

The Role of High Flow Nasal Oxygen in the Management of Severe COVID-19: A Systematic Review



O Papel do Oxigénio Nasal de Alto Fluxo no Tratamento da COVID-19 Grave: Uma Revisão Sistemática

Themistoklis PARASKEVAS¹, Eleousa OIKONOMOU¹, Maria LAGADINO¹, Vasileios KARAMOUZOS², Nikolaos ZAREIFOPOULOS¹, Despoina SPYROPOULOU³, Dimitrios VELISSARIS^{✉1}
Acta Med Port 2022 Jun;35(6):476-483 ▪ <https://doi.org/10.20344/amp.16686>

ABSTRACT

Introduction: Oxygen therapy remains the cornerstone for managing patients with severe SARS-CoV-2 infection and several modalities of non-invasive ventilation are used worldwide. High-flow oxygen via nasal cannula is one therapeutic option which may in certain cases prevent the need of mechanical ventilation. The aim of this review is to summarize the current evidence on the use of high-flow nasal oxygen in patients with severe SARS-CoV-2 infection.

Material and Methods: We conducted a systematic literature search of the databases PubMed and Cochrane Library until April 2021 using the following search terms: "high flow oxygen and COVID-19" and "high flow nasal and COVID-19".

Results: Twenty-three articles were included in this review, in four of which prone positioning was used as an adjunctive measure. Most of the articles were cohort studies or case series. High-flow nasal oxygen therapy was associated with a reduced need for invasive ventilation compared to conventional oxygen therapy and led to an improvement in secondary clinical outcomes such as length of stay. The efficacy of high-flow nasal oxygen therapy was comparable to that of other non-invasive ventilation options, but its tolerability is likely higher. Failure of this modality was associated with increased mortality.

Conclusion: High flow nasal oxygen is an established option for respiratory support in COVID-19 patients. Further investigation is required to quantify its efficacy and utility in preventing the requirement of invasive ventilation.

Keywords: Cannula; COVID-19; Critical Care; Noninvasive Ventilation; Oxygen/therapeutic use; Respiration, Artificial; Respiratory Distress; Syndrome

RESUMO

Introdução: A oxigenoterapia continua a ser o pilar do tratamento de doentes com infecção grave por SARS-CoV-2 e várias modalidades de ventilação não invasiva são usadas em todo o mundo. O oxigénio de alto fluxo via cânula nasal é uma opção terapêutica que pode, em certos casos, evitar a necessidade de ventilação mecânica.

Material e Métodos: Realizámos uma pesquisa sistemática da literatura nas bases de dados PubMed e Cochrane Library até abril de 2021 usando os seguintes termos de pesquisa: "oxigénio de alto fluxo e COVID-19" e "alto fluxo nasal e COVID-19".

Resultados: Vinte e três artigos foram incluídos nesta revisão, em quatro dos quais a posição de decúbito ventral foi usada como medida adjuvante. A maioria dos artigos eram estudos de coorte ou séries de casos. A oxigenoterapia nasal de alto fluxo pode reduzir a necessidade de ventilação invasiva em comparação com a oxigenoterapia convencional e pode melhorar os resultados clínicos. A eficácia da oxigenoterapia nasal de alto fluxo é comparável à de outras opções de ventilação não invasiva, embora a sua tolerabilidade seja provavelmente superior. O insucesso dessa modalidade está associado ao aumento da mortalidade.

Conclusão: O oxigénio nasal de alto fluxo é uma opção estabelecida para suporte respiratório em doentes com COVID-19. É necessária investigação adicional para medir a sua eficácia e utilidade na prevenção da necessidade de ventilação invasiva.

Palavras-chave: Cânula; COVID-19; Cuidados Intensivos; Oxigénio/uso terapêutico; Respiração Artificial; Síndrome do Desconforto Respiratório; Ventilação não Invasiva

INTRODUCTION

Appropriate antiviral and immunomodulatory treatment in combination with respiratory support are the cornerstones of the COVID-19 therapy. Conventional respiratory support strategies have been used since the onset of the pandemic in an attempt to decrease the need for mechanical ventilation. However, despite intensive research in this field and the application of several modalities, the best option treatment, the timing of initiation, escalation and de-escalation of each type of conventional respiratory support modality is still under investigation. The benefits of such treatment could reduce many of the financial consequences of the pandemic but remain a matter of debate.

Management of critically ill COVID-19 patients with respiratory failure includes standard procedures such as limited administration of intravenous crystalloid fluids, tracheal intubation, and invasive mechanical ventilation in the event of clinical deterioration, and muscle relaxants. Protocols of administration of dexamethasone, low weight molecular heparin and pharmacological agents such as remdesivir have also been applied. Conventional treatment for COVID-19 respiratory failure includes conventional oxygen therapy through face or venturi mask, high flow nasal cannula (HFNC) oxygen delivery and non-invasive ventilation (NIV) modalities such as continuous positive airway pressure (CPAP) or bi-level

1. Department of Internal Medicine. University Hospital of Patras. Patras. Greece.

2. Intensive Care Unit. University Hospital of Patras. Patras. Greece.

3. Department of Radiation Oncology. University Hospital of Patras. Patras. Greece.

✉ **Autor correspondente:** Dimitrios Velissaris. dvelissaris@upatras.gr

Recebido/Received: 07/06/2021 - **Aceite/Accepted:** 26/08/2021 - **Publicado Online/Published Online:** 14/01/2022 - **Publicado/Published:** 01/06/2022

Copyright © Ordem dos Médicos 2022



positive- airway pressure (BiPAP) ventilation. HFNC support has been proposed as an alternative non-invasive option to support the respiratory system and reduce the need for mechanical ventilation. HFNC oxygen support is a widely used modality of delivering high concentrations of oxygen for treating patients with hypoxemic respiratory failure. This support is achieved via a device which provides humidified and heated oxygen at high flows through nasal cannulas. These cannulas can provide oxygen in concentrations between 21% and 100%, at a flow of up to 60 L/min and temperatures between 31 and 37°C. The main benefit of HFNC is that compared to other forms of oxygen supplementation, it increases patient's comfort and tolerance and does not induce claustrophobia, thus solving a frequent issue during clinical practice.

The aim of this review is to summarize the current evidence on the use of high-flow nasal oxygen in patients with severe SARS-CoV-2 infection.

MATERIAL AND METHODS

Literature search

We conducted a systematic literature search of PubMed and Cochrane Library databases through April 2021 using the following search terms: "high flow oxygen and COVID-19" and "high flow nasal and COVID-19".

Inclusion criteria

We included the intervention studies that met the following criteria: a) preliminary and clinical trials as well as case series and any observational studies that report the efficacy of high-flow oxygen therapy, alone or in combination with prone positioning, only for COVID-19; b) studies that report significant outcomes such as clinical improvement, length of stay, discharge rate, mortality rate, intubation rate and ventilator-free days; c) studies written in English; d) studies enrolling adult population. We excluded the following studies: those with no sufficient efficacy endpoints; case reports, conference abstracts, thesis, review articles, editorials, and duplicate studies.

Study selection

We performed title and abstract screening, and after that we conducted a full-text screening for eligibility.

Data extraction

For studies that report the efficacy of high-flow nasal oxygen (HFNO) therapy for COVID-19, we extracted the following data: article title, author, study type, country, number of patients, main findings.

Quality assessment.

Quality assessment of observational cohorts was performed by two independent authors using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies. Case series and studies that did not compare HFNO to another oxygen treatment modality were considered of poor quality (Table 1).

We decided to use a narrative synthesis of the results instead of a quantitative synthesis/meta-analysis. The reason behind this decision, is that in our exploratory search, there was a great heterogeneity in the measures of outcomes used in the studies on HFNO.

RESULTS

The systematic search yielded a total of 883 results, 327 were rejected as duplicated, 556 were screened and based on their title and abstract 141 reports were sought for retrieval. This allowed us to identify 116 successfully retrieved reports that were assessed for eligibility. After a detailed review process, 23 articles were included in this rapid review, four of which studied the combination of prone positioning and HFNO therapy. Of the 93 excluded studies, 51 studies did not meet a sufficient endpoint, three studies were written in languages other than English and 39 were case reports, reviews, editorials, comments, or guidelines (Fig. 1).

We identified eight studies that compared HFNO with another option for respiratory support (Table 2). Compared to standard oxygen therapy, HFNO leads to a significant reduction in the rate of intubation, but its effect on mortality was not clear.¹⁻³ In a study by Teng *et al* with a small number of patients (n = 22), in addition to an improvement to respiratory indexes, the researchers also found a significant decrease in lymphocytes and CRP after 72 hours of HFNO

Table 1 – Quality assessment of the included studies

First author	Quality assessment
Bonnet ¹	good
Sayan ²	good
Demoule ³	good
Teng ⁴	good
Duan ⁵	fair
Franco ⁶	good
Grieco ⁷	good
Mellado-Artigas ⁸	good
Simioli ⁹	poor
Procopio ¹⁰	poor
Guy ¹¹	poor
Panadero ¹²	poor
Xia ¹³	poor
Vianello ¹⁴	poor
Hu ¹⁵	poor
Chandel ¹⁶	poor
Patel ¹⁷	poor
Calligaro ¹⁸	poor
Lagier ¹⁹	poor
Tu ²⁰	poor
Ferrando ²¹	good
Tonelli ²²	good
Xu ²³	poor

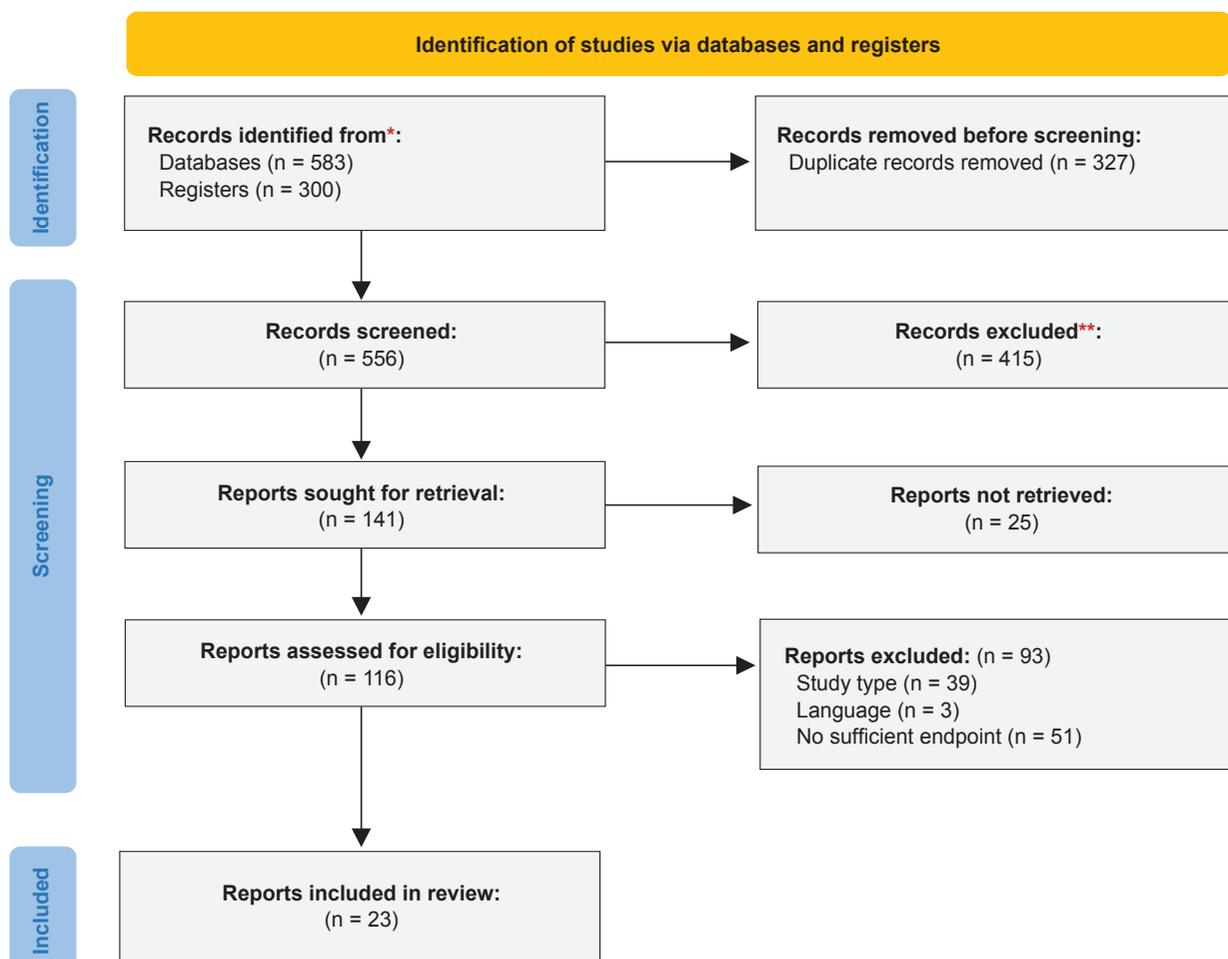


Figure 1 – Flowchart describing the literature search

* At this point, we describe the number of records that were identified using our search criteria, either in Databases such as pubmed or Registries such as <http://clinicaltrials.gov>.

** At this point, we describe the number of records that were excluded from our paper using the prespecified exclusion criteria.

treatment compared to conventional oxygen therapy.⁴ The rates of intubation and mortality did not differ between patients receiving NIV or HFNO but a randomized study reported that HFNO was associated with an increased intubation rate compared to Helmet NIV.⁵⁻⁷ Finally, patients treated with HFNO instead of being intubated early, stayed less time in the ICU and the use of this modality was associated with an increase in ventilator-free days.⁸

Additionally, 11 cohort studies and case series reported the clinical outcomes of patients receiving HFNO treatment (Table 3). Shortly after the application of HFNO, oxygenation indexes showed an upwards trend.^{9,10} The lowest percentage of HFNO failure (26%) was described in a case series of 27 patients by Guy *et al*,¹¹ while in the other included studies it ranged between 32% and 53%.¹²⁻¹⁸ Failure of this modality is consistently associated with poor prognosis in all the aforementioned studies, reaching 92% in a cohort from a resource-constrained setting by Calligaro *et al*.¹⁸ When measured between two and six hours after application of this modality, the ROX index could predict HFNO failure and need for invasive ventilation. Different cut-off points are suggested in the reviewed literature. Lagier *et al*¹⁹ reported a 36% rate of HFNO success in patients with

severe disease, who were not eligible for ICU-transfer due to comorbidities and in a case series of patients who did not tolerate CPAP or other NIV modalities, successful treatment was achieved with HFNO instead.¹⁰

High flow oxygen therapy in combination with prone positioning

Lastly, we identified four studies reporting on the clinical outcomes of the combination of HFNO combined with prone positioning (Table 4). In a case study by Tu *et al*, nine patients (mean age = 51) treated with HFNO and prone positioning were included. Each patient received a median of five prone positioning procedures, averaging two hours each.²⁰ After the first procedure, mean SpO₂ was increased from 90% ± 2% to 96% ± 3% ($p < 0.001$), and the mean PaO₂ was increased from 69 ± 10 to 108 ± 14 mmHg ($p < 0.001$). Mean PaCO₂ was also significantly decreased ($p = 0.007$).

A prospective, multicentre, observational cohort study in consecutive COVID-19 patients with acute respiratory failure (ARF) receiving support with HFNO investigated whether the combination of HFNO with awake-prone positioning prevented the need for intubation when compared to HFNO

Table 2 – Summary of studies that compared HFNO with another option for respiratory support

Title	First author	Publication date	Main finding
High flow nasal oxygen therapy to avoid invasive mechanical ventilation in SARS-CoV-2 pneumonia: a retrospective study.	Bonnet ¹	Feb 2021	High flow nasal cannula oxygen for acute respiratory failure due to COVID-19 was associated with a lower rate of invasive mechanical ventilation.
Impact of HFNC application on mortality and intensive care length of stay in acute respiratory failure secondary to COVID-19 pneumonia.	Sayan ²	May 2021	Administration of HFNC in respiratory failure secondary to COVID-19 pneumonia decreased the need for intubation and mortality.
High flow nasal cannula in critically ill patients with severe COVID-19.	Demoule ³	Oct 2020	HFNC significantly reduced intubation and subsequent invasive mechanical ventilation but did not affect case fatality
The value of high flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia.	Teng ⁴	Oct 2020	In severe patients, early application of HFNO improved oxygenation and respiratory rate and reduced the length of stay in the ICU.
Use of high-flow nasal cannula and noninvasive ventilation in patients with COVID-19: a multicenter observational study.	Duan ⁵	Jul 2020	In critically ill patients with COVID-19 who used HFNC and NIV as first-line therapy, the duration of HFNC + NIV, intubation rate and mortality did not differ between two groups.
Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia.	Franco ⁶	Nov 2020	30-day mortality rates using HFNC, CPAP and NIV were not significantly different.
Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: The HENIVOT Randomized Clinical Trial.	Grieco ⁷	May 2022 ¹	Among critically ill patients with moderate to severe hypoxemic respiratory failure due to COVID-19, helmet noninvasive ventilation, compared with high-flow nasal oxygen, resulted in no significant difference in the number of days free of respiratory support within 28 days.
High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure.	Mellado-Artigas ⁸	Feb 2021	The use of HFNO upon ICU admission in adult patients with COVID-19 related acute hypoxemic respiratory failure led to an increase in ventilator-free days and a reduction in ICU length of stay, when compared to early initiation of invasive mechanical ventilation.

alone.²¹ A total of 1076 patients with COVID-19 ARF were admitted, of which 199 patients received HFNO. Fifty-five of them (27.6%) were pronated during HFNO, while 60 (41%) and 22 (40%) patients from the HFNO and HFNO + awake-prone position groups were intubated. The results showed that the use of awake-prone position as an adjunctive therapy to HFNO did not prevent deterioration and need for intubation. Patients treated with HFNO + awake-prone position showed a trend for delay in intubation compared to HFNO alone, but the awake-prone position maneuver did not affect the 28-day mortality rate. It was concluded that in COVID-19 ARF patients who were treated with HFNO, the use of awake-prone positioning did not reduce the need for intubation or affect mortality.

A study by Tonelli *et al*,²² assessed the efficacy of prone positioning compared to standard care in patients receiving non-invasive respiratory support. From a total of 76 patients in the standard care group and 38 in the prone position group, 46 and 23 patients respectively were treated with HFNC. Patients in the prone position group were significantly younger and had worse respiratory profile. The

authors reported that awake prone positioning significantly reduced the need for endotracheal intubation in patients receiving HFNC therapy.

A retrospective observational case series was conducted by Xu *et al* which included 10 severe COVID-19 patients who received a combination of HFNC and prone positioning.²³ Compared to baseline, prone positioning led to a significant increase in PaO₂/F_{IO}2 and a slight increase in PaCO₂ (32.3 vs 29.7, $p < 0.001$). All patients enrolled in the study survived without progressing to critical condition and none required invasive ventilation.

DISCUSSION

The results of the studies included in this review are in favour of the use of HFNO in the treatment of patients with COVID-19 infection. HFNO usage is associated with a significant decrease in the rate of invasive ventilation compared to conventional oxygen therapy. Randomized controlled trials must be conducted before this modality can be confidently deemed not-inferior compared to more commonly used methods of ventilation in patients with severe disease.

Table 3 – Summary of studies that reported the clinical outcomes of patients receiving HFNO treatment, but do not compare it to another option for respiratory support

Title	First author	Publication date	Main finding
Clinical outcomes of high-flow nasal cannula in COVID-19 associated postextubation respiratory failure. A single-centre case series.	Simioli ⁹	Jan 2020	HFNO improved oxygenation and could be helpful in weaning patients.
Oxygen therapy via high flow nasal cannula in severe respiratory failure caused by SARS-CoV-2 infection: a real-life observational study.	Procopio ¹⁰	Dec 2020	HFNC can be used successfully in selected patients with COVID-19-related ARDS.
High-flow nasal oxygen: a safe, efficient treatment for COVID-19 patients not in an ICU.	Guy ¹¹	Nov 2020	The results of this single-centre study (23 out of 27 patients recovered, 19 out of 27 patients weaned from HFNO, including nine discharged) suggested that HFNO is effective.
High-flow nasal cannula for acute respiratory distress syndrome (ARDS) due to COVID-19.	Panadero ¹²	Sep 2020	HFNO therapy may be used to avoid intubation or as a bridge therapy, and no increased mortality was observed secondary to the delay in intubation.
High-flow nasal oxygen in coronavirus disease 2019 patients with acute hypoxemic respiratory failure: a multicenter, retrospective cohort study.	Xia ¹³	Nov 2020	HFNO failure was associated with a poor prognosis. Male and lower oxygenation at admission were the two strong predictors of HFNO failure.
High-flow nasal cannula oxygen therapy to treat patients with hypoxemic acute respiratory failure consequent to SARS-CoV-2 infection.	Vianello ¹⁴	Nov 2020	HFNC may be a safe treatment for less severe patients with SARS-CoV-2 respiratory failure.
Application of high-flow nasal cannula in hypoxemic patients with COVID-19: a retrospective cohort study.	Hu ¹⁵	Dec 2020	HFNC was an effective way of respiratory support in the treatment of COVID-19 patients.
High-flow nasal cannula therapy in COVID-19: using the ROX index to predict success.	Chandel ¹⁶	Dec 2020	60% of the patients were successfully weaned from HFNC. HFNC failure was associated with a high mortality rate (45.5%), but mortality did not differ between the early and late failure groups.
Retrospective analysis of high flow nasal therapy in COVID-19-related moderate-to-severe hypoxemic respiratory failure.	Patel ¹⁷	Aug 2020	HFNO use was associated with a reduction in the rate of invasive mechanical ventilation and overall mortality in patients with COVID-19 infection.
The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: a multi-centre prospective observational study.	Calligaro ¹⁸	Nov 2020	In a resource-constrained setting, 47% of the patients were successfully weaned from HFNO. HFNO failure was associated with increased mortality (83%).
High-flow oxygen therapy in elderly patients infected with SARS-CoV2 with a contraindication for transfer to an intensive care unit: a preliminary report.	Lagier ¹⁹	Apr 2021	Out of 44 patients who were treated with HFNO and were not eligible for ICU transfer, 36% of the patients had been weaned from HFNO and 64% had died.

Failure of this modality is associated with increased mortality, but the ROX index could potentially identify patients that will need intensification of oxygen support, early.

Some concerns have been raised regarding the increased transmission of the SARS-CoV-2 to healthcare workers when this respiratory modality is used, as well as its true efficacy in reducing the mechanical support of the respiratory function.²⁴ Clinicians are becoming more familiar with the use of HFNC in COVID-19 patients and hypoxic respiratory failure.

However, the use of personal protective equipment against SARS-CoV-2 transmission is deemed necessary when treating this group of patients. The risk of transmission is greater compared to patients treated with conventional oxygen supplementation and mechanically ventilated individuals due to increased aerosol generation. It is, however, unclear whether HFNC is associated with a higher risk of transmission compared with NIV modalities such as CPAP for which the increased rate of aerosol generation was singled out from the outset of the pandemic. The

Table 4 – Summary of studies of HFNO combined with prone positioning

Title	First author	Publication date	Main finding
Prone positioning in high-flow nasal cannula for COVID-19 patients with severe hypoxemia: a pilot study.	Tu ²⁰	May 2020	Prone positioning was safe and associated with improved oxygenation in HFNC patients with severe hypoxemia.
Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study.	Ferrando ²¹	Oct 2020	In patients with COVID-19 ARF treated with HFNO, the use of awake-PP did not reduce the need for intubation or affect mortality.
Early awake proning in critical and severe COVID-19 patients undergoing noninvasive respiratory support: a retrospective multicenter cohort study.	Tonelli ²²	Mar 2021	Prone positioning reduced the length of ICU and hospital stay, while mortality and tracheostomy rate was not significantly reduced.
Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19: a case series.	Xu ²³	May 2020	After prone positioning, the median PaCO ₂ increased slightly [32.3 (29.3 – 34.0) vs 29.7 (28.0 – 32.0), $p < 0.001$] and the median PaO ₂ /FIO ₂ (PF) was elevated significantly.

benefits of using HFNC oxygen are the patient's respiratory work reduction and increased comfort, an increased clearance of the pharyngeal mucous secretions and provision of a positive end –expiratory pressure effect. This modality, however, is associated with increased aerosol generation and the World Health Organization (WHO) has acknowledged airborne transmission as a possible mode of transmission. In order to avoid this, the maximum possible sealing between the device and the interface of the patient as well as the use of a mask by the patient and limiting the required flow rate by applying a higher FIO₂ have been recommended. In any case, patients developing signs of clinical deterioration and increased work of breathing should immediately proceed to intubation and invasive ventilation. However, the use of HFNC in previous SARS outbreaks suggest a low risk of transmission and effectiveness in selected respiratory failure cases. A 2012 meta-analysis found no increased risk of healthcare professional infection with SARS when using this modality.²⁵

International organizations have proposed guidelines for the use of HFNC. Experts of the Assembly of Intensive Care and Rehabilitation of the Polish Respiratory Society suggest that in patients with worsening respiratory failure the use of HFNC may be an effective initial management strategy.²⁶ The German Respiratory Society has also developed treatment strategies for these patients. In those who do not improve clinically or as assessed by arterial blood gas measurements, escalation to more advanced conventional treatment is indicated with the use of CPAP or non-invasive ventilation before intubation.²⁷ A position paper of the Respiratory Support and Chronic Care Group of the French Society of Respiratory Diseases proposes the use of HFNC as part of the conventional respiratory support techniques as a first line therapy outside the ICU, especially in cases where resources are limited or if there is no immediate access to invasive ventilation.²⁸

Awake prone positioning has emerged as a promising adjunctive therapy in non-intubated COVID-19 patients, but the efficacy of prone positioning combined with HFNO has not been systematically investigated. By reducing the pleural pressure gradient from non-dependent to dependent regions, dorsal lung regions are recruited, and lung perfusion is subsequently redistributed, leading to improved oxygenation.²⁹ In fact, the studies included in this review show an improvement in the respiratory profile of patients after prone positioning manoeuvres and a reduction of the intubation rate. More clinical trials must be performed on this subject before conclusions can be drawn, but prone positioning appears to be a safe adjunctive treatment to HFNO therapy.

Despite the encouraging evidence of the efficacy of HFNC, there is a lack of uniformity in clinical practice. On this matter, Subramaniam reports significant variations in practice among first responders and private hospital doctors, with the latter being less comfortable using HFNO in neutral pressure rooms.³⁰ This could be indicative of the controversial evidence on the safety of HFNC for healthcare workers. Some studies concluded that HFNC benefits patients without increasing the risk of contamination compared to standard oxygen mask, provided that precautionary measures have been taken,³¹ but Elshof *et al*³² argue that the issue of HFNC-generated droplet aerodynamics might be more complicated. The current literature considers the use of a medical mask over the HFNC device as the main precautionary measure against droplet dispersion and a recently published study reported that this method almost completely suppresses dispersion induced by coughing.³³ An environmental study by Ahn *et al* found extensive contamination in the room of a patient receiving NIV and HFNC, and even viable viruses on contaminated surfaces.³⁴ Therefore, future experimental and clinical research should focus not only on the benefits of this modality, but also on its safety for healthcare workers.

The main limitation of this review is that a quantitative synthesis was not conducted and, as far as the efficacy of HFNO is concerned, multiple measures of outcomes were reported, and different comparators were used by the included studies. However, we have excluded studies with conditions other than COVID-19, thus limiting the amount of heterogeneity to some extent.

CONCLUSION

High flow nasal cannula oxygen is now recognised as an effective option of respiratory support in COVID-19 patients. Further investigation is required to determine its efficacy compared to other non-invasive modalities and whether its use could prevent the need for mechanical ventilation.

AUTHORS CONTRIBUTION

TP: Literature review and analysis, draft of the manuscript.

EO: Literature review and analysis, critical review of the manuscript.

ML, NZ, DS: Literature review, critical review of the manuscript.

VK: Design of the review, critical review of the manu-

script.

DV: Conception and design of the review, draft of the manuscript.

PROTECTION OF HUMAN SUBJECTS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration issued by World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors report no competing interests.

FUNDING SOURCES

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

- Bonnet N, Martin O, Boubaya M, Levy V, Ebstein N, Karoubi P, et al. High flow nasal oxygen therapy to avoid invasive mechanical ventilation in SARS-CoV-2 pneumonia: a retrospective study. *Ann Intensive Care*. 2021;11:37.
- Sayan İ, Altınay M, Çınar AS, Türk HŞ, Peker N, Şahin K, et al. Impact of HFNC application on mortality and intensive care length of stay in acute respiratory failure secondary to COVID-19 pneumonia. *Heart Lung*. 2021;50:425-9.
- Demoule A, Vieillard Baron A, Darmon M, Beurton A, Géri G, Voiriot G, et al. High-flow nasal cannula in critically ill patients with severe COVID-19. *Am J Respir Crit Care Med*. 2020;202:1039-42.
- Teng XB, Shen Y, Han MF, Yang G, Zha L, Shi JF. The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. *Eur J Clin Invest*. 2021;51:e13435.
- Duan J, Chen B, Liu X, Shu W, Zhao W, Li J, et al. Use of high-flow nasal cannula and noninvasive ventilation in patients with COVID-19: A multicenter observational study. *Am J Emerg Med*. 2020; 2021;46:276-81.
- Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, et al. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. *Eur Respir J*. 2020;56:2002130.
- Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: The HENIVOT Randomized Clinical Trial. *JAMA*. 2021;325:1731-43.
- Mellado-Artigas R, Ferreyro BL, Angriman F, Hernández-Sanz M, Arruti E, Torres A, et al. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. *Crit Care*. 2021;25:58.
- Simioli F, Annunziata A, Langella G, Polistina GE, Martino M, Fiorentino G. Clinical outcomes of high-flow nasal cannula in COVID-19 associated postextubation respiratory failure. A single-centre case series. *Anaesthesiol Intensive Ther*. 2020;52:373-6.
- Procopio G, Cancelliere A, Trearichi EM, Mazzitelli M, Arrighi E, Perri G, et al. Oxygen therapy via high flow nasal cannula in severe respiratory failure caused by Sars-Cov-2 infection: a real-life observational study. *Ther Adv Respir Dis*. 2020;14:1753466620963016.
- Guy T, Créac'hcadec A, Ricordel C, Salé A, Amouat B, Bizet JL, et al. High-flow nasal oxygen: a safe, efficient treatment for COVID-19 patients not in an ICU. *Eur Respir J*. 2020;56:2001154.
- Panadero C, Abad-Fernández A, Rio-Ramirez MT, Acosta Gutierrez CM, Calderon-Alcala M, Lopez-Riolobos C, et al. High-flow nasal cannula for Acute Respiratory Distress Syndrome (ARDS) due to COVID-19. *Multidiscip Respir Med*. 2020;15:693.
- Xia J, Zhang Y, Ni L, Chen L, Zhou C, Gao C, et al. High-flow nasal oxygen in coronavirus disease 2019 patients with acute hypoxemic respiratory failure: a multicenter, retrospective cohort study. *Crit Care Med*. 2020;48:e1079-86.
- Vianello A, Arcaro G, Molena B, Turato C, Sukthi A, Guarnieri G, et al. High-flow nasal cannula oxygen therapy to treat patients with hypoxemic acute respiratory failure consequent to SARS-CoV-2 infection. *Thorax*. 2020;75:998-1000.
- Hu M, Zhou Q, Zheng R, Li X, Ling J, Chen Y, et al. Application of high-flow nasal cannula in hypoxemic patients with COVID-19: a retrospective cohort study. *BMC Pulm Med*. 2020;20:324.
- Chandel A, Patolia S, Brown AW, Collins AC, Sahjwani D, Khangoor V, et al. High-flow nasal cannula therapy in COVID-19: using the ROX index to predict success. *Respir Care*. 2021;66:909-19.
- Patel M, Gangemi A, Marron R, Chowdhury J, Yousef I, Zheng M, et al. Retrospective analysis of high flow nasal therapy in COVID-19-related moderate-to-severe hypoxaemic respiratory failure. *BMJ Open Respir Res*. 2020;7:e000650.
- Calligaro GL, Lalla U, Audley G, Gina P, Miller MG, Mendelson M, et al. The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: a multi-centre prospective observational study. *EclinicalMedicine*. 2020;28:100570.
- Lagier JC, Amrane S, Mailhe M, Gannier M, Arlotto S, Gentile S, et al. High-flow oxygen therapy in elderly patients infected with SARS-CoV2 with a contraindication for transfer to an intensive care unit: A preliminary report. *Int J Infect Dis*. 2021;108:1-3.
- Tu GW, Liao YX, Li QY, Dong H, Yang LY, Zhang XY, et al. Prone positioning in high-flow nasal cannula for COVID-19 patients with severe hypoxemia: a pilot study. *Ann Transl Med*. 2020;8:598.
- Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Adalia R, et al. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. *Crit Care*. 2020;24:597.
- Tonelli R, Pisani L, Tabbi L, Comellini V, Prediletto I, Fantini R, et al. Early awake proning in critical and severe COVID-19 patients undergoing noninvasive respiratory support: a retrospective multicenter cohort study. *Pulmonology*. 2021 (in press). doi: 10.1016/j.pulmoe.2021.03.002.

23. Xu Q, Wang T, Qin X, Jie Y, Zha L, Lu W. Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19: a case series. *Crit Care*. 2020;24:250.
24. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. *Lancet Respir Med*. 2020;8:433-4.
25. Tran K, Cimon K, Severn M, Pessoa-Silva C, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*. 2012;7:e35797.
26. Czajkowska-Malinowska M, Kania A, Kuca PJ, Nasiłowski J, Skoczyński S, Sokołowski R, et al. Treatment of acute respiratory failure in the course of COVID-19. Practical hints from the expert panel of the Assembly of Intensive Care and Rehabilitation of the Polish Respiratory Society. *Adv Respir Med*. 2020;88:245-66.
27. Pfeifer M, Ewig S, Voshaar T, Randerath WJ, Bauer T, Geiseler J, et al. Position paper for the state-of-the-art application of respiratory support in patients with COVID-19. *Respiration*. 2020;99:521-42.
28. Rabec C, Gonzalez-Bermejo J, Respiratory Support Chronic Care Group AVO2 of the French Society of Respiratory Diseases SPLF; GAVO2 collaborators. Respiratory support in patients with COVID-19 (outside intensive care unit). A position paper of the Respiratory Support and Chronic Care Group of the French Society of Respiratory Diseases. *Respir Med Res*. 2020;78:100768.
29. Pelosi P, Caironi P, Taccone P, Brazzi L. Pathophysiology of prone positioning in the healthy lung and in ALI/ARDS. *Minerva Anesthesiol*. 2001;67:238-47.
30. Subramaniam A, Haji JY, Kumar P, Ramanathan K, Rajamani A. Noninvasive oxygen strategies to manage confirmed COVID-19 patients in Indian intensive care units: a survey. *Indian J Crit Care Med*. 2020;24:926-31.
31. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. *Eur Respir J*. 2020;55:2000892.
32. Elshof J, Hebbink R, Duiverman ML, Hagmeijer R. High-flow nasal cannula for COVID-19 patients: risk of bio-aerosol dispersion. *Eur Respir J*. 2020;56:2003004.
33. Hamada S, Tanabe N, Inoue H, Hirai T. Wearing of medical mask over the high-flow nasal cannula for safer oxygen therapy in the COVID-19 era. *Pulmonology*. 2021;27:171-3.
34. Ahn JY, An S, Sohn Y, Cho Y, Hyun JH, Baek YJ, et al. Environmental contamination in the isolation rooms of COVID-19 patients with severe pneumonia requiring mechanical ventilation or high-flow oxygen therapy. *J Hosp Infect*. 2020;106:570-6.