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Review

High flow nasal oxygen (HFNO) in the treatment of COVID-19 infection of adult patients from – An emergency perspective: A systematic review and meta-analysis

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2, which was first discovered in Wuhan, China. The disease has grown into a global pandemic causing mild to moderate symptoms in most people. The disease can also exhibit serious illnesses, especially for patients with other chronic diseases such as cardiovascular diseases, diabetes, chronic respiratory disease, or cancer. In such cases of severe illness, high flow nasal oxygen (HFNO) has been used to provide oxygenation to COVID-19 patients. However, the efficiency of HFNO remains uncertain, prompting the conduction of this systematic review to evaluate the effectiveness of the therapy.

A thorough search for relevant and original articles was carried out on five electronic databases, including ScienceDirect, PubMed, Cochrane Library, Embase, and Google Scholar. No time limitation was placed during the search as it included all the articles related to COVID-19 from 2019 to 2022. The search strategy utilized in this systematic review yielded 504 articles, of which only 10 met the eligibility criteria and were included. Our meta-analysis reveals that HFNO success rate was higher than HFNO failure rates (0.52 (95% CI; 0.47, 0.56) and 0.48 (95% CI; 0.44, 0.53), respectively), however, the difference was statistically insignificant. HFNO was associated with a significant decrease in mortality and intubation rates (0.28 (95% CI; 0.19, 0.39) and 0.28 (95% CI; 0.18, 0.41), respectively). Our statistical analysis has shown that significantly lower ROX index (5.07 ± 1.66, $p = 0.028$) and PaO_2/FiO_2 (100 ± 27.51, $p = 0.031$) are associated with HFNO failure, while a significantly lower respiratory rate (RR) (23.17 ± 4.167, $p = 0.006$) is associated with HFNO success. No statistically significant difference was observed in SpO_2/FiO_2 ratio between the HFNO success and failure groups (154.23 ± 42.74 vs. 124.025 ± 28.50, $p = 0.62$, respectively).

Based on the results from our meta-analysis, the success or failure of HFNO in treating COVID-19 adult patients remains uncertain. However, HFNO has been shown to be an effective treatment in reducing mortality and intubation rates. Therefore, HFNO can be recommended for COVID-19 patients but with close monitoring and should be carried out by experienced healthcare workers.

Abbreviations: ARDS, **Adult Respiratory Distress Syndrome**; CI, confidence interval; COVID-19, **Coronavirus disease 2019**; **CPAP**, **positive airway pressure**; HFNO, **High Flow Nasal Oxygen**; ICU, **Intensive Care Unit**; **IQR**, **interquartile range**; **IMV**, **invasive mechanical ventilation**; **FiO2**, **inspiratory oxygen fraction**; **NIV**, **Non-invasive ventilation**; NIPPV, **non-invasive positive pressure ventilation**; PEEP, **end-expiratory pressure**; **PRISMA**, **Preferred Reporting Items for Systematic Reviews and Meta-analysis**; **RR**, **Respiratory rate**; **ROX index**, **Respiratory Rate Oxygenation Index**; **SOFA**, **Sequential Organ Failure Assessment**; **SpO2**, **Oxygen saturation**; WHO, **World Health Organization**.

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Contents

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. This disease was first recorded on a small scale in November 2019, followed by a massive large-scale appearance in Wuhan, China December 2019. Since then, COVID-19 has grown to be a global public health problem. According to the World Health Organization (WHO) statistics, as of July 2022, the number of confirmed COVID-19 cases worldwide was 545, 226, 550, including 6,334,728 deaths [1]. Most people with the disease exhibit mild to moderate symptoms and recover without requiring special medication. However, in some patients, COVID-19 causes serious illnesses that require medical attention. The WHO has reported that older patients and patients with underlying conditions such as cardiovascular diseases, diabetes, chronic respiratory disease, or cancer are more likely to develop severe illnesses [2].

COVID-19 patients usually require oxygen therapy due to type 1 respiratory failure, and when the disease progresses to a serious condition, then a difficult choice between invasive and non-invasive ventilation therapies is usually made [3]. Several non-invasive therapies, including High flow nasal oxygen (HFNO), Non-invasive ventilation (NIV), or continuous positive airway pressure (CPAP) devices, have been used as therapeutic options for COVID-19 patients, especially in the treatment of medium to severe Adult Respiratory Distress Syndrome (ARDS). HFNO is described as an innovative therapy in which 30–60 Liters/min of heated and fully humidified gas with an inspiratory oxygen fraction (FiO_2) of 21%–100% is administered [4]. HFNO is considered to have numerous physiological benefits including, reducing the anatomical dead space and work of breathing, providing a constant fraction of inspired oxygen (FiO2) with sufficient humidification, and a degree of positive end-expiratory pressure (PEEP) [3,5].

Although HFNO has its benefits, there is a concern on when to switch COVID-19 patients from the treatment to either invasive mechanical ventilation (IMV) or NIV. Research shows that even though HFNO might help avoid the need for IMV in some patients [6,7], it might result to delayed initiation of IMV and worsen their outcomes [8]. Therefore, it is essential to identify and describe accurate predictors for the need of IMV in spontaneously breathing patients. The WHO has pointed out that when using HFNO in COVID-19 patients, the oxygenation status should be closely monitored in order to adjust the respiratory support programs at the appropriate time. Some indicators including Oxygen saturation index (SpO_2/FiO_2), ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO2), Respiratory rate (RR), and respiratory rate oxygenation index (ROX index) have been reported to be useful in monitoring oxygenation status and are effective in predicting the outcomes of HFNO [9,10]. However, it is unclear whether these predictors are applicable in COVID-19 patients.

Therefore, this systematic review was designed to evaluate the efficacy of HFNO in treating COVID-19 adult patients and the predictive values of ROX index, SpO_2/FiO_2, PaO_2/FiO2 and RR on the outcomes of HFNO in these patients.

2. Methods

2.1. Literature search

Following the guidelines outlined in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis), a thorough search was conducted through 5 electronic databases, including ScienceDirect, PubMed, Cochrane Library, Embase, and Google Scholar. The search criteria involved using the Boolean expressions "AND" and "OR" together with specific keywords. The detailed search strategy utilized in this systematic review to identify relevant and original articles was as follows; ("High flow nasal oxygen" OR "High flow nasal cannula" OR "High flow nasal cannula oxygen therapy") AND ("Management" OR "Treatment") AND ("Coronavirus" OR "COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2"). The search query was not limited as it included all articles on COVID-19 published between 2019 and 2022.

2.2. Eligibility criteria

All the articles from the databases outlined in the literature search were assessed using the inclusion and exclusion criteria. For studies to be included in this systematic, they had to satisfy the following criteria.

1. Include adult patients (aged $\geq$18 years)
2. Studies independently evaluating HFNO in COVID-19 patients.
3. Studies written and Published in English language. The reviewers made this consideration to avoid the direct translation

of Scientific terms, which could lead to loss of meaning or context.

Studies were excluded based on the following criteria.

1. Studies including young patients (<18 years)
2. Studies evaluating HFNO in the treatment of patients with other diseases other than COVID-19
3. Studies published in languages other than English.
4. Systematic reviews, case reports, letters to the editor, and abstracts without evidence of full articles were also excluded.
5. Studies comparing HFNO to other treatment options in COVID-19 patients.

2.3. Data extraction and definition

Two reviewers were tasked with the retrieval and compilation of relevant data from the included studies. The data extracted included; Author ID (Autor(s) and year of publishment), Study design, Characteristics of the study participants, intervention, follow-up period, and main outcomes. The characteristics of the participants included; age, sex, and sample size, while the follow-up period represented the time after HFNO initiation. Any inconsistencies in the data were reconciled by consulting a third reviewer. The main outcomes of this systematic review were the number of COVID-19 patients successfully or unsuccessfully treated using the HFNO, mortality rates, and intubation rates. The other outcomes were oxygen and respiratory parameters, including Oxygen saturation to a fraction of inspired oxygen ratio (SpO_2/FiO_2), respiratory rate (RR), the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO2), and ROX index (measured as the ratio of SpO_2/FIO_2 to the respiratory rate.) (Table 1).

Successful HFNO treatment was defined priori as the withdrawal of HFNO with improved oxygenation, no need for NIV and/or Invasive mechanical ventilation (IMV), and discharge from the hospitals alive. On the other hand, HFNO failure was defined as the need for NIV and/or IMV and death while on HFNO support.

2.4. Quality assessment

Studies included in this systematic review were non-randomized; therefore, the quality assessment was done using Newcastle-Ottawa appraisal tool. The two reviewers tasked with the quality assessment procedure evaluated each study based on three categories including selection, comparability and outcomes. Under the selection category, four questions were used, while for comparability and outcome, 1 and 3 questions were used, respectively. During the assessment, the reviewers assigned rating scores to each study. A quality rating of "1" was used for a fully answered question, while a rating score of "0" was used for "unclear" or "no" responses. Studies with a quality rating scores of 0–2, 3–5 and > five were deemed to have poor, moderate and high methodological quality, respectively (Table 2).

2.5. Data analysis

The meta-analysis of pooled data was conducted using RevMan software (version 4.2.1). A random-effect model was implemented because it efficiently considers the study sample size and heterogeneity. Given that the groups analyzed in this systematic review were retrieved from the same population, a paired sample *t*-test was used for the statistical analysis. All the statistical analyses were conducted using SPSS (Version 28.0.0). The outcomes of mortality, intubation, success, and failure rates were pooled together and presented in forest plots in which a 95% confidence interval was used. Data heterogeneity was measured using I^2 statistics of which heterogeneity of 25%, 50%, and above 70% was considered low, moderate, and substantial, respectively. A *P*-value of less than 5% ($P < 0.05$) was used to indicate a significant difference in both meta-analyses and statistical analyses.

3. Results

3.1. Search results

The search strategy outlined earlier yielded 504 articles from the 5 electronic databases. The studies were screened for duplicates, of which 23 duplicate articles were identified and excluded. The remaining 481 articles had their titles and abstracts screened, of which 203 articles were excluded. 190 articles were not retrieved, and the remaining articles were assessed using the eligibility. Assessing the articles using eligibility criteria led to the exclusion of 78 articles, of which 11 were excluded because they were published in languages other than English, 22 evaluated the use of HFNO in the treatment of other diseases, 1 included young patients, 36 compared HFNO to other treatment options and 8 were either systematic reviews, case reports, letters to the editor or Abstracts without full articles (Fig. 1).

3.2. Clinical outcomes

A meta-analysis of 10 studies showed that 591 of 1148 COVID-19 patients subjected to HFNO therapy were successfully treated with a success rate of 0.52 (95% CI; 0.47, 0.56) (Fig. 2).

On the other hand, out of 1148 COVID-19 patients, HFNO failure was observed in 557 patients at a failure rate of 0.48 (95% CI; 0.44, 0.53) (Fig. 3). Comparing the two rates (analyzed in Figs. 2 and 3), there is no significant difference.

The meta-analysis of data from 7 studies shows that of 1007 patients treated using HFNO therapy, 367 patients eventually died at a mortality rate of 0.28 (95% CI; 0.19, 0.39) (Fig. 4).

Similarly, a meta-analysis of data from 8 studies has shown that of 1048 patients treated using HFNO, 246 required intubations at a rate of 0.28 (95% CI; 0.18, 0.41) (Fig. 5).

Our statistical analysis showed that significantly higher ROX index, and PaO_2/FiO_2 ratio and lower RR were observed in the HFNO success group than failure group (Table 3). The ratio SpO2/FiO2 was higher in the success group; however, when compared with the failure group, no statistically significant difference was observed (Table 3).

4. Discussion

The primary aim of conducting this systematic review and meta-analysis was to understand the effectiveness of HFNO in treating COVID-19. The results of our meta-analysis have shown high success rates of HFNO; however, compared to the failure rates, there was no significant difference. The high success rate can be attributed to the fact that all the studies used in this review used HFNO as the first-line therapy for the treatment of patients with COVID-19. Indeed, this finding is corroborated by previous large cohort studies, which show that when HFNO is used as the first-line therapy, then the success rate can range from 44% to 62% [21,22]. The statistical analysis of respiratory and oxygen requirements after treatment with HFNO has shown that significantly higher ROX index, higher PaO_2/FiO2 ratio, and lower RR were observed in the HFNO success group than in the failure group. However, no significant difference was observed in SpO2/FiO2 ratio in the two groups after treatment with HFNO.

Our statistical analysis has shown that a significantly lower ROX index is associated with HFNO failure among COVID-19 patients.

Table 1
Study characteristics.

Author ID	Study Design	Participants	Intervention	Follow-up (Hours)	Main Outcomes
Calligaro et al., 2020 [11]	Multicenter Prospective observational Study	293 COVID-19 patients (163 males and 130 females) aged 44–58 years	HNFO was initiated at 50–60 L/min with FiO_2 0.8–1.0, titrated with the aim of achieving $SpO_2 \geq 92\%$	6	137 of 293 (47%) patients were successfully treated with HFNO, while HFNO failure was observed in 156 patients. The median HFNO duration for patients successfully treated was 6 (3–9) days versus 2 (1–5) days in those who failed. Compared with HFNO failure patients, those successfully treated with HFNO were recorded to have higher oxygen saturations (91% vs. 89%), lower respiratory rates (32 vs. 40 breaths/min), and lower oxygen requirements at 6 h of HFNO initiation.
Kerai et al., 2022 [12]	Retrospective study	85 critically ill COVID-19 patients (age ≥18 years) met the inclusion criteria of this study	HFNO was administered using two devices capable of delivering FiO_2 from 21 to 100% and maximum flow rates of 80 L/min and 60 L/min with the aim of maintaining $SpO_2 > 90\%$	12	Successful HFNC treatment was observed in 41 patients, while HNFC failure was observed in 44 patients. ROX indices at 2, 6, and 12 h after HFNO initiation were significantly higher in the success group compared failure group (5.43 ± 1.42 vs. 4.44 ± 1.13, 5.74 ± 1.53 vs. 4.59 ± 1.06, and 6.12 ± 1.54 vs. 4.72 ± 1.32 at 2, 6 and 12 h respectively). Higher PaO_2/FiO_2 was observed in the success group compared with the failure group (115 ± 54 vs. 87 ± 41.3, respectively.)
Takeshita et al., 2022 [13]	Retrospective cohort study	39 COVID-19 patients (35 men and 4 women) with a mean age of 57.9 ± 12.7 years were studied.	HFNC was initiated at a temperature of 31 °C–37 °C with high-flow oxygen at 40 L/min and an adjustment of FiO_2 to maintain the $SpO_2 > 94\%$	24	24 patients were successfully treated using the HFNO, while HFNO treatment failed in 15 patients. The respiratory rate was significantly higher among patients in the HFNC failure group compared with the success group (23 vs. 20 breaths/min, respectively). The ROX index was significantly higher among the success group than the failure group (9.11 vs. 5.74)
Duan et al., 2021 [14]	Multicenter retrospective study	66 patients were enrolled in this study.	HFNC flow and FiO_2 were adjusted to maintain a $SpO_2 > 93\%$	24	37 patients were successfully treated using HFNC oxygen therapy, while HFNC failure was recorded in 29 patients. A significantly higher mortality rate was observed among patients in the failure group than the success group (28% vs. 0% $p < 0.01$). ROX index was significantly lower in the failure group than in the success group. The results of multivariate analysis showed that the ROX index was independently related to the HFNC failure (odds ratio [OR] = 0.65; 95% confidence interval [CI]: 0.45–0.94)
Wang et al., 2020 [15]	Retrospective study	17 COVID-19 patients (7 males and 10 females) with a mean age of 65 years	HFNO therapy was initiated at a temperature of 31–37 °C, a flow rate of 30–60 L/min, and FiO_2 adjusted to maintain the $SpO_2 > 93\%$	2	HFNC success was recorded in 10 patients, while HFNC failure was recorded in 7 patients. A higher failure rate was observed in 64% of the patients with $PaO_2/FiO_2 \leq 200$ mmHg. The respiratory rate showed no statistically significant difference between the success and failure groups after 1–2 h of HFNO administration.
Hu et al., 2020 [16]	Retrospective cohort study	105 hypoxemic patients with COVID-19 (51 males and 54 females) with a mean age of 64.0 ± 11.3 years.	The HFNC was initially set to a gas flow rate of 30 L/min, and FiO_2 of 1.0 was adjusted to maintain the SpO_2 at 92–96%.	24	65 of 105 patients were successfully treated with HFNC, while 40 recorded an HFNC failure. Significantly higher SpO_2/FiO_2 and PaO_2/FiO_2 were observed in the success group than failure group after 6, 12, and 24 h of HFNC initiation. Significant lower respiratory rates were observed in the Success group after 6, 12, and 24 h of HFNC initiation (22 vs. 24, 22 vs. 25, and 21 vs. 25 breaths/min after 6, 12, and 24 h, respectively.)
Xu et al., 2020 [17]	Retrospective Study	324 COVID-19 patients (219 males and 105 females) aged above 60 years.	HFNC oxygen therapy was initiated at a temperature of 31–37 °C, and a minimum flow rate of 30 L/min; the FiO_2 was adjusted to maintain $SpO_2 > 90\%$	48	HFNC failure was observed in 147 patients, while HFNC success was observed in 177 patients. A significantly lower rate of respiratory was observed in the HFNC success group than in the HFNC failure group (22 vs. 23 breaths/min, respectively.) A significantly higher ROX index was recorded in the success group than the failure group (5.9 vs. 4.8, respectively.)
Kim et al., 2022 [18]	Multicenter retrospective Study	133 hypoxemic COVID-19 patients (79 males and 54	HFNC oxygen therapy	12	HFNC success was observed in 63 patients, while failure was observed in 70 patients.

Table 1 (*continued*)

Author ID	Study Design	Participants	Intervention	Follow-up (Hours)	Main Outcomes
		females) with a mean age of 70 years were analyzed			Significantly higher ROX indices were observed in the success group than in the failure group (8.77 vs. 6.85, 9.33 vs. 7.67, 9.70 vs. 8.64 after 1, 4, and 12 h, respectively.) No statistically significant difference was observed in the rate of respiratory for HFNC success and failure groups (21 vs. 21, 20 vs.20, and 20 vs. 20 breaths/min after 1, 4, and 12 h. Significantly higher SpO_2/FiO_2 ratios were observed in the HFNC success group than in the failure group (196 vs. 160, 194 vs. 159, and 196 vs. 163 after 1, 4, and 12 h, respectively.
Alshahrani et al., 2021 [19].	Prospective Cohort Study	44 COVID-19 patients (38 males and 6 females) with a mean age of 57 ± 14 years.	HFNC gas flow rate was initiated at a flow rate of 30–60 L/min, and FiO_2 adjusted to maintain SpO_2 between 92% and 96%	24	29 patients experienced HFNC failure, while 15 patients recorded HFNC success. ROX index was significantly higher in the success group than the failure group but not statistically significant (4.98; IQR, 3.94–7.8 vs. 3.69; IQR, 2.96–4.96, respectively). Higher rates of respiratory and SOFA scores were significantly associated with HFNC therapy failure
Goury et al., 2021 [20]	Retrospective study	42 COVID-19 patients (28 males and 14 females) aged between 59 and 72.5 years	HFNC flow rate was initiated at 50 L/min with FiO_2 of 50%, which was adjusted to maintain SpO_2 greater than 92%	12	22 patients were successfully treated using HFNC oxygen therapy, while 20 patients experienced HFNC failure. Patients in the success group had a significantly shorter ICU stay duration than those in the failure group (7 days [4–8] vs. 23 days [18–42], P = 0.0015). The ROX index at 12 h was significantly associated with the successful treatment of COVID-19 patients using HFNC oxygen therapy.

Note: COVID-19; Coronavirus disease 2019: SpO_2; Oxygen saturation: FiO_2; Fraction of inspired Oxygen: HFNO; High Flow Nasal Oxygen: HFNC; High Flow Nasal Cannula: $PaO_2/FiO2$; ratio of arterial oxygen partial pressure to fractional inspired oxygen: SpO_2/FiO_2; Oxygen saturation to fraction of inspired oxygen ratio: ROX (Ratio of SpO_2/FiO_2 to respiratory rate); IQR; interquartile range: ICU; Intensive Care Unit: SOFA; Sequential Organ Failure Assessment.

Table 2
Methodological Quality using the Newcastle Ottawa Scale for cohort studies.

Author ID	Selection (Maximum 4)	Comparability (Maximum 1)	Outcome (Maximum 3)	Total Score	Quality
Calligaro et al., 2020 [11]	2	1	2	5	Moderate
Kerai et al., 2022 [12]	2	1	1	4	Moderate
Takeshita et al., 2022 [13]	2	1	2	5	Moderate
Duan et al., 2021 [14]	3	1	1	5	Moderate
Wang et al., 2020 [15]	3	1	1	5	Moderate
Hu et al., 2020 [16]	3	1	3	7	High
Xu et al., 2020 [17]	3	1	2	6	High
Kim et al., 2022 [18]	2	1	1	4	Moderate
Alshahrani et al., 2021 [19]	2	1	2	5	Moderate
Goury et al., 2021 [20]	2	1	2	5	Moderate

These results are supported by previous studies which show that ROX index is a good predictor for HFNO failure. For example, Xu et al. [23] after evaluating HFNC treatment in 2851 patients with COVID-19 found that patients in the HFNC failure group showed a significantly lower ROX index than those in the success group (4.9 ± 2.5 vs. 6.1 ± 2.7 (P < 0.01), respectively). This study also suggested that the high sensitivity observed in the ROX index was sufficient to detect HFNO failure in COVID-19 patients. Similarly, another study conducted on 157 COVID-19 pneumonia patients with hypoxemic respiratory failure reported that ROX index was a better predictor of HFNC success compared to RR and SpO_2/FiO_2 [24]. Results depicted by the receiver operating characteristic curves (ROC) and area under the curves (AUROC) showed that after 12 h of HFNC initiation, the ROX index produced the best prediction accuracy (AUROC 0.74). Similarly, results after 18 and 24 h showed better accuracy. This study also suggested that ROX index ≥4.88 was related to increased chances of HFNC success in the treatment of hypoxemic respiratory failure. Prakash and colleagues also undertook the analysis of ROX index in the prediction of HFNC failure among COVID-19 patients with acute hypoxemic respiratory failure and found out that ROX index was a good predictor for distinguishing COVID-19 patients that require hospitalization (ROX index <25.7) [25].

Additionally, our statistical analysis shows that the SpO_2/FiO_2 after HFNO initiation showed no statistically significant difference between the success and failure groups (154.23 ± 42.74 vs. 124.025 ± 28.50, p = 0.62, respectively). However, some studies have shown that SpO_2/FiO_2 after HFNO initiation might be a good indicator of HFNO success in treating COVID-19 patients. Kim et al. [18] reported that ROX index and SpO_2/FiO_2 were acceptable predictors for HFNC failure among COVID-19 patients. Results of AUROC revealed that the ratio SpO_2/FiO_2 at 1 and 4 h were 0.762 (95% CI: 0.679–0.846) and 0.733 (95% CI: 0.640–0.826), respectively, signifying better prediction accuracy. Similarly, evidence has

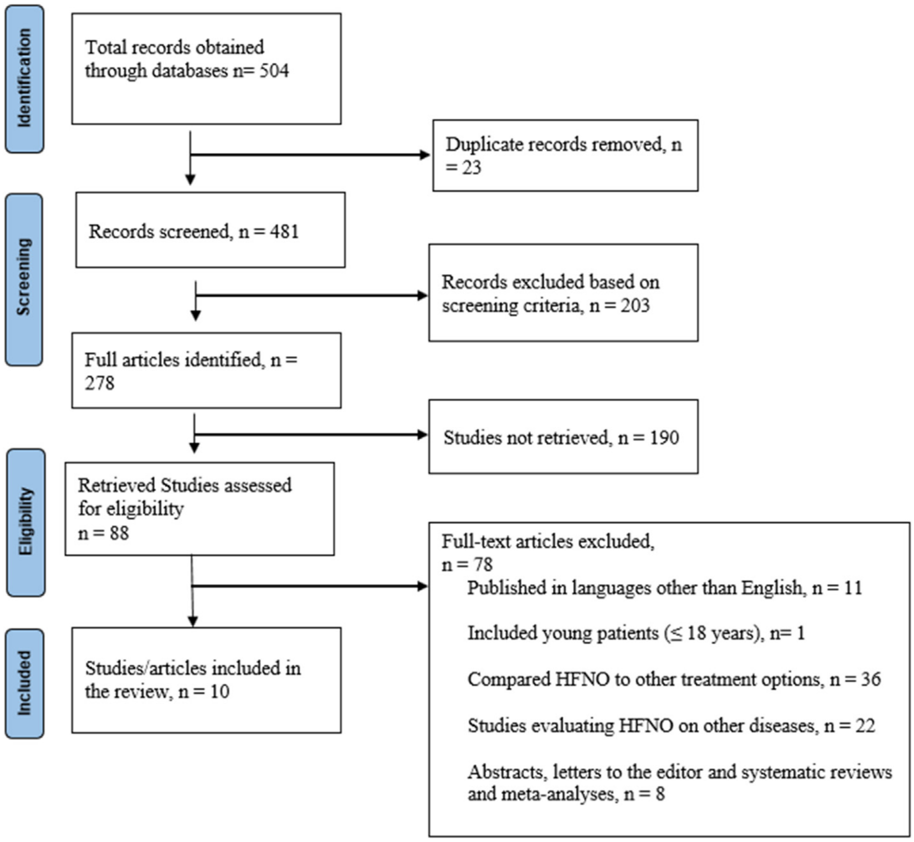

Fig. 1. Prisma flow diagram.

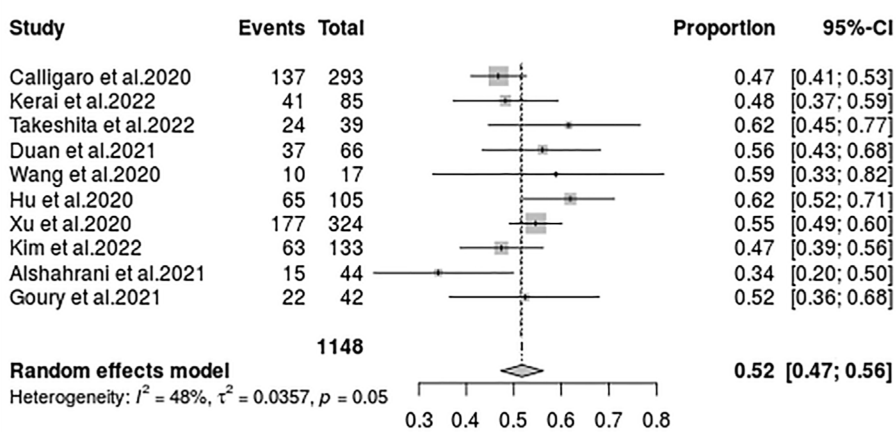

Fig. 2. Forest Plot showing HFNO Success rates.

shown that PaO_2/FiO_2 may be a useful predictor in determining the success of HFNO treatment. Our statistical analysis has shown that a significantly higher PaO_2/FiO_2 was associated with HFNO success than failure (144.75 ± 45.54 vs. 100 ± 27.51, respectively). These results are in line with the results from a previous study which showed that $PaO_2/FiO_2 \leq 100$ mmHg was a significant predictor of HFNC failure [26]. A 2020 study also reported no HFNC failure was observed in patients with $PaO_2/FiO_2 > 200$ mmHg, while 63% of HFNC failure was observed in patients with $PaO_2/FiO_2 \leq 200$ mmHg [15].

The respiratory rate has also been used as a clinical outcome to predict the success of HFNC treatment. Our statistical analysis shows that a significantly lower RR was associated with HFNO success than failure. These results are supported by a recent study that reported that the reduction of RR 18–24 h after HFNO initiation was clinically reasonable to predict the success of HFNC [13]. The study also reported that the RR at the initiation in the HFNC success and failure groups were 23 and 20 breaths/min,

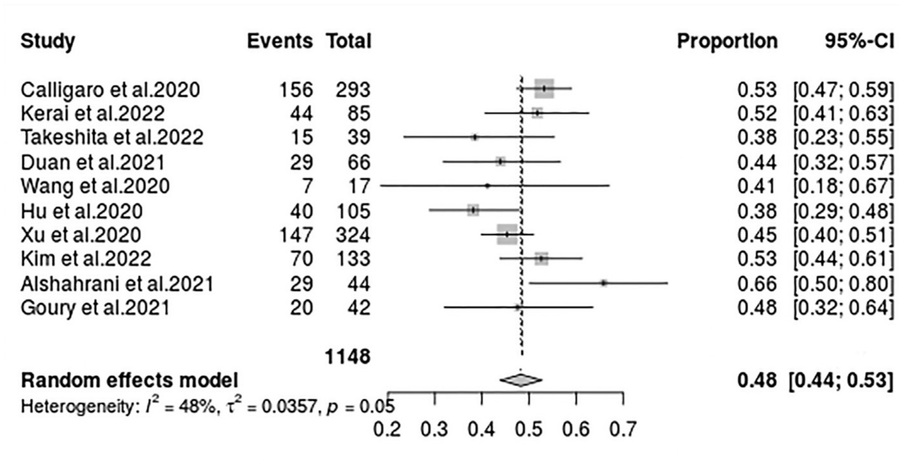

Fig. 3. Forest Plot showing HFNO Failure Rates.

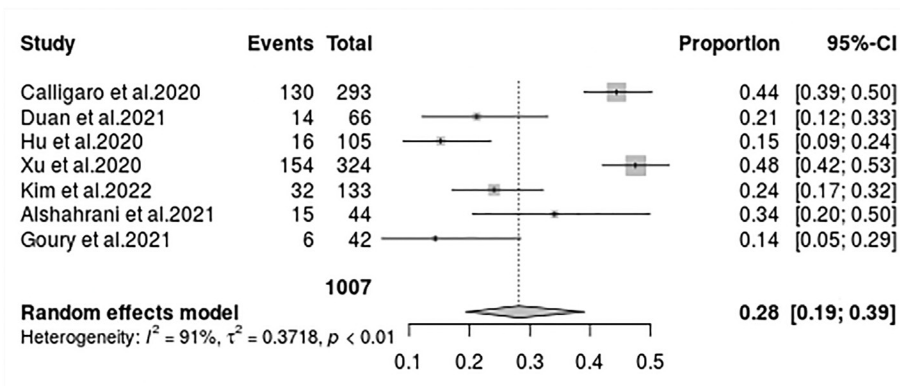

Fig. 4. Forest Plot showing mortality rates associated with HFNO treatment.

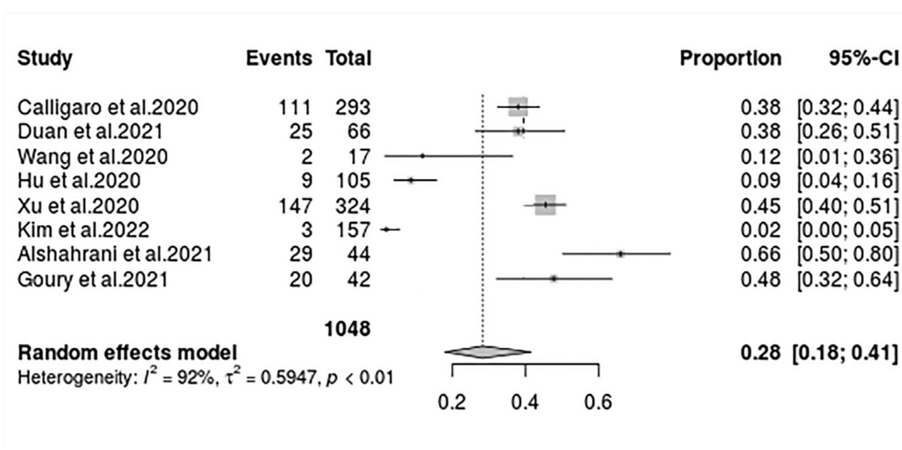

Fig. 5. Forest Plot showing Intubation rates.

Table 3
Statistical Analysis of respiratory and oxygen requirements after HFNO initiation.

Respiratory and oxygen requirement parameters	Articles reported, n	HFNO Success (Mean ± SD)	HFNO failure (Mean ± SD)	*P*-value
ROX index	9	7.67 ± 3.36	5.07 ± 1.66	0.028
RR (breaths/min)	6	23.17 ± 4.167	25.083 ± 4.61	0.006
PaO_2/FiO_2	4	144.75 ± 45.54	100 ± 27.51	0.031
SpO_2/FiO_2	4	154.23 ± 42.74	124.025 ± 28.50	0.62

respectively. After the HFNC treatment, the RR was found to be 20 and 23 breaths/min in success and failure groups. Furthermore, it was reported that RR improvement was observed in 14 (58.3%) patients in the HFNC success group, while only 1 (6.7%) patient in the failure group experienced RR improvement. A previous study by Sztrymf et al. [27] also reported that a significant decrease in RR 48 h after HFNC initiation was associated with success.

Despite using ROX index, RR, PaO_2/FiO_2 and SpO_2/FiO_2 to predict the success or failure of HFNO, evidence shows that the use of HFNO in the treatment of COVID-19 remains controversial. Our meta-analysis shows that HFNO treatment can significantly reduce the intubation and mortality rates. Similar results were reported in a previous meta-analysis which revealed that HFNC usage in COVID-19 patients was associated with reduced intubation and mortality rates. The results of that meta-analysis showed that the mortality rate after HFNC treatment was 0.23 (95% CI; 0.19, 0.29) while the intubation rates were 0.44 (95% CI; 0.38, 0.51) [23]. Similarly, a previous literature review evaluating the use of HFNC in COVID-19 reported that HFNC treatment could reduce the need for intubation and decrease the length of hospital stay [28]. He et al. [29] also evaluated the use of HFNO in 36 critically ill COVID-19 patients and found that 26 (72%) patients were successfully cured while 10 required invasive mechanical ventilation. It was reported that this high success rate and reduced need for intubation was because the HFNO treatment was initiated at a flow rate of 60 L/min and 37 °C while the oxygen saturation was maintained above 95% for patients without lung diseases. Other previous studies have shown that HFNC is efficient in reducing intubation rates in patients without COVID-19. For instance, a meta-analysis conducted by Bocchile et al. reported that HFNC was associated with significant decrease in intubation rates (OR 0.66; 95%CI 0.45−0.96; $p = 0.031$). The success of HFNC in this study was attributed to sufficient minute ventilation and constant oxygenation.

On the other hand, compared to other treatments such as conventional oxygen therapy (COT) and NIV, HFNO effect on the rates of intubation and mortality remain uncertain. Bonnet et al. [30] compared the HFNO therapy to COT among 138 patients with COVID-19 pneumonia and found that there was no significant difference in the intubation rates. Of the 76 patients treated using the HFNO therapy, 39 eventually required intubation, while 46 of 62 patients treated with COT were intubated. The study also reported that the mortality rates at 28 and 60 days showed an insignificant difference in the HFNO and COT groups (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). However, a study that included 43 patients with acute respiratory failure due to COVID-19 pneumonia showed a significant difference between HFNO and COT [31]. Of the 25 patients enrolled in the HFNO therapy, 12 eventually died, while 16 of 19 patients in the COT group died. The need for intubation was also decreased by using HFNO than COT (13 (54.2%) vs. 16 (84.2%), respectively). Additionally, Franco et al. [32] compared HFNC to NIV and CPAP in 670 COVID-19 pneumonia patients and found that the crude 30-day mortality was higher in CPAP patients than in HFNC and NIV patients (100 vs. 26 vs. 54, respectively). The need for intubation was also significantly lower in patients treated using HFNC than CPAP (47 vs. 82, respectively). A recent randomized trial has also shown no significant difference in the mortality rates whether treated by NIV or HFNO (13 vs. 12, $p = 0.82$, respectively) [33].

Notwithstanding the evidence showing that the use of HFNO in COVID-19 is controversial, other studies have recommended the use of HFNO over other treatment options. Alhazzani and colleagues recommended that adult patients with acute hypoxemic respiratory failure due to COVID-19 can be treated using HFNO over COT or non-invasive positive pressure ventilation (NIPPV) [34]. The recommendation of HFNC over NIPPV was attributed to several factors. The study claimed that there is limited experience with NIPPV, suggesting that high failure rates may be experienced. Supporting this claim was a recent meta-analysis comparing HFNC to NPPIV showed that HFNC was significantly associated with decreased mortality rates and the need for intubation [33−35]. Evidence also shows that patients may find using HFNC more comfortable than NIPPV [36]. However, the WHO recommends that HFNO used in treating COVID-19 patients should only be monitored using the health workers experienced with the HFNO [37].

There is little evidence that HFNC oxygen therapy is associated with an increased risk of COVID-19 transmission. Takeshita et al. [13] reported none of the healthcare workers tending to the COVID-19 patients using HFNO was infected with COVID-19. This trend was because all the patients were accommodated in negative pressure rooms during hospitalization and the healthcare providers used surgical masks when they came into contact with the patients. Similarly, the results of a 2021 study conducted on 15 COVID-19 patients showed that no COVID-19 transmission infections were reported during the entire study [38]. However, antibody tests on 1228 health workers showed that two patients tested positive for COVID-19. These infections were unrelated to any interaction with COVID-19 patients in the hospital. Furthermore, the study claims that the lack of COVID-19 transmission among health workers was because the environment and facilities were managed sufficiently. Vianello et al. [26] also evaluated COVID-19 infection in 73 healthcare workers who came in contact with COVID-19 patients over 48 (44−52) hours and found that none of the healthcare workers tested positive for COVID-19. This lack of COVID-19 transmission among healthcare workers was attributed to the use of appropriate protective equipment.

Our research is beneficial for clinical decision making on when to continue or switch HFNO with invasive ventilation. In previous studies, it has been reported that the gold standard for monitoring oxygenation status of patients on HFNO was PaO_2/FiO_2. [16] However, our analysis shows that in addition to PaO_2/FiO_2, ROX index and RR are important predictors for the outcomes of HFNO in COVID-19 patients. It should be noted that a high RR is associated with failure, therefore, medical physicians can switch HFNO with invasive ventilation when a rapid increase in RR is observed. It is also worth noting that in patients without lung diseases, HFNO treatment initiated at a flow rate of 60 L/min and 37 °C can be recommended to reduce the rate of intubation in COVID-19 patients.

4.1. Limitations

Like any other systematic review, this study was subject to several limitations which should be considered when interpreting the results. The primary limitation of this systematic review was the high heterogeneity observed in the meta-analysis of mortality and intubation rates. This heterogeneity can be attributed to the fact that this review included studies with observational design, small sample sizes and lack of control arms; thus, limiting the study results. The results in these studies can be improved only if further prospective randomized trials with controlled arms are carried out for the confirmation of the results. Furthermore, the decision to switch to IMV in some of the studies was left to attending physicians who had different opinions on the point of switching the treatment [16]. Our results may have also been affected by the fact that there was no clear protocol for initiating HFNO therapy was provided. In most cases, the HFNO protocol provided to the patients depended on the judgment of the physicians or hospital, resulting in varied outcomes in the treatment results. This study also did not directly compare HFNO to other treatments such as COT, NIV, or

CPAP, making it challenging to identify the effectiveness of HFNO in the treatment of COVID-19. Lastly, the eligibility criteria provided in this systematic review only allowed the inclusion of studies published in English. This may have led to the omitting of some significant results in studies published in other languages that would have otherwise formed the basis of our analysis.

5. Conclusion

Our analysis shows that there is no significant difference in the success and failure rate of HFNO; however, HFNO demonstrated a remarkable ability to significantly reduce the mortality and intubation rates suggesting that it can be considered as the first-line therapy for patients with COVID-19. In a clinical setting, close monitoring of respiratory parameters by experienced physicians is very vital in determining the next course of treatment, with parameters such as ROX index, PaO_2/FiO_2, and RR being the most important predictors of the HFNO outcomes and the need to switch to IMV.

CRediT authorship contribution statement

Nabil Shallik: Writing – review & editing. **Khalid Bashir:** Conceptualization, Methodology, Software. **Amr Elmoheen:** Data curation, Writing – original draft. **Haris Iftikhar:** Visualization, Investigation. **Hany A. Zaki:** Supervision, Writing – original draft, Writing – review & editing.

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