



Various Aspects of Non-Invasive Ventilation in COVID-19 Patients: A Narrative Review

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Abstract

Non-invasive ventilation (NIV) is primarily used to treat acute respiratory failure. However, it has broad applications to manage a range of other diseases successfully. The main advantage of NIV lies in its capability to provide the same physiological effects as invasive ventilation while avoiding the placement of an artificial airway and its associated life-threatening complications.

The war on the COVID-19 pandemic is far from over. The present narrative review aimed at identifying various aspects of NIV usage, in COVID-19 and other patients, such as the onset time, mode, setting, positioning, sedation, and types of interface. A search for articles published from May 2020 to April 2021 was conducted using MEDLINE, PMC central, Scopus, Web of Science, Cochrane Library, and Embase databases. Of the initially identified 5,450 articles, 73 studies and 24 guidelines on the use of NIV were included. The search was limited to studies involving human cases and English language articles. Despite several reported benefits of NIV, the evidence on the use of NIV in COVID-19 patients does not yet fully support its routine use.

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What's Known

- Over the last two decades, non-invasive ventilation (NIV) has dramatically changed the management of many diseases, such as chronic obstructive pulmonary disease and weaning failure.
- Routine use of NIV in the management of COVID-19 patients is still controversial.

What's New

- NIV can be used under certain conditions and initiated based on the PaO₂/FiO₂ ratio instead of SpO₂ alone.
- Key NIV recommendations: Select a mode based on the type of respiratory failure and comorbidities, the helmet interface is preferred, and enteral or parenteral feeding should be balanced against susceptibility to airway complications.

Introduction

Non-invasive ventilation (NIV) is a procedure to support the respiratory system and breathing effort, improve gas exchange, and enhance patients' comfort using an oxygen delivery device with an easy-to-use interface.¹ NIV is well recognized as an effective strategy to avoid endotracheal intubation with adverse complications (e.g., ventilator-associated pneumonia) in patients with various forms of hypercapnic respiratory failure, immunosuppression, and specific postoperative conditions.² During the past few years, the main application of NIV has been in chronic obstructive pulmonary disease (COPD) exacerbations. In addition to being a weaning strategy for COPD patients from invasive mechanical ventilation (IMV), the use of NIV has resulted in a significant reduction in mortality rate, nosocomial pneumonia, and weaning failure.^{3, 4} NIV is currently utilized in intensive care units (ICUs), emergency departments, and in the home setting.⁵ However, the use of NIV in patients with severe respiratory failure is still controversial. A high rate of NIV failures has been reported to occur during the treatment of patients with Middle East Respiratory Syndrome (MERS).⁶

In December 2019, the first cases of the novel coronavirus were identified in Wuhan, China, and the infection was referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Shortly thereafter, the World Health Organization (WHO) called the virus the coronavirus disease 2019 (COVID-19). SARS-CoV-2 was considered highly contagious⁷ to the extent that the WHO declared it as a global pandemic in March 2020.⁸ COVID-19 may cause respiratory failure such that patients need respiratory support using NIV or IMV. According to guidelines on the treatment and management of patients with COVID-19, controlling the duration of hypoxemia is important for a favorable outcome.⁹ However, clinicians resort to various protocols for using NIV. The present review is primarily aimed at identifying the effectiveness of NIV in COVID-19 patients. In addition, we investigated and compared different protocols from various national and international organizations on various aspects such as the onset and offset times, modes of ventilation, sedative drugs and dosage, patient positioning, types of interface, and nutritional management of patients receiving NIV support.

Search Strategy

A search was performed to identify suitable articles on NIV in COVID-19 patients using MEDLINE, PMC central, Scopus, Web of Science, Cochrane Library, and Embase databases. Publications from May 2020 to April 2021 were included, and a total of 5,450 articles were identified during the initial search. The search was limited to English language studies that included adults (age > 18 years), and those published in peer-reviewed journals to minimize possible sources of bias and exclude erroneous data.

The search strategy included a combination of keywords and terms: "coronavirus", "novel CoV", "SARS-CoV-2", "COVID-19", "acute respiratory failure"; "non-invasive mechanical ventilation", "NIV", "CPAP", "BiPAP", "onset", "position"; "sedation", "interface", "AHRF", "acute hypoxemic respiratory failure", "nutrition support", "enteral nutrition"; "parenteral nutrition", and "intensive care". The appropriateness of each article was determined based on the relevancy of its title and a detailed review of the reference list. The authors then independently reviewed the abstract and full-text of each article with a specific focus on NIV in COVID-19 patients. Accordingly, the final list of articles was made. In addition, we collected and compared the most important recommendations from prominent organizations on the application and management of NIV in patients with respiratory failure, including COVID-19 patients.

NIV Over the Years

During the past two decades, NIV has dramatically contributed to the treatment of patients with acute and chronic respiratory failure.¹⁰ The concept of bellows-powered face masks dates back to the early 19th century, when Chaussier described the application of a device during resuscitation.¹¹ During the 1930s and 1940s, recommendations were made to use NIV in treating pneumonia, pulmonary edema, and asthma. However, these were not widely supported or accepted for several decades. In the 1980s, NIV was proposed for chronic conditions such as treating obstructive sleep apnea (OSA) using continuous positive airway pressure (CPAP). Eventually, in the 1990s, NIV was widely used in ICUs to treat chronic respiratory failure in patients with neuromuscular diseases.¹² It was then that manufacturers started to produce ventilatory support devices, including adjustable inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) or bi-level positive pressure (BiPAP).¹³ Nowadays, NIV is an integral part of clinical equipment and used as the first-line treatment for patients with acute respiratory failure due to COPD, weaning from IMV,^{14, 15} and immunocompromised conditions.¹¹

Some studies have reported strong evidence in support of NIV usage, over IMV, in patients with cardiogenic pulmonary edema¹² and specific forms of acute respiratory failure.¹¹ The use of NIV in the United States has increased by 462% over the last 10 years, which led to a 42% reduction in IMV use and decreased in-hospital mortality.¹⁶ Some specialists have proposed research concepts for the design of a more comfortable NIV interface for patients with *de novo* respiratory failure and to improve NIV settings for better patient-ventilator synchrony.³

COVID-19 has been shown to cause acute hypoxemic respiratory failure (AHRF), necessitating respiratory support.¹⁷ A previous study reported a high mortality rate in patients with AHRF, who received IMV.¹⁸ One of the reasons for the high mortality rate may be due to ventilator-induced lung injury, which is an IMV complication. As an alternative, NIV is a safe, feasible, and useful strategy for COVID-19 patients. However, there are different perspectives on the effectiveness of NIV in COVID-19 associated AHRF patients, and the data on its efficacy are still insufficient.^{19, 20} Considering the high mortality rate in COVID-19 patients due to intubation,²¹ clinicians tend to utilize NIV. However, there are uncertainties about its effectiveness and a lack of reported evidence on its use in COVID-19 patients.

Different Perspectives

Supportive therapies such as NIV and IMV are essential in the management of COVID-19 respiratory failure. Although NIV has fewer adverse effects than IMV, it may put healthcare providers at risk of contracting the disease due to virus-laden aerosols.²² This is probably the most controversial issue regarding the use of NIV in COVID-19 patients. Table 1 presents an overview of research studies with different perspectives and recommendations on the application of NIV in COVID-19 patients.

NIV Interfaces

The success of the NIV procedure depends on several factors, the most prominent of which is the type of interface used, as it greatly affects the comfort of patients. The main disadvantages of NIV interfaces are air leakage, facial skin erythema, claustrophobia, eye irritation, skin breakdown, and acneiform rash.⁵ There are many types of NIV interfaces, and new formats are in development. The most common types are oral interfaces (mouthpieces placed between the patient's lips and held in place by lip-seal

or teeth), nasal masks (cover the nose but not the mouth), nasal pillows (plug inserted into the nostrils), full-face masks (cover the mouth, nose, and eyes), oronasal masks (cover the nose and mouth), and helmets (cover the whole head and all or part of the neck without any contact with the face or head).^{29, 30}

Unlike traditional masks, the helmet interface can be used in abnormal anatomical situations and is applicable to all patients. This interface is a transparent plastic hood that does not contact the patient's face, especially the nasal bridge, and thus prevents skin lesions. The fixation system is not as complex as traditional masks. A recently developed helmet interface features an annular openable ring placed underneath an inflatable cushion. This type reduces discomfort and axillary skin lesions caused by the padded armpit braces of a standard helmet. However, complications might occur in the neck area.³¹⁻³³ The main advantage of the helmet interface is minimal air leakage (i.e., no aerosol dispersion from the interface). It reduces the dispersion distance to 27 cm and becomes undetectable, if a leak-free seal is deployed. This range can go

Table 1: Recommendations of research papers regarding the use of non-invasive ventilation in COVID-19 patients

Organization	Author	Country	Recommendations and comments
Society of Critical Care Medicine (SCCM)	Alhazzani W et al. ⁴	Multinational	Use NIV if HFNC is unavailable or in case of patient intolerance. Prompt intubation if no oxygenation improvement is observed after utilizing NIV for 1-2 hours.
Australian and New Zealand Intensive Care Society (ANZICS)	ANZICS group ⁵	Australia and New Zealand	Not routine usage Use NIV and HFNC if health services are unable to provide invasive ventilation
Sociedad Española de Neumología y Cirugía Torácica, Spain	Raof S et al. ²³	Spain	Supportive of the use of NIV
Asociación Argentina de Medicina Respiratoria		Argentina	Supportive for the use of NIV. A short trial (one hour)
Associação Brasileira de Fisioterapia Cardiopulmonar e Fisioterapia em Terapia Intensiva		Brazil	Supportive of the use of NIV in certain situations. A short trial (30 min).
Italian Thoracic Society and Italian Respiratory Society		Italy	Supportive of the use of NIV.
Irish Thoracic Society		Ireland	Supportive of the use of NIV. Helmet interface suggested.
Sociedade Portuguesa de Pneumologia		Portugal	NIV can be used in specific patients and conditions. A short trial (one hour) using a facial mask is suggested.
European Society of Intensive Care Medicine and the Society of Critical Care Medicine 2020	Alhazzani W et al. ²⁴	Multinational	In adults with COVID-19 and acute hypoxemic respiratory failure, a short trial NIPPV with close monitoring is suggested, but only in the absence of urgent indication for endotracheal intubation and HFNC is not available.
ICM Anaesthesia ²⁵	-	United Kingdom	A short trial with a well-fitting interface (full face mask or helmet) is recommended as a bridge to invasive mechanical ventilation.
Military Medical Research	Jaber S et al. ⁶	Multinational	In case of ineffectiveness of nasal cannula or mask oxygen therapy, HFNC or NIV can be considered. In the absence of improvement in respiratory failure or continuous worsening within one hour after HFNC or NIV, intubation should be performed straightaway.

National COVID-19 Clinical Evidence Taskforce	Shereen MA et al. ⁷	Australia	NIV should only be considered in concomitant COPD with type 2 respiratory failure or cardiogenic pulmonary edema (CPE)
National Health Care System guidelines	Velly L et al. ⁸	United Kingdom	NIV can be used for mild hypoxia and acute or chronic respiratory failure (selected patients). The use of NIV (BiPAP) should be reserved for those with acute hypercapnic respiratory failure or chronic ventilatory failure. CPAP is the preferred form of NIV support in the management of hypoxemic COVID-19 patients.
State Administration of Traditional Chinese Medicine in China and the National Health Commission	Suen CM et al. ⁹	China	NIV is recommended and routinely use (invasive ventilation is recommended, only if NIV failed to enhance respiratory distress or hypoxemia).
World Health Organization	Scala R et al. ¹⁰	Multinational	NIV usage: No recommendation for a pandemic viral illness (some confined data showed a high failure rate in patients with respiratory viral infections (MERS-CoV) receiving NIV). CPAP usage: For selected patients with close monitoring.
JAMA Clinical Guidelines Synopsis	Fakharian A et al. ¹¹		NIV usage: A trial period with close monitoring is recommended, but only if HFNC is not available.
The ÖGARI (Österreichische Gesellschaft für Anästhesiologie, Reanimation und Intensivmedizin), FASIM (Federation of Austrian Societies of Intensive Care Medicine) and ÖGIAM (Österreichische Gesellschaft für Internistische und Allgemeine Intensivmedizin und Notfallmedizin)	Pierson DJ et al. ¹²	Austria	Consider a short trial only if HFNC is not suitable. When stabilization is not achieved within an hour, endotracheal intubation should be performed immediately.
Pakistan Chest Society	Bach JR et al. ¹³	Pakistan	Against using NIV for COVID-19 patients.
Department Of Defense COVID-19 practice management guide	Ward NS et al. ¹⁴	United States	Recommended avoiding NIV because of increased aerosolization generated by the face mask and lack of an exhalation filter. In exceptional cases, such as patients that chronically use NIV, isolation with airborne precautions is required regardless of ICU/acute care status.
European Respiratory Society (ERS)	MacIntyre N et al. ¹⁵	Multinational	Recommended NIV as a preventive strategy for avoiding intubation in hypoxemic ARF only when performed by experienced teams in specifically selected cooperative patients with community-acquired pneumonia or early ARDS without any associated major organ dysfunction.
National Institutes of Health	Bellani G et al. ²⁶	United States	For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV)
Department of Biopathology and Medical Biotechnologies (DIBIMED), Section of Anesthesia, Analgesia, Intensive Care and Emergency, Policlinico P. Giaccone, University of Palermo, Palermo, Italy	Cortegiani A et al. ²⁷	Italy	Due to the lack of exhalation filters and aerosols generated for face mask ventilation, it is recommended to avoid NIV. Moreover, it is suggested that patients, who regularly receive NIV should be isolated regardless of ICU/acute care status.
China Medical Treatment Expert Group for COVID-19	Guan WJ et al. ²⁸	China	A preemptive NIV to prevent intubation in case of hypoxemic acute respiratory failure can be considered. Only when performed by experienced teams in specifically elected cooperative patients with community-acquired pneumonia or early ARDS without any associated major organ dysfunction.
The Northwell COVID-19 Research Consortium	Richardson S et al. ¹⁸	United States	If conventional oxygen therapy does not improve oxygenation in acute hypoxemic respiratory failure in adults, HFNC oxygen may be preferred over NIPPV.

COVID-19: Coronavirus disease 2019, HFNC: High-flow nasal cannula, NIV: Non-invasive ventilation, NIPPV: Non-invasive positive pressure ventilation, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit

up to 91.6 cm with the addition of a face mask interface.^{34, 35}

Previous studies have reported that using helmet NIV may improve the outcome in COVID-19 patients. In Italy, the most commonly used interface for COVID-19 patients is the helmet interface. Some studies have suggested that helmet NIV may be better than other traditional interfaces, as it prevents intubation and reduces the mortality rate in patients with hypoxemic respiratory failure.^{36, 37} Other studies found that a helmet is generally well-tolerated, has fewer air leaks and pressure ulcer complications, is suitable for prolonged therapy, and may provide better tolerance with prolonged usage.^{38, 39} A recent study by Raouf and colleagues recommended the use of helmet NIV in COVID-19 patients.²³ The results of a randomized controlled trial showed that the use of a helmet significantly reduced the intubation rate in patients with acute respiratory distress syndrome (ARDS) than the face masks (from 61% to 18%, respectively). Several supporting statements in favor of helmet interface have been reported, including its effectiveness, well-tolerated by patients,⁴⁰ fit-for-purpose, as it acts as a reservoir,⁴¹ and being the interface of first choice.⁴⁰⁻⁴²

NIV Modes and Settings

The most common NIV modes are CPAP and BiPAP (or BPAP). These modes can provide respiratory support and a fraction of inspired oxygen (FiO_2) equal to 100% in a closed-loop.^{6, 42} CPAP is used to provide continuous positive airway pressure to patients with spontaneous breathing. This mode can support breathing at high flow rates of air or a mixture of air and oxygen as one set pressure, typically between 3 and 20 cmH_2O .⁴³ By improving the ventilation-perfusion mismatch and respiratory compliance, CPAP reduces the degree of hypoxemia through alveolar recruitment. It has been shown that CPAP delivered by helmet interface is safer and more effective than a face mask, and is better tolerated over prolonged ventilation periods.⁴⁴

BiPAP mode is considered when applying CPAP to non-intubated adult patients through different interfaces. It allows clinicians to control ventilation using two different pressures (IPAP and EPAP) to improve ventilation and make breathing easier. High inspiratory pressure offloads the patient's breathing effort, while the lower pressure preserves an acceptable alveolar volume and prevents the collapse of unstable alveoli during expiration. Pressure support (PS) is calculated by the difference between IPAP and EPAP, where the difference should be at

least 8 cmH_2O .^{45, 46} Early pressure setting for EPAP and IPAP is 3 and 10 cmH_2O , respectively, followed by up-titration every 10-30 minutes to reach adequate chest expansion (maximum IPAP of 30 cmH_2O).⁴⁷ BiPAP is regularly used in treating COPD patients and thus may also benefit COVID-19 patients with comorbidities, as it improves their breathing.^{46, 48} However, there is a potential risk of incorrect settings whereby a patient is given a tidal volume (VT) that is too large causing barotrauma and volutrauma.⁴⁹ Since COVID-19 patients have less lung compliance, they are at risk of developing barotrauma and pneumothorax. Since the condition of these patients can rapidly deteriorate, they should be closely monitored for early intervention.⁵⁰

Some BiPAP ventilators include a 'ramp' or 'rise time' setting to slowly increase the pressure over the first few minutes of ventilation until the required pressure is reached. This has the benefit of preventing barotrauma and is less distressing to patients at the early stage of mechanical ventilation. By doing so, a 25% rise time will take up 25% of the total inspiratory time before the peak pressure is reached.⁴⁹ Respiratory support for COVID-19 patients is challenging due to differences in their lung pathologies and respiratory dysfunction. These patients require individualized lung-protective strategies to enhance outcomes. The setting and timing of respiratory support should be closely tailored to the specific demands of each patient, taking into account the phase and progression of the disease.⁵¹

Due to the lack of guidelines on how to manage a large number of COVID-19 patients with hypoxemic respiratory failure in a short time frame, an Emergency Department in Northern Italy proposed a procedure to standardize the process. They recommended the initiation of a CPAP trial of 120 minutes with the initial settings of positive end-expiratory pressure (PEEP) of 7.5 cmH_2O , flow rate ≥ 60 L/min, titrating the FiO_2 to reach pulse oximetry (SpO_2) $\geq 94\%$, and respiratory rate (RR) ≤ 25 bpm. They recommended that during the trial period, patients should be monitored closely, and all vital signs re-assessed every 30 minutes. In case of failure to reach the established target for RR, PEEP should be elevated by 2.5 cmH_2O up to a maximum of 12.5 cmH_2O . If the target is reached after the trial period, CPAP alternated with high-flow nasal oxygen should be continued, while vital signs are continuously monitored. In case of failure to reach the specified target after the CPAP trial, early intubation should be considered.⁴⁴

Compared to CPAP, BiPAP is the preferred mode in patients with respiratory acidosis ($\text{PCO}_2 > 40$ mmHg and $\text{pH} < 7.35$), COPD, obesity, and respiratory muscle fatigue. The initial settings in BiPAP mode are PS of 5 cmH_2O , PEEP of 5-10 cmH_2O , and titrating the FiO_2 to reach $\text{SpO}_2 \geq 94\%$, $\text{RR} \leq 25$ bpm, and a VT of 6 mL/Kg predicted body weight. Moreover, monitoring should be done every 30 minutes during the 60 minutes trial duration.^{44, 48, 52, 53}

Novel modes of NIV are proportional assist ventilation (PAV), average volume assured pressure support (AVAPS), and assist/control. However, there is not enough evidence to support their application in COVID-19 patients with respiratory failure.³⁸

Sedation in Patients Receiving NIV

Whether sedative medications can be used to improve NIV interface tolerance is still under debate. The goal of sedation is to reduce the patient's discomfort and reach a level of awake sedation without significant effects on respiratory drive, respiratory pattern, blood gases, minute volume, hemodynamics, and airway reflexes.⁵⁴ A small dose of sedation, while vital signs and oxygenation are closely monitored, could be considered on a case-by-case basis to help ease some of the adverse effects of the NIV interface and thus improve patient compliance.²³ Many physicians in Europe and North America oppose the use of sedatives, as they may interfere with their ability to protect airways or depress the respiratory system. However, to prevent NIV failure due to low patient tolerance, mild sedation is suggested in selected patients in the ICU provided close monitoring of the patient's airway and consciousness.⁵⁴

Agitation is one of the most common causes of low tolerance to or failure of NIV. The term 'agitation' refers to a state of high anxiety that causes patients to become uncooperative. Agitation prevents patients from relaxing and synchronizing their breathing with the ventilator, and they often tend to remove the NIV interface. Agitation may also be related to the underlying delirium, a condition of inattention and disorientation, which becomes apparent, when a patient is stressed by the necessity to use NIV. In general, the management strategy in these patients focuses on non-pharmacological measures like verbal reassurance, giving the patient control over the mask, or improving comfort by frequent disconnection from NIV, if the respiratory insufficiency is not too severe.^{55, 56} However, sedatives are also used to improve tolerance to NIV. The preferred agents are small doses of benzodiazepines (lorazepam or midazolam)

and/or narcotics (fentanyl or morphine sulfate). Other agents commonly used to calm patients with delirium to accept NIV include haloperidol, propofol, and dexmedetomidine. However, patients receiving propofol must be carefully observed for potential respiratory depression or apnea. In contrast, dexmedetomidine causes minimal respiratory depression and has sedative and analgesic sparing properties, but it is relatively expensive.^{30, 56, 57} The Richmond agitation-sedation scale (RASS) is commonly used as an index for adjusting sedation levels. A score of +1 or higher on RASS is an indicator for sedation.⁵⁸ Patients are usually managed between -2 and 0 on the RASS during sedation. Sedation usually starts intermittently, but continuous administration is initiated, if the target sedation level is not reached.⁵⁹

Prone ventilation can be performed with minimum effort, if sedatives (e.g., dexmedetomidine) are used. A previous study showed the benefits (e.g., mortality reduction and enhanced oxygenation) of prone position (PP) in patients with severe ARDS if applied early and for prolonged periods.⁶⁰ A case study on a COVID-19 patient in Canada likewise reported that PP prevented the use of IMV.⁶¹ Another case series hypothesized an association between awake early self-proning in the emergency department and improved oxygen saturation in COVID-19 patients.⁶²

Dexmedetomidine is a centrally acting, highly selective alpha-2 adrenoreceptor agonist that inhibits the release of norepinephrine from synaptic vesicles. It improves analgesic, anxiolytic, and sedative effects without depressing the respiratory system.^{63, 64} A previous study compared the infusion of different loading doses of dexmedetomidine and midazolam over 24 hours in patients receiving NIV. Both agents were reported to be effective sedatives without significant differences in their effects on ventilation and oxygenation. However, dexmedetomidine required significantly fewer dosage adjustments to maintain adequate sedation, and patients receiving NIV were more cooperative.⁶⁵ Dexmedetomidine was also reported to be more effective than haloperidol in preventing delirium during NIV use with a lower incidence of intubation, NIV failure, and the requirement for supplementary sedation and analgesia. Dexmedetomidine was associated with a shorter hospital stay and lower incidence of respiratory tract infections.⁵⁶ A group of Italian physicians recommended bolus dosing of fentanyl or hydromorphone for analgesia and midazolam for sedation/anxiolysis as the best first-line agents in non-intubated patients. Additionally, they suggested dexmedetomidine

infusion as an effective alternative for medium sedation, particularly in the case of patients at risk of or already experiencing alcohol withdrawal symptoms.⁶⁶

In the case of psychosis and/or unmanageable disruptive behavior, pharmacological treatment is required. Antipsychotic agents are suggested as the first-choice intervention. Existing guidelines vary in terms of the preferred first-line agents, but in general haloperidol, olanzapine, risperidone, and quetiapine are recommended.⁶⁷ The causes of delirium in COVID-19 patients are not clear. However, contributing factors include systemic inflammation and neuroinflammation, multi-organ failure, coagulation abnormalities, deep sedative strategies, mechanical ventilation, and social isolation.⁶⁸ The risks of delirium and coma in COVID-19 patients can be reduced by avoiding the use of deep sedative drugs. The type, duration, and depth of sedation also play an important role. The results of a multicenter cohort study, involving 69 adult ICUs across 14 countries, recommended the avoidance of benzodiazepines for a prolonged period, as it was associated with a 59% higher risk of developing delirium.⁶⁹

The combined effects of inflammation and several other factors cause an increase in capillary permeability. These effects are not only confined to the lungs, but may also cause damage to the vascular endothelium, which in turn result in leakage from the vascular compartment into the interstitial tissues.⁷⁰⁻⁷² These variations increase the volume of distribution of water-soluble drugs and subsequently decrease their systemic exposure.⁷³ Sedative and analgesic agents with a low volume of distribution at steady-state (VD_{ss}) such as midazolam (0.7-1.2 L/Kg) are prone to under-exposure linked to a hyper-inflammatory state. However, other drugs widely distributed in the extravascular space, such as propofol (1.8-5.3 L/Kg), sufentanil (VD_{ss} 4.9 L/Kg), and fentanyl (VD_{ss} 5.5 L/Kg), are theoretically less affected by these variations.

From the perspective of metabolic interactions, some combination drugs such as midazolam, extensively metabolized by cytochrome P450 3A4/5 (CYP3A4/5), can probably be modified by CYP inducers or inhibitors. This could be increased significantly by combining midazolam with lopinavir/ritonavir.⁷⁴ Therefore, it is important to adjust drug dosages since high doses or prolonged infusions of midazolam in patients receiving lopinavir/ritonavir may cause delayed recovery, long-lasting hypnotic effects, and respiratory depression. Propofol and fentanyl have a lower risk of metabolic interactions, as their clearance is dependent on hepatic blood

flow (not only on intrinsic metabolic activity), although they can be metabolized by CYP 3A4. However, fentanyl has a high hepatic extraction rate (0.7-0.8) and is therefore not affected by variations in metabolic enzyme activity. Since propofol and fentanyl clearance is dependent on hepatic blood flow, any reduction in hepatic blood flow in the event of circulatory insufficiency (e.g., ARDS) could increase systemic exposure to the molecules of these drugs.⁷⁵⁻⁷⁷ The bradycardizing effects of dexmedetomidine must be taken into account in patients receiving azithromycin and hydroxychloroquine, as it may prolong the QT interval.⁷⁴ Accordingly, sedative and analgesic dosing should be adjusted to the patient's response in real-time. Based on clinical experience, COVID-19 patients may require higher doses of sedation than the patients with ARDS secondary to other etiologies (e.g., pneumonia).²⁸

Positioning

Previous studies have shown that awake PP in non-intubated COVID-19 patients with severe hypoxemic respiratory failure improves oxygen saturation than the supine position. Moreover, repositioning can improve the respiratory status and oxygenation in patients with normal mental status.^{62, 78} It is recommended that patients change position every 30-120 minutes (e.g., right lateral recumbent, prone, left lateral recumbent, sitting upright at 60-90 degrees). During and immediately after every position change, the oxygen supply should be checked. Health care workers should evaluate patients' respiratory status and oxygen saturation about 10 to 15 minutes after each position change.⁷⁹ It has been reported that awake PP may improve oxygenation, ventilation/perfusion mismatch, and breathing.⁸⁰ Besides, the early application of PP with HFNC or NIV, particularly in patients with non-intubated moderate ARDS and with SpO₂ >95%, may reduce intubation incidence.⁸¹ Another study recommended the semi-sitting or sitting position but avoiding the supine position in COVID-19 patients receiving NIV. These positions should be considered whenever possible and in close consultation with the medical team.⁸¹ It is important to ensure that a patient has to exert as little effort as possible, even when maintaining a posture. Therefore, the use of cushions/pillows is recommended to allow a stable position without active use of muscles by the patient and to reduce shortness of breath and energy expenditure.^{41, 82} Moreover, the position should be passive to reduce muscular activity and relax the accessory muscles to facilitate the ventilation/perfusion ratio.⁸³ Repositioning should be performed according

to clinical protocols to ensure its efficiency and patient safety.⁸⁴

The results of an observational prospective study, conducted in patients with COVID-19 on helmet CPAP therapy, showed that only a small proportion of patients prone/lateral positioning resulted in a significant improvement in gas exchange. Additionally, a decrease in the alveolar-arterial oxygen gradient (A-a O₂) of <20% (an important minimal but clinically relevant difference) was reported.⁸⁵ In another study, results showed that PP in conjunction with NIV can improve oxygenation in COVID-19 patients. This can be achieved without significant adverse effects, particularly in those with a sustained response, and may even avoid intubation. When used in a suitably monitored environment, with access to experienced clinicians able to facilitate IMV if required, PP alongside NIV may be a useful tool in treating COVID-19 patients with moderate AHRF. The reported change in the PaO₂/FiO₂ ratio was 28.7 mmHg in PP without any notable change in heart or respiratory rate.⁸⁶

Monitoring

Patients on NIV support should be monitored closely in order to take immediate action in case of NIV failure and to be able to switch to invasive ventilation. Health care providers should remain at the patient's bedside for constant monitoring of respiratory rate and breathing status. They should check arterial blood gases (ABG) every 30 min and alternate between CPAP and pressure support ventilation (PSV) to improve SpO₂ and reduce RR. Furthermore, patients should be checked, if administration of small doses of sedatives is needed and directly control delivered VT with high pressure.^{23, 47} Another serious concern is the possible presence of 'happy or silent hypoxemia'. For clinicians, the presence of happy or silent hypoxemia in COVID-19 patients, despite marked arterial hypoxemia, can incorrectly lead to the conclusion that the patient is not in a critical condition. Such cases can quickly jump clinical evolution stages and suffer ARDS with the associated cardiorespiratory arrest and death.⁸⁷

SpO₂ is used to measure oxygen saturation and to detect hypoxemia. However, SpO₂ levels should be interpreted cautiously in COVID-19 patients with hypoxemia. The sigmoid-shaped oxyhemoglobin dissociation curve moves to the left because of induced respiratory alkalosis (decrease in PaCO₂) due to hypoxemia-driven tachypnea and hyperpnea. During periods of hypocapnia, the ionization of hemoglobin and thus oxygen saturation increases for a given

degree of PaO₂. This explains why SpO₂ can be well-preserved in the face of a profoundly low PaO₂.⁸⁸ Falsely high SpO₂ and low RR can be seen in COVID-19 patients due to secondary causes such as diarrhea, dehydration, and hypoalbuminemia. It is therefore recommended to initiate respiratory support based on the PaO₂/FiO₂ ratio rather than SpO₂ levels alone.⁸⁹ It is suggested that the ratio should be above 150 mmHg, since NIV is associated with higher ICU mortality in patients with a ratio below this level.²³

Nutrition

Oral intake of food and drinks by COVID-19 patients in the ICU remains inadequate due to disease-related loss of appetite, nausea, and loss of taste. NIV interface (full-face or helmet) also makes it difficult to eat and drink, and its removal will reduce arterial oxygen saturation. The English National Health Service has recommended the administration of opioids when using NIV interfaces to reduce the perception of breathlessness and high VT; however, it can negatively affect bowel motility.⁹⁰ ⁹¹ In COVID-19 patients at the risk of malnutrition due to insufficient oral nutritional intake, oral nutritional supplementation (ONS) should be initially considered and then enteral nutrition (EN) should be used. In case of restrictions through the EN route, peripheral parenteral nutrition (PN) may be considered in patients who fail to meet their energy-protein needs through ONS or EN.⁹² In patients who cannot tolerate a full dose of EN during the first week in ICU, initiation of PN should be weighed on a case-by-case basis. PN should not be initiated until all strategies to maximize EN tolerance have failed. At every phase of disease progression, ICU patients with COVID-19 must be carefully evaluated for the risk of malnutrition and the need for nutritional support. Any delay will result in increased energy and protein deficiency, leading to extended hospitalization and rehabilitation of the surviving patients. Metabolism control and nutritional support play an important role in managing critically ill COVID-19 patients.⁹³

Unlike IMV, patients treated with NIV have no airway protection and may experience airway-related problems (increased sputum, vomiting, atelectasis, and mucus plugging) and other complications such as discomfort, hypotension, pneumothorax, anxiety, and cardiac rhythm disturbances. EN may exacerbate these complications, especially those that are airway-related, and potentially lead to critical complications such as pneumonia and airway obstruction.^{94, 95} Therefore, COVID-19 patients

receiving NIV support are predominantly fed with PN to avoid the gastrointestinal complications associated with EN.⁹⁶ However, liquid ONS is also given in an effort to meet energy needs, if it cannot be fulfilled with PN alone, and to maintain intestinal mucosal tropism.⁹⁷ An observational study found that inadequate oral intake was associated with prolonged NIV and hospital stay, whereby about 78% of patients received less than 80% of their energy requirements. Of the 150 patients receiving NIV support longer than 48 hours, 107 were unable to take oral nutrition to the extent that the medical staff had to opt for EN.⁵⁹

EN is recommended as the preferred route for critically ill patients without contraindications, as it provides the required calories. However, EN may elevate residual gastric volume leading to bacterial colonization and increase the risk of aspiration pneumonia and ventilator-associated pneumonia (VAP).⁹⁸ In cases where patients receive both EN and NIV support, nasogastric (NG) tubes may undermine interface sealing and consequently, reduce the effectiveness of the ventilation. Moreover, NIV may cause abdominal distension due to positive air pressure in the stomach, which results in diaphragmatic dysfunction. Therefore, the use of EN on its own is associated with airway complications, prolonged NIV, and lengthy hospital stays.^{59, 24, 99} It is recommended to initiate EN only during the first 48 hours of ICU stay, despite the risk of malnutrition and complications. Alternatively, peripheral or central PN may be considered.^{99, 100}

Various measures have been proposed to minimize risks to patients receiving NIV in case of EN using NG tubes:

- Silicone dressings can be applied to tight-fitting masks to minimize air leakage and pressure on the skin.⁵⁴
- If possible, a fine bore NG tube (size 8Fr) should be used for feeding.
- Position the patient in supine upright at an angle of 30-40 degrees during EN feeding. PP is not the preferred position.
- Use an EN pump for accurate and consistent delivery of feed, alternatively, gravity drip-feeding should be considered. The use of bolus feeding is not recommended, as it increases the risk of aspiration.⁹¹
- In the case of feeding intolerance, prokinetics metoclopramide (10 mg three times a day) and erythromycin (100-250 mg three times a day) can be used in patients without acute abdominal complication.⁹⁷
- Use post-pyloric feeding in patients with gastric intolerance after treatment with prokinetic agents or in patients at risk of aspiration.
- The prone position does not show any

limitations or contraindications to EN.¹⁰¹ Patients in the prone position should begin EN according to the preceding guidelines, keeping in mind that the prone posture is related to greater stomach residual volumes and an increased risk of vomiting. It is critical to examine the location of the NGT at the point of entry into the nasal cavity after placing the patient in the prone position to determine the possible risk of pressure damage.

- If the above procedures fail, use gastric aspiration to decompress the stomach and check feed absorption.⁹⁷

PN support should be considered when EN and ONS are not effective, especially in those patients already suffering from malnutrition at admission.¹⁰² This is also recommended in patients with long-term swallowing disorders for whom the re-introduction of an NG tube may reduce the rate of success of swallowing rehabilitation. An effective combination of new respiratory support strategies with a suitable route is suggested as nutritional therapy.¹⁰³ It should be noted that the use of peripheral PN (<850 mOsm/l) is not recommended as the first choice in patients receiving NIV due to its high fluid volume and low nutrition density.¹⁰⁴

In all COVID-19 patients, critical or non-critical, carbohydrate intake should be reduced. High carbohydrate has been associated with deteriorating ARDS because of an increase in CO₂ production and subsequent hypercapnia.¹⁰⁵ Moreover, ESPEN guidelines on clinical nutrition in the ICU recommend a low-carbohydrate diet to avoid insulin resistance and hyperglycemia, as repeatedly observed in critically ill patients.⁹⁷ The guidelines also recommend 1.3 g protein equivalents per Kg body weight per day delivered progressively. However, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends 1.2-2 g/Kg of body weight.^{97, 106} On a final note, one should be aware of using 0.9% saline as routine maintenance for COVID-19 patients, as it can increase sodium and chloride load, potentially cause bowel edema, and impair gastrointestinal function.¹⁰⁷

Conclusion

The application of NIV in the management of COVID-19 patients remains controversial. So far, the evidence on the use of NIV in patients with COVID-19 does not fully encourage its routine use. Some studies have revealed the benefits of using NIV in selected patients with respiratory failure. The main findings of our review are:

- NIV could be a useful respiratory support in the early stages of infection to prevent silent hypoxia as a complication of COVID-19.

- Patients receiving NIV support should be closely monitored during the trial period. Intubation should always remain an option, since any delay in intubation increases the risk of complications and may result in unfavorable outcomes.
- Early prone positioning can be deployed without significant adverse effects, mainly in patients with a sustained response, as it may help to increase oxygenation and thus avoid intubation.
- With close monitoring to prevent any complications, a small dose of sedation may be used in patients with agitation and delirium. The sedative dose should be adjusted for COVID-19 patients according to their response, as it is not a one-size-fits-all.
- Enteral feeding in patients receiving NIV support is associated with airway complications, prolonged NIV, and hospital stay, especially when initiated within the first two days of NIV use. However, it can still be considered for selected patients.
- Among all NIV interfaces, the helmet involves fewer complications and provides more comfort to patients.

Further studies are required to better understand the role and advantages of NIV in COVID-19 patients and to develop clear strategies (i.e., optimal settings, duration of therapy, sedation plane, and patient selection).

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Authors' Contribution

M.M: Study concept and design, re-analyzed the clinical and statistical data, drafting and critical revision of the manuscript for important intellectual content; Z. H.K: Study concept and design, drafting and critical revision of the manuscript for important intellectual content; H.A.V: Study concept and design, statistical analysis and re-analyzed the clinical and statistical data, drafting and revising the manuscript; A.M.A: Study concept and design, re-analyzed the clinical and statistical data, drafting and critical revision of the manuscript for important intellectual content.

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