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Comparison between high-flow nasal cannula and noninvasive ventilation in COVID-19 patients: a systematic review and meta-analysis

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Abstract

Background: High-flow nasal cannula (HFNC) and noninvasive ventilation (NIV) are important treatment approaches for acute hypoxemic respiratory failure (AHRF) in coronavirus disease 2019 (COVID-19) patients. However, the differential impact of HFNC *versus* NIV on clinical outcomes of COVID-19 is uncertain.

Objectives: We assessed the effects of HFNC *versus* NIV (interface or mode) on clinical outcomes of COVID-19.

Methods: We searched PubMed, EMBASE, Web of Science, Scopus, MedRxiv, and BioRxiv for randomized controlled trials (RCTs) and observational studies (with a control group) of HFNC and NIV in patients with COVID-19-related AHRF published in English before February 2022. The primary outcome of interest was the mortality rate, and the secondary outcomes were intubation rate, PaO_2/FiO_2, intensive care unit (ICU) length of stay (LOS), hospital LOS, and days free from invasive mechanical ventilation [ventilator-free day (VFD)].

Results: In all, 23 studies fulfilled the selection criteria, and 5354 patients were included. The mortality rate was higher in the NIV group than the HFNC group [odds ratio (OR) = 0.66, 95% confidence interval (CI): 0.51–0.84, $p = 0.0008$, $I^2 = 60\%$]; however, in this subgroup, no significant difference in mortality was observed in the NIV-helmet group (OR = 1.21, 95% CI: 0.63–2.32, $p = 0.57$, $I^2 = 0\%$) or NIV-continuous positive airway pressure (CPAP) group (OR = 0.77, 95% CI: 0.51–1.17, $p = 0.23$, $I^2 = 65\%$) relative to the HFNC group. There were no differences in intubation rate, PaO_2/FiO_2, ICU LOS, hospital LOS, or days free from invasive mechanical ventilation (VFD) between the HFNC and NIV groups.

Conclusion: Although mortality was lower with HFNC than NIV, there was no difference in mortality between HFNC and NIV on a subgroup of helmet or CPAP group. Future large sample RCTs are necessary to prove our findings.

Registration: This systematic review and meta-analysis protocol was prospectively registered with PROSPERO (no. CRD42022321997).

Keywords: CPAP, COVID-19, helmet, high-flow nasal cannula, noninvasive mechanical ventilation

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Introduction

Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may develop coronavirus disease 2019 (COVID-19) with viral pneumonia, acute hypoxemic respiratory failure (AHRF), or acute respiratory distress syndrome (ARDS) and may require hospital admission.[1–3] About 15–30% of COVID-19 patients experience hypoxemia and progress to ARDS.[4] These patients require oxygen and possibly ventilatory support, which can be delivered using different devices. Noninvasive oxygenation strategies, such as

high-flow nasal cannula (HFNC) and noninvasive ventilation (NIV), have been widely adopted in patients with AHRF secondary to COVID-19.[5,6]

HFNC is a noninvasive respiratory support modality that delivers warm, humidified oxygen at a maximum flow rate of 60–100 l/min and up to 100% of the inspired oxygen fraction (FiO_2) through nasal probes.[7] NIV refers to the application of mechanical ventilatory support using a nasal, oronasal, or full face mask or a helmet.[8] HFNC and NIV are the main forms of treatment for AHRF and associated with favorable outcomes in COVID-19 patients.[9] Many recent studies have compared the effects of HFNC and NIV in COVID-19 patients, but the use of HFNC *versus* NIV for COVID-19-related AHRF remains controversial.[5,6] Current clinical practice is based on prior experience, personal medical opinion, and local availability. Therefore, this meta-analysis compared HFNC *versus* NIV with respect to the risk for mortality and intubation in patients with COVID-19-related AHRF.

Methods

Search strategy

We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[10] PubMed, EMBASE, Web of Science, Scopus, ClinicalTrials.gov, MedRxiv, BioRxiv, and the Cochrane Central Register of Controlled Trials were searched for relevant studies published before February 2022. Two trained investigators (W.T. and Y.P.) independently performed the searches, screening, and identification. Discrepancies were resolved by discussion and consensus.

The search combinations adopted were as follows: ('Ventilation, Noninvasive' OR 'Non Invasive Ventilation' OR 'Ventilation, Non Invasive' OR 'Noninvasive Ventilation') OR ('HFNC' OR 'high-flow nasal cannula' OR 'high-flow nasal oxygen' OR 'high-flow oxygen') AND ('COVID 19' OR 'SARS CoV 2' OR '2019 Novel Coronavirus' OR '2019 nCoV' OR 'Coronavirus Disease 2019' OR 'Coronavirus Disease 19' OR 'Severe Acute Respiratory Syndrome Coronavirus 2 Infection' OR 'SARS Coronavirus 2 Infection' OR 'COVID 19 Pandemic OR COVID-19'). In addition, the reference lists of all primary studies and review articles were evaluated to locate additional relevant studies.

Study selection

The inclusion criteria were as follows: randomized controlled trials (RCTs) and observational studies; adult patients (⩾18 years old) with laboratory-confirmed COVID-19; HFNC compared with a control group receiving NIV; and outcomes, including aggregated mortality rate, intubation rate, or both.

The exclusion criteria were as follows: patients who did not meet the screening criteria; studies that were not in English or commentaries, reviews, or duplicate publications from the same study; and data that could not be extracted by the reported statistical methods or non-targeted outcomes.

The ultimate decision to include or exclude any study was made following a full-text review of the article by two investigators (W.T. and Y.P.) focusing on publication date, study type, study design, and outcomes. Discrepancies were resolved by consensus.

The primary outcome of interest was the mortality rate, and the secondary outcomes were the intubation rate, PaO_2/FiO_2, intensive care unit (ICU) length of stay (LOS), hospital LOS, and days free from invasive mechanical ventilation [ventilator-free day (VFD)].

Data extraction and study quality

Using a standardized form, two investigators (W.T. and Y.P.) independently extracted data with no blinding of trials (e.g. authors, institutions, or publication sources). Some data not provided in the published reports were obtained by contacting authors by email. To assess the quality of eligible RCTs, we used the Cochrane collaboration risk of bias tool, which considers allocation sequence generation, concealment of allocation, masking of participants and investigators, incomplete outcome reporting, selective outcome reporting, and other sources of bias. Potential sources of bias were graded as high, low, or unclear to assign the studies to high, low, or moderate risk of bias groups. The Newcastle-Ottawa quality assessment scale (NOS) checklist was used to assess the quality of observational studies. Using this scale, each study was assessed on nine items and categorized into three groups, as follows: selection, comparability, and outcomes. Stars were awarded

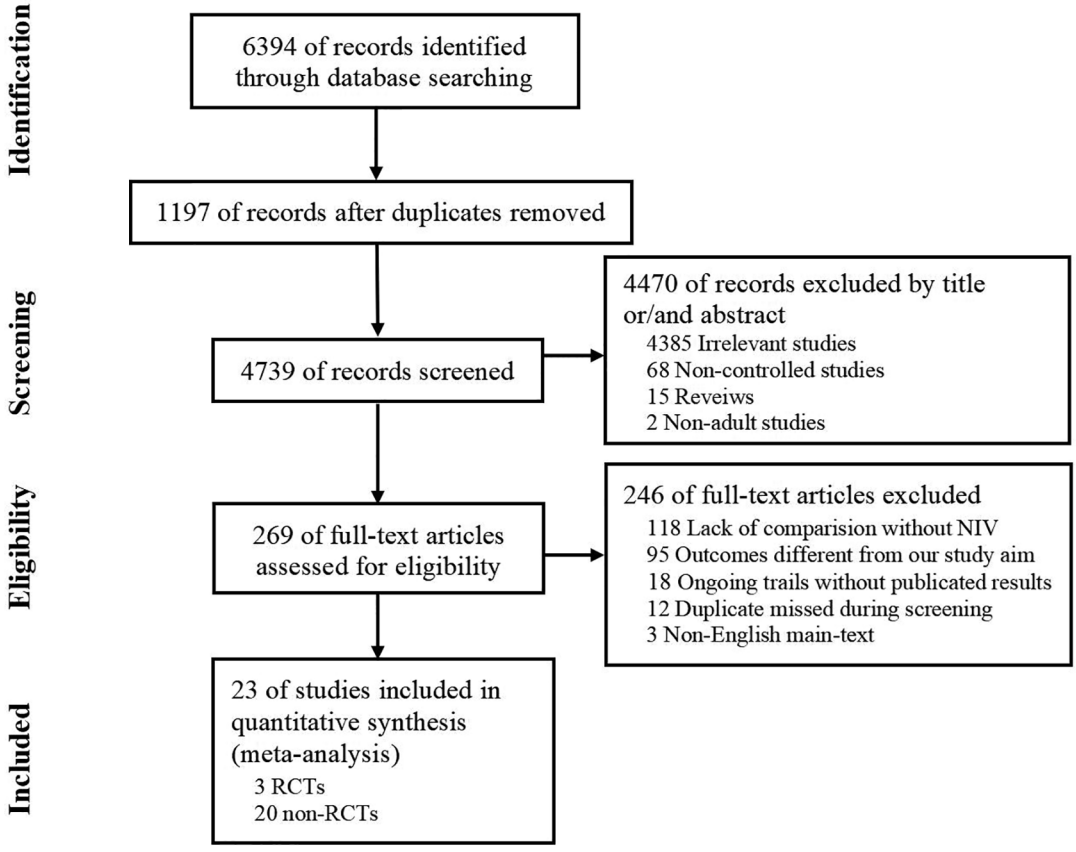

Figure 1. Study flow diagram.

for each quality item, and the highest-quality studies were awarded nine stars. A study was considered to be of low, moderate, or high quality when it achieved 0–4, 5–7, or 8–9 stars, respectively.

Data synthesis and analysis

The meta-analysis was performed using available data from the primary studies with the RevMan Review Manager (version 5.4.1; Nordic Cochrane Review Centre, Copenhagen, Denmark). Dichotomous outcomes are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Continuous outcomes are presented as weighted mean differences (MDs) and 95% CIs. Data were assessed in median-interquartile ranges and were transformed into standard mean difference formats for further comparison.

The results were analyzed using the random-effects model and are presented in a forest plot. The I^2 statistical index (ranges from 0% to 100%) was used to measure heterogeneity among the studies in each analysis, with values of 25%, 50%, and 75% corresponding to degrees of low, moderate, and high heterogeneity, respectively. Publication bias was assessed using a funnel plot. In addition, subgroup analysis was performed to investigate the different effects of interface and mode of NIV on treatment outcomes. A p-value of less than 0.05 was considered to represent a significant difference.

Results

Search results

A total of 6394 relevant studies were obtained from the databases. After excluding duplicates and evaluating the full texts of articles, we identified 23 eligible studies[9,11–32] (3 RCTs,[20,24,26] 8 prospective observational studies,[13,16,18,19,22,25,28,30] and 12 retrospective observational studies).[9,11,12,14,15,17,21,23,27,29,31,32] The process of searching and screening is described in Figure 1. The main characteristics of the articles included in the meta-analysis are shown in Table 1.

Table 1. Characteristics of included studies.

Author	Country	Study design	Setting	Study period	No. of patients Total (HFNC/ NIV)	Outcomes[a]
Alharthy *et al.*[11]	Saudi Arabia	Retrospective observational study	ICU	As of 30 April 2020	30 (15/15)	②
Alkouh *et al.*[12]	Morocco	Retrospective observational study	ICU	1 March 2020–31 December 2021	233 (162/71)	①②
Costa *et al.*[9]	Brazil	Retrospective observational study	ICU	March 2020–April 2020	37 (23/14)	①②④⑤
COVID-ICU group[13]	France, Belgium, Switzerland	Prospectively observational study	ICU	25 February 2020–4 May 2020	725 (567/158)	①②④⑤
Duan *et al.*[14]	China	Retrospective observational study	Ward/ ICU	January 2020–March 2020	36 (23/13)	①②③
Fernández *et al.*[15]	Spanish	Retrospective observational study	Ward/ ICU	1 March 2020–1 April 2020	594 (431/163)	①②
Franco *et al.*[16]	Italy	Prospectively observational study	ED/ICU	1 March 2021–1 April 2020	667 (163/507)	①②⑤
Gaulton *et al.*[17]	US (most)	Retrospective observational study	ICU	MD	59 (42/17)	①②
Ghani *et al.*[18]	UK	Prospectively observational study	Non-ICU	March 2020–January 2021	130 (35/95)	①②
Gough *et al.*[19]	Ireland	Prospectively observational study	Non-ICU	March 2020–April 2020	117 (32/85)	①②
Grieco *et al.*[20]	Italy	RCT, multicenter	ICU	October 2020–December 2020	109 (54/55)	①②③④⑤⑥
Mahroof *et al.*[21]	UK	Retrospective observational study	ICU	MD	45 (32/13)	②
Menga *et al.*[22]	Italy	Prospectively observational study	ICU	12 March 2021–20 April 20	85 (24/61)	②
Nadeem *et al.*[23]	UK	Retrospective observational study	RSU	1 March 2020–28 February 2021	100 (44/56)	①
Nair *et al.*[24]	India	RCT, single center	ICU	Auguts 2020–December 2020	109 (55/54)	①②③⑤⑥
Pearson *et al.*[25]	US	Prospectively observational study	ICU	1 March 2020–31 July 2020	62 (31/31)	①②
Perkins *et al.*[26]	UK	RCT	Non-ICU	MD	797 (417/380)	①②④
Ranieri *et al.*[27]	Italy	Retrospective observational study	MD	February 2020–December 2020	315 (184/131)	①②
Rodrigues Santos *et al.*[28]	Egypt	Retrospective observational study	ICU	May 2020–August 2020	63 (37/26)	①②③

(Continued)

Table 1. (Continued)

Author	Country	Study design	Setting	Study period	No. of patients Total (HFNC/ NIV)	Outcomes[a]
Shoukri[29]	Portugal	Prospectively observational study	RICU	18 November 2020–18 February 2021	190 (139/51)	①②⑤
Sykes *et al.*[30]	UK	Prospectively observational study	Non-ICU	April 2020–March 2021	140 (48/92)	①
Wendel Garcia *et al.*[31]	Spain	Retrospective observational study	ICU	As of 1 October 2020	174 (87/87)	①②④
Wendel Garcia *et al.*[32]	Spain	Retrospective observational study	ICU	14 March 2020–15 April 2020	540 (439/101)	①②④⑥

ED, emergency department; HFNC, high-flow nasal cannula; ICU, intensive care unit; MD, missing data; NIV, noninvasive ventilation; No, number; RCT, randomized controlled trial; RICU, respiratory intermediate care units; RSU, respiratory support unit; UK, the United Kingdom; USA, the United States.
[a]Outcome measures include: ① mortality rate; ② Intubation rate; ③ PaO_2/FiO_2; ④ ICU length of stay; ⑤ Hospital length of stay; and ⑥ days free from invasive mechanical ventilation.

Author	HFNC						NIV					
	Age	Male %	BMI, kg/m²	APACHE Ⅱ	SOFA	P/F, mmHg	Age	male%	BMI, kg/ m²	APACHE Ⅱ	SOFA	P/F, mmHg
Alharthy *et al.*[11]	46 (16.4)	86.7	24.3 (7.4)	MD	9 (1.6)	217.7 (34.4)	46.3 (13.9)	80	24.3 (7.4)	MD	9 (1.6)	214.7 (30.3)
Alkouh *et al.*[12]	66.32 (12.8)	72.2	27.59 (4.7)	MD	MD	MD	64.7 (14.97)	69	27.5 (4.9)	MD	MD	MD
Costa *et al.*[9]	65.3 (17.7)	91.3	29.4 (5.5)	11.2 (8.5)	3.7 (5.7)	MD	74.5 (19)	35.7	32.4 (4.7)	20.7 (12.4)	2.7 (1)	MD
COVID-ICU group[13]	63.7 (12.6)	75	28 (4.5)	MD	3 (1.5)	105 (42.3)	64.3 (12)	71	28 (4.5)	MD	2.7 (1.5)	127.7 (62)
Duan *et al.*[14]	50 (14)	52	MD	10 (5)	4 (2)	165 (48)	65 (14)	92	MD	8 (2)	4 (1)	196 (46)
Fernández *et al.*[15]	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD
Franco *et al.*[16]	65.7 (14.7)	69.9	MD	MD	2.5 (0.9)	166 (65)	69.08 (12.6)	69	MD	MD	3.5 (1.8)	147 (82.4)
Gaulton *et al.*[17]	61 (16)	33.3	35.8 (9)	MD	MD	MD	56 (15)	82.3	34.8 (7.8)	MD	MD	MD
Ghani *et al.*[18]	MD	68	MD	MD	MD	MD	MD	68	MD	MD	MD	MD
Gough *et al.*[19]	74 (28.7)	51.6	29.6 (7.8)	MD	MD	180.3 (150)	61.7 (13.6)	43.4	30.2 (5.3)	MD	MD	180.5 (101.3)
Grieco *et al.*[20]	62 (10.7)	84	28.3 (3.8)	MD	2.3 (0.8)	102 (33.5)	65 (11.4)	77	27.7 (3)	MD	2.3 (0.8)	104 (32)
Mahroof *et al.*[21]	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD
Menga *et al.*[22]	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD
Nadeem *et al.*[23]	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD

(Continued)

Author	HFNC						NIV					
	Age	Male %	BMI, kg/m²	APACHE Ⅱ	SOFA	P/F, mmHg	Age	male%	BMI, kg/m²	APACHE Ⅱ	SOFA	P/F, mmHg
Nair *et al.*[24]	56.7 (13)	80	MD	MD	MD	112.1 (36)	56.2 (13)	64.8	MD	MD	MD	115.3 (42)
Pearson *et al.*[25]	66 (12.4)	61.3	32.5 (9.5)	MD	3 (1.6)	MD	60.7 (18.7)	81.3	27.7 (4.8)	MD	2.3 (0.8)	MD
Perkins *et al.*[26]	57.6 (13)	65.2	MD	MD	MD	138.5 (87.6)	56.7 (12.5)	68.4	MD	MD	MD	131.8 (67.8)
Ranieri *et al.*[27]	62.7 (12.7)	78.3	27.7 (4.6)	MD	3 (1.5)	132.7 (41.8)	66.3 (10.5)	75.6	27.6 (3.2)	MD	2.3 (0.7)	148.7 (42.7)
Rodrigues Santos et al.[28]	67.94 (7.82)	62.2	MD	9.8 (3.2)	3 (0.9)	191.1 (37.8)	64.1 (9.81)	65.4	MD	11 (3.2)	2.7 (0.8)	190.38 (42.47)
Shoukri[29]	65.7 (12.2)	68.3	28.2 (5.7)	MD	MD	MD	69.6 (10.2)	68.6	29.5 (6.2)	MD	MD	MD
Sykes *et al.*[30]	71.3 (13.9)	75	MD	MD	MD	77.3 (38.2)	70.7 (10.0)	60	MD	MD	MD	76.0 (34.5)
Wendel Garcia *et al.*[31]	64 (14.3)	75	28 (5.3)	9.7 (5.3)	5.3 (3)	124.7 (67.8)	65.7 (15.8)	71	26.3 (3.8)	11 (6.8)	5.7 (2.3)	133.3 (53.5)
Wendel Garcia *et al.*[32]	62 (11.9)	68	28.3 (3.7)	MD	MD	MD	61.7 (12)	68	28.3 (3.8)	MD	MD	MD

APACHE, acute physiology and chronic health evaluation; BMI, body mass index; HFNC, high-flow nasal cannula; MD, missing data; NIV, noninvasive ventilation; P/F, oxygenation index (PaO_2/FiO_2); SOFA, sequential organ failure assessment.
Values are given as mean (standard deviation).

Author	HFNC			NIV				
	Setting	Intervention	Duration, days	NIV mode	NIV interface	Setting	Intervention	Duration, days
Alharthy *et al.*[11]	Mean flow rate, 60 l/min; median FiO_2, 40%	Received HFNC	9 (3.3)	CPAP	Helmet	Mean flow rate, 45 l/min; median FiO_2, 40%	Received helmet-CPAP	8.3 (4.1)
Alkouh *et al.*[12]	Flow rate, 60–80 l/min; FiO_2, maintain SpO_2 ⩾92%	Received HFNC	MD	MD	MD	MD	Received NIV	MD
Costa *et al*[9]	Flow rate, 40–50 l/min; FiO_2, maintain SpO_2 >92%	Received HFNC	MD	BiPAP	Face mask	PEE ⩾8 cmH_2O; PS, for a TV ⩽8 ml/kg; FiO_2, maintain SpO_2 >92%	Received NIV	MD
COVID-ICU group[13]	Flow rate, 50 (40–60) l/min; FiO_2, 70 (60–90) %	HFNC was the most invasive treatment	MD	MD	Face mask	PEEP, 7 (6–8) cmH_2O; PS, 8 (6–10) cmH_2O; FiO_2, 60 (50–80)%	NIV was the most invasive treatment	MD
Duan *et al.*[14]	Flow rate: 30–60 l/min; FiO_2, maintain SpO_2 >93%	HFNC as first-line therapy	4.5 (5.3)	CPAP/BiPAP	Face mask	Initial: CPAP or PEEP, 4 cmH_2O; initial inspiratory pressure, 8–10 cmH_2O; FiO_2, maintain SpO_2 >93%	NIV as first-line therapy	7.1 (4.6)
Fernández *et al.*[15]	MD	HFNC only		CPAP/BiPAP	Face mask	MD	NIV and/or CPAP with or without HFNC	MD
Franco *et al.*[16]	MD	Received HFNC	MD	CPAP/BiPAP	MD	MD	Received CPAP or NIV	MD

(Continued)

Author	HFNC			NIV				
	Setting	Intervention	Duration, days	NIV mode	NIV interface	Setting	Intervention	Duration, days
Gaulton, 2020[17]	Flow rate, 40–60 l/min; FiO_2, maintain SpO_2 >92%	HFNC as first-line therapy	MD	CPAP	Helmet	CPAP, 5–10 cmH_2O; FiO_2, maintain SpO_2 >92%	Helmet as first-line therapy. Patients on helmet therapy were provided breaks with intervening HFNC use	MD
Ghani *et al.*[18]	Initial flow rate, 60 l/min; FiO_2, maintain SpO_2 92–96%	Received HFNC	MD	CPAP	Face mask	PEEP, 8 (6–12) cmH_2O; FiO_2, maintain SpO_2 92–96%	Received CPAP	MD
Gough *et al.*[19]	Flow rate, capped at 30 l/min, limiting PEEP to < 3 cmH_2O	Received HFNC	MD	CPAP	Face mask	PEEP ⩾ 10 cmH_2O	Received CPAP	MD
Grieco *et al.*[20]	Initial flow rate, 60 l/min; FiO_2, maintain SpO_2 92–98%	Randomized	⩾ 2	BiPAP	Helmet	PEEP, 10–12 cmH_2O; initial PS, 10–12 cmH_2O; FiO_2, maintain SpO_2 92–98%	Randomized. After interruption of NIV, patients underwent continuous Venturi mask or HFNC	⩾
Mahroof *et al.*[21]	MD	Initial mode of support was HFNC	MD	MD	MD	MD	Initial mode of support was NIV	MD
Menga *et al.*[22]	MD	HFNC as first-line treatment	MD	BiPAP	Helmet/ Face mask	MD	NIV as first-line treatment	MD
Nadeem *et al.*[23]	MD	Received HFNC	MD	CPAP/BiPAP	MD	MD	Received CPAP or NIV	MD
Nair *et al.*[24]	Initial: flow rate, 50 l/min; FiO_2, 1.0, target SpO_2 >94%	HFNC only	MD	BiPAP	MD	PEEP, 5–10 cmH_2O; PS, 10–20 cmH_2O; FiO_2, 0.5–1.0, target SpO_2 >94%	Received NIV	MD
Pearson *et al.*[25]	MD	HFNC as initial therapy	MD	CPAP	Helmet	MD	Helmet NIV as initial therapy	MD
Perkins *et al.*[26]	MD	Randomized. Crossover was observed between allocated treatment arms	3.7 (4.1)	CPAP	Face mask	MD	Randomized. Crossover was observed between allocated treatment arms	3.5 (4.6)
Ranieri *et al.*[27]	Flow rate, 55 (50–60) l/min	Patients initially treated for ⩾12 continuous hours with HFNC using gas flows ⩾40 l/min	MD	BiPAP	MD	PEEP, 10 (10–12) cmH_2O PS, 10 (10–12) cmH_2O	Patients initially treated with NIV with PEEP ⩾5 cmH_2O	MD
Rodrigues Santos *et al.*[28]	Flow rate, 30–60 l/min; FiO_2, maintain SpO_2 >93%	HFNC as initial therapy	5.53 (1.11)	BiPAP	Face mask	Initial PEEP, 4 cmH_2O; initial inspiratory pressure, 8–10 cmH_2O; FiO_2, maintain SpO_2 >93%	NIV as initial therapy	5.86 (1.10)
Shoukri[29]	Maximum: flow, 59.2 (1.0) l/min; FiO_2, 0.9 (0.1), SpO_2, 92–96%	Received HFNC	5.5 (4.4)	MD	Face mask	Maximum: CPAP/EPAP, 10.0 (1.9) cmH_2O; IPAP, 14.8 (2.4) cmH_2O; FiO_2, 1.0 (0.1), SpO_2, 92–96%	Received CPAP or NIV	5.2 (4.3)
Sykes *et al.*[30]	Mean FiO_2, 79.5 (23) %	HFNC was the highest level of treatment	6 (9.8)	CPAP	Face mask	Mean FiO_2, 83.8 (26.1) %	CPAP with or without HFNC	9 (17.4)

(Continued)

Author	HFNC			NIV				
	Setting	Intervention	Duration, days	NIV mode	NIV interface	Setting	Intervention	Duration, days
Wendel Garcia *et al.*[31]	Flow rate >30 l/min; mean FiO_2, 60 (44–80)%	HFNC was maximal respiratory support at ICU admission	MD	MD	MD	MD	NIV was maximal respiratory support at ICU admission	MD
Wendel Garcia *et al.*[32]	Flow rate >30 l/min; mean FiO_2 ⩾50%	HFNC only	MD	MD	Face mask	Mean FiO_2, at least 50%	NIV only	MD

BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; EPAP, expired positive airway pressure; FiO_2, Fraction of inspiration O_2; HFNC, high-flow nasal cannula; ICU, intensive care unit; IPAP, inspired positive airway pressure; MD, missing data; NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure; PS, pressure support; SpO_2, oxygen saturation; TV, tidal volume.
Values are given as mean (standard deviation).

Literature quality and bias assessment

The quality evaluation results of the three RCTs[20,24,26] are shown in Figure 2. None of the included studies were performed with double blinding. Two studies were considered to have an unclear risk of bias. The 20 observational[9,11–19,21–23,25,27–32] studies were assessed using the NOS checklist, and the results are shown in the Table 2. All studies were of medium quality (⩾5 stars) or above, and 10 were considered high quality (⩾8 stars). We generated a funnel plot for intubation and mortality rates; visual inspection of this plot indicated no evidence of publication bias for intubation rate, but we did observe a possible bias for mortality rate (Figure 3).

Clinical outcomes

A total of 5354 patients participated in the 23 studies[9,11–32] of the present meta-analysis, all of whom were adult COVID-19 patients. The patients were admitted to different hospital settings and received noninvasive respiratory support at the time of admission. In 4 studies,[11,17,20,25] a helmet was applied, in 11 studies,[9,13–15,18,19,26,28,29,30,32] a face mask was used, 1 study[22] reported applying both a helmet and a face mask, 7 studies[12,16,21,23,24,27,31] did not report whether a helmet or a facemask was used, in 6 studies,[9,20,22,24,27,29] BiPAP was applied, 7 studies[11,17–19,25,26,30] featured CPAP, 4 studies[14–16,23] reported applying both BiPAP and CPAP, and 6 studies[12,13,21,28,31,32] did not report whether they applied BiPAP or CPAP (Table 1).

A total of 5196 patients participated in 20 studies[9,12–20,23–32] that reported mortality, and the pooled estimates demonstrated that mortality rate was lower in HFNC groups than in NIV groups [OR = 0.66, 95% CI: 0.51–0.84, $p = 0.0008$, $I^2 = 60\%$, Figure 4(a)]. However, in subgroup analysis, no significant differences in mortality were observed in the HFNC group relative to NIV-helmet group [OR = 1.21, 95% CI: 0.63–2.32, $p = 0.57$, $I^2 = 0\%$, Figure 5(a)] or the NIV-CPAP group [OR = 0.77, 95% CI: 0.51–1.17, $p = 0.23$, $I^2 = 65\%$, Figure 5(b)], but significant differences in mortality were observed in the HFNC group relative to the NIV-facemask group [OR = 0.58, 95% CI: 0.41–0.81, $p = 0.001$, $I^2 = 63\%$, Figure 5(a)] or the NIV-BiPAP group [OR = 0.60, 95% CI: 0.45–0.79, $p = 0.0003$, $I^2 = 5\%$, Figure 5(b)].

Intubation was reported in 5114 patients in 21 studies[9,11–22,24–29,31,32] and pooled estimates demonstrated that there were no significant differences in the intubation rate between the HFNC and NIV groups [OR = 0.93, 95% CI: 0.73–1.20, $p = 0.59$, $I^2 = 63\%$, Figure 4(b)]. No significant differences in intubation requirements were found in subgroup analyses by interface [helmet: OR = 1.54, 95% CI: 0.72–3.29, $p = 0.27$, $I^2 = 55\%$; facemask: OR = 0.81, 95% CI: 0.57–1.15, $p = 0.24$, $I^2 = 65\%$, Figure 5(c)] or mode [CPAP: OR = 0.90, 95% CI: 0.57–1.40, $p = 0.62$, $I^2 = 66\%$; BiPAP: OR = 1.16, 95% CI: 0.85–1.58, $p = 0.35$, $I^2 = 35\%$, Figure 5(d)] relative to the HFNC group.

PaO_2/FiO_2 ratio (24 h after treatment) was reported in 317 patients in four studies,[14,20,24,29] and no significant differences were found between the HFNC group and NIV group [MD = −22.63, 95% CI: −47.21 to 1.95, $p = 0.07$, $I^2 = 64\%$, Figure 6(a)]. A total of 2382 patients from six

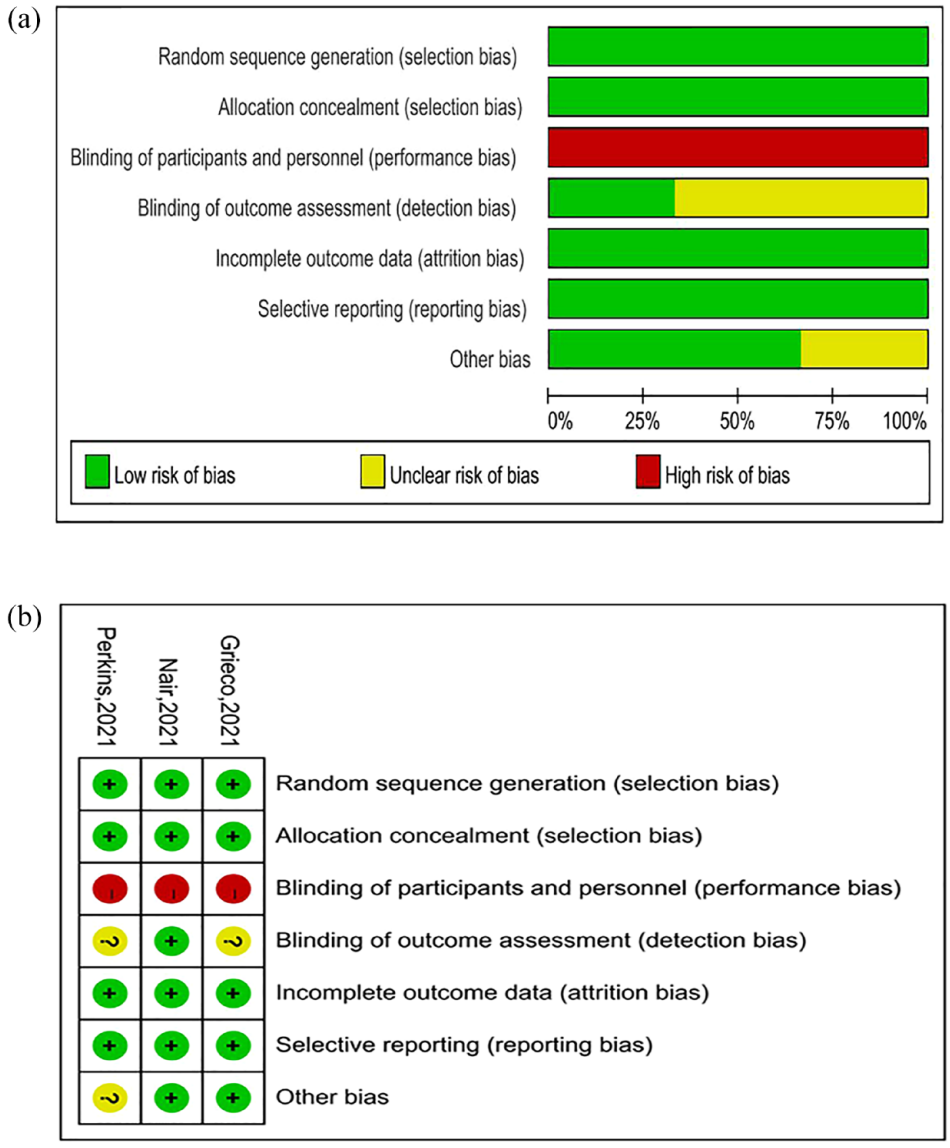

Figure 2. The quality evaluation results of the three RCTs: (a) risk of bias graph and (b) risk of bias summary.

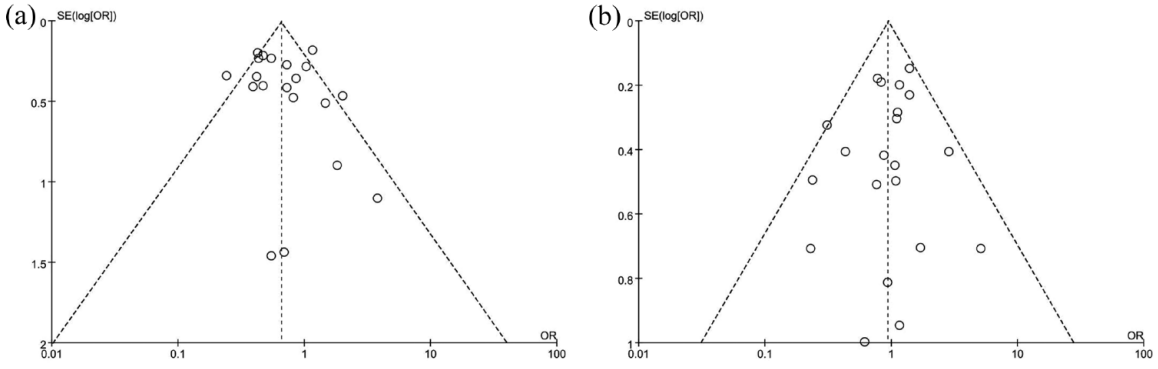

Figure 3. Funnel plots of the (a) proportion *versus* the standard error of mortality, (b) intubation. Circles indicate studies included in the meta-analysis.

Table 2. The NOS quality of included studies.

Study	Selection				Comparability		Outcome			Total	Quality
	REC	SNEC	AE	DO	SC	AF	AO	FU	AFU		
Alharthy *et al.*[11]	1	1	1	1	1	1	1	0	1	8	High
Alkouh *et al.*[12]	1	1	1	1	0	0	0	1	1	6	Moderate
Costa *et al.*[9]	1	1	1	1	1	1	0	1	1	8	High
COVID-ICU group[13]	1	1	1	1	1	1	1	1	1	9	High
Duan *et al.*[14]	1	1	1	1	1	1	1	1	1	9	High
Fernández *et al.*[15]	1	1	1	1	0	0	1	1	1	5	Moderate
Franco *et al.*[16]	1	1	1	1	1	1	1	1	1	8	High
Gaulton *et al.*[17]	1	1	1	1	1	0	1	0	1	7	Moderate
Ghani *et al.*[18]	1	1	1	1	1	1	0	1	1	8	High
Gough *et al.*[19]	1	1	1	1	0	0	1	0	1	6	Moderate
Mahroof *et al.*[21]	1	1	1	1	0	0	1	0	1	5	Moderate
Menga *et al.*[22]	1	1	1	1	1	1	0	0	0	6	Moderate
Nadeem *et al.*[23]	1	1	1	1	1	1	0	0	1	7	Moderate
Pearson *et al.*[25]	1	1	1	1	1	1	1	0	1	7	Moderate
Ranieri *et al.*[27]	1	1	1	1	1	1	1	1	1	9	High
Rodrigues Santos *et al.*[28]	1	1	1	1	1	1	1	0	1	8	High
Shoukri[29]	1	1	1	1	1	0	1	0	1	7	Moderate
Sykes *et al.*[30]	1	1	1	1	1	1	1	0	1	8	High
Wendel Garcia *et al.*[31]	1	1	1	1	1	1	0	1	0	7	Moderate
Wendel Garcia *et al.*[32]	1	1	1	1	1	1	1	0	1	8	High

AE, ascertainment of exposure; AF, study controls for any additional factors; AFU, adequacy of follow-up of cohorts (⩾90%); AO, assessment of outcome; DO, demonstration that outcome of interest was not present at start of study; FU, follow-up long enough for outcomes to occur; REC, representativeness of the exposed cohort; SC, study controls for age, sex; SNEC, selection of the non-exposed cohort.
'1' means that the study is satisfied with the item and '0' means the opposite situation.

studies[9,13,20,26,31,32] reported ICU LOS, and no significant differences were found between those two groups [MD = 0.31, 95% CI: −0.81 to 1.43, $p = 0.59$, $I^2 = 0\%$, Figure 6(b)]. The results were similar for hospital LOS: no difference in this value was reported in a total of 1840 patients in six studies[9,13,16,20,24,28] between those two groups [MD = 0.76, 95% CI: −0.33 to 1.85, $p = 0.17$, $I^2 = 0\%$, Figure 6(c)]. A total of 758 patients in three studies[20,24,32] reported VFD, and again there were no significant differences between those two groups [MD = 0.17, 95% CI: −2.63 to 2.96, $p = 0.91$, $I^2 = 55\%$, Figure 6(d)].

Discussion

In this meta-analysis of 23 studies with 5354 patients who were hospitalized for COVID-19, NIV was associated with higher mortality than HFNC. However, no significant differences in

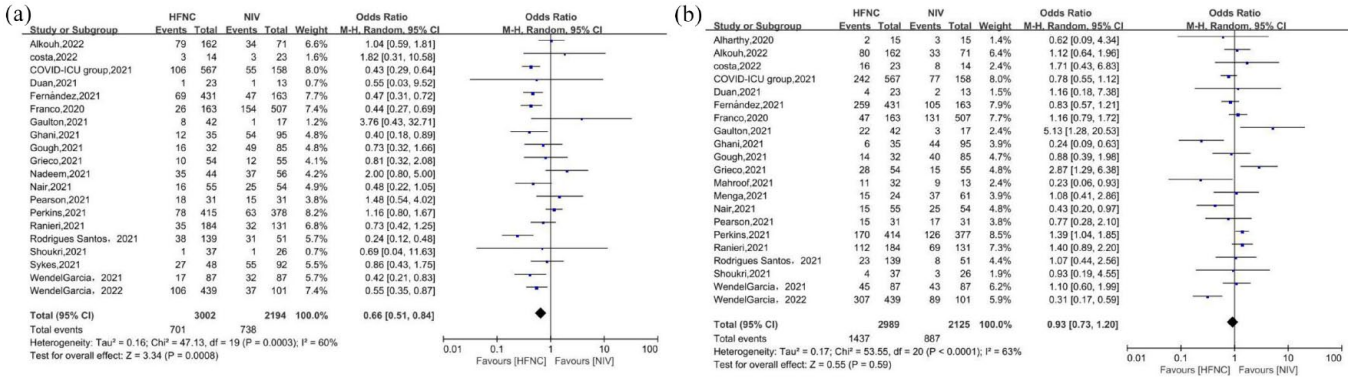

Figure 4. Mortality (a) and intubation (b) for included studies.
HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

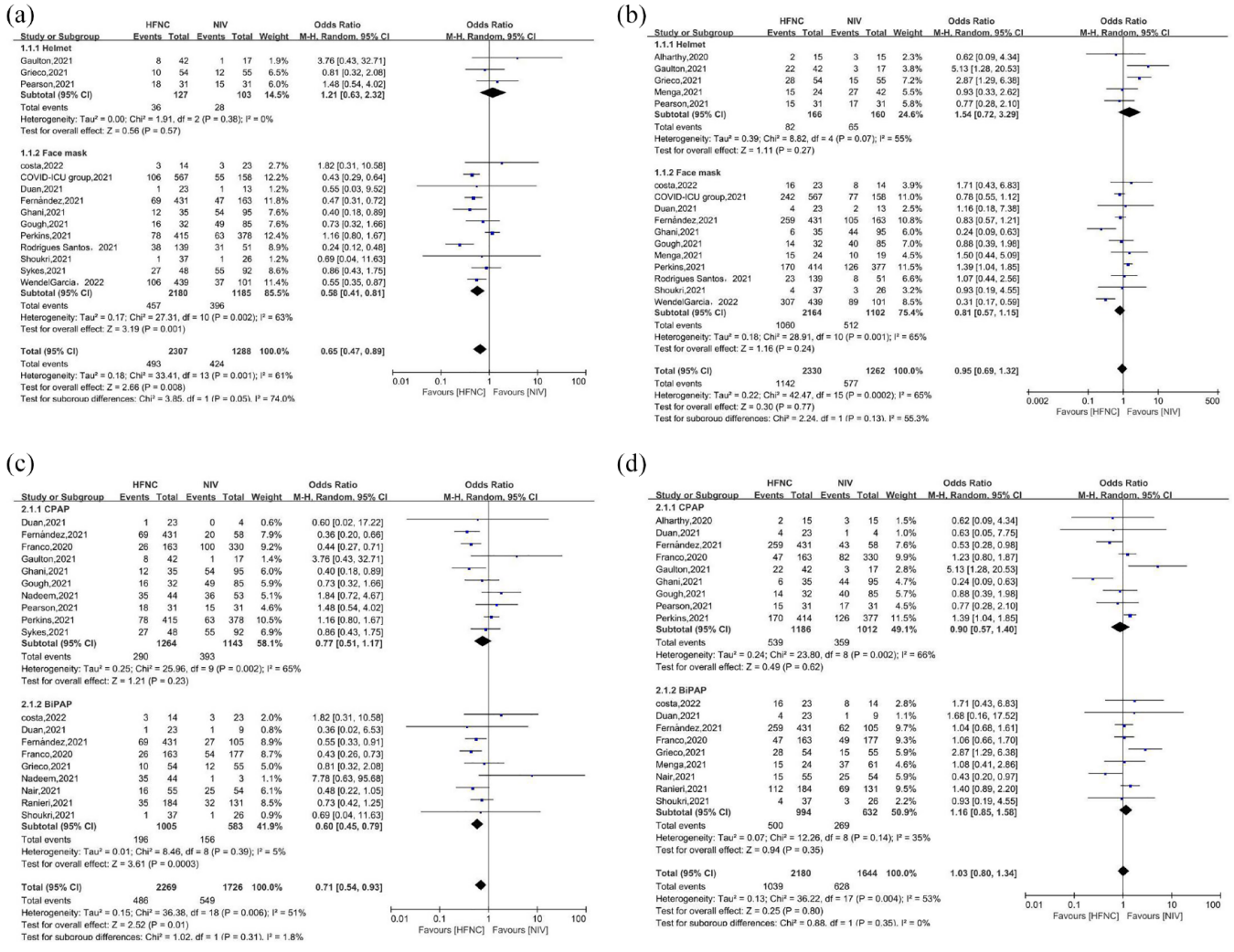

Figure 5. (a, b) Subgroup analysis of mortality and (c, d) intubation.
BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

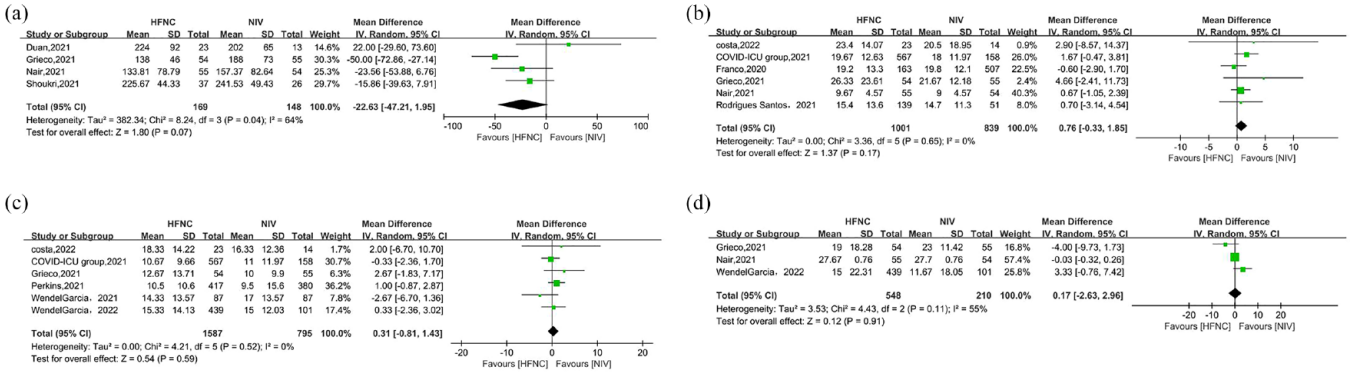

Figure 6. The secondary outcomes for included studies: (a) PaO_2/FiO_2, (b) ICU length of stay, (c) hospital length of stay, and (d) days free from invasive mechanical ventilation.
HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

mortality were observed between the NIV-helmet group and the NIV-CPAP group compared with HFNC group. There were also no significant differences in the intubation rate, PaO_2/FiO_2, ICU LOS, hospital LOS, and VFD between the HFNC and NIV groups.

Noninvasive respiratory support, including the use of HFNC and NIV, has increasingly been used in the management of COVID-19-associated acute respiratory failure.[5,6] A literature review found that HFNC can reduce the need for intubation in patients with COVID-19 and can decrease the LOS in the ICU as well as complications related to mechanical ventilation.[33] A population-based study involving 1400 patients found a similar 60-day mortality risk for patients undergoing immediate invasive mechanical ventilation (IMV) and those intubated after an NIV trial,[34] suggesting that NIV can be safely used in patients with COVID-19 AHRF. However, questions remain about the utility, safety, and outcome benefit of noninvasive respiratory strategies, as there was little high-quality evidence. In patients who do not have COVID-19, the European Respiratory Society recommends HFNC therapy to patients with hypoxic respiratory failure over conventional nasal cannula therapy and NIV.[35] Since then, many studies have compared HFNC and NIV and have produced conflicting findings in patients with COVID-19[13,18,20] for these patients, there is not enough evidence to prove which approach is better.

In our meta-analysis, we found that there were no differences in intubation rate, PaO_2/FiO_2, ICU LOS, hospital LOS, or VFD between the NIV and HFNC group, but mortality was significantly higher among COVID-19 patients in the NIV group, consistent with three recent meta-analyses.[36–38] Whether this was because of the delayed intubation and increased mortality in the NIV group is still unclear. In general, the role of NIV is indeed controversial. The success of NIV, however, depends on several factors, such as, for example, the underlying causes of AHRF, patient cooperation, staff experience, interface, mode, and so forth.[8] Our meta-analysis included more studies than recent meta-analyses; more importantly, we performed subgroup analyses to evaluate the factors affecting the efficiency of NIV.

NIV ventilates by applying positive pressure to the lungs through a mask or a helmet. In the pre-COVID-19 era, a meta-analysis demonstrated that helmet NIV may reduce mortality and the need for intubation relative to conventional oxygen therapy in patients with purely AHRF.[39] Nonetheless, all included trials and observational studies were small, and helmet NIV was not compared with HFNC. In one other recent meta-analysis of adult patients with AHRF of all types, it was found that relative to facemask NIV, helmet NIV may reduce mortality and intubation; however, the effects of helmet NIV compared with HFNC remain uncertain.[40] The use of helmet NIV has steadily increased throughout the COVID-19 pandemic,[10] Our meta-analysis found that there were no differences in mortality rate between helmet NIV and HFNC, while face mask NIV had a higher mortality than HFNC. Previous study found that helmet NIV may be more

comfortable and allow the application of a more 'protective' ventilation with higher PEEP (i.e. 8–12 cmH_2O) and lower pressure support values with fewer air leaks and interruptions.[39,41] However, only two small sample size RCTs[20,26] and one observational study[17] comparing helmet NIV and HFNC were included in the analysis, and there was no study to comparing the differences of mode and ventilator parameters between helmet NIV and face mask NIV. High-quality RCTs in COVID-19 patients comparing helmet NIV with both face mask NIV and HFNC are needed, including patient-important outcomes and attention to possible adverse events.

NIV can deliver airflow through the CPAP and BiPAP modes. Largely because of an early negative report,[42] CPAP remains largely undocumented in ARDS. Recently, one multicenter adaptive RCT compared the use of CPAP, HFNC, and standard oxygen therapy. The results showed that treating hospitalized COVID-19 patients who had AHRF with continuous CPAP reduced the need for IMV.[26] Our meta-analysis found that there were no differences in mortality between CPAP and HFNC, while BiPAP had a higher mortality than HFNC. This may be for two reasons. On the one hand, patients' conditions may have been relatively mild in the CPAP group; for these patients, medical personnel often choose the CPAP mode first as the majority of patients with COVID-19 who are offered continuous CPAP therapy (83–97%) can tolerate the treatment.[43,44] On the other hand, the risks of BiPAP include delayed intubation, large tidal volumes, and injurious transpulmonary pressures;[6] many guidelines describe BiPAP as the first-line treatment for AHRF caused by acute exacerbations of chronic obstructive pulmonary disease or acute cardiogenic pulmonary edema.[45] RCTs with large samples to compare CPAP with BiPAP or HFNC based on patient populations in COVID-19 patients are still lacking.

Therefore, routinely offering HFNC as the main form of noninvasive respiratory support for patients with respiratory failure due to COVID-19 may not be recommendable.[46] We need to fully consider the underlying cause of AHRF, the severity and cooperation of patients, and the advantages of each noninvasive oxygen strategy. For patients with COVID-19-associated AHRF, the way forward may be a stepwise treatment approach that is based on patient status/commodities, includes several consecutive ventilation strategies,[47] uses multiple oxygen strategies based on patients' lifestyle and oxygenation status, and uses objective criteria when observing patients.

The present study had several limitations. First, our results were based mostly on cohort and case-control studies, and the quality of the evidence in these studies was low. The lack of RCTs may have reduced overall accuracy and increased heterogeneity. Some variables are likely skewed and would best be reported as medians with interquartile ranges and compared using a non-parametric statistical test, but this may be related to the original data provided by the included study. Second, few studies have been conducted on the use of a helmet in COVID-19 patients, and high-quality RCTs comparing helmet NIV to both face mask NIV and HFNC are needed. Third, population-based studies of evaluation of CPAP and BiPAP are lacking, such as BiPAP for COVID-19-associated AHRF patients with COPD and cardiogenic pulmonary edema, or CPAP for COVID-19 patients with purely AHRF. For this reason, we could not conduct subgroup analysis based on the patient population.

Conclusion

In this meta-analysis, we found although mortality was lower with HFNC than NIV, there was no difference in mortality between HFNC and NIV on a subgroup of helmet or CPAP group. The lack of RCTs may have reduced overall accuracy and increased heterogeneity. Future large sample RCTs are necessary to prove our findings.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Yun Peng: Formal analysis; Methodology; Resources; Writing – original draft; Writing – review & editing.

Bing Dai: Formal analysis; Resources; Writing – original draft; Writing – review & editing.

Hong-wen Zhao: Formal analysis; Resources; Writing – original draft; Writing – review & editing.

Wei Wang: Formal analysis; Resources; Writing – original draft; Writing – review & editing.

Jian Kang: Formal analysis; Resources; Writing – original draft; Writing – review & editing.

Hai-jia Hou: Formal analysis; Resources; Supervision; Writing – original draft; Writing – review & editing.

Wei Tan: Formal analysis; Methodology; Resources; Supervision; Writing – original draft; Writing – review & editing.

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