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 ($PaO_2/FiO_2 < 200$ 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 $PaO_2/FiO_2 < 200$ 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

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KEY POINTS

- Maintenance of spontaneous breathing hypoxemic 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 hypoxemic 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.

care unit (ICU)-acquired pneumonia, diaphragmatic atrophy and ICU-induced delirium, with detrimental effects on clinical outcome [4,5]. During the COVID-19 pandemic, the unprecedented lack of mechanical ventilators and ICU beds led clinicians to extensively use noninvasive respiratory support for the treatment of hypoxemic respiratory failure [6–9].

Patients with hypoxemic 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 hypoxemic 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 $PaCO_2$, 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 hypoxemic 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 $PaO_2/FiO_2 > 200$mmHg, noninvasive respiratory support is safe and effective. Differently, in patients

with $PaO_2/FiO_2 \leq 200$ 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 (60 L/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 PaO_2/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 PaO_2/FiO_2 ratio > 200 mmHg [38,41], whereas it may be associated to higher risk of failure when PaO_2/FiO_2 < 200 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 At admission O2 flow rate 9 lt/min and PaO_2 69 [63–82]	SOT $n=62$ HFNO $n=76$	SOT 74% [95% CI 62 to 83] HFNO 51% [95% CI 40 to 62]	SOT 26% [95% CI 17 to 38] HFNO 16% [95% CI 9 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.
Chandel *et al.* [49], 2021	33328179	Multicentered retrospective study	Mixed population	COVID-19 AHRF PaO_2/FiO_2 not reported ROX index after 2 h of HFNO 4.5 [3.3–6.0]	HFNO $n=272$	40% [95% CI 34 to 46]	17% [95% CI 13 to 21]	Prolonged usage of HFNO was not associated with worse clinical outcomes compared with shorter trials in those that ultimately required mechanical ventilation	The ROX index was sensitive for the identification of subjects who were successfully managed with HFNO and a cut off of 3.67 at 12 h was identified
Demoule *et al.* [31], 2020	32758000	Retrospective study	ICU	COVID-19 AHRF HFNO: PaO_2/FiO_2 126 [86–189] No-HFNO: PaO_2/FiO_2 130 [97–195]	Matched sample: HFNO $n=137$ no-HFNO $n=137$	HFNO 55% [95% CI, 46 to 63] no-HFNO 72% [95% CI, 64 to 79]	HFNO 21%, [95% CI 15 to 29] 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	
Ehrmann *et al.* [128▪▪], 2021	34425070	Prospective collaborative randomized controlled meta trial,	Mixed setting	COVID-19 AHRF SpO_2/FiO_2 awake PP 147.9 (43.9) SpO_2/FiO_2 standard care148.6 (43.1)	Awake PP $n=564$ Standard care $n=557$ All patients treated with HFNO FiO_2 0.6 [0.5 – 0.8] Awake PP HFNO flow 50 l/min [40–55] Standard care HFNO flow 40 l/min [40–50]	Treatment failure Awake PP 40% [95% CI 36 to 44] Treatment failure Standard care 46% [95% CI 42 to 50] IMV Awake PP 33% [95% CI 29 to 37] IMV Standard care 40% [95% CI 36 to 44]	Awake PP 21% [95% CI 18 to 24] Standard care 24% [95% CI 20 to 27]	Awake PP reduces the proportion of patients intubated or dying within 28 days of enrolment, 223 (40%) in the awake PP group vs 257 (46%) in the standard of care, $P=0.007$, relative risk reduction 0.86 [95% CI 0.75 to 0.98]. Patients that received PP for longer sessions had lower treatment failure rate.	Awake PP significantly improves blood oxygenation, 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 PaO_2/FiO_2 138 (66)	HFNO $n=163$ CPAP $n=330$ PEEP 10.2 (1.6) cmH_2O Helmet 149 (99%) Face mask 2 (1%) NIV $n=177$ PEEP 9.5 (2.2) cmH_2O Pressure Support 17.3 (3) cmH_2O Helmet 15 (21%) Face mask 57 (79%)	Recieved IMV: HFNO 29% [95% CI 24 to 36] 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]	30 day mortality: HFNO 16% [95% CI 11 to 22] CPAP 30% [95% CI 26 to 35] NIV 31% [95% CI 24 to 38] Difference not significant at adjusted analysis	Noninvasive respiratory support outside of ICU is feasibile, 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.* [87], 2020	32984836	Retrospective, multicenter study	ICU	COVID-19 AHRF $SpO_2<92\%$ 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 cmH_2O	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]	Difference in the intubation rate was significant after adjustment for age.	In obese patients Helmet CPAP is effective in reducing the ETI rate.
Geng *et al.* [37], 2020	32295710	Case series	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 259.88 (58)	HFNO $n=8$	0% [95% CI 0 to 32]	0% [95% CI 0 to 32]	HFNO is safe and effective in mild AHRF of COVID-19 etiology	

Table 1 (*Continued*)

Publication	PMID	Study design	Setting	Patient Population	Treatment	Intubation Rate	Mortality Rate	Main finding	Secondary findings
Grieco *et al.* [70▪▪], 2021	33764378	Randomized controlled multicenter trial	ICU	COVID-19 AHRF NIV PaO_2/FiO_2 105 [83–125] HFNO PaO_2/FiO_2 102 [80–124]	Helmet NIV $n=54$ Continuous treatment PEEP 12 [10–12] cmH_2O Pressure Support 10 [10–12] cmH_2O HFNO $n=55$	Helmet NIV 30% [95% CI 19 to 43] HFNO 51% [95% CI 38 to 64]	HFNO 25% [16 to 38] Helmet NIV 24% [95% CI 15 to 37]	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.
Hernandez-Romieu *et al.* [30], 2020	32804790	Retrospective study	ICU	COVID-19 AHRF PaO_2/FiO_2 not reported for the overall cohort. At intubation, PaO_2/FiO_2 148 [111–205]	HFNO $n=109$ Only IMV $n=97$	72% [95% CI 62 to 79]	HFNO 22% [95% CI 15 to 31] Only IMV 40% [95% CI 31 to 50]	A trial of noninvasive respiratory support, including HFNO, in an attempt to avoid intubation, is not associated with increased mortality.	Use of noninvasive respiratory support is not associated with worse pulmonary compliance and oxygenation, among those who eventually require mechanical ventilation.
Liu *et al.* [40▪▪], 2021	33573999	Retrospective multicentre study	ICU	COVID-19 AHRF PaO_2/FiO_2 HFNO 116 [66–252] PaO_2/FiO_2 NIV 113 [68–183]	HFNO $n=366$ NIV $n=286$ Type and setting of NIV is not reported	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, ROX 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
Mellado-Artigas *et al.* [33], 2021	33573680	Prospective observational study	ICU	COVID-19 AHRF Only IMV PaO_2/FiO_2 117 (51) HFNO PaO_2/FiO_2 121 (49)	HFNO $n=61$ Only IMV $n=61$	38% [95% CI 27 to 50]	Only IMV 21% [95% CI 13 to 33] HFNO 15% [95% CI 8 to 26]	HFNO was associated with an increase in VFDs at 28 days when compared with early IMV and with reduction in ICU length of stay.	Mortality was not different in the patients that were intubated early and in the patients that failed HFNO.
Montiel *et al.* [30], 2020	32990864	Prospective observational study	ICU	COVID-19 AHRF PaO_2/FiO_2 83 (±22)	HFNO $n=21$	Not reported	Not reported	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.	The oxygenation improvement is associated with neither a clinically significant change in the $PaCO_2$ nor subjective patient complaints.
Panadero *et al.* [44], 2020	32983456	Retrospective study	Non-ICU	COVID-19 AHRF SpO_2/FiO_2 in HFNO success 103.0 (3.4) ROX index in HFNO success 4.0 (1.4) SpO_2/FiO_2 in HFNO failure 101.4 (5.1) ROX index in HFNO failure 3.7 (1.0)	HFNO $n=40$	52% [95% CI 37 to 67]	22% [95% CI 12 to 37]	HFNO therapy is a useful treatment in ARDS in order to avoid ETI or as a bridge therapy, and no increased mortality was observed secondary to delayed intubation	After initiating HFNO, a ROX index below 4.94 predicts the need for intubation.
Rosén *et al.* [127▪], 2021	34127046	Multicenter randomized clinical trial	Non-ICU	COVID-19 AHRF Standard care $n=39$ PaO_2/FiO_2 standard care 115 [94–130] Prone $n=36$ PaO_2/FiO_2 prone 115 [86–130]	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 33% [95% CI 20 to 49] Prone group 33% [95% CI 20 to 50]	Control group 8% [95% CI 3 to 20] Prone group 17% [95% CI 8 to 22]	The implemented protocol for awake PP increased duration of awake PP but did not reduce the rate of intubation in patients with AHRF due to COVID-19 compared to standard care.	Nine patients (23%) in the control group had pressure sores compared with two patients (6%) in the prone group, $P=0.03$, there were no difference in the use of NIV, vasopressors, continuous renal-replacement therapy, ECMO, VFD, hospital and ICU length of stay and mortality among the two groups.

Table 1 (*Continued*)

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 $n=69$	59% [95% CI 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 SpO_2/FiO_2 155 [106–190]	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 SpO_2/FiO_2 had greater predictive value
Vianello *et al.* [35], 2020	32703883	Retrospective study	ICU	COVID-19 AHRF PaO_2/FiO_2 108 [52–296]	HFNO $n=28$ Rescue 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 18% [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 AHRF secondary to COVID-19 not responding to conventional oxygen therapy	Severity of hypoxemia and C reactive protein level were correlated with HFNO failure
Wang *et al.* [41], 2020	32232685	Retrospective study	Mixed population	COVID-19 AHRF PaO_2/FiO_2 209 [179–376] in success patients PaO_2/FiO_2 142 [130–188] in failure patients	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 PaO_2/FiO_2 were more likely to experience HFNO failure
Wang *et al.* [39], 2020	32267160	Retrospective study	ICU	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] HNFO failure 77% [95% CI 61 to 88] NIV failure 79% [95% CI 63 to 90]	HFNO 80% [95% CI 64 to 90] 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 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 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 $P=016$ 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]	32% [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.

Table 1 (*Continued*)

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 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] HNFO failure 77% [95% CI 61 to 88] NIV failure 79% [95% CI 63 to 90]	HFNO 80% [95% CI 64 to 90] 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	PaO_2/FiO_2 100 [66.6–126.7] in survivors PaO_2/FiO_2 62 [52–74] nonsurvivors	Overall cohort $n=52$ HFNO $n=33$ NIV $n=29$ IMV n=22	The progression among the interfaces is not reported	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 COVID-19 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% [CI66 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.
Zucman *et al.* [42], 2020	32671470	Retrospective study	ICU	COVID-19 AHRF FiO_2 at admission 0.8 [0.6–1] Median SpO_2 96% [94–98]	HFNO $n=60$	65% [95% CI 52 to 76]	17% [9 to 28]	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_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.

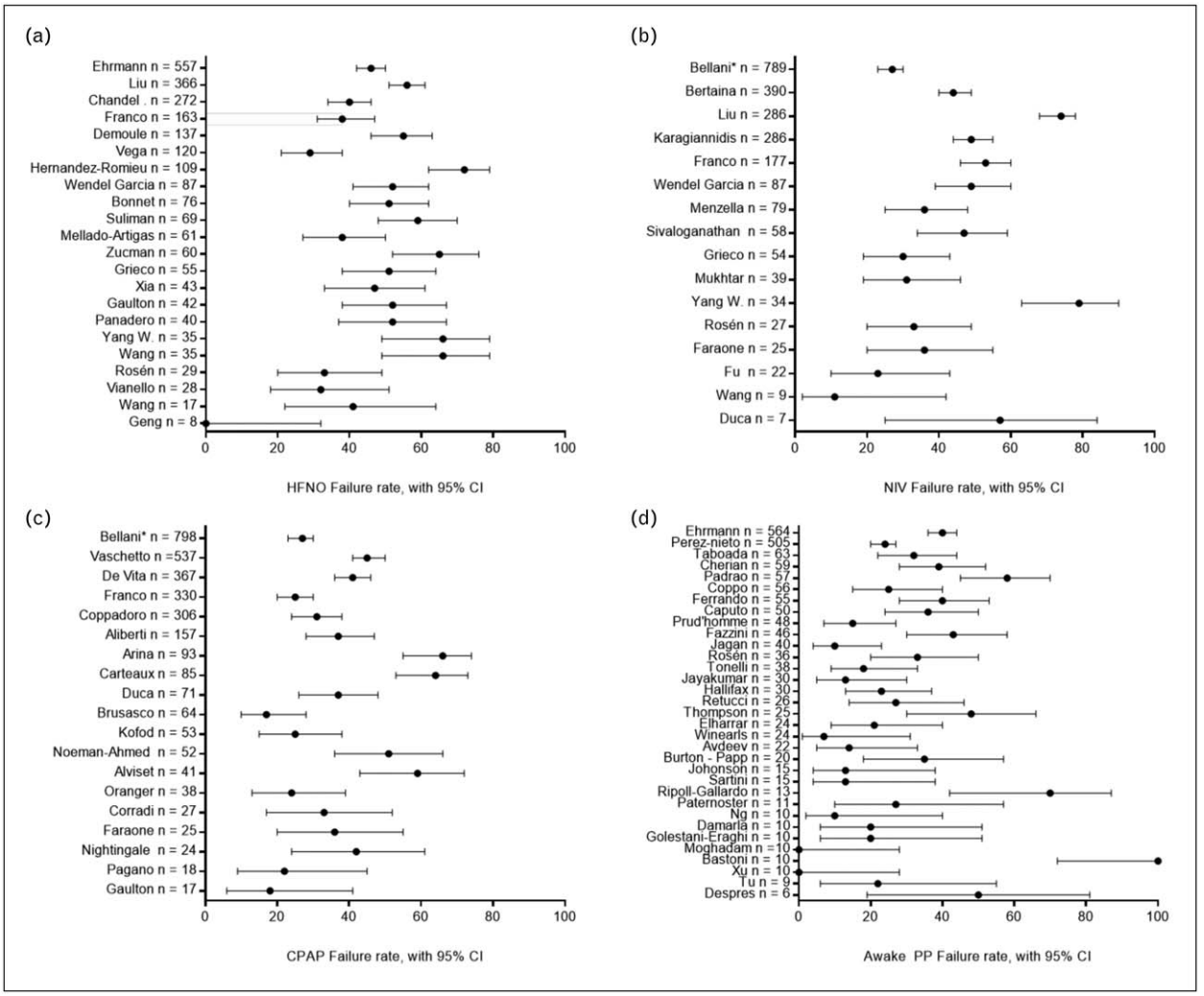

FIGURE 1. Panel reporting the failure rate [95% CI] of patients with hypoxemic respiratory failure treated with noninvasive respiratory support. Failure rate was defined as occurrence of endotracheal intubation or death. Only the patients without limitation of treatment were considered for the figure. 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.

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_2O, patients treated with face mask received a median PEEP of 5.1 cmH_2O [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

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.* [69▪], 2021	33395553	Single day observational study	Ward	COVID-19 AHRF PaO_2/FiO_2 172 (102)	NIV + CPAP $n=798$ 215 (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	Noninvasive respiratory support failure 38% [95% CI 34 to 41] in the overall cohort Noninvasive respiratory support failure 27% [23 to 30] in patients with no limitations of treatment cohort Noninvasive respiratory support failure 67% [61 to 73] in patients with limitations of treatment cohort	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.
Bertaina *et al.* [59], 2021	33727235	Observational prospective registry	Mixed setting	COVID-19 AHRF 51% of patients had SpO2 < 92% on room air	NIV $n=390$ NIV settings, interfaces, and whether CPAP is codified as NIV is not know	NIV failure 44% [95% CI 40 to 49] Received ETI 16% [95% CI 13 to 20]	Overall cohort 38% [95% CI 33 to 43] Among intubated patients 58% [95% CI 46 to 70%]	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 SpO_2 at presentation, lymphocytopenia, in-hospital use of antibiotics were independently associated with NIV failure.
Burns *et al.* [78], 2020	32624494	Retrospective study	Non-ICU	COVID-19 AHRF SpO2 < 94% in Venturi Mask 40%	CPAP $n=23$ BIPAP $n=5$ BIPAP settings: max PEEP = 10.2 (2.9) cmH_2O max Pinsp = 22.4 (6) cmH_2O CPAP settings: Max PEEP = 12.7 (2.1) cmH_2O	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' imaging appearances, $P=0.034$.
Duca *et al.* [60], 2020	32766538	Retrospective study	Non-ICU	COVID-19 AHRF CPAP PaO_2/FiO_2 131 [97–190] NIV PaO_2/FiO_2 87 [53–120] IMV at arrival PaO_2/FiO_2 76 [60–177]	CPAP $n=71$ Helmet CPAP, PEEP = 15 [12–18] cmH_2O NIV $n=7$ NIV, PEEP = 16 [12–20] cmH_2O IMV at arrival = 7 IMV at arrival, PEEP = 18 [10–18] cmH_2O	CPAP intubation rate 37% [95% CI 26 to 48] NIV intubation rate 0% [95% CI 0 to 35] 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] IMV 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 PaO_2/FiO_2 130 (65) 25 (50%) patients had patients with limitations of treatment	NIV $n=25$ CPAP $n=25$ Interface: full face or oro-nasal mask Duration of treatment in the overall cohort: 187 (181) hours PEEP started at 5 cmH_2O, up to 12 cmH_2O IPAP set at 15cmH_2O, up to 20–25 cmH_2O	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 was useful in avoiding intubation in patients with no limitations of treatment.	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.* [67▪▪], 2020	32747398	Retrospective multicenter study	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 138 (66)	HFNO $n=163$ CPAP $n=330$ PEEP 10.2 (1.6) cmH_2O Helmet 149 (99%) Face mask 2 (1%) NIV $n=177$ PEEP 9.5 (2.2) cmH_2O Pressure Support 17.3 (3) cmH_2O Helmet 15 (21%) Face mask 57 (79%)	Recieved IMV: HFNO 29% [95% CI 24 to 36] 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]	30 day mortality: HFNO 16% [95% CI 11 to 22] CPAP 30% [95% CI 26 to 35] NIV 31% [95% CI 24 to 38] Difference not significant at adjusted analysis	Noninvasive respiratory support outside of ICU is feasibile, 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.
Fu *et al.* [62], 2021	34109190	Retrospective study	Mixed population	COVID-19 AHRF NIV as initial therapy PaO_2/FiO_2 174.4 [158.0–208.7] NIV as rescue therapy PaO_2/FiO_2 179.27 [165.9–224.1]	NIV as initial therapy $n=22$ NIV as rescue therapy $n=17$ PEEP in NIV success: 6 [6–7] PEEP in NIV failure: 6 [6–6.3] Pressure Support in NIV success: 7 [6–7] Pressure Support in NIV failure: 6 [6–6.3]	NIV as initial therapy 23% [95% CI 10 to 43] NIV as rescue therapy 65% [95% CI 41 to 83]	NIV initial therapy 5% [95% CI 8 to 22] NIV as rescue therapy 12% [95% CI 3 to 34]	Close attention should be paid to patients with $PaO_2/FiO_2<200$ 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.
Grieco *et al.* [70▪▪], 2021	33764378	Randomized controlled multicenter trial	ICU	COVID-19 AHRF NIV PaO_2/FiO_2 105 [83–125] HFNO PaO_2/FiO_2 102 [80–124]	Helmet NIV $n=54$ Continuous treatment PEEP 12 [10–12] cmH_2O Pressure Support 10 [10–12] cmH_2O HFNO $n=55$	Helmet NIV 30% [95% CI 19 to 43] HFNO 51% [95% CI 38 to 64]	HFNO 25% [16 to 38] Helmet NIV 24% [95% CI 15 to 37]	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.
Hua *et al.* [63], 2020	32546258	Retrospective, multicenter study	ICU	COVID-19 AHRF PaO_2/FiO_2 not reported	SOT $n=204$ IMV $n=113$ NIV $n=152$ NIV settings, interfaces, and whether CPAP is codified as NIV is not reported	Not reported	SOT 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 outcome.	
Karagiannidis *et al.* [68▪▪], 2020	32735842	Retrospective, nation-wide study	Mixed population	COVID-19 AHRF PaO_2/FiO_2 not reported	NIV $n=286$ IMV only $n=1318$ NIV settings, interfaces, and whether CPAP is codified as NIV is not reported	NIV failure 49% [95% CI 44 to 55]	NIV 51% [95% CI 45 to 56] 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.* [40▪▪], 2021	33573999	Retrospective multicentre study	ICU	COVID-19 AHRF PaO_2/FiO_2 HFNO 116 [66–252] PaO_2/FiO_2 NIV 113 [68–183]	HFNO $n=366$ NIV $n=286$ NIV settings, interfaces, and whether CPAP is codified are NIV is not reported	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, ROX 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.

Table 2 (*Continued*)

Publication	PMID	Study design	Setting	Patient Population	Treatment	Intubation Rate	Mortality Rate	Main finding	Secondary findings
Menzella *et al.* [64], 2021	33728822	Retrospective cohort study	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 120.1 (41.6)	NIV $n=79$ PEEP: 9.46 (2.37) cmH_2O IPAP: 17.7 (2.2) cmH_2O	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 63]	Mortality 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	32736030	Retrospective study	ICU	COVID-19 AHRF PaO_2/FiO_2 in NIV success 170 [112–224] PaO_2/FiO_2 in NIV failure 175 [118–205]	NIV $n=39$ NIV settings, interfaces, and whether CPAP or HNFO are codified as NIV is not reported	Need for ETI 23% [13 to 38] NIV failure 31% [95% CI 19 to 46]	26% [15 to 41]	The use of NIV was successful in 77% of patients	
Rosén *et al.* [127▪], 2021	34127046	Multicenter randomized clinical trial	Non-ICU	COVID-19 AHRF Standard care $n=39$ PaO_2/FiO_2 standard care 115 [94–130] Prone $n=36$ PaO_2/FiO_2 prone 115 [86–130]	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 33% [95% CI 20 to 49] Prone group 33% [95% CI 20 to 50]	Control group 8% [95% CI 3 to 20] Prone group 17% [95% CI 8 to 22]	The implemented protocol for awake PP increased duration of awake PP but did not reduce the rate of intubation in patients with AHRF due to COVID-19 compared to standard care.	Nine patients (23%) in the control group had pressure sores compared with two patients (6%) in the prone group, $P=0.03$, there were no difference in the use of NIV, vasopressors, continuous renal-replacement therapy, ECMO, VFD, hospital and ICU length of stay and mortality among the two groups.
Sivaloganathan *et al.* [75], 2020	32811662	Retrospective Study	Mixed population	COVID-19 AHRF Worst PaO_2/FiO_2 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–limitations 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: 5% [95% CI 2 to 14] Patients with limitations of treatment: 83% [95% CI 64 to 93]	NIV is safe and has low failure and mortality rate especially in patients with no limitations of treatment.	The only variable associated with risk of intubation was admission SOFA
Vianello *et al.* [35], 2020	32703883	Retrospective study	ICU	COVID-19 AHRF PaO_2/FiO_2 108 [52–296]	HFNO $n=28$ Rescue 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 18% [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 AHRF secondary to COVID-19 not responding to conventional oxygen therapy	Severity of hypoxemia and C reactive protein level were correlated with HFNO failure
Wang *et al.* [41], 2020	32232685	Retrospective study	Mixed population	COVID-19 AHRF PaO_2/FiO_2 209 [179–376] in success patients PaO_2/FiO_2 142 [130–188] in failure patients	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 PaO_2/FiO_2 were more likely to experience HFNO failure

Table 2 (*Continued*)

Publication	PMID	Study design	Setting	Patient Population	Treatment	Intubation Rate	Mortality Rate	Main finding	Secondary findings
Wendel Garcia *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 $P=016$ 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] HNFO failure 77% [95% CI 61 to 88] NIV failure 79% [95% CI 63 to 90]	HFNO 80% [95% CI 64 to 90] 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_2 100 [66.6–126.7] in survivors PaO_2/FiO_2 62 [52–74] nonsurvivors	Overall cohort $n=52$ HFNO $n=33$ NIV $n=29$ IMV $n=22$	The progression among the interfaces is 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% [CI66 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 hypoxemic 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 PaO_2/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
Aliberti *et al.* [81], 2020	32747395	Observational prospective multicenter cohort study	High dependency unit	COVID-19 AHRF PaO_2/FiO_2 142 [97–203] 65 patients with limitations of treatment 92 patients with no limitations of treatment	Helmet CPAP $n=157$ PEEP 10.8 (2.3) cmH_2O 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]	Helmet CPAP is feasible in the high dependency unit and is associated with a failure rate $< 40\%$ in patients with no limitations of treatment with moderate to severe AHRF.	CPAP failure was associated with the severity of pneumonia on admission and higher baseline values of interleukin-6.
Alviset *et al.* [82], 2020	33052968	Retrospective study	Mixed setting	COVID-19 AHRF SpO2 $< 90\%$ oxygen therapy 15lt/min with nonrebreather face mask	Face Mask CPAP $n=41$ PEEP 5–10 cmH_2O 2 cases discontinued CPAP for intolerance	59% [95% CI 43 to 72]	29% [18 to 44]	CPAP is feasible outside of the ICU	The intubation rate was lower than 60%, with a mortality rate less than 1/3.
Arina *et al.* [79], 2020	33196858	Retrospective study	ICU	COVID-19 AHRF PaO_2/FiO_2 97 [75–135]	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 (15%) had CPAP as ceiling of treatment	43% [33 to 53]	At a multivariate model C-reactive protein and NT-proBMP had sensitivity of 0.75 [95% CI 0.62 to 0.86] and specificity of 0.83 [95% 0.61–0.95].	After 6 h of treatment in patients of the CPAP success group a PaO_2/FiO_2 raise of 77% was observed, while a raise of only 38% in patients that failed CPAP.
Bellani *et al.* [69▪], 2021	33395553	Single day observational study	Ward	COVID-19 AHRF PaO_2/FiO_2 172 (102)	NIV + CPAP $n=798$ 215 (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	Noninvasive respiratory support failure 38% [95% CI 34 to 41] in the overall cohort Noninvasive respiratory support failure 27% [23 to 30] in patients with no limitations of treatment cohort Noninvasive respiratory support failure 67% [61 to 73] in patients with limitations of treatment cohort	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 PaO_2/FiO_2 119 [99–153]	CPAP $n=64$ PEEP 10 cmH_2O in all patients	CPAP failure 17% [10 to 28] ETI 11% [5 to 21]	Overall mortality 14% [95% CI 8 to 25] Died on CPAP 6% [95% CI 2 to 15] Died on IMV 8% [95% CI 4 to 17]	CPAP was feasible in patients with moderate to severe AHRF	At univariate analysis CPAP failure correlated 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, $P=0.012$).

Table 3 (*Continued*)

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 SpO2 < 94% in Venturi Mask 40%	CPAP $n = 23$ BIPAP $n = 5$ BIPAP settings: max PEEP = 10.2 (2.9) cmH_2O max Pinsp = 22.4 (6) cmH_2O CPAP settings: Max PEEP = 12.7 (2.1) cmH_2O	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 PaO_2/FiO_2 160 [115–258]	CPAP $n = 85$ Interface: oro-nasal 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. 64% [95% CI 53 to 73]	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 PaO_2/FiO_2 103 [79–176]	CPAP $n = 306$ Patients with no limitations of treatment $n = 176$ Patients with limitations of treatment $n = 130$ PEEP 10 [7–10] cmH_2O 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%. It 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 PaO_2/FiO_2 during CPAP and number of comorbidities.
Corradi *et al.* [77], 2020	33197604	Single-center pilot study	ICU	COVID-19 AHRF PaO_2/FiO_2 195 [168–246]	Helmet CPAP $n = 27$ PEEP = 10 cmH_2O	Predefined criteria for ETI 33% [95% CI 17 to 52]	11% [95% CI 4 to 28]	CPAP failure was significantly associated with diaphragmatic thickening fraction at multivariate analysis, the best threshold was 21.4%	
De vita *et al.* [80], 2021	33500220	Retrospective multicenter study	High Intensity Unit	COVID-19 AHRF PaO_2/FiO_2 success 120 [75–160] PaO_2/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 cmH_2O, to be increased up to 15cmH_2O	Predefined criteria for intubation 41% [95% CI 36 to 46]	Not reported	In patients treated with CPAP, age, LDH and percentage change in PaO_2/FiO_2 after starting are predictors of intubation.	The use of CPAP avoided IMV in more than half of the patients.

Table 3 (*Continued*)

Publication	PMID	Study design	Setting	Patient Population	Treatment	Intubation Rate	Mortality Rate	Main finding	Secondary findings
Duca *et al.* [60], 2020	32766538	Retrospective study	Non-ICU	COVID-19 AHRF CPAP PaO_2/FiO_2 131 [97–190] NIV PaO_2/FiO_2 87 [53–120] IMV at arrival PaO_2/FiO_2 76 [60–177]	CPAP $n=71$ Helmet CPAP, PEEP = 15 [12–18] cmH_2O NIV $n=7$ NIV, PEEP = 16 [12–20] cmH_2O IMV at arrival = 7 IMV at arrival, PEEP = 18 [10–18] cmH_2O	CPAP intubation rate 37% [95% CI 26 to 48] NIV intubation rate 0% [95% CI 0 to 35] 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] IMV 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 PaO_2/FiO_2 130 (65) 25 (50%) patients had patients with limitations of treatment	NIV $n=25$ CPAP $n=25$ Interface: full face or oro-nasal mask Duration of treatment in the overall cohort: 187 (181) hours PEEP started at 5 cmH_2O, up to 12 cmH_2O IPAP set at 15cmH_2O, up to 20–25 cmH_2O	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 was useful in avoiding intubation in patients with no limitations of treatment.	The rate of infection among healthcare workers was low.
Franco *et al.* [67▪▪], 2020	32747398	Retrospective multicenter study	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 138 (66)	HFNO $n=163$ CPAP $n=330$ PEEP 10.2 (1.6) cmH_2O Helmet 149 (99%) Face mask 2 (1%) NIV $n=177$ PEEP 9.5 (2.2) cmH_2O Pressure Support 17.3 (3) cmH_2O Helmet 15 (21%) Face mask 57 (79%)	Recieved IMV: HFNO 29% [95% CI 24 to 36] 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]	30 day mortality: HFNO 16% [95% CI 11 to 22] CPAP 30% [95% CI 26 to 35] NIV 31% [95% CI 24 to 38] Difference not significant at adjusted analysis	Noninvasive respiratory support outside of ICU is feasibile, 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.* [87], 2020	32984836	Retrospective, multicenter study	ICU	COVID-19 AHRF $SpO_2 < 92\%$ 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 cmH_2O	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]	Difference in the intubation rate was significant after adjustment for age.	In obese patients Helmet CPAP is effective in reducing the ETI rate.
Kofod *et al.* [84], 2021	33889343	Retrospective study	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 101 (36) Patients with no limitations of treatment $n=27$ Patients with limitations of treatment $n=26$	CPAP $n=53$ Interface: Face Mask 30 patients received CPAP between 18 and 24 h a day. PEEP 10.5 [10–12] cmH_2O	CPAP failure overall cohort 72% [49 to 87] CPAP patients with no limitations of treatment 25% [95% CI 15 to 38]	Overall mortality 58% [45 to 71] CPAP limitations of treatment 92% [95% CI 76 to 98] CPAP patients with no limitations of treatment 13% [7 to 25]	CPAP seems to have positive effect on oxygenation and respiratory rate in most patients with severe respiratory failure caused by COVID-19, but the prognosis for especially elderly patients with high oxygen requirement and with a ceiling of treatment in the ward is poor.	A positive and significant ($P=0.002$) immediate response of CPAP was seen on respiratory rate, decreased from 28.6 (7.6) to 26.9 (6.2), and SpO_2, increased from 90.7 (3.5) to 92.7 (3.2) with a decrease of oxygen flow rate from 27.4 (13.3) to 23.3 (10.7).

Table 3 (*Continued*)

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 PaO_2/FiO_2 122 [97–175]	CPAP $n=24$ Interface: face mask PEEP 8.75 [7.5–10] cmH_2O	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.
Noeman-Ahmed *et al.* [86], 2020	33140491	Retrospective study	Acute Respiratory Care Unit	COVID-19 AHRF PaO_2/FiO_2 123.15 (59.56) Patients with no limitations of treatment $n=41$ Patients with limitations of treatment $n=11$	CPAP $n=52$ Interface: full-face mask Starting PEEP 10 cmH_2O titrated to 12.5 cmH_2O or 15 cmH_2O if SpO_2 is $\leq$ 94% with a FiO2 of 60%.	Patients with no limitations of treatment CPAP failure 51% [95% CI 36 to 66]	Patients with no limitations of treatment 20% [95%CI 10 to 34] 20% Patients with limitations of treatment 91% [95% CI 62 to 98]	CPAP success rate in the overall cohort was 40% with a mortality of 23%.	Predictors of success were: SpO2/FiO2, PaO_2/FiO_2, respiratory rate, neutrophil to lymphocyte ratio.
Oranger *et al.* [86], 2020	32430410	Retrospective study with short term historical control	Non-ICU	COVID-19 AHRF $O_2>6$ l/min to maintain $SpO_2\geq92\%$	case CPAP $n=38$ control SOT $n=14$ Interface: face mask with high end domiciliary ventilator PEEP 10 (adjusted between 8 and 12) cmH_2O CPAP was delivered for 8 [4–11] hours per day	Day 7 follow-up control SOT failure 54% [95% CI 33 to 79] case CPAP 24% [95% CI 13 to 39]	Day 7 follow-up control SOT 21% [95% CI 8 to 48] case CPAP 0 [95% CI 0 to 9%]	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 prospective study	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 152 (82)	CPAP $n=18$ Interface: Helmet PEEP 10 cmH_2O FiO_2 titrated to $SpO_2>93\%$.	CPAP ETI rate 22% [95% CI 9 to 45] The number of patients with no limitations of treatment and patients with limitations of treatment is not clearly defined.	Overall mortality 61% [95% CI 39 to 80]	Eleven patients died (61%), 4 among the responders (defined as patients with an improve of PaO_2/FiO_2 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.
Vaschetto *et al.* [74▪], 2021	33527074	Retrospective multicenter study	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 108 [71–157] Patients with no limitations of treatment $n=397$ Patients with limitations of treatment $n=140$	CPAP $n=537$ Interface: Helmet $n=399$ (74%) Face mask $n=123$ (23%) Both $n=15$ (3%) PEEP 10 [10–12] cmH_2O	Patients with no limitations of treatment 45% [95% CI 41 to 50]	Overall mortality 34% [95% CI 30 to 38] Patients with no limitations of treatment group mortality 21% [95% CI 17 to 25] Limitations of treatment mortality 73% [95% CI 65 to 79]	CPAP is feasible outside the ICU, with overall in-hospital mortality similar to that reported in other studies. Mortality is closely related to the therapeutic goal, patients having limitations of treatment being affected by much higher mortality.	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 hypoxemic 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.

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	33494771	Prospective multicenter observational study	Non-ICU	COVID-19 AHRF Responders PaO_2/FiO_2 136 [118–172] Non-Responders PaO_2/FiO_2 138 [113–177]	Awake PP $n=22$ CPAP $n=16$ STO $n=6$	14% [95% CI 5 to 33]	9% [95% CI 3 to 28]	Response to awake PP depends on localization of aeration loss, and lung ultrasound can predict it.	Sixteen (73%) patients improved oxygenation with awake PP, 3 patients (14%) improved dyspnea in 15 min, 12 (54%) improved dyspnea at 3 h. Responders (patient with a decrease in lung ultrasound score with PP) had shorter disease duration.
Bastoni *et al.* [102], 2020	32748797	Prospective observational study	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 68 (5)	Attempted awake PP $n=10$ Awake PP failed in 4 (40%) patients. Helmet NIV or helmet CPAP, PEEP ranging from 10 to 20 cmH2O	100% [95% CI 72 to 100]	Not available	Awake PP was feasible in 4 out of 10 patients	Awake PP improved the PaO_2/FiO_2 to 97 (8) but there was no difference in lung ultrasound
Burton-Papp *et al.* [103], 2020	33110499	Retrospective study	ICU	COVID-19 AHRF PaO_2/FiO_2 123 (28)	Attempted awake PP $n=20$ CPAP $n=4$ CPAP: PEEP 10 [8–10] cmH_2O BIPAP and CPAP $n=16$ EPAP 10 [10–10] cmH_2O IPAP 15 [14–16] cmH_2O Median duration of each cycle 3 (IQR 2) hours Number of cycles 5 (IQR 6.3) per patients Time spent prone 18% (IQR 31)	35% [95% CI 18 to 57]	0% [95% CI 0 to 16] ECMO 10% [3 to 30]	In patients with moderate AHRF treated with CPAP or NIV awake PP can improve oxygenation without relevant adverse events.	Patients that needed ETI did not had a significant improvement during prone position in PaO_2/FiO_2 [5, 95% CI -9 to 20] vs nonintubated [41, 95% CI 29 to 53].
Caputo *et al.* [104], 2020	32320506	Pilot study	Non-ICU	COVID-19 AHRF SpO_2 with supplemental oxygen was 82% [72–85]	Awake PP $n=50$	36% [95% CI 24 to 50]		Awake early prone position in the emergency department demonstrated improved oxygen saturation in COVID-19 patients.	
Cherian *et al.* [95], 2021	33845325	Retrospective study	Non-ICU	COVID-19 AHRF Patients that required IMV PaO_2/FiO_2 100 [95–155] Patients that did not required IMV PaO_2/FiO_2 206 [100–293]	Awake PP $n=59$ PP for at least 3 h/day. HFNO $n=52$ NIV $n=20$	IMV in the overall cohort 39% [95% CI 28 to 52]	32% [95% CI 22 to 45]	Awake PP can be safely performed with improvement in oxygenation. However, its institution may be beneficial only in patients with mild to moderate AHRF.	To avoid the risk of delayed intubation ROX index, improvement in PaO_2/FiO_2, reduction of LDH and D-Dimer should be monitored.
Coppo *et al.* [96], 2020	32569585	Prospective, feasibility study	Respiratory High Dependency Unit	COVID-19 AHRF PaO_2/FiO_2 standard care 180.5 (76.6)	Attempted awake PP $n=56$ PP was maintained for 3 [3–4] hours in 47 patients (84%) Helmet CPAP $n=44$ (79%) PEEP 8.3 (2.3) Reservoir mask 9 (16%) Venturi Mask 3 (5%)	25% [95% CI 15 to 40]	11% [95% CI 5 to 23]	PP was feasible and effective in rapidly ameliorating blood oxygenation in awake patients with COVID-19-related pneumonia requiring oxygen supplementation. The effect was maintained after resupination in half of the patients.	PaO_2/FiO_2 improvement in PP 104.9 [95% CI 70.9 to 134], PaO_2/FiO_2 not improved after resupination 12.3 [95% CI -10.9 to 35.5]. Only 23 (50%) of patients (responders) mainted the improvement, but it was was not significant. LDH and C-reactive protein were higher in responders.
Damarla *et al.* [105], 2020	32551807	Retrospective study	Mixed setting	COVID-19 AHRF Median oxygen requirement was 40% to achieve SpO_2 94% (91 to 95)	Awake PP $n=10$ HFNO $n=4$ Nasal cannula $n=5$ Room air $n=1$	20% [95% CI 6 to 51]	0% [95% CI 0 to 28]	PP is potentially a low-cost, easily implemented, and scalable intervention, particularly in low- and middle-income countries.	After 1h of PP SpO_2 improved to 98% [97–99] and respiratory rate was reduced to 22 [18–25] from 31 [28–39].

Table 4 (*Continued*)

Publication	PMID	Study design	Setting	Patient Population	Treatment	Intubation Rate	Mortality Rate	Main finding	Secondary findings
Despres *et al.* [106], 2020	32456663	Case series	ICU	COVID-19 AHRF PaO_2/FiO_2 183 (144 to 212)	Awake PP $n=6$ A total of 9 PP sessions were performed. HFNO in 4 sessions. SOT in 5 sessions.	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.	The proportion of patients with PaO_2/FiO_2 ratio improvement after PP appeared to be higher with HFNO compared to conventional oxygen therapy.
Ehrmann *et al.* [128▪▪], 2021	34425070	Prospective collaborative randomized controlled meta trial,	Mixed setting	COVID-19 AHRF SpO_2/FiO_2 awake PP 147.9 (43.9) SpO_2/FiO_2 standard care148.6 (43.1)	Awake PP $n=564$ Standard care $n=557$ All patients treated with HFNO FiO_2 0.6 [0.5 – 0.8] Awake PP HFNO flow 50 l/min [40–55] Standard care HFNO flow 40 l/min [40–50]	Treatment failure Awake PP 40% [95% CI 36 to 44] Treatment failure Standard care 46% [95% CI 42 to 50] IMV Awake PP 33% [95% CI 29 to 37] IMV Standard care 40% [95% CI 36 to 44]	Awake PP 21% [95% CI 18 to 24] Standard care 24% [95% CI 20 to 27]	Awake PP reduces the proportion of patients intubated or dying within 28 days of enrolment, 223 (40%) in the awake PP group vs 257 (46%) in the standard of care, $P=0.007$, relative risk reduction 0.86 [95% CI 0.75 to 0.98]. Patients that received PP for longer sessions had lower treatment failure rate.	Awake PP significantly improves blood oxygenation, respiratory rate and ROX index during PP. The benefit was maintained after supination.
Elharrar *et al.* [97], 2020	32412581	Prospective before after	ICU	COVID-19 AHRF O_2 supplement < 4l/min in 16 (67%) patients O_2 supplement ≥ 4l/min in 8 (33%) patients PaO_2 78 (14)	Attempted awake PP $n=24$ PP was maintained for: less than 1 h $n=4$ (17%) for 1 to 3 h $n=15$ (63%) for more than 3 h $n=5$ (21%)	Follow up to 10 days 21% [95% CI 9 to 40]	Not reported	Responders (increased $PaO_2>20\%$ from standard care) n = 6 [25%, 95% CI 12–45]; 3 patients were persistent responders.	63% of patients were able to prone for more than 3 h, and 42% reported back pain.
Fazzini *et al.* [107], 2021	https://doi.org/10.1177/1751143721996542	Prospective observational	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 115 (43)	Awake PP $n=46$ 12 (26%) patients could not tolerate PP for > 1 h. 34 (74%) awake PP for 5 h per session, 1 to 6 sessions daily. Interface: HFNO, CPAP, face mask oxygen; HFNO was the most used.	Overall cohort 43% [95% CI 30 to 58] Awake PP for > 1 h 29% [95% CI 17 to 46] Awake PP for < 1 h 83% [95% CI 55 to 95]	Overall cohort 30% [95% CI 19 to 45] Awake PP for > 1 h 26% [95% CI 15 to 43] Awake PP for < 1 h 42% [95% CI 19 to 68]	Patients that were pronated for more than 1 h had less need for endotracheal intubation than patients that were proned for less than 1 h.	PaO_2/FiO2 standard care 115 (43) vs 148 (70); Respiratory rate standard care 34 (7) vs 25 (7); Prone position > 1 h less need for ICU than prone position < 1hour (41% vs 83%).
Ferrando *et al.* [108], 2020	33023669	Prospective, multicenter, adjusted observational study	ICU	COVID-19 AHRF PaO_2/FiO_2, HFNO 111 [83–144] PaO_2/FiO_2, HFNO + PP 125 [99–187]	Overall cohort $n=199$ HFNO $n=144$ HFNO + PP $n=55$ Patients in group HFNO + PP underwent pronation for at least 16h/die	HFNO 42% [34 to 50%] HFNO + PP 40% [95% CI 28 to 53]	HFNO 10% [95% CI 6 to 16] HFNO + PP 11% [95% CI 5 to 22]	The combined approach of HFNO and PP did not decrease the risk of endotracheal intubation	Patients treated with HFNO + awake PP showed a trend for delay in intubation compared to HFNO alone [median 1 (interquartile range, IQR 1.0–2.5) vs 2 IQR 1.0–3.0] days ($P=0.055$), but Awake PP did not affect 28-day mortality ($P=0.92$).
Golestani-Eraghi *et al.* [109], 2020	32473503	Prospective, observational	ICU	COVID-19 AHRF $PaO_2/FiO_2<150$	Awake PP $n=10$ Helmet NIV (settings are not reported) Mean PP duration was 9 h	20% [95% CI 6 to 51]	20% [95% CI 6 to 51]	Authors report low intubation rate and high compliance to the intervention, suggesting that PP might be a useful tool to increase blood oxygenation in patients with moderate to severe AHRF related to COVID-19.	Improvement in oxygenation after PP: standard care PaO_2 46.34 (5.2) vs PP PaO_2 62.5 (4.6).
Hallifax *et al.* [110], 2020	32928787	Retrospective study	Respiratory High Dependency Unit	COVID-19 AHRF $FiO_2 \leq 60\%$ $n=22$ (46%) $FiO_2>60\%$ $n=26$ (54%) The proportion between patients with no limitations of treatment and patients with limitations of treatment is not specified.	Overall cohort $n=48$ Attempt awake PP $n=30$ Successfull proning defined as at least 2 h twice a day for 2 consecutive days. Full proning $n=11$ Semiproning $n=17$ Refused $n=2$ CPAP only $n=22$ HFNO + CPAP $n=26$ CPAP PEEP ranging from 6–8 cmH_2O	23% [95% CI 13 to 37]	Patients with limitations of treatment 54% [95% CI 40 to 67] 6% [95% CI 2 to 19] died on IMV 4% [95% CI 1 to 14] still on IMV	Data from this cohort of patients managed on respiratory high dependency unit show that CPAP and awake proning are possible in a selected population of COVID-19.	Increasing age and the inability to awake prone were the only independent predictors of COVID-19 mortality.

Table 4 (*Continued*)

Publication	PMID	Study design	Setting	Patient Population	Treatment	Intubation Rate	Mortality Rate	Main finding	Secondary findings
Jagan *et al.* [111], 2020	33063033	Retrospective study	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 not reported	Overall cohort $n=105$ Standard care $n=65$ Self-proning $n=40$ Self-proning was defined as a time spent PP greater or equal to 1 h, for at least 5 times/day, and for at least 1 h overnight. Interface not specified	Standard care 27% [95% CI 18 to 40] Self-proning 10% [95% CI 4 to 23]	Standard care 25% [95% CI 16 to 36] Self-proning 0% [95% CI 0 to 9]	Awake self-proning was well tolerated, with good compliance in 38% of patients and was associated with lower intubation rates, that remained significant after adjustment for SOFA and APACHE II.	The difference in mortality was significant at the univariate analysis but become nonsignificant after adjustment for SOFA and APACHE II.
Jayakumar *et al.* [125], 2021	33949237	Multicenter, randomized, controlled feasibility trial with 3 parallel groups	Non-ICU	COVID-19 AHRF Standard care PaO_2/FiO_2 185.6 (126) Awake PP PaO_2/FiO_2 201 (119) Discharged against medical advice: 2 patients in each group.	Overall cohort $n=60$ Standard care group $n=30$ PP group $n=30$ Encouraged to PP for at least 6 h/day. Median duration of PP per session was 2 h. 3 progressive interfaces: low flow oxygen (nonrebreather face mask) -> HFNO -> NIV (oronasal interface)	Standard care 13% [95% CI 5 to 30] Awake PP 13% [95% CI 5 to 30]	Standard care 7% [95% CI 2 to 21] Awake PP 10% [3 to 26]	In the prone group, 43% (13 out of 30) of patients were able to self-prone for 6 or more hours a day. 70% of the patients in the prone group were able to lie prone for 4 h a day. In the standard care group, 47% (14 out of 30) were completely supine and 53% spent some hours in the prone position, but none exceeded 6 h.	PaO_2/FiO_2 after 2 h was not different in the two groups: Standard care 171.7 (100.6) vs awake PP 198 (87.6), $P=0.3$. There were no adverse events in both groups.
Johonson *et al.* [126], 2021	33596394	Pragmatic randomized controlled trial	Non-ICU	COVID-19 AHRF FiO_2 at admission 21 [21–29], SpO2 at admission 94% [90–96]. Requiring supplemental O_2 at admission: 11 (36.7%) patients.	Overall cohort $n=30$ Standard care $n=15$ Awake PP $n=15$ Self-driven protocol. Only 6/15 (40%) patients were observed in PP in the first 72 h. Cumulative time spent in PP was 2.4% of total time (1.6 [95% CI 0.2 to 3.1] hours).	Standard care 7% [95% CI 12 to 30] Awake PP 13% [95% CI 4 to 38]	Standard care 0% [95% CI 0 to 20] Awake PP 13% [95% CI 4 to 38]	Patient-directed PP is not feasible in spontaneously breathing, nonintubated patients hospitalized with COVID-19.	No improvements in oxygenation were observed at 72 or 48 h.
Moghadam *et al.* [112], 2020	32427179	Prospective observational study	Non-ICU	COVID-19 AHRF Mean SpO_2 at arrival 85.6%	Awake PP $n=10$	0% [95% CI 0 to 28]	0% [95% CI 0 to 28]	SpO_2 improved from 85.6% to 95.9% after awake PP. 40% of patients reported improved dyspnea.	
Ng *et al.* [113], 2020	32457195	Case series	Non-ICU	COVID-19 AHRF Median room air SpO_2 at arrival 91% (91 to 94) Oxygen supplementation at arrival 2l/min [2–3]	Awake PP $n=10$ Cumulative median time in PP 21 h. Three (10%) patients were transferred to ICU: 1 (10%) HFNO 1 (10%) Venturi Mask 1 (10%) IMV	10% [95% CI 2 to 40]	10% [95% CI 2 to 40]	Awake PP can be a low-risk, low-cost maneuver which can help patients with COVID-19 pneumonia delay or reduce the need for intensive care.	Three out of 10 patients were transferred to ICU, and one died.
Padrao *et al.* [114], 2020	33107664	Retroscpetive study	Non-ICU	COVID-19 AHRF Standard care SpO_2 92.5% [90–94] O_2 flow rate 6 l/min [5–10] $SpO_2/FiO_2<235$ in 56 (53%) patients Awake PP SpO_2 92% [88–93] O_2 flow rate 7 l/min [5–13.5] $SpO_2/FiO_2<235$ in 36 (63%) patients SpO_2/FiO_2 196 [128–254]	Overall cohort $n=166$ Standard care $n=109$ Awake PP $n=57$ Nasal cannula 44% Venturi mask 10% Nonrebreather face mask 46% First session awake PP duration: < 1h (6%) 1–2h (14%) 2–3h (12%) 3–4h (10%) > 4h (58%)	Awake PP 58% [95% CI 45 to 70] Standard care 49% [95% CI 39 to 58]	Awake PP 11% [95% CI 5 to 21] Standard care 20% [95% CI 14 to 29]	Awake PP was not associated with a reduction of need of intubation, both at univariate or multivariate analysis.	Awake PP led to improvement in ROX index (from 5.7 [3.9–7.7] to 7.7 [5.4–11], SpO_2/FiO_2 (from 196 [128–254] to 224 [159–307]) and respiratory rate (from 34 [30–38] to 29 [26–32])

Table 4 (*Continued*)

Publication	PMID	Study design	Setting	Patient Population	Treatment	Intubation Rate	Mortality Rate	Main finding	Secondary findings
Paternoster *et al.* [98], 2020	33067029	Case series	High Dependency Unit	COVID-19 AHRF PaO_2/FiO_2 107.5 (21)	Awake PP $n=11$ Awake PP cycles of 13 (1.2) hours Helmet CPAP PEEP 9.6 (1.74) cmH_2O Seven (63.6%) patients needed dexmedetomidine during awake PP	27% [95% CI 10 to 57]	18 [95% CI 5 to 48]	In conclusion, helmet CPAP in prone position for COVID-19 severely hypoxemic acute respiratory failure resulted feasible and without complications; the infusion of dexmedetomidine to improve patients' compliance to pronation was well tolerate.	PaO_2/FiO_2 at enrollment 107 (20) PaO_2/FiO_2 after 24 h 214.6 (73) PaO_2/FiO_2 after 48 h 224.6 (86.6) PaO_2/FiO_2 after 72 h 244.4 (106.2) $P<0.001$ Respiratory rate at enrollment 27 (4) Respiratory rate after 24 h 24 (5) Respiratory rate after 48 h 22 (4) Respiratory rate after 72 h 20 (5) $P<0.001$
Perez-nieto *et al.* [124▪▪], 2021	34266942	Retrospectivemulticenter study	Non-ICU	COVID-19 AHRF SpO_2/FiO_2 189.5 (81.6)	Awake PP $n=505$ Standard care $n=322$ Awake PP group was prones for at least 2 consecutive hours. Awake PP Nasal Cannula 50% HFNO 12.1% Nonrebreather face mask 37.6% Standard care Nasal Cannula 46.3% HFNO 6.8% Nonrebreather face mask 46.9%	Awake PP 24% [95% CI 20 to 27] Standard care 40% [95% CI 35 to 46]	Awake PP 20% [95% CI 17 to 24] Standard care 38% [33 to 43]	Awake PP reduces the risk for endotracheal intubation and for mortality. The reduction of risk remained significant at multivariate, and after propensity score match.	Main risk factors associated with endotracheal intubation were age, $SpO_2/FiO_2<100$, and the use of nonrebreather mask.
Prud'homme *et al.* [115], 2021	33516704	Retrospective multicenter matched cohort study	Non-ICU	COVID-19 AHRF SpO_2/FiO_2 standard care 299 (45) SpO_2/FiO_2 awake PP 279 (84)	Awake PP $n=48$ Standard care $n=48$ Oxygen supplementation strategy: first line oxygen therapy, escalation to HFNO, escalation to NIV, escalation to IMV. 32 (67%) patients underwent PP from 3 to 8 h/day 16 (32%) patients underwent PP for >8 h/day	Follow up to day 14 Awake PP 15% [95% CI 7 to 27] Standard care 17% [95% CI 9 to 30]	Follow up to day 14 Awake PP 8% [95% CI 3 to 20] Standard care 12% [6 to 25]	Awake PP reduced the need of upgrading oxygen delivery method at day 14 (15 (31.2%)) compared with conventional treatment (25 (52.1%)), $P=0.038$ with a hazard ratio of 2.03 [95% CI, 1.07–3.86; $P=0.003$].	Awake PP did not decrease the need for endotracheal intubation or the mortality rate.
Retucci *et al.* [99], 2020	32679237	Pilot prospective observational study	High Dependency Unit	COVID-19 AHRF PaO_2/FiO_2 143 [97–204]	Awake PP $n=26$ Helmet CPAP Prone or lateral position lasted 1h Helmet CPAP PaO_2/FiO_2 180 [155–218] 39 sessions of attempted PP: 12 prone and 27 lateral positioning.	27% [95% CI 14 to 46]	8% [95% CI 2 to 24]	The target was an alveolar-arterial gradient decrease of more than 20% before and after PP. Of the 12 sessions of PP 33.3% of trials succeeded, 41.7% decrease in alveolar-arterial gradient of $<20\%$ from supine position, and 25% failed. Of the 39 sessions of lateral positioning: 8% succeeded, 52% decrease in alveolar-arterial gradient $<20\%$ from supine position, 40% failed.	Respiratory rate: standard care 23.7 (4.7), during PP 23.1 (4.5), after resupination 23.6 (4.7). PaO_2/FiO_2 182.9 (43), during awake PP 220 (64.5), after resupination 179.3 (43.9).
Ripoll-Gallardo *et al.* [116], 2020	32713387	Retrospective case series	Non-ICU	COVID-19 AHRF PaO_2/FiO_2, 115 (13)	Awake PP $n=13$ Interface: Helmet CPAP PEEP 10 cmH_2O	70% [95% CI 42 to 87]	54% [95% CI 29 to 77]	Patients with moderate to severe AHRF have a high intubation rate, despite the treatment with CPAP and awake PP.	PaO_2/FiO_2, improved before and after PP ($P=0.003$), but there was no difference in respiratory rate before and after.

Table 4 (*Continued*)

Publication	PMID	Study design	Setting	Patient Population	Treatment	Intubation Rate	Mortality Rate	Main finding	Secondary findings
Rosén *et al.* [127▪], 2021	34127046	Multicenter randomized clinical trial	Non-ICU	COVID-19 AHRF Standard care n = 39 PaO_2/FiO_2 standard care 115 [94–130] Prone n = 36 PaO_2/FiO_2 prone 115 [86–130]	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 33% [95% CI 20 to 49] Prone group 33% [95% CI 20 to 50]	Control group 8% [95% CI 3 to 20] Prone group 17% [95% CI 8 to 22]	The implemented protocol for awake PP increased duration of awake PP but did not reduce the rate of intubation in patients with AHRF due to COVID-19 compared to standard care.	Nine patients (23%) in the control group had pressure sores compared with two patients (6%) in the prone group, P = 0.03, there were no difference in the use of NIV, vasopressors, continuous renal-replacement therapy, ECMO, VFD, hospital and ICU length of stay and mortality among the two groups.
Sartini *et al.* [117], 2020	32412606	Cross sectional	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 157 (43)	Awake PP n = 15 Interface: NIV, PEEP 10 cmH_2O Number of PP cycles 2 [1–3], for a total duration of 3 [1–6] hours	Follow-up 14 days Awake PP failure 13% [95% CI 4 to 38]	Follow-up 14 days 7% [95% CI 1 to 30]	All patients had improvement in PaO_2/FiO_2 during PP, and 12 (80%) had maintained PaO_2/FiO_2 improvement after resupination.	All patients had a reduction in respiratory rate during PP, that was maintained after resupination.
Taboada *et al.* [118], 2021	33839432	Prospective observational study	ICU	COVID-19 AHRF PaO_2/FiO_2 93 [72–108]	Awake PP n = 63 Treated with HFNO and dexmedetomidine For a median of 4 [2.5–8] sessions, each lasting 36 [24–72] hours.	HFNO and awake PP failure 32% [95% CI 22 to 44]	11% [95% CI 5 to 21]	In patients with mild to moderate AHRF treatment with a combination of dexmedetomidine, HFNO and long periods of PP led to a mortality rate of 11%.	Application of HFNO, awake PP and dexmedetomidine was relatively safe, as bradycardia (<40 bpm) during DEX infusion was observed in 5 patients (7.9%).
Thompson *et al.* [119], 2020	32584946	Prospective observational study	Intermediate Care Unit,	COVID-19 AHRF SpO2 ≤ 93% in nasal cannula 6 l/min or 15 l/min via nonrebreather face mask)	Awake PP n = 25 At least 1 session lasting at least 1hour	48% [95% CI 30 to 66]	12% [95% CI 4 to 30]	During awake PP the range of improvement in SpO_2 was 1% to 34% (median [SE], 7% [1.2%]; 95% CI, 4.6%-9.4%).	An SpO_2 of 95% or greater after 1 h of PP was associated with a lower rate of intubation.
Tonelli *et al.* [120], 2021	33824084	Retrospectivemulticenter study	Respiratory ICU	COVID-19 AHRF PaO_2/FiO_2 overall cohort 149 [78–232] PaO_2/FiO_2 awake PP 141 [73–223] PaO_2/FiO_2 standard care 153 [84–232]; P = 0.03	Awake PP n = 38 Standard care n = 76 Awake PP encouraged for at least 3 h; number of daily PP sessions: 1 to 4 Interface: HFNO 69 (61%) Helmet CPAP 25 (22%) CPAP 8 cmH_2O and then adjusted Oro-nasal NIV 19% (17) PEEP 8 cmH_2O and then adjusted Pressure support 10 cmH_2O and then adjusted	Awake PP 18% [95% CI 9 to 33] Standard care 39% [95% CI 29 to 51]	Awake PP 13% [95% CI 6 to 27] Standard care 22% [95% CI 14 to 33]	Awake PP in awake and spontaneously breathing Covid-19 patients is feasible and can significantly reduce intubation rate (HR = 0.59 95% CI [0.3 to 0.94], P = 0.03 after adjustment) especially in those patients undergoing HFNO (HR = 0.34 95% CI [0.12 to 0.84], P = 0.04).	Awake PP increased the respiratory support free days (standard care 15 [2–22] vs 20 [2–24] P = 0.03) and decreased the respiratory ICU (standard care 15 [3–26] vs 10 [3–21] P = 0.02) and the hospital length of stay (standard care 24 [3–45] vs 20 [3–41], P = 0.03).
Tu *et al.* [121], 2020	32566624	Pilot retrospective study	ICU	COVID-19 AHRF PaO_2/FiO_2 lower 150	Awake PP n = 9 Treated with HFNO Awake PP sessions applied for 5 [3–8] times, with a duration 2 [1–4] hours.	22% [95% CI 6 to 55]	Not reported	Awake PP could improve blood oxygenation and potentially avoid endotracheal intubation.	Mean PaO_2 increased from 69 (10) to 108 (14) with awake PP (P < 0.00) and $PaCO_2$ decreased from 47 (7) to 39 (5) (P = 0.007).
Winearls *et al.* [100], 2020	32895247	Retrospective Study	Non-ICU	COVID-19 AHRF PaO_2/FiO_2 112 [106–194] Patients with no limitations of treatment n = 14 Patients with limitations of treatment n = 10	Attempted awake PP n = 24 Treated with CPAP, maximum PEEP 12 [12–15] cmH_2O Interface not specified 2 patients did not tolerate Awake PP 12 patients received full awake PP, 10 patients semiprone lateral position The mean (SD) time of awake PP was 8 (5) hours in first day.	Patients with no limitations of treatment 7% [95% CI 1 to 31]	Patients with limitations of treatment 40% [95% CI 17 to 69]	Awake PP alongside CPAP significantly increased both the ROX index and the PaO_2/FiO_2 from baseline values (ROX index: 7.0 (2.5) baseline vs 11.4 (3.7) CPAP + PP, P < 0.0001; PaO_2/FiO_2 143 (73) mm Hg baseline vs 252 (87) mm Hg CPAP + PP, P < 0.01).	No difference in respiratory rate at any timepoint was found.

Table 4 (*Continued*)

Publication	PMID	Study design	Setting	Patient Population	Treatment	Intubation Rate	Mortality Rate	Main finding	Secondary findings
Xu *et al.* [122], 2020	32448330	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	32699915	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] Standard care 76% [60 to 87], $P < 0.001$	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 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.

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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Conflicts of interest

There are no conflicts of interest.

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