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Management of Patients with COVID-19 in the Intensive Care Unit

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ABSTRACT

Coronavirus disease-19 (COVID-19), which was first seen in Wuhan, China in December 2019, caused a pandemic. According to the data of the World Health Organization, it has been reported to caused 6,566,610 deaths since the day it was defined. COVID-19 causes a wide variety of clinical conditions in adults, ranging from asymptomatic infection, mild respiratory symptoms, acute respiratory distress syndrome and multi-organ dysfunction to severe pneumonia. All these conditions require multidisciplinary patient care. Intensive care units (ICU) play a critical role for treating the most severe cases. In this process, it has been difficult for clinicians to meet the increasing need for hospitalization and intensive care, to provide clinical management of patients by following the current case approach. In our country, according to the constantly renewed COVID-19 guidelines of the Ministry of Health, the clinical follow-up of the patients was carried out. In this review, our aim is to present the management of patients with a diagnosis of COVID-19 who were followed up in ICUs.

Keywords: Coronavirus disease-19 (COVID-19), Intensive care unit, ARDS, ventilation

Introduction

Coronavirus disease-19 (COVID-19), first identified in China's Wuhan province in December 2019, has since become a serious health problem and caused a pandemic (1). The entire world has been affected economically, socially and psychologically.

It was declared a "public health emergency of international concern" by the World Health Organization in January 2020, and as of July of the same year, approximately more than 10 million cases recorded in 6 months, and more than 6,500,000 deaths have been reported to date (2). COVID-19 causes a wide variety of clinical conditions in adults, ranging from asymptomatic infection, mild respiratory symptoms, acute respiratory distress syndrome and multi-organ dysfunction to severe pneumonia (3). In this process, healthcare practitioners are making a high level of effort to respond to the increasing demand; on the other hand, they are following the scientific literature with new clinical and experimental studies and benefiting from the experiences of clinicians from worldwide about the pandemic. In this article, our aim is to present the management of patients with a diagnosis of COVID-19 who were followed up in the intensive care units (ICU).

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Risk Factors for Severe COVID-19

Many risk factors and comorbidities, such as old age, male gender, obesity, hypertension, diabetes, chronic lung diseases, heart, liver and kidney diseases and tumors have been identified in the progression of COVID-19 to a severe and critical stage (Table 1). Additionally, clinically significant immunodeficiencies and pregnancy are also considered important risk factors (4).

Table 1. Definitions of critical and severe COVID-19

Category	Definiton
Severe	Clinical manifestations of pneumonia (fever, cough, shortness of breath, rapid breathing) and any of the following: • Respiratory rate >30 breaths/min; • Severe respiratory distress; or • Oxygen saturation in room air <90%
Critical	ARDS*, sepsis or septic shock or presence of respiratory failure requiring ventilation

*ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus disease-2019

Indications for the Admission to the ICU

Patients with severe pneumonia and COVID-19 should be followed up in the ICU (1).

- Severe pneumonia,
- Acute respiratory distress syndrome,
- Sepsis, septic shock,
- Myocarditis, arrhythmia, cardiogenic shock or
- Multiple organ failure can be observed in severe clinical conditions.

According to the intensity of the required treatment and ideally where it should occur (out of hospital, emergency room, service, ICU and after discharge), COVID-19 patients are followed and treated; admissions to the ICU depend on the severity of the disease and the ICU capacity of the health system. According to the COVID-19 guideline of the Ministry of Health dated April 12, 2022, ICU admission should be considered in the following cases (5):

Patients Who Need to be Treated in the ICU:

- Dyspnea and respiratory distress
- Respiratory rate >30 breaths/min
- PaO_2/FiO_2 <300
- Increased oxygen requirement during follow-up
- SpO_2 <90% and PaO_2 <70 mmHg despite 5 L/min oxygen therapy

- Hypotension (SBP <90 mmHg and more than 40 mmHg decrease from normal SBP and MAP <65 mmHg, tachycardia >100/min)
- Patients with acute kidney and liver injury, confusion, other acute organ dysfunction (acute bleeding diathesis and immunosuppression)
- Cardiac biomarkers elevation and arrhythmia
- Lactate >2 mmol/L
- Skin disorders (prolonged capillary refill time and cutis marmaratus.

Patient Follow-up in the ICU

Monitoring

Standard monitoring parameters; non-invasive or invasive arterial pressure, oxygen saturation, electrocardiogram, body temperature, urine output monitoring. Additionally, end-tidal CO_2 monitoring should be applied to patients on mechanical ventilator support with severe respiratory failure (1).

In patients with critical illness with hemodynamic unstability (Table 1), it is important to monitor dynamic parameters that can evaluate cardiac output, at least with central venous catheterization and even invasive and non-invasive methods. In this group of patients, the results obtained from these parameters are critical both in the decision of vasopressor and inotropic treatment and in fluid management. The National Institutes of Health (NIH) states that dynamic parameters (body temperature, capillary refill time, and/or lactate level) should be preferred over static parameters in fluid response (6). Other tools that guide treatment are echocardiography and lung ultrasonography (1).

Laboratory

In laboratory monitoring; with daily hemogram; white blood cell, lymphocyte, neutrophil lymphocyte ratio, thrombocyte and erythrocyte amount are important in clinical follow-up (1). Laboratory findings in critically ill patients with COVID-19 include leukopenia or leukocytosis, lymphopenia, and elevated D-dimer, aminotransferases, lactate dehydrogenase, and ferritin levels. Abnormalities are typically more pronounced in critically ill patients, although these can also be seen with less severe COVID-19 (7).

Arterial blood gas measurement; they are also precious parameters in terms of oxygenation, ventilation, acid-base status, blood lactate level, and thus the appropriate management of respiratory support in the patient, and tissue perfusion, fluid, sepsis, septic shock management (1).

Critically ill patients diagnosed with COVID-19 may also have an elevated procalcitonin (PCT) level. PCT indicates that there is a secondary bacterial infection focus, which is important for antibiotic selection. Coagulation parameters are important for the follow-up of processes such as coagulopathy and vasculitis that may develop in these patients. Monitoring of prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer and ferritin is recommended (1).

In some patients with severe COVID-19, there is laboratory evidence of a severe inflammatory response similar to cytokine release syndrome, with persistent fever, elevated inflammatory markers (e.g., D-dimer, ferritin, interleukin-6). Abnormalities in laboratory results indicate a poor prognosis.

Clinic

Deterioration in the respiratory system is associated with mechanical ventilation, which we can consider as the beginning of the ICU period.

Frequently, lung gas volume and respiratory system compliance are decreased, oxygenation impaired, and $PaCO_2$ may rise.

Applied sedation and neuromuscular blocking causes loss of skeletal and diaphragmatic muscle mass, resulting in insufficient understanding of the actual driving pressure applied during spontaneous breathing, resulting in hypoventilation at lower tidal volumes and protective driving pressures (8). These changes trigger atelectasis formation and resulting loss of lung gas volume. It is possible that the additional fluid load during this phase is at least one factor that contributes to the increase in pulmonary edema and impaired lung function. This condition, defined as type H lung by Gattinoni et al. (8), is characterized by high elastance, high lung weight, high right-to-left shunt, and a high rate of recovery.

Radiological Imaging

Bedside lung imaging should be performed daily or every other day order to monitor the underlying viral pneumonia and acute respiratory distress syndrome (ARDS) course, as well as to monitor complications such as atelectasis and pneumothorax. Reports of a few patients showing computed tomography (CT) scan image properties consistent with fibrosis but showing near-normal improvement in chest radiography, caution should be exercised against the early prognosis of irreversibility and established fibrosis (8).

Chest radiography: Chest radiography may be normal in early or mild disease. In a retrospective study of 64 patients diagnosed with COVID-19, Wong et al. (9) reported that 20%

of the patients did not have any abnormality in the chest radiography throughout the disease. Common abnormal radiographic findings increased throughout the disease course with a peak in severity 10 to 12 days after symptom onset; it is a lung involvement with bilateral, peripheral and lung bases consolidation and ground glass opacities (Figure 1) (9).

Lung CT: Although more sensitive than chest radiography and some CT findings are characteristic of COVID-19, no findings can completely rule out the possibility of COVID-19.

Ground-glass opacification with or without consolidative abnormalities is most commonly seen on lung CT in patients with a diagnosis of COVID-19, which is consistent with viral pneumonia (Figure 2). As an example, in a systematic review of studies evaluating lung CT findings in more than 2.700 COVID-19 patients, the following abnormalities were noted (10).

- Ground glass opacification-83%
- Mixed consolidation ground glass opacities-58%
- Pleural thickening-52%
- Interlobular septal thickening-48%
- Air bronchograms-46%

Lung ultrasound (LUS): COVID-19 has bilateral, asymmetric and patchy involvement in the periphery of the lungs is involved, which can increase the effectiveness of LUS. Some findings detected with LUS are as follows: B lines (It is the most important ultrasonographic finding of the disease. Although these lines are the typical finding of the disease, they can also be seen in different interstitial diseases, therefore, their specificity is low). Irregular pleural line (may be regular or

Figure 1. Bilateral, peripheral and lung bases consolidation and ground glass opacities
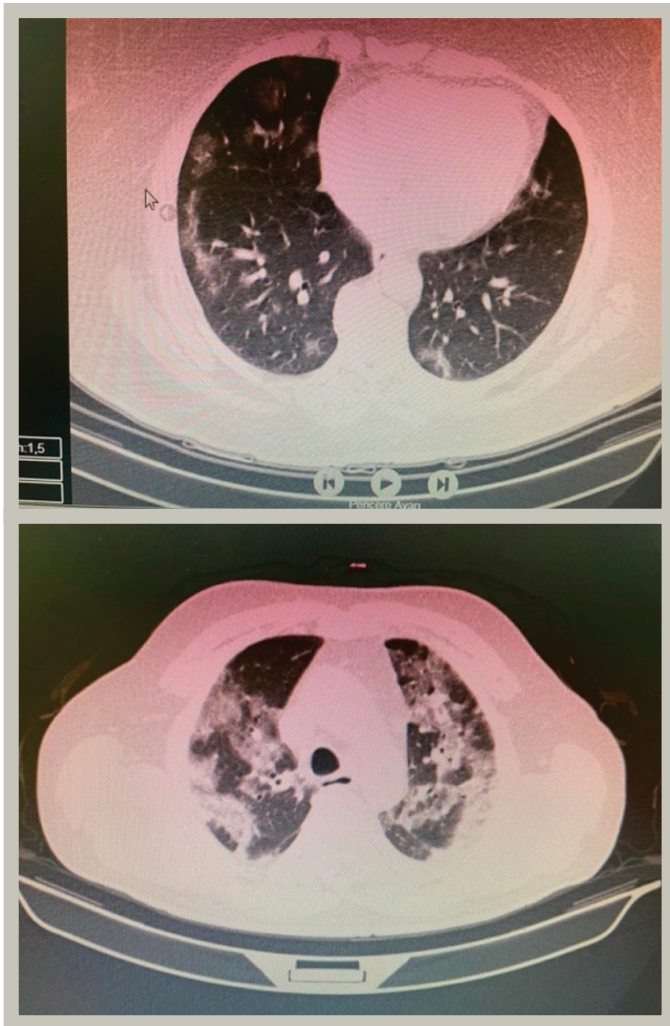
Table 2. The Berlin definition of the ARDS

Timing	Respiratory distress that has occurred or worsened in the past week
Chest imaging	Bilateral opacities not explained radiologically by volume overload, lobar or lung collapse, or nodules
Origin of edema	Respiratory failure cannot be explained by heart failure or fluid overload alone
Hypoxemia	
• Mild ARDS	200 mmHg <PaO_2/FiO_2 ≤300 mmHg (PEEP ≥5 cm H_2O)
• Moderate ARDS	100 mmHg <PaO_2/FiO_2 ≤200 mmHg (PEEP ≥5 cm H_2O)
• Severe ARDS	PaO_2/FiO_2 ≤100 mmHg (PEEP ≥5 cm H_2O)

ARDS: Acute respiratory distress syndrome, PEEP: Positive end-expiratory pressure

While some patients recover and the need for respiratory support can be reduced; in some, oxygenation continues to deteriorate; a decision needs to be made regarding intubation and mechanical ventilation. In the ICU, treatment principles should not differ significantly from those recommended for treating ARDS. However, close attention should be paid to the PEEP setting, as prerequisites for PEEP efficacy (i.e., pulmonary edema or atelectasis) exist only in the intermediate stages of COVID-19 and are less common too early or too early stages. Optimally, the hemodynamics and respiratory system mechanics should be carefully monitored and the patient should be given the most appropriate ventilator therapy.

Respiratory Support in Patients Diagnosed with COVID-19 Pneumonia

Awake prone position

For hospitalized patients with hypoxemic respiratory failure due to COVID-19, an awake/sedated prone position receiving oxygen or non-invasive support methods [including low-flow oxygen, high-flow oxygen delivered via nasal cannula (HFNC), or NIV] is recommended. Titration of oxygen therapy is highly recommended to prevent hypoxemia in acute hypoxemic respiratory failure. A range of 90-96% oxygen saturation confirmed by pulse oximetry is a reasonable target (12).

While an optimally beneficial time has not been established, the prone position should be encouraged in the eligible patient for at least 6 to 8 hours, typically within a 24-hour period. However, it has been experienced in clinics that some patients have difficulty in the prone position due to personal ailments (e.g., face, neck or arm pain, inability to sleep prone) or discomfort from external equipment (e.g., mask and tube).

Figure 2. Ground-glass opacification with or without consolidative abnormalities

fragmented), punctate defect, subpleural consolidation, air bronchogram, and in severe cases, pleural sliding movement ("sliding") deterioration can be observed (11).

Management of Acute Respiratory Failure and Acute Respiratory Distress Syndrome

ARDS: The diagnosis of ARDS, which can occur in patients with severe pneumonia and has a high mortality rate, is defined according to the Berlin criteria (Table 2) (3).

As patients' clinic worsens, increased respiratory support is required, often requiring the level of ICU care, depending on hospital and patient characteristics.

Respiratory support includes oxygenation with low-flow and high-flow systems, non-invasive ventilation (NIV), and the use of other adjunctive therapies (e.g., nebulized medications) and rescue therapies (e.g., prone positioning).

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Although oxygenation can be partially restored, a progressive rise in $PaCO_2$ and dead space, as commonly described, becomes evident in connection with structural changes in the lung parenchyma. Responses to recruitment, higher PEEP, and the prone position gradually fades. Indeed, in nearly 50% of patients, oxygenation may decrease rather than increase. This phenomenon is consistent with a progressive shift from edema to a fibrotic state (8). The NIH does not recommend the awake prone position as a salvage therapy to avoid intubation in patients with refractory hypoxemia with indications for intubation and mechanical ventilation (6).

Low flow oxygen

For patients with hypoxemic respiratory failure due to COVID-19, supplemental oxygenation via a nasal cannula with a low-flow system (i.e., up to 6 L/min) is appropriate as an initial strategy. The degree of viral aerosolization at low flow rates is unknown but probably minimal (13).

High Flow Nasal Cannula Oxygen Therapy

If SpO_2 continues to be low despite O_2 treatment with a nasal cannula and mask with sufficient flow, HFNC can be given up to 20-80 L/min, FiO_2 up to 21-100% O_2 can be given. HFNC devices are systems that provide clearing of the anatomical dead space from CO_2, positive nasopharyngeal pressure, a more stable FiO_2 and improvement in mucociliary function. It can give about 30-40 L/min O_2 and 4-7 cmH_2O positive end-expiratory pressure (PEEP) (14). This helps open collapsed alveoli by reducing physiological dead space and maintaining a modest PEEP, resulting in better comfort by reducing the work of breathing (12).

At the onset of the COVID-19 pandemic, fear of disease transmission by exhaled aerosol led to avoidance of HFNC use and preference for early intubation in patients. However, observations of aerosol concentrations in the environment of COVID-19 patients in clinical studies show that aerosol masses are not significantly different before and after HFNC use and are further reduced when a surgical mask is worn on the patient's face (15). For this reason, experts recommend that clinicians use HFNC therapy for COVID-19 patients, with attention to the correct use of personal protective equipment, no different from those without infection (16).

Despite the lack of controlled studies in COVID-19, large case series have reported positive outcomes for patients treated with HFNC. A recent computer simulation study concluded that strategies involving HFNC may result in greater mechanical ventilator availability and fewer deaths for patients who do not need emergency intubation (17).

Non-invasive Mechanical Ventilation (NIMV)

NIMV is defined as positive pressure respiratory support administered through a mask instead of an endotracheal tube as the interface. Positive airway pressure can be applied either continuously (continuous positive airway pressure, CPAP) or bilevel (bilevel positive airway pressure, BiPAP; different pressures in inspiration and expiration). CPAP maintains a constant level of pressure throughout the respiratory cycle. BiPAP, on the other hand, provides different levels of positive airway pressure during inspiration (IPAP) and expiration (EPAP). The difference between IPAP and EPAP is called pressure support and it increases ventilation. With NIMV application, functional residual capacity increases, collapsed or non-ventilated alveoli open, oxygenation improves, respiratory work load, respiratory muscle fatigue and upper airway resistance decrease.

NIMV indications:

• Dyspnea (moderate-severe),

• Tachypnea (>24/minute obstructive pulmonary diseases, >30/minute restrictive lung diseases)

• Increased respiratory workload (use of accessory respiratory muscles, abdominal paradoxal breathing),

• Impaired gas exchange (acute respiratory failure of acute or chronic background);

• $PaCO_2$ >45 mmHg, pH <7.35)

• Hypoxemia (PaO_2/FiO_2 <200)

Respiratory arrest and the presence of an obstacle to applying the mask to the face (such as burns, trauma) are absolute contraindications for NIMV application. There are also relative contraindications; hemodynamic instability, uncontrolled myocardial ischemia or arrhythmia, uncontrolled upper gastrointestinal bleeding, agitation, lack of cooperation, inability to protect the airway, difficulty swallowing, excessive secretion, multiple organ failure, recent upper airway or upper gastrointestinal tract surgery.

In a multicenter randomized study (the RECOVERY-RS randomized clinical trial) conducted in the UK, tracheal intubation and 30-day mortality were found to be statistically significantly lower in the CPAP-applied group when CPAP was compared with conventional oxygen therapy in acute respiratory failure due to COVID-19 infection. NIMV can be applied within a protocol in intermediate intensive care or ward conditions outside the ICU but intubation should not be delayed in case of failure criteria (18).

Invasive mechanical ventilation (IMV)

In patients who will undergo IMV, endotracheal intubation should be performed by trained and experienced practitioners with a rapid sequential intubation protocol. To provide balanced anesthesia in these patients who will undergo elective endotracheal intubation, induction should be performed using anesthetic agents to be selected according to patient characteristics. If possible, the use of bag-mask should be avoided during preoxygenation. Intubation should be performed with a video laryngoscope, if possible. Unless necessary, the mechanical ventilator circuit should not be disconnected, and if disconnection is necessary, personal protective equipment must be used. If possible, the closed system aspiration method should be used (5).

In COVID-19 patients who require endotracheal intubation, lung protective mechanical ventilation should be applied in patients who undergo IMV for ARDS. Tidal volume should be set at 4-8 mL/ideal body weight. The plateau pressure should be <30 cmH$_2$O and the driver pressure (plateau pressure-PEEP) <15 cmH$_2$O.

The ventilation frequency can be adjusted 16-24/min. In cases with pH <7.15 and hypercapnia, the respiratory rate may increase up to 30/min. Permissive hypercapnia can be applied unless the pH is <7.15. If the tidal volume, plateau pressure and driving pressure are too high and patient ventilator dyssynchrony occurs sedation, analgesia or neuromuscular blocking agents can be administered. Excessive sedation should be avoided (5).

If hypoxemia progresses to a ratio below PaO$_2$:FiO$_2$ <100-150 mmHg, there are several treatment options. The PEEP level can be increased by 2-3 cm H$_2$O every 15-30 minutes to keep the plateau airway pressure below 30 cm H$_2$O to increase oxygen saturation to 88-90%. The use of high PEEP versus a low PEEP strategy is recommended by the NIH (6). Recruitment maneuvers may have little effect, but moderate pressures of about 30 cm H$_2$O for 20-30 seconds following hemodynamics can be applied (19). If static compliance is >40 mL/cm H$_2$O, recruitment and high PEEP values may not be required. However, patients with low compliance should be treated like classical ARDS, especially in moderate-severe ARDS, PEEP should be applied, which will prevent atelecto-trauma and provide alveolar patency, but at pressures that will not cause excessive stretching and will not disrupt hemodynamics, which will provide the best compliance and oxygenation. Additionally, the prone position should be applied if there are no specific contraindications and in conjunction with the previously described interventions (19). A prone position of 12-16 hours per day is recommended for mechanically ventilated patients. Although the use of neuromuscular blocking agents is not routinely recommended, use of neuromuscular blockers as bolus or infusion (up to 48 h if persistent patient ventilator dyssynchrony) is recommended during lung protective ventilation (6).

The prone position may improve oxygenation of 5-20 ppm inhaled as an alternative if persistent refractory hypoxemia persists despite efforts to optimize neuromuscular blockade and PEEP therapy (Table 3) (19). However, routine use of inhaled nitric oxide is not recommended (6).

Extracorporeal membrane oxygenation (ECMO)

Although ECMO is often life-saving, it represents a form of support that sometimes takes several weeks to allow for recovery and recovery, or time to determine the potential reversibility of lung injury (Table 3). No NIH recommendation due to insufficient evidence on the benefits of using ECMO in patients with refractory hypoxemia (6).

Weaning

Preparation for extubation should be performed after standard spontaneous breathing trials (SBT) applications. Weaning and extubation should be performed when clinical (neurological well-being, good hemodynamics, improved

Table 3. Treatment options for severe acute respiratory distress syndrome due to COVID-19 (19)

Treatment	Implementation
HFNC	This may have prevented or delayed the need for intubation
Tidal volume	Use 6 mL/kg of predicted body weight (may decrease to 4 mL/kg of predicted body weight)
Plateau airway pressure	<30 cm H$_2$O
Positive end-expiratory pressure	Consider moderate to high levels if needed
Recruitment maneuvers	At low pressures
Use of neuromuscular blockers	For ventilator non-compliance, increased airway pressure, hypoxemia
Prone position	For worsening hypoxemia, PaO$_2$:FiO$_2$ <100-150 mmHg
Inhaled NO	Use 5-20 ppm*
Fluid management	Aim for a negative fluid balance of 0.5-1.0 L per day
Renal replacement therapy	For oliguric renal failure, acid-base management, negative fluid balance
ECMO	Use the EOLIA criteria (23)

*ppm: Parts per million, HFNC: High-flow oxygen delivered via nasal, ECMO: Extracorporeal membrane oxygenation, COVID-19: Coronavirus disease-2019

respiratory distress) and laboratory parameters (pH >7.35 in arterial blood gas, $PaCO_2$ <45 mmHg, PaO_2 >60 mmHg) are appropriate.

However, attention should be paid to infection control measures changes for COVID-19. Equipment; while we recommend using closed systems, and T-track testing is not recommended for SBTs. To reduce the risk of reintubation following extubation, patients with COVID-19 should have a higher degree of extubation readiness. The implementation may vary and may include higher criteria for passing an SBT. For example, some experts use lower pressure assisted ventilation parameters (e.g., 0-5 cm H_2O) instead of the typical high PEEP to overcome endotracheal tube resistance during extubation, while others use SBT for longer durations (e.g., typical two four hours instead of one hour) they deem appropriate (20). Newer procedures such as "mask-on-tube" extubation can reduce exposure to droplets and aerosols. We recommend that the steps for weaning from mechanical ventilation not be changed unless there is evidence to the contrary. Extubation can be performed safely by adhering to standard PPE (personal protective equipment) practices.

Extubation

Extubation in the isolation room should be preferred in patients with continued infection control measures for COVID-19. Close communication with a clinician experienced in intubation when extubating a patient with a diagnosis of COVID-19 is advocated, especially for patients with predetermined difficulty in airway when rapid reintubation is required (1).

Tracheostomy

Approximately 10% of patients followed in the ICU with a diagnosis of COVID-19 require tracheostomy (21).

• **Indications:** Similar to patients without COVID-19 (e.g., weaning failure, failed extubation, secretion management, airway edema, failure to protect the airway (e.g., poor mental state) (22).

• **Timing:** The optimal timing for tracheostomy in COVID-19 patients is uncertain, but it is usually delayed until after 10 days of intubation (14-21 days or longer) although the practice varies (22).

• **Procedure;** for patients who are contagious during the procedure, tracheostomy is considered a high-risk procedure for aerosolization (22).

Nutritional support

The same nutritional principles used in critically ill patients without COVID-19 should be applied to critically ill patients with COVID-19 (24).

Fluid and Electrolyte Management

Conservative fluid management with crystalloids is recommended for patients with acute respiratory distress syndrome unless patients have sepsis or hypovolemia due to high fever or gastrointestinal losses (1).

While the NIH recommends the use of balanced/buffered solutions for acute fluid resuscitation of patients in shock due to COVID-19, it does not recommend the use of albumin. Norepinephrine is recommended as a first-line vasopressor. It is recommended to keep the MAP around 60-65 mmHg. The use of hydroxyethyl starch solution is not recommended for intravascular volume support. If norepinephrine is available in shock patients with a diagnosis of COVID-19, the use of dopamine is not recommended. Vasopressin and epinephrine are recommended as second-choice vasopressors. The use of low-dose dopamine is not recommended for the preservation of kidney functions. The use of dobutamine is recommended in patients with cardiac dysfunction who show signs of hypoperfusion despite adequate fluid therapy and vasopressor support. Invasive blood pressure monitoring is recommended in patients on vasopressor support. Low-dose corticosteroid therapy is recommended in patients with refractory septic shock who have completed corticosteroid therapy (6).

If there is no shock picture in patients with pulmonary edema, it is recommended to stay negative for 500 mL in the acute period. Renal function should be carefully monitored (6).

Complications

In addition to the difficulties experienced in the clinical management of COVID-19, many complications caused by the disease itself have been reported (Table 4). Common complications of acute respiratory distress syndrome associated with COVID-19 include acute kidney injury (AKI), elevated liver enzymes, delirium/encephalopathy, heart damage (e.g., cardiomyopathy, arrhythmia, and sudden cardiac death), and thrombosis (25,26).

• **AKI:** It occurs in 15 to 30% of critically ill patients with COVID-19. Some of these patients require renal replacement therapy (27). In a cohort study of 40,000 critically ill patients, Cummings et al. (28) reported that one-third (31%) of patients required renal replacement therapy for AKI.

• **Gastrointestinal complications:** Gastrointestinal complications appear more common in patients with ARDS due to COVID-19 than in patients with ARDS for other reasons (74% vs. 37%) These rates include high aminotransferase levels (55%), severe ileus (48%) and mesenteric ischemia (4%) clinics (29).

• **Neurological complications:** Neurological complications are common in critically ill patients hospitalized in the ICU (30). Delirium or encephalopathy is the most common complications and present with marked agitation and confusion and corticospinal system findings (hyperreflexia). Consistent with this, ICUs have observed that sedation requirements are high in this population, particularly immediately after intubation. Other common complications include acute ischemic stroke, myositis, Guillain-Barré, and focal neuropathy. Encephalitis is rare (31).

• **Cardiovascular complications:** In critically ill patients, it may develop after heart damage, a complication that is concurrent with respiratory disease, or after respiratory disease has resolved. Cardiomyopathy, atrial arrhythmias, myocardial infarction, acute right heart failure and cardiac arrest are cardiac complications seen in patients with COVID-19 (32).

• **Thrombosis:** Hypercoagulable state resulting in arterial and venous thrombosis is common in critically ill patients with COVID-19. The actual incidence is unknown, although some studies report an incidence as high as 30% (33).

• **Sepsis, shock, multi-organ failure:** Sepsis, shock, and multi-organ failure may occur in critically ill patients with COVID-19, but appear less common compared with non-COVID-19-related ARDS. The need for vasoactive agents is variable (32,34). According to the literature, hypotension is unusual in the absence of a specific cause and the need for vasoactive agents is typically associated with sedative agents, cardiac dysfunction, or secondary bacterial infections.

• **Secondary infections:** Although our data is limited, critically ill patients with COVID-19 are at risk of secondary infections. Secondary infections include pneumonia (e.g., bacterial, fungal), vascular catheter infections, urinary tract infections, Epstein-Barr and cytomegalovirus reactivation, and rarely strongyloides reactivation (20). Empirical antibiotic therapy should be avoided unless there is a proven or suspected focus of bacterial infection. Patients receiving antibiotic therapy during hospitalization should be evaluated daily and unnecessary antibiotic use should be avoided (6).

• **Pneumothorax and barotrauma:** Pneumothorax may occur in critically ill patients with a diagnosis of COVID-19 who is spontaneously breathing or mechanically ventilated. Patients with COVID-19-related ARDS under mechanical ventilation therapy may have an increased risk of barotrauma compared with patients with other ARDS, but data are variable, ranging from 2 to 40%. Patients undergoing invasive ventilation have higher rates than NIV, and those undergoing invasive ventilation have a higher risk of death compared with non-COVID-19 patients with barotrauma (35).

Prognosis

• **Mortality:** Retrospective studies have reported variable mortality in ARDS associated with COVID-19 (27,34). The death rate from COVID-19 appears to be due to the presence of severe ARDS, and the rate ranges from 12 to 78%, with an average of 25 to 50%. However, death can occur from certain other conditions such as cardiac arrhythmia, cardiac arrest, and pulmonary embolism. Limited data show that there is no difference in mortality among people with ARDS between those with COVID-19-related ARDS and those with non-COVID-19-related ARDS (36).

• **Mortality risk factors:** Globally, the major mortality-related risk factor in critically ill patients with COVID-19 is advanced age. In a study by Gupta et al. (37) on 2.215 patients diagnosed with COVID-19, mortality was associated with ≥80 years of age, and it was stated that the risk of death increased 11 times. Other risk factors associated with death in critically ill patients are (37):

• ARDS, particularly severe ARDS development and the need for mechanical ventilation,

• Comorbidities (e.g.: Obesity, chronic heart and lung conditions, hypertension, diabetes, chronic kidney disease, renal replacement therapy, cancer),

• Markers of inflammation or coagulation (e.g.: Fever, D-dimer level >1 microg/mL, high fibrin degradation products, long-term activated partial thromboplastin, and prothrombin times),

• Laboratory parameters (e.g.: Worsening lymphopenia, neutrophilia, troponin elevation),

• Male gender,

• Severity of organ dysfunction at admission,

• Right ventricular dysfunction.

Table 4. Difficulties in clinical management (38)

Epidemiology and clinical features	Suggestions
• It is difficult to predict the course of the disease from the onset of symptoms.	• Support research to develop and validate prognostic tools and biomarkers.
Diagnosis	
• Clinical features are not specific; the risk of missing an early case in a local outbreak should not be ignored. The sensitivity of RT-PCR tests for critically ill patients unknown. • RT-PCR tests may not be available in many intensive care units; if any, the assays will take time to complete.	• Adopt a low threshold for diagnostic testing, if applicable. • Repeat sampling, preferably from the lower respiratory tract, if necessary. • Maintain a high index of suspicion for COVID-19.
Management of acute respiratory failure	
• The benefits of NIV and HFNC and the risks of viral transmission via aerosolization are unclear. • Intubation poses a risk of viral transmission to healthcare workers. • ECMOs are a limited number centralized in designated centers.	• Reserve for mild ARDS with airborne measures, preferably in single rooms and at low intubation threshold. • Perform intubation drills; the most experienced practitioner should intubate with full PPE and limited balloon-mask ventilation. • Balance the needs of more patients with less severe disease (unproven) against the few benefits.
Other intensive care management	
• These patients often develop myocardial dysfunction in addition to acute respiratory failure.	• Care should be taken in fluid management due to hypovolemia; myocardial involvement should be detected early by troponin and betanatriuretic peptide measurements and echocardiography.
• Bacterial and influenza pneumonia or co-infection is difficult to distinguish from COVID-19 alone.	• Consider empirical broad-spectrum antibiotics and neuraminidase inhibitors and then taper them off quickly.
• The benefits and risks of systemic corticosteroids are unclear.	• Routine use should be avoided until further evidence is available.
• Transfer from the intensive care unit for investigations such as CT scans carries a risk of viral transmission	• Minimize transfers by using alternative methods such as bedside ultrasound.
• In severe COVID-19, viral transmission in the upper respiratory tract continues 10 days after the onset of symptoms.	• The isolation of patients should be terminated after clinical recovery and after two negative RT-PCR tests 24 h apart.
• The use of purposeful and experimental treatments unsupported by strong evidence.	• Seek expert guidance from local or international communities and enroll patients in clinical trials if possible.

ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus disease-2019, ECMO: Extracorporeal membrane oxygenation, HFNC: High-flow nasal cannula, ICU: Intensive care unit, NIV: Non-invasive ventilation, PPE: Personal protective equipment, CT: Computed tomography, RT-PCR: Reverse transcription-polymerase chain reaction

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