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Safety and Efficacy of High-flow Nasal Cannula (HFNC) Versus Non-invasive Ventilation in Patients with Respiratory Failure: A Meta-analysis

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Abstract: *Respiratory failure can be caused by a variety of diseases and can lead to death due to poor oxygenation. The role of non-invasive respiratory support has been debated. This meta-analysis assesses the effectiveness and reliability of HFNC, standard oxygen (SO) treatment and non-invasive ventilation (NIV) in patients with respiratory failure respectively. The PubMed, Cochrane library, and CNKI databases were systematically searched from the inception dates to March 1, 2022. The primary randomized clinical trials included in meta-analyses were identified. The participants were patients with acute respiratory failure. Hospitalization mortality was defined as the primary outcome. Secondary outcomes were Failure of ventilation, Infection. The PROSPERO database has been registered with this meta-analysis. (registration number: CRD42022320088, 03/26/2022). A total of 26 RCTs involving 6518 patients were included. HFNC did not differ from NIV or SO therapy in terms of hospitalization mortality, ventilation failure, or lung infection. Patients with acute respiratory failure treaded with HFNC were more likely to develop remaining organ failure during hospitalization than those treated with NIV (P = 0.002, I^2 = 0%). Compared to SO, the use of HFNC leads to a more comfortable experience to patients (P=0.0003, I^2=0%) and increase the oxygen partial pressure (P=0.001, I^2=0%). In the subgroup analysis results of COVID-19, there were no significant differences between the HFNC, SO, and NIV for intervention failure, hospital mortality and oxygenation index. In hemodynamically stable patients with acute respiratory failure, there was no significant difference in in-hospital mortality and intervention failure rates between HFNC and SO and NIV. HFNC was superior to SO in improving patient oxygen partial pressure and comfort. In addition, there was no significant efficacy difference between NIV and SO for HFNC in the treatment of acute respiratory failure in COVID-19 patients.*

Keywords: *High-flow Nasal Cannula; Non-invasive ventilation; Respiratory failure; Randomized controlled trial; Standard oxygen therapy*

1. Introduction

Respiratory failure or respiratory distress is a common symptom in hospitals and even intensive care units[1, 2] It can lead to systemic organ failure and even life-threatening complications in severe cases[3-7]. Most patients with respiratory failure are characterized by hypoxemia, pulmonary ground-glass pulmonary lesions, and pulmonary edema[8-14]. Furthermore, such patients require assisted ventilation to increase the body's oxygen demand. Intubation and tracheostomy, as invasive procedures, cause some patients to be unable to tolerate being taken off-line, to the point of lifelong ventilator therapy.[15-18]. The lung-protective ventilator strategy is the first therapy found to improve outcomes in acute respiratory distress syndrome (ARDS)[2, 19-21]. Thus, the patient or physician should improve oxygenation with a non-invasive, efficient and comfortable ventilation mode.

HFNC[22, 23] as a novel respiratory support system has become well-known in clinics in recent years. This treatment device, which primarily consists of a high flow nasal congestion, a humidification therapy instrument, an air oxygen hybrid device, and a connecting respiratory line, primarily provides stable oxygen concentrations (21 % to 100 %), humidity (8-80 L/min) of high-flow gas, and temperature (31-37°C), as well as oxygen therapy via nasal congestion with great comfort. Since

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HFNC only delivers elevated flow gas transnasally, patients are required to have better spontaneous breathing and airway self-cleaning capabilities.

Consequently, situations requiring the urgent establishment of an artificial airway are absolute contraindications to HFNC, such as respiratory cardiac arrest, acute respiratory obstruction, significant hemodynamic instability, and weak spontaneous breathing[24-26]. Some clinical situations foresee a high rate of HFNC treatment failure or the presence of conditions affecting the proper use of HFNC and are relative contraindications, such as severe hypoxemia (oxygenation index < 100 mmHg), significant CO_2 retention (pH < 7.25), paradoxical respiratory exercise, additional airway secretions and no ability to excrete sputum, nasal facial surgery or trauma, significant nasal obstruction, and HFNC intolerance.

It remains debatable about the impacts of HFNC used on patients with acute respiratory failure(ARF)[27]. Compared to the meta-analysis from Lewis SR et al.[28, 29], the current investigation included additional RCT trials, increased the sample size, and included a subunit analysis of patients with 2019 novel coronavirus. Non-invasive ventilation measures included standard oxygen therapy and non-invasive ventilator-assisted. These two ventilation modes have also been used in the treatment of patients with mild to moderate respiratory failure who require ventilation assistance. There is still disagreement between the safety and efficacy of HFNC versus non-invasive ventilation for improving patients with respiratory distress. Schmid, B[28] considered both HFNC and NIV to have a substantial risk of harm. Lewis, SR et al. [30]suggested that HFNC may have little effect on treatment failure when compared to conventional oxygen therapy (SO) than NIV or NIPPV. Therefore, the primary objective of this study was to evaluate the survival and safety of HFNC in patients with ARF in this relative contraindication to alternative non-invasive ventilation methods.

2. Methods

2.1 Search strategy

The PROSPERO database (www.crd.york.ac.uk/prospero/) has been registered with this meta-analysis. CRD42022320088 was filed and done in accordance with Preferred Reporting Items for Meta-Analysis Protocols (PRISMA-P). PRISMA's process flow diagram is shown in Figure 1.

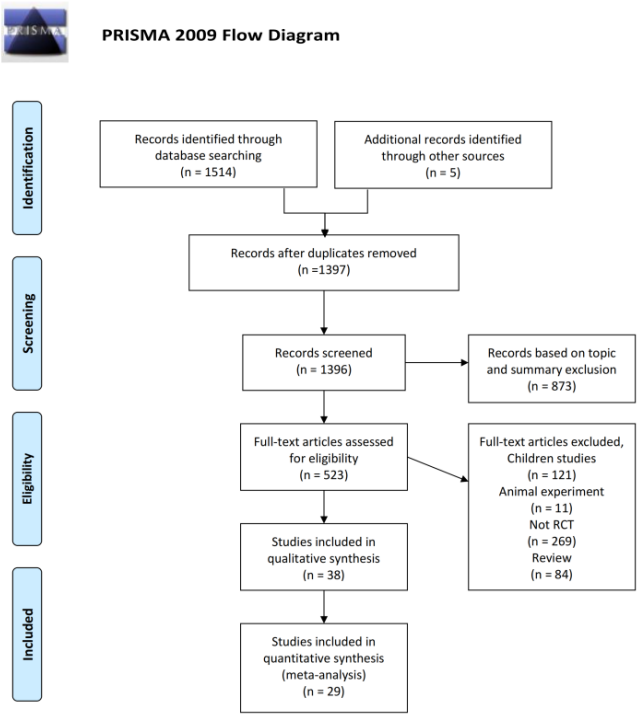

Figure 1: PRISMA process flow diagram.

A systematic search of randomized controlled trials was performed (RCTs). Then, in patients with respiratory failure, we looked at the effects of HFNC and alternative non-invasive ventilation options.

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A literature search strategy was developed based on this framework from PICO (patient questions, interventions, comparisons, and outcomes) [34]. I.e., Patient concerns included "adults with respiratory failure or respiratory distress," with interventions including " standard oxygen therapy, non-invasive ventilator assisted ventilation, and High-flow Nasal Cannula (HFNC)" and comparisons of "what ventilation mode is optimal" yielded "risk of in-hospital mortality, endotracheal intubation, ICU mortality, hospital days, PaO_2, PaO_2 / FiO_2," and "risk of in-hospital mortality, in-hospital mortality. We scoured the CNKI, MEDLINE, and Cochrane Central Register of Controlled Trials (Central) for the phrases "HFNC, NIV, oxygen, ARDS, COVID-19, respiratory failure." Until March 1, 2022, the EU clinical trials registration and government database were utilized to offer relevant research. No language restrictions were placed on the studies. A review of previous meta-analyses and relevant reviews identified additional relevant studies based on references in those studies.

The Review Manager Database was used to assess chosen examinations (Review Manager 5.3; The Cochrane, 2022). Each research arm was represented by its mean and standard deviation (SD), while the therapeutic outcome was represented by mean differences. In general, dichotomous data are reported as proportions or risks for each arm of research. The authors were contacted to obtain missing data. In case of not following the rules or losing track of people, intent-to-treat principles were used. The I^2 and C2 tests were used to assess the statistical heterogeneity. Random-effects modeling was used to estimate statistical heterogeneity when the I^2 numerical was more than 50% and the P numerical was less than 0.01. The fixed effect model will be utilized as an alternative. In contrast, a non-significant C2 ($P > 0.1$ and $I^2 > 50\%$) just showed that there was no indication of heterogeneity: While there was a possible lack of power to detect heterogeneity, it did not necessarily mean that there was homogeneity. The main outcome was inpatient mortality following randomization. The incidence of hospitalization mortality, failure of ventilation, Infection, organ failure, and continuous type variables such as number of days without ventilator support within 28 days were all secondary outcomes. Based on the available data, we performed a subgroup analysis on the COVID-19 ARF population to explain the efficiency and security of non-invasive breathing therapy following a change in the type of disease.

2.2 Search selection

The meta-analysis was performed using the Cochrane's methodology. This study was limited to randomized controlled trials. Participants with ARDS or respiratory failure were considered. Selected studies were analyzed using the Review Manager Database (Review Manager 5.3, Cochrane Collaboration, 2022). The search strategy used the electronic databases CNKI (1978 to March 2022), Cochrane Library (2022), and PubMed (1985 to March 2022) to search the published literature. No date restrictions or language were applied. "HFNC " or " high flow " and " respiratory distress syndrome " were used to search the keywords and Medical Subject Headings (MESH). We used the online databases Note Express and Endnote to look at the complete text of all articles' references that were linked to any studies that were not sure. A total of 1519 pieces of literature were initially retrieved. Finally, there was a total of 26 trials with 6518 patients enrolled in randomized controlled trials.

The Cochrane risk of bias assessment tool was used to evaluate the methodology of randomized controlled trials. Nevertheless, as the intervention could not be blinded, we did not expect this to affect the outcome data. We chose to ignore the blinding issue to include all RCTs. Three investigators (DQH, LSH, and HW) collected all included studies independently after a full-text review. A data extraction table was designed and agreed upon by the authors, and five articles were pilot-tested to ensure consistency. Any differences were settled via consensus.

2.3 Data processing

Based on aggregated data from individual patients, statistical analyses were carried out independently for the outcomes of interest. All outcomes were analyzed with treatment intent and all patients were analyzed at randomization. Treatment effect was measured by the hazard ratio of outcomes for dichotomous variables, hazard ratio of outcomes for time-to-event, and the mean difference for quantitative outcomes. A dichotomous variable was used to define the primary endpoint, and it was examined in two steps (primary analysis and sensitivity analysis). We first evaluated each experiment individually using the aggregated data from individual patients. Then, to combine them and account for between-study variability, we utilized a random-effects meta-analysis technique. Between these analyses of heterogeneity are used Cochran's Q test, I^2 statistic, and study variance.

In diverse populations, we conducted sensitivity analyses for the main result (post-treatment, per

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protocol). The per-protocol population includes all randomized patients who embraced randomization (i.e., patients in the clinical trial who received HFNC and patients from the comparative subject who did not receive HFNC). Patients receiving HFNC therapy will be compared randomly with non-invasive ventilator-assisted ventilation (or standard oxygen therapy). In the sensitivity analysis, we also removed studies with a high probability of bias. Treatment-subgroup interactions were examined for each subgroup.

Based on quantitative baseline features, we employed mean and variance to describe results of subgroup analyses. These subgroup analyses were all prepared ahead of time. Alpha risk for the primary outcome was set at 5%. We did not conduct multiple testing for all secondary outcomes. Sensitivity and subgroup analyses should thus be regarded as exploratory.

2.4 Data extraction

Study characteristics and length, illness features, age, gender, Sa, PaO_2, $PaCO_2$, PaO_2 / FiO_2, and respiratory rate were all examined in order to collect data from the included RCTs. If standard deviations were not mentioned for the continuous type variables in the trial, inclusion was not considered because there is a bias in the standard deviation calculated as the median, which could affect the results.

The included studies were screened according to the principle of PICO：the population that was included had to fulfill the following requirements: acute respiratory distress syndrome or acute lung damage, defined as PaO_2/FiO_2 300 mmHg, must be present in patients older than 18 years old; if acute respiratory failure start suddenly, the patient's level of consciousness is clear, and no invasive ventilation pointers such as immediate tracheal intubation and tracheotomy; ICU admission. Patients with severe chronic lung illness, asthma, cardiogenic pulmonary edema, and those in need of rapid invasive ventilation were also not included. All included studies were randomized controlled trials, and each study was required to provide at least one required outcome indicator. Articles with repetitive reporting, defects in research design, poor quality of articles, incomplete data and unclear outcome effects were not included. In addition, case studies, literature reviews and observational studies were also excluded. The study had no restrictive language and all experiments were carried out on people, excluding animal experiments.

In-hospital mortality was the main outcome of this meta-analysis. Secondary outcomes included the rate of the ventilation failure (including intubation, intubation for recurrent acute respiratory failure after extubation), as well as continuous type variables such as hospital stay length, the time of ICU stay, PaO_2 to FiO_2 ratio, SaO_2 value, and respiratory rate, among others. In addition, we also compare SO with HFNC, patients with failed ventilation will receive non-invasive ventilation as a result of ventilation failure.

3. Results

Up to March 2022, 6518 patients with respiratory failure were chosen from 26 studies. 49.72% were treated with HFNC, 34.74% were given standard oxygen therapy, and 15.54% were helped to breathe by a ventilator without being invasive. (Some patients received more than one mode of ventilation, so there was a deviation in the percentage of people of each type.) The supplemental table lists relevant research and patient characteristics. HFNC was compared to SO in 19 trials, and NIV or NIPPV in 8 investigations. One study (Frat et al.[31]) did both types of comparatives. We report these as two independent comparisons. The demographic characteristics of the studies that were included were summarized. It was unable to obtain demographic characteristics from several research since they simply gave data findings. (Table 1 Characteristics of the included studies)

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Table 1: Characteristics of the included studies.

Author and Year	Country	Number	Intervention	Age years	RR min/per	BMI kg/m^2	PaO_2/FIO_2 mmHg
Jean 2022	France	711	HFNC/SO	[49.0,73.0]	[22.0,35.0]	[23.0,35.0]	[97.0,163.0]
Perkins 2022	UK	783	HFNC/NIV	[56.7,57.6]	[23,24]	NA	[112.5,115.0]
Luca 2021	Italian	109	HFNC/NIV	[55.0,72.0]	[23,32]	[26.0,31.0]	[83.0,125.0]
Nair 2021	India	109	HFNC/NIV	[47.0,65.0]	[28,38]	NA	[89.8,145.0]
Ospina 2021	Colombia	199	HFNC/SO	[49.0,69.0]	NA	[26.2,33.1]	[85.0,141.0]
Teng 2021	China	22	HFNC/SO	[48.0,59.6]	[21.2,23.5]	NA	[212.08,236.85]
Wu 2020	China	58	HFNC/SO	[52.7,77.0]	NA	NA	[118.3,162.3]
HU 2020	China	56	HFNC/NIV	[59.8,86.3]	NA	NA	[188.4,409.6]
Azoulay 2018	France	776	HFNC/SO	[55.0,71.0]	[27,39]	NA	[92.0,187.0]
Shebl 2018	Saudi Arabia	70	HFNC/NIV	[48.3,74.3]	NA	[18.8,28.0]	[123.0,233.0]
MakdeeO	Thailand	128	HFNC/SO	[54.5,86.3]	[27,35]	NA	NA
Song 2018	China	60	HFNC/NIV	[52.0,84.0]	NA	NA	NA
Yu 2017	China	109	HFNC/SO	[47.9,63.7]	[14,22]	[20.17,30.21]	[300.3,381.6]
Futier 2016	France	220	HFNC/SO	[48.0,74.0]	NA	[21.0,29.0]	NA
Hernandez 2016	Spain	527	HFNC/SO	[37.9,64.0]	NA	NA	[202.0,271.0]

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Jones 2016	New Zealand	303	HFNC/SO	[55.4,90.2]	[27,31]	NA	NA
Frat 2015	France and Belgium	310	HFNC/SO	[42.0,78.0]	[26,40]	[16,32]	[77.0,246.0]
Hernandez 2015	Spain	604	HFNC/SO	[48.6,80.2]	NA	NA	[157.0,231.0]
Lemiale 2015	France	100	HFNC/SO	[43.0,72.0]	[22,32]	NA	[40.0,178.0]
Stephan 2015	France	830	HFNC/NIV	[62.5,65.2]	[22,24]	[27.6,28.8]	[187.0,212.0]
maggiore 2014	Rome and Novara	107	HFNC/SO	[57.0,83.0]	[17,29]	NA	[197.0,292.2]
Corley 2014	Australian and NewZealand	155	HFNC/SO	[51.6,76.1]	NA	NA	NA
Rittayamai 2013	Thailand	17	HFNC/SO	[53.0,147.4]	NA	NA	NA
Zhan 2012	China	40	HFNC/NIV	[30.1,62.8]	[22,37]	[18.9,26.9]	[207.8,261.0]
Idone 2014	NA	35	HFNC/SO	No difference was observed in the baseline characteristics at inclusion.			
Antonicelli 2014	NA	80	HFNC/SO	No difference was observed in the baseline characteristics at inclusion.			

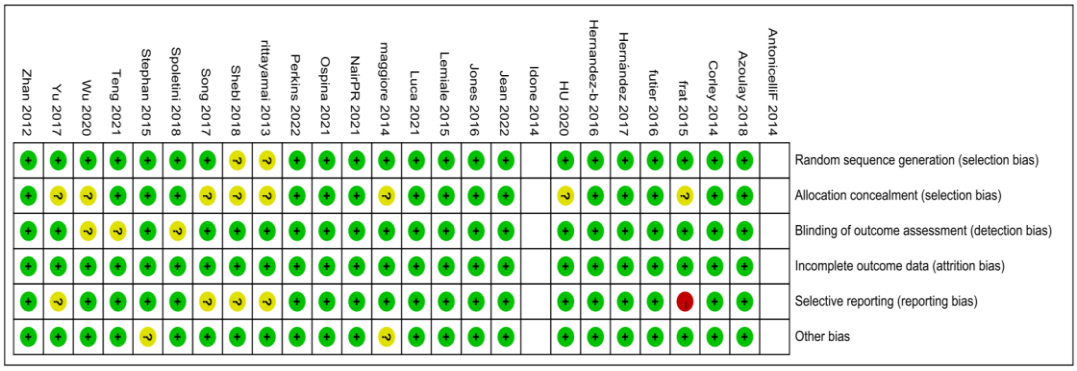

Figure 2: Risk of bias assessment.

Summary of bias risk: For each research study, the investigators' perspectives on each potential

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source of bias was included. We only assessed the likelihood of bias in studies that included outcome information and domains that were relevant to the reported results (especially for detection bias of objective and subjective measures). Blank spaces mean that the assessment of bias risk was not done for the outcome or a particular domain (Figure 2 Risk of bias assessment)

3.1 Hospitalization mortality

When noninvasive ventilation support and HFNC are used in individuals with acute respiratory insufficiency, 5 trials[31-35] that provided pertinent data on hospitalization mortality comprised all 544 individuals. In the HFNC group, 57 of 269 people died in the hospital, compared with 81 of 275 in the control group. In-hospital mortality was not statistically different between the two groups(RR=0.76, 95 % CI 0.48 to 1.21, P=0.25, I^2=52%). After sensitivity analysis, none of the literature caused significant interference with the results of this meta-analysis, with RR fluctuating between 0.48-1.21 and no significant change in I^2 and P values.

Similarly, we including a total of 5 publications with 2650 patients, examined the difference between in-hospital mortality in patients receiving HFNC versus regular oxygen therapy ventilation, which can be seen to be largely symmetrically distributed on both sides of the midline。

In the initial results, one of the studies with asymmetrical distribution locations and a small sample size Hu et al. considered this study as having some error, so we excluded this study. There was minimal heterogeneity among the 5 studies' final outcomes[31, 36-39], and no significant statistical distinction between the HFNC group and the group receiving conventional oxygen therapy in terms of minor outcomes(RR=0.87, 95 % CI 0.72 to 1.05, P=0.16, I^2=16%)

3.2 Failure of ventilation (including intubation, intubation for recurrent acute respiratory failure after extubation, non-invasive ventilation)

Compared to the NIV group, a total of 5 trials[31-35] with 544 patients were included. Since I^2 > 50 %, to reduce bias, we choose the random effect model. The findings revealed no significant difference between the two groups in the risk of failure of interventions for patients with ARF in the ICU (RR=0.98, 95% CI 0.60 to 0.59, P = 0.04, I^2 = 69%).

For the comparison with the standard oxygen therapy group, we included 13 publications, a total of 3440 eligible patients[31, 36-47]. Due to the large heterogeneity differences between the literature and the inability to exclude the primary literature that caused the heterogeneity differences after the sensitivity analysis, we chose a random effects model, the results demonstrated that individuals receiving normal oxygen therapy had a higher intervention failure rate than patients in the HFNC group. (RR=0.94, 95% CI 0.78 to 1.12, P = 0.49, I^2 = 66%).

3.3 Infection

The incidence of infection did not differ statistically significantly(RR=1.08, 95% CI 0.76 to 1.54, P = 0.65, I^2 = 0%) as well as ventilator-associated pneumonia (RR=1.5, 95% CI 64 to 3.49, P = 0.35, I^2 = 0%) in HFNC versus NIV, and there was no significant heterogeneity between the literature.

When compared to the incidence of pulmonary infections in patients undergoing HFNC ventilation, the prevalence of pulmonary infections in patients with acute respiratory failure getting normal oxygen therapy was not clinically meaningful (RR=1.02, 95% CI 0.86 to 1.21, P = 0.84, I^2 = 0%).

3.4 Number of days without ventilator support within 28 days

We included 2 studies that reported the days' length of ventilator-support-free treatment during the acute respiratory collapse of patients over a 28-day period[31, 34]. Of the 286 patients who participated in the randomized controlled trial, the number of days off ventilator support therapy was on average 4.52 days longer in the HFNC group compared to the NIV group, and this result was statistically different, with a heterogeneity of 0 between the two papers (MD 4.52, 95% CI 2.56 to 6.48, P＜0.00001, I^2=0%). (Figure 3)

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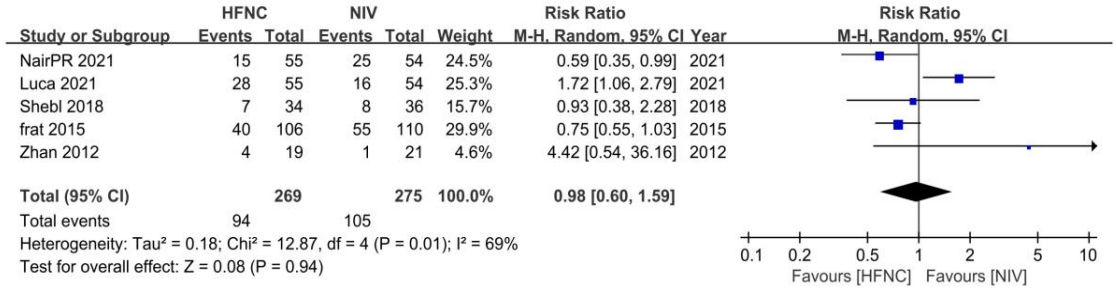

Figure 3: HFNC_Failure of ventilation.

3.5 Organ Failure

This outcome statistic is provided in 3 studies. However, in the end, the paper by Hernández et al[48]. They were not included due to the large population heterogeneity between their study population and the literature we included. The study by Luca[35] and Zhan[33], which included a total of 149 patients, were selected for inclusion. There was no homogeneity between the two studies, reporting data from Luca et al. for patients with liver failure, while Zhan reported data on how many organ failures occurred there are overall in the heart, liver, kidney, central nervous system and blood. We can see that more organ failure occurred in the HFNC group compared to the pilot group receiving non-invasive ventilation, and this result is statistically significant (RR=5.13, 95% CI 1.85 to 14.2, P = 0.002, I^2 = 0%). (Figure 4)

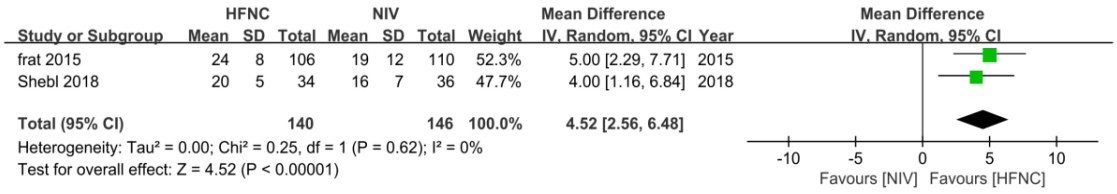

Figure 4: HFNC_Number of days without ventilator support.

3.6 Subgroup analysis: individuals with COVID-19

Changes in the disease profile of the acute respiratory failure population since the 2019 epidemic of new coronavirus pneumonia. With COVID-19, we performed a subgroup study of the acute respiratory failure sample.

3.6.1 Interventional treatment failure

We defined failure of intervention as failure of assisted ventilation, requiring immediate invasive ventilator-assisted ventilation, tracheal intubation, and tracheotomy. A total of 2 randomized controlled trials of HFNC versus noninvasive ventilator-assisted ventilation in patients with confirmed neocoronary pneumonia were included luca et al.[35] and Nair et al.[32] In total, there are 218 patients participated in the experiment, of whom 41 failed in the control group and 43 failed in the experimental group, with a large heterogeneity between the two literatures, which was statistically insignificant (P = 0.99, I^2=89%).

A total of 3 studies[36-38] comparing HFNC with the standard oxygen therapy group were included, with a total of 1693 patients participating, with an I^2 of 50% between the literature, with some heterogeneity, P=0.07 > 0.05, which did not meet statistical significance (RR 0.86, 95% CI 0.73 to 1.01, P=0.09, I^2=50%).

3.6.2 Hospital mortality

HFNC in patients with neocoronary pneumonia is not statistically different from standard oxygen therapy (RR 0.87, 95% CI 0.70 to 1.10, P=0.24, I^2=2%) and non-invasive ventilator-assisted ventilation(RR 0.78, 95% CI 0.52 to 1.15, P=0.21, I^2=35%) in terms of in-hospital mortality.

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3.6.3 PaO_2*/Fi*O_2

The experimental results of oxygenation index were reported by Jean et al.[38] and Teng et al.[49] respectively. After treatment, there was no significant difference in mean oxygen saturation between the HFNC group and the usual oxygen therapy group. These two papers also showed the results of the experiments in the new crown pneumonia population did not differ significantly in the oxygenation index between the HFNC and SO groups (MD 4.80, 95% CI -53.53 to 63.12, P=0.87, I^2=99%).

4. Discussion

Our meta-analysis results included 26 articles and 6518 patients. For patients with acute respiratory failure who were hemodynamically stable and did not require immediate tracheal intubation, tracheotomy, non-acute pulmonary edema, and aggravated chronic lung disease, the results showed that the mortality and intervention failure rates for HFNC were not clinically significant compared to NIV. Alternatively, the number of days without ventilator-assisted breathing was longer in the HFNC group compared to the NIV group. And the HFNC group had an increased risk of organ failure. Compared with SO group, HFNC group could improve the oxygen partial pressure and discomfort of patients, and shorten the time of ICU stay. In addition, we performed subgroup analyses of patients with COVID-19. Nevertheless, we did not get meaningful results in the subgroup analysis of patients infected with the novel coronavirus.

Because a rising quantity of research papers have shown the impact of HFNC usage on infant respiratory distress in recent years[50, 51]. During the search, a meta-analysis[51] of HFNC therapy for neonatal respiratory distress syndrome mentioned that HFNC should not be used as primary respiratory support for newborns with respiratory distress syndrome. Because of the different physiological structures of newborns and adults, we excluded the population <18 years old in the early search. Due to the simplicity and effectiveness of HFNC, it is as respiratory assistance could be used in adult hypoxemia patient[52] and is suggested utilized in COVID-19 patients[53, 54]. Previously, the effects of HFNC and other forms of non-invasive ventilation were compared in three meta-analyses for the treatment of patients with respiratory failure: Lewis, S.R et al. (31 RCTs), Schmid, B et al. (5 RCTs), Yasuda, H et al. (27 RCTs). Lewis, S.R et al. [30]found that HFNC may produce minor treatment failure when compared to regular oxygen therapy, but that it makes few differences when compared to NIV and NIPPV. Consistent with our meta-analysis, HFNC use did not significantly reduce in-hospital mortality, intubation rates, or adverse events in individuals with acute respiratory failure, when compared to NIV and regular oxygen. We conclude that the limited sample size and the variability in the population are to blame for the lack of statistical significance of the outcome indicators. Schmid, B. et meta-analysis[28] found no convincing evidence of the differential efficacy of HFNC or NIV in neonatal pneumonia patients. They also found that the use of both may even harm patients with new crown pneumonia. But our results show that NIV is superior to HFNC, and that treatment effect and the occurrence of non-pulmonary organ failure and ventilator infection in the HFNC group may be greater than in the NIV group. A meta-analysis study by Yasuda, H et al. [55] considered that the use of NPPV and HFNC to reduce the risk of endotracheal intubation. But our results were not statistically significant. The reason may be that due to classify the population more accurately, to expand the sample size and reduce the bias.

Treatment of HFNC has been shown to cause patients with acute respiratory failure to miss the optimal period for non-invasive ventilatory assisted ventilation, resulting in a poor prognosis such as multi-organ failure. In a randomized controlled trial by Hernández et al.[56], patients treated with HFNC required re-intubation, while patients treated with NIV had shorter hospital stays. This conclusion is supported by the findings of our most recent meta-analysis, which showed that even in the absence of significant differences in survival analysis, the risk of hospitalization and the likelihood of adverse outcomes was higher in the HFNC group. Therefore, in the absence of statistically significant mortality and intervention failure rates in either groups, patients had better outcomes when noninvasive ventilator-assisted ventilation was used early in the course of severe respiratory failure. In contrast to the recipients of conventional oxygen therapy, we found that the HFNC group had an advantage over the standard oxygen therapy in terms of outcomes such as reduced mortality and intervention failure rate, but lacked significant statistical significance. After using HFNC as well as SO intervention for hypoxemia, the HFNC group improved hypoxemia better than the standard oxygen therapy group. We therefore believe that the use of HFNC to improve hypoxemia is a more cost-effective course of intervention than the choice of standard oxygen therapy, when the mortality and failure rates of interventions are not significantly different.

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5. Limitations

The limited sample size of each trial, the short follow-up period, and the high variability in ICU days were all limitations of this meta-analysis. In addition, insufficient data were available for the analysis of COVID-19 patients, too few RCT trials were included, and existing randomization errors may not be avoidable. We lack the refinement of population characteristics, such as classification of patients with respiratory failure as mild, moderate and severe. Even though our sample size has grown, RCTs with people who suffer acute respiratory failure or even ARDS are still insufficient. We need large prospective RCTs to figure out the best way to enhance ventilation in patients with respiratory failure through non-invasive ventilation.

6. Conclusion

In hemodynamically stable patients with acute respiratory insufficiency who did not require tracheotomy or emergency tracheal intubation, non-acute pulmonary edema, or a flare-up of a long-term lung condition, there was no discernible difference in the rates of intervention failure or in-hospital mortality between HFNC, SO, and NIV. When non-invasive ventilator-assisted ventilation was used sooner, patients with acute respiratory failure had a better prognosis. At the same time, the use of HFNC resulted in a more comfortable experience for the patient and increased the oxygen partial pressure. Moreover, there was no significant efficacy difference between NIV and SO for HFNC in COVID-19 patients. Large randomized controlled trials are still needed to confirm the ideal ventilation mode for individuals with acute respiratory failure.

7. Declarations

Authors' contributions: TJX and XF contributed to the definition of the meta-analysis. DQH gathered the information, carried out the evaluation and interpretation, and then DQH, LSH, and HW wrote the paper's content. LSH and HW were involved in the analysis of the data. Both XF and TJX were involved in interpreting the data. The final document was reviewed and approved by all of the writers.

Reporting Checklist: The authors have completed the PRISMA reporting checklist.

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All authors agree to the publication of this article.

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