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# Non-invasive ventilation in patients with novel coronavirus infection COVID-19

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**Abstract**

In the early stages of the COVID-19 pandemic, many guidelines for the management of patients with new coronavirus infection did not include recommendations for the use of non-invasive ventilation (NIV) due to the concerns that NIV could be accompanied by high tidal volumes that could cause lung damage. In addition, there was an opinion that NIV increases the risk of spreading bioaerosol containing the SARS-CoV-2 virus. At the same time, NIV was widely used in real clinical practice in the management of severe patients with COVID-19 (in some countries, up to 60% of all respiratory support methods). The accumulated experience demonstrates that when applying NIV, the risk of contamination with viral infections is minimized with adequate use of personal protective equipment. To date, the results of a limited number of studies about effectiveness of NIV in hypoxemic acute respiratory failure (ARF) in patients with COVID-19 are available. In most studies, the need for tracheal intubation and hospital mortality, were on average, 20 – 30%, that suggests a fairly high effectiveness of NIV in ARF in patients with COVID-19.

**Key words:** coronavirus infection SARS-CoV-2, COVID-19, acute respiratory failure, non-invasive ventilation, continuous positive airway pressure.
**Conflict of interests.** The author declares the absence of conflict of interests.

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# Неинвазивная вентиляция легких при новой коронавирусной инфекции COVID-19

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**Резюме**

На начальных этапах пандемии COVID-19 во многих руководствах по ведению пациентов с новой коронавирусной инфекцией отсутствовали рекомендации по использованию неинвазивной вентиляции легких (НВЛ) из опасений, что последняя может сопровождаться высокими дыхательными объемами, способными вызвать повреждение легких. Кроме того, существовало мнение, что при НВЛ повышается риск распространения биоаэрозоля, содержащего вирус SARS-CoV-2. В то же время НВЛ достаточно широко используется в реальной клинической практике при ведении тяжелых пациентов с COVID-19 (в некоторых странах – до 60 % всех методов респираторной поддержки). Накопленный опыт показывает, что при работе с НВЛ риск контаминации вирусными инфекциями сводится к минимуму при адекватном использовании средств индивидуальной защиты. К настоящему времени доступны результаты небольшого числа исследований, посвященных эффективности НВЛ при гипоксемической острой дыхательной недостаточности у пациентов с COVID-19. По результатам большинства исследований показано, что потребность в интубации трахеи и госпитальная летальность в среднем составляют 20–30 %. Это позволяет сделать вывод о достаточно высокой эффективности НВЛ при острой дыхательной недостаточности у пациентов с COVID-19.

**Ключевые слова:** коронавирусная инфекция SARS-CoV-2, COVID-19, острая дыхательная недостаточность, неинвазивная вентиляция легких, постоянное положительное давление в дыхательных путях.
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Viral pneumonia and acute respiratory distress syndrome (ARDS) are the most common complications of the new SARS-CoV-2 coronavirus infection (COVID-19), leading to hypoxemic acute respiratory failure (ARF), in most cases requiring oxygen therapy and respiratory support [1–3]. Hypoxemic ARF is the leading cause of death in patients with severe COVID-19 referred to intensive care units (ICU). Thus, study by *Ruan et al.*, showed that ARF was the leading cause of mortality in 88% of patients suffering COVID-19 [4].

Traditionally, early intubation and mechanical ventilation (MV) were considered to improve survival in patients with ARDS [5]. However, recently published studies from UK, USA, and China, including COVID-19 patients, showed an extremely high mortality rate (65 – 92%) among patients receiving mechanical ventilation [6–8].

Currently, there is increasing interest in non-invasive respiratory modalities, e.g., high-flow nasal oxygen therapy (HFNO) and non-invasive ventilation (NIV).

NIV is a respiratory support method where the main interfaces (mask or helmet) can be easily applied and thereafter easily disconnected from the patient airways [9]. NIV has significant advantages over traditional mechanical ventilation, as the application of artificial airways (endotracheal tube, tracheostomy) is not required, thus increasing patient comfort, reducing the need for sedatives, preserving eating and swallowing functions, and most importantly, significantly reducing the risk of respiratory tract direct injuries and the risk of nosocomial infections [10, 11].

Most often in patients with ARF, the following NIV modes are used: Continuous Positive Airway Pressure (CPAP) and pressure support (PS) or a close similar mode – Bilevel Positive Airway Pressure (BiPAP) [11, 12]. CPAP provides a constant flow of oxygen at a given pressure, which remains constant during inspiration and expiration [11, 12]. PS mode is an assissted mode-in response to the patient's inspiratory effort, the ventilator creates a predetermined level of positive pressure in the airways during the inspiration phase [11, 12].

The role of NIV in COVID-19 patients with hypoxemic ARF is a subject for discussion and debate. Consensus guidelines issued by the Intensive Care Society, the Association of Anesthesiologists and the Royal College of Anesthesiologists states that the use of non-invasive modalities "should be avoided", and also states "There is no survival benefit compared to conventional oxygen therapy, and the risk of environmental viral contamination may be higher" [13]. The guideline "Surviving Sepsis Campaign" recommends attempting NIV only in cases where "high-flow oxygen therapy is not available and there is no urgent indication for tracheal intubation", and under the close monitoring and frequent assessment for progression of respiratory failure [14]. The World Health Organization (WHO) recommends to use NIV only in selected patients with hypoxemic respiratory failure, under close monitoring by experienced medical staff who can perform tracheal intubation in case of rapid deterioration or no improvement after a short trial period [15]. The National Health Service (UK) recommendations consider NIV as the first line respiratory support for COVID-19 patients with hypoxemic ARF [16]. A similar approach was also adopted in the recommendations from Italy, Spain and Russia [17–20].

On the other hand, in real clinical practice NIV for severe COVID-19 is widely used almost everywhere. The proportion of patients requiring non-invasive respiratory support in published studies varies greatly, from 11% to 96%, with higher rate in China (62% on average) and lower in North America (20%) [21]. According to a survey including 1,215 Italian doctors, most of the responders (62%) used NIV (CPAP and BiPAP) as a first-line therapy for patients with hypoxemic ARF associated with COVID-19; 60% of doctors considered indications for endotracheal intubation (EI) and mechanical ventilation only 1 – 8 h after no response to NIV therapy [22]. A summary of non-invasive respiratory modalities use is presented in Table 1 [21].

## Bioaerosols and protection of healthcare professionals

It is generally accepted that SARS-CoV-2 spreads mainly through airborne droplets or through direct contact, and nosocomial virus transmission from the patient to medical professionals can be a serious challenge [23]. Biologically hazardous aerosols are usually formed as a result of so-called aerosol-generating procedures, such as nebulizer therapy, oxygen therapy, including HFNC, NIV, tracheotomy [24], and these procedures can expose health care workers (HCWs) to viral pathogens that cause acute respiratory infections. According to published data,

***Table 1***
***Respiratory support in cohort studies of SARS-CoV-2 infection***
***Таблица 1***
***Респираторная поддержка в когортных исследованиях по инфекции SARS-CoV-2***

| Study | | Country | Design | Patient population (N) | Respiratory support, *n* (%) | Non-invasive support methods, *n* (%) | | |
|---|---|---|---|---|---|---|---|---|
| Author | Edition, year | | | | | HFOT | NIV | NIRS |
| *Wang D.* | *JAMA*, 2020 | China | Retrospective SC | 138 | 36 (26) | 4 (11) | 15 (42) | – |
| *Arentz M.* | *JAMA Netw. Open*, 2020 | USA | Retrospective SC | 21 | 20 (95) | 1 (5) | 4 (20) | – |
| *Grasselli G.* | *JAMA*, 2020 | Italy | Retrospective MC | 1,591 | 1,287 (99) | – | 137 (11) | – |
| *Huang C.* | *Lancet*, 2020 | China | Prospective | 41 | 14 (34) | – | – | 10 (71) |
| *Wang K.* | *Ann. Intensive Care*, 2020 | China | Retrospective | 318 | 27 (8) | 17 (63) | 9 (3) | |
| *Zhou F.* | *Lancet*, 2020 | China | Retrospective MC | 191 | 99 (52) | 41 (41) | 26 (26) | |
| *Guan W.* | *NEJM*, 2020 | China | Retrospective MC | 1,099 | 67 (6.1) | – | 56 (83) | |
| *Liao X.* | *MedRixv*, 2020 | China | Retrospective MC | 81 | 63 (77) | 31 (49) | 22 (35) | |
| *Zheng Y.* | *MedRixv*, 2020 | China | Retrospective SC | 34 | 34 (100) | 18 (53) | 1 (3) | |
| *Xu Yang* | *MedRixv*, 2020 | China | Retrospective MC | 69 | 5 (7) | – | 3 (60) | |
| *Xu Yonghao* | *MedRixv*, 2020 | China | Retrospective MC | 45 | 39 (86) | 13 (33) | 6 (15) | |

Note: SC, single-center; MC, multi-center; HFOT, high-flow oxygen therapy; NIV, non-invasive ventilation; NIRS, non-invasive respiratory support methods

3.8% of Chinese HCWs were infected with SARS-CoV-2 virus [25]. 63% of these cases occurred in Wuhan city; Italian data are even worse – 14% of HCWs were infected [26]. How can we reduce the exposure of bioaerosols on HCWs? The basic protective measure is the wearing of effective personal protective equipment (PPE) such as $FPP_2$/N95 respirators, medical suits, gloves, and eye and face shields [27].

As it was reported by *K.E.Remy et al.*, the risk of virus spreading in living patients (and not in surrogate inanimate body models) on NIV has not been studied [28]. In fact, a number of studies was carried out in healthy volunteers, using smoke laser lighting techniques on patient simulators, showing changes and increase of droplet dispersion along with increasing NIV flow rate [29]. Droplets are particles > 5 μm in diameter that quickly fall to the ground due to gravity; therefore, they are only transmitted over a limited distance (e.g. ⩽ 1 meter). On the other hand, airborne transmission refers to the presence of microbes in droplet cores, which are particles less than 5 μm in diameter that can remain in the air for a long time and can be transmitted to other people over distances of more than 1 m [30].

*D.S.Hui et al.* [31] measured airflow using smoke as a marker, and confirmed the difference between ventilated and non-ventilated masks by measuring maximum exhaled air distances using various oxygen therapy devices: nasal cannula, Venturi mask, and reservoir mask. The helmet has been demonstrated to be the preferred NIV interface in reducing patient aerosol leakage (with dual circuit NIV configuration) [32]. These authors also demonstrated that exhaled air dispersion during NIV using various interfaces, including the oronasal mask, is also significantly limited, provided that the mask fits well to the patient face [33]. In a real human model (control group of healthy volunteers, patients with catarrhal symptoms and patients with an acute infectious exacerbation of chronic obstructive pulmonary disease) *A.K.Simonds et al.* demonstrated that NIV using a vented mask produced large fraction droplets (> 10 μm) compared to baseline amount of droplets (without any intervention) [34]. Such an increase in the number of large drops was not observed in case of NIV when using unvented mask and in-line filter in the circuit.

The maximum distance values of exhaled air spreading for different procedures and devices are presented in Table 2.

A more prominent diffusion and contamination by the exhaled air is likely in units not equipped with negative pressure rooms. If negative pressure rooms are not available, it is recommended to use rooms with natural ventilation with an air flow of at least 160 L/s per patient, as well as High Energy Particulate Arresting (HEPA) filters [35].

In an observational study by *M.Oranger et al.*, the proportion of HCWs infected with SARS-CoV-2 was similar before and after the introduction of CPAP therapy in the COVID-19 department (6% *vs* 10%) [36]. In a Wuhan study investigating ingress of infection in HCWs, the SARS-CoV-2 infection rate was only 1.1% of the total hospital staff [23], where with most healthcare worker infections occurring in the early stages of the COVID-19 outbreak, resulting from the absent awareness of the high contagiousness of coronavirus infection, and, therefore, not sufficient use of individual protection at that time. Infections in HCWs can be avoided with appropriate personal protection, even when working with patients on NIV. As evidenced by only a few cases of infection of healthcare workers in the later period of the pandemic [37].

*Table 2*
*Maximum distance of spread of exhaled air when using various procedures and devices*
*Таблица 2*
*Максимальная дистанция распространения выдыхаемого воздуха при различных процедурах и использовании тех или иных устройств*

| Method | Maximum distance of exhaled air spread, cm |
|---|---|
| Nasal cannula oxygen 5 L/min | 100 |
| Face mask oxygen 4 L/min | 40 |
| Venturi mask oxygen $FiO_2$ 40% | 33 |
| Oxygen through mask with reservoir 12 L/min | < 10 |
| CPAP using oronasal mask 20 cm $H_2O$ | Minimal |
| CPAP through nose cones | 33 |
| HFOT 60 L/min | 17 |
| NIV through full face mask: IPAP 18 cm $H_2O$, EPAP 5 cm $H_2O$ | 92 |
| NIV through a helmet without a tight fit: IPAP 20 cm $H_2O$, EPAP 10 cm $H_2O$ | 27 |
| NIV through a tight-fitting helmet: IPAP 20 cm $H_2O$, EPAP 10 cm $H_2O$ | Minimal |

Note: NIV, non-invasive ventilation; HFOT, high-flow oxygen therapy; CPAP, continuous positive airway pressure; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

Thus, even when using NIV in patients, the risk of contamination with viral infections is minimized in case of adequate use of PPE.

## Benefits of non-invasive ventilation in hypoxemic acute respiratory failure patients

Despite controversial recommendations, NIV is regularly used in hypoxemic ARF patients [38]. Study by *G.Bellani et al.*, showed that NIV was used in 14.4% of patients with ARDS (436 of 3,022), and 69% of them (300 of 436) were treated only using exclusively NIV [39].

In hypoxemic ARF, the main goals are to improve oxygenation, reduce the work of breathing, and reduce dyspnea [40]. The first goal can usually be achieved by using higher levels of positive end-expiratory pressure (PEEP) to recruit non-ventilated or poorly ventilated alveoli [41]. Increased PEEP may help to keep the alveoli open, leading to increased functional residual capacity, to decreased ventilation-perfusion imbalance and shunt, and hence to an improved oxygenation [40]. In addition, PEEP stabilizes the airway and reduces the heterogeneity of lung volumes distribution [42]. NIV also decreases respiratory muscles load. The main component reducing the work of breathing in NIV is a positive pressure on inspiration (pressure support) [40, 43].

Recently, a physiological randomized crossover study concluded that patients with $PaO_2/FiO_2$ < 200 mm Hg the use of NIV with a helmet is preferable to HFCN in terms of optimizing oxygenation and reducing inspiratory effort, especially in patients with more severe hypoxemia and a higher work of breathing [44].

In patients with severe community-acquired pneumonia, NIV significantly improved arterial blood oxygenation compared to standard oxygen therapy [45]. In addition, it was shown that the use of CPAP therapy in patients with pneumonia and severe hypoxemic ARF, compared to oxygen therapy, leads to a decreased risk of endotracheal intubation and invasive mechanical ventilation [46].

The use of NIV in patients with some types of ARF, including ARDS, reduces the need for EI and mechanical ventilation. Meta-analysis by *R.Agarwal et al.*, showed that NIV can improve oxygenation and reduce the risk of EI in patients with mild ARDS ($PaO_2/FiO_2 \geqslant 150$ mm Hg) [47]. In a recent meta-analysis by *B.L.Ferreyro et al.*, including 25 studies with 3,804 hypoxemic ARF patients, it was shown that NIV using helmets (risk ratio [RR] 0.26) and face masks (RR 0.76) was associated with a lower risk of EI compared to standard oxygen therapy [48]. NIV using both helmets (RR 0.40) and face masks (RR 0.83) was also associated with a lower risk of hospital mortality.

## Limitations of non-invasive ventilation in hypoxemic acute respiratory failure patients

In contrast to patients with invasive mechanical ventilation, for whom there are established protective ventilation protocols, there are currently no ventilation protocols for NIV aimed at reducing the risk of ventilator-associated lung injury. This is possibly one of the main challenges using NIV in hypoxemic ARF patients. Consequently, unsafe settings are usually used. For example, in the recent European cohort of hypoxemic ARF patients in more than half of cases tidal volumes greater than 10 ml/kg of ideal body weight were used [49]. In this study, tidal volumes greater than 9.5 ml/kg were a strong predictor of NIV failure, indicating that close monitoring of tidal volume is necessary. In patients with persistently high tidal volumes, early invasive ventilation may be a reasonable option to reduce the risk of ventilator-induced lung injury.

Often too high inspiratory pressures are used for NIV in severe ARDS patients, leading to an increased transpulmonary pressure (the difference between end-inspiratory pressure and intrathoracic pressure). Increased transpulmonary pressure, on the one hand, can lead to excessive overdistension of alveoli in non-gravity-dependent areas of the lungs, and on the other hand, it can cause a significant increase in dead space. Excessive pressure support can lead to barotrauma and lung biotrauma [50]. A recently published study by *R.Tonelli et al.*, showed that hypoxemic ARF patients with NIV failure had higher transpulmonary pressure levels (39.5 cm $H_2O$ *vs* 30.5 cm $H_2O$), and decreased esophageal pressure fluctuations (ΔPes) during NIV were a clear indicator of NIV success and improvement of lung X-ray pattern [51].

The main risk of using NIV in hypoxemic ARF may be associated with the delayed intubation despite indications present [52]. Early signs of NIV failure include a higher score when assessing condition severity using scales (e.g., APACHE or SAPS II), and also the absence of improvement in patient condition 1 hour after starting NIV [53]. Studies have shown that the NIV failure is an independent risk factor for death in this patient population. But this risk possibly may be decreased via careful selection of patients for NIV [54].

## First data on the use of non-invasive ventilation in COVID-19

To date, only a small number of studies are available on NIV efficacy in hypoxemic ARF patients with COVID-19 [36, 55–61] (Table 3).

All the published studies were open-label, observational. And until today there are no randomized controlled clinical trial. And this can be explained by only a short period of time that NIV was used in COVID-19 clinical practice.

It should be pointed out, that only one of the studies presented included patients from the intensive care unit (ICU) [61], and all the other studies were conducted not in ICU, but in emergency department, pulmonology department, specialized departments for patients with COVID-19 and in intermediate care units (non-invasive respiratory support department).

This practice reflects modern tendencies, according to which, as experience accumulates, the use of NIV is possible not only in the ICU, but also at a "lower level" units, i.e. in units with less monitoring capacity and a lower nurse-to-patient ratio [62]. In addition, today the use of NIV in acute cases is not limited only to in patient departments, but is successfully applied at earlier stages, for example, in the emergency department [63].

In published studies, in the majority of COVID-19 cases, the CPAP mode was used (average pressure about 10 cm $H_2O$), which is explained by its high efficiency in hypoxemic ARF, and, by the fact that this mode can be implemented using simpler equipment-flow generators (and not necessarily ventilators). An example of such a flow generator is the UCL – Ventura Breathing Aid, developed by Mercedes AMG High Performance Powertrains, specifically for CPAP therapy in critically ill patients with COVID-19 [64].

Either face masks (oronasal masks) or helmets were used as the main interfaces in the abovementioned studies. Potential advantages of the helmet are the possibility of airtight fastening of this interface in patients with virtually any facial shape, exclusion of any damage to the facial skin, and greater comfort for patient [65]. In a study by *B.K.Patel et al.* helmet use in patients with ARDS compared to facial masks was associated with a lower need for EI (18.2% *vs* 61.5%) [66]. Another helmet advantage when working with COVID-19 is the minimal bioaerosol spreading [27, 32]. Given the fact that helmets are still rarely used in our medical institutions, it should be emphasized that non-vented facial masks are also effective interfaces for NIV in severe COVID-19 patients.

*Table 3*
*Studies on the effectiveness of non-invasive ventilation in COVID-19*
*Таблица 3*
*Исследования по эффективности неинвазивной вентиляции легких при COVID-19*

| Study | Design | Patients | Department | $PaO_2/FiO_2$ | Respirators | Interfaces | Regimens | Duration | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| *Oranger et al.* | Observational, historical control | 38 (NIV) | Pulmonology department | ? | Portable NIV respirators | Facial masks | CPAP: 10 cm $H_2O$ | 5 (2 – 7.5) days | EI – 23% |
| | | 14 (control) | | | | | | | Died – 0% |
| *Duca et al.* | Observational, retrospective | 78 | Emergency department | 131 mm Hg (CPAP) | NA | Helmets | CPAP (*n* = 71) | NA | Failure – 88% |
| | | | | 87 mm Hg (NIV) | | | NIV (*n* = 7) | | EI – 33% |
| | | | | | | | | | Died – 74% |
| *Pagano et al.* | Observational, prospective | 18 | COVID-19 department | 153 mm Hg | NA | Helmets | CPAP: 10 cm $H_2O$ | NA | Died – 61% |
| *Burns et al.* | Observational, retrospective | 28 | COVID-19 department | NA | NA | Masks | CPAP (*n* = 23): 12.7 ± 2.1 cm $H_2O$ | 5 days | Died – 50% |
| | | | | | | | BiPAP (*n* = 5): IPAP 22.4 ± 6.0 cm $H_2O$/ PEEP 10.2 ± 2.9 cm $H_2O$ | | |
| *Nightingale et al.* | Observational, retrospective | 24 | COVID-19 department | 122 mm Hg | portable NIV respirators | Non-vented masks | CPAP 8.75 (7.5 – 10) cm $H_2O$ | 4.5 days | EI – 38% |
| | | | | | | | | | Died – 21% |
| *Aliberti et al.* | Observational, prospective | 157 | HDU | 142 mm Hg | Flow generators, | Helmets | CPAP 10.8 ± 2.3 cm $H_2O$ | 6 (3 – 10) days | Failure – 44.6% |
| | | | | | | | | | EI – 21.7% |
| | | | | | | | | | Died – 22.9% |
| *Franco et al.* | Observational, retrospective | 330 (CPAP) | Respiratory Disease Units | 151 mm Hg (CPAP) | Flow generators, portable NIV respirators | Helmets, masks | CPAP 10.2 ± 1.6 cm $H_2O$ | NA | EI – 24.8% (CPAP) |
| | | | | | | | | | 27.7% (NIV) |
| | | 177 (NIV) | | 138 mm Hg (NIV) | | | NIV: IPAP 17.3 ± 3.0 cm H2O/ PEEP 9.5 ± 2.2 cm $H_2O$ | | Died – 30.3% (CPAP) |
| *Mukhtar et al.* | Observational, retrospective | 39 | ICU | 170 mm Hg | NA | NA | NA | 2 (2 – 5) дней | EI – 23% |
| | | | | | | | | | Died – 26% |
| Собственные данные | Observational, retrospective | 61 | COVID-19 department | 164 mm Hg | NIV respirators | Non-vented masks | CPAP (*n* = 55): 10.0 (10.0 – 12.2) cm $H_2O$ | 8.0 (6.3 – 11.0) days | EI – 27.9% |
| | | | | | | | NIV (*n* = 6): PS 10.0 (8.0 – 12.1) cm $H_2O$ / PEEP 10.0 (10.0 – 10.3) cm $H_2O$ | | Died – 24.6% |

Note: NIV, Non-invasive Ventilation; ICU, intensive care unit; HDU, high dependency unit; CPAP, continuous positive airway pressure; IPAP, inspiratory positive airway pressure; PS, pressure support; PEEP, positive end-expiratory pressure; EI, endotracheal intubation; NA, not available.

All of these studies included COVID-19 patients with severe hypoxemic ARF, who met Berlin classification criteria for moderate-to-severe ARDS [67]: the mean baseline $PaO_2/FiO_2$ ratios ranged from 87 to 170 mm Hg, i.e., according to the classical canons, these patients had indications for invasive mechanical ventilation. The efficacy of NIV in hypoxemic ARF patients with COVID-19 can be assessed using data on the proportion of intubated and deceased patients. Of course, the results presented are rather heterogeneous – patient mortality ranged 0 to 74%, and the need for EI ranged from 22 to 38%. The highest mortality rate (74%) was observed in emergency department patients with severe hypoxemia ($PaO_2/FiO_2$ 87 mm Hg) in Bergamo (Italy). But these results are explained by the extreme shortage of hospital beds in the Italian ICUs during the explosive increase of COVID-19 incidence [55]. In general, in most studies, the need for EI and hospital mortality rates, on average, were 20 – 30%, thus suggesting a fairly high NIV efficacy in ARF patients with COVID-19.

Interestingly, previous experience with NIV in hypoxemic ARF patients with severe community-acquired pneumonia and ARDS is difficult to transfer to patients with COVID-19. For example, according to generally-accepted concepts, the $PaO_2/FiO_2$ ratio below 150 mm Hg is regarded as a reliable predictor of NIV failure, i.e., it is a direct indication for immediate EI [47, 53]. On the other hand, it is most likely that baseline $PaO_2/FiO_2$ ratio in COVID-19 patients, is not a predictor of NIV success or failure. For example, in a study by *S.Aliberti et al.*, including 157 patients, baseline $PaO_2/FiO_2$ values in the success group were even lower than in the failure group (136 *vs* 152 mm Hg) [59]. And in the study by *C.Franco et al.*, including 507 COVID-19 patients, there was also no difference in mortality among patients with baseline $PaO_2/FiO_2$ rations of 201 – 250, 151 – 200 and 101 – 150 mm Hg (20.3, 25.2 and 24.2%, respectively); mortality was higher (45.5%) only at $PaO_2/FiO_2$ below 50 mm Hg [60].

Experience gained in managing COVID-19 patients showed that NIV may not be a sufficient universal respiratory support method for absolutely all patients with severe COVID-19. In some patients, NIV can temporarily improve oxygenation and respiratory work, but has no influence on natural disease progression, and ultimately does not prevent the need for EI and invasive ventilation. Unfortunately, today we don't have yet any reliable markers of disease progression in NIV patients. In a study by *W.Wang et al.*, including a nationwide cohort of critically ill COVID-19 patients from China, an elevated D-dimer level (> 1.5 mg/L) on admission was an indicator of a high probability of a ventilator requirement [37]. These results are consistent with evidence that increased D-dimer levels in COVID-19 patients are associated with disease progression [68].

Large randomized controlled trials are currently in progress to assess the NIV efficacy in critically ill COVID-19 patients [69–70]. And results of these studies will help to improve our knowledge of optimal respiratory support in new coronavirus infection patients.

## Conclusion

In the early stages of the COVID-19 pandemic, most of guidelines for the management of patients with new coronavirus infection did not contain recommendations for the use of non-invasive ventilation, due to concerns that NIV may require high tidal volumes that could cause lung damage. And also there was an opinion that NIV increases the risk of bioaerosol spreading, containing the SARS-CoV-2 virus. At the same time, NIV is widely used in real clinical practice for the management of severe COVID-19 patients (up to 60% of all respiratory support methods in some countries). The accumulated experience showed that when working with NIV, the risk of contamination with viral infections is minimized with adequate use of personal protective equipment. To date, there are available results of a limited number of studies on NIV efficacy in hypoxemic ARF patients with COVID-19. In most studies, the need for endotracheal intubation and hospital mortality rates, on average, were 20 – 30%, thus suggesting a fairly high NIV efficacy in ARF patients with COVID-19.

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