Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Non-invasive oxygenation strategies for respiratory failure with COVID-19: A concise narrative review of literature in pre and mid-COVID-19 era

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ABSTRACT

The coronavirus disease 2019 (COVID-19) has spread globally and can cause a shortage of medical resources, in particular, mechanical ventilators. High-flow nasal cannula oxygen therapy (HFNC) and non-invasive positive pressure ventilation (NPPV) are frequently used for acute respiratory failure patients as alternatives to invasive mechanical ventilation. They are drawing attention because of a potential role to save mechanical ventilators. However, their effectiveness and risk of viral spread are unclear. The latest network meta-analysis of pre-COVID-19 trials reported that treatment with non-invasive oxygenation strategies was associated with improved survival when compared with conventional oxygen therapy. During the COVID-19 pandemic, a lot of clinical research on COVID-19 related acute respiratory failure has been reported. Several observational studies and small trials have suggested HFNC or NPPV as an alternative of standard oxygen therapy to manage COVID-19 related acute respiratory failure, provided that appropriate infection prevention is applied by health care workers to avoid risks of the virus transmission. Awake proning is an emerging strategy to optimise the management of patients with COVID-19 acute respiratory failure. However, the benefits of awake proning have yet to be assessed in properly designed clinical research. Although HFNC and NPPV are probably effective for acute respiratory failure, the safety data are mostly based on observational and experimental reports. As such, they should be implemented carefully if adequate personal protective equipment and negative pressure rooms are available.

Contents

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care medicine; HFNC, high-flow nasal cannula; NPPV, non-invasive positive pressure ventilation; ARF, acute respiratory failure; RCT, randomised clinical trial; COT, conventional oxygen therapy; PPE, personal protective equipment; AGPs, aerosol-generating procedures; AE-COPD, acute exacerbation of chronic obstructive pulmonary disease; DNI, do not intubate; IMV-after-NPPV, invasive mechanical ventilation after NPPV; IMV-only, invasive mechanical ventilation only.

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1. Introduction

The coronavirus disease 2019 (COVID-19) is a disease caused by a new type of coronavirus, SARS-CoV-2. It was first reported in Wuhan, China, in December 2019 and has spread globally in several months. SARS-CoV-2 can spread through contact with an infectious person and contact with droplets from an infected person's cough or nasal discharge, besides aerosol spread is considered possible route of transmission [1]. The virus infects respiratory systems and can cause mild to severe pneumonia. The onslaught of patients with acute respiratory failure forcefully demands intensive care with mechanical ventilation with a subsequent overwhelming need for ventilators and exceeding the capacity of the intensive care unit (ICU) [2–4]. The devastating situation inevitably drove attention to other available equipment.

High-flow nasal cannula oxygen therapy (HFNC) and non-invasive positive pressure ventilation (NPPV) are widely used in patients having acute respiratory failure (ARF) as alternatives to standard oxygen therapy to avoid invasive mechanical ventilation [5]. HFNC and NPPV require less staff resource and sedation than invasive mechanical ventilation and may provide benefits to patients who have the limitation of life-sustaining therapies [5–8]. Another therapeutic intervention re-explored for COVID-19 respiratory failure is awake prone positioning in spontaneously breathing patients. Awake proning is expected to reduce treatment failure when combined with HFNC or NPPV [9].

Under an emergency at risk of a shortage of a mechanical ventilator, strategies using HFNC or NPPV, so as to reduce the need for mechanical ventilation in patients with COVID-19, are appealing. However, significant concern exists about the risk of viral transmission to health care professionals as high-flow oxygen supply and positive pressure ventilation provided by HFNC and NPPV could spread aerosols suspending the virus [10]. We searched PubMed using the following keywords to obtain relevant articles: COVID-19, SARS-CoV-2, NPPV, NIV, non-invasive positive pressure ventilation, non-invasive ventilation, HFNC, NHF, HFT, HFNO, high-flow nasal cannula, nasal high flow, high-flow therapy, high-flow nasal oxygen. This concise review summarises existing literature about the efficacy and safety of HFNC or NPPV use and awake prone positioning in patients with COVID-19 respiratory failure.

2. Reports on the use of HFNC and NPPV by countries and COVID-19 guidelines

Attitude and recommendations towards the use of HFNC and NPPV for COVID-19 respiratory failure varie across countries and regions (Table 1) [11–17]. HFNC and NPPV were frequently used in hospitalised patients in the UK but less frequently in the US. In European ICUs, 10–25% of critically ill patients with COVID-19 received HFNC or NPPV.

Development of recommendations for COVID-19 management is a major but complex challenge. Despite the commonality of HFNC and NPPV for COVID-19, a few organisations or country guidelines suggest using HFNC [11], and another guideline supports the use of NPPV [18]. Most guidelines from major intensive care societies do not support the benefits of HFNC or NPPV, instead emphasising the risk of the virus transmission to health care workers [19–22]. The available evidence on the benefits and harms of HFNC and NPPV in patients infected by COVID-19 are based on case reports, expert opinions and observational studies. As such, the recommendations should have reflected the locally available resources and capacities of critical care, and values of the societies.

3. HFNC

3.1. What was known in the pre-COVID-19 era

HFNC is widely used for acute respiratory failure [23] because of its favourable tolerability [24] and physiologic support [25–27]. The first randomised clinical trial comparing HFNC with conventional oxygen therapy (COT) and NPPV in patients with ARF was conducted in France and reported that HFNC improved mortality (N = 310, 12% *vs.* 23% *vs.* 28%, $p = 0.02$) [28]. However, another trial conducted in emergency department by Jones et al., comparing COT with HFNC in adult patients with ARF, found that HFNC did not reduce the need for invasive mechanical ventilation (N = 303) [29]. Similarly, Azoulay et al. conducted a large RCT in immunocompromised patients with ARF (N = 776) and did not find any difference in mortality at day 28 and intubation rates between patients treated with HFNC or COT [30]. The latest

Table 1
The frequency of HFNC and NPPV use in patients with COVID-19 related acute respiratory failure.

Countries	HFNC	NPPV
US [12]	12 (4.7%)	3 (1.2%)
UK [13]	9244 (54.9%)	2670 (15.9%)
Germany [14]	286 (16.6%)	
Italy [15]	137 (10.6%)	
France, Switzerland, and Belgium [16]	786 (19%)	230 (6%)
China [17]	33 (63.5%)	29 (55.8%)

network meta-analysis showed that HFNC was associated with a lower risk of intubation in patients with ARF compared with COT (N = 3804, 25 RCTs, RR 0.76 [95% CI, 0.55–0.99]) [5]. However, the reduced risk of mortality was not observed in a subgroup of severe ARF defined as PaO2/FiO2 $<$ 200 [5]. A multicentre randomised controlled trial is ongoing in France with the aim to compare HFNC with COT in severe hypoxaemic acute respiratory failure [31] and therefore helping to find an appropriate target population.

3.2. What COVID-19 studies have shown

Only one small randomised trial conducted in China compared the efficacy of HFNC and COT in 32 patients infected by COVID-19. HFNC significantly improved oxygenation (PaO2/FiO2 ratio at 72 h, 321 $\pm$ 5 *vs.* 286 $\pm$ 7, p = 0.001), but did not reduce significantly length of ICU stay (4.0 $\pm$ 0.7 *vs.* 4.9 $\pm$ 1.0 days, p = 0.24) [32]. However, this trial was at high risks of biases, *i.e.*, unclear random sequence generation, unclear allocation concealment, and unclear definition of data set sent to analysis.

Other observational studies provided heterogeneous results on intubation rates using HFNC ranging from 30 to 60%. A Spanish retrospective observational study including 40 patients with COVID-19 managed using HFNC reported an intubation rate of 52% [33], while another retrospective observational study from Wuhan reported a 30% rate of intubation in 43 COVID-19 patients [34]. A larger retrospective observational study of two hospitals in China reported in 105 patients with ARF (pulse oxymetry $\leq$ 92% or respiratory rate $\geq$ 25 under 10 L/min) treated with HFNC a failure treatment of 38% [35]. A prospective observational study from two hospitals in South Africa including 293 patients treated with HFNC for severe respiratory failure (respiratory rate $\geq$ 30 with pulse oxymetry $\leq$ 92% despite oxygen at 15 L/min) reported a failure treatment of 53% [36]. Two French observational studies comparing HFNC with COT, using propensity score, in a larger number of patients treated for acute hypoxaemic respiratory failure due to COVID-19 reported benefits in terms of intubation rates with HFNC, but no difference in mortality rates between the two strategies [37,38].

One potential risk using HFNC is to delay intubation and to increase mortality [39]. A North American study from six COVID-19 specific ICUs included 231 patients of whom 175 were intubated. Timing of intubation was not associated with mortality. Indeed, patients under HFNC even intubated after 24 h of treatment had not a higher risk of mortality than those intubated earlier [40]. Another retrospective observational study compared the intubation and mortality rates before and after implementing non-invasive respiratory support protocol, which encouraged the use of HFNC, NPPV, and self-proning [41]. The study reported that the need for intubation decreased from 25% (64/254) to 11% (23/215) without increasing mortality (25% before implementation *vs.* 28.8% after implementation; p = 0.14) [41].

These findings imply that HFNC could be an effective strategy of oxygenation for respiratory failure in patients with COVID-19. However, these observational studies cannot mitigate the risk of bias due to confounding factors, *i.e.*, confounding by indications. In addition, clinicians should carefully use HFNC because most studies on the efficacy of HFNC were conducted in ICUs or respiratory wards, where medical staffs were familiar with HFNC.

Some severe hypoxic COVID-19 patients do not present the increased work of breathing, as generally observed in ARF patients from other causes. Such patients may not require mechanical pressure support, thus, may as well benefit from HFNC. However, using HFNC in such patients inherits the risk of harm from delayed intubation as the appropriate timing of intubation is still being discussed. Further studies are needed to investigate the benefits and harms of using HFNC for severe COVID-19 ARF.

3.3. Risks of virus transmission

According to the risk of the virus transmission to HCWs through aerosol dispersed from oxygenation supports, guidelines recommend appropriate personal protective equipment (PPE) and airborne precaution during aerosol-generating procedures (AGPs) [19–22]. Indeed, the risk of transmission depends on environmental conditions (humidity, local ventilation) and also on the anatomic location of the aerosol generation (form bronchioles to vocal cord) or on the action of patient (breathing, speaking or coughing) [42]. To better describe this risk, several experimental studies have assessed particle concentration in room air, the distance of dispersion from patient airways using different oxygenation supports. Gaeckle et al. reported in 10 healthy volunteers while breathing, talking, and coughing the size and concentration of particles and droplets generated from the respiratory tract with HFNC, non-humidified nasal cannula [10]. The experiment was conducted in a negative-pressure room with 15 air exchanges per hour. Use of HFNC did not significantly increase aerosol generation from the respiratory tract. When the participants were breathing normally, the median exhaled particle concentrations were 0.068, 0.050, 0.046, and 0.041 particles/cm^3 with room air, HFNC 10 L/min, HFNC 30 L/min, HFNC 50 L/min, respectively [10]. Even when the participants coughed, no difference in the size and concentration of exhaled particle was observed. Jie et al. summarised the results from reported in vitro studies of exhaled smoke dispersion with different oxygen devices [43]. Provided that the same study method and similar breathing patterns were applied, authors found that the exhaled smoke dispersion distance with HFNC ranged from 13 to 17 cm at 30 and 60 L/min. This was similar to the one observed with a simple oxygen mask around 10 cm and even smaller than with other oxygenation devices, as non-rebreathing 25 cm, or Venturi masks, up to 40 cm.

Using a surgical mask with HFNC may decrease the risk of aerosol spread. Leonard et al. showed that a surgical mask captured 67.6% of exhaled small particles ($\leq$ 5 μm) and 93.4% of large particles ($>$ 5 μm) during HFNC [44]. In the experiment, a particle size more than and equal to 5 μm was used to mimic the transmission conditions of COVID-19. Moreover, wearing a surgical mask does not harm patients with respiratory failure. Montiel et al. evaluated oxygenation parameters in 21 hypoxemic COVID-19 patients wearing a surgical mask for $\geq$ 30 min with HFNC. PaO2 increased significantly from 59 mmHg ($\pm$ 6) to 79 mmHg ($\pm$ 16), whereas PaCO2 increased from 31 mmHg ($\pm$ 3) to 32 mmHg ($\pm$ 4) ($p < 0.002$) [45]. The change in PaCO2 was small and may not be clinically relevant. However, it should be noted that the data supporting the safety of a surgical mask on top of HFNC for patients are scarce.

The safety of HFNC for bedside HCWs in clinical settings has been investigated in several observational studies. A retrospective before-after study at a tertiary care hospital in the United States reported that the incidence of infection did not increase in clinical staff after the implementation of COVID-19 respiratory protocol [46]. The protocol included encouragement of HFNC and NPPV for COVID-19 patients with hypoxaemic respiratory failure and PPE and N95/KN95 for hospital staff to wear. Also, the incidence did not increase in clinicians working in the COVID-19 unit using HFNC or NPPV compared to those working in the COVID-19 unit where HFNC or NPPV was not used (2/79, 2.5% *vs.* 4/67, 6.0%) [46]. Another multicentre survey reported no medical staff that participated in HFNC and NIV management of COVID-19 patients got infected where PPE and N95 mask were provided [47].

Although most reports were single-centre study, no or very few HCWs contracted COVID-19 where patients wore a surgical mask

on top of HFNC in negative pressure rooms, and HCWs wore PPE and N95 or FFP2 masks [48–50]. These results suggest that HCWs may not be at greater risk of COVID-19 infection.

3.4. Limitations of the studies on HFNC

RCTs in the pre-COVID-19 era may provide high-quality evidence to support the use of HFNC in ARF [5,28–30]. However, the beneficial effect on mortality over conventional oxygen therapy has yet to be confirmed in patients with severe ARF. COVID-19 studies are mostly experimental or retrospective observational.

3.5. Implications for future COVID-19 research

Proper RCTs of high quality that focused on the effectiveness of HFNC in patients with COVID-19 respiratory failure are warranted. Such trials should also assess the safety not only for patients but for virus transmission to HCWs. As the incidence of virus transmission from patients to HCWs appears low, large-size multicentre observational studies would also provide precise data on the safety of HFNC for ARF with COVID-19. Seven RCTs [51–57] are ongoing. Severity of patients who are beneficial to use HFNC will be found if any positive data come and risk of transmission to HWCs also needs to be evaluated.

4. NPPV

4.1. What was known in pre-COVID-19 era

NPPV helps to recruit collapsed alveoli and relieves work of breathing [58]. RCTs and guidelines support NPPV use as first line therapy for ARF due to acute heart failure and acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) with hypercapnic respiratory acidosis [59–61]. Two meta-analyses showed that NPPV significantly reduced mortality and intubation rate in AE-COPD with hypercapnic or acute heart failure patients [62,63].

However, the beneficial effects of NPPV in acute hypoxaemic respiratory failure are controversial.

Frat et al. reported that, in patients with hypoxaemic ARF, NIV was associated with a higher risk of mortality as compared to HFNC or COT and a higher risk of intubation in severe hypoxaemic patients [28]. However, Lemiale et al. reported that, in 374 immunocompromised patients with AR, NPPV did not increase the risks of intubation or mortality, as compared to COT, which reduced those risks [64]. Similarly, a RCT including 200 patients with pneumonia did not find significant decrease either in the proportion of patients requiring intubation (9.2 *vs.* 10.8%, $p = 0.706$) or ICU mortality (3.1 *vs.* 4.9%, $p = 0.721$) [65].

A recent meta-analysis showed that face mask NPPV was associated with lower risk of mortality (N = 3370, 21 RCTs, RR 0.83 [95% CI, 0.68–0.99]) and lower risk of intubation compared with COT (N = 3082, 25 RCTs, RR 0.76 [95% CI, 0.62–0.90] [5]. This meta-analysis excluded RCTs, which had included 50% or more patients suffering from AE-COPD or chronic heart failure patients. However, these results were based on the analysis with heterogeneity, which was derived from including AE-COPD or chronic heart failure patients partially. In fact, sensitivity analysis which excluded RCTs including at least one patient with AE-COPD or chronic heart failure patients showed that mortality did not significantly decrease (RR 1.2 [95% CI, 0.89–1.6]) and the rate of intubation significantly decreased (RR 1.3 [95% CI, 1.1–1.7]) in comparing face mask NPPV with COT. These results support that NPPV may decrease intubation rate compared to COT in adult patients with ARF not due to AE-COPD with hypercapnic respiratory acidosis or acute heart failure.

4.2. What COVID-19 studies have shown

An intubation rates of patients with COVID-19 using NPPV were reportedly 10.9–44.6% [66–72]. The efficacy of NPPV for COVID-19 ARF is unclear because there is little high-quality evidence. A population-based study involving 1,400 patients in a province in Italy surveyed 520 symptomatic in-hospital patients with COVID-19 ARF [73]. Of the 520 patients, 408 (78.5%), 46 (8.8%), 25 (4.8%) and 41 (7.9%) patients were treated with COT only, NPPV only, invasive mechanical ventilation after NPPV (IMV-after-NPPV), and invasive mechanical ventilation only (IMV-only), respectively. Mortality at 60-day did not increase in IMV-after-NPPV (32.0%) compared with IMV-only (36.6%) ($p = 0.165$) [73], suggesting NPPV may be safely used in patients with COVID-19 ARF. A similar result was also shown in the other observational trial in which the overall mortality was compared between NPPV only, IMV-after-NPPV and IMV-only including 87, 44 and 91 patients respectively [72]. Mortality at 30-day in IMV-after-NPPV (84%) did not be worsened compared with IMV-only (82%) ($p = 0.05$).

Several observational studies should be highlighted as they provided data on how NPPV was used in patients with the limitation of medical treatment. A retrospective observational study in a UK hospital reported that 24 patients with the ceiling of ventilation care were treated with NPPV in a Level 2 area. Twenty patients (83.3%) died in the hospital, and four patients (16.7%) discharged home [69]. Another retrospective observational study in Italy showed in 27 patients with a "Do Not Intubate (DNI)" order managed with NPPV an in-hospital mortality rate of 89% [74]. On the other hand, two reports from UK and France reported better outcomes [75,76]. Twenty-eight patients with COVID-19 ARF who were too frail to receive the potential benefit from intubation were managed with NPPV, of whom 50% survived to discharge [75]. In a before-after study conducted in France, intubation or death in patients with a DNI order had decreased after NPPV was introduced as a part of respiratory therapy for COVID-19 ARF [76].

These studies used CPAP or BiPAP mode except for two studies [73,76], which used CPAP only and showed that NPPV use did not increase mortality.

4.3. Risk of virus transmission

Two experimental studies [10,77] and two observational studies [46,47] reported that NPPV did not significantly increase aerosol production compared with the low-flow nasal cannula and would not increase the risk of infection to HCWs. In the experiment by Gaeckle et al., the particle concentrations generated by NPPV were also measured for HFNC in ten healthy participants in a negative-pressure room. Median particle concentrations were 0.068, 0.056, and 0.057 particles/cm^3 with no oxygen, NPPV 12/5 cm H_2O and NPPV 20/10 cm H_2O, respectively, and there was no significant difference between the three groups [10]. A similar experiment by Millar et al. concluded that the use of NPPV did not significantly increase aerosol production compared to low-flow nasal cannula [77].

The largest data on the safety of NPPV for HCWs are available from the single-centre retrospective study comparing before and after the implementation of the COVID-19 respiratory protocol, which included wearing PPE and N95/KN95 mask during AGPs. The incidence of COVID-19 infection was similar between HCWs in a COVID-19 unit where HFNC or NPPV were used and a COVID-19 unit where those devices were not used as described above [46].

Two reports from France supported the results [68,76]. A retrospective study was conducted where all HCWs who took care of patients on NPPV for COVID-19 ARF used appropriate PPE, *i.e.*, FFP2/FFP3 masks, eye and head protection, disposable protective suits, gloves, and overshoes. During the study period, 61 patients with COVID-19 ARF were managed with NPPV; however, none of the HCWs was infected [68]. In the before-after study of NPPV implementation for COVID-19 ARF, the proportion of HCWs who had contracted COVID-19 did not increase (before 10%, after 6%) [76].

4.4. Limitations of the studies

Contrary to the pre-COVID-19 studies, COVID-19 studies are all experimental or observational studies with small sizes. The observational studies inherit indication/selection biases, which leads to the overestimation of the efficacy of NPPV. If NPPV is to be used for COVID-19 ARF, close monitoring will be mandatory when NPPV is used at the discretion of treating clinicians. Given the possible biases in the available evidence, the expected benefits may not outweigh the risk of worsening respiratory failure due to displacement of a facial mask by accident or intolerance particularly in general wards. Furthermore, safety data of virus transmission could be subject to underreporting.

4.5. Implications for future COVID-19 research

A number of RCTs have been registered in trial registries. High-quality, adequately powered, multicentre RCTs assessing patient-centred outcomes are important; furthermore, the safety assessment for HCWs is warranted. To assess the incidence of the virus transmission, unit-level or team-level randomisation is required, thus cluster randomised trial would be desirable. Five RCTs [53–57] are ongoing. The most effective superiority in type of device will be revealed if any beneficial outcomes are found and the degree of greater risk of infection in HWCs also needs to be assessed.

4.6. *Helmet NPPV* versus *HFNC*

A recent open-label RCT that recruited 109 patients with COVID-19 ARF (ratio of PaO2/FiO2 $\leq$ 200) compared the effects of helmet NPPV and HFNC on 28-day respiratory support free days [78]. Helmet NPPV did not significantly improved the primary outcome (20 *vs.* 18 days, $p = 0.26$). However, helmet NPPV significantly reduced the rate of endotracheal intubation (30 *vs.* 51%, $p = 0.03$) and increased 28-day invasive mechanical ventilation free days (28 *vs.* 25 days [mean difference, 3 days, 95% CI, 0–7, $P = 0.04$]). The trial sample size was calculated under the assumption that helmet HPPV can increase 28-day respiratory support free days by 3 days (14 days *vs.* 11 days). As the primary outcome data in patients with COVID-19 ARF were limited before the trial, the sample size calculation would not have been feasible. Also, co-intervention imbalance might have affected the results, as the trial interventions could not be blinded. Despite these limitations, the results suggested that helmet NPPV might be the preferable NIV strategy to improve outcomes of patients with COVID-19 ARF. Adequately powered larger trials are expected to apply helmet NPPV into clinical practice [79].

5. Preference of NPPV *versus* HFNC

Since the Helmet NPPV led to less need for invasive mechanical ventilation than HFNC in the open label RCT, Helmet NPPV may be preferable for the management of ARF in COVID-19 patients, if available. However, given the small sample size and the limited availability, it would also be reasonable for clinicians to choose other non-invasive ventilation strategies based on the physiological effects, patient tolerability, and familiarity at facilities.

6. Awake proning

6.1. What was known in pre-COVID-19 era

Since first described in the 1970s in patients on invasive mechanical ventilation [80], prone positioning has been used for hypoxaemic respiratory failure requiring mechanical ventilation. The suggested mechanisms to improve oxygenation include better ventilation-perfusion matching [81] and alterations in end-expiratory lung volume and chest wall compliances [82]. Prone positioning in patients with severe ARDS on invasive mechanical ventilation improved survival in several RCTs [83–85]. In contrast, there have been no RCTs assessing the impact of awake proning for ARF.

Awake proning may safely improve oxygenation and decrease respiratory effort in patients with ARF without any additional resources. A retrospective study including 15 non-intubated patients receiving oxygen or HFNC/NPPV for moderate to severe ARF reported the clinical courses of 43 awake proning procedures [86]. Two interruptions due to intolerance occurred; however, no complications were documented. Awake proning improved oxygenation, but the oxygenation improvement was not maintained after resupination (PaO_2/FiO_2 124 $\pm$ 50 mmHg, 187 $\pm$ 72 mmHg, and 140 $\pm$ 61 mmHg, during pre-proning, proning, and post-proning procedures, respectively) [86].

Ding et al. reported a series of 20 non-intubated patients with moderate to severe ARDS in a respiratory ICU of two university teaching hospitals [87]. The main causes of ARDS were infectious pneumonia due to influenza (9 cases, 45%) or other viruses (2 cases, 10%). Patients were placed in awake proning with NPPV or with HFNC, and the efficacy in improving oxygenation with each support methods was evaluated. In both HFNC/NPPV patients, PaO2/FiO2 ratio demonstrated an upward trend with awake proning. Among these patients, 11 were avoided intubation, and nine patients were intubated. All 7 patients with a PaO2/FiO2 $<$ 100 mmHg on NIV required intubation [87].

6.2. What COVID-19 studies have shown

An international survey was conducted in 40 countries, to which 502 respondents completed. The survey reported that 46.2% had tried awake proning with HFNC or NPPV for COVID-19 ARF [88]. Despite the strong interest in awake proning for COVID-19 ARF among medical communities and social media, evidence that supports the use of prone positioning in non-intubated COVID-19 patients is still limited. A number of reports have been published; however, all are small case series or observational studies [89].

A prospective observational study, including 56 non-intubated patients with COVID-19 ARF, reported feasibility and physiological effect on gas exchange of awake prone positioning [90]. The awake proning was feasible in 47 of the 56 patients for at least 3 h (median 3 h [IQR 3–4]). PaO2/FiO2 ratio significantly improved with awake proning (180.5 mm Hg [SD 76.6] in supine position *vs.* 285.5 mm Hg [112.9] in prone position; $p < 0.0001$). When resupinated, oxygenation level was maintained only in 23 patients (41%). Overall, oxygenation improvement was not maintained after resupination (PaO2/FiO2 ratio 192.9 mm Hg [100.9] 1 h after resupination; $p = 0.29$ [*vs.* pre-proning]) [90].

On the other hand, some studies have shown negative results. A larger retrospective observational study including 166 cases of

Table 2
Key articles for the interventions in patients with COVID-19 covered in this review.

	Study?	Design	Method	Main result	Key point
HFNC	Teng [32]	RCT	Population, severe COVID-19 patients (n = 22); intervention, HFNC (n = 12) *vs.* COT (n = 10)	P/F ratio at 72 h 321 ± 5 *vs.* 286 ± 7 (p = 0.001)	This is the only available RCT that compared the efficacy of HFNC and COT.
	Hernandez-Romieu [40]	Retrospective observational study	Population, COVID-19 patients admitted to ICUs; exposure, HFNC prior to intubation (n = 78) *vs.* intubated without preceding HFNC (n = 97)	Mortality 30.8% *vs.* 40.2% (p = 0.2)	This is the largest study which explored the safety of HFNC use before the intubation
NPPV	Grieco [78]	RCT	Population, COVID-19 ARF patients (n = 109); intervention, Helmet NPPV (n = 54) *vs.* HFNC (n = 55)	Intubation rate 30 *vs.* 51% (95% CI, −38 to −3%, p = 0.03)	This is the only RCT, which investigated the efficacy of helmet NPPV *vs.* HFNC
	Potalivo [73]	Retrospective observational study	Population, COVID-19 ARF patients who needed respiratory support; exposure IMV after NIV (n = 25) *vs.* IMV only (n = 41)	Overall 60-day mortality 32.0 *vs.* 36.6% (p = 0.165)	This is the largest study, which explored the safety of preceding NPPV use before the intubation
Awake proning	Coppo [90]	Prospective observational study	Population, non-intubated patients with COVID-19 ARF; exposure awake proning (n = 47)	P/F ratio before *vs.* after 180.5 *vs.* 285.5 ($p < 0.001$)	This study reported that the awake proning improved P/F ratio in patients with COVID-19
	Padrão [91]	Retrospective observational study	Population, patients with COVID-19 ARF (n = 166); exposure, awake proning (n = 57) *vs.* usual care (n = 109)	Intubation rate 58 *vs.* 49% (95% CI, 0.78–1.88, p = 0.39)	This larger study investigated the effect of awake proning in patients with COVID-19, reporting no benefits to avoid the intubation

confirmed or suspected COVID-19 ARF in need of oxygen supplementation (> 3 L/min) and tachypnoea (> 24 bpm) reported no difference in intubation rates between awake proning (33/57, 58%) and usual care (53/109, 49%) (adjusted hazard ratio 0.90; 95% CI, 0.55–1.49; p = 0.69) [91]. A multicentre observational study from Spain assessed the effect of awake proning in patients with COVID-19 ARF on HFNC [92]. Of 199 patients who received HFNC, 55 patients (27.6%) were pronated during HFNC, and 144 patients were managed only with HFNC. The use of awake proning as adjunctive therapy to HFNC did not reduce the risk of intubation (RR, 0.87; 95% CI, 0.53–1.43; p = 0.60]. Furthermore, awake proning did not affect 28-day mortality (RR 1.04; 95% CI, 0.40–2.72, p = 0.92] [92]. Thus, the benefits of awake proning in patients with COVID-19 ARF have yet to be confirmed.

Adverse events during awake proning should be noted. The reported adverse events were discomfort, nosebleeds, sternal pain, back pain, pressure ulcers, intolerance of awake prone positioning, and deaths [89]. Gastric distention, gastroesophageal reflux, vomiting, accidentally disconnection of oxygen supplement can also occur during prone positioning [93].

There is no consensus on the selection of appropriate patient for awake proning. Awake prone positioning has been applied to patients with mild to moderate hypoxic failure in most studies. Patients requiring urgent intubation or patients with altered mental status, haemodynamic instability, trauma, or intra abdominal hypertension were not eligible for proning [89].

Similarly, there is no consensus on appropriate duration and frequency during the procedure. The duration of awake proning for each session varied from < 1 h [94] to > 18 h [95], and the proning session was applied repeatedly in a day. Xu et al. applied awake proning with HFNC in 10 patients with COVID-19 ARF more than 16 h per day. They reported mean PaO2/FiO2 improved after a prone position, and none of them required invasive mechanical ventilation [96], suggesting that a longer duration of prone positioning is associated with treatment success.

6.3. Limitations of the studies

Studies in both the pre-COVID-19 and COVID-19 era are all observational studies; as such, there is insufficient evidence that supports or is against the application of awake proning in patients with ARF. Selected observational studies reported the improved oxygenation during awake proning. However, it has been consistently reported that the improved oxygenation could not be maintained after resupination. Furthermore, the expected benefits to reduce mortality and endotracheal intubation are yet to be determined. Also, the procedures of awake proning varied across the studies, which made it difficult to meta-analyse the effect on clinical outcomes.

6.4. Implications for future COVID-19 research

Adequately powered, multicentre RCTs assessing patient-centred outcomes, *e.g.*, mortality, intubation rate, are warranted. Of note, given the PROSEVA trial in sedated, intubated, and mechanically ventilated patients applied long duration of prone positioning protocol for more than 16 h and demonstrated mortality benefit, future research on awake proning in patients with COVID-19 ARF should consider long intervention. In applying such long intervention, patients' needs to be on close monitoring as patient intolerance and adverse events will occur frequently.

More than 10 RCTs [97–101] are ongoing. The optimal duration and frequency of awake proning will be explored if any beneficial effects will be observed.

7. Summary

Key articles in this review are summarised in Table 2. HFNC and NPPV for moderate ARF were suggested to be beneficial to avoid intubation and improve mortality from the meta-analysis of pre-COVID RCTs. A number of observational studies reported possible benefits of HFNC or NPPV for COVID-19 ARF. In particular, HFNC or NPPV may be considered for patients with a DNI order. Despite that conducting proper RCTs amid pandemic is challenging, many trials are reported to be completed. Findings from the trials should be reported with transparency to provide minimally biased information.

Also, strong interest should focus on the safety of HFNC and NPPV for HCWs when the positive pressure ventilation devices are applied to COVID-19 patients. From the currently available epidemiological data, the risks of virus spread and transmission to HCWs appear low when HCWs wear appropriate PPE with N95/FFP2 mask in a negative pressure room. The safety of HCWs is of

top priority, as such any RCTs or observational studies on the clinical impact of HFNC and NPPV should assess the possible risk of COVID-19 transmission to HCWs to provide precise and reliable data. Finally, awake proning should not be implemented into clinical practice until further research provides high-quality data of benefits and safety for patients with ARF.

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Author contributions

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KO and TF conceived the topic and frame of the article. KO, KA, and JI retrieved all the relevant reports and research articles and retrieved the data. KO and TF drafted the manuscript. KA and JI provided critical intellectual input to the manuscript. All the authors approved the final manuscript

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