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## Consensus and Guideline

## Expert consensus on the diagnosis and treatment of severe and critical coronavirus disease 2019 (COVID-19) ☆



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## Introduction

Coronavirus disease 2019 (COVID-19), a disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is highly contagious<sup>[1]</sup> and has developed into a global pandemic. Up to July 1, 2022, COVID-19 has affected >200 countries and regions across the globe and caused 545,226,550 confirmed cases and 6334,728 deaths,<sup>[2]</sup> seriously compromising human life, public properties, and medical and health care sys-

tems. The emerged SARS-CoV-2 variants (Delta and Omicron), which are variants of concern with progressively increased transmissibility between humans and potential problems with vaccine effectiveness pose new challenges for global pandemic prevention and control efforts.<sup>[3–6]</sup> Although the disease severity is lower with the Omicron variant, the high volume of emergency department visits and hospitalizations places pressure on local health care systems and is a marked threat to global public health.

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This consensus focuses on severe and critical cases of COVID-19, predominantly based on the consideration that the mortality of severe and critical cases is higher compared with mild and moderate cases of COVID-19. In addition, no significant time window exists between severe and critical cases. Therefore, healthcare workers (HCWs) should increase their vigilance over this group of patients and pool the best expertise and resources to treat severe and critical cases in the early stage. The vast majority of patients with COVID-19 have mild symptoms and a usually favorable prognosis; however, some older patients with COVID-19 and underlying medical conditions may rapidly develop severe illness. Severely affected patients usually developed dyspnea and/or hypoxemia in a short period of time, and in some cases progressively developed respiratory failure, septic shock, coagulation disorders, and multi-organ dysfunction.<sup>[7–9]</sup> One study reported a mortality of 2.3% in mild patients and high mortality of 50% in critically ill patients.<sup>[10]</sup> At the time of writing, the causes underlying the progression to severe and critical illness have yet to be elucidated. Besides, viral load, abnormal immune response in the COVID-19 patient is believed to be the major cause of progression to severe, critical illness and even death.<sup>[11]</sup>

No antiviral drugs specifically effective for COVID-19 were available until three new oral antiviral treatments (molnupiravir, fluvoxamine, and Paxlovid) were clinically proven to be effective.<sup>[12,13]</sup> Organ support therapy (respiratory, circulatory, and other organs) is a vital treatment for severe and critical cases. To better standardize and guide the diagnosis and treatment of severe and critical patients with COVID-19, and improve the treatment success rate, we organized a group of critical care medicine experts across China to formulate this consensus based on a literature review, the clinical experience gained in the fight against the pandemic in China, and several expert workshops to guide clinical practice.

### Part I: Methods for Formulating This Consensus

This consensus is the result of the concerted efforts of front-line medical experts across China. The expert group first identified the problems relevant to the diagnosis and treatment of severe and critical COVID-19, then defined the clinical problems using the population, interventions, comparisons, and outcomes (PICO) framework to guide the literature search. The databases searched included PubMed, Web of Science, and Embase. The keywords searched included SARS-CoV-2, novel coronavirus, nCoV, COVID-19, critically ill, severely ill, novel coronavirus pneumonia, severe and critical, diagnosis, and treatment

and management. The keywords were searched in combination with free terms. The time period searched was from the date the databases were established to June 2022. All search results were pooled, including systematic reviews, meta-analyses, randomized, controlled studies, cohort studies, case reports, and guidelines. Publications not in English or Chinese, publications where full text was not available and the authors could not be reached were excluded. Based on a comprehensive review (analysis, consolidation, and summarization) of the treatment protocols, management consensuses, and relevant literature on COVID-19 and the experience gained from the diagnosis and treatment of severe and critical COVID-19 patients during the fight with the pandemic in China, a draft of this consensus was produced. The draft was subsequently discussed at face-to-face and online video expert workshops, underwent several rounds of revision (including repeated searching and updating of references), and finally formulated the current shape based on a consensus reached using the Delphi method. This consensus comprises 49 recommendations.

The strength of the recommendations was graded using the grading of recommendations assessment, development, and evaluation (GRADE) approach. The recommendations were graded into three levels: strong recommendation, optional recommendation, and expert opinion, as shown in [Table 1](#).

### Part II: Etiology, Pathology, and Pathophysiology

Based on current research findings, three main pathophysiological mechanisms have involved the onset of severe COVID-19. First, SARS-CoV-2 enters host cells and directly causes cell injury. When the virus encounters cell receptors, angiotensin-converting enzyme 2 (ACE2) is richly expressed in respiratory cells such as goblet cells, ciliated epithelial cells, and type-II alveolar epithelial cells. Therefore, in SARS-CoV-2-infected patients, the respiratory system is usually the first affected organ. In addition, ACE2 may also be expressed in various other human tissues, such as small intestines, vascular endothelial cells, olfactory neurons, kidneys, heart, thyroid gland, testes, and adipose tissues. This indicates that the virus can enter the human body through other pathways and directly compromise the function of various organs.<sup>[14]</sup> The second pathophysiological mechanism is that SARS-CoV-2-induced immune responses further aggravate pulmonary injury. The process is extremely complex, involving the generation of massive amounts of proinflammatory cytokines and chemokines, recruitment of immunocytes (monocytes, macrophages, and T cells), progressive reduction of lymphocytes, and antibody-dependent enhancement.<sup>[15]</sup> These re-

**Table 1**  
Strength of recommendation grading using the GRADE system.

Evidence	Recommendation	Grade
High level of evidence	Strong recommendation “... should be done...”	Grade 1+
Moderate level of evidence	Optional recommendation “... should probably be done...”	Grade 2+
Low level of evidence	Recommendation in the form of an expert opinion “The experts suggest...”	Expert opinion
Moderate level of evidence	Optional recommendation “... should probably not be done...”	Grade 2–
High level of evidence	Strong recommendation “... should not be done...”	Grade 1–

GRADE: Grading of recommendations assessment, development, and evaluation.

sponses and subsequent interactions promote systemic inflammation and finally cause multi-organ dysfunction. Third, coagulation mechanism abnormalities are accelerated in multi-organ dysfunction. In particular, hypercoagulation and microthrombosis in pulmonary arteriole vessels are the typical manifestations of severe and critical COVID-19.<sup>[16]</sup> The pathogenesis may be closely related to endothelial injury, neutrophil recruitment, cytokine release, and complement activation. Finally, the impaired organs interact and evolve into a vicious circle of multi-organ dysfunction. Investigating the pathogenesis of severe COVID-19 facilitates the development of new prevention and treatment methods, including the development of vaccines, antiviral drugs, anti-inflammatory drugs, immunomodulators, and anti-coagulants.

### Part III: Clinical Features, Classification and Diagnostic Criteria, and Early Warning of Severe and Critical Illness

#### Clinical features

Patients with COVID-19 had non-specific clinical manifestations. Symptoms of severe COVID-19 include fever (81.73%), cough (65.41%), dyspnea (51.50%), fatigue (38.34%), and expectoration (35.10%).<sup>[17]</sup> Critical cases may develop respiratory failure and multi-organ dysfunction. Hospitalized COVID-19 patients developed organ dysfunctions including acute kidney injury (AKI) (9%), hepatic dysfunction (19%), coagulation disorder (10–25%), and septic shock (6%).<sup>[18]</sup>

In addition, clinical symptoms do not match disease severity in some patients. Despite severe hypoxemia (oxygenation index <200 mmHg or even 150 mmHg), these patients presented a relatively normal respiratory state and did not have typical clinical symptoms such as dyspnea and increased heart rate. Some researchers refer to this clinical manifestation as “silent hypoxemia.”<sup>[19]</sup> Early identification of this type of patient, early adoption of oxygen therapy, and avoidance of delayed treatment are critical to improving prognosis.

**Recommendation 1: The experts suggest that patients aged >65 years, immunocompromised, unvaccinated, or with comorbidities could be at higher risk of developing severe COVID-19 after infection with Delta and Omicron variants. (Expert opinion)**

Recently designated variants of concern by the World Health Organization (WHO) include Alpha, Beta, Gamma, Delta, and Omicron.<sup>[6]</sup> In December 2020, the first case of the Delta infection was detected in India. Since then, the Delta variant has been rapidly spreading across the world. The Delta variant is estimated to be more than twice infectious as previous variants, with a higher probability of hospitalization and intensive care unit (ICU) admission for unvaccinated people.<sup>[6]</sup> The Omicron variant, a new and markedly mutated SARS-CoV-2 variant, has become the predominant variant worldwide since it was first reported in November 2021.<sup>[6]</sup> The Omicron variant is 100-fold greater in the rate of infection compared with the Delta variant.<sup>[20]</sup> However, compared with Delta, Omicron infection is reported to have a lower risk for ICU admission (adjusted difference=11.4%, 95% confidence interval [CI] : 8.4–14.4), mechanical ventilation (MV) (adjusted difference = 3.6%, 95%

CI :1.7–5.6), and in-hospital death (adjusted difference = 4.2%, 95% CI: 2.0–6.5).<sup>[21]</sup> Vaccinated patients admitted to hospitals in the United States with COVID-19, including Delta and Omicron variants, have significantly lower risk for ICU admission and invasive MV (IMV).<sup>[22,23]</sup> China-made COVID-19 vaccines were associated with a 70–80% lower risk of severe COVID-19 among adults, and full vaccination and booster doses reduced the risk of developing serious COVID-19 among ≥60-year-old patients infected with the Omicron variant.<sup>[24]</sup> The risk of severe COVID-19 among vaccinated patients aged <65 years was low during Omicron infection, even in the presence of comorbidities. However, the risk of severe COVID-19 remained elevated among vaccinated patients aged ≥65 years during Omicron infection only in the presence of comorbidities,<sup>[25]</sup> indicating that the degree of disease severity is related to vaccination, age, and comorbidities. In-hospital death or respiratory failure treated with IMV that were associated with SARS-CoV-2 variant (including Delta and Omicron) infections can occur in those who are older, more likely to be immunocompromised, and have more chronic medical conditions.<sup>[23,26]</sup>

#### Rapid etiological diagnosis of COVID-19

**Recommendation 2: Nucleic acid amplification testing (NAAT) for COVID-19 nucleic acid detection should probably be used as the first-choice method for the diagnosis of COVID-19. (Grade 2+, weak recommendation)**

NAAT such as real-time fluorescence reverse-transcription polymerase chain reaction (RT-PCR) is a reliable and rapid ribonucleic acid (RNA) testing technique that is capable of high-throughput direct detection of viral nucleic acid and can establish a diagnosis within a few hours. NAAT is currently designated as the gold standard for the detection of SARS-CoV-2 in various countries.<sup>[27–29]</sup> NAAT can be used on samples collected from various parts of the human body, including oropharyngeal and nasal swabs, upper and lower respiratory tract secretions, bronchoalveolar lavage fluid, sputum, and rectal swabs. However, the test-positive rate differs significantly between specimens collected from distinct parts of the body at different times.<sup>[30]</sup> Viral load was reported to be high in the nasopharynx and oropharynx in early pathogenesis (days 4–5) and consequently, the use of nasopharyngeal and oropharyngeal samples was advised for the diagnosis and screening of early COVID-19.<sup>[31]</sup> During the later stages of infection, the viral load in alveolar lavage fluid was significantly higher compared with that in the nasopharynx and oropharynx.<sup>[32]</sup> A study by Xu et al.<sup>[33]</sup> demonstrated that positive results on rectal swabs can remain for a long duration. Therefore, rectal swabs can be used for assessing potential infectivity and determining the quarantine period.

**Recommendation 3: SARS-CoV-2-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies assay should probably be used as an auxiliary method for the rapid diagnosis of COVID-19. (Grade 2+, weak recommendation)**

Common antibody targets for SARS-CoV-2 include the nucleocapsid (anti-N)-, receptor-binding domain (RBD)-, and Spike



(anti-S)-specific IgM, IgA, and IgG. Anti-N is produced in response to natural infection, while the anti-S is produced in response to either natural infection or vaccination. Both IgG and IgM begin to appear 1–2 weeks after the onset of symptoms, with IgM lasting several weeks and IgG lasting longer. The diagnostic sensitivity at 2–3 weeks post-infection is approximately 76.4–95.0%.<sup>[34,35]</sup> Therefore, serological testing has limited value for early diagnosis, and testing is generally recommended 3–4 weeks after infection.<sup>[35]</sup> However, given the variability in measurements by different analytical methods, there is currently no consensus on the optimal diagnostic cut-off value. Clinicians should be aware of the assays used by their institution to interpret test results. Additionally, patients who are immunocompromised or on immunosuppressants may have difficulty producing antibodies. Therefore, serological testing has a limited role in the diagnosis of acute infection and is more used as an auxiliary diagnosis.<sup>[36]</sup>

**Recommendation 4: SARS-CoV-2-specific antigen assays should probably not be used as a method for the rapid diagnosis of COVID-19. (Grade 2–, weak recommendation)**

Antigen assays directly detect viral components (*i.e.*, glycoprotein, M protein, or released N protein) or viruses. Like antibody assays, antigen assays are prone to false-positive results due to cross-reactions between antigens. At present, only a small quantity of assay kits has been approved by the Food and Drug Administration (FDA) for clinical testing of SARS-CoV-2 nucleocapsid protein (N protein) using nasopharyngeal swabs. Compared with nucleic acid assays, this method has a sensitivity of 80% and a specificity of 100%.<sup>[37]</sup> However, due to the availability of only limited data at present, WHO does not recommend the use of antigen assays for the diagnosis of COVID-19 but encourages further research on this topic.

**Classification and diagnostic criteria**

The following criteria, as described in the Diagnosis and Treatment Protocol for COVID-19 (trial version 9) published by China's National Health Commission<sup>[38]</sup> and the Expert Recommendations for the Management of Severe and critical COVID-19 published by the Chinese Society of Critical Care Medicine, Chinese Medical Association<sup>[39]</sup> are recommended to be used as the diagnostic criteria for severe and critical COVID-19.

**Severe cases**

Adults with any of the following symptoms: (1) Shortness of breath, respiration rate  $\geq 30$  breaths/min; (2) oxygen saturation  $\leq 93\%$  when breathing air in a resting state; (3) arterial partial pressure of oxygen (PaO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>)  $\leq 300$  mmHg; for high-altitude (altitude  $> 1000$  m), the PaO<sub>2</sub>/FiO<sub>2</sub> index should be corrected using the following formula: PaO<sub>2</sub>/FiO<sub>2</sub>  $\times (760/\text{atmospheric pressure [mmHg]})$ ; and (4) progressive deterioration of clinical symptoms, with prominent ( $> 50\%$ ) lesion progression within 24–48 h as shown by lung imaging. In addition, patients with the following conditions are recommended to be managed as severe cases: patients aged  $> 70$  years and complicated with a severe chronic disease such as hypertension, diabetes mellitus, coronary artery disease, malignant tumor, chronic lung diseases, or cor pulmonale, and immunocompromised patients. These criteria facilitate the early identification of high-risk patients with severe COVID-19.

**Critical cases**

Patients with any of the following symptoms: (1) onset of respiratory failure necessitating MV; (2) onset of shock; and (3) complication through dysfunction of other organs necessitating monitoring and treatment in the ICU.

**Early warning of severe and critical cases**

Due to the high mortality in severe and critical COVID-19 cases, early warning of severe cases facilitates their early identification and prompting treatment, and thus has important clinical values and implications.

Commonly used predictors of severe cases include X-ray chest radiographic abnormalities, age, hemoptysis, shortness of breath, hypoxemia, state of consciousness, number of chronic comorbidities, history of diabetes mellitus, history of cancer, neutrophil/lymphocyte ratio (NLR), lactate dehydrogenase, D-dimer C-reactive protein (CRP), and direct bilirubin.<sup>[40,41]</sup>

In addition, traditional early warning scoring systems— such as MEWS, APACHE II, SOFA, PSI, qSOFA, and NEWS— have been trialed and applied in the early warning of severe and critical COVID-19.<sup>[42,43]</sup>

**Part IV: Clinical Monitoring and Treatment**

**Etiological treatment (antiviral treatment)**

**Antiviral drugs**

**Recommendation 5: Nirmatrelvir plus ritonavir should be recommended for use within 3 days after the onset of symptoms for COVID-19 patients at risk of progression to severe COVID-19. (Grade 1+, strong recommendation)**

Nirmatrelvir is an orally administered SARS-CoV-2 main protease inhibitor with potent pan-human-coronavirus activity *in vitro*. A phase 2–3 double-blind, randomized, controlled trial was conducted in symptomatic, unvaccinated, non-hospitalized adults who were at high risk for progression to severe COVID-19.<sup>[44]</sup> A total of 2246 patients were enrolled in the trial and were assigned in a 1:1 ratio to receive either 300 mg nirmatrelvir plus 100 mg of ritonavir (Paxlovid) or placebo every 12 h for 5 days. The incidence of COVID-19-related hospitalization or death by day 28 was lower in the nirmatrelvir group compared with the placebo group by 5.81% (95% CI:  $-7.78$  to  $-3.84$ ;  $P < 0.001$ ; relative risk reduction, 88.9%); the incidence was 0.72% (5 of 697 patients) in the nirmatrelvir group, with zero death, as compared with 6.53% (44 of 682 patients) in the placebo group, with thirteen deaths. Furthermore, the viral load was lower on day 5 of treatment in the group administered with nirmatrelvir plus ritonavir compared with the placebo group, with an adjusted mean difference of  $-0.868$  log(10) copies per milliliter when treatment was initiated within 3 days after the onset of symptoms. The incidence of adverse events during the treatment period was similar in the two groups (any adverse event, 22.6% with nirmatrelvir plus ritonavir vs. 23.9% with placebo; serious adverse events, 1.6% vs. 6.6%).<sup>[44]</sup> Najjar-Debbiny et al.<sup>[45]</sup> used population-based real-world data to evaluate the effectiveness of Paxlovid. Patients were included irrespective of their COVID-19 vaccination status. Both Paxlovid and adequate COVID-19 vaccination status were associated with

a significant decrease in the rate of severe COVID-19 or mortality with adjusted hazard ratio (HR) of 0.54 (95% CI: 0.39–0.75) and 0.20 (95% CI: 0.17–0.22), respectively. Paxlovid appeared to be more effective in older patients, immunosuppressed patients, and patients with underlying neurological or cardiovascular disease (interaction  $P < 0.05$  for all). A meta-analysis of eight studies, involving 4788 COVID-19 patients, was conducted to evaluate the efficacy and safety of three new oral antiviral treatments (molnupiravir, fluvoxamine, and Paxlovid).<sup>[13]</sup> The overall odds ratio (OR) of mortality or hospitalization was 0.33 (95% CI: 0.22–0.49) for COVID-19 patients in the drug group and placebo group, indicating that oral antiviral drugs were effective for COVID-19 patients and reduced mortality or hospitalization by approximately 67%.<sup>[13]</sup> Paxlovid consists of two separate antiviral medications—ritonavir and nirmatrelvir. The ritonavir component boosts plasma concentrations of nirmatrelvir through potent and rapid inhibition of the key drug-metabolizing enzyme cytochrome P450 3A4. Thus nirmatrelvir/ritonavir, even given as a short course treatment, has a high potential to cause harm due to drug-drug interactions with other drugs metabolized through this pathway.<sup>[46]</sup> New oral antiviral drugs are still being studied and might bring new hope for COVID-19 treatment and recovery.<sup>[47]</sup>

**Recommendation 6: The following antiviral drugs should not be selected for the treatment of severe COVID-19: remdesivir, lopinavir/ritonavir, favipiravir, and arbidol. (Grade 1–, strong recommendation)**

Remdesivir inhibits the replication of SARS-CoV-2 by terminating the transcription of its RNA. A randomized, double-blind trial involving 1062 patients demonstrated that the remdesivir group had shorter recovery time (10 days vs. 15 days;  $P < 0.001$ ) and a lower 29-day all-cause mortality (11.4% vs. 15.2%).<sup>[48]</sup> However, another randomized, double-blind trial showed that remdesivir was not associated with the time to clinical improvement (HR=1.23, 95% CI: 0.87–1.75) and did not reduce 28-day mortality (14% vs. 13%).<sup>[49]</sup> In addition, remdesivir had a higher proportion of side effects (12% vs. 5%).<sup>[49]</sup> The Interim WHO Solidarity trial showed that, compared with the placebo group, remdesivir had no significant benefits in mortality (risk ratio [RR] = 0.95, 95% CI: 0.81–1.11), risk of MV (RR=0.91, 95% CI: 0.79–1.05), and initiation of MV. Several subsequent meta-analyses demonstrated that remdesivir did not improve clinical outcomes and reduce the risk of MV, duration of MV, and mortality in critical cases; therefore, the use of remdesivir for the treatment of critical cases was not recommended.<sup>[50]</sup>

Lopinavir/ritonavir is an anti-HIV drug and a candidate drug against SARS-CoV-2.<sup>[51]</sup> In a randomized, controlled, open-label, platform trial, 1616 patients received a lopinavir/ritonavir treatment, while 3424 patients received a conventional treatment. Results of the trial showed that there was no significant difference in time of discharge alive from the hospital (median= 11 days, interquartile range [IQR]: 5–28 days) in both groups and in the proportion of patients discharged from the hospital alive within 28 days (RR=0.98, 95% CI: 0.91–1.05;  $P=0.53$ ). Among patients did not receive IMV at baseline, there was no significant difference in the proportion who met the composite endpoint of IMV or death (RR = 1.09, 95% CI: 0.99–1.20;  $P=0.092$ ). Meta-analyses showed that lopinavir/ritonavir had no significant benefits in

clinical outcomes such as mortality, risk of MV, time to clinical recovery, and length of hospital stay.<sup>[50–52]</sup>

Similarly, other drugs—such as favipiravir and arbidol, used alone or in combination—are not recommended for the antiviral treatment of COVID-19.<sup>[53,54]</sup> Therefore, the following antiviral drugs are not recommended for the treatment of severe and critical COVID-19: remdesivir, lopinavir/ritonavir, favipiravir, and arbidol.<sup>[54]</sup>

### Interferons

**Recommendation 7: Interferons should probably not be used as standard care for severe COVID-19. (Grade 2–, weak recommendation)**

Interferons have immunoregulatory and antiviral effects. In a randomized, open-label, small-sample Phase II clinical trial, one group of patients received interferon  $\alpha$ -2b plus standard care treatment, while the other group received standard care treatment only. The interferon group achieved clinical improvement at day 15 (95% vs. 68%;  $P < 0.05$ ) and higher viral nucleic acid-negative rates at days 7 (80% vs. 63%;  $P < 0.05$ ) and 14 (95% vs. 68%;  $P < 0.05$ ).<sup>[55]</sup> However, meta-analyses showed that interferons had no benefits in MV and mortality in patients with COVID-19. Therefore, interferons are not recommended to be used as standard care for severe COVID-19.

### Chloroquine/hydroxychloroquine

**Recommendation 8: Chloroquine/hydroxychloroquine should not be used as standard care for severe COVID-19. (Grade 1–, strong recommendation)**

*In vitro* tests showed that other pharmacological drugs such as chloroquine/hydroxychloroquine may have effects against SARS-CoV-2. A multicenter, randomized, open-label, controlled trial revealed that, compared with standard care, the proportional odds of having a higher score on the seven-point ordinal scale at 15 days was not affected by either hydroxychloroquine alone (OR=1.21, 95% CI: 0.69–2.11;  $P=1.00$ ) or hydroxychloroquine plus azithromycin (OR=0.99, 95% CI: 0.57–1.73;  $P=1.00$ ). Prolongation of the corrected QT interval on an electrocardiogram and elevation of liver-enzyme levels were more frequently observed in patients receiving hydroxychloroquine, alone or with azithromycin, compared with those who were not receiving either agent.<sup>[56]</sup> A randomized, open-label, controlled Phase III trial enrolling 105 patients hospitalized with severe COVID-19 showed that the patients receiving chloroquine or hydroxychloroquine in combination with standard care for 5 days had worse clinical outcomes at days 14 (OR=2.45, 95% CI: 1.17–4.93;  $P = 0.016$ ) and 28 (OR=2.47, 95% CI: 1.15–5.30;  $P = 0.020$ ). Moreover, the intervention group had higher incidences of IMV use (RR=2.15, 95% CI: 1.05–4.40;  $P=0.030$ ) and severe renal dysfunction (KDIGO stage 3) (RR=2.24, 95% CI: 1.01–4.99;  $P = 0.042$ ) until the 28th day of follow-up.<sup>[57]</sup> A meta-analysis that included 28 randomized controlled trials (RCTs) involving a total of 10,319 patients showed that hydroxychloroquine was associated with mortality in patients with COVID-19 and that chloroquine had no benefits.<sup>[58]</sup> Moreover, chloroquine and hydroxychloroquine might cause arrhythmia and other severe adverse events.<sup>[59]</sup> Therefore, chloroquine/hydroxychloroquine is not recommended to be used as standard care for severe COVID-19.

### Neutralizing antibody

**Recommendation 9: Neutralizing antibodies should probably be used for the treatment of patients with early severe or advanced COVID-19. (Grade 2+, weak recommendation)**

Neutralizing antibodies can block SARS-CoV-2 from binding with ACE2. An interim analysis of a 275-patient trial showed that the use of neutralizing antibody REGN-COV2 (a 1:1 mixture of casirivimab [REGN10933] and imdevimab [REGN10987]) slightly decreased viral load (the time-weighted average change in viral load from day 1 through day 7 was  $-0.56 \log_{10}$  copies/mL, 95% CI:  $-1.02$  —  $-0.11$ ) but did not improve disease severity.<sup>[60]</sup> A randomized trial with 577 enrolled patients revealed that treatment with bamlanivimab and etesevimab combination therapy, but not bamlanivimab monotherapy, significantly reduced viral load at day 11 (between-group difference =  $-0.57$ , 95% CI:  $-1.00$  —  $-0.14$ );  $P = 0.01$ ).<sup>[61]</sup> A phase 3 portion of this adaptive, randomized, master protocol trial involving 4057 COVID-19 outpatients with one or more risk factors for severe disease showed that interventions using 2400 mg and 1200 mg REGN-COV significantly reduced COVID-19-associated hospitalization or all-cause mortality by 71.3% (1.3% vs. 4.6%;  $P < 0.0001$ ) and 70.4% (1.0% vs. 3.2%;  $P = 0.0024$ ), compared with the placebo, respectively. Both doses shortened the median time to resolution of COVID-19 symptoms by 4 days (10 days and 14 days;  $P < 0.0001$ ).<sup>[62]</sup> Furthermore, in a randomized, controlled, open-label platform trial, 9785 hospitalized COVID-19 patients were randomly allocated (1:1) to receive either usual care alone or usual care plus a single dose of REGN-COV (casirivimab 4 g and imdevimab 4 g). Compared with patients receiving usual care, seronegative patients receiving usual care plus REGN-COV exhibited a lower frequency of progression to MV (28% vs. 32%; RR=0.87, 95% CI: 0.77–0.98) and significantly lower mortality (24% vs. 30%; RR=0.80, 95% CI: 0.70–0.91;  $P = 0.001$ ).<sup>[63]</sup> However, a multinational, double-blind, randomized, placebo-controlled, clinical trial with 546 enrolled inpatients at 43 hospitals, found that neither sotrovimab nor BRII-196 plus BRII-198 showed efficacy in improving clinical outcomes among adults hospitalized with COVID-19.<sup>[64]</sup> In an analysis involving all randomized patients (regardless of baseline antibody status), the REGN-COV group and usual care group did not differ significantly in mortality (20% vs. 21%; RR=0.94, 95% CI: 0.86–1.03;  $P = 0.17$ ) and the frequency of MV (23% vs. 24%; RR=0.95, 95% CI: 0.87–1.04). These results indicate that neutralizing antibodies may benefit seronegative COVID-19 patients, but not other patient groups.<sup>[63]</sup>

A meta-analysis found low consistency in the trial results for neutralizing antibodies and failed to draw a deterministic conclusion.<sup>[65]</sup> Research is therefore ongoing.<sup>[60,66]</sup> However, despite the need for additional research to determine the efficacy of neutralizing antibodies in severe cases, existing evidence indicates that neutralizing antibodies can lower viral load, reduce the hospitalization rate, and decrease the frequency of MV. Therefore, neutralizing antibodies are recommended for the treatment of patients with early severe or advanced COVID-19. In addition, neutralizing antibodies may benefit seronegative patients.

### Convalescent plasma

**Recommendation 10: Convalescent plasma is not used as standard care for COVID-19; however, severe COVID-19 patients should probably benefit from early infusion of high-titer convalescent plasma. (Grade 2+, weak recommendation)**

Convalescent plasma contains neutralizing antibodies and thus facilitates virus clearance. A study with propensity score-matched controls showed that 73 patients with COVID-19 who received convalescent plasma within 72 h of hospital admission exhibited no difference in mortality ( $P = 0.47$ ). However, a stratified analysis showed that convalescent plasma recipients <65 years old had a four-fold lower risk of mortality and a four-fold lower risk of deterioration in oxygenation or mortality at day 28.<sup>[67]</sup> Univariate analysis showed that titers of spike protein antibodies (IgG, IgM, and IgA) were associated with mortality at day 28 ( $P < 0.05$ ), while multi-factor analysis revealed that age and time from symptom onset to transfusion were associated with mortality at day 28.<sup>[67]</sup> A randomized, double-blind trial with 74 enrolled patients showed that recipients of convalescent plasma had lower 90-day all-cause mortality, but the difference was not statistically significant (27% vs. 33%;  $P = 0.63$ ).<sup>[68]</sup> However, among the 14 intubated patients, recipients of convalescent plasma had significantly lower 90-day all-cause mortality (5 [45%] vs. 3 [100%];  $P = 0.05$ ). In addition, patients with severe or life-threatening COVID-19 who received convalescent plasma had a lower proportion of oxygen requirements and higher survival rate at day 14.<sup>[69]</sup> Another study showed that high-titer convalescent plasma helped reduce the ratio of severe respiratory disease (16% vs. 31%;  $P = 0.03$ ), the ratio of ICU transfer (14% vs. 27%), and 28-day mortality (6.9% vs. 10.4%).<sup>[70]</sup> Therefore, early (within 72 h) administration of high-titer convalescent plasma may benefit patients with severe illness or those aged <65 years.

However, other studies showed inefficacy of convalescent plasma.<sup>[71–74]</sup> A randomized, embedded, multifactorial, adaptive, platform trial for community-acquired pneumonia (REMAP-CAP) enrolled 4673 patients with suspected or confirmed COVID-19. The experimental group was administered two units of high-titer convalescent plasma, but this group exhibited no improvement in in-hospital mortality, number of days alive, and number of days free of organ support.<sup>[71]</sup> A single-center prospective observational study with 113 enrolled patients showed that compared with the control group, 41 recipients of convalescent plasma had no significant improvement in 28-day mortality (49% vs. 56%). In addition, subgroup analysis revealed no improvement in outcomes among patients with moderate-to-severe acute respiratory distress syndrome (ARDS).<sup>[72]</sup> Patients who received early or deferred administration of convalescent plasma also presented no significant difference in in-hospital mortality and MV requirement.<sup>[73]</sup> Similarly, a multicenter, open-label, randomized clinical trial involving 103 patients with severe COVID-19 and an RCT with 333 enrolled patients confirmed no benefits of convalescent plasma in clinical improvement and mortality.<sup>[71]</sup> Moreover, an experimental study showed that SARS-CoV-2 can escape the immune response through mutation even in patients administered high-titer polyclonal convalescent plasma.<sup>[75]</sup>



Based on the above evidence, convalescent plasma is not recommended to be used as standard care for COVID-19. However, early administration of convalescent plasma may benefit patients with severe illness or those aged <65 years. The efficacy of convalescent plasma in the treatment of severe COVID-19 is subject to confirmation by future large-sample RCTs.<sup>[76]</sup>

In summary, etiological therapy has an important role in the treatment of patients with severe COVID-19, and candidate drugs against SARS-CoV-2 were once given high expectations. However, the results of existing clinical trials showed that, compared with the control or placebo group, the above drugs or modes of therapy presented a low certainty of substantial benefits to patients. Despite ongoing studies on this topic, which hopefully may bring encouraging results, the current reality reminds us that in the absence of effective etiological therapy, supportive therapy is of particular importance in the treatment of COVID-19, especially in severe cases.

### Symptomatic therapy

#### Immunoregulatory therapy

##### Corticosteroids

**Recommendation 11: Corticosteroids should probably not be used as standard care for patients with COVID-19 (Grade 2+, weak recommendation); however, low-dose, short-course use of dexamethasone should be used for the treatment of patients with severe and critical COVID-19. (Grade 1+, strong recommendation)**

These recommendations are based on high-quality clinical studies conducted early in the COVID-19 pandemic and at a time of high fatality rates. At the time of writing (June 2022), both the prevalence and mortality of severe COVID-19 are low in China, *i.e.*, the conditions on which these studies were based have changed. Therefore, discretion should be exercised in clinical application of corticosteroids by weighing the pros and cons and considering the patient's inflammation status, underlying disease, and other factors.

Dexamethasone has high glucocorticosteroid activity, particularly anti-inflammatory activity, but mineralocorticoid activity-induced water and sodium retention are negligible. Theoretically, increasing water and sodium retention better facilitate the anti-inflammatory treatment of COVID-19, and failure to increase water and sodium retention may lead to disease deterioration. In clinical practice, the use of dexamethasone for the treatment of severe COVID-19 has the highest level of evidence. However, dexamethasone should be used in low doses (6 mg daily, intravenous or oral) for only a short course (not exceeding 10 days).

The RECOVERY Collaborative Group conducted a multicenter RCT using a large sample of 6425 patients in the United Kingdom (UK).<sup>[77]</sup> Oral or intravenous dexamethasone (at a dose of 6 mg once daily for up to 10 days) significantly reduced length of hospital stay, invasive ventilation ratio, and 28-day mortality. Among critical patients undergoing IMV, the dexamethasone group had lower mortality compared with the usual care group (29.3% vs. 41.4%; RR=0.64, 95% CI: 0.51–0.81). Similar results were found among severe patients receiving oxygen (23.3% vs. 26.2%; RR=0.82, 95% CI: 0.72–0.94). However, the use of

dexamethasone may increase the risk of mortality in patients with non-severe COVID-19 (RR=1.19, 95% CI: 0.91–1.55). After the publication of this trial, some ongoing clinical RCTs were stopped early.<sup>[78,79]</sup> A Brazilian multicenter RCT showed that critical patients ( $n=151$ ) receiving intravenous dexamethasone (20 mg/day) had a lower median number of ventilator-free days (defined as the number of days surviving and free of MV for a continuous 48 h within the first 28 days; a patient who died within 28 days was defined as having zero ventilator-free days) as compared with patients receiving usual care (6.6 days vs. 4.0 days, 95% CI: 0.2–4.4;  $P=0.04$ ).<sup>[80]</sup> This indicated the superiority of dexamethasone in treating COVID-19. A meta-analysis that included seven RCTs and 1703 enrolled patients with severe or critical COVID-19 showed that systemic corticosteroids reduced 28-day all-cause mortality in patients with severe COVID-19 (32.7% vs. 41.5%; OR=0.66, 95% CI: 0.53–0.82;  $P<0.001$ ).<sup>[81]</sup> In a network meta-analysis that compared various treatments for COVID-19, 11 RCTs comparing corticosteroids with standard care/placebo were included. Compared with standard care/placebo, corticosteroids reduced the risk of death ( $n=2975$ ; OR=0.83, 95% CI: 0.69–0.98; moderate certainty) and MV ( $n=2425$ ; OR=0.76, 95% CI: 0.59–0.99; moderate certainty) and increased the number of ventilator-free days in mechanically ventilated patients ( $n=151$ ; mean difference=2.6 days, 95% CI: 0.3–4.9 days; moderate certainty).<sup>[50]</sup> Other meta-analyses reached similar conclusions.<sup>[82]</sup> All these meta-analyses suggested that corticosteroids improved the prognosis in severe and critical patients but most data about the efficacy of corticosteroids came from the RECOVERY study.

Some RCTs and retrospective studies did not prove the efficacy of glucocorticosteroids. A Brazilian double-blind RCT showed that the difference in mortality at day 28 between the intravenous methylprednisolone (0.5 mg/kg, bid) group ( $n=194$ ) and the placebo group ( $n=199$ ) was not statistically significant (37.1% vs. 38.2%;  $P=0.629$ ) in severe or critical patients.<sup>[83]</sup> A Chinese retrospective study that included 1514 severe and 249 critical patients revealed that after adjustment for confounding factors, the use of corticosteroids (methylprednisolone at an average daily dose of 40 mg) was associated with increased in-hospital mortality among severe and critical cases.<sup>[84]</sup> Among 774 COVID-19 patients with ARDS, the use of corticosteroids increased 28-day all-cause mortality (44.3% vs. 31.0%; OR=1.77, 95% CI: 1.32–2.38;  $P<0.001$ ). A Cox proportional hazards logistic regression model indicated that corticosteroids treatment might increase mortality (adjusted HR=1.45, 95% CI: 1.06–1.99;  $P=0.021$ ). Furthermore, compared with the control group, corticosteroids treatment delayed virus clearance (subhazard ratio=1.59, 95% CI: 1.17–2.15;  $P=0.003$ ).<sup>[85]</sup> A retrospective study that included 428 severe or critical patients showed that after adjustment for confounding factors, corticosteroids treatment was not significantly associated with 28-day mortality (HR=0.80, 95% CI: 0.54–1.18;  $P=0.26$ ); however, a subgroup analysis demonstrated that corticosteroids treatment was associated with decreased 28-day mortality in patients with a hyperinflammatory response (D-dimer >2.0  $\mu\text{g/mL}$  or NLR >6.9).<sup>[86]</sup> A Wuhan multicenter large-sample ( $n=12,862$ ) retrospective analysis showed that corticosteroids treatment might be effective in severe patients with NLR >6.11 but possibly not effective in patients with NLR <6.11 or type 2 diabetes.<sup>[87]</sup>



## Monoclonal antibody

### **Recommendation 12: Interleukin (IL)–6 receptor monoclonal antibodies should probably be used for the treatment of severe or critical patients under specific conditions. (Grade 2+, weak recommendation)**

For patients receiving oxygen therapy, when the clinical status tends to progress after the use of dexamethasone and CRP level is  $\geq 75$  mg/L, a dose of tocilizumab (if available) can be given based on the specific conditions. However, this treatment is not recommended for patients with allergy to tocilizumab, uncontrolled severe infections other than COVID-19, and immunosuppression.

The RECOVERY Collaborative Group conducted a large-sample RCT that included 4116 severe or critical patients with hypoxia (oxygen saturation  $< 92\%$  or requiring oxygen therapy) and systemic inflammation (CRP  $\geq 75$  mg/L).<sup>[88]</sup> The treatment group ( $n=2022$ , usual care plus 400–800 mg intravenous tocilizumab) exhibited lower 28-day mortality compared with the usual care group (31% vs. 35%; RR=0.85, 95% CI: 0.76–0.94;  $P=0.0028$ ). In patients (82%) receiving systemic corticosteroids, improved prognosis might be additional to the benefits of systemic corticosteroids. In addition, a REMAP-CAP study designed to investigate the efficacy of two IL-6 receptor antagonists (tocilizumab and sarilumab) in severe or critical patients showed that, compared with the control group ( $n=402$ ), both tocilizumab ( $n=353$ , 8 mg/kg body weight, administered intravenously  $> 1$  h) and sarilumab ( $n=48$ , 400 mg, administered intravenously in one injection) treatments increased the number of organ support-free days up to day 21 and in-hospital survival rate.<sup>[89]</sup> The WHO Rapid Evidence Appraisal for COVID 19 Therapies (REACT) Working Group made a prospective meta-analysis of the associations between IL-6 receptor antagonists and 28-day mortality in severe or critical patients. The IL-6 receptor antagonist treatment group had lower 28-day absolute mortality risk than the usual care/placebo group (22% vs. 25%, OR=0.86, 95% CI: 0.79–0.95;  $P = 0.003$ ). However, patients treated with antagonists might have higher risk of secondary infections after 28 days compared with patients treated with standard care/placebo (21.9% vs. 17.6%; OR=0.99, 95% CI: 0.85–1.16).<sup>[90]</sup> A recent meta-analysis included 10 RCTs on tocilizumab involving 6493 enrolled patients with severe or critical COVID-19.<sup>[91]</sup> Tocilizumab was found to potentially improve mortality (24.4% vs. 29.0%; OR=0.87, 95% CI: 0.74–1.01;  $P = 0.07$ ) and reduce the MV ratio in severe patients (8.7% vs. 10.5%; OR=0.70, 95% CI: 0.54–0.89;  $P = 0.004$ ).

However, other studies reached alternative conclusions. An RCT ( $n=131$ ) found that tocilizumab had no effect on 28-day mortality in severe patients (HR=0.92, 95% CI: 0.33–2.53),<sup>[92]</sup> while another four RCTs (comprising 129, 126, 243, and 452 severe or critical patients, respectively) showed that tocilizumab (at a dose of 8 mg/kg to a maximum of 800 mg/day) treatment was not associated with improved 28-day survival rate.<sup>[93–96]</sup> The Sarilumab COVID-19 Global Study Group conducted a 60-day, randomized, double-blind, placebo-controlled, multinational phase 3 trial at 45 hospitals globally, enrolling 416 severe or critical patients. No significant difference in 28-day survival rate was observed.<sup>[97]</sup>

At present, there is no evidence that gamma globulins, thymosin alpha-1, and granulocyte colony-stimulating factors improve the prognosis of patients with severe COVID-19.

### *Respiratory function monitoring and supportive therapy*

High-flow nasal cannula (HFNC) oxygen therapy

### **Recommendation 13: HFNC oxygen therapy should probably be selected as the first treatment choice for patients with oxygenation index ( $\text{PaO}_2/\text{FiO}_2$ ) = 200–300 mmHg. (Grade 2+, weak recommendation)**

Beneficial therapeutic effects of HFNC on mild to moderate respiratory failure in non-COVID-19 diseases have been demonstrated. A meta-analysis showed that compared with conventional oxygen therapy (COT), HFNC reduced intubation rate (RR=0.46, 95% CI: 0.30–0.70) and length of hospital stay (0.98 day on average), and compared with non-invasive ventilation (NIV), did not differ in mortality (RR=1.12, 95% CI: 0.82–1.53) and intubation rate (RR=1.16, 95% CI: 0.86–1.57).<sup>[98]</sup> However, another meta-analysis found that HFNC improved patient-reported comfort and dyspnea scores.<sup>[99]</sup> Discretion should be exercised in the application of HFNC in patients with moderate-to-severe hypoxemia ( $\text{PaO}_2/\text{FiO}_2 \leq 200$  mmHg). A study on high-flow nasal oxygen in the resuscitation of patients with acute lung injury (FLORALI-2) revealed that patients receiving NIV had a lower frequency of severe hypoxemia compared with those receiving HFNC (24% vs. 35%; OR=0.56, 95% CI: 0.32–0.99;  $P=0.0459$ ).<sup>[100]</sup> Wang et al.<sup>[101]</sup> reported that among 17 COVID-19 patients receiving HFNC, all six patients with  $\text{PaO}_2/\text{FiO}_2 > 200$  mmHg experienced HFNC success, whereas seven (63%) of the 11 patients with  $\text{PaO}_2/\text{FiO}_2 \leq 200$  mmHg experienced HFNC failure ( $P=0.04$ ). In a multicenter randomized clinical trial including 109 patients with COVID-19 and  $\text{PaO}_2/\text{FiO}_2 \leq 200$  mmHg, the rate of endotracheal intubation was significantly lower in the helmet NIV group compared with the HFNC group (30% vs. 51%; difference=–21%, 95% CI: –38% – –3%;  $P=0.03$ ). The median number of days free of IMV at day 28 was significantly higher in the helmet group compared with the HFNC group (28 [IQR: 13–28] days vs. 25 [IQR: 4–28] days; difference=3 days, 95% CI: 0–7;  $P=0.04$ ).<sup>[102]</sup>

### **Recommendation 14: Close monitoring of patients undergoing HFNC therapy is necessary to prevent delayed intubation, and the respiratory rate-oxygenation (ROX) index (defined as $[\text{SpO}_2/\text{FiO}_2]/\text{respiratory rate}$ ) should probably be a potential predictor of HFNC success. (Grade 2+, weak recommendation)**

Oxygenation index,  $\text{SpO}_2$ , and respiratory rate are closely associated with HFNC success. However, no single index is an effective predictor of HFNC success. A non-COVID-19 study showed that the ROX index had greater prediction power for HFNC outcome, with a ROX index of  $< 2.85$ ,  $< 3.47$ , and  $< 3.85$  within 2 h, 6 h, and 12 h of HFNC initiation, respectively, predicting a high risk of HFNC failure.<sup>[103]</sup> A retrospective study by Xu et al.<sup>[104]</sup> collected clinical data from 324 COVID-19 patients receiving HFNC therapy. A ROX index  $< 5.31$  at 4 h after HFNC initiation is a predictor of HFNC failure (OR=5.22, 95% CI: 2.96–9.20).

## MV

**Recommendation 15: NIV support should probably be tried in COVID-19 patients with a PaO<sub>2</sub>/FiO<sub>2</sub> ≤200 mmHg. (Grade 2+, weak recommendation)**

Published guidelines and consensus suggest that NIV support can be tried in COVID-19 patients with a PaO<sub>2</sub>/FiO<sub>2</sub> ≤200 mmHg.<sup>[105–107]</sup> A multicenter RCT (the HENIVOT study) compared helmet continuous positive airway pressure (CPAP) and HFNC for efficacy in COVID-19 patients ( $n=109$ ) with PaO<sub>2</sub>/FiO<sub>2</sub> <200 mmHg. The PaO<sub>2</sub>/FiO<sub>2</sub> in the helmet CPAP group increased to 188 mmHg within 48 h, which was significantly higher compared with that in the HFNC group (138 mmHg;  $P < 0.001$ ). In addition, the intubation rate in the helmet CPAP group was significantly lower compared with that in the HFNC group (30% vs. 51%;  $P = 0.03$ ), while there was no significant difference in in-hospital mortality between the two groups (24% vs. 25%;  $P > 0.99$ ).<sup>[102]</sup> A single-center retrospective study on the efficacy of NIV among patients with COVID-19-associated acute hypoxemic respiratory failure enrolled 64 patients who received CPAP support with indications of PaO<sub>2</sub>/FiO<sub>2</sub> ≤200 mmHg, respiratory rate >30 breaths/min, and respiratory distress. The CPAP group had a mean PaO<sub>2</sub>/FiO<sub>2</sub> of 119 mmHg and a mean respiratory rate of 33 breaths/min at baseline. Among the CPAP group, 53 (83%) patients were discharged from the hospital within 28 days, 4 died, and 7 underwent IMV (among them, 5 patients died).<sup>[108]</sup>

Despite the efficacy of NIV in improving oxygenation in patients with COVID-19, the failure rate should not be ignored. A cohort study enrolled 670 COVID-19 patients receiving out-of-ICU non-invasive respiratory support (HFNC, CPAP, or NIV) and found that patients receiving CPAP or NIV (507 patients in total) had an intubation rate of 25–28% and a 30-day mortality of approximately 30%.<sup>[109]</sup> The failure of NIV in these studies might be attributed to the unique pathophysiology of COVID-19 and the delayed intubation due to the scarcity of resources during the pandemic. Meanwhile, the high failure rates of NIV indicate that close monitoring and a quick initiation of IMV when necessary are required. A published study on patients with ARDS showed that the average failure rate of NIV was 37.5% (22.2%, 42.3%, and 47.1% for mild, moderate, and severe ARDS, respectively). Among ARDS patients with PaO<sub>2</sub>/FiO<sub>2</sub> <150 mmHg, the ones that received NIV had higher mortality compared with those that received IMV (45.0% vs. 14.6%;  $P < 0.001$ ). In addition, patients who received NIV before IMV also exhibited higher mortality (45.4% vs. 16.1%;  $P < 0.001$ ) compared with those that received IMV without NIV intervention.<sup>[110]</sup>

**Recommendation 16: The experts suggest that IMV with tracheal intubation is used in patients with PaO<sub>2</sub>/FiO<sub>2</sub> <150 mmHg, consciousness disorder, hemodynamic instability, respiratory distress, or hypoxemia after receiving NIV or HFNC. (Expert opinion)**

At present, there is no RCT on the effects of the timing of intubation on the prognosis of COVID-19. Observational studies have provided inconsistent results. A recently published meta-analysis that included 12 observational studies, with a total of 8944 enrolled patients, showed that the timing of intubation did not affect mortality in patients with COVID-19.<sup>[111]</sup> Moreover, inconsistent definitions of the timing of intubation were pro-

vided in existing studies. Clinical practice determines the need for intubation based on the severity of respiratory failure and clinical manifestations of the patient.

For patients with critical COVID-19, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio is an indicator of the severity of respiratory failure. A cohort study enrolled 9990 patients with COVID-19 from 258 ICUs and showed that the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was an independent risk factor for 30-day mortality.<sup>[112]</sup> The NIV failure rate increases significantly when PaO<sub>2</sub>/FiO<sub>2</sub> <150 mmHg.<sup>[112]</sup> A retrospective study of 859 COVID-19 patients receiving NIV or HFNC demonstrated that NIV and HFNC had high failure rates of 75% and 55%, respectively.<sup>[113]</sup>

Patients with respiratory distress and spontaneous vigorous inspiratory effort have significantly increased pulmonary stresses, significantly increased transpulmonary vascular pressures, aggravated pulmonary edema, and ventilator-induced lung injury. Therefore, for patients whose respiratory distress is not alleviated after the use of HFNC or NIV and who use auxiliary respiratory muscles and have vigorous inspiratory effort, invasive ventilation therapy needs to be initiated.<sup>[114]</sup>

**Recommendation 17: The experts suggest that rapid sequence induction intubation in patients with COVID-19 is performed after pre-oxygenation. (Expert opinion)**

Typical clinical manifestations in patients with COVID-19 are dyspnea and hypoxemia. Among critically ill patients, approximately 3.2% required tracheal intubation and MV therapy.<sup>[115]</sup> Patients usually experienced severe hypoxemia before tracheal intubation and might easily develop arrhythmia, hypotension, and even sudden cardiac arrest and sudden death during intubation. Decreasing the hypoxemia risk during intubation can be realized by increasing the flow and fraction of inspired oxygen or using balloon mask manual positive-pressure ventilation or non-invasive ventilator positive-pressure ventilation, thereby maximizing the pre-oxygenation level before intubation. These measures were confirmed to improve oxygenation and decrease the hypoxemia incidence rate during intubation.<sup>[116–120]</sup> Rapid sequence induction tracheal intubation refers to the selection of different induction drugs based on the patient's hemodynamic state after pre-oxygenation and the administration of opiates to repress the pharyngeal reflex and muscle relaxants to repress the cough reflex, thereby enabling rapid completion of intubation. Rapid sequence induction intubation shortens the non-effective ventilation time (from the patient's loss of consciousness to the establishment of effective ventilation) and reduces the requirement for oxygen reserve.<sup>[121,122]</sup> Intubation using rapid sequence induction in one study of patients with COVID-19 had a first-attempt success rate of 89.3% and an overall success rate of 100%.<sup>[123]</sup>

**Recommendation 18: Timely tracheotomy should probably be used for critical COVID-19 patients when failure of timely extubation is expected. (Grade 2+, weak recommendation)**

A retrospective study by Hernandez et al.<sup>[124]</sup> of 1939 patients with COVID-19 showed that early tracheotomy (<7 days) improved 28-day ventilator-free days, ICU days, and total length of hospital stay as compared with deferred tracheotomy (>7 days). Furthermore, in a retrospective study of 38 patients with COVID-19 by Livneh et al.,<sup>[125]</sup> early tracheotomy (<7 days)

led to higher decannulation rates. Kwak et al.<sup>[126]</sup> reported that the timing of tracheotomy was related to the length of hospital stay in patients with COVID-19. Compared with patients receiving late (15.83 days) tracheotomy, patients receiving early (5.58 days) tracheotomy had shorter hospital stays (40 days vs. 49 days for early vs. late tracheotomy, respectively). A recent prospective study showed that, compared with late (19 days) percutaneous tracheotomy, early (9 days) percutaneous tracheotomy reduced the duration of MV and tended to reduce mortality.<sup>[127]</sup> At the time of writing, there are controversies over the exact timing of tracheotomy in patients with COVID-19, and moreover, different thresholds between early and late tracheotomy were defined in different studies. However, evidence from the published research supports that late or deferred tracheotomy is detrimental to the prognosis of patients with COVID-19. Relevant international consensuses and guidelines recommend to perform tracheotomy for COVID-19 patients who need secondary tracheal intubation or are expected to need venovenous extracorporeal membrane oxygenation (VV-ECMO) or other forms of long-term MV and do not recommend deferred tracheotomy.<sup>[128,129]</sup>

**Recommendation 19: Low-tidal-volume ventilation should probably be used for COVID-19 patients with ARDS undergoing IMV. (Grade 2+, weak recommendation)**

There are currently limited studies on the effects of tidal volume on prognosis in mechanically ventilated patients with COVID-19. Relevant guidelines suggest a tidal volume of 6 mL/kg predicted body weight (kg.PBW) for initial treatment of ARDS. Ferrando et al.<sup>[130]</sup> found that COVID-19-associated ARDS was not significantly different from conventional ARDS in clinical features and respiratory mechanics and suggested a tidal volume of 6.9 (IQR: 6.3–7.8) mL/kg.PBW. A Dutch study suggested a tidal volume of 6.3 (IQR: 5.7–7.1) mL/kg.PBW.<sup>[131]</sup> A recent review included 26 studies that enrolled 14,075 patients receiving invasive ventilation and found that the tidal volume was set in the range of 5.6–7.5 mL/kg.PBW in the different studies.<sup>[132]</sup> Based on research on non-COVID-19-associated ARDS and the current tidal volume settings for mechanically ventilated patients with COVID-19-associated ARDS, small-tidal-volume ventilation is recommended for mechanically ventilated patients with COVID-19.

**Recommendation 20: For COVID-19 patients with ARDS undergoing IMV, plateau pressure should probably be set <30 cmH<sub>2</sub>O and the driving pressure <15 cmH<sub>2</sub>O. (Grade 2+, weak recommendation)**

There is presently no consensus on the effects of plateau pressure and driving pressure configurations on prognosis in COVID-19 patients with ARDS. Based on research on non-COVID-19-associated ARDS, for low-tidal-volume ventilation, lowering plateau and driving pressures can alleviate ventilator-associated lung injury. A meta-analysis by Amato et al.<sup>[133]</sup> that included nine RCTs with a total of 1629 patients showed that lowering the plateau pressure to <15 cmH<sub>2</sub>O significantly reduced mortality in patients with ARDS (RR=0.80, 95% CI: 0.66–0.98). Another meta-analysis that included 15 RCTs revealed that increasing the plateau pressure >32 cmH<sub>2</sub>O significantly increased patient mortality. In addition, driving pressure is significantly associated with mortality in patients with ARDS. In-

creasing the driving pressure >15 cmH<sub>2</sub>O significantly increased patient mortality. Observational studies of mechanically ventilated patients with COVID-19 showed that the clinical practice was to adopt lung-protective ventilation strategies using a plateau pressure of <30 cmH<sub>2</sub>O and a driving pressure of <15 cmH<sub>2</sub>O. Ferrando et al.<sup>[130]</sup> found that in mechanically ventilated patients with COVID-19, the plateau pressure was set at 25 (22–29) mmHg and the driving pressure at 12 (10–16) mmHg, while a study by Botta et al.<sup>[131]</sup> reported that clinicians set peak airway pressure at 27 (IQR: 24–31) cmH<sub>2</sub>O and driving pressure at 14 (IQR: 11.2–16) cmH<sub>2</sub>O in mechanically ventilated COVID-19 patients. Based on existing research findings and the clinical application of IMV in pneumonia patients, we recommend the plateau pressure be set <30 cmH<sub>2</sub>O and the driving pressure <15 cmH<sub>2</sub>O for COVID-19 patients with ARDS undergoing IMV.

**Recommendation 21: For COVID-19 patients with ARDS undergoing IMV, positive end-expiratory pressure (PEEP) should probably be initially set according to the ARDS-net low PEEP/FiO<sub>2</sub> table and subsequently titrated according to the patient's respiratory system compliance, oxygenation, and dead space. (Grade 2+, weak recommendation)**

PEEP is an important parameter of MV in patients with ARDS. However, there are no studies comparing the effects of PEEP on the prognosis of patients with COVID-19-associated ARDS. A meta-analysis of 2299 ARDS patients showed that a high PEEP significantly decreased mortality in patients with moderate-to-severe ARDS.<sup>[134]</sup> A review by Grasselli et al.<sup>[132]</sup>, which included 26 studies, showed that PEEP was set at 9–16.5 cmH<sub>2</sub>O in patients with COVID-19. However, some patients with severe COVID-19 have low lung recruitability. In these patients, a high PEEP may lead to alveolar hyperinflation. In a study of eight COVID-19 patients with ARDS, Grasso et al.<sup>[135]</sup> found that a high PEEP improved oxygenation to a certain degree but easily led to alveolar hyperinflation and affected hemodynamics. Ball et al.<sup>[136]</sup> titrated PEEP using the electrical impedance tomography (EIT) method and found that a high PEEP did not effectively promote alveolar recruitment; therefore, the research group suggested PEEP should be set below a certain level unless a higher PEEP is required to sustain oxygenation. Gattinoni et al.<sup>[137]</sup> classified COVID-19-associated ARDS into two phenotypes—H and L—and found that a high PEEP was not suitable for Type L ARDS. Grasselli et al.<sup>[138]</sup> reported that, compared with a PEEP <10 cmH<sub>2</sub>O, a PEEP >13 cmH<sub>2</sub>O was significantly associated with mortality. Therefore, we recommend PEEP be initially set using the low PEEP/FiO<sub>2</sub> table. After this initial setting, and considering the low lung recruitability of patients, the PEEP should be titrated based on the patient's respiratory system compliance, oxygenation, and dead space.

**Recommendation 22: Recruitment maneuver (RM) should probably not be used as standard care for COVID-19 patients with ARDS undergoing IMV. (Grade 2–, weak recommendation)**

To date, no study has provided conclusive evidence on the effects of RM on the prognosis of patients with COVID-19-associated ARDS. Existing research demonstrates that RM can significantly improve oxygenation in patients with ARDS. However, a high horizontal pressure can significantly increase



transpulmonary pressure and cause lung injury. One study even showed that lung recruitment strategies increased mortality in patients with ARDS.<sup>[134]</sup> Some patients with COVID-19-associated ARDS have low lung recruitability. By using EIT, Mauri et al.<sup>[139]</sup> found high inhomogeneity in lung recruitability among patients with severe COVID-19. Therefore, we do not recommend RM should be used as a standard treatment. If deemed necessary based on clinical conditions, RM should be used after an assessment of the patient's lung recruitability.

**Recommendation 23: The experts suggest that bedside bronchoscopy could improve sputum suction in mechanically ventilated patients with severe COVID-19. (Expert opinion)**

Patients with severe COVID-19 usually receive deep sedation and even muscle relaxation therapies. In these patients, sputum suction is a common problem. Bronchoscopy and sputum suction are beneficial for airway clearance and prognosis improvement in patients with COVID-19.<sup>[140]</sup> However, the potential risk brought by the relevant operations to patients in the same ward and HCWs should be considered. He et al.<sup>[141]</sup> elaborated the basic principles and methods for the preparation, preventive strategies, and environment cleaning required for the use of bronchoscopy in patients with COVID-19. Wang et al.<sup>[142]</sup> reported a study of 33 patients with COVID-19 receiving fiberoptic bronchoscopic sputum suction and found that airway secretion clearance effectively improved oxygenation and that third-level protection facilitated the prevention of nosocomial cross-infection. Some researchers proposed the use of disposable fiberoptic bronchoscopy for sputum suction therapy where conditions permit.<sup>[143]</sup> At present, there is a lack of large-sample clinical studies on the therapeutic and prognostic effects of bronchoscopy in patients with COVID-19. Expert opinions suggest bedside bronchoscopy improves sputum suction in mechanically ventilated patients with severe COVID-19; however, relevant operating procedures must be strictly followed to prevent nosocomial infection.

Prone positioning

**Recommendation 24: Awake prone positioning should probably be used for non-intubated severe COVID-19 patients with persistent hypoxemia. (Grade 2+, weak recommendation)**

A systematic review of three studies showed that non-intubated COVID-19 patients had a high tolerance to awake prone positioning (63.0–83.9%) and that prone positioning improved percutaneous oxygen saturation, oxygenation index, and lung recruitment.<sup>[144]</sup> At the time of writing, there is no conclusive evidence as to whether awake prone positioning decreases intubation rate and mortality in patients with severe COVID-19. A prospective, multicenter cohort study—involving 199 COVID-19 patients with acute respiratory failure receiving HFNC, with 55 (27.6%) patients receiving prone positioning—showed that prone positioning did not decrease intubation rate and 28-day mortality.<sup>[145]</sup> A recent systematic review found that the difference in intubation rate between non-intubated COVID-19 patients with acute respiratory failure receiving standard care ( $n=852$ ) and prone positioning ( $n=870$ ) was not statistically significant (27% vs. 30%;  $P=0.71$ ).<sup>[146]</sup> In a prospective and col-

laborative meta-trial of six randomized controlled open-label superiority trials, 1126 patients with acute respiratory failure requiring nasal high-flow oxygen were enrolled and randomly assigned to awake prone positioning ( $n=567$ ) or standard care ( $n=559$ ). The intubation rate in the awake prone positioning group was lower compared with that in the standard care group (HR=0.75, 95% CI: 0.62–0.91) within 28 days of enrollment but no significant difference in 28-day mortality was observed.<sup>[147]</sup> Nevertheless, a retrospective multicenter observational study through propensity score analyses found that awake prone positioning is associated with a lower risk of intubation and mortality in hospitalized non-intubated patients with COVID-19.<sup>[148]</sup>

Prone positioning could improve oxygenation in COVID-19 patients with acute respiratory failure but did not decrease mortality. This may be related to the patients with COVID-19 having high pulmonary compliance and low recruitability during the early stage of illness and therefore awake prone positioning can provide temporary improvements in ventilation/perfusion mismatching but not continuous benefits.<sup>[149]</sup> In addition, the daily duration of awake prone positioning could impact prognosis. Although the optimal daily duration of awake prone positioning is unclear, a randomized, controlled, multinational, open-label meta-trial showed a median of 3.0 (IQR: 1.2–4.0) h of awake prone positioning with HFNC could improve the oxygenation index. Patients in awake prone positioning for at least 8 h daily on average had a higher rate of treatment success (patient was alive and did not require intubation after 28 days) compared with those patients in awake prone positioning for <8 h daily.<sup>[147]</sup> Therefore, based on current understanding,<sup>[150]</sup> the longer the duration of prone positioning, the more benefits could be obtained.

Existing relevant studies are mostly observational and have high heterogeneity, necessitating future RCTs to provide conclusive evidence on the optimal daily duration and effects of awake prone positioning on the prognosis of severe COVID-19 patients with persistent hypoxemia requiring no immediate intubation. Prone positioning is a non-invasive therapy that is well tolerable and can improve oxygenation. Consequently, this therapy may prevent a need for intubation in some patients with severe COVID-19 and thus is of particular value in situations with scarce ICU bed resources.<sup>[151]</sup> Therefore, we recommend a trial of awake prone positioning in severe COVID-19 patients with persistent hypoxemia requiring no immediate intubation.

**Recommendation 25: For invasively ventilated patients with critical COVID-19, prone positioning no less than 16 h daily should probably be used. (Grade 2+, weak recommendation)**

Prone positioning for at least 12 h daily can decrease mortality in patients with moderate-to-severe ARDS.<sup>[150,152]</sup> Therefore, prone positioning has been adopted as one of the major therapies for patients with severe and critical COVID-19. A multicenter, prospective cohort study showed that 70% of 4244 invasively ventilated adult patients with critical COVID-19 received prone positioning.<sup>[153]</sup> Prone positioning can promote lung recruitment and improve oxygenation.<sup>[154]</sup>

At present, there are some controversies over the effects of prone positioning on mortality in invasively ventilated patients with critical COVID-19. An Italian multicenter retrospective study included 1057 severe COVID-19 patients, 61% of whom



received prone positioning. The study showed that prone positioning decreased ICU mortality only after this therapy had significantly improved oxygenation.<sup>[155]</sup> A US multicenter cohort study included 2338 patients with critical COVID-19 undergoing IMV at 68 hospitals, of whom 702 (30%) received prone positioning within 2 days of hospitalization. The patients who received prone positioning within the first 2 days of ICU admission had a low adjusted risk of death (HR=0.84, 95% CI: 0.73–0.97) and in-hospital mortality was lower in mechanically ventilated COVID-19 patients treated with early prone positioning.<sup>[156]</sup>

The duration of continuous prone positioning may affect the prognosis in mechanically ventilated patients with critical COVID-19. A recent retrospective cohort study included 261 mechanically ventilated patients with moderate-to-severe ARDS due to COVID-19, of whom 62 received prone positioning for at least 16 h daily. This prone positioning improved oxygenation-associated physiological indexes in the patients and significantly reduced mortality.<sup>[157]</sup> Based on the beneficial time of prone positioning in patients with moderate-to-severe ARDS,<sup>[150]</sup> we recommend prone positioning no <16 h daily for mechanically ventilated patients with severe and critical COVID-19.

Extracorporeal membrane oxygenation (ECMO)

**Recommendation 26: For critical COVID-19 patients with refractory hypoxemia and/or hypercapnia after fully optimized lung-protective ventilation and prone positioning, ECMO should probably be used as early as possible at experienced centers. (Grade 2+, weak recommendation)**

ECMO is a major life rescue therapy for patients with critical COVID-19. A meta-analysis included 45 studies that enrolled 16,561 patients with severe and critical COVID-19 from 17 countries, and the analysis showed that 6.4% of the patients received ECMO therapy.<sup>[158]</sup> A 2021 European multicenter, prospective cohort study included 4244 adults with severe and critical COVID-19 and showed that 11% (235/2153) of patients with critical COVID-19 received ECMO therapy.<sup>[153]</sup> Meanwhile, a study using data from the Extracorporeal Life Support Organization (ELSO) registry revealed that 1035 critical COVID-19 patients treated with ECMO from 36 countries had a 90-day in-hospital mortality of 37.4%.<sup>[159]</sup>

Some cohort studies have provided evidence of the benefits of ECMO in improving the prognosis in patients with critical COVID-19. A multicenter, retrospective cohort study of critical COVID-19 patients treated with ECMO in Wuhan, China before June 30, 2020, showed that ECMO therapy was significantly associated with decreased 120-day mortality.<sup>[160]</sup> In addition, a 2021 multicenter cohort study of 302 patients with critical COVID-19 treated with ECMO in Greater Paris found that early ECMO was significantly associated with decreased 90-day mortality at medical centers experienced in ECMO application.<sup>[161]</sup> A recent multicenter clinical trial used a cohort simulation method to analyze 5122 patients with critical COVID-19 admitted to 68 hospitals across the US. Results of the trial showed that patients with critical COVID-19 who received ECMO in the first week of ICU admission had lower 60-day mortality.<sup>[162]</sup>

VV-ECMO is predominantly applicable to the following indications: PaO<sub>2</sub>/FiO<sub>2</sub> <50 mmHg for >3 h, or PaO<sub>2</sub>/FiO<sub>2</sub> <80 mmHg for >6 h, or artery pH <7.25 and PaCO<sub>2</sub> >60 mmHg for >6 h. Application of venoarterial (VA)-ECMO can be consid-

ered at the onset of severe heart failure.<sup>[163]</sup> At the time of writing, there remains a lack of RCTs on the effects of ECMO on the prognosis of patients with severe COVID-19 as compared with using MV alone. However, for critical COVID-19 patients with respiratory failure and refractory hypoxemia and/or hypercapnia after fully optimized lung-protective ventilation and prone positioning, ECMO is recommended to be initiated as early as possible at hospitals with relevant experience and expertise.

*Analgesia and sedation therapy*

**Recommendation 27: Close monitoring and evaluation of patients with severe COVID-19 undergoing HFNC oxygen therapy and NIV are indispensable, and a light sedation protocol should probably be used for less-tolerable patients. (Grade 2+, weak recommendation)**

Prone positioning, HFNC, and NIV are major therapies for the treatment of patients with moderate-to-severe COVID-19. Awake prone positioning in combination with HFNC was safe and effective for treating patients with severe COVID-19, prevented the disease from progressing to critical conditions, and avoided the need for intubation.<sup>[164]</sup> A multicenter, prospective cohort study of unsedated patients with moderate-to-severe ARDS found that early prone positioning in combination with HFNC or NIV avoided the need for tracheal intubation and the incidence of adverse complications.<sup>[165]</sup> However, another study reported no significant difference in 90-day mortality between mechanically ventilated patients treated with light sedation with daily interruption and those not treated with sedation.<sup>[166]</sup> Therefore, sedation is not recommended as standard care for patients that can tolerate the prone positioning and HFNC or NIV; for less-tolerable patients, a light sedation protocol can be applied to the patients without anxiety and pain.<sup>[167]</sup>

**Recommendation 28: For mechanically ventilated patients with early COVID-19 and moderate-to-severe ARDS, adequate analgesia and deep sedation should probably be used. (Grade 2+, weak recommendation)**

The Surviving Sepsis Campaign COVID-19 expert panel suggests that mechanically ventilated patients with COVID-19 should be treated with similar therapies to those used for ICU patients with non-COVID-19-associated ARDS.<sup>[107]</sup> Appropriate analgesia and sedation can eliminate pain and discomfort, reduce sympathetic nerve excitation, and lower metabolism, oxygen consumption, and systemic inflammation. However, patients with critical COVID-19-associated severe ARDS have more severe lung injury, stronger respiratory drive, and even spontaneous respiration-associated lung injury (P-SILI)<sup>[114]</sup>; thus, these patients require a more aggressive MV strategy and deep sedation protocol.<sup>[168]</sup> A deep sedation protocol that decreases oxygen consumption, improves patient-machine coordination, and reduces P-SILI should therefore be an important component of a protective ventilation strategy for COVID-19 patients with severe ARDS.<sup>[169]</sup> In addition, adequate analgesia should be administered before deep sedation. Moreover, due to the unique pathophysiology<sup>[170]</sup> and different clinical features<sup>[137]</sup> in patients with COVID-19, the level and duration of sedation for severe and critical COVID-19 patients with ARDS may be different from the sedation used for other patients. P-SILI has been recognized as the predominant cause behind disease deteriora-

tion during the first week of COVID-19 infections.<sup>[171]</sup> Therefore, for the early-stage patients with severe ARDS undergoing deep sedation, to prevent deterioration in P-SILI-induced lung injury, daily awakening and sedation interruption are not recommended to be used as standard care.

**Recommendation 29:** For COVID-19 patients with moderate-to-severe ARDS ( $\text{PaO}_2/\text{FiO}_2 \leq 150$  mmHg) who have respiratory distress and tidal volume  $\geq 8$  mL/kg.PBW after appropriate sedation and analgesia, neuromuscular blockers (NMBs) should probably be used based on the patient's conditions. (Grade 2+, weak recommendation)

Currently, the effects of NMBs on the prognosis of patients with COVID-19 are lacking. The ACCURASY trial<sup>[172]</sup> and Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial<sup>[173]</sup> investigated the effects of early use (within 48 h) of cisatracurium on the prognosis of patients with moderate-to-severe ARDS. Despite inconsistent findings,<sup>[174]</sup> conditional use of NMBs is still recommended for COVID-19-associated moderate-to-severe ARDS at present.<sup>[175,176]</sup> Large clinical observational studies showed varied use of NMBs in patients with severe COVID-19, with the ratio ranging between 22% and 88%.<sup>[132]</sup> A Spanish multicenter, prospective observational study reported that 76% (536/742) of patients with COVID-19-associated ARDS received NMBs, with ratios of 77.7%, 70%, and 64% use in critical, moderate, and mild ARDS, respectively.<sup>[177]</sup> A European multicenter clinical observational study included 407 patients with COVID-19 who were followed up for 28 days, 342 (84%) of whom received NMBs.<sup>[178]</sup> The most common indications for NMBs included  $\text{PaO}_2/\text{FiO}_2 \leq 150$  mmHg and prone positioning. Current data from COVID-19 studies showed a higher proportion of NMBs use as compared with classical ARDS studies (approximately 26% of patients received NMBs in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure [LUNG SAFE]). Further investigation is required to ascertain the difference in usage of NMBs between COVID-19 and traditional ARDS cohorts. One possibility is that NMBs were employed to inhibit the strong respiratory drive and P-SILI in patients with COVID-19 and that a relatively large proportion of patients with COVID-19 received prone positioning.

Although other types of NMBs, such as rocuronium, vecuronium, and pancuronium, have not yet been validated by clinical studies, they can still be considered as alternatives.<sup>[179]</sup> However, attention should be directed to the metabolism and adverse events of different drugs. In conclusion, the use and withdrawal of muscle relaxants should be determined according to the patient's clinical manifestations, oxygenation status, lung compliance, and degree of respiratory distress.

**Recommendation 30:** For invasively ventilated COVID-19 patients with moderate-to-severe ARDS who have entered the convalescent period, the experts suggest a light sedation strategy is used to prevent delayed ventilator removal. (Expert opinion)

COVID-19 spreads through respiratory droplets and air and requires third-level protection, increasing the workload and difficulty of HCWs, who may be concerned by the risk of accidental extubation-caused environmental and nosocomial infection. Consequently, the HCWs may promote the adoption of a deep

sedation strategy in severe and critical COVID-19 patients with ARDS more frequently. Abundant evidence shows that deep sedation leads to longer MV duration, longer ICU stay, and higher mortality, while light sedation shortens MV duration and reduces tracheotomy rate. Therefore, for patients who have entered the convalescent period, a light sedation strategy should be initiated promptly to prevent delayed extubation, provided that MV has lung-protective effects.

**Recommendation 31:** The experts suggest that screening and evaluation of delirium are used as standard care for patients with severe and critical COVID-19. (Expert opinion)

Coronaviruses were proved to be neurotropic in the SARS and Middle East Respiratory Syndrome (MERS) pandemics. SARS-CoV-2 also has similar potential neuroinvasive effects, *i.e.*, acute mental dysfunction, manifesting as delirium (also referred to as encephalopathy).<sup>[180]</sup> The proportion of COVID-19 patients with nervous symptoms has been reported to be as high as 45%.<sup>[181]</sup> The risk factors for delirium in patients with COVID-19 include age, Simplified Acute Physiology Score II (SAPS II), tobacco use, and excessive alcohol use.<sup>[182]</sup> Family visits might reduce the risk of delirium. Therefore, considering the high incidence of delirium in patients with COVID-19, delirium screening is recommended as standard care for patients with severe and critical COVID-19.

#### *Hemodynamic monitoring*

**Recommendation 32:** Close monitoring of COVID-19 patients for hypoxia and inflammatory response-induced myocardial injury should probably be performed. (Grade 2+, weak recommendation)

Myocardial injury is a major life-threatening complication in patients with COVID-19.<sup>[183]</sup> The prevalence of myocardial injury was as high as 19.7% (82/416) in hospitalized COVID-19 patients, and patients with cardiac injury had significantly higher mortality compared with those patients without myocardial injury.<sup>[184]</sup> Bansal et al.<sup>[185]</sup> found that mortality, ICU stay, MV, and coagulation disorders significantly increased in patients with myocardial injury. However, the mechanisms underlying the myocardial injury in patients with COVID-19 have yet to be elucidated.<sup>[184]</sup> For patients with severe COVID-19, persistent hypoxia and inflammatory response-induced myocardial injury mandates close attention.

Increased aerobic metabolism in myocardial tissues may lead to myocardial hypoxia. After the onset of systemic viral infection-induced acute respiratory failure, this change further damages the supply-demand relationship in the myocardium and causes acute myocardial injury.<sup>[186]</sup> In addition, increased cytokine secretion may also be responsible for myocardial injury in COVID-19 patients.<sup>[7,184,186]</sup> Huang et al.<sup>[7]</sup> confirmed that unbalanced T-helper-1 and T-helper-2 responses lead to cytokine storms, which may induce myocardial injury in patients with COVID-19. The release of inflammatory cytokines may lead to decreased coronary blood flow and oxygen supply.

**Recommendation 33:** Considering that acute right ventricular impairment is not uncommon in patients with COVID-19, optimization of right ventricle-pulmonary artery cou-

**pling should probably be used to improve cardiac efficiency. (Grade 2+, weak recommendation)**

COVID-19 predominantly affects the respiratory system, with 19.6–31.0% of patients presenting with ARDS, which is a manifestation of severe COVID-19. Cardiac injury is another common manifestation in COVID-19 patients, with right ventricular impairment being the most prevalent cardiac injury.<sup>[187,188]</sup> Mortality was reported to be significantly higher in COVID-19 patients with right ventricular impairment as compared with those without right ventricular impairment and the risk of death further increased in patients who also exhibited pulmonary hypertension.<sup>[189]</sup>

The major cause of right ventricular impairment in patients with COVID-19 is distressed pulmonary circulation. The mechanisms predominantly include hypoxia/respiratory acidosis-induced pulmonary vasoconstriction, pulmonary interstitial edema-induced pulmonary capillary compression, pulmonary capillary microthrombosis, and the effects of positive-pressure ventilation.<sup>[190,191]</sup> The diagnostic criteria for right ventricular impairment are also based on echocardiographic indications, including right ventricular dilation, decreased tricuspid annular plane systolic excursion, and decreased right ventricular fractional area change.<sup>[192]</sup>

COVID-19 may cause right ventricular-pulmonary arterial uncoupling. Therefore, therapies that can optimize right ventricular-pulmonary arterial coupling and improve right ventricular function are important for the treatment of COVID-19.<sup>[193]</sup> Detailed methods are summarized as follows. First, a strategy that prevents positive-pressure ventilation from further increasing pulmonary vascular resistance and deteriorating right ventricular function—that is, a circulation-protective ventilation strategy—should be adopted, including maintaining plateau pressure <28 cmH<sub>2</sub>O, driving pressure <15 cmH<sub>2</sub>O, and CO<sub>2</sub> level between 40 mmHg and 49 mmHg. This strategy also includes prone positioning, which can significantly improve ventilation–perfusion ratio and thereby improve oxygenation.<sup>[194]</sup> Next, in addition to proactive correction of hypoxemia and acidosis, prevention of fluid overload while ensuring tissue perfusion is another important strategy to alleviate pulmonary interstitial edema. Moreover, SARS-CoV-2 causes vascular endothelial injury and vascular inflammation, leading to hypercoagulation in many patients and a high prevalence of pulmonary embolism.<sup>[190]</sup> Therefore, proactive preventive or therapeutic anticoagulation is an important method to prevent oxygenation deterioration and decrease right ventricular overload.

**Recommendation 34: For COVID-19 patients with abnormal pulmonary blood flow distribution, optimization of the MV strategy should probably be used to improve abnormal pulmonary blood distribution-induced dead space ventilation. (Grade 2+, weak recommendation)**

COVID-19-induced hypoxemia differs from commonly seen typical ARDS.<sup>[195]</sup> Some patients with severe and critical COVID-19 developed “silent hypoxemia,” a severe hypoxemia but with normal respiratory rate and essentially normal pulmonary compliance.<sup>[19]</sup> Gattinoni et al.<sup>[196]</sup> classified COVID-19-associated ARDS into two types according to pulmonary compliance: Type 1 (basically normal compliance) and Type 2 (low compliance). Type 2 is similar to typical ARDS,

while Type 1 patients have a respiratory system compliance >50 mL/cmH<sub>2</sub>O while presenting with severe hypoxemia.<sup>[197]</sup>

Based on the pathophysiological characteristics of COVID-19, close attention should be directed to abnormal pulmonary blood flow distribution-induced dead space ventilation to facilitate timely identification of patients with severe or critical conditions, implement personalized therapeutic strategies, and improve prognosis. For respiratory function support in Type 1 patients, high-PEEP therapies have poor effects due to the abnormal pulmonary blood distribution-induced dead space ventilation and normal pulmonary compliance; therefore, therapies that can improve the ventilation–perfusion ratio should be adopted. Prone positioning is effective in improving ventilation–perfusion ratio. Researchers monitored the ventilation and perfusion in a COVID-19 patient before and after prone positioning using EIT and found that prone positioning increased ventilation in the dorsal half by 20% and decreased perfusion in the same area by 11%, thus prone positioning improved ventilation–perfusion matching.<sup>[198]</sup> In addition, Type 1 patients did not present with significantly increased respiratory rate but usually had a large tidal volume, vigorous spontaneous respiration, and large negative intrathoracic pressure. The presence of inhomogeneous pulmonary lesions under these conditions means uncontrolled inspiratory effort may further aggravate excessive dilation of the relatively normal pulmonary tissues, vascular leakage in pulmonary tissues, and thus ventilation–perfusion mismatching. Considering that it is currently difficult to evaluate pulmonary blood flow in COVID-19 patients under spontaneous respiration, controlling inspiratory effort presents as a good option.

*Anticoagulation therapy*

**Recommendation 35: Screening the risk of venous thromboembolism (VTE) in patients with severe and critical COVID-19 and dynamically evaluating its evolutions should probably be performed. (Grade 2+, weak recommendation)**

Hospitalized COVID-19 patients often developed thromboembolism. A retrospective cohort study of hospitalized COVID-19 patients from New York showed a VTE prevalence of 2.9% and a high mortality of 26.1%. The major predictors of VTE include high age, history of cardiovascular disease, and high D-dimer (critical value four times or greater than the upper limit of normal).<sup>[199]</sup> A French multicenter prospective study showed that the prevalence of pulmonary embolism was as high as 16.7%, and that compared with patients with non-COVID-19-associated ARDS, patients with COVID-19-associated ARDS were more prone to pulmonary embolism (11.7% vs. 2.1%;  $P=0.008$ ).<sup>[200]</sup> A Chinese retrospective study showed that the ORs for developing symptomatic VTE in severe and non-severe hospitalized COVID-19-patients were 5.94 and 2.79, respectively.<sup>[201]</sup> Thromboprophylaxis with rivaroxaban 10 mg/day for 35 days after discharge from the hospital improved clinical outcomes, including reducing arterial events, compared with no post-discharge anticoagulation therapy.<sup>[202]</sup> Despite a lack of large-sample, randomized, controlled studies, considering the high prevalence of thrombus events in patients with COVID-19, we recommend screening patients with COVID-19 for the risk of VTE and dynamic evaluation of its evolutions as standard care.



**Recommendation 36: Anticoagulation interventions using low-molecular-weight heparins (LMWHs) or unfractionated heparins (UFHs) should probably be used for severe and critical COVID-19 patients without contraindications to anticoagulation. (Grade 2+, weak recommendation)**

A Chinese retrospective study found no difference in 28-day mortality between patients with COVID-19 who received heparin and those who did not; however, when sepsis-induced coagulopathy (SIC) score  $\geq 4$  or D-dimer  $>6$ , 28-day mortality was lower in the heparin users.<sup>[203]</sup> In an open-label, adaptive, multiplatform, controlled trial, non-critically ill patients with COVID-19 received pragmatically defined regimens of either therapeutic-dose anticoagulation with heparin or usual-care pharmacologic thromboprophylaxis. Among 2219 non-critically ill patients, the probability that therapeutic-dose anticoagulation increased organ support-free days as compared with usual-care thromboprophylaxis was 98.6% (adjusted OR=1.27, 95% CI: 1.03–1.58).<sup>[204]</sup> A US cohort study showed that 84.4% of 4297 hospitalized COVID-19 patients received prophylactic anticoagulation treatment within 24 h of admission and had a 30-day cumulative incidence of mortality of 14.3%, indicating that prophylactic anti-coagulation reduced 30-day mortality.<sup>[205]</sup> At present, there is no definitive evidence comparing different types of anticoagulants. Parenteral anticoagulants such as UFHs or LMWHs are recommended.<sup>[206]</sup>

Currently, there are some controversies surrounding the dosage of anticoagulants. In a large observational study of hospitalized COVID-19 patients, the strategy of intermediate compared with prophylactic-dose anticoagulation improved the probability of survival. These findings suggest that increased-intensity anticoagulation may be beneficial in the treatment of COVID-19.<sup>[207]</sup> Therapeutic-dose anticoagulation may reduce the risk of all-cause mortality, but the evidence is very uncertain (adjusted OR=0.86; 95% CI: 0.73–1.02).<sup>[208]</sup> At present, clinical studies do not support this approach in critically ill patients, suggesting an increased risk of bleeding in patients with more severe COVID-19. An Iranian multicenter, open RCT (the INSPIRATION trial) compared 30-day intermediate-dose (enoxaparin, 1 mg/kg daily) and standard-dose (enoxaparin, 40 mg daily) anticoagulation treatments and found that increasing the dosage provided no benefits in decreasing venous or arterial thrombus, treatment with ECMO, and 30-day mortality.<sup>[209]</sup> Furthermore, a therapeutic-dose heparin anticoagulation strategy did not increase the probability of survival to hospital discharge, reduce cardiovascular or respiratory organ support compared with usual-care pharmacologic thromboprophylaxis.<sup>[210]</sup>

To reduce the incidence of VTE, standard prophylactic anticoagulation with LMWH is recommended as a frontline treatment in patients with COVID-19.<sup>[211]</sup> Enoxaparin (40 mg) was injected subcutaneously every 24 h for the prophylactic anticoagulation. Therapeutic-dose anticoagulation was administered according to local protocols for the treatment of VTE. Enoxaparin 40 mg was injected subcutaneously every 12 h for the therapeutic anticoagulation. Dosing should be adjusted according to body weight/BMI and renal function.

At present, there is inadequate medical evidence on the different effects of different anticoagulants or the benefits of increasing the dosage of prophylactic anticoagulation.

*Use of antimicrobial agents*

COVID-19 infection leads to immune function impairment, which makes the patient vulnerable to secondary infections, a factor associated with increased mortality.<sup>[212]</sup> In previous influenza pandemics, secondary bacterial, viral, and fungal infections were common.<sup>[213]</sup> However, there are limited data on the prevalence of secondary infections in patients with COVID-19. An early retrospective study of COVID-19 patients admitted to the Wuhan Jinyintan Hospital reported that the prevalence of bacterial and fungal secondary infections was 1% and 4%, respectively.<sup>[214]</sup> A systematic meta-analysis that included 30 clinical studies of patients with COVID-19 showed that 7% of hospitalized COVID-19 patients had a bacterial secondary infection.<sup>[215]</sup> Other retrospective and clinical studies also reported that the proportion of COVID-19 patients with a secondary infection was  $<10\%$ .<sup>[213–215]</sup>

**Recommendation 37: Prophylactic antimicrobial agents should probably not be used as standard care for patients with COVID-19 unless definitive evidence of bacterial or fungal secondary infections is available. (Grade 2–, weak recommendation)**

Among 4267 patients recruited in a single-center study, 3.6% of the confirmed cases of COVID-19 were positive in a screen (using blood or respiratory secretion cultures) for bacterial infection. Among them, 65% were transferred to the ICU, and 74% received MV.<sup>[7]</sup> Another study recruited almost 4000 patients, among which, 7% of the hospitalized COVID-19 patients developed a bacterial secondary infection, with the prevalence higher in ICU patients compared with non-ICU patients (14% vs. 4%).<sup>[215]</sup> Based on current research data, the risk factors for secondary infections are ICU admission, indwelling catheter, and MV. WHO does not recommend empirical broad-spectrum antibiotic therapy for COVID-19 patients without indications.<sup>[216]</sup>

*Acute renal injury and continuous renal replacement therapy (CRRT)*

**Recommendation 38: The experts suggest that renal replacement therapy (RRT) is initiated promptly for COVID-19 patients with AKI and indications of RRT. (Expert opinion)**

The optimal time to initiate RRT in critical COVID-19 patients with AKI remains unclear. However, when an AKI patient develops a life-threatening complication such as severe metabolic disorder (e.g., refractory acidosis, hyperpotassaemia, and uremia) or diuretic-unresponsive fluid overload, RRT should be initiated promptly. Nevertheless, there are considerable controversies over the timing to initiate RRT in moderate-to-severe patients. A single-center, randomized study by Zarbock et al.<sup>[217]</sup> showed that, compared with late RRT, early RRT decreased the 90-day mortality in AKI patients. However, the artificial kidney initiation in kidney injury (AKIKI)–1 study by Gaudry et al.<sup>[218]</sup> found that among patients with severe AKI but no life-threatening complication, the mortality was not significantly different between early and delayed RRT strategies. The AKIKI-2 study showed that longer postponing of RRT did not confer additional benefits and was associated with increased 60-day mortality.<sup>[219]</sup> Therefore, the use of RRT in COVID-19 patients with AKI requires rigorous evaluation of the



indications, and the mode and dosage of RRT should reference its use in non-COVID-19 patients.

**Recommendation 39: Blood purification therapy should probably not be used as standard care for clearing inflammatory mediators and cytokines in COVID-19 patients. (Grade 2–, weak recommendation)**

With the development of membrane materials and blood purification devices and technologies, current CRRT technology is capable of simultaneous RRT and clearance of endotoxins and/or cytokines. Case studies showed that CRRT significantly decreased inflammatory cytokine levels and provided benefits in stabilizing the oxygenation level and hemodynamic state in patients with COVID-19.<sup>[220–222]</sup> However, the CYCOV trial reported that early cytokine absorption did not reduce blood IL-6 concentration in severe COVID-19 patients undergoing VV-ECMO and was associated with increased 30-day mortality.<sup>[223]</sup> Therefore, cytokine clearance using blood purification alone is not recommended for patients with COVID-19.

#### *Nutrition support therapy*

**Recommendation 40: Early nutritional risk assessment and therapy should probably be performed for patients with severe and critical COVID-19. (Grade 2+, weak recommendation)**

Nutritional therapy is an important component of the treatment of severe and critical COVID-19. Deepening research on the nutritional therapy for patients with COVID-19 has revealed a high prevalence of high nutritional risk in severe and critical COVID-19 patients at hospital admission, and its significant association with mortality and longer hospital stays has been recognized. A multicenter, retrospective study that included 523 patients with severe and critical COVID-19 showed that the Nutrition Risk in Critically ill (NUTRIC) score is an independent predictor of in-hospital mortality (OR=1.20, 95% CI: 1.09–1.45;  $P = 0.006$ ) and that patients with a high Nutritional Risk Screening (NRS) score had a higher risk of poor prognosis in the ICU (OR=1.88, 95% CI: 1.15–3.07;  $P=0.012$ ).<sup>[224]</sup> Another single-center, retrospective study showed that 92% of severe and critical COVID-19 patients had nutritional risk (NRS score  $\geq 3$ ) and 16% had high nutritional risk (NRS score  $\geq 5$ ). In regression models, one unit increase in the NRS score was associated with a 1.23-fold increase in mortality.<sup>[225]</sup> Furthermore, a retrospective cohort study of patients with critical COVID-19 revealed that, compared with low nutritional risk, high nutritional risk was associated with a higher risk of death (OR=2.40, 95% CI: 1.06–5.47;  $P=0.036$ ) and higher 28-day mortality (HR=2.05, 95% CI: 1.01–4.23;  $P=0.04$ ).<sup>[226]</sup> Therefore, early nutritional risk assessment and therapy are necessary for patients with severe COVID-19. Recommended assessment tools include NRS2002, NUTRIC, and modified NUTRIC.

**Recommendation 41: The experts suggest a target calorie intake of 20–25 kcal/kg (actual body weight if BMI  $<30 \text{ kg/m}^2$ ; adjusted body weight for obese patients) is used for the early stage (first week) of ICU stay, with calorie intake to be increased appropriately in later stages based on the patient's clinical status. The daily protein intake is 1.2–1.5 g/kg. For patients with a 25-hydroxyvitamin D level**

**$<50 \text{ nmol/L}$ , 500,000 UI complement vitamin D3 is suggested to be given within one week. (Expert opinion)**

Patients with severe and critical COVID-19 usually had a prolonged, significant systemic inflammatory response, which led to hypermetabolism that persisted longer as compared with other ICU patients.<sup>[227]</sup> This has been confirmed by a prospective study, in which the measured resting energy expenditure (mREE) of critical COVID-19 patients undergoing tracheal intubation was observed to be 15–20 kcal/kg in the first week, which increased continuously with wider variability after the first week, and increased to 1.5-fold (2-fold for some patients) the prediction of REE (pREE) in the third week.<sup>[228]</sup> Therefore, by referencing the European Society for Clinical Nutrition and Metabolism (ESPEN)/American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, we recommend a target calorie intake of 20–25 kcal/kg for the early stage of ICU stay for patients with COVID-19. Considering that patients with severe COVID-19 exhibited persistent hypermetabolism, calorie intake should be increased appropriately in the subsequent stages of the disease.

At present, there are few studies on the protein intake in COVID-19 patients. A small-sample, retrospective study showed that a daily protein provision  $>0.8 \text{ g/kg}$  decreased the in-hospital mortality in ICU COVID-19 patients.<sup>[229]</sup> Another small-sample retrospective study suggested that a daily protein provision of 1.5 g/kg contributed to nitrogen balance.<sup>[230]</sup> By referencing the ESPEN's expert consensus on the nutrition in COVID-19 patients, we recommend a daily protein provision of 1.2–1.5 g/kg for COVID-19 patients in the ICU.

Among micronutrients, vitamin D deficiency is associated with the risk and severity of COVID-19 infection. A prospective study showed that vitamin D deficiency was associated with poor prognosis in COVID-19 patients  $>65$  years and vitamin D status might be a reliable prognosticator.<sup>[231]</sup> We recommend that for patients with a 25-Hydroxyvitamin D level  $<12.5 \text{ ng/mL}$  or  $<50 \text{ nmol/L}$ , 500,000 UI compliment vitamin D3 should be given within 1 week.

**Recommendation 42: The experts suggest that enteral nutrition (EN) is administered to severe and critical COVID-19 patients within 24–48 h of ICU admission, and parenteral nutrition (PN) is administered to ICU patients intolerable to all-calorie tube feeding of EN. (Expert opinion)**

ESPEN/ASPEN guidelines recommend EN within 48 h of ICU admission. At present, there is a lack of studies on the timing of delivering EN to patients with COVID-19. By referencing existing guidelines, we recommend the delivery of EN to patients with severe COVID-19 within 48 h of ICU admission based on a comprehensive evaluation of the patient's severity of illness, mode of respiratory support, and gastrointestinal function. When the patient has a complication such as uncontrolled shock, severe hypoxemia, severe acidosis, upper gastrointestinal hemorrhage or a gastric residual volume  $>500 \text{ mL/6 h}$ , intestinal ischemia, intestinal obstruction, or abdominal compartment syndrome, EN should be temporarily suspended.<sup>[232–234]</sup> For patients capable of self-feeding, the best option is oral feeding or oral nutritional supplement (ONS). When oral delivery does not meet the energy requirement, EN should be delivered by tube feeding.

Many factors may lead to drastically decreased food intake in patients with COVID-19. Therefore, we recommend PN be given to patients with severe COVID-19 in ICU who are intolerable to all-calorie tube feeding of EN.

- (1) **Total PN (TPN):** For patients with contraindications to EN, TPN should be delivered immediately after ICU admission when the patient presents with severe malnutrition or high nutritional risk (NRS 2002  $\geq 5$  or NUTRIC score  $\geq 5$ ) and within 3–7 days of ICU admission when the nutritional risk is low (NRS 2002  $\leq 3$  or NUTRIC score  $< 5$ ).<sup>[232]</sup>
- (2) **Supplemental PN (SPN):** For patients presenting with high nutritional risk, SPN should be delivered as soon as possible when EN fails to reach 60% of the target amount within 48–72 h; SPN is also recommended when EN fails to reach 60% of the target amount within 7–10 days.<sup>[234,235]</sup>

### Part V: Traditional Chinese Medicine (TCM)

TCM therapy has been adopted in China for COVID-19 prevention and control. In TCM, COVID-19 is classified as a *yi* disease and is diagnosed and treated based on an overall analysis of the patient's illness and constitution in the light of the local climatic characteristics. Precise treatment of severe and critical COVID-19 under the guidance of a TCM doctor includes Chinese patent medicine, decoction, and other TCM therapies, with the medication adjusted over time based on the changing clinical status. For detailed TCM therapies, see the Diagnosis and Treatment Protocol for COVID-19 (trial version 9).<sup>[38]</sup>

Xuebijing (XBJ) can antagonize endotoxin, inhibit the inflammatory response, improve immune function, regulate coagulation balance, and protect tissues and organs. The efficacy of XBJ has been demonstrated in its use for the treatment of severe pneumonia and sepsis. A single-center RCT by Wen et al.<sup>[236]</sup> investigated the clinical effects of XBJ injection in the treatment of severe COVID-19. Compared with patients receiving standard care, the patients receiving standard care in combination with XBJ injection had significantly decreased CRP, erythrocyte sedimentation rate (ESR), and acute physiology and chronic health evaluation (APACHE) II score, confirming the effects of XBJ in improving the prognosis of patients with COVID-19. A single-center, double-blind RCT by Luo et al.<sup>[237]</sup> showed that XBJ significantly suppressed inflammatory mediator levels and improved clinical symptoms in patients with COVID-19. However, these two trials are single-center trials that enrolled only a small number of patients, and further clinical research evidence is needed. Patients with severe and critical COVID-19 can be treated using XBJ under the guidance of a TCM expert based on the disease status.

### Part VI: Rehabilitation Therapy for Severe and Critically Ill Patients

**Recommendation 43: Early mobilization in patients with severe COVID-19 is safe and effective, and early initiation of rehabilitation therapy should probably be used in patients with stable clinical status and indications to early mobilization. (Grade 2+, weak recommendation)**

Early active mobilization is associated with improved muscular strength, better mobility status at discharge from the hospital, and the number of post-discharge days of survival, and is the most basic and important means of rehabilitation therapy. Early rehabilitation therapy provides proven benefits in patients with ARDS, including improving respiratory function, promoting redistribution of body fluids, and reducing immobilization-induced complications.<sup>[238]</sup> However, when the disease is unstable or progressively deteriorating, early mobilization may further increase oxygen consumption and lead to further disease deterioration. Early mobilization can only be initiated after confirming that the disease is relatively stable.

In a British prospective, observational study, 110 mechanically ventilated patients with severe COVID-19 were evaluated by rehabilitation therapists within 24 h of ICU admission. Once the clinical status stabilized, rehabilitation therapy was initiated and carried forward under the coordination of rehabilitation therapists. All patients performed rehabilitation motions in the ICU, with the first mobilization performed within  $14 \pm 7$  days of ICU admission. This indicates that patients with severe COVID-19 may experience delayed rehabilitation due to severe illness but are capable of early rehabilitation in the ICU that can improve the mobilization levels in patients at ICU discharge.<sup>[239]</sup> Early chest physiotherapy is effective in improving gas exchange, reversing pathological progression, and alleviating or avoiding the need for artificial ventilation in other respiratory diseases. Furthermore, a study by Abdullahi et al.<sup>[240]</sup> showed that chest physiotherapy improved the respiratory function and quality of life in patients with COVID-19.

**Recommendation 44: Patients with severe and critical COVID-19 should probably receive psychological rehabilitation therapy during hospitalization and after discharge. (Grade 2+, weak recommendation)**

After discharge from the hospital, a proportion of patients with COVID-19 had mental disorders, including anxiety and depression. Halpin et al.<sup>[241]</sup> followed 100 survivors of COVID-19 and found that 46.9% of ICU patients and 23.5% of ordinary ward patients had psychological distress. A follow-up study of COVID-19 patients discharged from the hospital between January 7, 2020, and May 29, 2020, revealed that 23% of the patients had anxiety and depression 6 months after acute infection.<sup>[242]</sup> A study by Liu et al.<sup>[243]</sup> showed that the prevalence of depression and anxiety in patients with COVID-19 increased after quarantine treatment but a respiratory rehabilitation program significantly improved their quality of life and anxiety (SAS score:  $47.4 \pm 6.3$  vs.  $54.9 \pm 7.3$ ;  $P < 0.05$ ).

### Part VII: Transfer of Severe and Critically Ill Patients

Patients with severe and critical COVID-19 may require an in-hospital or inter-hospital transfer, which leads to risks associated with the disease itself, as well as the risk of viral transmission. Such a transfer should be performed by a transfer team with the appropriate expertise to ensure safety. In addition to following the best practice for the transfer of severe and critically ill patients with a conventional disease, special precautions

should be incorporated and followed for the transfer of patients with severe and critical COVID-19.

**Recommendation 45:** The experts suggest that diagnostic and therapeutic operations are performed at bedside as far as possible to avoid unnecessary transfer. If the situation does warrant a transfer, it can be performed after an adequate risk assessment, formulation of a transfer program, and preparation of an emergency response plan for potential risks. In addition, life-threatening medical conditions need to be corrected as far as possible before a transfer. (Expert opinion)

A study showed that among 250 patients with severe COVID-19 who were transported between hospitals, 9 (3.5%) had cardiac arrest before transport, 29 (11.6%) had hypotension, and 22 (8.8%) had a critical desaturation during transport.<sup>[244]</sup> Therefore, inter- and intra-hospital transfers of COVID-19 patients should be minimized. Therapeutic and diagnostic methods that can be performed at the bedside should be adopted as far as possible.<sup>[245]</sup>

**Recommendation 46:** The experts suggest necessary monitoring and therapeutic measures should be taken during transport, and the original monitoring and therapeutic measures should be maintained as far as possible; negative-pressure transfer devices should be used, such as negative-pressure transfer vehicles and beds; HCWs should use third-level protection. (Expert opinion)

When a transfer is necessary, it should only be conducted after an adequate assessment of the pros and cons and correction of life-threatening medical conditions as far as possible. In addition, a transfer should be well planned, including an emergency response plan for potential risks. The planning should cover the transport route, elevators, quarantine room, bed, drugs, devices, and personnel. The original monitoring and treatment should be maintained as far as possible. The transfer plan should be communicated to the HCWs in the receiving department/hospital in advance. During transport, contact with irrelevant persons should be minimized. The use of negative-pressure transfer devices can avoid the discharge of virus-polluted gas and thus minimize the possibility of environmental pollution.<sup>[39]</sup>

At present, no transfer-associated infection in HCWs has been reported. However, considering the high infectivity of COVID-19, we still recommend that HCWs involved in a transfer use third-level protection.<sup>[246]</sup>

#### Part VIII: Protection of HCWs in the ICU

**Recommendation 47:** The experts suggest that ICUs hosting patients with severe COVID-19 have a “three zones, two lines, three passages” layout. (Expert opinion)

ICUs hosting patients with severe COVID-19 must strictly adhere to the standard “three zones, two lines, three passages” layout for infectious disease wards.<sup>[246,247]</sup> “Three zones” refers to a clean zone, a semi-polluted zone, and a polluted zone; “Two lines” refers to the two lines demarcating the three zones; and “Three passages” refers to the three separate passages for patients, HCWs, and polluted materials, respectively.<sup>[248,249]</sup>

The clean zone includes a locker room for HCWs, a supplies storage room, and a shower room. The semi-polluted zone includes HCWs’ duty room, toilet, office, and internal corridor. The polluted zone includes wards, treatment rooms, nurse stations, outer corridors, and pollution sources. A buffer room and an isolation door should be configured between the clean zone and semi-polluted zone and between the semi-polluted zone and polluted zone, respectively.

**Recommendation 48:** The experts suggest that ICU HCWs involved in the treatment of COVID-19 assess the risk of the medical operations and use appropriate personal protective equipment (PPE). Third-level protection is used when performing high-risk operations such as tracheal intubation, tracheotomy, and tracheoscopy. (Expert opinion)

Before entering a patient treatment zone, HCWs should wear third-level PPE, including a disposable leak-proof isolation gown, a disposable cap, an N95 mask, disposable shoe covers, sterile gloves, a protective face shield, and goggles.<sup>[250]</sup> An air-purifying respirator (if available) can be used when performing high-risk or aerosol-generating operations, such as non-closed sputum suction, non-invasive ventilator positive-pressure ventilation, tracheal intubation, tracheotomy, fiberoptic bronchoscopy, collection of diagnostic respiratory tract samples, tracheal incision care, and cardio-pulmonary resuscitation (CPR).<sup>[123,246,248,251–253]</sup> When using third-level protection, the relevant procedures must be strictly adhered to, and the PPE should be worn and removed according to the specified sequence.<sup>[119,254]</sup>

#### Part IX: Vaccines

**Recommendation 49:** COVID-19 vaccination should probably be used to reduce the proportion of breakthrough infections that progress to severe and critical illness. (Grade 2+, weak recommendation)

At the time of writing, vaccination is the most effective method for prevention and control of COVID-19. A vaccine initiates a primary immune response by introducing modified or weakened forms of the disease-causing antigen (or part of it) and stimulating the host to produce immunological memory under the conditions of a natural infection. Numerous countries around the world have developed and tested many different vaccine platforms [Table 2], predominantly including: (1) live attenuated vaccine and inactivated vaccine; (2) protein subunit and vector-based vaccine; and (3) nucleic acid and nanomaterial vaccine. COVID-19 vaccines that have recently passed Phase 3 trials include three inactivated vaccines (WIV04, HB02, and CoronaVac), two mRNA vaccines (BNT162b2 and mRNA-1273), and three adenovirus vector vaccines (ChAdOx1-nCoV-19, Gam-COVID Vac [Sputnik V], and Ad26.COV2.S).<sup>[255–258]</sup> The overall efficacy of the various vaccines falls in the range of 62.1–95.0%. Compared with the infection rate among unvaccinated populations, the breakthrough infection rate is lower (0.04–0.6%). Most breakthrough infections occurred before the full immunity of the vaccine and individuals experienced milder symptoms and a shorter course, with few progressing to severe illness. Therefore, we believe that vaccination can reduce the pro-



**Table 2**  
Multinational Phase 3 trials of COVID-19 vaccines.

Vaccines	Infections		Severe cases		Breakthrough infections (%)
	Vaccine group	Control group	Vaccine group	Control group	
WIV04/HB02	26/21	95	0	2	0.20/0.04
CoronaVac	9	32	0	3	0.15
BNT162b2	8	162	1	9	0.05
mRNA-1273	11	185	0	30	0.06
Ad26.COV2.S	117	351	14	60	0.42
Gam-COVID-Vac	16	62	0	20	0.10
ChAdOx1 nCoV-19	30	101	0	2	0.50

portion of breakthrough infections that progress to severe and critical illnesses.

## Conclusions

In summary, this expert consensus focuses on the diagnosis and treatment of severe and critical COVID-19. We hope the consensus will provide clinical direction for these patients. Strong evidence from high-quality clinical trials is needed to clarify the remaining uncertainties, and many trials are currently in progress worldwide. This is a changing statement that will be updated as new evidence emerges.

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## Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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