusions may be associated with the selection of correct patient groups. In the RECOVERY study, mortality benefits were only observed in patients receiving IMV or oxygen alone (2). Many other studies have adopted partial pressure of oxygen (PaO_2)/fraction of inspiration O_2 (FiO_2) in their inclusion criteria. However, targeting this particular physiological marker may not be enough to filter potential groups who could likely benefit from GCs, whatever the regimen is. Finally, systemic variations, such as differences between healthcare systems and practice norms may also have an impact.

Despite considerable efforts, it is extremely difficult to derive definitive conclusions on GC timing, dosage, and duration from the literature. Firstly, completed RCTs still focus on the effectiveness of GCs in general rather than specific regimens during treatment. Also, GC type, timing, dosage, and duration vary greatly between studies, making it difficult to draw conclusions due a lack of high-quality evidence. Lastly, some RCTs (64) completed early due to issues with patient recruitment and the publication of results (e.g., RECOVERY), thereby questioning the strength of study outcomes.

At the same time, potential severe adverse effects associated with GCs need to be considered and cost-benefit analysis should be made when substantial uncertainty occurs. Traditionally, long-term use of GC is associated with various complications, such as infections, diabetes and osteoporosis, psychiatric disorders, and adrenal crisis (84,85). High-dose GCs is related to many metabolic disorders, such as hypokalemia and intravenous pulse GCs have been associated with hypotension, electrolyte disorders, anaphylactic shock, and abnormal behavior (86). For patients with severe COVID-19, one systemic review including 6 trials concluded that there was no suggestion that the risk of serious adverse events was higher in patients treated with GCs except for the 2 smallest trials (68). A further systemic review published recently draw the conclusion that there were unclear differences in rates of neuromuscular weakness and gastrointestinal bleeding with GCs. Increase in superinfection was not observed. But there was probably an increase in hyperglycemia (87).

Unequivocally, GC benefits in patients with severe COVID-19 are dependent on the selection of the right dose, at the right time, in the right patient group. Using new methods to target specific patient groups, guiding GC treatments based on disease progression, and evaluating treatment effectiveness should be key research objectives in future research.

Tailoring GC treatments

GC regimens lasting 7–10 days have been recommended in updated WHO guidelines for treating patients with severe COVID-19 (3), but the exact timing, duration, and dosage remain, and whether proper weaning should be considered unclear. As more clinical trials are being conducted, it appears that in a short period of time, the concept of "one regimen fits all" cannot be adequately addressed in current RCT models.

Previously, it was reported that patients with ARDS receiving similar GC doses experienced a substantial variability in plasma concentrations due to between-patient variability, plus additional disease effects from GC pharmacokinetics were also observed, potentially affecting clinical responses (88). Therefore, tailored dosages and therapy durations based on individual patient responses are essential.

Undoubtedly, current clinical research has generated beneficial parameters to evaluate end-point incidents (2,62-67). Several RCTs and observational studies have adopted mortality rates and ventilation status as primary or secondary outcomes (2,65,67). However, a lack of evaluation and assessment tools during disease progression means physicians are less likely to adequately assess ambulatory characteristics and decide when, how much, and how long GCs should be administered.

Several biological markers have been adopted to reflect disease severity and may help tailor GC treatments. Of these, C-reactive protein (CRP) (89-91), lactate dehydrogenase (LDH) (92,93), neutrophil lymphocyte ratios (94), and D-dimers (90,95,96) alone are all associated with disease progression severity. Other markers, such as the interleukins (97), ferritin (98,99), and several cardiac markers (100) have also been explored. In one study, a combination of two markers (neutrophil-to-lymphocyte ratio and CRP) correlated with disease severity, similar to individual use (101). For patients with elevated CRP, GC treatment was linked to reduced mortality risk or MV (102), suggesting this marker may help select patients benefitting from GCs. However, several limitations to this approach must be considered. Firstly, as several biomarkers reflect disease severity, with no consensus on superiority, it is difficult for clinicians to decide on the importance of one marker and associated changes during infection.

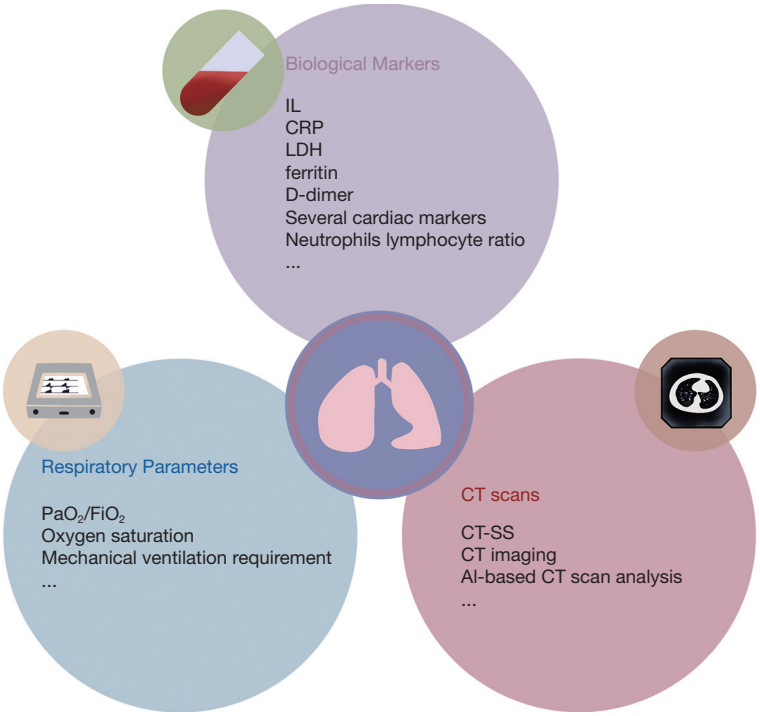

Figure 2 Three dimensions of tailoring glucocorticoids. The efficacy of glucocorticoid (GC) treatment can be monitored by taking three perspectives, biological markers, respiratory parameters and radiological evidence into consideration. CRP, C-reactive protein; LDH, lactate dehydrogenase; IL, Interleukin; PaO_2, partial arterial pressure of oxygen; FiO_2, fraction of inspiration oxygen; CT, computed tomography; CT-SS computed tomography severity score, AI, artificial intelligence.

Additionally, biological markers tend to be influenced by a number of factors, e.g., CRP is elevated during multiple inflammatory conditions, including rheumatoid arthritis and some cardiovascular diseases, besides COVID-19 (103). Thus, more studies are required to investigate the potential impact of these markers on COVID-19.

Respiratory parameters could also be used to define severe COVID-19 infections. In general, such parameters are defined by at least one of the following characteristics: respiratory distress (≥30 times/min), oxygen saturation ≤93% at rest, respiratory failure requiring MV, and PaO_2/FiO_2 ≤300 mmHg (62,104-106). The use of GCs for patient receiving IMV resulted in a lower 28-day mortality (2), suggesting that respiratory parameters could be adopted to select patients for GC treatment. However, clinical hazards must be indicated if these parameters are used. Undesirable changes in PaO_2/FiO_2 or oxygen saturation levels in patients on oxygen therapies do not necessarily reflect progression of an initial infection. Ventilator-induced lung injury caused by inappropriate tidal volume or positive end-expiratory pressure could worsen the ventilation status of patients (104,107). Other complications, such as ventilator-related infections by bacteria, may also affect respiratory status (108).

In addition, most clinical trials (2,62-64,67) have included inflammatory markers and ventilation status to their study designs, but the benefit of adding radiological evidence to guide GC treatment is warranted (*Figure 2*).

Chest computed tomography (CT) has been used in the diagnosis and evaluation of many respiratory diseases, such as pneumonia (109) and interstitial lung disease (110). It is accepted that monitoring responses to GC treatment during intervention, using daily assessments of lung, multiple organ function, and systemic inflammation marker measurements are essential (31,111).

Lung infection severity may be assessed using CT imaging in a comparatively objective manner. A chest CT severity score (CT-SS) has been proposed to evaluate patient severity upon diagnosis, and importantly provides crucial prognostic information. The score uses lung opacification as a surrogate for extension of the disease, and could be used to rapidly and objectively evaluate the severity of pulmonary involvement (112). Also, these scores

have implications for predicting the progression risk of patients with COVID-19 pneumonia at admission, risk-stratification, and admission timing (113).

CT not only offers crucial information on lung pathology, but is also a good indicator of systemic characteristics. CT-SS is positively associated with several inflammatory indices (e.g., neutrophil counts, LDH, and CRP) and negatively associated with lymphocyte counts (114,115). Thus, CT-SS provides considerable morphological information on lung inflammation progression as well as systemic inflammatory status.

Modern technology may help increase evaluation accuracy based on CT analyses. Artificial Intelligence (AI)-guided severity assessments and patient-following could have promising roles in guiding GC treatments. Thus, AI and CT could help precisely evaluate COVID-19 pneumonia severity and also patient clinical surveillance (116). As the role of AI in patient diagnostics has already been confirmed (117), its combination with CT-SS as an AI-guided GC treatment could offer more precise clinical options for clinicians.

In their study, Su *et al.* reported several cases where AI-based CT scans were used to adjust GC parameters (dosage and duration) in patients, with the authors concluding that sufficient GCs may be effective in treating patients with COVID-19, concomitant with frequent evaluation and timely adjustment (118). However, further research is required to investigate how GCs may be adjusted based on a combinatorial approach of physiological markers, laboratory results, and CT analysis. Similarly, limitations to this approach exist, e.g., appropriate algorithms must be tested to objectively and precisely reflect lung opacification. More importantly, in hospitals with limited capacity to separate patients, the risk of spreading disease while transferring patients should also be considered. For patients, frequent CT scans may generate radiation exposure risks, and treatment costs not covered by healthcare systems may generate increased economic burdens to patients outside these systems. Lastly, these approaches are limited to facilities where CT technologies are readily available.

Conclusions

GCs play key roles in treating severe COVID-19 infections. We investigated the unique properties of GCs toward immune cell modulation, cytokine reduction, and improved endothelial function, which reflect the major pathophysiological processes induced by COVID-19. The clinical studies reviewed here have somewhat proven the efficacy of GCs in patients with severe COVID-19. However, timing, dosage, and duration varied considerably among studies. GC treatment initiation is relatively late when compared with ARDS, with a tendency to administer low-to-moderate GC doses. Importantly, tapering as an administrative method is not widely accepted. Thus, early treatment initiation and a tailored dosage with appropriate tapering may be of particular relevance. Equally, biological markers, respiratory parameters, and radiological evidence may be used in a combinatorial manner to tailor GC treatments to patients with COVID-19.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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