

Respiratory support for pneumonia patients in the COVID-19 pandemic

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Abstract

The COVID-19 respiratory disease pandemic caused by a type of Coronavirus, SARS-CoV 2, not previously known to infect humans, began in late 2019 and continues to this day. The clinical picture of the disease in adults is already well understood; risk factors for infection, disease severity, and mortality have been identified; diagnostic methods have been developed and successfully applied; virus spread control procedures are in place. However, despite such impressive advances, there is still no standard antiviral drug therapy nor recommendations for respiratory support for COVID-19 with proven effectiveness in pneumonia. There are currently several non-invasive respiratory support options for COVID-19 patients with mild to moderate respiratory disorders. These may significantly reduce the number of patients needing intubation and mechanical ventilation due to severe acute respiratory failure. That is why for patients with COVID-19 when choosing respiratory support, a balance must be struck between the clinical benefit of the intervention and the risk of intra-hospital spread of infection. It is important to note that during the treatment of COVID-19 patients with respiratory failure, the full range of invasive and non-invasive lung ventilation options should be considered.

Keywords: COVID-19, respiratory support, pneumonia, oxygenation, mechanical ventilation, non-invasive ventilation (NIV), acute respiratory distress syndrome (ARDS).

INTRODUCTION

Due to the rapid spread of the novel Coronavirus (SARS-CoV-2) pandemic and exponential growth in the number of patients with coronavirus disease 2019 (COVID-19), health care systems in affected countries are facing an increase in the number of patients admitted to intensive care units (ICUs) with hypoxic respiratory failure. Since the beginning of the pandemic, understanding of this pathology has proliferated. The need for respiratory support and mechanical ventilation for these patients became a matter of survival and often exceeded the resources available for health care systems. Although large, randomized trials are currently underway, survival depends mainly on providing supportive care. Pertinently, current recommendations for supportive care are based on treatment guidelines for other viral pneumonia and sepsis, but COVID-19 differs from pneumonia and sepsis in several fundamental ways. In this clinical review, we tried to analyze domestic and foreign practical recommendations for respiratory support for patients with COVID-19.

Overview of COVID-19

The number of COVID-19 patients worldwide is growing [1, 3], including Kazakhstan. COVID-19 is characterized by a severe course and high mortality than flu [4, 5]. The most common complication is viral pneumonia, which leads to the development of acute respiratory failure (ARF) and acute respiratory distress syndrome (ARDS), which necessitate oxygen therapy and respiratory support in most cases [6, 8].

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In South Korea, only 6.3% of approximately 7,000 cases were younger than 20 [38]. The most common comorbidity was Hypertension (31.2% to 81%) [17]. Li H, Liu L, Zhang D, et al. [20] reported a 40.3% incidence of cerebrovascular and cardiovascular diseases in patients with COVID-19; others have noted a high incidence of diabetes mellitus, from 10% to 21% [31, 24]. However, according to Korean researchers, the proportion with a history of chronic lung diseases ranged from 1 to 2.8% [20], which did not exceed the average prevalence of this pathology in Korea. COVID-19 infection has variable clinical presentations: from mild (asymptomatic) forms to a severe fulminant course [23]. A study of 43,000 patients in China showed that 82% had mild or moderate disease, 13% had a severe course, and 5% required critical intensive care [31]. The most commonly reported clinical presentations were fever (86.7%), cough (66.8%), weakness and fatigue (37.1%), sputum production (34.4%), shortness of breath (17, 6%), sore throat (12.9%), headache (12.6%), muscle pain (12%), and confusion (8%). There were also gastrointestinal manifestations: diarrhoea (3.7%) and vomiting (5.2%) [14, 12]. Feeling “heaviness in the chest” and dyspnea have been described [2]. The authors noted the rare occurrence of upper respiratory tract symptoms, such as a runny nose [13]. Folegatti PM, Ewer KJ, Aley PK, et al.[4] described the clinical progression of the first cases as beginning with respiratory symptoms (cough) followed by abdominal discomfort, diarrhoea, nausea, and vomiting. The absence of fever in approximately 11% of patients with COVID-19 distinguished this disease from severe acute respiratory syndrome caused by SARS-CoV and Middle East respiratory syndrome caused by MERS-CoV, in which the proportions of patients without fever were approximately 1% and 2%, respectively [8]. Unlike SARS-CoV and MERS-CoV, chills were less common with COVID-19 [5].

According to many authors, elderly patients with comorbidities such as Hypertension and other cardiovascular diseases, diabetes mellitus, or chronic obstructive pulmonary disease (COPD) had a severe disease course, often with the development of acute respiratory distress syndrome (ARDS), septic shock and metabolic disorders, acidosis and coagulopathy [6]. According to Zhu F-C, Guan X-H, Li Y-H, et al., the median time from symptom onset to hospitalization was approximately seven days – 31% of those hospitalized needed artificial lung ventilation (ALV) [5]. According to Wang D, Hu B, Hu C, et al., the average period from the onset of clinical presentations to the development of ARDS was about 7-8 days [12]. Deterioration of patients’ condition correlates with rising plasma levels of the pro-inflammatory cytokine IL-6 from days 6 to 14 of symptomatic illness [5]. The average times elapsed from the onset of symptoms to implementation of ALV and death were ten days and 23 days, respectively [14].

ARF is the leading cause of death in patients with severe COVID-19 admitted to an intensive care unit (ICU).

According to Zhou F, Yu T, Du R, et al., ARF was the leading cause of death in 87% of patients with COVID-19 [21]. The following study [9] showed that hypoxemia was the main predictor of poor outcomes in hospitalized patients with COVID-19; thus, lethality was 68.5% at saturation of arterial blood with oxygen (SpO₂) < 89%, but only 1.2% at SpO₂ > 90%. In the case of ARDS and severe pneumonia, early intubation and ALV are believed to improve patient survival [10]. However, studies in the United Kingdom and the USA found very high mortality of COVID-19 patients on ALV, from 64% to 87% [5, 11]. Early oxygen therapy and respiratory support initiation should commence at the pre-resuscitation stage while reducing the need for transfer to intensive care, tracheal intubation and ALV, improving the outcome [12].

Critical recommendations for oxygen therapy

The main task of treating patients with hypoxemic ARF is to oxygenate the body because severe hypoxemia leads to serious and often irreversible functional disorders of organs and systems and is also potentially lethal [14, 17]. The leading treatment for ARF is oxygen therapy (O₂ therapy) [18]. According to Huang C, Wang Y, Li X, et al., 41.2% of patients with SARS-CoV-2 required oxygen therapy, 35.6% of whom received oxygen outside the ICU [9].

Indications for starting O₂ therapy are SpO₂<90% or partial oxygen pressure (PaO₂) <60 mm Hg, guided by specific criteria:

- An essential condition for oxygen therapy is patency of the airways;
- O₂ therapy should not be used as an alternative to respiratory support if the latter is indicated;
- Optimal is maintaining SpO₂ 91–95%, PaO₂ 63–80 mm Hg (in COPD and other chronic respiratory diseases, SpO₂ is 87–92%, PaO₂ 56–65 mm Hg) [13, 19, 20].

When monitoring O₂ therapy, authors make the following recommendations:

- In case of hypoxemia, constantly monitor the SpO₂ level using pulse oximetry;
- When prescribing oxygen therapy, analyze the gas composition of arterial blood as often as possible, followed by monitoring the oxygen concentration in the inhaled mixture (FiO₂);
- In patients with a risk of hypercapnia (obesity/hypoventilation syndrome, COPD, neuromuscular diseases), determine PaO₂, PaCO₂, pH, and analyze the arterial blood gas composition;
- A re-analysis can be prescribed 30–60 minutes after starting oxygen therapy or a change in the FiO₂ value [14, 20].

Oxygen delivery methods

Systems for delivering oxygen to the respiratory tract can be divided into low-flow (nasal cannulas, nasal catheters, simple masks) and high-flow (Venturi masks, masks with a reservoir

or masks without rebreathing) [13, 19]. Both methods provide different FiO₂ values; The terms “low flow” and “high flow” do not refer to the FiO₂ value but to the amount of O₂-air mixture flowing through the system. FiO₂ depends not only on the flow of oxygen but also on the individual patient’s condition (minute ventilation and respiratory pattern should be taken into account) [22].

O₂ delivery systems include:

- Nasal cannulas are easy to use and well tolerated by most patients. The approximate FiO₂ value is calculated according to the following formula [24]: $FiO_2 = 20\% + 4 \times O_2 \text{ flow}$;
- A simple mask with 50-100 ml of additional “dead space”. To ensure “washing out” of CO₂, it is recommended to set a minimum flow of O₂ > 5 lt/min;
- The Venturi mask has the advantage of providing reasonably accurate FiO₂ values that do not depend on the patient’s minute ventilation and inspiratory flow; this is recognized as the safest and most effective way to deliver O₂ to the respiratory tract in patients at risk of O₂-induced hypercapnia [25];
- Mask with a reservoir (mask without rebreathing) creates higher concentrations of O₂, 60–80% on average [16]. Typically, an O₂ flow >10–15 Lt/min is used; the O₂ flow must be greater than the patient’s minute ventilation, and the mask reservoir must always be filled before the patient inhales.

Choice of a delivery system

A delivery system should be chosen by following these criteria [16, 18]:

- In patients with hypoxemia and without hypercapnia, O₂ therapy is carried out using masks or nasal cannulas (initial flow of O₂ is 5–6 lt/min);
- In hypoxemic patients at risk of hypercapnia, O₂ therapy should be started with low O₂ concentrations using nasal cannulas (flow 1–4 lt/min) or a Venturi mask (FiO₂– 24 or 28%);
- FiO₂ flow should be increased to SpO₂ levels of 92–96% (for COPD and other chronic lung diseases, 88–92%);
- In case of severe hypoxemia (SpO₂ <74% in air), it is recommended to start O₂ therapy with a reservoir mask (initial O₂ flow 10 lt/min).

High-flow oxygen therapy

High-flow oxygen therapy (HFOT) delivers a heated and humidified oxygen-air mixture through nasal cannulas at high flow rates (up to 60 lt/min). At the same time, it is possible to provide up to 100% FiO₂ [27]. In ARF, the peak inspiratory rate is high and often exceeds the flow of oxygen delivered by traditional oxygen devices, resulting in a subjective sensation of lacking air [28, 29]. Using HFOT overcomes these limitations. The main indication for HFOT is hypoxemic ARF (PaO₂/FiO₂– 150–300 mmHg) [30, 33].

Additional physiological benefits of HFOT are as follows [24, 29]:

- Gas conditioning prevents drying of the respiratory tract, improves mucociliary function, facilitates secretion mobilization and reduces atelectasis;
- A high level of oxygen flow ensures washing out CO₂ from the nasopharynx and oropharynx, while the functional “dead space” and breathing effort are reduced;
- HFOT creates a trim level of positive end-expiratory pressure (PEEP) in the airways, which increases the final expiratory volume and the opening of collapsed alveoli. At a flow rate of 35-60 lt/min, an average pressure of 2-3 cm of w.c. is created when the patient breathes with an open mouth and 5–7 cm of w.c. when breathing with a closed mouth;
- There is no metabolic burden associated with warming and humidifying the inspired gas, as the gas is optimally conditioned before it enters the HFOT.

The following complications may occur during O₂ therapy:

- High O₂ concentrations can lead to damage to the epithelium of the mucous membranes and lungs from mild tracheobronchitis to diffuse alveolar damage [36];
- Absorptive atelectasis and O₂-induced hypercapnia may develop at high FiO₂ levels [30].

Recommendations for non-invasive ventilation

Data validating non-invasive lung ventilation (NIV) in acute hypoxemic ARF are patchy [24, 25]. The first guidelines for managing COVID-19 did not recommend NIV support due to concerns that it may be accompanied by high tidal volume and transpulmonary pressure, which can cause further lung damage [11, 17, 36]. NIV methods have also been discouraged because they are aerosol-generating procedures with the potential to increase the risk of spreading the SARS-CoV-2 virus [36]. Evidence supporting the use of NIV during the COVID-19 pandemic is now emerging [38]. According to reports from Italy and China, the condition of many patients improved after NIV; up to 48% of patients treated with NIV in Italy did not require ALV [12, 14, 21].

The following NIV regimens are most often used in patients with ARF [15]:

- Continuous positive airway pressure (CPAP);
- Pressure support (PS);
- Auxiliary-controlled mode with pressure regulation (pressure-assisted/controlled ventilation, often referred to as PA/C);
- Bi-level positive airway pressure (BiPAP) mode;

In CPAP mode, the patient breathes spontaneously while a positive pressure relative to atmospheric pressure is maintained in his airways throughout the respiratory cycle. The PS mode is auxiliary in response to the patient’s respiratory effort. A predetermined airway pressure level is created in the respirator, and inspiration stops when the

inspiratory flow drops to a particular value (for example, 25% of the peak flow) [13]. BiPAP mode is the same as PS mode expiratory pressure (EPAP) corresponds to positive end-expiratory pressure (PEEP), and inspiratory pressure (IPAP) corresponds to the sum of PEEP + PS. The R-A/C mode is auxiliary. However, it allows you to set guaranteed negative-pressure ventilation (NPV) (back-up rate). If the patient's spontaneous NPV is below a predetermined level, the respirator automatically switches to controlled mode [14]. In many portable respirators, this mode is called Spontaneous-Timed mode (S/T), which is essentially PS with guaranteed NPV. Given these data, it is recommended to consider NIV in cases that do not require urgent intubation [35] and in patients without significant hemodynamic impairment and severe metabolic acidosis [36].

Recommendations for the prone position in non-intubated patients

The prone position (patients lying on their front) is widely used in treating patients with COVID-19 complicated by ARF. Typically, the prone position is used in patients with moderate to severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$ mmHg) who are on ALV [16]. When using the prone position, ARDS mortality can be reduced due to improved oxygenation [26, 32, 33]. The prone position can also be used in non-intubated patients receiving oxygen therapy or NIV [7,9,14]. Early use of the prone position in combination with oxygen therapy and NIV can avoid the need for intubation in many patients with moderate ARDS; when added to oxygen therapy or NIV, the prone position $\text{PaO}_2/\text{FiO}_2$ increases by 25–35 mm Hg compared with previous indicators [20, 21]. Early use of pronation in patients with COVID-19 receiving oxygen therapy or NIV has been shown to improve oxygenation parameters, reduce the need for tracheal intubation and ALV, and possibly reduce mortality [22, 34]. The prone position is well tolerated by spontaneously breathing patients. The objective of the prone position is to maintain SpO_2 in the range of 92–96% (88–92% in COPD).

A retro- and prospective study was performed in the ICU Department of the City Clinical Hospital No. 1 of Almaty based on S.D.Asfendiyarov KazNMU. The study included all patients with known outcomes (death from any cause or recovery) of SARS-CoV-2 pneumonia complicated by acute respiratory distress syndrome (ARDS) from March 26 to September 28, 2021. Risk factors of death were analyzed using a multivariate Cox regression model.

Results. The study included 311 patients, 177 (56.9%) men and 134 (43.1%) women. The median age was 63 years. 186 (59.8%) patients were in the ICU of the City Clinical Hospital No. 1 of Almaty. In 298 (95.8%) patients, the diagnosis of SARS-CoV-2 infection was confirmed by PCR. 127 (40.8%) patients died, 183 (59.2%) survived. The main causes of death were ARDS (93.4%), cardiovascular events (3.2%), and pulmonary embolism (1.0%). Mortality was low in patients receiving oxygen therapy (10.4%) and significantly increased in patients who received had to be

transferred to non-invasive (36.5%) or invasive (84.5%) ventilation of the lungs. The risk of death increased with age, and in the age groups over 50 years, men were significantly higher than women. In univariate models, diseases associated with the development of a lethal outcome were arterial Hypertension, coronary artery disease, stroke, atrial fibrillation, type 2 diabetes mellitus and obesity. However, in a multivariate model built on all grounds with correction for sex and age, only CHD retained statistical significance (relative risk [RR] 1.256, 95% confidence interval [CI] 1.064-1.484, $p=0.007$), type 2 diabetes mellitus (RR 1.300, 95% CI 1.131-1.494, $p<0.0001$) and obesity (RR 1.347, 95% CI 1.166-1.556, $p<0.0001$).

Conclusion. In the ICU of the City Clinical Hospital No. 1 of Almaty, the lethality of patients with SARS-CoV-2 pneumonia who needed respiratory support averaged 40.8%. Mortality largely depended on the severity of ARDS and indications for hospitalization in the ICU. Thus, it was significantly higher in patients who were transferred to ALV, especially in the presence of signs of septic shock. Mortality in patients older than 50, especially men, was higher than in younger patients. According to Cox multivariate analysis, the factors associated with a higher risk of death in patients with severe SARS-CoV-2 pneumonia complicated by ARDS were CHD (myocardial infarction and/or interventions on the coronary arteries in history), obesity ($\text{BMI} \geq 35$ kg/m²) and type 2 diabetes.

Risk factors for complications and lethality of COVID-19

COVID-19 complications include developing ARDS (29%) and secondary infections (10%) [25], sepsis, and acute kidney and liver damage [26, 28]. Lighter J, Phillips M, Hochman S, et al. report that acute cardiac injury was often observed, which may indicate viral infection of the heart muscle and a significant cardiac risk in patients [16]. The first wave of COVID-19 in Wuhan, China, included 71,333 cases and caused 1,775 deaths, although most cases were moderate. Among 44,672 cases, approximately 5% had a severe course, almost half ending in death [15]. On average, according to different authors, mortality from COVID-19 was no more than 4%, which is much less compared with coronaviruses SARS-CoV (about 10%) and MERS-CoV (about 37%) [19, 21, 24]. Preliminary studies revealed mortality rates from pneumonia caused by SARS-CoV-2 ranging from 12 to 16% [16], but more recent studies have indicated mortality in the region of 1.3% to 4.2% [19]. The considerable difference in mortality rates between different studies is likely due to methodological reasons. An analysis of fatalities showed that in patients older than 70 years, there was a shorter interval between the first clinical presentations and death (about ten days) compared with younger patients (about 21 days) [29].

An informative retrospective study was performed at the Federal Remote Consultative Center for Anesthesiology and Resuscitation for Adult Patients with COVID-19 at the Sechenov First Moscow State Medical University [17]. That study included all patients with known outcomes (death from

any causes or complete recovery) of SARS-CoV-2 pneumonia complicated by ARDS, who were examined from March 16 to May 3, 2020. Risk factors for death were analyzed using a multivariate Cox regression model (table 1). The study included 1522 patients, 863 (56.7%) men and 659 (43.3%) women, with a median age of 62. 922 (60.5%) patients were in the ICU of hospitals in Moscow and the Moscow region, and 600 (39.4%) were at medical institutions in 70 regions of the Russian Federation. In 995 (65.4%), the diagnosis of SARS-CoV-2 infection was confirmed by PCR. 995 (65.4%) patients died, 527 (34.6%) survived. The leading causes of death were ARDS (93.2%), cardiovascular events (3.7%), and pulmonary embolism (1.0%). Mortality was low in patients on oxygen therapy (10.1%) and significantly increased in patients who had to be transferred to NIV (36.8%) or invasive (76.5%) ventilation.

Table 1. Risk factors for death

Characteristics	n	%
Gender		
male	863	56.7
female	659	43.3
Median age 62 years	1522	100
Causes of death		
ARDS	1418	93.2
cardiovascular events	56	3.7
pulmonary embolism	16	1
others	32	2.1
Delivery systems of O2		
oxygen therapy	153	10.1
NIV	560	36.8
invasive ventilation	1164	76.5

The risk of death increased with age, and in age groups over 50, men were significantly more likely to die than women. In univariate models, fatality-related diseases were arterial Hypertension, coronary artery disease, stroke, atrial fibrillation, type 2 diabetes mellitus, obesity, and solid tumours. However, in a multivariate model corrected for sex and age, only coronary heart disease (hazard ratio [RR] 1.257, 95% confidence interval [CI] 1.064–1.485, $p=0.007$), and type 2 diabetes mellitus (RR 1.300, 95% CI 1.131–1.494, $p<0.0001$), remained statistically significant.

These data show that the main risk factors for death among patients with COVID-19 transferred to the ICU for respiratory support were the severity of ARDS – primarily the need for ALV – advanced age, male sex, coronary artery disease, obesity, and diabetes mellitus 2 type.

However, these data are incongruent with another study by Huang C, Wang Y, Li X, et al.[9]; among 710 patients with confirmed COVID-19, 52 were admitted to the ICU in Wuhan, China, of whom 29 (56%) were on NIV at admission to the ICU, and 22 (76%) of these required further orotracheal intubation and ALV. ICU mortality among those requiring ALV was 23/29 (79%). The authors did not recommend high-flow nasal prongs or NIV while the patient has viral clearance. NIV is not recommended for patients

with viral infections complicated by pneumonia because non-invasive ventilation temporarily improves oxygenation and reduces respiratory muscle function in these patients. However, this method will not necessarily change the natural course of the disease. Finally, using NIV in COVID-19 patients in the ICU is controversial.

Guan WJ, Ni ZY, Hu Y, et al. reported the presence of ARDS in 100% of cases among 112 deceased patients [8]. Petrilli CM, Jones SA, Yang J, et al. analyzed 44,673 cases of confirmed COVID-19 infection, according to the Chinese Center for Disease Control and Prevention, and showed that 41% of all hospitalized patients and more than 70% with severe infection had signs of respiratory failure [15]. In another study, invasive ventilation and NIV were used in 38.6% of cases of severe infection, and five patients (2.8%) were treated with extracorporeal membrane oxygenation [33].

Most authors of studies on COVID-19 have reported risk factors for respiratory failure, including older age (>60 years), male sex, and comorbidities such as diabetes mellitus, malignant neoplasms, and immunodeficiency [21, 25, 28]. Patient's condition can deteriorate very quickly: at the time of admission to ICU, most patients had absolute indications for invasive ventilation due to severe ARDS, and several patients were clinically [5, 8, 14, 26].

Conclusion

The COVID-19 pandemic requires a more comprehensive analysis of the risks and benefits of providing respiratory support, including NIV and ALV. Implementing respiratory support with modern options for oxygen therapy and NIV will require a thorough assessment of the risks of infection of medical workers, the nosocomial spread of infection, the availability of healthcare resources and the clinical spectrum of comorbid diseases in patients with COVID-19 [3, 5].

The main task of treating patients with ARF is to ensure sufficient since severe hypoxemia leads to serious and often irreversible functional disorders of vital organs and systems. The initiation of oxygen therapy and respiratory support in patients with COVID-19 should be carried out at the pre-resuscitation stage. The most accessible treatment for ARF is urgent oxygen therapy. Additional physiological benefits during HFOT include improved mucociliary function, reduced functional “dead space”, and a trim level of positive pressure created in the airways. NIV not only improves gas exchange but also reduces the load on the respiratory apparatus and the work of the respiratory muscles. In spontaneously breathing patients with COVID-19, using the prone position may improve oxygenation, reducing the need for tracheal intubation and ALV.

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