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High-Flow Nasal Oxygen and Noninvasive Ventilation for COVID-19

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KEYWORDS

• COVID-19 • Noninvasive ventilation • HFNO
• Acute hypoxemic respiratory failure (AHRF)

KEY POINTS

- Invasive mechanical ventilation has been associated with high mortality in patients with acute hypoxemic respiratory failure due to COVID-19.
- Hence, High flow nasal oxygen and noninvaive ventilation were increasing used as first-line respiratory support in most affceted patients.
- Based on observational studies, the use of high flow nasal oxygen and noninvasive ventilation have been associated with a reduction in the need for invasive mechanical ventilation and possibly mortality.
- Results from ongoing randomized controlled trials are awaited.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to more than 347 million cases of coronavirus disease 2019 (COVID-19) and approximately 5.7 million fatalities by January 22, 2022.[1] COVID-19 is a systemic disease, with a wide spectrum of disease severity ranging from asymptomatic to life-threatening. The main reason for hospitalization and admission to an intensive care unit (ICU) is the development of acute hypoxemic respiratory failure (AHRF),[2] which is frequently severe.[3,4] The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) database suggests that 15% of hospitalized patients with COVID-19 are admitted to an ICU or a high dependency unit at some point during their illness.[5]

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Abbreviations	
COVID-19	Coronasvirus Disease 2019
AHRF	acute hypoxemic respiratory failure
SARS-CoV-2	acute respiratory syndrome coronavirus 2
HFNO	high-flow nasal oxygen
NIV	noninvasive ventilation
ARDS	acute respiratory distress syndrome
CPAP	continuous positive airway pressure
ICU	intensive care unit
RCT	randomized controlled trial
HR	hazard ratio
CI	confidence interval
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
HCW	health care worker

Respiratory support options for patients with AHRF in COVID-19 pneumonia include conventional oxygen therapy, high-flow nasal oxygen (HFNO), and noninvasive positive pressure ventilation (NIV) in addition to invasive mechanical ventilation.[6–8] The ISARIC database showed that HFNO was used in 20.3%, NIV was used in 9.8%, and invasive mechanical ventilation was used in 9.3% of hospitalized patients.[5] Early in the pandemic, invasive mechanical ventilation was the preferred modality for treating severe cases, partly because of the concerns over aerosolization associated with other forms of oxygen therapy, especially with reports of intrahospital transmission among health care workers (HCWs).[9] Early clinical practice guidelines on the use of NIV and HFNO in COVID-19 were cautious. For example, the World Health Organization interim guidelines published in May 2020 stated that a trial of HFNO and NIV may be used in selected patients with COVID-19 and mild acute respiratory distress syndrome (ARDS).[10] As high mortality was observed in intubated patients (**Table 1**), NIV and HFNO were increasingly used,[11] which paved the way for conducting clinical studies.

In this review, the authors focus on the published evidence of the safety and effectiveness of HFNO and NIV for the management of patients with AHRF owing to COVID-19.

MECHANISMS OF ACTION OF HIGH-FLOW NASAL OXYGEN AND NONINVASIVE VENTILATION IN ACUTE HYPOXEMIC RESPIRATORY FAILURE

HFNO achieves its main beneficial effects through the provision of high flow of gases. It uses humidification and heat to allow the delivery of up to 100% oxygen at high-flow rates (usually 40–60 L/min) that can be tolerated by patients for extended time periods. The main mechanisms of action are the following: (1) washout of nasopharyngeal dead space, thus reducing the overall dead space, improving the elimination of carbon dioxide and enhancing oxygenation; (2) attenuation of the inspiratory resistance of the nasopharynx, and thus reducing the related work of breathing; (3) improving conductance and pulmonary compliance by the adequately warmed and humidified gas compared with dry, cooler gas; (4) reducing the metabolic work associated with gas conditioning; and (5) the application of positive distending pressure for lung recruitment.[12] HFNO generates a very low positive end-expiratory pressure (PEEP) effect (3 cm H_2O on average), although it is higher with increasing flow.[13] The utilization of delivered oxygen is higher with HFNO compared with NIV at the same set fraction of inspired oxygen (Fio_2), hence increasing the risk of depletion of hospital oxygen supply.

Table 1
Studies that reported the use of high-flow nasal oxygen and/or noninvasive positive pressure ventilation for patients with COVID-19

Study	Study Type	Patients/Setting/Country	Respiratory Support	Outcomes
Chen et al,[61] 2020	Retrospective observational (single-center)	145 patients with COVID-19 (43 severely ill) (China)	HFNO: 6 patients IMV: 1 patient	Not reported
Lagi et al,[62] 2020	Retrospective observational (single-center)	84 patients with COVID-19 admitted to the Infectious and Tropical Disease Unit in February–March 2020; nurse and physician coverage intensified with time (Italy)	HFNO: 9 patients IMV: 1 patient	1/9 (11.1%) patients treated with HFNO required ICU admission and intubation[a]
Calligaro et al,[63] 2020	Prospective observational (multicenter)	293 consecutive patients with COVID-19 and AHRF in April–June 2020 (South Africa)	HFNO: 293 patients	HFNO success: 134/293 (47%) HFNO failure: 156/293 (53%) with 111 received IMV and 45 died without intubation 84/111 (75,7%) who received IMV died[a]
Zhou et al,[64] 2020	Retrospective observational (multicenter)	191 patients with COVID-19 admitted to 2 hospitals in December 2019–January 2020; 50 were admitted to ICU (Wuhan, China)	HFNO: 41 patients NIV: 26 patients IMV: 32 patients	33/41 (80.5%) patients treated with HFNO died 24/26 (92.3%) patients treated with NIV died 31/32 (96.9%) patients treated with IMV died
Yang et al,[65] 2020	Retrospective observational (single-center)	52 critically ill patients with COVID-19 December 2019–January 2020 (Wuhan, China)	HFNO: 33 patients NIV: 29 patients IMV: 22 patients	16/33 (48.5%) patients treated with HFNO died 23/29 (79.3%) patients treated with NIV died 19/22 (86.4%) patients treated with IMV died

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Table 1
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Study	Study Type	Patients/Setting/Country	Respiratory Support	Outcomes
Grasselli et al,[2] 2020	Retrospective observational (multicenter)	1591 patients admitted to the ICU in February–March 2020 (Italy)	NIV: 137 (11%) patients IMV: 1150 (88%) patients	No outcome reported for patients who were treated with NIV or IMV[a]
Avdeev et al,[66] 2021	Retrospective observational (multicenter)	61 patients receiving NIV for AHRF in wards in April–June 2020 (Russia)	NIV: 61 patients	44/61 (72.1%) patients had NIV success 17/61 (27.9%) patients treated with NIV required intubation Mortality was 24.6%
Forrest et al,[45] 2021	Retrospective observational (multicenter)	688 adult patients with confirmed COVID-19 and hypoxia in March–April 2020 (New York City, USA)	NIV: 534 patients IMV: 154 patients	171/534 (32.0%) patients treated with NIV died 128/154 (83.1%) patients treated with IMV died Across all subgroups and propensity-matched analysis, IMV was associated with a greater risk of death than NIV
Bellani et al,[67] 2021	Prospective, single-day observational study (multicenter)	8753 patients with COVID-19 present in the participating hospitals on the study day in March 2020 (Italy)	909 (10%) patients received NIV outside the ICU (85%) with CPAP; delivered by helmet in 617 (68%) patients	300/909 (37.6%) patients had NIV failure 498/909 (62.4%) patients were discharged alive without intubation C-reactive protein, PF ratio, and platelet counts were independently associated with increased risk of NIV failure

Franco et al,[36] 2020	Retrospective observational (multicenter)	670 consecutive patients with confirmed COVID-19 in pulmonology units in 9 hospitals in March–May 2020 (Italy)	HFNO: 163 patients CPAP/NIV: 507 patients	Intubation: 47 (28.8%) patients on HFNO, 82 (24.8%) patients on CPAP, and 49 (27.7%) patients on NIV Mortality: 16%, 30%, and 30% for HFNO, CPAP and NIV, respectively
Karagiannidis et al,[11] 2021	Retrospective observational (multicenter)	Nationwide cohort of 7490 patients with COVID-19 hospitalized in 2 periods (February–May and October–November 2020) with hospital setting not specified (Germany)	NIV only: 1614 (21.5%) patients NIV followed by intubation: 1247 (16.6%) patients IMV: 3851 (51.4%) patients	1247/2861 (43.6%) patients had NIV failure 624/1614 (38.7%) patients treated with NIV only died 818/1247 (65.6%) patients with NIV failure died 2003/3851 (52.0%) patients treated with IMV died
Faraone et al,[37] 2021	Retrospective observational (single-center)	50 consecutive patients with COVID-19 admitted to the general wards in March–May 2020 (Italy)	NIV: 50 patients	25 (50%) patients had do-not-intubate order 22 patients were weaned from NIV and did not require intubation (6/25 patients with treatment limitation and16/25 without treatment limitation) 9 (36%) patients had NIV failure and needed IMV
Menga et al,[68] 2021	Prospective observational (single-center)	85 consecutive patients with COVID-19 admitted to the ICU in March–April 20 (Italy)	Helmet NIV: 42 patients Face-mask NIV: 19 patients HFNO: 24 patients	Helmet NIV failure: 27/42 (64.3%) Face-mask NIV failure: 10/19 (52.6%) HFNO failure: 15/24 (62.5%) 21/52 (40.4%) of patient with NIV/HFNO failure died Higher illness severity predicted NIV/HFNO failure

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Study	Study Type	Patients/Setting/Country	Respiratory Support	Outcomes
Burns et al,[69] 2020	Retrospective observational (single-center)	28 patients with COVID-19 admitted to the ward in March–April 2020 (United Kingdom)	NIV: 28 patients	14/28 (50%) patients treated with NIV died
Xie et al,[70] 2020	Retrospective observational (multicenter)	733 patients with COVID-19 admitted to the ICU in January-February 2020 (China)	HFNO: 320 patients NIV: 164 patients IMV: 100	144/320 (%) patients treated with HFNO died 107/164 (%) patients treated with NIV died 75/100 (75%) patients treated with IMV died
Garcia et al,[71] 2020	Prospective observational (multicenter)	639 patients with COVID-19 admitted to the ICU after April 2020 (Europe)	HFNO: 25 patients NIV: 27 patients IMV: 317 patients	4/25 (16.0%) patients treated with HFNO died in the ICU[a] 9/27 (33.3%) patients treated with NIV died in the ICU[a] 58/317 (18.3%) patients treated with IMV died in the ICU[a]
Elhadi et al,[72] 2021	Prospective observational (multicenter)	465 consecutive COVID-19 critically ill patients May-December 2020 (Libya)	HFNO:20 patients NIV/CPAP: 20 patients	15/20 (75%) patients treated with HFNO died 18/20 (90%) patients treated with NIV died
Rahim et al,[73] 2020	Cross-sectional (single)	204 patients admitted to the ICU April–August 2020 (Pakistan)	NIV: 126 patients IMV: 78 patients	84/126 (66.7%) patients treated with NIV died 73/78 (93.6%) patients treated with IMV died
Carpagnano et al,[74] 2021	Retrospective (single-center)	78 consecutive patients with COVID-19 and moderate to severe ARDS hospitalized in an intermediate respiratory ICU, in March–April 2020 (Italy)	HFNO: 7 patients NIV: 61 patients	2/7 (28.6%) patients treated with HFNO died 25/61 (41.0%) patients treated with NIV died

Rodríguez et al,[75] 2021	Prospective observational (multicenter)	1362 critically ill patients with confirmed COVID-19 disease and acute respiratory failure in February–May 2020 (Spain)	HFNO: 375 patients NIV: 140 patients IMV: 1172 patients	80/375 (21.3%) patients treated with HFNO died in ICU 42/140 (30.0%) patients treated with NIV died in ICU 458/1172 (39.1%) patients treated with IMV died in ICU
Roomi et al,[76] 2021	Retrospective observational (multicenter)	1204 patients with COVID-19 admitted to the ICU in March–August 2020 (Philadelphia area, USA)	HFNO: 573 patients NIV: 399 patients IMV: 713 patients	203/573 (35.4%) patients treated with HFNO died 187/399 (46.9%) patients treated with NIV died 373/713 (52.3%) patients treated with IMV died
Grosgurin et al.[77] 2021	Retrospective observational (single-center)	157 patients with COVID-19 admitted to the intermediate care unit in March–April 2020 (Switzerland)	HFNO alternating with NIV was provided to 85 patients with worsening respiratory failure	33/85 (39%) required ICU admission and IMV 52 (61%) were discharged to the ward without ICU admission
Grieco et al,[47] 2021	Randomized controlled trial (multicenter)	109 patients with COVID-19 and moderate-severe AHRF (PF ratio < 200) admitted to 4 ICUs (Italy)	Helmet-NIV group: helmet applied continuously for the first 48 h (PEEP: 10–12 cmH_2O; pressure support: 10–12 cmH_2O) followed by HFNO: 54 HFNO group at 60 L/min: 55	No difference in the duration of respiratory support at 28 d (primary outcome): mean difference 2 d, 95% CI, −2 to 6, $P = .26$) Intubation rate: 16/54 (30%) vs 28/55 (51%); $P = .03$ in favor of the Helmet NIV group Ventilator-free days within 28 d (median of 28 vs 25 d; mean difference; $P = .04$) 13/54 (24%) patients in the helmet-NIV group and 14/55 (25%) patients in HFNO group died in the hospital ($P = 1.0$)

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Table 1
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Study	Study Type	Patients/Setting/Country	Respiratory Support	Outcomes
Perkins et al,[48] 2021	Randomized controlled trial (multicenter)	1272 hospitalized patients with acute respiratory failure due to COVID-19 (United Kingdom)	CPAP: 380 patients HFNO: 417 patients Conventional oxygen therapy: 475 patients	The primary outcome (composite of tracheal intubation or mortality within 30 d) was lower in the CPAP group (36.3%) compared with conventional oxygen therapy (44.4%; $P = .03$), but similar in the HFNO and conventional oxygen therapy groups ($P = .85$). The difference in between CPAP and HFNO was due to tracheal intubation Safety events were most common in the CPAP group (CPAP 34.2%; HFNO 20.6%; conventional oxygen therapy 13.9%, $P<.001$)

Abbreviation: IMV, invasive mechanical ventilation.
[a] Outcome data incomplete at the time of publication.

NIV is primarily a pressure-targeted modality delivered as continuous (CPAP) or biphasic positive airway pressure (mainly as pressure support ventilation). It improves arterial oxygenation by increasing functional residual capacity, shifting the tidal volume to a more compliant part of the pressure-volume curve, thus reducing both the work of breathing and the tidal opening and closure of the airways.[14] The face-mask and helmet interfaces are commonly used to deliver NIV. The helmet has the advantage of less air leaks and better tolerability in many patients, thus facilitating prolonged NIV treatments at higher PEEP.[15]

The main settings, strengths, and risks of HFNO, face-mask NIV, and helmet NIV are presented in **Fig. 1**.

SAFETY OF NONINVASIVE VENTILATION AND HIGH-FLOW NASAL OXYGEN IN PATIENTS WITH COVID-19

Both NIV and HFNO can avoid the complications associated with invasive mechanical ventilation, most importantly, ventilator-induced lung injury, cardiovascular decompensation, and infectious complications.[16,17] However, the concerns associated with NIV and HFNO use in patients with COVID-19 include patient self-inflicted lung

	High-flow nasal oxygen	Mask NIV/CPAP	Helmet NIV/CPAP
Picture			
Main settings	FiO_2: 0.21-1.0 start high and titrate to achieve SpO2 92-96% (usual target for most patients) Flow: 40-60 L/min Temperature: 31-37° C	FiO_2: 0.21-1.0; start high and titrate to achieve SpO2 92-96% (usual target for most patients) PSV/ PEEP: 8-10/5-8 cmH2O or CPAP 8-10 cmH2O	FiO_2: 0.21-1.0; start high and titrate to achieve SpO2 92-96% (usual target for most patients) PSV/PEEP 10-12/ 10-12 cmH2O or CPAP10-12 cmH2O Flow:≥60 L/min
Advantages/ strengths			
Easy to apply	+++	++	+
Easy to monitor	+++	++	+
Ability to drink and eat	+++	0	+
Ability to communicate	+++	+	++
Risks			
Mucosal irritation/ dryness	+	++	+
Claustrophobia	0	++	+++
Skin Injury	0/+	+++	+
pneumothorax	0	++	++
Minimizing the associated risks	Caution in patients with hemodynamic instability, decreased level of consciousness Monitoring mental status, respiratory rate, PF ratio, ROX index	Caution in patients with hemodynamic instability, decreased level of consciousness, agitation Monitoring mental status, work of breathing, respiratory rate, PF ratio, ROX index, HACOR scale, pressure-induced skin injury (nose bridge, face)	Caution in patients with hypercapnia, hemodynamic instability, decreased level of consciousness, agitation Monitoring mental status, work of breathing, respiratory rate, PF ratio, ROX index, pressure-induced skin injury (axilla)

Fig. 1. Settings, strengths, risks, and monitoring of HFNO and NIV/CPAP via face mask and helmet in patients with COVID-19 and AHRF. PF ratio, the ratio of arterial oxygen partial pressure to fractional inspired oxygen; PSV, pressure support ventilation.

injury, delayed intubation in the case of treatment failure, and virus nosocomial transmission.[18]

Patient Self-Inflicted Lung Injury

In patients with AHRF, hypoxemia and dysregulated inspiratory effort may induce spontaneous vigorous inspiratory efforts. The resulting high transpulmonary pressures along with altered respiratory mechanics and inhomogeneous lung inflation may induce further injury to the lung, which is described as patient self-inflicted lung injury.[15,19,20] HFNO and NIV may mitigate partially, but not fully, these pathophysiologic abnormalities. Patient self-inflicted lung injury is difficult to quantify or even detect, and related studies that compare noninvasive respiratory support versus invasive mechanical ventilation are lacking. From a mechanistic point of view, NIV has theoretic advantages over HFNO for the management of patients with COVID-19 and AHRF.[21] The ability of NIV to deliver higher PEEP compared with HFNO may render spontaneous breathing less injurious.[22]

Delayed Intubation

One of the concerns with the use of HFNO or NIV is delayed intubation that may worsen outcomes. Related studies showed mixed results and are based mainly on observational data. In a propensity score-matched retrospective study of 175 patients with non-COVID-19 respiratory failure who required intubation after HFNO failure (2013–2014), patients with early HFNO failure (intubated < 48 hours after initiation; n = 130) had significantly lower mortality compared with those failing greater than 48 hours after initiation (n = 45; 39.2% vs 66.7%, $P = .001$).[23] In a multicenter retrospective study, 164 out of 272 patients with COVID-19 managed with HFNO inside (n = 161) and outside (n = 111) the ICU were successfully weaned from HFNO.[24] HFNO failure occurred in 108 (39.7%) patients: 61 had early failures (< 48 hours) and 47 late failures.[24] Mortality after HFNO failure was high (45.4%) with no significant difference in hospital mortality (39.3% vs 53.2%; $P = .18$) or any of the secondary end points between early and late HFNO failure groups. The trend in mortality difference, although not statistically significant, raises the question of whether a larger trial might show a difference. Much larger trials will be needed to answer this question.[24]

Nosocomial Transmission

The viral dispersion with HFNO has been evaluated in simulation and clinical studies. A study measured smoke dispersion distance from a manikin model with HFNO at 60 L/min and demonstrated that smoke dispersion distance was limited, suggesting that dispersion was similar to the one observed with simple oxygen mask.[25,26] Wearing a surgical mask on top of HFNO further reduces the aerosol transmission during coughing or sneezing.[27] An experiment in healthy volunteers showed that cough-generated droplets spread to a mean (standard deviation) distance of 2.48 ± 1.03 m at baseline and 2.91 ± 1.09 m with HFNO (maximum cough distance of 4.50 m).[28] Face-mask NIV delivered through devices with single-limb circuits has been associated with more viral dispersion than HFNO.[29,30] Using a human-patient simulator on face-mask NIV, the exhaled air dispersion distance was shown to increase with higher inspiratory positive airway pressures and was within a 1-m region.[30] It has been suggested that NIV delivered through devices that use double-tube circuits (which includes selected NIV machines and ICU ventilators) is associated with less aerosol generation compared with single-tube circuits (only inspiratory tube).[31] Helmet NIV is associated with less viral dispersion than HFNO and face-mask NIV.[29] On the other hand, a study found that HFNO and NIV did not increase aerosol

generation from the respiratory tract in healthy participants with no active pulmonary disease measured in a negative-pressure room.[32]

Clinical studies that link HFNO or NIV with nosocomial transmission of viruses are limited by their size and methodology.[33] These studies suggest that transmission to HCWs is uncommon with the use of infection control precautions, but it does exist. One study evaluated 73 HCWs exposed to patients with confirmed COVID-19 (n = 28) treated with HFNO for a median of 48 hours per person.[34] All HCWs wore appropriate personal protective equipment and underwent weekly COVID-19 polymerase chain reaction testing, and all HCWs had negative tests in the 14 days following exposure.[34] A study in 27 patients with confirmed COVID-19 treated with HFNO outside the ICU found that 1 nurse became infected among 44 exposed HCWs.[35] The HCWs applied airborne precautions, and the patients wore a surgical mask when an HCW entered the room.[35] In a cohort of 670 patients with confirmed COVID-19, closely monitored and treated in respiratory units outside the ICU with either HFNO (N = 163, 24.3%) or CPAP/NIV (n = 507, 75.7%; using helmet or face-mask interfaces), 42 (11.1%) HCWs tested positive for infection, despite appropriate protective equipment.[36] Only 3 HCWs required hospitalization.[36] In another study in which 50 patients with COVID-19 received NIV, HCWs caring for them underwent nasopharyngeal swabs for SARS-CoV-2 in case of COVID-19 symptoms and had periodic SARS-CoV-2 screening serology, and 2/124 (1.6%) HCWs were diagnosed with COVID-19.[37]

As the potential of nosocomial transmission of SARS-CoV-2 exists, it is prudent that HFNO and NIV are used with proper infection control precautions, that is, in single rooms or negative pressure airborne isolation rooms when possible.[28] Careful fitting of the interfaces on supported patients is recommended.[38] The risk of transmission may be decreased by using NIV devices that use double-tube circuits without exhalation ports.[31] The use of viral filters at exhalation ports may further reduce nosocomial transmission. HCWs caring for patients with COVID-19 using NIV or HFNO should be wearing full airborne personal protective equipment.[28]

Other Safety Concerns

The prolonged use of NIV and to a lesser extent HFNO in patients with COVID-19 is associated with the risk of pressure injury, especially in the nasal area, and with an increased risk of pulmonary barotrauma.[39] Helmet-NIV eliminates the risk of pressure injury associated with face-mask interfaces, but may uncommonly be associated with other pressure injuries around the neck seal and underneath the axillary straps.

EFFECTIVENESS OF HIGH-FLOW NASAL OXYGEN AND NONINVASIVE VENTILATION IN PATIENTS WITH ACUTE HYPOXEMIC RESPIRATORY FAILURE

Evidence from Randomized Controlled Trials in Non-COVID-19 Population

A meta-analysis of 9 randomized controlled trials (RCTs; n = 2093 patients) found no difference in mortality in patients with AHRF treated with HFNO (relative risk, 0.94; 95% confidence interval [CI], 0.67–1.31, moderate certainty) compared with conventional oxygen therapy, but a decreased risk of intubation (relative risk, 0.85; 95% CI, 0.74–0.99).[40] A meta-analysis of 8 RCTs comparing high-flow nasal cannula with other noninvasive methods of oxygen delivery after extubation in critically ill adults found that HFNO compared with conventional oxygen therapy decreased reintubation (relative risk, 0.46; 95% CI, 0.30–0.70; moderate certainty) and postextubation respiratory failure, but had no effect on mortality (relative risk, 0.93; 95% CI, 0.57–1.52; moderate certainty), or ICU length of stay (mean difference, 0.05 days fewer;

95% CI, 0.83 days fewer to 0.73 days more; high certainty).[41] In this population, HFNO compared with NIV had no effect on reintubation, mortality, or postextubation respiratory failure.[41]

A systematic review and network meta-analysis that included 25 RCTs and 3804 patients with AHRF owing to causes other than COVID-19 found lower mortality risk associated with face-mask NIV (risk ratio, 0.83; credible interval, 0.68–0.99) and helmet NIV (risk ratio, 0.40; credible interval, 0.24–0.63) compared with conventional oxygen therapy.[42] The benefit of helmet NIV but not face-mask NIV was maintained after excluding patients with chronic obstructive pulmonary disease exacerbation or cardiogenic pulmonary edema.[42] Face-mask NIV, helmet NIV, and HFNO were associated with lower risk of endotracheal intubation.[42]

Evidence from Observational Data in Patients with COVID-19

A simulation model projected that a scenario in which HFNO is available would result in 10,000 to 40,000 fewer deaths in the United States compared with a scenario in which HFNO was unavailable and in fewer days without available ventilators.[43] A retrospective study evaluated 379 consecutive patients with COVID-19 admitted to 4 ICUs for AHRF in Paris, France, between February 21 and April 24, 2020. The 146 (39%) patients who received HFNO within the first 24 hours after ICU admission were compared with the 233 patients who did not. Propensity-score adjusted analysis showed that HFNO was associated with fewer patients requiring invasive mechanical ventilation by day 28 (55% vs 72%; $P < .0001$) with similar 28-day mortality (21% in the HFNO group vs 22% in the other group).[44] Other studies on the outcomes associated with HFNO in patients with COVID-19 are summarized in **Table 1**.

There are multiple observational studies that evaluated NIV in the management of COVID-19 in different settings that vary between ICU and wards, mostly owing to unavailability of ICU beds (see **Table 1**).[36] One multicenter retrospective observational study found that patients treated with NIV had significantly lower mortality (171/534; 32.0%) than those who received invasive mechanical ventilation (128/154; 83.1%). Although the multivariable regression attempted to address bias inherent in this nonrandomized study, it is not clear whether the higher mortality in this study reflects severity of illness in those intubated or a true cause and effect.[45] In patients with confirmed COVID-19 treated in respiratory units outside the ICU with either HFNO (n = 163, 24.3%) or CPAP/NIV (n = 507, 75.7%), the intubation rate was similar in the 2 groups, but the mortality was lower in the HFNO group.[36] In an interim analysis of the international, multicenter HOPE COVID-19 cohort (1933 patients), 390 (20%) patients were treated with NIV, 44.4% of whom had the composite outcome of death or need for intubation.[46] Other studies on the outcomes associated with NIV in patients with COVID-19 are summarized in **Table 1**.

Evidence from Randomized Controlled Trials in Patients with COVID-19

A recent RCT conducted in patients with COVID-19 admitted to 4 Italian ICUs with moderate to severe AHRF found that helmet NIV did not result in significantly fewer days of respiratory support at 28 days (primary outcome) as compared with HFNO alone (mean difference, 2 days; 95% CI, −2 to 6; $P = .26$).[47] However, the helmet NIV group had a lower intubation rate (30% vs 51%; $P = .03$) and more days free of invasive mechanical ventilation within 28 days (median of 28 vs 25 days; $P = .04$).[47] The hospital mortality was 24% in the helmet NIV group and 25% in the HFNO group.[47] In the RECOVERY-Respiratory Support multicenter RCT, 1272 hospitalized patients with acute respiratory failure owing to COVID-19 were randomized to CPAP (n = 380; 29.9%), HFNO (n = 417;

32.8%), or conventional oxygen therapy (n = 475; 37.3%).[48] The composite outcome (tracheal intubation or mortality within 30 days) was lower in the CPAP group compared with conventional oxygen therapy (CPAP group, 36.3%; conventional oxygen therapy, 44.4%; unadjusted odds ratio, 0.72; 95% CI, 0.53–0.96; $P = .03$), but similar in the HFNO and conventional oxygen therapy groups (HFNO, 44.4%; vs conventional oxygen therapy, 45.1%; unadjusted odds ratio, 0.97; 95% CI, 0.73–1.29; $P = .85$).[48] There are no data from RCTs that compare CPAP with pressure support mode.

PRONE POSITIONING WITH HIGH-FLOW NASAL OXYGEN AND NONINVASIVE VENTILATION

Awake prone positioning can easily be performed in patients receiving HFNO. In a pilot study of 9 patients with COVID-19 and AHRF requiring HFNO for greater than 2 days, prone positioning led to an increase in blood oxygen saturation (Sao_2) from 90% ± 2% to 96% ± 3% ($P<.001$) and in blood oxygen partial pressure (Pao_2) from 69 ± 10 to 108 ± 14 mm Hg ($P<.001$).[49]

Awake prone positioning has also been used in patients with COVID-19 while receiving NIV, but data are limited. Small observational studies have shown that NIV in the prone position is feasible and is probably safe, even outside the ICU.[50,51] In an a priori collaborative metatrial of 6 RCTs, adults who required respiratory support with high-flow nasal cannula for AHRF owing to COVID-19 (n = 1126) were randomly assigned to awake prone positioning or standard care.[52] The primary composite outcome was treatment failure (intubation or death within 28 days), which was lower with awake prone positioning compared with standard care (40% vs 46%; relative risk, 0.86; 95% CI, 0.75–0.98).[52]

MONITORING OF PATIENTS DURING HIGH-FLOW NASAL OXYGEN AND NONINVASIVE VENTILATION

The success of the new modalities of noninvasive respiratory support starts with ensuring availability, having the needed infrastructure and resources, and establishing programs that train HCWs as well as creating protocols, policies, and procedures on their use (see **Fig. 1**). Close monitoring and short-interval assessments for worsening of respiratory failure are critical for patients receiving noninvasive respiratory support (see **Fig. 1**).[53] Monitoring during HFNO and NIV should encompass monitoring the inspiratory effort, respiratory rate, tidal volume, Fio_2, and oxygenation parameters (Sao_2/Fio_2 or Pao_2/Fio_2 ratio), as these variables may indicate HFNO or NIV failure and the need for intubation.[15] A small retrospective study evaluated 17 patients with ARDS secondary to COVID-19 who were managed with HFNO.[54] The HFNO failure rate, defined by the need of NIV or intubation as rescue therapy, was 0% (0/6) in patients with Pao_2/Fio_2 greater than 200 mm Hg versus 63% (7/11) in those with $Pao_2/Fio_2 \leq 200$ mm Hg ($P = .04$).[54] The ROX ($[Spo_2/Fio_2]$/respiratory rate) index has been validated to predict the success of HFNO in non-COVID-19 patients. A 2-year multicenter prospective cohort study validated the ability of the ROX index to predict intubation in 191 patients with non-COVID-19 pneumonia treated with HFNO.[55] ROX ≥ 4.88 at 2 hours (hazard ratio [HR], 0.434; 95% CI, 0.264–0.715), 6 hours (HR, 0.304; 95% CI, 0.182–0.509), or 12 hours (HR, 0.291; 95% CI, 0.161–0.524) after HFNO initiation was associated with a lower intubation risk. An ROX less than 2.85 at 2 hours, less than 3.47 at 6 hours, and less than 3.85 at 12 hours predicted HFNO failure (specificities 98%–99%).[55] A single-center retrospective study of 196 patients with ARDS secondary to COVID-19 observed that 40 patients were treated with HFNO.[56] The ROX index was significantly higher in the group that did not require intubation

Table 2
Randomized controlled trials (recruiting or nonrecruiting) evaluating noninvasive respiratory support (high-flow nasal oxygen or noninvasive ventilation) in patients with COVID-19 and acute hypoxemic respiratory failure

Trial	Identifier/Status	Country	Design	Population	Sample Size	Intervention	Primary Outcome
Comparison of HFNO, face-mask NIV and helmet NIV in COVID-19 ARDS patients (NIV COVID-19)	ClinicalTrials.gov Identifier: NCT04715243 Recruiting	Oman	Multicenter RCT	Patients with confirmed COVID-19 in the emergency department, the ward, high dependency, or ICU with ARDS requiring NIV	360	Patients assigned to 1 of 3 arms: HFNO, face-mask NIV, or helmet NIV	Rate of endotracheal intubation
Helmet noninvasive ventilation for COVID-19 patients (Helmet-COVID)	ClinicalTrials.gov Identifier: NCT04477668 Recruiting	Saudi Arabia	Multicenter RCT	COVID-19 with AHRF	320	Pragmatic parallel RCT that will compare helmet NIV with standard of care to standard of care alone in 1:1 ratio. The trial will be implemented in multiple centers	28-d all-cause mortality
Early CPAP in COVID-19 patients with respiratory failure (EC-COVID-RCT)	ClinicalTrials.gov Identifier: NCT04326075	Italy	Single-center RCT	Patients in the emergency department with confirmed or suspected COVID-19 and Spo_2 < 95% with PF ratio > 200	900	Early helmet CPAP vs usual care	Death or need of intubation
High-flow nasal oxygen vs CPAP helmet in COVID-19 pneumonia (COVIDNOCHE)	ClinicalTrials.gov Identifier: NCT04381923 Not recruiting (by August 26, 2021)	USA	Single-center RCT	Patients with COVID-19 and refractory hypoxemia ($Spo_2 \leq 92\%$ on $O_2 \geq 6$ L/min by nasal cannula)	200	Advanced respiratory units will be assigned to use 1 of 2 default interventions (helmet CPAP vs HFNO) as the first-line treatment	Ventilator-free days within 28 d

High-flow nasal therapy vs conventional oxygen therapy in COVID-19 (COVID-HIGH)	ClinicalTrials.gov Identifier: NCT04655638 Recruiting	Italy	Multicenter RCT (Europe)	Patients with confirmed COVID-19–related AHRF in any hospital ward caring for COVID-19 patients	364	HFNO vs conventional oxygen therapy	Proportion of patients needing escalation of treatment (ie, NIV, including CPAP, or intubation) by 28 d

The search was performed on August 26, 2021, in ClinicalTrials.gov, using the following terms: adults (≥18 y), COVID, interventional studies, all countries, recruiting or nonrecruiting, and each of the following: noninvasive ventilation (yielded 167 studies) OR high-flow nasal oxygen (yielded 26 studies) OR continuous positive airway pressure (yielded 15 studies). Only 5 studies were RCTs as reported. Additional search on September 15, 2021, in International Clinical Trials Registry Platform and ISRCTN registry, did not yield any additional studies.

(5.0 ± 1.6 vs 4.0 ± 1.0 for those who required intubation; $P = .02$).[56] An ROX index less than 4.94 measured 2 to 6 hours after the start of therapy was associated with increased risk of intubation (HR, 4.03; 95% CI, 1.18–13.7).[56] A multicenter retrospective study of 272 patients with COVID-19 managed with HFNO found that ROX index greater than 3.0 at 2, 6, and 12 hours after initiation of HFNO was 85.3% sensitive for identifying subsequent HFNO success. Another study found that at 6 hours ROX score ≥ 3.7 was 80% predictive of successful weaning, whereas ROX ≤ 2.2 was 74% predictive of failure. A systematic review that included 8 cohort studies (n = 1301 patients) showed that ROX index had a sensitivity of 0.70 (95% CI, 0.59–0.80) and specificity of 0.79 (95% CI, 0.67–0.88) for predicting HNFC failure, resulting in a good discriminatory value, with a summary area under the curve of 0.81 (95% CI, 0.77–0.84).[57]

There is evidence that the ROX index may also predict the success of NIV to avoid delay in intubation.[58] Another index, the HACOR scale, which incorporates heart rate, acidosis, consciousness, oxygenation, and respiratory rate, may also predict NIV failure.[59]

FUTURE DIRECTIONS

Multiple RCTs on noninvasive respiratory support in patients with COVID-19 are ongoing (**Table 2**).[60] These trials are addressing the effectiveness of HFNO, facemask NIV, and helmet NIV. Other studies are needed to evaluate the safety and effectiveness of noninvasive respiratory support outside of the ICU setting and validate the predictors of success or failure of HFNO and NIV.

SUMMARY

HFNO and NIV are used as first-line respiratory support in most patients with AHRF owing to COVID-19. The increasing use during the pandemic was associated with a reduction in the need for invasive mechanical ventilation and mortality, although causal inferences cannot be made. Results from ongoing RCTs are awaited to answer questions regarding the effects of HFNO and NIV on patient-centered outcomes.

CLINICS CARE POINTS

- Both NIV and HFNO are associated with better survival than invasive ventilation in COVID-19. It is not clear if this is cause and effect or merely a reflection of lesser severity of illness.
- Early intubation (<48 hours) seems to result in better outcomes in those who fail NIV and HFNO.
- In one trial, continuous positive airway pressure (CPAP), but not HFNO, resulted in a lower composite endpoint of tracheal intubation or mortality compared to conventional oxygen therapy.
- Data on the effectiveness of helmet NIV compared to mask NIV or HFNO in COVID-19 are limited.
- The risk of nosocomial transmission of COVID-19 is low with NIV or HFNO.

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