Noninvasive respiratory support for acute respiratory failure due to COVID-19

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Purpose of review
Noninvasive respiratory support has been widely applied during the COVID-19 pandemic. We provide a narrative review on the benefits and possible harms of noninvasive respiratory support for COVID-19 respiratory failure.

Recent findings
Maintenance of spontaneous breathing by means of noninvasive respiratory support in hypoxemic patients with vigorous spontaneous effort carries the risk of patient self-induced lung injury: the benefit of averting intubation in successful patients should be balanced with the harms of a worse outcome in patients who are intubated after failing a trial of noninvasive support.

The risk of noninvasive treatment failure is greater in patients with the most severe oxygenation impairment ($\text{PaO}_2/\text{FiO}_2 < 200$ mmHg).

High-flow nasal oxygen (HFNO) is the most widely applied intervention in COVID-19 patients with hypoxemic respiratory failure. Also, noninvasive ventilation (NIV) and continuous positive airway pressure delivered with different interfaces have been used with variable success rates. A single randomized trial showed lower need for intubation in patients receiving helmet NIV with specific settings, compared to HFNO alone.

Prone positioning is recommended for moderate-to-severe acute respiratory distress syndrome patients on invasive ventilation. Awake prone position has been frequently applied in COVID-19 patients: one randomized trial showed improved oxygenation and lower intubation rate in patients receiving 6-h sessions of awake prone positioning, as compared to conventional management.

Summary
Noninvasive respiratory support and awake prone position are tools possibly capable of averting endotracheal intubation in COVID-19 patients; carefully monitoring during any treatment is warranted to avoid delays in endotracheal intubation, especially in patients with $\text{PaO}_2/\text{FiO}_2 < 200$ mmHg.

Keywords
acute respiratory failure, awake prone position, COVID-19, high flow nasal oxygen, noninvasive respiratory support

INTRODUCTION
The optimal management of hypoxemic respiratory failure is debated. Most recent guidelines suggest caution in using noninvasive respiratory support – namely high-flow nasal oxygen (HFNO), noninvasive ventilation (NIV) or continuous positive end-expiratory pressure (CPAP) – for the early treatment of hypoxemic respiratory failure due to COVID-19 [1] and non-COVID-19 etiology [2]. Early endotracheal intubation has been advocated in the early phases of the pandemic to limit the risks related to prolonged exposure of injured lungs to the potential harms of intense inspiratory efforts and high tidal volumes [3].

However, intubation with invasive mechanical ventilation can lead to serious complications, including ventilator-induced lung injury, intensive
KEY POINTS

- Maintenance of spontaneous breathing hypoxic patients carries the risk of patient self-induced lung injury, but avoidance of intubation can lead to improved outcomes.
- High-flow nasal oxygen is the most widely applied intervention for the treatment of hypoxic respiratory failure due to COVID-19.
- Helmet NIV and Helmet CPAP allow to improve blood oxygenation and deliver high-PEEP in the early phases of respiratory failure; to date only one randomized controlled trial supports the use of Helmet NIV compared to high-flow nasal oxygen.
- Awake prone position is a promising, physiologically sound, cost-effective intervention; one randomized controlled trial showed its possible positive effects in reducing the need for endotracheal intubation.
- The benefit of averting intubation by means of noninvasive respiratory support should be balanced with the harms of a worse outcome in patients who are intubated after failing a trial of noninvasive support, warranting careful monitoring of treated patients.

Respiratory system

Patients with hypoxic respiratory failure often show dysregulated respiratory drive. The harmful effects of spontaneous breathing with intense inspiratory effort can result in self-induced lung injury (P-SILI). P-SILI may worsen the clinical outcome of patients who require endotracheal intubation after having received noninvasive respiratory support [10,11].

As the debate remains open, we searched MEDLINE-PubMed databases for the relevant articles (up to August 2021) assessing the physiological and clinical effects of noninvasive respiratory support in patients with acute respiratory failure of COVID-19 etiology.

In this review, we provide an overview of the available evidence regarding the use of noninvasive respiratory support in COVID-19 patients, highlighting its benefits and potential risks.

PATIENT SELF-INDUCED LUNG INJURY

In hypoxic respiratory failure, lung injury yields altered respiratory mechanics and increased dead space; inflammation combined to biochemical stimuli induced by hypoxemia, respiratory acidosis with hypercarbia, and the ‘chemomechanical’ variations due to atelectasis and alveolar derecruitment increase patient’s ventilatory demand. This results in a shift of brain homeostasis toward a lower level of PaCO₂, which can cause spontaneous ventilation with high inspiratory effort, large tidal volumes and tachypnea, leading to abnormal inspiratory swings of pleural pressure and consequent increment of the transpulmonary pressure (alveolar pressure – esophageal pressure as a surrogate of the pleural pressure). As a consequence, baro-, volu- and atelec-trauma are generated. These mechanisms lead to the progression of lung injury [12*,13*,14–18]. Additionally, the increase in transmural pressure of lung vessels combined with their increased permeability concur to alveolar flooding and negative pressure pulmonary edema [15,19].

Under this scenario, the damaged lung can exhibit two distinct patterns: the healthy lung has a more fluid-like condition in the nondependent regions, whereas the most damaged and atelectatic regions have a solid-like pattern (the dependent regions). The solid-like regions transmit pleural pressure differently from the fluid-like regions, finally generating intra-tidal heterogeneity of transpulmonary pressure. This causes an intra-tidal shift of gas from nondependent regions of the lung to the dependent regions; this occult movement of air is called ‘pendelluft’, and can overstretch dependent lung regions independently from the size of inspired volume, increasing inflammation and regional strain [20].

Delivering high positive end-expiratory pressure (PEEP) during spontaneous breathing might render spontaneous effort noninjurious through different mechanisms: (1) it increases functional residual capacity, reducing the extension of atelectatic regions, finally decreasing the mechanical stimuli yielding the increase of respiratory drive, (2) it yields diaphragmatic uncoupling, reducing the inspiratory effort, (3) it limits the occurrence of pendelluft phenomenon by favoring a more homogeneous transmission of the pleural pressure across the lung tissue [12*,21,22].

Although these considerations may advocate against the use of noninvasive respiratory support, it appears that patients with hypoxic respiratory failure due to COVID-19 exhibit average lower inspiratory effort than non-COVID-19 patients with similar oxygenation impairment, possibly indicating a reduced risk of P-SILI [23].

Available data indicate that, in patients with PaO₂/FiO₂ > 200mmHg, noninvasive respiratory support is safe and effective. Differently, in patients...
with \( \text{PaO}_2/\text{FiO}_2 \leq 200 \text{mmHg} \), the best balance between the benefits and harms of maintaining spontaneous breathing with noninvasive respiratory support has yet to be identified [8,24]. When considering a noninvasive respiratory support trial, the optimal strategy should aim to limit the risk of endotracheal intubation, without increasing the risk of P-SILI: [25] this is of particular importance given the high failure rate of noninvasive respiratory support in COVID-19 hypoxemic respiratory failure when compared to non-COVID-19 patients [26*].

**HIGH-FLOW NASAL OXYGEN**

HFNO is a technique that delivers high flow rates (60L/min) of humidified and heated oxygen at adjustable FiO\(_2\) through nasal cannula. HFNO allows (1) accurate delivery of the set FiO\(_2\) by limiting dilution of inhaled gas, (2) provides carbon dioxide washout of the upper airways and reduction of physiological dead space when the flow rates is > 30 L/min (3) and variable PEEP that increases with flow rates, ultimately reducing inspiratory effort [27,28].

A randomized trial showed that HFNO might reduce intubation rate and mortality in moderate-to-severe hypoxemic respiratory failure when compared to low flow oxygen and face mask NIV [24], and the latest guidelines [2,29] suggest HFNO as the optimal first line intervention to correct hypoxemia during de novo respiratory failure.

Despite the initial concerns about the risk of viral aerosolization and transmission to healthcare workers – that can be mitigated by a surgical mask on top of high-flow nasal cannula, which also improves oxygenation [30]—HFNO has been widely applied in patients with acute respiratory failure due to COVID-19 in heterogeneous clinical scenarios, with highly variable outcomes in terms of endotracheal intubation and mortality rate [31–37] (Table 1).

In ICU and non-ICU settings, patients with COVID-19 and \( \text{PaO}_2/\text{FiO}_2 \) ratio < 300 mmHg have been treated with HFNO, showing rates of endotracheal intubation and mortality rate as low as 0% in very mild patients [38] up to a failure rate as high as 80% in the most severe ones [39,40**] (Fig. 1a).

Indeed, during the COVID-19 pandemic, HFNO has shown a great efficacy in patients with a \( \text{PaO}_2/\text{FiO}_2 \) ratio > 200 mmHg [38,41], whereas it may be associated to higher risk of failure when \( \text{PaO}_2/\text{FiO}_2 < 200 \text{mmHg} \) [42–45].

Overall, available data indicate that HFNO in COVID-19 patients with acute respiratory failure do not increase mortality rate and may be an effective strategy in mild-to-moderate cases to reduce the need for mechanical ventilation and critical care support [46,47].

As any other form of noninvasive respiratory support, HFNO should be applied under strict clinical monitoring to promptly detect treatment failure and reduce the risks related to delayed endotracheal intubation, P-SILI and poor prognosis. The ROX index, which is the SpO\(_2\) normalized to FiO\(_2\) times respiratory rate has been validated in the non-COVID setting [48], has been examined by several authors to be adapted to COVID-19 patients. Preliminary data show that ROX index in COVID-19 patients could be a simple marker to predict the risk of HFNO failure and could be used to prevent the delay in endotracheal intubation: however, different thresholds have been suggested, ranging from 3.67 to 5.37, and the optimal cut-off for COVID-19 patients remains to be clarified [42–44,47,49].

**NONINVASIVE VENTILATION**

NIV has progressively been identified in the last 20 years as valid treatment in the management of acute respiratory failure.

Specific indications are exacerbation of chronic obstructive pulmonary disease, cardiogenic pulmonary edema, pneumonia in immunocompromised patients and weaning of previously intubated stable patients with chronic obstructive pulmonary disease.

Conversely, in the treatment of hypoxemic respiratory failure, NIV use has been associated with conflicting results, and the most recent guidelines suggest caution in its application [2,29]. Clinical outcome improves when NIV allows to avoid endotracheal intubation. Differently, if intubation is needed after NIV, mortality is increased, possibly due to delayed intubation and the prolonged exposure of injured lungs to P-SILI [50].

In the recent years, various interfaces have been used, as face (or oro-nasal/full-face) mask, nasal masks, mouthpieces, nasal pillows or plugs, and helmet; each has its own peculiarities and pitfalls, that must be part of the clinician’s evaluation.

NIV improves oxygenation, reduces dyspnea, inspiratory effort and work of breathing [51], and might reduce the rate of endotracheal intubation and ICU mortality rate [52**]; however, in case of failure, it leads to delayed intubation, worsening clinical outcome [50].

Oro-nasal or full-face masks, when compared to the helmets, allow greater unloading of respiratory muscles [53], unless specific settings – including high PEEP, high-pressure support and low pressurization time – are used [54].

The helmet allows to deliver relatively high PEEP with minimum air leakage and good
### Table 1. Clinical trials of HFNO in acute hypoxemic respiratory failure of COVID-19 etiology

| Publication | PMID          | Study design           | Setting                        | Patient Population                  | Treatment                   | Intubation Rate | Mortality Rate | Main finding                                                                 | Secondary findings                                                                                                                                 |
|------------|---------------|------------------------|--------------------------------|-------------------------------------|-----------------------------|-----------------|----------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Bonnet et al. [47], 2021 | 33638752      | Retrospective multicenter study | ICU                            | COVID-19 AHRF                      | HFNO n = 62                | SOT 7.4% [95% CI 7.0 to 7.8] | HFNO 16% [95% CI 9.0 to 26] | HFNO oxygen for AHRF due to COVID-19 is associated with a lower rate of invasive mechanical ventilation compared to SOT | Mortality and ICU LOS did not differ. The number of VFD was lower in the HFNO group. A ROX index higher than 4.88 and higher SAPSII were associated with IMV use. |
| Chandel et al. [49], 2021 | 33328179      | Multicentered retrospective study | Mixed population                | COVID-19 AHRF                      | HFNO n = 272              | 40% [95% CI 34 to 46] | No-HFNO 72% [95% CI 64 to 79] | Prolonged usage of HFNO was not associated with worse clinical outcomes compared to SOT. | The ROX index was sensitive for the identification of subjects who were successfully managed with HFNO and a cut off of 3.67 or 12 h was identified. |
| Demoule [31], 2020          | 32758000      | Retrospective study     | ICU                            | COVID-19 AHRF                      | Matched sample: HFNO n = 113 | 17% [95% CI 13 to 21] | No-HFNO 22% [95% CI 16 to 30] | HFNO significantly reduces intubation and subsequent invasive mechanical ventilation compared to standard oxygen therapy, but does not affect case fatality. | Awake PP reduces the proportion of patients intubated or dying within 28 days of enrolment. 223 (40%) in the awake PP group vs 257 (45%) in the standard of care. F = 0.007, relative risk reduction 0.86 (95% CI 0.75 to 0.98). Patients that received PP for longer sessions had lower treatment failure rate. |
| Brimme et al. [128], 2021   | 34425027      | Prospective collaborative randomized controlled meta trial, Mixed setting | COVID-19 AHRF SpO2/FiO2: awake PP: 147/9 (43.9) | All patients treated with HFNO SpO2/FiO2: standard care 148.6 (43.1) | Awake PP: n = 564            | HFNO 55% [95% CI 46 to 63] | No-HFNO 72% [95% CI 64 to 79] | Awake PP 31% [95% CI 18 to 47] | Awake PP significantly improves blood gas analysis, respiratory rate and ROX index during PP. The benefit was maintained after supination. |
| Franco et al. [67], 2020    | 32747398      | Retrospective multicenter study | Non-ICU COVID-19 AHRF | HFNO n = 163 | CPAP Failure 47% [95% CI 42 to 53] | 30 day mortality: HFNO 16% [95% CI 11 to 20] | Noninvasive respiratory support outside of ICU is feasible, and mortality rate compare favourably with previous reports. There was no difference among the interfaces at the adjusted analysis. | Noninvasive respiratory support was associated with risk of staff contamination. |
| Gaulin et al. [87], 2020    | 32984836      | Retrospective, multicenter study | ICU                            | COVID-19 AHRF SpO2 < 92% with 6 min nasal cannula Body mass index, kg/m2, mean (sd) 22 – 32.5 (8.6) | Helmet CPAP 117 | 56% [95% CI 48 to 64] | CPAP 30% [95% CI 26 to 35] | Noninvasive respiratory support was associated with risk of staff contamination. |
| Gegg et al. [37], 2020      | 32295710      | Case series             | Non-ICU COVID-19 AHRF          | HFNO n = 8 | 0% [95% CI 0 to 32] | Death of 7 days: HFNO 19% [10 to 32] | HFNO is safe and effective in mild AHRF of COVID-19 etiology | Noninvasive respiratory support was associated with risk of staff contamination. |
| Publication Details | PMID | Study design | Setting | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main finding | Secondary findings |
|---------------------|------|--------------|---------|--------------------|-----------|----------------|---------------|--------------|--------------------|
| Grinao et al. [70](#) | 33764378 | Randomized controlled multicenter trial | ICU | COVID-19 AHF due to AHRF | Helmet NIV n = 54 | Continuous treatment PEEP 12 [10–12] cmH2O Pressure Support 10 [10–12] cmH2O | HFNO n = 55 | Helmet NIV 30% [95% CI 19 to 40] | Helmet NIV alone do not affect respiratory support free days. |
| Hernandez-Romieu et al. [30], 2020 | 32804790 | Retrospective study | ICU | COVID-19 AHRF | Helmet NIV 30% | Only IMV n = 97 | HFNO n = 109 | Helmet NIV 22% [95% CI 15 to 31] | A trial of noninvasive respiratory support, including HFNO, in an attempt to avoid intubation, is not associated with increased mortality. Modern nomogram and online calculator are simple to use and able to predict the risk of failure in patients with COVID-19 treated with HFNO and NIV. |
| Liu et al. [40](#) | 33573999 | Retrospective multicentre study | ICU | COVID-19 AHRF | Helmet NIV 24% | Only IMV 40% [95% CI 31 to 50] | HFNO n = 56 | Helmet NIV 49% [95% CI 44 to 54] | Use of noninvasive respiratory support is not associated with worse pulmonary compliance and oxygenation among those who eventually require mechanical ventilation. |
| Mellado-Artigas et al. [33], 2021 | 33573680 | Prospective observational study | ICU | COVID-19 AHRF | Helmet NIV 21% | Only IMV 24% [95% CI 17 to 33] | HFNO n = 61 | Helmet NIV 22% [95% CI 17 to 32] | The nomogram and online calculator are simple to use and able to predict the risk of failure in patients with COVID-19 treated with HFNO and NIV. |
| Montiel et al. [30], 2020 | 32990864 | Prospective observational study | ICU | COVID-19 AHRF | Helmet NIV 21% | Only IMV 21% [95% CI 12 to 32] | HFNO n = 21 | Helmet NIV 49% [95% CI 44 to 54] | Mortality was not different in the patients that were intubated early and in the patients that failed HFNO. |
| Panadero et al. [44], 2020 | 32983456 | Retrospective study | NonICU | COVID-19 AHRF | Helmet NIV 39% | Only IMV 39% [95% CI 33 to 45] | HFNO n = 40 | Helmet NIV 52% [95% CI 37 to 67] | A surgical mask placed on patient's face already treated by a HFNO device would offer an advantage in terms of oxygenation in COVID-19 patients admitted in ICU with severe AHRF. |
| Rask et al. [12](#) | 34127046 | Multicenter randomized clinical trial | NonICU | COVID-19 AHRF | Standard care n = 39 | No intervention | HFNO standard care n = 29 | Helmet NIV 8% [95% CI 3 to 20] | Nine patients (23%) in the control group had pressure scores compared with two patients (6%) in the prone group, P = 0.03, there were no differences in the use of NIV, vasopressors, continuous renal replacement therapy, ECMO, VFD, hospital and ICU length of stay and mortality among the two groups. |
| Publication | PMID | Study design | Setting | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main finding | Secondary findings |
|-------------|------|--------------|---------|-------------------|-----------|----------------|---------------|-------------|-------------------|
| Suliman et al. [43], 2021 | 33471350 | Diagnostic research | Mixed population | COVID-19 AHRF at intubation PaO$_2$/FiO$_2$ 91 [60–110] | HFNO n = 69 | 5% [95% CI 1.48 to 70] | Not reported | ROX index is a simple noninvasive promising tool for predicting discontinuation of high-flow oxygen therapy and could be used by clinicians in the assessment of progress and the risk of intubation in COVID-19 patients with pneumonia | The ROX index on the 1st day of admission was significantly associated with the presence of comorbidities, COVID-19 clinical classification, CT findings and intubation |
| Vega et al. [34], 2021 | 34049831 | Retrospective analysis of prospectively collected data | Non-ICU COVID-19 AHRF | HFNO n = 120 | 29% [95% CI 21 to 38] | 7.5% [95% CI 4 to 14] | ROX index with cut off of 5.99 may be useful in guiding clinicians in their decision to intubate patients especially in moderate acute respiratory failure treated outside ICU | Among the components of the index, PaO$_2$/FiO$_2$ had greater predictive value |
| Vianello et al. [35], 2020 | 32703883 | Retrospective study | ICU COVID-19 AHRF | HFNO n = 28 | Rescue NIV n = 9 | NIV settings, interfaces, and whether CPAP is codified as NIV is not reported | HFNO failure 3.2% [95% CI 1.8 to 5.1] | HFNO can be considered an effective and safe means to improve oxygenation in less severe forms of AHRF secondary to COVID-19 not responding to conventional oxygen therapy | Severity of hypoxemia and C reactive protein level were correlated with HFNO failure |
| Wong et al. [41], 2020 | 32232885 | Retrospective study | Mixed population | COVID-19 AHRF PaO$_2$/FiO$_2$ 209 [179–376] in success patients PaO$_2$/FiO$_2$ < 142 [130–186] in failure patients | HFNO n = 17 | only IMV n = 1 | only NIV n = 9 | rescue NIV n = 7 | First line NIV failure 11% [2 to 42] | rescue NIV failure 29% [8 to 64] | HFNO was the most common ventilation support for patients, and rescue NIV was often used in case of HFNO failure | Patients with lower PaO$_2$/FiO$_2$ were more likely to experience HFNO failure |
| Wong et al. [34], 2020 | 32267160 | Retrospective study | ICU | SpO$_2$/FiO$_2$ in the overall cohort 279 [157–328] IMV n = 100 | HFNO 66% [95% CI 49 to 79] | HFNO failure 77% [95% CI 61 to 88] | Not reported | Older patients with comorbidities are at increased risk of mortality. Real-time monitoring of SpO$_2$/FiO$_2$ and regular measurements of lymphocyte count and inflammatory markers may be essential to disease management | A total of 128 out of 145 (88.3%) patients who developed ARDS died at or before 28 days. |
| Wendel Garcia et al. [36], 2021 | 34034782 | Retrospective subanalysis of data | ICU COVID-19 AHRF | SOT n = 87 | HFNO n = 87 | HFNO n = 92 | HFNO 80% [95% CI 64 to 93] | A trial of HFNO appeared to be the most balanced initial respiratory support strategy. | Compared to the other respiratory support strategies, NIV was associated with a higher overall ICU mortality P = 0.16 and should be avoided. |
| Xia et al. [46], 2020 | 32826432 | Retrospective multicenter study | Mixed population COVID-19 AHRF PaO$_2$/FiO$_2$ available in only 12 patients 122 [51] | HFNO n = 43 | 30% [95% CI 19 to 45] | HFNO failure 47% [95% CI 33 to 61] | 3.2% [95% CI 20 to 48] | Early HFNO may be an effective respiratory support modality for COVID-19 patients with mild to moderate AHRF, most severe cases need IMV or NIV | Male and lower oxygenation at admission were the two strongest predictors of HFNO failure. |
| Publication          | PMID         | Study design            | Setting          | Patient Population | Treatment | Intubation Rate | Mortality Rate     | Main Finding                                                                                                                                            | Secondary Findings                                                                                                                                   |
|---------------------|--------------|-------------------------|------------------|--------------------|------------|-----------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Yang W. et al. [39], 2020 | 32267160     | Retrospective study     | ICU               | COVID-19 AHRF       | HFNO n = 35 | NIV n = 34       | IMV n = 100   | Older patients with comorbidities are at increased risk of mortality. Real-time monitoring of S/F and regular measurements of lymphocyte count and inflammatory markers may be essential to disease management. | A total of 128 out of 145 (88.3%) patients who developed ARDS died at or before 28 days.                                                                 |
| Yang X. et al. [66], 2020 | 32105632     | Retrospective study     | ICU               | PaO<sub>2</sub>/FiO<sub>2</sub> in survivors | HFNO n = 33 | NIV n = 29       | IMV n = 22     | The progression among the interfaces is not reported.                                                                                                       | Among 52 critically ill patients with COVID-19 infection, 32 (61.5%) patients had died at 28 days.                                                                 |
| Zhou et al. [37], 2020 | 32171076     | Retrospective multicenter study | Mixed Population | PaO<sub>2</sub>/FiO<sub>2</sub> at enrollment is not reported | HFNO n = 41 | NIV n = 26       | IMV n = 32     | Older, high SOFA score, and d-dimer greater than 1 µg/mL could help clinicians to identify patients with poor prognosis at an early stage. | Noninvasive respiratory support and invasive mechanical ventilation have high mortality rate.                                                                 |
| Zucman et al. [42], 2020 | 32671470     | Retrospective study     | ICU               | COVID-19 AHRF       | HFNO n = 60 | 65% [95% CI 52 to 76] | IMV = 60     | Early application of NHF as first-line ventilatory support during COVID-19-related AHRF may have obviated the need for intubation in up to a third of cases. | The ROX index measured within the first 4 h after NHF initiation could be an easy-to-use marker of early ventilatory response.                                                                 |

Values are displayed as means (SD) or medians [Interquartile range].

Failure was defined as either intubation, death while still on noninvasive respiratory support, or escalation to other noninvasive respiratory support to avoid endotracheal intubation. AHRF, acute hypoxemic respiratory failure; ARDS, acute respiratory distress syndrome; awake PP, awake prone position; CPAP, continuous positive end-expiratory pressure; FiO<sub>2</sub>, fraction of inspired oxygen; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IQR, interquartile range; NIV, noninvasive ventilation; PaO<sub>2</sub>, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; SpO<sub>2</sub>, peripheral capillary oxygen saturation; VFD, Ventilatory Free Days.
tolerability, allowing the patient to receive continuous treatments with enhanced comfort [55]; this is particularly important in the early phases of hypoxemic respiratory failure, when high PEEP seems a promising tool to mitigate the risk of P-SILI [21,56,57].

In 2016, a randomized study showed lower intubation rate and improved outcome in hypoxemic patients treated with helmet NIV vs those treated with face-mask NIV; whereas patients with helmet received a median sustained PEEP of 8 cmH$_2$O, patients treated with face mask received a median PEEP of 5.1 cmH$_2$O [58].

During the COVID-19 pandemic, NIV has been used both as a first-line therapy and as rescue therapy after HFNO, in patients with wide range of severity [59–65] (Table 2).

NIV showed variable success rates during the pandemic, possible due to the heterogeneous interfaces, settings and protocols applied; Wang et al. report a failure rate of 11% in mild-to-moderate patients when NIV is used as first-line therapy.

**FIGURE 1.** Panel reporting the failure rate [95% CI] of patients with hypoxemic respiratory failure treated with noninvasive respiratory support. Failure rate was defined as occurrence of endotracheal intubation or death. Only the patients without limitation of treatment were considered for the figure. Except from the bottom – right figure, nonrandomized studies including awake prone position were excluded from the figure, due to the possible selection bias of patients treated with conventional therapy. The studies with the bigger sample size are displayed at the top of the figure. (a) Forest plot of patients treated with HFNO in the supine position. (b) Forest plot of patients treated with NIV as first line of therapy. (c) Forest plot of patients treated with CPAP as first line of therapy. (d) Forest plot of patients treated with awake prone position, regardless of the kind of noninvasive respiratory support used. *It was not possible to differentiate between CPAP and NIV that were both considered as noninvasive respiratory support. CPAP, continuous positive end-expiratory pressure; HFNO, high-flow nasal oxygen; NIV, noninvasive ventilation.*
Table 2. Clinical trials of NIV in acute hypoxemic respiratory failure of COVID-19 etiology

| Publication | PMID    | Study design          | Setting                 | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main finding                                                                 | Secondary findings                                                                                                           |
|------------|---------|-----------------------|-------------------------|--------------------|-----------|-----------------|----------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Bellani et al. [59], 2021 | 33727235 | Observational prospective registry | COVID-19 AHRF | NIV = 390 NIV settings, interfaces, and whether CPAP is codified as NIV is not know | NIV failure 44% [95% CI 40 to 49] | Overall cohort 38% [95% CI 33 to 43] | NIV may have a significant role in supporting patients with COVID-19-related respiratory failure. It effectively supported and prevented the need for intubation of more than half of those treated. Those failing had a very poor in-hospital survival rate. | After adjustment, age, hypertension, room air \(\text{SpO}_2\), at presentation, lymphopenia, in-hospital use of antibiotics were independently associated with NIV failure. |
| Burns et al. [78], 2020 | 32624494 | Retrospective study | Non-ICU | COVID-19 AHRF \(\text{SpO}_2 < 94\%\) in Venturi Mask | Not reported | BIPAP 40% [95% CI 12 to 77] | CPAP 52% [33 to 71] | Ward based noninvasive respiratory is a good treatment option, with a mortality around 50%. | The only statistically significant difference between survivors and nonsurvivors was the presence of “classical” radiological imaging appearances, \(P=0.034\). |
| Duca et al. [60], 2020 | 33222116 | Retrospective study | Non-ICU | COVID-19 AHRF \(\text{PaO}_2/\text{FiO}_2\) 131 [97–190] NIV \(\text{PaO}_2/\text{FiO}_2\) 87 (53–120) IMV at arrival \(\text{PaO}_2/\text{FiO}_2\) 76 (50–177) | CPAP failure rate 3.7% [95% CI 2.6 to 4.8] | Overall cohort 76% [95% CI 65 to 84] | CPAP failure occurred in a high percentage of patients. | | |
| Faraone et al. [61], 2020 | 33222116 | Retrospective study | Non-ICU | COVID-19 AHRF \(\text{PaO}_2/\text{FiO}_2\) 130 (69) | NIV n = 25 | IMV at arrival 100% [95% CI 65 to 100] | CPAP failure in patients with limitations of treatment was used in both intubated and non-intubated patients. | The rate of infection among healthcare workers was low. |
### Table 2 (Continued)

| Publication | PMID | Study design | Setting | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main finding | Secondary findings |
|-------------|------|--------------|---------|--------------------|-----------|-----------------|---------------|---------------|-------------------|
| Franco et al. [62-64], 2020 | 32747398 | Retrospective multicenter study | Non-ICU | COVID-19 AHRF | HFNO n = 163 CPAP n = 330 RECP 102 (146) cmH2O Helmet 149 (99%) Face mask 2 (1%) NIV n = 177 RECP 95 (2.2) cmH2O Pressure Support 172 (3) cmH2O Helmet 15 (21%) Face mask 57 (7%) | 30 day mortality: HFNO 29% [95% CI 24 to 34] CPAP 25% [95% CI 20 to 30] NIV 28% [95% CI 22 to 35] HFNO Failure 38% [CI 31 to 47] CPAP Failure 47% [95% CI 42 to 53] NIV Failure 53% [95% CI 46 to 60] | Noninvasive respiratory support outside of ICU is feasible, but mortality rates compare favourably with previous reports. There was no difference among the interfaces at the adjusted analysis. | Noninvasive respiratory support was associated with risk of staff contamination. |
| Fu et al. [62], 2021 | 34109190 | Retrospective study | Mixed population | COVID-19 AHRF | HFNO as initial therapy n = 22 HFNO as rescue therapy n = 17 RECP in NIV success: 6 (6–7) RECP in NIV failure: 6–6.3 Pressure Support in NIV success: 7 (6–7) Pressure Support in NIV failure: 6–6.3 | 30 day mortality: HFNO 23% [95% CI 10 to 43] HFNO as rescue therapy 46% [95% CI 41 to 83] | HFNO initial therapy 5% [95% CI 8 to 22] HFNO as rescue therapy 12% [95% CI 3 to 34] | Close attention should be paid to patients with PaO2/FiO2 < 200 mmHg after 1–2 h of NIV. | Using NIV as rescue therapy after HFNO failure is associated with higher risk of IOT and detrimental outcomes. |
| Giacco et al. [70], 2021 | 33764378 | Randomized controlled multicenter trial | ICU | COVID-19 AHRF | HFNO n = 54 Continuous treatment RECP 12 (10–12) cmH2O Pressure Support 10 (10–12) cmH2O Helmet NIV n = 55 | 30 day mortality: HFNO 44% [95% CI 38 to 64] NIV 62% [95% CI 55 to 69] | HFNO 22% [16 to 38] NIV 50% [15 to 75] | Helmet NIV = HFNO or HFNO alone do not affect respiratory support free days. | Helmet NIV reduces rate of ETI and increases invasive VFD at day 28. |
| Hu et al. [63, 2020 | 32546258 | Retrospective, multicenter study | ICU | COVID-19 AHRF | SO2 n = 204 IMV n = 113 NIV n = 152 NIV settings, interfaces, and whether CPAP is codified as NIV is not reported | 30 day mortality: SO2 6% [95% CI 4 to 11] IMV 92% [95% CI 86 to 96] NIV 41% [95% CI 33 to 49] | Patients who were invasively ventilated exhibited pessimistic outcomes. | | |
| Karagkaidis et al. [66-68], 2020 | 32735842 | Retrospective, nationwide study | Mixed population | COVID-19 AHRF | NIV n = 286 IMV only n = 1318 NIV settings, interfaces, and whether CPAP is codified as NIV is not reported | 30 day mortality: NIV failure 49% [95% CI 44 to 55] NIV Failure 51% [95% CI 45 to 55] IMV only 53% [95% CI 50 to 55] | In the German health-care system, in which hospital capacities have not been overwhelmed by the COVID-19 pandemic, mortality has been high for patients receiving mechanical ventilation. | Mortality in patients aged 80 or older was 72%. |
| Liu et al. [69], 2021 | 33573999 | Retrospective multicenter study | ICU | COVID-19 AHRF | HFNO n = 366 IMV n = 286 NIV settings, interfaces, and whether CPAP is codified are NIV is not reported | 30 day mortality: HFNO 56% [95% CI 51 to 61] NIV 74% [95% CI 68 to 78] | HFNO 49% [95% CI 44 to 54] NIV 62% [95% CI 56 to 67] | The nomogram and online calculator are simple to use and able to predict the risk of failure in patients with COVID-19 treated with HFNO and NIV. | Age, number of comorbidities, ROC index, Glasgow coma scale score, and use of vasopressors on the first day of noninvasive respiratory support were independent risk factors for noninvasive respiratory support failure. |
| Publication                      | PMID       | Study design            | Setting   | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main finding                                                                 |
|---------------------------------|------------|-------------------------|-----------|--------------------|-----------|-----------------|----------------|-----------------------------------------------------------------------------|
| Mentaella et al. [64], 2021      | 33278822   | Retrospective cohort study | NonICU    | COVID-19 ARF       | NIV n=79 PEEP: 9.46 (2.37) cmH2O IPAP: 17.7 (2.2) cmH2O | ETI rate after the exclusion of patients with limitations of treatment and 2 sudden deaths 36% [95% CI 25 to 48] NIV failure in the overall cohort 52% [95% CI 41 to 65] | Morality in the 20 intubated patients was 43% [95% CI 25 to 63] 18 (23%) patients had patients with limitations of treatment 2 (3%) patients died of sudden death | NIV was effective in almost half of the patients. At a multivariate Cox regression model only SOFA score at admission was significantly associated with the risk of failure. |
| Mukhtar et al. [65], 2020        | 32738030   | Retrospective study      | ICU       | COVID-19 ARF       | NIV n=39 NIV settings, interfaces, and whether CPAP or HFNO are codified as NIV is not reported | Need for ETI 23% [13 to 38] NIV failure 31% [95% CI 19 to 46] | 26% [1.5 to 41] | The use of NIV was successful in 77% of patients.                          |
| Rosén et al. [127], 2021         | 34127046   | Multicenter randomized clinical trial | NonICU    | COVID-19 ARF       | HFNO standard care n=29 HFNO prone n=31 NIV standard care n=27 PEEP 8 [6-8] NIV prone n=21 PEEP 7 [6-10] | Standard care group 3.3% [95% CI 20 to 49] Prone group 3.3% [95% CI 20 to 50] | Control group 8% [95% CI 3 to 20] Prone group 17% [95% CI 8 to 22] | The implementation protocol for awake PP increased duration of awake PP but did not reduce the rate of intubation in patients with ARHF due to COVID-19 compared to standard care. |
| Sivaganganathan et al. [73], 2020 | 32811682  | Retrospective Study      | Mixed population | COVID-19 ARF Waste PaO2/FiO2 ratio: NIV only: 127.5 [107-153] NIV = MV: 104.26 [96-126] IMV only: 115 [92-134] NIV = limitations of treatment: 75 [61-104] | NIV only n=31 NIV = MV: n=27 IMV only n=21 NIV-limitions of treatment n=24 NIV settings, interfaces, and whether CPAP is codified as NIV is not reported | Patients with no limitations of treatment: 47% [95% CI 34 to 59] Patients with no limitations of treatment: 3% [95% CI 2 to 14] Patients with limitations of treatment: 83% [95% CI 64 to 93] | Patients with no limitations of treatment: 5% [95% CI 2.1 to 14] | The use of NIV and has low failure and mortality rate especially in patients with no limitations of treatment. NIV is safe and has low failure and mortality rate especially in patients with no limitations of treatment.|
| Vianello et al. [35], 2020       | 32703883   | Retrospective study      | ICU       | COVID-19 ARF       | HFNO n=28 Resuce NIV n=9 NIV settings, interfaces, and whether CPAP is codified as NIV is not reported | HFNO failure 32% [95% CI 18 to 51] Rescue NIV failure 56% [95% CI 27 to 81] (ETI 16% [95% CI 8 to 36] | 11% [95% CI 4 to 27] | HFNO can be considered an effective and safe means to improve oxygenation in less severe forms of ARHF secondary to COVID-19 not responding to conventional oxygen therapy | The only variable associated with risk of intubation was admission SOFA |
| Wang et al. [41], 2020           | 32232685   | Retrospective study      | Mixed population | COVID-19 ARF | HFNO n=17 only IMV n=1 First line NIV n=9 rescue NIV n=7 | HFNO failure and rescue NIV 41% [95% CI 22 to 64] HFNO 12% [95% CI 3 to 34] First line NIV failure 11% [2 to 42] Rescue NIV failure 29% [8 to 64] | Not reported | HFNO was the most common ventilation support for patients, and rescue NIV was often used in case of HFNO failure | Patients with lower PaO2/FiO2 were more likely to experience HFNO failure |
| Publication | PMID | Study design | Setting | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main finding | Secondary findings |
|-------------|------|--------------|---------|--------------------|-----------|----------------|---------------|--------------|--------------------|
| Wendel García et al. [36], 2021 | 34034782 | Retrospective subanalysis of data | ICU | COVID-19 AHRF | PaO\(_2\)/FiO\(_2\) 123 [92, 167] | SOT n = 87 | HFNO n = 87 | NIV n = 87 | MV n = 92 | SOT 64% [95% CI 53 to 63] | HFNO 52% [95% CI 41 to 62] | NIV 49% [95% CI 39 to 60] | SOT 18% [95% CI 11 to 27] | HFNO 20% [95% CI 13 to 29] | NIV 37% [27 to 47] | A trial of HFNO appeared to be the most balanced initial respiratory support strategy. | Compared to the other respiratory support strategies, NIV was associated with a higher overall ICU mortality, P = 0.016 and should be avoided. |
| Yang W. et al. [37], 2020 | 32267160 | Retrospective study | ICU | COVID-19 AHRF | SpO\(_2\)/FiO\(_2\) in the overall cohort 279 [157–328] | HFNO n = 35 | NIV n = 34 | IMV n = 100 | HFNO 66% [95% CI 49 to 79] | HFNO failure 77% [95% CI 61 to 88] | NIV failure 79% [95% CI 63 to 90] | HFNO 80% [95% CI 64 to 92] | NIV 77% [95% CI 61 to 88] | IMV 97% [95% CI 92 to 99] | Older patients with comorbidities are at increased risk of mortality. Real-time monitoring of S/F and regular measurements of lymphocyte count and inflammatory markers may be essential to disease management. | A total of 128 out of 145 (88.3%) patients who developed ARDS died at or before 28 days. |
| Yang X. et al. [66], 2020 | 32105632 | Retrospective study | ICU | COVID-19 AHRF | PaO\(_2\)/FiO\(_2\) at enrollment is not reported | Overall cohort n = 52 | HFNO n = 33 | NIV n = 29 | IMV n = 22 | Not reported | Mortality at 28 days | HFNO 48% [95% CI 32 to 65] | NIV 79% [95% CI 62 to 90] | IMV 86% [95% CI 67 to 95] | Among 52 critically ill patients with SARS-CoV-2 infection, 32 (61.5%) patients had died at 28 days. | Older patients (>65 years) with comorbidities and ARDS are at increased risk of death. |
| Zhou et al. [37], 2020 | 32171076 | Retrospective multicenter study | Mixed Population | PaO\(_2\)/FiO\(_2\) at enrollment is not reported | HFNO n = 41 | NIV n = 26 | IMV n = 32 | NIV settings, interfaces, and whether CPAP is codified as NIV is not know | Not reported | HFNO 80% [95% CI 76 to 90] | NIV 92% [95% CI 96 to 98] | IMV 97% [95% CI 84 to 99] | Older age, high SOFA score, and d-dimer greater than 1 μg/mL could help clinicians to identify patients with poor prognosis at an early stage. | Noninvasive respiratory support and invasive mechanical ventilation have high mortality rate. |

Values are displayed as means (SD) or medians (Interquartile range).

Failure was defined as either intubation, death while still on noninvasive respiratory support, or escalation to other noninvasive respiratory support to avoid endotracheal intubation. AHRF, acute hypoxic respiratory failure; ARDS, acute respiratory distress syndrome; awake PP, awake prone position; CPAP, continuous positive end-expiratory pressure; FiO\(_2\), fraction of inspired oxygen; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IQR, interquartile range; NIV, noninvasive ventilation; PaO\(_2\), partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; SpO\(_2\), peripheral capillary oxygen saturation; VFD, Ventilatory Free Days.
[39], but in the most severe patients it can be as high as 80% [40,66]; to date, the largest observational studies have found consistent failure rates, ranging between 40% and 50% [67,68,69] (Fig. 1b).

Lastly, a randomized controlled trial compared the efficacy of continuous helmet NIV vs HFNO alone in COVID-19 patients affected by moderate-to-severe hypoxemia. In this study, despite the lack of a significant difference on the primary outcome (median days free of respiratory support at 28 days, helmet group 20 [interquartile range (IQR), 0–25] vs HFNO group 18 [IQR, 0–22]), the authors reported a significant difference in the intubation rate (30% in the helmet group vs 51% in the HFNO group; \( P = 0.03 \)), with no difference in mortality [70**].

NIV can be a powerful instrument as optimal settings and adequate interface are provided, but careful selection and strict clinical monitoring of patients are mandatory to reduce the risk of delayed intubation.

**CONTINUOUS POSITIVE AIRWAY PRESSURE**

The use of CPAP in hypoxemic respiratory failure has been proposed more than 20 years ago, but a randomized controlled trial failed to prove its efficacy in reducing the intubation rate in patients with hypoxemic respiratory failure of other etiologies [71].

Nevertheless, in the subsequent years, Helmet CPAP has become increasingly used to increase blood oxygenation and reduce the risk of intubation in patients with moderate-to-severe hypoxemia compared with standard oxygen [72,73].

Traditionally CPAP is provided with a device able to provide high flow rates of fresh gas flow (inlet port) and an adjustable PEEP valve (outlet port), being highly cost-effective in the emergency context and easily used outside the ICU.

CPAP has been adopted to increase blood oxygenation and to avoid endotracheal intubation and as ceiling of treatment in patients with limitation of care: in patients who were not candidate for receiving invasive mechanical ventilation, CPAP has been used as a rescue therapy, with mortality ranging from 0% to 90% [67**,74*,75–85] (Table 3).

In patients where escalation to invasive mechanical ventilation was appropriate, CPAP has been used with encouraging results: largest trials showed a failure rate of the technique ranging between 20% and 40%, mostly depending on hypoxemia severity and patients’ overall clinical condition [67**,69*,80].

When compared to other noninvasive respiratory support strategies or to standard oxygen, early case-series showed a trend to a reduction in the intubation rate in patients treated with CPAP [86,87], but the largest observational trial to date [67**] showed no difference in intubation and mortality rates (Fig. 1c).

Nevertheless, CPAP is a powerful instrument that can be safely used outside of the ICU, with good success in the less severe patients, especially when the Helmet interface is used. However, the increase in the \( \text{PaO}_2/\text{FiO}_2 \) ratio induced by PEEP might generate a false sense of security, possibly causing delays in the decision to intubate the patient: the clinician should pay close attention to the change of physiological variables over time [77,88] and, when available, should consider evaluating diaphragm thickening fraction [89,90] and lung ultrasound [91] to enhance early detection of treatment failure.

**NEW STRATEGIES: AWAKE PRONE POSITIONING**

In moderate-to-severe acute respiratory distress syndrome patients receiving invasive mechanical ventilation, prone positioning improves oxygenation, reduces ventilator-induced lung injury, finally reducing mortality [92**,93,94**].

In the midst of the pandemic, awake prone positioning was initially used on the most severe patients that required noninvasive respiratory support as a rescue strategy to avoid intubation, both in the ICU and in the non-ICU setting.

Prone positioning in spontaneously breathing patients improves oxygenation and lowers inspiratory effort [94**] and respiratory rate, but the improvement is often transient, and only a minority of patients show sustained benefit after resupination [95–123] (Table 4).

Several pilot studies have investigated whether it could improve patient-centered outcomes, but results are conflicting (Fig. 1d). The largest retrospective, multicenter, observational study showed a reduction in the intubation rate in patients who received awake prone position for at least 2 consecutive hours, compared to patients who did not receive this intervention [124**]. Three small, randomized feasibility trials available showed no benefit on endotracheal intubation rate and on mortality [125,126,127**]. In the trial designed by Rosén et al. [127**], the intervention group should have undergone prone positioning for at least 16 h per day, and the control group was allowed both the supine and the prone position, albeit the last one was not actively encouraged; this yielded relevant incidence of cross-over in the control group that, combined with relatively low time spent in prone position in
### Table 3. Clinical trials of CPAP in acute hypoxemic respiratory failure of COVID-19 etiology

| Publication                  | PMID        | Study design              | Setting                        | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main finding                                                                 | Secondary findings                                                                 |
|------------------------------|-------------|---------------------------|--------------------------------|--------------------|-----------|-----------------|----------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Alberti et al. [81], 2020    | 32747395    | Observational prospective multicenter cohort study | High dependency unit         | COVID-19 AHRF      | Helmet CPAP n = 157 PEEP 10.8 (2.3) cmH\(_2\)O 4 cases discontinued CPAP for intolerance | Overall population, CPAP failure 45% [37 to 52] Patients with no limitations of treatment, CPAP failure 37% [95% CI 28 to 47] | Overall cohort 29% [95% CI 22 to 36] Patients with limitations of treatment 55% [95% CI 43 to 67] Patients with no limitations of treatment 10% [95% CI 5 to 18] | CPAP failure was associated with the severity of pneumonia on admission and higher baseline values of interleukin-6. |
| Aliveti et al. [82], 2020    | 33052968    | Retrospective study       | Mixed setting                 | COVID-19 AHRF      | Face Mask CPAP n = 41 PEEP 5–10 cmH\(_2\)O 2 cases discontinued CPAP for intolerance | Overall population, CPAP failure 45% [37 to 52] Patients with no limitations of treatment, CPAP failure 37% [95% CI 28 to 47] | Overall cohort 29% [95% CI 22 to 36] Patients with limitations of treatment 55% [95% CI 43 to 67] Patients with no limitations of treatment 10% [95% CI 5 to 18] | CPAP failure was associated with the severity of pneumonia on admission and higher baseline values of interleukin-6. |
| Arina et al. [79], 2020      | 33196858    | Retrospective study       | ICU                            | COVID-19 AHRF      | CPAP n = 93 CPAP settings are not provided The exact number of patients with limitations of treatment is not provided | Failure in the overall cohort was 66% [55 to 74] 47 [51%] of patients were intubated, while 14 [13%] had CPAP as ceiling of treatment | Overall mortality was 25% [95% CI 22 to 28] Noninvasive respiratory support outside the ICU is feasible and approximately 10% of COVID-19 patients present in the hospital were treated with noninvasive respiratory support, with a predominant use of helmet CPAP | Overall rate of success was > 60% in the overall cohort and 73% in patients with no limitations of treatment. |
| Bellani et al. [69*], 2021   | 33395553    | Single day observational study | Ward                          | COVID-19 AHRF      | NIV = CPAP n = 798 213 [27%] patients with limitations of treatment Helmet was used for 617 patients, face mask for 248 Noninvasive respiratory support initiated 1 [0–4] days after hospital admission PEEP was 10.8 (2.6), ranging from 2 to 20 | Overall mortality was 25% [95% CI 22 to 28] Noninvasive respiratory support outside the ICU is feasible and approximately 10% of COVID-19 patients present in the hospital were treated with noninvasive respiratory support, with a predominant use of helmet CPAP | Overall mortality was 25% [95% CI 22 to 28] Noninvasive respiratory support outside the ICU is feasible and approximately 10% of COVID-19 patients present in the hospital were treated with noninvasive respiratory support, with a predominant use of helmet CPAP | Overall rate of success was > 60% in the overall cohort and 73% in patients with no limitations of treatment. |
| Brusasco et al. [89], 2021   | 33033151    | Retrospective multicenter study | Non ICU                        | COVID-19 AHRF      | CPAP n = 64 PEEP 10 cmH\(_2\)O in all patients | CPAP failure 17% [10 to 28] ETI 11% [9 to 21] | Overall mortality 14% [95% CI 8 to 23] Died on CPAP 6% [95% CI 2 to 15] Died on MV 8% [95% CI 4 to 17] | CPAP was feasible in patients with moderate to severe AHRF | At univariate analysis CPAP failure was associated with sex, hypertension, diabetes, COPD, three or more comorbidities and lung weight, but at multivariate analysis only hypertension remained significant (OR 7.33, 95% CI 1.5 to 34, P < 0.012) |

**Note:** COVID-19 AHRF, acute hypoxemic respiratory failure of COVID-19 etiology; CPAP, continuous positive airway pressure; ETI, extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; PaO\(_2\)/FiO\(_2\), partial pressure of arterial oxygen/fraction of inspired oxygen; NIV, noninvasive ventilation.
| Publication | PMID | Study design | Setting | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main Finding | Secondary Findings |
|-------------|------|--------------|---------|--------------------|-----------|----------------|---------------|-------------|--------------------|
| Burns et al. [78], 2020 | 32624494 | Retrospective study | Non-ICU COVID-19 AHRF | CPAP n = 23 | CPAP n = 5 BIPAP settings: max PEEP 10–12 (2.9) cmH₂O max Pinsp = 22.4 (6) cmH₂O CPAP settings: Max PEEP = 12.7 (2.1) cmH₂O | Not reported | BIPAP 40% [95% CI 12 to 77] | CPAP 52% [33 to 71] | Ward-based noninvasive respiratory support is a good treatment option, with a mortality around 50%. The only statistically significant difference between survivors and nonsurvivors was the presence of “classical” imaging appearances, \( P = 0.034 \). |
| Carteaux et al. [81], 2021 | 33655452 | Retrospective study | Intermediate Care Unit and ICU | COVID-19 AHRF \( \text{PaO}_2/\text{FiO}_2 \geq 160 \) [115–258] | CPAP n = 85 Interface: oronasal mask CPAP was designed with a Boussignac valve protected by a filter, and free flow oxygen rate of 15 l/min [15–15] | Predefined criteria for intubation were present | 27% [95% CI 19 to 37] | Adding a filter to the Boussignac valve does not affect the delivered pressure but may variably increase the resistive load depending on the filter used. | Clinical assessment suggests that CPAP designed with a Boussignac valve and a filter is a frugal solution to provide a ventilatory support and improve oxygenation during a massive COVID-19 outbreak. |
| Coppadoro et al. [77], 2021 | 33627169 | Retrospective multicenter study | Non-ICU COVID-19 AHRF \( \text{PaO}_2/\text{FiO}_2 \geq 103 \) [79–176] | CPAP n = 306 Patients with no limitations of treatment n = 176 Patients with limitations of treatment n = 130 PEEP 10 [7–11] cmH₂O Helmet CPAP was delivered for 21 h/day, for the first 48 h, and from day 3 to 5 for 19 h/day | CPAP failure overall cohort 48% [95% CI 42 to 54] CPAP failure in patients with no limitations of treatment 31% [24 to 38] | Hospital mortality in patients with no limitations of treatment 12% [95% CI 8 to 18] Hospital mortality in patients with limitations of treatment 72% [95% CI 64 to 79] | Treatment of COVID-19 AHRF outside the ICU is feasible with Helmet CPAP, with a mortality rate of 12%, was also used in patients with limitations of treatment, improving survival in almost 1/3 of cases. | CPAP failure was independently associated with C-reactive protein, time to oxygen mask failure, lower \( \text{PaO}_2/\text{FiO}_2 \) during CPAP and number of comorbidities. |
| Corradi et al. [77], 2020 | 33197604 | Single-center pilot study | ICU COVID-19 AHRF \( \text{PaO}_2/\text{FiO}_2 \geq 103 \) [85–246] | Helmet CPAP n = 27 PEEP = 10 cmH₂O | Predefined criteria for intubation | 11% [95% CI 4 to 28] | CPAP failure was significantly associated with diaphragmatic thickening fraction at multivariate analysis, the best threshold was 21.4% | The use of CPAP avoided IMV in more than half of the patients. |
| De vita et al. [80], 2021 | 33500220 | Retrospective multicenter study | High Intensity Unit COVID-19 AHRF \( \text{PaO}_2/\text{FiO}_2 \) success 120 [75–160] \( \text{PaO}_2/\text{FiO}_2 \) failure 103 [60–152] | CPAP n = 367 Helmet was applied in 281 (77%) patients and face mask in 71 (19%) patients. Values from 15 patients were missing. Initial PEEP was 10–12 cmH₂O, to be increased up to 15 cmH₂O | Predefined criteria for intubation | Not reported | In patients treated with CPAP, age, LDH and percentage change in \( \text{PaO}_2/\text{FiO}_2 \) after starting are predictors of intubation. | The use of CPAP avoided IMV in more than half of the patients. |
| Publication | PMID | Study design | Setting | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main finding | Secondary findings |
|-------------|------|--------------|---------|--------------------|-----------|----------------|---------------|--------------|-------------------|
| Duca et al. [60], 2020 | 32766638 | Retrospective study | Non-ICU | COVID-19 AHRF CPAP PaO₂/FiO₂ 131 [97–193] | CPAP n = 71 Helmet CPAP, PEEP = 15 [12–18] cmH₂O NIV n = 7 NIV, PEEP = 16 [12–20] cmH₂O IMW at arrival PaO₂/FiO₂ 76 [60–177] | CPAP intubation rate 37% [95% CI 26 to 48] NIV intubation rate 0% [95% CI 0 to 33] CPAP failure 92% [95% CI 83 to 96] NIV failure 57% [95% CI 25 to 84] | CPAP 76% [95% CI 65 to 84] NIV 57% [95% CI 25 to 84] IMW at arrival 100% [95% CI 65 to 100] | In case of limited resources, the use of early CPAP or NIV in the ward or in the emergency department could be a valid strategy. | CPAP failure occurred in a high percentage of patients. |
| Faraone et al. [61], 2020 | 33222116 | Retrospective study | Non-ICU | COVID-19 AHRF PaO₂/FiO₂ 130 (85) | CPAP n = 25 CPAP intervention full face or oro-nasal mask Duration of treatment in the overall cohort: 167 [18] hours PEEP started at 5 cmH₂O, up to 12 cmH₂O IPAP set at 1.5cmH₂O, up to 30–25 cmH₂O | Patients with no limitations of treatment 36% [95% CI 20 to 55] CPAP failure 44% [95% CI 27 to 63] NIV failure 68% [95% CI 48 to 83] | Patients with limitations of treatment 88% [95% CI 70 to 96] Patients with no limitations of treatment 12% [95% CI 4 to 30] | Noninvasive respiratory support was useful in avoiding intubation in patients with no limitations of treatment. | The rate of infection among healthcare workers was low. |
| Franco et al. [62*], 2020 | 32747398 | Retrospective multicenter study | Non-ICU | COVID-19 AHRF PaO₂/FiO₂ 138 (64) | HFNO n = 163 CPAP n = 330 PEEP 10.2 [1] cmH₂O Helmet 149 [99%] Face mask 2 [1%] NIV n = 177 PEEP 9.5 [2] cmH₂O Pressure Support 17.3 [3] cmH₂O Helmet 15 [21%] Face mask 57 [79%] | Received IMW HFNO 29% [95% CI 24 to 36] CPAP 25% [95% CI 20 to 30] NIV 28% [95% CI 22 to 33] HFNO Failure 38% [CI 31 to 47] CPAP Failure 47% [95% CI 42 to 53] NIV Failure 53% [95% CI 46 to 60] | 30 day mortality: HFNO 16% [95% CI 11 to 22] CPAP 30% [95% CI 26 to 33] NIV 31% [95% CI 24 to 38] Difference not significant | Noninvasive respiratory support outside of ICU is feasible, and mortality rates compare favourably with previous reports. There was no difference among the interfaces at the adjusted analysis. | Noninvasive respiratory support was associated with risk of staff contamination. |
| Gaulton et al. [67], 2020 | 32984836 | Retrospective, multicenter study | ICU | COVID-19 AHRF SpO₂ < 92% with 6l/min nasal cannula Body mass index, kg/m², mean (sd) 35.5 (8.6) | Helmet CPAP n = 17 HFNO n = 42 PEEP 5–10 cmH₂O ETI at 7 days CPAP 18% [6 to 41] HFNO 52% [38 to 67] Death at 7 days CPAP 6% [1 to 27] HFNO 19% [10 to 33] | Pressure Support 17.3 cmH₂O (3) cmH₂O Pressure Support 17.3 cmH₂O | Difference in the intubation rate was significant after adjustment for age. | In obese patients Helmet CPAP is effective in reducing the ETI rate. | A positive and significant (P < 0.002) immediate response of CPAP was seen on respiratory rate, decreased CSpO₂ from 28.6 (7.6) to 26.9 (6.2), and SpO₂, increased from 90.7 (3.4) to 92.7 (3.2) with a decrease of oxygen flow rate from 27.4 (13.3) to 23.3 (10.7). |
| Publication                          | PMID        | Study design          | Setting                        | Patient Population | Treatment                                                                 | Intubation Rate | Mortality Rate | Main finding                                                                 | Secondary findings                                                                                   |
|------------------------------------|-------------|-----------------------|--------------------------------|--------------------|---------------------------------------------------------------------------|----------------|----------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Nightingale et al. [85], 2020      | 32624495    | Retrospective study   | Non-ICU COVID-19 AHRF         | CPAP n=24           | Interface: face mask PEEP 8.75 [7.5–10] cmH₂O                             | CPAP failure 42% [95% CI 24 to 61] | 21% [9 to 40] | Over half of patients (58%) avoided mechanical ventilation and a total of 19 out of 24 (79%) were discharged | There have been no cases of COVID-19 among nursing staff who looked after this cohort of patients.     |
| Norman-Ahmed et al. [86], 2020     | 33140691    | Retrospective study   | Acute Respiratory Care Unit   | CPAP n=52           | Interface: full face mask starting PEEP 10 cmH₂O titrated to 12.5 cmH₂O or 15 cmH₂O if SpO₂ < 94% with a FiO₂ of 60%. | Patients with no limitations of treatment CPAP failure 51% [95% CI 36 to 66] | Patients with limitations of treatment CPAP failure 20% [95% CI 10 to 34] | Overall mortality rate in the overall cohort was 40% with a mortality of 23%. | Predictors of success were: SpO2/FiO2, respiratory rate, neutrophil to lymphocyte ratio.               |
| Oranger et al. [86], 2020          | 32430410    | Retrospective study   | Short term historical control | CPAP n=38           | Control SOT n=14 Interface: face mask with high end domiciliary ventilator. PEEP 10 (adjusted between 8 and 12) cmH₂O | Day 7 follow-up control SOT failure 54% [95% CI 33 to 79] | Day 7 follow-up control SOT failure 21% [95% CI 8 to 48] | CPAP is feasible in deteriorating COVID-19 patients managed in a pulmonology unit. | None of the CPAP patients had to be intubated under cardiac arrest or high emergency conditions.       |
| Pagano et al. [91], 2020           | 32629100    | Observational study   | Non-ICU COVID-19 AHRF         | CPAP n=18           | Interface: Helmet PEEP 10 cmH₂O FiO₂ titrated to SpO₂ > 93%               | Case CPAP 24% [95% CI 13 to 39] | Overall mortality 61% [95% CI 39 to 80] | Eleven patients died (61%), 4 among the responders (defined as patients with an improvement of SpO₂/FiO₂ of at least 15% after 1 h of CPAP) and 7 in nonresponders | Among responders 5 (27.7%) patients showed improvement in lung ultrasound score.                        |
| Vanzutletto et al. [74*], 2021     | 33527074    | Retrospective multicenter study | Non-ICU COVID-19 AHRF         | CPAP n=537          | Interface: Helmet n=399 [74%] Face mask n=123 [23%] Both n=15 [3%] PEEP 10 [10–12] cmH₂O | Patients with no limitations of treatment CPAP failure 45% [95% CI 4.1 to 50] | Overall mortality 34% [95% CI 30 to 38] | CPAP is feasible outside the ICU, with overall in-hospital mortality similar to that reported in other studies | Intubation delay represents a risk factor for mortality (hazard ratio 1.093, 95% CI 1.010–1.184).         |

Values are displayed as means (SD) or medians [Interquartile range].
Failure was defined as either intubation, death while still on noninvasive respiratory support, or escalation to other noninvasive respiratory support to avoid endotracheal intubation. AHRF, acute hypoxic respiratory failure; ARDS, acute respiratory distress syndrome; awaken PP, awaken prone position; CPAP, continuous positive end-expiratory pressure; FiO₂, fraction of inspired oxygen; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IQR, interquartile range; NIV, noninvasive ventilation; PaO₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; SpO₂, peripheral capillary oxygen saturation; WFD, Ventilatory Free Days.
### Table 4. Clinical trials of awake prone position in acute hypoxemic respiratory failure of COVID-19 etiology

| Publication | PMID | Study design | Setting | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main finding | Secondary findings |
|------------|------|--------------|---------|--------------------|-----------|----------------|---------------|-------------|-------------------|
| Avdeev et al. [101], 2021 | 32748797 | Retrospective | Non-ICU COVID-19 ARF | | Awake PP | 36% [95% CI 24 to 50] | 9% [95% CI 3 to 28] | Response to awake PP depends on localization of aeration loss, and lung ultrasound can predict it. | |
| Bastani et al. [102], 2020 | 33845325 | Retrospective | Non-ICU COVID-19 ARF | | Awake PP | 43% [95% CI 28 to 57] | 0% [95% CI 0 to 16] | PP was feasible and effective in rapidly improving oxygenation without relevant adverse events. | |
| Burton-Papp et al. [103], 2020 | 32748797 | Retrospective | ICU | COVID-19 ARF | | 10.5% [95% CI 5.0 to 21.1] | 0% [95% CI 0 to 21.1] | In patients with moderate ARF treated with CPAP or NIV awake PP can improve oxygenation without relevant adverse events. | |
| Capito et al. [104], 2020 | 32220356 | Pilot study | Non-ICU | COVID-19 ARF | | Awake PP | 36% [95% CI 24 to 50] | Awake early prone position in the emergency department demonstrated improved oxygenation in COVID-19 patients. | |
| Chetan et al. [95], 2021 | 33845325 | Retrospective | Non-ICU COVID-19 ARF | | Awake PP | 31% [95% CI 22 to 45] | 2% [95% CI 1 to 4] | Awake PP can be safely performed with improvement in oxygenation. However, no mortality benefit was observed in patients with mild to moderate ARF. | |
| Cappiello et al. [96], 2020 | 32509585 | Retrospective, feasibility study | Respiratory High Dependency Unit | COVID-19 ARF | | Awake PP | 25% [95% CI 15 to 35] | PP was feasible and effective in rapidly improving oxygenation in awake patients with COVID-19-related pneumonia requiring oxygen supplementation. | |
| Domati et al. [105], 2020 | 32551807 | Retrospective | ICU | COVID-19 ARF | | Awake PP | 20% [95% CI 5 to 35] | PP is potentially a low-cost, easily implemented, and scalable intervention, particularly in low and middle-income countries. | |
### Table 4 (Continued)

| Publication | PMID | Study design | Setting | Patient Population | Treatment | Imposition Rate | Mortality Rate | Main finding | Secondary findings |
|-------------|------|--------------|---------|--------------------|-----------|----------------|---------------|--------------|-------------------|
| Despre et al. [156], 2020 | 3245566-3 | Case series | ICU | COVID-19 AHRF | HPnO2/FiO2 > 1.83 (144 to 212) | Awake PP n = 6 | 50% [95% CI 19 to 81] | Not reported | Considering these observations, PP combined with either HFNO or SOT could be proposed in spontaneously breathing, severe COVID-19 patients. |
| Ehmann et al. [128], 2021 | 34423570 | Prospective, collaborative, randomized and controlled meta trial, Mixed setting | COVID-19 AHRF | SpO2/FiO2, awake PP 1.67 (0.43), SpO2/FiO2, standard care 1.46 (0.61) | Awake PP n = 116 | Treatment failure: Awake PP 10% [95% CI 6 to 15], Standard care 24% [95% CI 17 to 30] | Standard care 46% [95% CI 36 to 56] | Not reported | Awake PP significantly improves blood oxygenation, respiratory rate and RDR index during PP. The benefit was maintained after 24 h. |
| Ehrmann et al. [917], 2020 | 33412581 | Prospective before after | ICU | COVID-19 AHRF | O2 supplement < 16/min in 15 (30%) patients, O2 supplement ≥ 16/min in 8 (16%) patients | Attempted awake PP n = 24 | Follow-up to 10 days 21% [95% CI 9 to 40] | Not reported | Responders (increased PaO2 > 20% from standard care n = 6 (26%), PaO2 12–45); 2 patients were persistent responders. |
| Feinberg et al. [109], 2020 | https://doi.org/10.1177/1751143719981042 | Prospective observational | NonICU | COVID-19 AHRF | PaO2/FiO2 115 (40) | Overall cohort 43% [95% CI 30 to 50], Awake PP for 1 h 29% [95% CI 17 to 40], Awake PP for 1 h 26% [95% CI 15 to 40], Awake PP for < 1 h 43% [95% CI 19 to 68] | Patients that were pronounced for more than 1 h had less need for endotracheal intubation than patients that were pronounced for less than 1 h. | Patients treated with HFNO for more than 3 h had lower treatment failure rate. | Patients treated with PP showed a trend for delay in intubation compared to HFNO alone (median in 1 (inter quartile range 1 to 2) days vs 2 (IQR 1 to 3) days, P = 0.05). Awake PP did not affect 28-day mortality (P = 0.92). |
| Fernandes et al. [108], 2020 | 33322426-9 | Prospective, multicenter, double-blind observational study | ICU | COVID-19 AHRF | PaO2/FiO2, HFNO 111 (35), PaO2/FiO2, HPnO2 + PP 125 (91–167) | Overall cohort n = 119 | HFNO: 43% [95% CI 34 to 50], HFNO + CFAP 40% [95% CI 30 to 50], HFNO + CFAP + PP 28% [95 to 38], HFNO + CFAP + PP 25% [95% CI 19 to 68] | The combined approach of HFNO and PP did not decrease the risk of endotracheal intubation. | Patients treated with HHnO2 + awake PP showed a trend for delay in intubation compared to HFNO alone (median in 1 (inter quartile range 1 to 2) days vs 2 (IQR 1 to 3) days, P = 0.05), but Awake PP did not affect 28-day mortality (P = 0.92). |
| Gubiani et al. [106], 2020 | 32345553 | Prospective, observational | ICU | COVID-19 AHRF | PaO2/FiO2 = 1.50 (0.5) | Awake PP n = 10 | Mean PP duration was 9 h | 20% [95% CI 6 to 51] | Authors report low intubation rate and high compliance in the intervention, suggesting that PP might be a useful tool to increase blood oxygenation in patients with moderate to severe AHFR related to COVID-19. |
| Hallak et al. [115], 2020 | 32920789-7 | Retrospective study | Respiratory High Dependency Unit | COVID-19 AHRF | PaO2/FiO2 < 2 (46%), PaO2/FiO2 < 60% (54%) | Overall cohort n = 48 | Patients with limitations of treatment 54% [95% CI 40 to 67], HFNO 4% [95% CI 2 to 19], CPAP 6% [95% CI 1 to 14] all on IMV | Increasing age and the inability to achieve prone were the only independent predictors of COVID-19 mortality. |

Acute respiratory failure due to COVID-19: Menga et al.
### Table 4 (Continued)

| Publication | Study Design | Setting | Patient Population | Interventions | Intubation Rate | Mortality Rate | Main Finding | Secondary Findings |
|-------------|--------------|---------|--------------------|---------------|----------------|---------------|--------------|-------------------|
| Jagan et al. [21], 2020 | Retrospective study | Non-ICU COVID-19 AHRF | Overall cohort | Standard care vs. Awake Self-proning | 27% [95% CI 16 to 36] | 16% [95% CI 0 to 28] | Awake self-proning was well tolerated, with good compliance in 38% of patients who were able to lie prone for 4 h a day. | No improvements in respiratory rate or oxygen saturation were observed at 72 or 48 h. |
| Jahanmir et al. [23], 2021 | Prospective, uncontrolled study | COVID-19 patients | Standard care vs. Awake PP | Standard care vs. PP | 53% spent PP greater or equal to 1 h, with 25% spending at least 5 times/day, and for 3 progressive interfaces: low flow (oronasal interface) > high flow (nonrebreather face mask) > pressure support ventilation (PSV) | 5% [95% CI 0 to 14] | In the prone group, 43% (13 out of 30) of patients were able to self-prone for 6 to 30 h, with 52% spending at least 5 times/day, and for 3 progressive interfaces: low flow (oronasal interface) > high flow (nonrebreather face mask) > pressure support ventilation (PSV). Three women achieved a supine position, but none exceeded 6 h. | No differences in oxygenation, respiratory rate, or dyspnea were observed in the two groups. |
| Jayakumar et al. [24], 2020 | Prospective, controlled trial with 3 parallel groups | Non-ICU COVID-19 AHRF | Awake PP vs. Standard care | Awake PP vs. Standard care | 5% [95% CI 0 to 28] | 2% [95% CI 0 to 14] | Awake PP can be a low-risk, low-cost maneuver which can help patients with COVID-19 pneumonia delay or reduce intubation, both at 48 and 72 h. | No differences in oxygenation, respiratory rate, or dyspnea were observed in the two groups. |
| Johnson et al. [25], 2020 | Prospective, uncontrolled study | COVID-19 patients | Standard care vs. Awake PP | Standard care vs. PP | 10% [95% CI 2 to 40] | 2% [95% CI 0 to 14] | Patient-directed PP is not feasible in all ICU patients hospitalized with COVID-19. | No differences in oxygenation, respiratory rate, or dyspnea were observed in the two groups. |
| Moghadam et al. [26], 2021 | Prospective, controlled trial with 3 parallel groups | Non-ICU COVID-19 AHRF | Awake PP vs. Standard care | Awake PP vs. Standard care | 5% [95% CI 0 to 28] | 2% [95% CI 0 to 14] | Awake PP led to no improvements in respiratory rate or oxygen saturation were observed at 72 or 48 h. | No differences in oxygenation, respiratory rate, or dyspnea were observed in the two groups. |
| Padrao et al. [27], 2020 | Prospective, uncontrolled study | COVID-19 patients | Awake PP vs. Standard care | Awake PP vs. Standard care | 5% [95% CI 0 to 28] | 2% [95% CI 0 to 14] | Awake PP was defined as a time spent PP greater or equal to 1 h, for at least 5 times/day, and for 3 progressive interfaces: low flow (oronasal interface) > high flow (nonrebreather face mask) > pressure support ventilation (PSV). | No differences in oxygenation, respiratory rate, or dyspnea were observed in the two groups. |
### Table 4 (Continued)

| Publication | PMID | Study design | Setting | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main Conclusion |
|-------------|------|--------------|---------|--------------------|-----------|----------------|---------------|----------------|
| Paternoster et al. [116], 2020 | 32713387 | Retrospective case series | Non-CU | COVID-19 ARHF | Awake PP n = 1.1 | 70% (95% CI 42 to 67) | 5.4% (95% CI 29 to 77) | Patients with moderate to severe ARHF have a high intubation rate, despite this treatment with CPAP and awake PP. |
| Paternoster et al. [114], 2020 | 31407129 | Case series | High Dependency Unit | COVID-19 ARHF | Awake PP n = 1.1 | 27% [95% CI 1 to 57] | 1.8 [95% CI 0.5 to 6] | In conclusion, helmet CPAP in prone position for COVID-19 severe hypoxemic acute respiratory failure resulted feasible and without complications, the induction of dosemademia due to improve patients' compliance to pronation was well tolerate. |
| Prud'homme et al. [115], 2021 | 30316704 | Retrospective multicenter matched cohort study | Non-CU | COVID-19 ARHF | Awake PP n = 5.05 | Standard care n = 322 | Awake PP group was prone for at least 2 consecutive hours. Awake PP | 18 (95% CI 17 to 22) | Standard care 20% (95% CI 13 to 27) | Awake PP reduces the need for endotracheal intubation and for mortality. The reduction of risk remained significant at multivariate, and after propensity score match. |
| Retucci et al. [99], 2020 | 2102 | Pilot prospective observational study | High Dependency Unit | COVID-19 ARHF | Awake PP n = 2.6 | Helmet CPAP | 27% (95% CI 1 to 46) | 8% (95% CI 2 to 24) | The target was an alveolar-arterial gradient less than 25 mmHg, despite more than 25% failure of nasal CPAP, the use of nasal CPAP was well tolerated. |
| Retucci et al. [99] | 2102 | Pilot prospective observational study | High Dependency Unit | COVID-19 ARHF | Awake PP n = 2.6 | Helmet CPAP | 27% (95% CI 1 to 46) | 8% (95% CI 2 to 24) | The target was an alveolar-arterial gradient less than 25 mmHg, despite more than 25% failure of nasal CPAP, the use of nasal CPAP was well tolerated. |
| Ripoll-Gallardo et al. [111], 2020 | 343266942 | Retrospective multicenter study | Non-CU | COVID-19 ARHF | Awake PP n = 4.8 | Standard care n = 48 | Oxygen supplementation strategy | 93% (95% CI 82 to 98) | Standard care 100% (95% CI 75 to 100) | Awake PP did not decrease the need for endotracheal intubation or the mortality rate. |
| Retucci et al. [99], 2020 | 32679237 | Retrospective multicenter matched cohort study | Non-CU | COVID-19 ARHF | Awake PP n = 114 | Standard care n = 160 | Awake PP group was prone for at least 2 consecutive hours. Awake PP | 16 (95% CI 7.2 to 31) | Standard care 39% (95% CI 23 to 61) | Awake PP reduces the need for endotracheal intubation and for mortality. The reduction of risk remained significant at multivariate, and after propensity score match. |
| Retucci et al. [99] | 2102 | Pilot prospective observational study | High Dependency Unit | COVID-19 ARHF | Awake PP n = 2.6 | Helmet CPAP | 27% (95% CI 1 to 46) | 8% (95% CI 2 to 24) | The target was an alveolar-arterial gradient less than 25 mmHg, despite more than 25% failure of nasal CPAP, the use of nasal CPAP was well tolerated. |

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### Table 4 (Continued)

| Publication | PMID | Study design | Setting | Patient Population | Treatment | Intubation Rate | Mortality Rate | Main Finding | Secondary Findings |
|-------------|------|--------------|---------|--------------------|-----------|----------------|--------------|--------------|-------------------|
| Rosini et al. [123], 2021 | 32581946 | Prospective observational study | Intermediate Care Unit | COVID-19: AHRF SpO₂ ≤ 93% in nasal cannula 6 l/min or 1.5 l/min via non-rebreathing face mask | Awake PP 11% | 22% [95% CI 12 to 33] Standard care 39% [95% CI 29 to 49] | 27% [95% CI 14 to 40] Standard care 39% [95% CI 29 to 49] | Improved PaO₂/FiO₂ ratio in awake PP group compared to standard care group. | No difference in hospital length of stay between groups. |
| Tonelli et al. [124], 2021 | 33034064 | Retrospective cohort study | Respiratory ICU | COVID-19: AHRF PaO₂/FiO₂ overall cohort 141 [79–202] PaO₂/FiO₂ awake PP 141 [73–223] PaO₂/FiO₂ standard care 153 [84–223] | Awake PP 17% [95% CI 8 to 29] Standard care 38% [95% CI 1 to 4] | 20% [95% CI 3 to 40] Standard care 39% [95% CI 29 to 49] | 17% [95% CI 3 to 40] Standard care 39% [95% CI 29 to 49] | Improved PaO₂/FiO₂ ratio in awake PP group compared to standard care group. | No difference in hospital length of stay between groups. |
| Tu et al. [125], 2020 | 32586624 | Pilot retrospective study | ICU | COVID-19: AHRF PaO₂/FiO₂ lower 150 | Awake PP 15% [95% CI 3 to 27] Standard care 13% [95% CI 6 to 22] | 30% [95% CI 1 to 4] Standard care 29% [95% CI 18 to 39] | Not reported | Improved PaO₂/FiO₂ ratio in awake PP group compared to standard care group. | No difference in hospital length of stay between groups. |
| Winarski et al. [126], 2020 | 32895367 | Retrospective Study | NonICU | COVID-19: AHRF PaO₂/FiO₂ 317 [156–194] | Next session of treatment n = 14 Patients with limitations of treatment n = 10 | Attemped Awake PP n = 24 Treated with CPAP, maximum PEEP 12 [0–21] PaO₂/FiO₂ standard care 13 [6–23] Awake PP 22% [95% CI 6 to 35] Not reported | Patients with limitations of treatment 7% [95% CI 1 to 17] Patients with limitations of treatment 40% [95% CI 17 to 62] | Improved PaO₂/FiO₂ ratio in awake PP group compared to standard care group. | No difference in hospital length of stay between groups. |
the intervention group (median [IQR] time in prone positioning was 3.4 h [1.8–8.4] vs 9 [4.4–10.6] respectively), resolved in no difference in intubation rate, and the trial was stopped early for futility.

Lately, a prospective, randomized, collaborative meta-trial compared awake prone position and conventional in patients treated with HFNO with acute respiratory failure of COVID-19 etiology. The authors found a reduction in the proportion of patients intubated or dying within 28 days from enrolment (40% in the awake prone position group vs 46% in the standard of care group, \( P = 0.007 \)) [128]. Interestingly, average duration of prone positioning sessions was 6 h, and longer sessions were associated with treatment success at 28 days: this finding should be interpreted as exploratory.

Awake prone position appears as a cost-effective technique that can improve the blood oxygenation and reduce the respiratory rate [129], and a recent randomized controlled trial support its routine use in patients with respiratory failure of COVID-19 etiology treated with HFNO [128].

**CONCLUSION**

Currently, noninvasive respiratory support is a safe option in patients with a PaO\(_2\)/FiO\(_2\) \(\geq\) 200 mmHg; in patients PaO\(_2\)/FiO\(_2\) < 200 mmHg most recent randomized controlled trials suggest HFNO or helmet NIV as the most promising techniques for a noninvasive respiratory support trial [24,51,56]. In the COVID-19 pandemic, awake prone position, which has a robust physiological rationale, has been widely applied with benefits on oxygenation and a possible reduction in the rate of endotracheal intubation [87]. During any treatment, careful clinical monitoring remains mandatory not to delay the intubation and protective ventilation, especially in patients with PaO\(_2\)/FiO\(_2\) < 200 mmHg.

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**Table 4** (Continued)

| Publication | Study design | Setting | Study aim | PaO\(_2\)/FiO\(_2\) | Treatment | Intubation Rate | Mortality Rate | Main finding | Secondary findings |
|-------------|-------------|---------|-----------|-------------------|-----------|----------------|---------------|--------------|------------------|
| Xu et al. [122], 2020 | Retrospective multicenter study | ICU COVID-19 AHRF | PaO\(_2\)/FiO\(_2\) 157 (46) | Awake PP \( n = 10 \) | Target time was \( > 16 \) h/day | 0% [95% CI 0 to 28] | 0% [95% CI 0 to 28] | Early awake PP combined with HFNO therapy could be used safely and effectively in young, fit, severe COVID-19 patients, and it may reduce the conversion to critical illness and the need for tracheal intubation. | After awake PP PaO\(_2\)/FiO\(_2\) and increased significantly, and respiratory alkalosis decreased significantly. |
| Zang et al. [123], 2020 | Prospective observational study | ICU COVID-19 AHRF | Patients with severe hypoxia | Awake PP \( n = 23 \) | Standard care \( n = 37 \) | Not reported | Awake PP 43% [95% CI 26 to 63], \( P < 0.001 \) | Early awake PP might reduce hypoxia and improve mortality. | In the awake PP group SpO\(_2\) increased from 91% (1.5) to 95.5 (1.7), \( P < 0.01 \), respiratory rate decreased from 28.2 (3) to 24.9 (1.8), \( P < 0.01 \), and ROX index increased from 3.3 (0.5) to 4 (0.5), \( P < 0.01 \). |

Values are displayed as means (SD) or medians [interquartile range]. Failure was defined as either intubation, death while still on noninvasive respiratory support, or escalation to other noninvasive respiratory support to avoid endotracheal intubation. AHRF, acute hypoxemic respiratory failure; ARDS, acute respiratory distress syndrome; awake PP, awake prone position; CPAP, continuous positive airway pressure; FiO\(_2\), fraction of inspired oxygen; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IQR, interquartile range; NIV, noninvasive ventilation; PaO\(_2\), partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; SpO\(_2\), peripheral capillary oxygen saturation; VFD, Ventilatory Free Days.
Respiratory system

Conflicts of interest

There are no conflicts of interest.

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