REVIEW ARTICLE

Effectiveness of high-flow nasal cannula therapy on clinical outcomes in adults with COVID-19: A systematic review

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Introduction/Background: Coronavirus disease 2019 (COVID-19) has high transmissibility and mortality rates. High-flow nasal cannula therapy (HFNC) might reduce the need for orotracheal intubation, easing the burden on the health system caused by COVID-19. The objective of the present study was to examine the effectiveness of HFNC in adult patients hospitalized with COVID-19. Specifically, the present study explores the effects of HFNC on rates of mortality, intubation and intensive care units (ICU) length of stay. The present study also seeks to define predictors of success and failure of HFNC.

Methods: A systematic literature search was conducted in the PubMed, EMBASE and SCOPUS databases, and the study was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Study quality was assessed using the National Heart, Lung, and Blood Institute's Study Quality Assessment Tools.

Results: The search identified 1,476 unique titles; 95 articles received full-text reviews and 40 studies were included in this review. HFNC was associated with a reduction in the rate of orotracheal intubation, notably when compared to conventional oxygen therapy. Studies reported inconsistency in whether HFNC reduced ICU length of stay or mortality rates. Among the predictors of HFNC failure/success, a ratio of oxygen saturation index of approximately 5 or more was associated with HFNC success.

Conclusion: In adult patients hospitalized with COVID-19, HFNC may prove effective in reducing the rate of orotracheal intubation. The ratio of the oxygen saturation index was the parameter most examined as a predictor of HFNC success. Low-level research designs, inherent study weaknesses and inconsistent findings made it impossible to conclude whether HFNC reduces ICU length of stay or mortality. Future studies should employ higher level research designs.

Key Words: *COVID-19; intensive care units; intratracheal; intubation; nasal cannula; oxygen inhalation therapy; respiratory insufficiency*

INTRODUCTION

The *Coronavirus Disease 2019* (COVID-19), which is an infection caused by the new coronavirus (2019-nCoV or SARS-CoV-2), rapidly evolved to pandemic levels because of its high rate of transmissibility and mortality [1]. In its most severe form, this viral pneumonia may evolve into acute respiratory distress syndrome (ARDS), septic shock, metabolic disorders and coagulopathy [2].

Respiratory failure is the leading cause of death in patients with severe COVID-19. This occurs because of a combination of two factors: viral pneumonia and ARDS. Therefore, an adequate ventilatory support strategy is essential for the treatment of COVID-19 [3].

High-flow nasal cannula therapy (HFNC) is a viable approach to the treatment of mild to moderate hypoxemic respiratory failure helping to reverse respiratory acidosis [4]. HFNC provides a flow of up to 60 L/min of heated and humidified oxygen with accurate titration of FiO_2 through a nasal cannula. The beneficial physiological effects include reducing oxygen dilution, reducing the physiological dead space, generating positive end-expiratory pressure, promoting secretion clearance and reducing the development of bronchial hyper-responsiveness symptoms, in addition to being more comfortable for the patient [5]; it can also reduce dyspnea [6].

Although the development of vaccines has reduced the number of deaths because of COVID-19 [7], the pandemic continues to be marked by individuals who commonly required intensive and specialized treatment, thus increasing the demand on the health system, generating a shortage of beds in intensive care units (ICU) [8], and consequently elevating health care costs. HFNC may be an effective resource, reducing the need for intubation and hospitalization time, thereby lessening the burden on the health system, particularly during the pandemic [9].

Since the beginning of the COVID-19 pandemic, many primary studies have explored clinical, service and safety outcomes associated with HFNC in patients with COVID-19 (10–32). Many of these studies are observational [10, 11) and possess methodological weaknesses [12–21), making it challenging to draw conclusions about HFNC effectiveness, safety [22, 23) or appropriateness [24]. Therefore, the purpose of this systematic review was to synthesize evidence pertaining to the effectiveness of HFNC in adults hospitalized for treatment of COVID-19. Specifically, the present study seeks to define the effects of HFNC on rates of mortality, orotracheal intubation and on ICU length of stay. It also seeks to define the predictors of success and/or failure of HFNC in COVID-19 patients.

METHODS

This systematic review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [25]. The Population, Intervention, Comparison and Outcome (PICO) strategy was designed containing descriptors associated with the objectives of the study, as summarized in Table 1.

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TABLE 1
PICO strategy

P = (Population, patient)	Older adult Adult COVID-19 Hospitalized patient
I = (Intervention)	High-flow nasal cannula (HFNC)
C = (Comparison)	------------------------------
O = Outcomes	Intubation rate Mortality Predictors of success/failure Length of stay in the intensive care unit (ICU)

TABLE 2
Search strategy used in PubMed

#1*	"coronavirus disease 2019" "severe acute respiratory syndrome coronavirus" "2019 new coronavirus" "sars-cov-2" "human coronavirus 2019" "COVID-19"
#2*	"high-flow nasal cannula therapy" "hfnc (high-flow nasal cannula)" "hfnc assisted ventilation" "hfnc therapy" "hfnc ventilation" "high flow nasal cannula respiratory support" "high flow nasal cannula therapy" "high flow nasal prong therapy"
Strategy	**#1 AND #2**
Filters	Humans; language: Portuguese, English, Spanish; year: 2019-2022; free and complete articles

*Keywords joined by the Boolean operator "OR".

Search strategies

A keyword adherence test was used to optimize and filter the selected databases. The purpose of the test is to examine the frequency of appearance in absolute numbers, of a descriptor that is strongly linked to the proposed research topic in the most accessed health sciences databases [26]. The following databases were selected: PubMed, EMBASE and SCOPUS. An electronic search was conducted between May 11 and 13, 2022. The search strategy summarized in Table 2 used PubMed as an example. The same rationale was used for EMBASE and SCOPUS databases.

Study selection

Study selection was independently conducted by two reviewers (DA & GK) according to the following inclusion criteria: 1) experimental (eg, randomized clinical trials) and observational studies (eg, prospective, retrospective and case-control studies) that were interventional; 2) full-text articles; 3) published between 2019 and 2022; 4) in English, Portuguese and Spanish; 5) studies with humans, limited to adults or older adults, hospitalized with COVID-19, using HFNC therapy; 6) with no restriction of race, sex or country. Individual studies contained in systematic reviews that appeared within the search strategy were examined separately as an additional selection (eg, outside of the search strategy). The exclusion criteria were 1) case studies and case series, comments, recommendations, letters to the editor and editorials; 2) studies containing protocols for randomized clinical trials; 3) descriptive studies; 4) studies with animals; and 5) incomplete studies and systematic reviews. The title and abstract of potentially eligible studies were read in full, according to the previously established criteria. Full-text articles were consulted when the information contained in the abstract was insufficient. Any discrepancies were mediated by a third reviewer (LM-D).

Data extraction

The ZOTERO and Access programs were used to manage data screening and extraction. All relevant data were extracted and organized in a table format. The methodological quality of the studies was assessed using the Study Quality Assessment Tools from the National Heart, Lung, and Blood Institute (NHLBI) [27]. It consists of 14 items, with each item being marked as "Yes", "No" or "Not reported". The "Yes" score is assigned a score of 1, while the other scores are assigned a score of 0. Therefore, the overall score represents the number of affirmative answers. For the qualitative assessment of the final scores, studies with scores above 12 were considered "good", studies between 9 and 12 were considered "fair", while those lower than 9 were considered "weak" [28]. The quality assessment was independently conducted by two authors (GK & LM-D). This systematic review was registered in The International Prospective Register of Systematic Reviews (PROSPERO) database (CRD420201270360).

RESULTS

Database searches yielded a total of 2,553 articles: 211 articles in PubMed, 878 articles in EMBASE and 1,464 articles in SCOPUS, published between 2020 and 2022. After excluding the duplicates, 1,476 articles remained. After the analysis of titles and abstracts, 581 potentially eligible articles remained. Following the analysis based on eligibility criteria, a total of 95 articles remained. During full-text review and data extraction, 55 were excluded for not meeting the eligibility criteria. A total of 40 studies were included in the review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart illustrates the selection process (Figure 1).

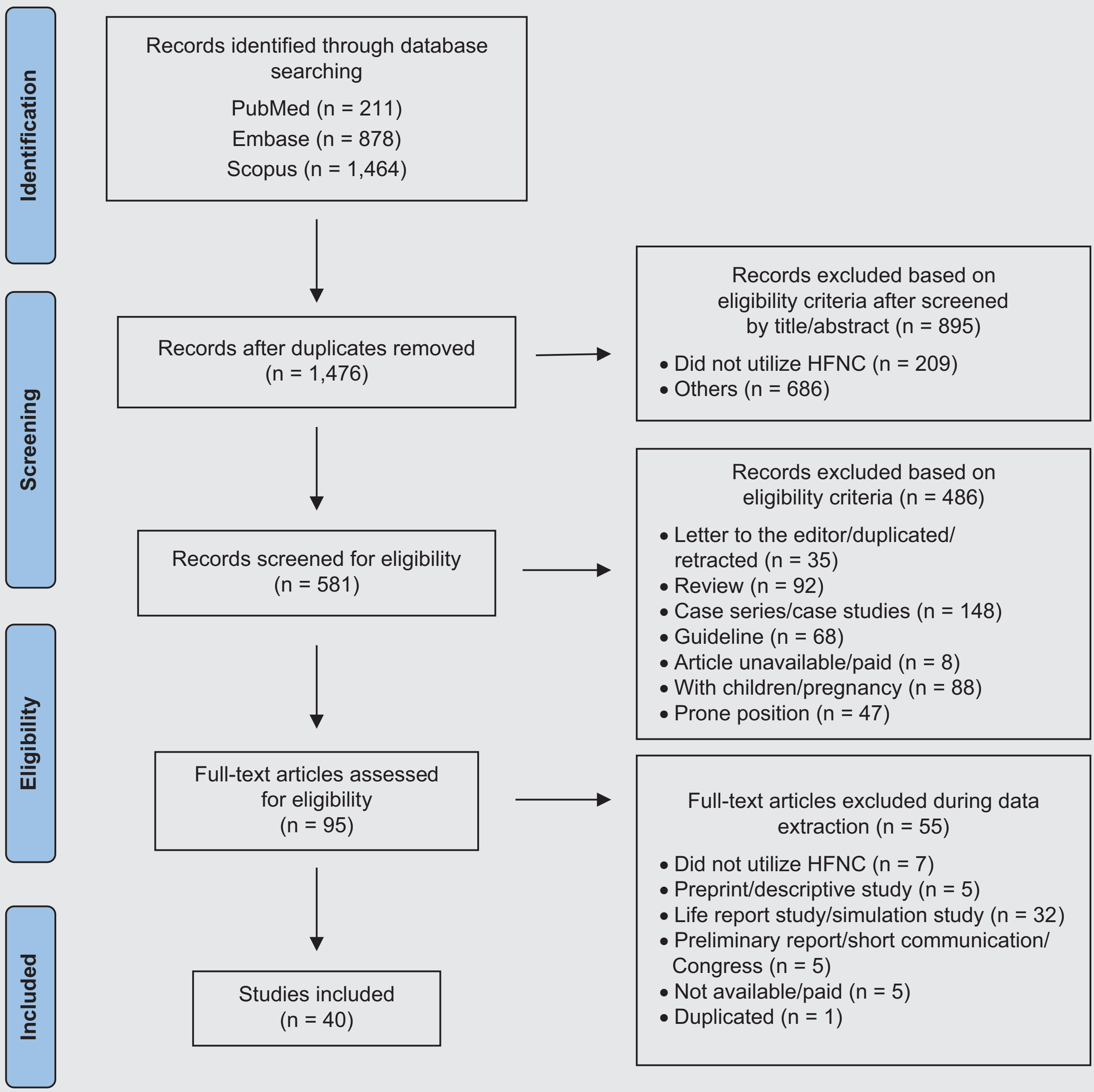
From the 40 studies included, 25 were observational retrospective, 13 were observational prospective and 2 were randomized controlled trials. A total of 18 studies were conducted in the ICU setting, 5 in a ward, 10 did not specify the location (hospital), 6 were conducted both in ICU and ward, and 1 in the emergency department. Five studies compared HFNC to conventional oxygen therapy, 8 compared the use of HFNC to invasive mechanical ventilation (eg, the first 24 h vs an early intubation approach or HFNC vs invasive mechanical ventilation), 3 compared HFNC to non-invasive ventilation (NIV), 1 compared HFNC to non-rebreather mask (NRM), 1 compared HFNC to helmet non-invasive ventilation (HNV), 6 compared HFNC to 3 or more forms of oxygen therapy (eg, continuous positive airway pressure [CPAP], NIV, HNV, NRM), 1 compared HFNC with and without use of medication (eg, tocilizumab) and 15 did not establish comparisons to other forms of oxygen therapy. Most of the studies [8] were conducted in China, followed by France, Spain and the United States (5 studies each), followed by Italy and Poland (2 studies each). Turkey, South Africa, Switzerland, Croatia, Saudi Arabia, Canada, Brazil, Germany, Mexico, the United Kingdom, India and Morocco had 1 study each. One was a multi-country study (France, Belgium and Switzerland). The number of participants in each study ranged between 16 [29] and 1,491 [30]. The mean interstudy age among patients who used HFNC ranged between 43.8 years [31] and 87 years [32]. Regarding the methodological quality, most of the studies (n=35) were classified as having fair quality, three studies were classified as having good quality and two studies were classified as having weak quality. The study characteristics and outcomes are summarized in Table 3.

The outcome "mortality" was evaluated in the majority (n=30) of studies [29–58]. Several studies compared mortality rates among those who were successfully managed with HFNC (ie, were weaned off HFNC) and those who failed. Most of these studies determined that HFNC failures [29, 37, 40, 41, 46, 51] were associated with higher rates of mortality. One study reported opposite findings [44], and another determined that the availability of HFNC in the emergency department was not associated with increased survival [50].

Regarding the type of oxygen therapy used, contrasting results were reported. Four studies reported that mortality was lower in patients who used HFNC compared to those who used conventional oxygen therapy [35, 58] and NRMs [32, 53]. However, studies with better methodological quality (n=8) found that mortality rate did not differ between those

FIGURE 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection.



who used HFNC and those who used conventional oxygen therapy [33, 49], HNV [48], CPAP [38, 52] or NIV [36, 38, 43]. Four studies found that mortality was higher among those who used NIV compared to those who used HFNC [30, 31, 55, 57].

Orotracheal intubation rate was analysed in 22 studies [29–31, 33–38, 43, 45, 46, 48, 50, 53, 54, 56–61], and in 12 of these studies, HFNC was associated with a reduction of orotracheal intubations. From these, five studies revealed that intubation rate was lower among those who were successfully managed with HFNC compared to those who failed it [29, 37, 59]. The need for intubation was also lower in those who received early HFNC treatment compared to those who received later treatment [45] or who had HFNC available in the emergency department [50]. The remaining seven studies revealed a decrease in intubation rate among those who used the HFNC compared to those who used either conventional oxygen therapy [33, 35, 57], NRM [31, 53], NIV [30] or early intubation approach [34]. However, the effectiveness of the HFNC in reducing orotracheal intubation may be comparable to that of the NIV, as five studies revealed no difference in intubation rates between the groups that used the HFNC compared to the NIV [36, 38, 43, 58] or CPAP [38]. Only one study compared the use of HNV therapy with HFNC and reported lower intubation rates among those who received HNV compared to those who received HFNC [48].

The outcome "predictors of HFNC success/failure" were examined in 12 studies [2, 29, 37, 39, 40, 46, 59, 62–66]. The ratio of oxygen saturation (ROX) index [67], measured at different intervals, was the most

TABLE 3
Summary of the characteristics and outcomes of included studies

Study characteristics				Intervention characteristics		Outcome characteristics
Author/Year/ Country	**Type of study/ context**	**Sample size/% males/mean age (±SD)**	**Quality assessment**	**Comparison**	**Outcome variables**	**Main findings (After statistical adjustments where applicable)**
Hu et al, 2020 China	Observational retrospective/ Ward	Sample size: 105 % males: 48.6 Mean age: 64 years (±11.3)	11 Fair	N/A	Predictors of success of HFNC	Predictors of HFNC success: Young age (OR = 0.83; 95%CI = 0.75 – 0.940; P = 0.003), female sex (statistics for male sex: OR = 0.17; 95%CI = 0.03–0.79; P = 0.02), lower SOFA index (OR = 0.38; 95%CI = 0.20–0.74; P = 0.004), and ROX index > 5.55, at hour 6 (OR = 17.82; 95%CI = 3.74–84.90; P<0.001.)
Bonnet et al, 2020 France	Observational retrospective/ ICU	Total sample size: 128 **HFNC** Sample size: 76 % males: 82 Median age: 60 years **COT** Sample size: 62 % males: 50 Median age: 60 years	10 Fair	HFNC × COT	Proportion of patients who required IMV after ICU admission (ie, intubation rate) Mortality 28 days and 60 days after ICU admission Length of stay in the ICU	Mortality at day 28 and day 60 (12% vs 24%; OR = 0.52; 95%CI = 0.2–1.34; P = 0.17 and 16% vs 26%; OR = 0.75; 95%CI = 0.32–1.8; P = 0.52, respectively) and the length of stay in the ICU (11 days vs 12.5 days; difference -0.23; 95%CI = -0.54 to -0.08; P = 0.14) did not differ between HFNC and COT groups. In the HFNC group, 51% required IMV; in the COT group, 74% required IMV (P = 0.007). The HFNC group had significant lower risk for IMV compared to COT (OR = 0.31; 95%CI = 0.14–0.66; P = 0.002). In the HFNC group, a ROX>4.88 was associated with low risk of intubation (OR = 0.23; 95%CI = 0.008–0.64; P = 0.006) and a higher SAPS II score was associated with higher risk of IMV (OR = 1.13; 95%CI = 1.06–1.20; P = 0.0002).
Mellado-Artigas et al, 2021 Spain	Observational prospective/ICU	Total sample size: 122 **HFNC** Sample size: 61 % males: 60 Mean age: 62 years (±11) **Early intubation** Sample size: 61 % males: 52%Mean age: 61(±11)	12 Fair	HFNC in the first 24 h × an early intubation approach in the first 24 h	Length of stay in the ICU Intubation All-cause in-hospital mortality	The use of HFNC remained associated with a shorter ICU length of stay (mean difference -9.4 days; 95%CI = -14.7 to -4.0) compared to an early intubation approach. No difference in all-cause in-hospital mortality was found between the two groups (OR = 0.75; 95%CI = 0.22–2.55).
Sayan et al, 2021 Turkey	Observational retrospective/ ICU	Total sample size: 43 **HFNC** Sample size: 24 % males: 70.8 Mean age: 63.3 years (±12.1) **COT** Sample size: 19 % males: 68.4 Mean age: 69.5 years (±12.3)	9 Fair	HFNC × COT	Length of stay in the ICU Intubation rate Short-term mortality	No statistically significant difference was found in length of stay in the ICU between HFNC and COT groups (9.8 days±4.8 v. 9 days±7.9; P = 0.18, respectively). Intubation rate (54.2% vs 84.2%; P = 0.03) and short-term mortality (50% vs 84.2%; P = 0.01) were lower in the HFNC group compared to the COT group.
Wang et al, 2020 China	Observational retrospective/ Hospital	Sample size: 17 % males: 41 Mean age: 65 years (N/A)	7 Weak	N/A	HFNC success or failure	No HFNC failure was registered in patients with PaO_2/FiO_2>200 mmHg. However, the failure rate was 64% in patients with PaO_2/FiO_2 ≤200 mmHg (P = 0.04).
Calligaro et al, 2020 South Africa	Observational prospective/ ward and ICU	Sample size: 293 % males: 56 Median age: 52 years	9 Fair	N/A	Predictors of HFNC failure	In multivariate analysis, poorly-controlled diabetes (adjusted HR = 1.56; 95%CI = 1.06 – 2.28; P = 0.023), treatment with steroids (adjusted HR = 0.25; 95%CI = 0.18–0.37; P<0.001), and the ROX index measured 6 h after therapy initiation (adjusted HR = 0.42; 95%CI = 0.33–0.53; P<0.001), were significantly associated with relative hazard of HFNC failure.

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Author/Year/ Country	**Type of study/ context**	**Sample size/% males/mean age (±SD)**	**Quality assessment**	**Comparison**	**Outcome variables**	**Main findings (After statistical adjustments where applicable)**
Xu et al, 2020 China	Observational retrospective/ ICU	Sample size: 324 % males: 67.6 Mean age: 63.2 years (±14.5)	11 Fair	N/A	Predictors of HFNC failure	Predictors independently associated with HFNC failure: Age >60 years (OR = 2.54; 95%CI = 1.39–4.65; P = 0.003); platelets <125 × 10^9/L; (OR = 3.18; 95%CI = 1.36–7.46; P = 0.008) interleukin 6>7.0 pg/mL (OR = 3.07; 95%CI = 1.67–5.62; P<0.001), and ROX index<5.5 within the first 4 h of HFNC initiation (OR = 5.92; 95%CI = 3.31–10.58; P<0.001). These four parameters had a strong predictive ability for the need of mechanical ventilation in patients treated with HFNC.
Teng et al, 2021 China	RCT/ICU	Total sample size: 22 **HFNC** Sample size: 12 % males: 66 Mean age: 56 years (±3) **COT** Sample size: 10 % males: 70 Mean age: 53 years (±5.5)	11 Fair	HFNC × COT	Length of stay in the ICU	The length of stay in the ICU was shorter and statistically significant in the HFNC group (4 days [±0.74]) compared to the COT group (4.9 days [±1] P = 0.02).
Duan et al, 2020 China	Observational retrospective/ Ward and ICU	Total sample size: 36 **HFNC** Sample size: 23 % males: 52 Mean age: 65 years (±14) **NIV** Sample size: 13 % males: 92 Mean age: 50 years (±14)	10 Fair	HFNC × NIV	Intubation rate Mortality Predictors of intubation	There was no difference in intubation rate (P>0.99) and mortality (P>0.99) between HFNC and NIV groups. In multivariate analysis, only C-reactive protein was independently associated with intubation, and it had high distinguishing power to predict intubation (OR = 1.04; 95%CI = 1.01–1.07; P<0.01).
Xia et al, 2020 China	Observational retrospective/ Hospital	Sample size: 43 % males: 58.1 Mean age: 63 years (±9.7)	12 Fair	HFNC (success/ failure) × IMV	Predictors of HFNC failure (survivors × non-survivors) Intubation rate Hospital mortality rate	The hospital mortality rate was higher among those failed HFNC (65%) compared to those who succeeded (0%; P<0.001). In addition, mortality was also higher among those who failed HFNC and underwent endotracheal intubation (75%; P<0.001) compared to those who were intubated without HFCN treatment (66.7%; P<0.04). Intubation rate was lower among those who succeeded HFNC (0%) compared to those who failed (65%; P<0.001). Being male was independently associated with HFNC failure (OR = 6.94; 95%CI = 1.12–42.75; P = 0.03). In contrast, a high SpO_2 value at admission was a protective factor associated with HFNC failure (OR = 0.56; 95%CI = 0.38–0.82; P = 0.03). Survivors were associated with younger age (60.97 [±9.7] vs 69.9 [±6.0] years; P = 0.003), fewer dyspnea symptoms (37% vs 76.9%; P = 0.01), higher SpO_2 (96% [93%–98%] vs 93% [91%–95%]; P = 0.04), and longer length of hospital stay (25.1 [±12.7] vs 10.8 [±4.7] days; P<0.001) compared to nonsurvivors.

(Continues)

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Franco et al, 2020 Italy	Observational prospective/ Ward	Total sample size: 670 **HFNC** Sample size: 163 % males: 69.9 Mean age: 65.7 years (±14.7) **NIV** Sample size: 177 % males: 71.8 Mean age: 66.8 years (±13.5) **CPAP** Sample size: 330 % males: 67.6 Mean age: 70.3 years (±12.1)	12 Fair	HFNC × NIV × CPAP	Intubation 30-day mortality rate	No statistically significant differences were found in intubation and mortality rates among patients treated with either type of oxygen therapy support, after adjusting for confounders (ie, age and number of comorbidities).
Chandel et al, 2021 United States	Observational retrospective/ Ward and ICU	Sample size: 272 % males: 66.2 Mean age: 57 (±13)	12 Fair	HFNC (success/ failure)+Failure: intubation ≤48 h vs intubation ≥48 h	Mortality Predictors of HFNC success/failure Length of stay in the ICU	Those who succeeded HFNC therapy were younger (54 [±14] years vs 60 [±13 years], P<0.001) and had no comorbidities (60 [36.6] vs 23 [21.3]*; P = 0.01) compared to those who failed. Additionally, those who succeed had less history of active cancer (1 [0.6] vs 6 [5.6]*; P = 0.02), lower initial SOFA score (2 [1–4] vs 4 [2–7], P<0.001), lower baseline lactate (1.5 [1.3–2.1] vs 1.9 [1.4–2.8]; P<0.005), lower pro-calcitonin (0.2 [0.1–0.5] vs 0.3 [0.1–1.0]; P = 0.033), and lower neutrophil to lymphocyte ratio (6.1 [3.9–1.60] vs 8.1 [4.9–12]; P = 0.02), and had a higher median ROX index at all-time points (2, 6 and 12 h; P<0.001) compared to those who failed HFNC therapy. ROX index of >3.67 at 12 h had the diagnostic accuracy (AUC 0.78 [95%CI 0.72–0.84) for predicting therapy success (sensitivity = 84.1%, specificity = 49.4%). Among those who succeeded HFNC within the first 12 h after HFNC initiation a ROX index>3.0 at each time point had good sensitivity and specificity for success (sensitivity = 85.3%; specificity = 51.1%) of HFNC success compared to those who failed the therapy. Hospital mortality and length of stay in the ICU were only measured among those who failed the HFNC therapy (not in comparison to those who succeed). No statistically differences were found among those who were intubated with ≤48 h or ≥48 h.
Alshahrani et al, 2021 Saudi Arabia	Observational prospective/ICU	Sample size: 44 % males: 86 Mean age: 57 years (±14)	12 Fair	HFNC (success/ failure)	Predictors of success/failure Mortality (30 days) Length of stay in the ICU	Higher SOFA score (HR = 1.42; 95%CI = 1.04–1.95; P = 0.02), and low ROX index (≥4.88) (HR = 0.61; 95%CI = 0.42–0.87; P = 0.008) were significant predictors of HFNC failure. HFNC failure was significantly associated with higher in-hospital mortality (0% in succeed vs 52% in failure; P = 0.001) and longer ICU stay (6 days in success vs 11 days in failure; P = 0.04).
Beduneau et al, 2021 France	Observational retrospective/ ICU	Sample size: 43 % males: 72 Median age: 61 years (51.5–69.5)	9 Fair	HFNC success × failure (eg, intubation)	Mortality (28 days) Length of stay in the ICU	Compared to the ones who succeeded, those who failed had longer median length of stay in the ICU (28 [19–28]) vs 6 [3–8] days; P = 0.00001) and increased mortality (3 vs 0; P = 0.013).

(Continues)

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Celejewska-Wójcik et al, 2021 Poland	Observational prospective/ Hospital	Sample size: 116 % males: 78.4 Median age: 61 years (51–70)	12 Fair	N/A	Mortality or intubation (30 days) (Composite measure)	Multivariate analysis showed that a ROX index below 3.85 was associated with increased mortality (HR = 6.1; 95%CI = 3.04–12.26), whereas the ROX index between 3.85 and 4.88 was not (HR = 1.46; 95%CI = 0.73–2.93), compared to ROX index of 4.88 or higher (as reference value).
Chavarria et al, 2021 Mexico	Observational prospective/ Ward and ICU	Sample size: 378 % males: 66.7 Median age: 54.5 years (46–64)	12 Fair	HFNC success × failure (eg, intubation)	Intubation	Success rate was 71.4% (n = 270/95%CI = 66.6–75.8) compared to 28% (n = 108/95% CI = 24.2–33.4) of patients who failed and were intubated.
					Predictors of success/failure	The difference in the ROX index between 2 and 16 h was statistically significant only among those who succeeded the HFNC (6.83 vs 8.20; P<0.0001), not among those who failed (5.88 vs 5.62; P = 0.91) the therapy. The disease progression risk at admission (HR 1.27; 95%CI = 1.09–1.47; P<0.01), ROX index at 1 h (HR 0.82; 95%CI = 0.70–0.96; P = 0.02), and absence of treatment with steroids (HR 0.34; 95%CI = 0.19–0.62; P<0.0001) were predictors of HFNC failure.
Costa et al, 2022 Brazil	Observational retrospective/ ICU	Sample size: 37 % males: 70.3 Mean age: 68.8 years (±18)	9 Fair	HFNC × NIV	Length of stay in the ICU Mortality Intubation rate	No significant differences were found in length of stay in the ICU, mortality and intubation rates among those who used HFNC or NIV.
Delbove et al, 2021 France	Observational retrospective/ ICU	Sample size: 46 % males: 76 Median age: 75 years (70–79)	11 Fair	HFNC success × DNIO × failure (eg, intubation)	Length of stay in the ICU Mortality	Compared to those who succeeded HFNC, those who failed spend longer days in the ICU (9 [7–13] vs 18 [14–25]; P<0.001). No differences were found for hospital mortality.
Deng et al, 2021 China	Observational retrospective/ hospital	Sample size: 110 % males: 65 Median age: 71 years (65–89)	9 Fair	HFNC early × late treatment	Length of stay in the ICU Intubation rate	Compared to those who received early HFNC treatment, those who received later HFNC treatment had longer length of stay in the ICU (12 days [10–15] vs 18 days [13–22]; P<0.001), required more intubation (4* vs 38*; P<0.001).
					Mortality	Multivariate analysis showed that mortality was associated with SpO_2 (OR 1.27; 95%CI = 1.05–1.55; P = 0.01), lactate (OR 3.08; 95%CI = 1.37–6.94; P = 0.006), and PaO_2/FiO_2 at HFNC onset (OR = 2.03; 95%CI = 2.00–2.06; P = 0.02).
Duan et al, 2021 China	Observational retrospective/ ICU and ward	Sample size: 66 Success: % males: 38 Median age: 63 years (±16) Failure: % males: 38 Median age: 73 years (±14)	12 Fair	HFNC success × failure (eg, intubation)	Predictors of HFNC failure	In multivariate analysis, the ROX index after 1 h (≤7.17) (OR = 0.65; 95%CI = 0.45–0.94; P = 0.02) and the SOFA score (OR = 2.16; 95%CI = 1.19–5.53; P = 0.02). Were independent predictors of HFNC failure (OR = 0.65; 95%CI = 0.45–0.94; P = 0.02).
					Length of stay in the ICU	Length of stay in the ICU and intubation rate did not differ among those who succeed and those who failed the therapy.
					Intubation rate Mortality	Mortality was higher among those who failed the therapy (28%) compared to those who succeeded (0%); P<0.01.
Ferrer et al, 2021 Spain	Observational prospective/ Hospital	Sample size: 85 % males: 69 Mean age: 64.51 years (±11.78)	13 Good	HFNC success × failure (eg, intubation)	Predictors of HFNC success/failure (the ROX index)	In adjusted multivariate analysis, the ROX index at 24 h (AUC = 0.82; 95%CI = 0.59– 1.00; P = 0.01) with a cut-off point of 5.35 was the best predictor of HFNC success.

(Continues)

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Summary of the characteristics and outcomes of included studies

Study characteristics				Intervention characteristics		Outcome characteristics
Author/Year/ Country	**Type of study/ context**	**Sample size/% males/mean age (±SD)**	**Quality assessment**	**Comparison**	**Outcome variables**	**Main findings (After statistical adjustments where applicable)**
Gaspic et al, 2021 Croatia	Observational prospective/ Hospital	Sample size: 102 % males: 71.6 Median age: 66 years (58–73)	12 Fair	N/A	Mortality (and predictors)	Multivariate analysis showed that Charlson Comorbity Index >4, a Rox index<4.11, LDB-WBC ratio, and age >65 years were the best predictors of in-hospital mortality among those using HFNC (AUC = 0.92; 0.80–0.98; P<0.001).
Grieco et al, 2021 Italy	RCT/ICU	Sample size: 109 HNV: % males: 77 Median age: 66 years (57–72) HFNC: % males: 84 Median age: 63 years (55–69)	11 Fair	HFNC × HNV	Intubation Mortality (in-hospital, 28-day, 60-day) Length of stay in the ICU	After post-hoc multivariate analysis, the intubation rate was lower in the HNV group compared to HFNC (OR = 0.27; 95%CI = 0.10–0.70; P<0.02). No statistically significant differences were found for mortality and length of stay in the ICU between both groups.
Hacquin et al, 2021 France	Observational retrospective/ Ward	Sample size: 67 NRM: % males: 54 Median age: 86 years (84–89) HFNC: % males: 66 Median age: 87 years (85–90)	12 Fair	HFNC × NRM	In-hospital 30-day survival	After adjustments, HFNC was associated with increased survival at 30-day compared to NRM (HR = 0.57; 95%CI = 0.33–0.99; P = 0.04). Although the majority of patients died within 10 days in both groups, HFNC was associated with increased 30-day survival (P = 0.03).
Hansen et al, 2021 USA	Observational prospective/ Hospital	Sample size: 91 % males: 58 Mean age: 68.4 years (±12)	12 Fair	HFNC × COT	Mortality	Multivariate analysis showed no difference in mortality rate between HFNC and COT (OR = 0.37; 95%CI = 0.12–1.15; P = 0.09).
Jarou et al, 2020 USA	Observational retrospective/ ED	Sample size: 123 % males: 64 Median age: 65 years (57–75)	12 Fair	HFNC available in the ED × HFNC not available in the ED	Intubation (in the ED and 24 h after hospitalization) Length of stay in the ICU Survival	HFNC available in the ED was associated with reduced rate of intubation in the ED (46.4% vs 26.3%, P<0.001) and with a decrease in the cumulative proportion of patients who required intubation with 24 h of hospitalization (85.7% vs32.6%, P<0.001) and throughout the entire hospital stay (89.3% vs 48.4%, P<0.001) compared to those who did not have HFNC available in the ED. No significant differences were found for ICU length of stay and survival.
Kerai et al, 2022 USA	Observational retrospective/ ICU	Sample size: 85 Success: % males: 68.2 Mean age: 53.9 years (±14.53) Failure: % males: 65.9 Mean age: 60.5 years (±13.90)	11 Fair	HFNC success × failure	Predictors of success/failure	Higher SpO_2 at baseline (OR = 0.83; 95%CI = 0.70–0.92; P = 0.02) and higher number of days on HFNC were associated decreased odds of failure (OR = 0.55; 95%CI = 0.33–0.93; P = 0.02). Not being in prone position was associated with increased odds of failure (OR = 4.55; 95%CI = 4.47–5.93; P = 0.006).
Nguyen et al, 2021 USA	Observational retrospective/ Hospital	Sample size: 104 % males: 57.7 Mean age: 67 years (±14.8)	11 Fair	HFNC success × failure	60-day mortality	After multivariate analysis, HFNC failure was significantly associated with increased 60-day mortality (OR = 12.48; 95%CI = 4.07 – 38.28; P<0.001).

(Continues)

TABLE 3
Summary of the characteristics and outcomes of included studies

Study characteristics				Intervention characteristics		Outcome characteristics
Author/Year/ Country	**Type of study/ context**	**Sample size/% males/mean age (±SD)**	**Quality assessment**	**Comparison**	**Outcome variables**	**Main findings (After statistical adjustments where applicable)**
Suryawanshi et al, 2022 India	Observational prospective/ Hospital	Sample size: 90 HFNC: % males: 76.7 Mean age: 43.8 years (±14.76) NIV: % males: 63.3 Mean age: 50.63 years (±15.32) NRM: % males: 57.7 Mean age: 35.8 years (±19.97)	9 Fair	HFNC × NIV × NRM	Intubation Mortality Length of stay in the ICU	Intubation rate was higher among HFNC (16.7%) and NIV groups (20%), compared to NRM (0%) (P = 0.04). Mortality was higher in the NIV group (20%) compared to HFNC (10%) and NRM (0%) groups (P<0.03). No difference was found for the length of stay in the ICU between HFNC and NIV groups (No results were reported for NRM).
Sykies et al, 2021 United Kingdom	Observational prospective/ Hospital	Sample size: 140 % males: 65 Mean age: 71.2 years (±11.1)	9 Fair	HFNC × CPAP	Mortality	There was no difference in mortality between the CPAP and HFNC groups (58% vs 64%/P = 0.53.
Wendel-Garcia et al, 2022 Spain	Observational retrospective/ ICU	Sample size: 1,093 % males: 68 Median age: 63 years (54–70)	10 Fair	HFNC × NRM × NIV	Intubation rate Mortality	Intubation rate was significantly lower for the HFNC (HR = 0.45; 95%CI = 0.39–0.53; P<0.0001) and NIV (HR = 0.67; 95%CI = 0.53–0.85; P<0.0001) groups, compared to NRM. Mortality was significantly lower for the HFNC (HR = 0.75; 95%CI = 0.58–0.98; P = 0.02) and NIV (HR = 1.21; 95%CI = 0.8–1.83; P = 0.02) groups, compared to NRM. Age (HR = 1.08;95% CI = 1.06–1.1; P<0.001), BMI (HR = 1.03;95% CI = 1.01–1.1; P = 0.009), high levels of C-reactive protein (HR = 1.14;95% CI = 1.05–1.2; P = 0.003), procalcitonin (HR = 1.09;95% CI = 1.04–1.1; P<0.001), ferritin (HR = 1.39;95% CI = 1.2–1.6; P<0.001), D-dimers (HR = 1.14; 95% CI = 1.03–1.3; P = 0.009), and presence of chronic obstructive pulmonary disease (HR = 1.67 95%CI = 1.12–2.5; P = 0.01) were highly predictive of ICU mortality.
Mellado-Artigas et al, 2021 Spain	Observational prospective/ICU	Sample size: 259 % males: 71 Median age: 62 (55–70)	11 Fair		Intubation rate (28 days) (through SOFA score and ROX index)	After multivariate analysis, baseline non-respiratory SOFA score (OR = 1.78; 95%CI = 1.41–2.35), ROX index (OR = 0.53; 95%CI = 0.38–0.72) were associated with the need for intubation.
Ouissa et al, 2022 France	Observational retrospective/ Ward	Sample size: 110 % males: 58 Mean age: 55 (±11)	11 Fair	HFNC with tocilizumab × HFNC without tocilizumab	Intubation rate Mortality	The only risk factor associated with the unfavorable outcome (intubation rate and mortality) was the absence of tocilizumab prescription with an adjusted odds ratio (95%CI = 3.50 [1.40–8.69]; P = 0.007).
Panadero et al, 2020 Spain	Observational restrospective/ Intermediate respiratory care unit	Sample size: 40* % males: 70 Mean age: 58.9 (11.8)	12 Fair	HFNC success × failure	Intubation rate (30 days) (and the ROX Index as predictor of intubation)	Twenty-one patients (52.5%) experienced therapy failure and required intubation at day 30. The ROX index was shown to have good diagnostic performance in predicting the need for intubation (AUC = 0.712). The optimal cut-off point was an ROX value of 4.94, measured 2–6 h after starting therapy. In the survival analysis, a ROX value of less than 4.94 was associated with increased risk of intubation (HR 4.03; 95% CI = 1.18–13.7; P = 0.026).

(Continues)

**If the PCR was not available, diagnosis was based on symptoms with compatible laboratory and radiology data and ARDS

TABLE 3
Summary of the characteristics and outcomes of included studies

Study characteristics				Intervention characteristics		Outcome characteristics
Author/Year/ Country	**Type of study/ context**	**Sample size/% males/mean age (±SD)**	**Quality assessment**	**Comparison**	**Outcome variables**	**Main findings (After statistical adjustments where applicable)**
Rorat et al, 2021 Poland	Observational retrospective/ Ward	Sample size: 200 % males: 67 Median age: 67.0 (60.0–74.0)	13 Good	HFNO × NIV × intubation	Mortality	Mortality in the group of patients treated with NIV was statistically significantly higher (HR = 2.20; 95%CI = 1.42–3.42; P<0.001) than when HFNO alone was used. In patients intubated mortality was statistically significantly higher (HR = 2.39; 95%CI = 1.53–3.73; P<0.001) than when only HFNO was used. No correlation was found between late intubation and the risk of death (P = 0.454).
Schmidt et al, 2022 Germany	Observational retrospective/ ICU and ward	Sample size: 16 % males: 68.7 Median age: 78.5 (61.25–81.0)	11 Fair	Group1: Efficient High-flow × Group2: High-flow failure	Predictors of HFNC success and failure (FiO_2, SpO_2 and PaO_2/FiO_2 ratio) Intubation rate Mortality	ROC analyses identified FiO_2 of > 0.58 (AUC 0.881; P = 0.022) to predict disease severity and consecutively HFNC failure on day 4. In addition, persistent oxygen saturation <89% and PaO_2/FiO_2 ratio<91 on day 4 were identified as significant predictors for HFNC failure (AUC = 0.933; P = 0.018; and 0.893; P = 0.038, respectively). In the HFNC group, 5 out of 9 (55.6%) patients died upon disease progression and HFNC failure (P = 0.017) (intubation rate).
Schmidt et al, 2021 France, Belgium and Switzerland	Observational prospective/ICU	Sample size: 1,491 % males: 73 Median age: 63 (54–71)	13 Good	COT × HFNC × NIV	Intubation rate Mortality	Intubation rate: For standard oxygen, HFNC, and NIV, oxygenation failure rate was 49%, 48%, and 60% (P<0.001). In multivariate analysis, HFNC (OR = 0.60; 95%CI = 0.36–0.99; P = 0.013) but not NIV (OR = 1.57; 95%CI = 0.78–3.21) was associated with a reduction in oxygenation failure). in multivariable analysis, HFNC was not associated with mortality (OR = 0.90; 95%CI 0.61–1.33), while NIV was associated with increased mortality (OR = 2.75, 95 CI = 1.79–4.21; P<0.001).
Schwartz et al, 2022 Canada	Observational retrospective/ ICU	Sample size: 142 % males: 71 Median age: 66 (59–73)	9 Fair	HFNC success × failure	Intubation rate Mortality	Intubated patients were older (mean [IQR] age, 70 [61–76] vs 65 [57–71] years; P = 0.02), had higher SOFA and 4C scores, and had worse oxygenation on the day of ICU admission (median [IQR] SpO_2/FiO_2 ratio 102 [88–144] vs 126 [108–182]; P = 0.01) compared with those who did not undergo intubation. Cohort mortality was well predicted by the 4C score (10–14 subgroup analysis: 17.6% (95%CI = 9.8–25.4) and 15 subgroup analysis: 26.7% (95%CI = 10.8–42.5) compared to 31% and 62% respectively in the internal validation cohort of the report initially describing the 4C score.
Wendel Garcia et al, 2021 Switzerland	Observational restrospective/ ICU	Sample size: 351 % males: 73 Median age: 63 (55–72)	11 Fair	COT × HFNC × NIV × IMV	Mortality Intubation rate	The intubation rate was lower in patients initially ventilated with HFNC and NIV compared to those who received COT (COT: 64%, HFNC: 52%, NIV: 49%; P = 0.025). Compared to the other respiratory support strategies, NIV was associated with a higher overall ICU mortality (COT: 18%, HFNC: 20%, NIV: 37%, IMV: 25%; P = 0.016).
Alkouh et al, 2022 Marroco	Observational retrospective/ ICU	Sample size: 265 HFNC: % males: 72.2 Mean age: 66.32 (±12.8) COT: % males: 69 Mean age: 64.66 (±14.9)	8 Weak	HFNC × COT	Mortality Intubation rate	HFNC was associated with lower mortality rate compared to those who used COT and failed and required NIV (98.6% vs 100%; P<0.0001, respectively). Neither HFNC nor NIV (those who failed COT) decreased the rate of mechanical ventilation (eg, intubation) (P = 0.08).

*Number of subjects.
95% CI 95% confidence interval; ARDS acute respiratory distress syndrome; AUC area under the curve; COT conventional oxygen therapy; CPAP continuous positive airway pressure; DNIO do not intubate order; ED emergency department; HFNC high-flow nasal cannula; HNV helmet noninvasive ventilation; HR hazard ratio; ICU intensive care unit; IMV invasive mechanical ventilation; N/A not applicable; NIV non-invasive ventilation; NRM non-rebreather mask; OR odds ratio; PaO_2/FiO_2 partial pressure of oxygen/fraction of inspired oxygen; RCT randomized controlled trial; ROX ratio of oxygen saturation; SOFA sepsis-related organ failure assessment.

often described potential predictor of HFNC success. In one study, a ROX index ≤ 7.17 within the first hour of therapy was predictive of HFNC failure [46], while a second study reported that a ROX index less than 5.5 within the first 4 h was predictive of HFNC failure [64]. Hu et al [62] and Calligaro et al [63] examined the ROX index, within the first 6 h of therapy, and showed that ROX indexes above 5.55 and above 3.26, respectively, were significantly associated with HFNC success. Chandel et al [39] showed that ROX index greater than 3.0, measured at several time points (ie, 2, 6 and 12 h) and at 12 h greater than 3.67 were significantly predictive of HFNC success. Similarly, Chavarria et al [59] found a statistically significant difference in ROX index scores, measured at 2 and 16 h post HFNC initiation, in those who succeeded the HFNC (6.83 vs 8.20) but not among those who failed it (5.88 vs 5.62). Ferrer et al [65] reported that a ROX index cut-off of 5.35, measured at 24 h, was the best predictor of HFNC success.

In addition to the ROX index, additional parameters such as age, sex, disease severity index, vital signs, ventilation/perfusion (P/F) ratio, blood sample parameters, comorbidities and drug treatment were also investigated as potential predictors of HFNC success or failure. Young age [37, 39, 62] and female gender [37, 62] were independent predictors of success. In contrast, advanced age was a predictor of failure [37, 64]. Regarding disease severity, a lower sepsis-related organ failure assessment (SOFA) score [68] was a predictor of HFNC success [39, 62], while a higher SOFA score was associated with HFNC therapy failure [40, 46].

Regarding vital signs and PF ratio, it was found that a higher SpO_2 at admission [37, 66] or in the first 6 h of HFNC [63] and a P/F ratio greater than 200 mmHg were significantly associated with HFNC success [2] or survival [37]. In contrast, a persistent SpO_2 less than 89% and a P/F ratio of less than 91, 4 days after therapy initiation, were associated with therapy failure [29].

In relation to blood sample parameters, elevated interleukin-6 [64] and C-reactive protein [36], in addition to thrombocytopenia [64], were independent predictors of HFNC failure. Chandel et al [39] showed that higher lactate, higher procalcitonin and a lower neutrophil to lymphocyte ratio were associated with HFNC failure. Regarding comorbidities, poorly controlled diabetes represented by glycated hemoglobin (HbA1c > 8%) [63] and a history of active cancer [39] were predictors of HFNC failure. Finally, in relation to medications, steroid treatment had conflicting results. Calligaro et al [63] showed that steroid treatment was a predictor of HFNC failure, while Chavarria et al [59] found that the absence of treatment with steroids was a predictor of HFNC failure.

The effects of HFNC on ICU "length of stay" was examined in 14 studies [31, 33–35, 39–41, 43–46, 48, 50, 69]. Some studies showed that persons who failed HFNC [40, 41, 44] or who received HFNC at later points in the course of their disease [45] had significant longer ICU stays when compared to those who succeeded HFNC (ie, were weaned off HFNC). Other studies found no difference [46, 50]. Mellado-Artigas et al [34] found that those treated with the HFNC had shorter ICU length of stays compared to those receiving an early intubation approach, whereas Chandel et al [39] found no difference in ICU length of stay among persons intubated 48 h before or after HFNC initiation. Regarding the type of oxygen therapy utilized, no differences in ICU length of stay were reported in studies that compared HFNC to NIV [31, 43] or HNV [48]. Furthermore, although one study found that patients treated with HFNC had a significant reduction in ICU length of stay [69], compared to those who were treated with conventional oxygen therapy, two other studies found no difference [33, 35].

DISCUSSION

The purpose of this systematic review was to synthesize the evidence pertaining to the effectiveness of HFNC on select clinical outcomes in adults hospitalized with COVID-19. The most examined outcomes were mortality followed by orotracheal intubation rates. Although select studies demonstrated positive associations between HFNC failure and mortality rates, this finding was not consistent across all studies. It is important to note that COVID-19 disease severity and co-morbidities were not accounted for in most of the included studies. Additionally, there is a lack of agreement across studies as to whether HFNC, compared to other types of oxygen therapy, is more effective in lowering the rates of mortality. For example, several studies showed no difference in mortality between those treated with the HFNC versus conventional oxygen therapy [70–72], whereas others showed that non-invasive oxygen therapy, including the HFNC, was associated with a lower risk of death [73]. Perhaps part of this inconsistency may be explained by the variety of time intervals for this particular outcome (eg, 30-day, 60-day, in-hospital and all-cause mortality).

The present study showed that the orotracheal intubation rate was lower among those for whom HFNC was successful (ie, successful weaning from HFNC) when compared to those who failed it. It also suggests that, when compared to other forms of oxygen therapy (ie, particularly conventional oxygen therapy), HFNC may be more effective in reducing oral intubation rates [70, 71]. However, compared with NIV, no differences in intubation rates were found [74, 75].

Regarding the predictors of HFNC success and failure, the ROX index, assessed at different time intervals, was the most commonly assessed measure. It was generally found that maintaining the ROX index around 5 was the best predictor of HFNC success. Recent studies, including two systematic reviews, have examined cut-off values for the ROX index at different time intervals, and determined that higher ROX index values were associated with greater chances of HFNC success and a lower risk of mortality [65, 76]. Ferrer et al [65] showed that a ROX index cut-off of 5.35 measured at 24 h post HFNC initiation was associated with HFNC success in COVID-19 patients, and Zucman et al [16] showed that a ROX index of greater than 5.37 in the first 4 h of HFNC was associated with a lower risk of intubation. Zhou et al [77] has shown that a range of ROX index values between 4.2 and 5.4, within 12 h of HFNC initiation, are predictive of HFNC success. In addition, in patients with hypoxemic respiratory failure because of pneumonia/ARDS, a ROX index greater than 4.88 measured at 2, 6 and 12 h post HFNC initiation was associated with a lower risk of HFNC failure [78]. These findings corroborate the results of this review, with the ROX index being a potentially valuable tool for predicting the failure of HFNC, and consequently the need for orotracheal intubation in patients with respiratory failure.

Younger age, female gender, lower SOFA scores and greater oxygenation profile were also described as predictors of the HFNC success; however, the evidence is limited by the small number of studies. Advanced age was shown to be a predictor of HFNC failure, and this finding has been supported by other studies. Lee et al [79] examined the clinical characteristics, the risk factors for mortality and the need for either mechanical ventilation or HFNC in older patients hospitalized with COVID-19. Results showed that patients with advanced age had a higher risk of need for mechanical ventilation or HFNC, in addition to a higher mortality risk, particularly in those over 80 and with comorbidities. Other studies have also shown an association between advanced age, especially over 70, and greater disease severity and mortality from COVD-19 [80, 81], speculating on a possible association between advanced age and oxygen therapy failure.

In the present study, we identified conflicting evidence regarding whether HFNC reduces ICU length of stay. The lack of consensus across studies prevented conclusions from being made. Nevertheless, there is emerging evidence, although still limited, suggesting that the ICU length of stay does not change regardless of the type of oxygen therapy utilized, whether it is HFNC, NIV or HNV. This finding was also supported by a prior systematic review [82], and future studies are strongly recommended.

The strengths of this systematic review include 1) a literature search in pre-selected databases through an adherence test, thus maximizing the chances of selecting studies relevant to the research topic; 2) the inclusion of four clinical outcomes widening the understanding of the HFNC's effectiveness, including a comparison among other forms of oxygen therapy. The present study had some limitations that must be acknowledged. Many of the included studies did not assess the severity of the hypoxemia or of COVID-19 itself. Therefore, it was not possible to determine the effectiveness of the HFNC in the context of COVID-19 severity. Depending on the severity of the hypoxemia caused by COVID-19, it is possible that the patient's condition will naturally worsen, leading to the need for orotracheal intubation, regardless of the type of oxygen therapy previously used [83].

Regarding inclusion/exclusion criteria and study selection, Chinese language studies were not included; therefore, it is possible that some studies were not included. The "grey" literature was not searched. Most of the studies included in this review were observational and retrospective. The low number of randomized controlled trials and the lower quality of many of the included observational studies reduce the strength of the evidence. Furthermore, the COVID-19 pandemic is still ongoing, and additional studies are likely to be published during the conduction of this systematic review.

Future randomized controlled trials are strongly recommended. Studies should consider the role of comorbidities and COVID-19 disease severity when seeking to determine the effectiveness of HFNC.

CONCLUSION

The use of HFNC in patients with respiratory failure because of COVID-19 may provide an effective approach to reducing the rate of orotracheal intubation, notably when compared to the use of conventional oxygen therapy, but not to NIV. Further studies that include consideration of the severity of COVID-19 disease and patient co-morbidities on HFNC ability to reduce intubation are warranted. Among predictors of HFNC success and failure, the ROX index was the parameter most examined. Current evidence does not support the determination of HFNC's ability to reduce ICU length of stay or mortality.

DISCLOSURES

Contributions

Dr M-D and Spec. K. designed the present study. Miss A searched the literature and performed data analysis. Dr M-D and Spec. K performed the data interpretation. Miss A drafted the manuscript. Dr M-D and Spec. K reviewed and revised the manuscript. All authors approved the final draft before submission.

Competing interests

All authors have completed the ICMJE uniform disclosure form and declare no conflict of interest.

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Ethical approval

Not required for this article type.

REFERENCES

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA 2020;324(8):782–93. htpps://doi.org/10.1001/jama.2020.12839
2. Wang K, Zhao W, Li J, Shu W, Duan J. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. Ann Intensive Care 2020;10(1):37. https://doi.org/10.1186/s13613-020-00653-z
3. Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): Clinical features and differences from typical pre-COVID-19 ARDS. Med J Aust 2020;213(2):54–6.e1. https://doi.org/10.5694/mja2.50674
4. Esquinas AM, Karim HMR. To: Efficacy and safety of high-flow nasal cannula oxygen therapy in moderate acute hypercapnic respiratory failure. Rev Bras Ter Intensiva 2020;32(1):163–64. https://doi.org/10.5935/0103-507x.20200026
5. Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. Respir Care 2010;55(4):408–13.
6. Nishimura M. High-flow nasal cannula oxygen therapy in adults: Physiological benefits, indication, clinical benefits, and adverse effects. Respir Care 2016;61(4):529–41.https://doi.org/10.4187/respcare.04577
7. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus pandemic (COVID-19). Our world in data. 2020 [accessed 15 May 2022]. <https://ourworldindata.org/coronavirus>.
8. Suffredini DA, Allison MG. A rationale for use of high flow nasal cannula for select patients with suspected or confirmed severe acute respiratory syndrome coronavirus-2 infection. J Intensive Care Med 2021;36(1):9–17. https://doi.org/10.1177/0885066620956630
9. Gürün Kaya A, Öz M, Erol S, Çiftçi F, Çiledağ A, Kaya A. High flow nasal cannula in COVID-19: A literature review. Tuberk Toraks 2020;68(2):168–74. https://doi.org/10.5578/tt.69807
10. Al-Dorzi HM, Aldawood AS, Almatrood A, et al. Managing critical care during COVID-19 pandemic: The experience of an ICU of a tertiary care hospital. J Infect Public Health 2021;14(11):1635–41. https://doi.org/10.1016/j.jiph.2021.09.018
11. Corrêa TD, Midega TD, Timenetsky KT, et al. Clinical characteristics and outcomes of COVID-19 patients admitted to the intensive care unit during the first year of the pandemic in Brazil: A single center retrospective cohort study. Einstein (Sao Paulo) 2021;19:eAO6739. https://doi.org/10.31744/einstein_journal/2021AO6739
12. Ángel Mejía VE, Arango Isaza D, Fernández Turizo MJ, Vasquez Trespalacios EM, Rincón JA. High flow nasal cannula useful for severe SARSs-CoV-2 pneumonia. Med Intensiva 2022;46(2):107–9. https://doi.org/10.1016/j.medine.2021.01.004
13. Chosidow S, Plantefève G, Fraissé M, Mentec H, Cally R, Contou D. Non-intubated COVID-19 patients despite high levels of supplemental oxygen. Crit Care 2021;25(1):170. https://doi.org/10.1186/s13054-021-03599-1
14. Swenson ER. Does inspiration of exhaled CO(2) explain improved oxygenation with a face mask plus high-flow nasal cannula oxygen in severe COVID-19 infection? Crit Care 2021;25(1):343. https://doi.org/10.1186/s13054-021-03771-7
15. Willems RAL, Spaetgens B, Conemans LH, Wesseling G, Stehouwer CDA, Alnima T. High flow nasal cannula in older vulnerable COVID-19 patients: A missed opportunity? Respir Med 2021;189:106666. https://doi.org/10.1016/j.rmed.2021.106666
16. Zucman N, Mullaert J, Roux D, et al. Prediction of outcome of nasal high flow use during COVID-19-related acute hypoxemic respiratory failure. Intensive Care Med 2020;46(10):1924–6. https://doi.org/10.1007/s00134-020-06177-1
17. Aguilar-Piedras MF, Porres-Aguilar M, Mukherjee D, Cueto-Robledo G, Roldan-Valadez E, Tapia-Vargas PA. High flow nasal cannula oxygenation successfully used as bridge therapy for systemic thrombolysis in COVID-19 associated intermediate-high risk pulmonary embolism. Curr Probl Cardiol 2022;47(2):101000. https://doi.org/10.1016/j.cpcardiol.2021.101000
18. Vadi S, Phadtare S, Shetty K. High-flow oxygen therapy via tracheostomy to liberate COVID-19-induced ARDS from invasive ventilation: A case series. Indian J Crit Care Med 2021;25(6):723–7. https://doi.org/10.5005/jp-journals-10071-23858
19. Vega ML, Pisani L. Nasal high flow oxygen in acute respiratory failure. Pulmonology 2021;27(3):240–7. https://doi.org/10.1016/j.pulmoe.2021.01.005
20. Şener MU, Aydemir S, Ozturk A. Effect of high-flow nasal oxygen therapy on tracheobronchial mucosa in COVID-19 cases. Respir Case Rep 2021;10(3):216–9. https://doi.org/10.5505/respircase.2021.35119
21. Mariati NMAS, Sugiarto A, Endriani E, Lestari R, Anindita K. High flow nasal cannula to prevent intubation in obese patient with COVID-19 induced ARDS: A case report. Anaesth Pain Intensive Care 2021;25(2):212–6. https://doi.org/10.35975/APIC.V25I2.1473
22. Madney YM, Esquinas AM, Saeed H, Harb HS, Abdelrahim MEA. Improving the safety of high-flow therapies in the management of patients with COVID-19. Chest 2020;158(4):1788–9. https://doi.org/10.1016/j.chest.2020.06.040
23. Kumar A, Kumar A, Kumar N, et al. Repackaging of malfunctioning high flow nasal cannula as a rescue oxygen therapy: Innovation amid COVID-19 crisis. Indian J Crit Care Med 2021;25(8):949–50. https://doi.org/10.5005/jp-journals-10071-23953.
24. Aguirre-García GM, Ramonfaur D, Torre-Amione G, et al. Stratifying risk outcomes among adult COVID-19 inpatients with high flow oxygen: The R4 score. Pulmonology October 30, 2021;22–58. https://reader.elsevier.com/reader/sd/pii/S2531043721001963?token=6D072EB7E17AAA2DD2F03B7F1F5E95F2405796257D960420C398B5218A5AC831E14EBB538A8E54C6219B2498406AE657&originRegion=us-east-1&originCreation=20221219141331
25. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71

26. Ruthes S. O uso de estudos prospectivos na análise de políticas públicas: uma análise bibliométrica. 19.pt. [accessed 11 Oct 2022]. http://altec2015.nitec.co/altec/papers/770.pdf
27. Study Quality Assessment Tools | NHLBI, NIH, [accessed 17 Oct 2022]. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
28. Ma L-L, Wang Y-Y, Yang Z-H, Huang D, Weng H, Zeng X-T. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: What are they and which is better? Mil Med Res 2020;7(1):7. https://doi.org/10.1186/s40779-020-00238-8
29. Schmidt F, Nowak L, Obereisenbuchler F, et al. Predicting the effectiveness of high-flow oxygen therapy in COVID-19 patients: A single-centre observational study. Anaesthesiol Tntens Ther 2022;54(1):12–7. https://doi.org/10.5114/ait.2022.113738
30. Schmidt M, Demoule A, Hajage D, et al. Benefits and risks of noninvasive oxygenation strategy in COVID-19: A multicenter, prospective cohort study (COVID-ICU) in 137 hospitals. Crit Care 2021;25(1):421. https://doi.org/10.1186/s13054-021-03784-2
31. Suryawanshi C, Narkhede H, Mahanta D. Clinical outcomes of COVID-19 patients after sequential oxygen therapy in Tertiary Medical College. Bali J Anesthesiol 2022;6(1):49–53. https://doi.org/10.4103/bjoa.bjoa_179_21
32. Hacquin A, Perret M, Manckoundia P, et al. High-flow nasal cannula oxygenation in older patients with sars-cov-2-related acute respiratory failure. J Clin Med 2021;10(16):3515. https://doi.org/10.3390/jcm10163515
33. Bonnet N, Martin O, Boubaya M, et al. High flow nasal oxygen therapy to avoid invasive mechanical ventilation in SARS-CoV-2 pneumonia: A retrospective study. Ann Intensive Care 2021;11(1):37. https://doi.org/10.1186/s13613-021-00825-5
34. Mellado-Artigas R, Ferreyro BL, Angriman F, et al. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. Crit Care 2021;25(1):58. https://doi.org/10.1186/s13054-021-03469-w
35. Sayan İ, Altınay M, Çınar AS, et al. Impact of HFNC application on mortality and intensive care length of stay in acute respiratory failure secondary to COVID-19 pneumonia. Heart & Lung 2021;50(3):425–9. https://doi.org/10.1016/j.hrtlng.2021.02.009
36. Duan J, Chen B, Liu X, et al. Use of high-flow nasal cannula and noninvasive ventilation in patients with COVID-19: A multicenter observational study. Am J Emerg Med 2021;46:276–81. https://doi.org/10.1016/j.ajem.2020.07.071
37. Xia J, Zhang Y, Ni L, et al. High-flow nasal oxygen in coronavirus disease 2019 patients with acute hypoxemic respiratory failure: A multicenter, retrospective cohort study. Crit Care Med 2020;48(11):E1079–86. https://doi.org/10.1097/CCM.0000000000004558
38. Franco C, Facciolongo N, Tonelli R, et al. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. Eur Respir J 2020;56(5):2002130. https://doi.org/10.1183/13993003.02130-2020
39. Chandel A, Patolia S, Brown AW, et al. High-flow nasal cannula therapy in COVID-19: Using the ROX index to predict success. Respir Care 2021;66(6):909–19. https://doi.org/10.4187/respcare.08631
40. Alshahrani M, Alshaqaq H, Alhumaid J, et al. High-flow nasal cannula treatment in patients with COVID-19 acute hypoxemic respiratory failure: A prospective cohort study. Saudi J Med Med Sci 2021;9(3):215–22. https://doi.org/10.4103/sjmms.sjmms_316_21
41. Beduneau G, Boyer D, Guitard PG, et al. Covid-19 severe hypoxemic pneumonia: A clinical experience using high-flow nasal oxygen therapy as first-line management. Res Med Res 2021;80:10083. https://doi.org/10.1016/j.resmer.2021.100834
42. Celejewska-Wójcik N, Polok K, Górka K, et al. High-flow nasal oxygen therapy in the treatment of acute respiratory failure in severe COVID-19 pneumonia: A prospective observational study. Polish Arch Intern Med 2021;131(7–8):658–65. https://doi.org/10.20452/pamw.16015
43. Costa WNDS, Miguel JP, Prado FDS, et al. Noninvasive ventilation and high-flow nasal cannula in patients with acute hypoxemic respiratory failure by covid-19: A retrospective study of the feasibility, safety and outcomes. Respir Physiol Neurobiol 2022;298:103842. https://doi.org/10.1016/j.resp.2022.103842
44. Delbove A, Foubert A, Mateos F, Guy T, Gousseff M. High flow nasal cannula oxygenation in COVID-19 related acute respiratory distress syndrome: A safe way to avoid endotracheal intubation? Ther Adv Respir Dis 2021;15:17534666211019555. https://doi.org/10.1177/17534666211019555
45. Deng L, Lei S, Wang X, et al. Course of illness and outcomes in older COVID-19 patients treated with HFNC: A retrospective analysis. Aging (Albany NY) 2021;13(12):15801–14. https://doi.org/10.18632/aging.203224
46. Duan J, Zeng J, Deng P, et al. High-flow nasal cannula for COVID-19 patients: A multicenter retrospective study in China. Front Mol Biosci 2021;8:639100. https://doi.org/10.3389/fmolb.2021.639100
47. Gaspic TK, Ivelja MP, Kumric M, et al. In-hospital mortality of COVID-19 patients treated with high-flow nasal oxygen: Evaluation of biomarkers and development of the novel risk score model CROW-65. Life 2021;11(8):735. https://doi.org/10.3390/life11080735
48. Grieco DL, Menga LS, Cesarano M, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: The HENIVOT randomized clinical trial. JAMA 2021;325(17):1731–43. https://doi.org/10.1001/jama.2021.4682
49. Hansen C, Stempek S, Liesching T, Lei Y, Dargin J. Characteristics and outcomes of patients receiving high flow nasal cannula therapy prior to mechanical ventilation in COVID-19 respiratory failure: A prospective observational study. Int J Crit Illn Inj Sci 2021;11(2):56–60. https://doi.org/10.4103/IJCIIS.IJCIIS_181_20
50. Jarou ZJ, Beiser DG, Sharp WW, et al. Emergency department-initiated high-flow nasal cannula for COVID-19 respiratory distress. West J Emerg Med 2021;22(4):979–87. https://doi.org/10.5811/WESTJEM.2021.3.50116
51. Nguyen PL, Osman H, Watza D, et al. High-flow nasal cannula therapy in a predominantly African American population with COVID-19 associated acute respiratory failure. BMJ Open Respir Res 2021;8(1):e000875. https://doi.org/10.1136/bmjresp-2021-000875
52. Sykes DL, Crooks MG, Thu KT, et al. Outcomes and characteristics of COVID-19 patients treated with continuous positive airway pressure/high-flow nasal oxygen outside the intensive care setting. ERJ Open Res 2021;7(4):00318-2021. https://doi.org/10.1183/23120541.00318-2021
53. Wendel-Garcia PD, Mas A, González-Isern C, et al. Non-invasive oxygenation support in acutely hypoxemic COVID-19 patients admitted to the ICU: A multicenter observational retrospective study. Crit Care 2022;26(1):37. https://doi.org/10.1186/s13054-022-03905-5
54. Ouissa R, Le Guillou C, Broudic M, Markowicz S, Curlier E, Roger PM. Successful high flow nasal cannula therapy for severe COVID-19 pneumonia is associated with tocilizumab use. Infect Dis Now 2022;52(3):145–8. https://doi.org/10.1016/j.idnow.2022.02.006
55. Rorat M, Szymański W, Jurek T, Karczewski M, Zelig J, Simon K. When conventional oxygen therapy fails—The effectiveness of high-flow nasal oxygen therapy in patients with respiratory failure in the course of COVID-19. J Clin Med 2021;10(20):4751. https://doi.org/10.3390/jcm10204751
56. Schwartz BC, Jayaraman D, Yang SS, Wong EG, Lipes J, Dial S. High-flow nasal oxygen as first-line therapy for COVID-19-associated hypoxemic respiratory failure: A single-centre historical cohort study. Can J Anesth 2022;69(5):582–90. https://doi.org/10.1007/s12630-022-02218-z
57. Wendel Garcia PD, Aguirre-Bermeo H, Buehler PK, et al. Implications of early respiratory support strategies on disease progression in critical COVID-19: A matched subanalysis of the prospective RISC-19-ICU cohort. Crit Care 2021;25(1):175.https://doi.org/10.1186/s13054-021-03580-y
58. Alkouh R, El Rhalete A, Manal M, et al. High-flow nasal oxygen therapy decrease the risk of mortality and the use of invasive mechanical ventilation in patients with severe SARS-CoV-2 pneumonia? A retrospective and comparative study of 265 cases. Ann Med Surg 2022;74:103230. https://doi.org/10.1016/j.amsu.2021.103230
59. Chavarria AP, Lezama ES, Navarro MG, et al. High-flow nasal cannula therapy for hypoxemic respiratory failure in patients with COVID-19. Ther Adv Infect Dis 2021;8:20499361211042959. https://doi.org/10.1177/20499361211042959
60. Mellado-Artigas R, Mujica LE, Ruiz ML, et al. Predictors of failure with high-flow nasal oxygen therapy in COVID-19 patients with acute respiratory failure: A multicenter observational study. J Intensive Care 2021;9(1):23. https://doi.org/10.1186/s40560-021-00538-8
61. Panadero C, Abad-Fernández A, Rio-Ramirez MT, et al. High-flow nasal cannula for acute respiratory distress syndrome (ARDS) due to COVID-19. Multidiscip Respir Med 2020;15(1):693. https://doi.org/10.4081/mrm.2020.693
62. Hu M, Zhou Q, Zheng R, et al. Application of high-flow nasal cannula in hypoxemic patients with COVID-19: A retrospective cohort study. BMC Pulm Med 2020;20(1):324. https://doi.org/10.1186/s12890-020-01354-w
63. Calligaro GL, Lalla U, Audley G, et al. The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study. E Clin Med 2020;28:100570. https://doi.org/10.1016/j.eclinm.2020.100570

64. Xu J, Yang X, Huang C, et al. A novel risk-stratification models of the high-flow nasal cannula therapy in COVID-19 patients with hypoxemic respiratory failure. Front Med (Lausanne) 2020;7:607821. https://doi.org/10.3389/fmed.2020.607821
65. Ferrer S, Sancho J, Bocigas I, et al. ROX index as predictor of high flow nasal cannula therapy success in acute respiratory failure due to SARS-CoV-2. Respir Med 2021;189:106638. https://doi.org/10.1016/j.rmed.2021.106638
66. Kerai S, Singh R, Saxena KN, Desai SD, Bhalotra AR. A retrospective study on experience of high-flow nasal cannula oxygen in critically ill COVID-19 adult patients admitted to intensive care unit. Indian J Crit Care Med 2022;26(1):62–66.. https://doi.org/10.5005/jp-journals-10071-24097
67. Roca O, Messika J, Caralt B, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index. J Crit Care 2016;35:200–205. https://doi.org/10.1016/j.jcrc.2016.05.022
68. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22(7):707–10.https://doi.org/10.1007/BF01709751
69. Teng Xb, Shen Y, Han Mf, Yang G, Zha L, Shi Jf. The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. Eur J Clin Invest 2021;51(3):e13435. https://doi.org/10.1111/eci.13435
70. Demoule A, Baron AV, Darmon M, et al. High-flow nasal cannula in critically ill patients with severe COVID-19. Am J Respir Crit Care Med 2020;202(7):1039–42. https://doi.org/10.1164/rccm.202005-2007LE
71. Rochwerg B, Granton D, Wang DX, Einav S, Burns KEA. High-flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: Author's reply. Intensive Care Med 2019;45(8):1171. https://doi.org/10.1007/s00134-019-05658-2
72. Rochwerg B, Granton D, Wang DX, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: A systematic review and meta-analysis. Intensive Care Med 2019;45(5):563–72. https://doi.org/10.1007/s00134-019-05590-5
73. Ferreyro BL, Angriman F, Munshi L, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: A systematic review and meta-analysis. JAMA 2020;324(1):57–67.https://doi.org/10.1001/jama.2020.9524
74. Zhang C, Ou M. Comparison of hypoxemia, intubation procedure, and complications for non-invasive ventilation against high-flow nasal cannula oxygen therapy for patients with acute hypoxemic respiratory failure: A non-randomized retrospective analysis for effectiveness and safety (NIVaHIC-aHRF). BMC Emerg Med 2021;21(1):6. https://doi.org/10.1186/s12873-021-00402-w
75. Zhao H, Wang H, Sun F, Lyu S, An Y. High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: A systematic review and meta-analysis. Crit Care 2017;21(1):184. https://doi.org/10.1186/s13054-017-1760-8
76. Claudi D, Arifin H, Prasetya RJ. The role of ROX index in predicting intubation in COVID-19 pneumonia receiving high flow nasal cannula: A systematic review. J Emerg Med Trauma Acute Care 2022;(2). https://www.qscience.com/content/journals/10.5339/jemtac.2022.8
77. Zhou X, Liu J, Pan J, Xu Z, Xu J. The ROX index as a predictor of high-flow nasal cannula outcome in pneumonia patients with acute hypoxemic respiratory failure: A systematic review and meta-analysis. BMC Pulm Med 2022;22(1):121. https://doi.org/10.1186/s12890-022-01914-2
78. Roca O, Caralt B, Messika J, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med 2019;199(11):1368–76. https://doi.org/10.1164/rccm.201803-0589OC
79. Lee JY, Kim HA, Huh K, et al. Risk factors for mortality and respiratory support in elderly patients hospitalized with COVID-19 in Korea. J Korean Med Sci 2020;35(23):e223. https://doi.org/10.3346/jkms.2020.35.e223
80. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239–242. https://doi.org/10.1001/jama.2020.2648
81. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323(18):1775–6. https://doi.org/10.1001/jama.2020.4683
82. Beran A, Srour O, Malhas SE, et al. High-flow nasal cannula oxygen versus non-invasive ventilation in subjects with COVID-19: A systematic review and meta-analysis of comparative studies. Respir Care 2022;67(9):1177–89. https://doi.org/10.4187/respcare.09987
83. Frat J-P, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372(23):2185–96. https://doi.org/10.1056/NEJMoa1503326