BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open: first published as 10.1136/bmjopen-2022-067879 on 30 March 2023. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

BMJ Open

High-flow nasal cannula reduces intubation rate in COVID-19 patients with acute respiratory failure: a meta-analysis and systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067879
Article Type:	Original research
Date Submitted by the Author:	01-Sep-2022
Complete List of Authors:	Li, Yang; Southeast University, Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine LI, Cong; Southeast University, Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine Chang, Wei; Southeast University, Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine Liu, Ling; Southeast University, Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine
Keywords:	COVID-19, Adult intensive & critical care < ANAESTHETICS, Respiratory infections < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2022-067879 on 30 March 2023. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

High-flow nasal cannula reduces intubation rate in COVID-19 patients with acute respiratory failure: a meta-analysis and systematic review

Yang Li,[1] Cong LI,[1] Wei Chang,[1] Ling Liu[1]

Author affiliations

1 Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, Jiangsu, China

***Corresponding author**

Ling Liu

Address: NO.87 Dingjiaqiao, Nanjing 210009, China.

E-mail: liulingdoctor@126.com.

Phone: 86-13851435472.

E-mail Adress

Yang Li: liyang2022@seu.edu.cn; Cong Li: congcongli2020@163.com; Wei Chang: ewei_0181@126.com; Ling Liu: liulingdoctor@126.com.

Keywords COVID-19 acute respiratory failure; high-flow nasal cannula; conventional oxygen therapy; meta-analysis

Word count 3799

For peer review only

ABSTRACT

Objective The aim was to investigate the effect of high-flow nasal cannula therapy (HFNC) versus conventional oxygen therapy (COT) on intubation rate, 28-day ICU mortality, 28-day ventilator-free days (VFDs) and ICU length of stay (ICU LOS) in adult patients with acute respiratory failure (ARF) by COVID-19.

Design Systematic review and meta-analysis.

Data sources PubMed, Web of Science, Cochrane Library, and Embase up to June 2022.

Eligibility criteria for selecting studies Only randomized controlled trials or cohort studies comparing HFNC with COT in COVID-19 patients were included up to June 2022. Studies conducted on children or pregnant women and not in English language were excluded.

Data extraction and synthesis Two reviewers screened the titles, abstracts and full texts independently. Relevant information was extracted and curated into tables. Cochrane collaboration tool and Newcastle-Ottawa scale were used to assess the quality of randomized controlled trials or cohort studies. Meta-analysis was conducted in RevMan 5.4 computer software using a random effects model with 95% CI. Heterogeneity was assessed using Cochrane's Q test (chi-square) and Higgins I^2 statistics, with subgroup analyses to account for sources of heterogeneity.

Results Nine studies involving 3370 (1480 received HFNC) subjects were included. HFNC reduced intubation rate compared with COT (OR = 0.44, 95% CI 0.28 to 0.71, P = 0.0007), decreased 28-day ICU mortality (OR = 0.54, 95% CI 0.30 to 0.97, P = 0.04), and improved 28-day VFDs (MD = 2.58, 95% CI 1.70 to 3.45, P < 0.00001). However, HFNC had no effect on ICU LOS versus COT (MD = 0.52, 95% CI -1.01 to 2.06, P = 0.50).

Conclusions Our study indicates that HFNC may reduce intubation rate and 28-day ICU mortality, and improve 28-day VFDs in patients with ARF due to COVID-19 compared with COT. To validate our finding, large-scale randomized controlled trials are necessary.

PROSPERO registration number CRD42022345713.

Keywords COVID-19; acute respiratory failure; high-flow nasal cannula; conventional oxygen therapy; meta-analysis

For peer review only

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This meta-analysis was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
2. Cochrane collaboration tool was used to assess the quality of randomized controlled trials, and Newcastle-Ottawa scale was used to evaluate the quality of cohort studies.
3. Subgroup analyses were performed to account for sources of heterogeneity.
4. Due to the limited number of relevant randomized controlled trials, our meta-analysis consisted mainly of cohort studies, which may still affect the accuracy of the results.
5. Significant differences between HFNC and COT made blinding of participants and personnel difficult, so the performance bias of all included RCTs was all at high risk.

For peer review only

INTRODUCTION

The outbreak of the novel coronavirus disease 2019 (COVID-19) has caused untold harm and challenges to people in more than 200 countries and territories around the world. As of 26 June 2022, over 541 million confirmed cases and over 6.3 million deaths have been reported globally.[1] Acute respiratory distress syndrome (ARDS) is a major complication of COVID-19 patients during hospitalization.[2, 3] And it can progress to acute respiratory failure (ARF), which presents with severe hypoxemia and dyspnea and is associated with higher mortality. Consequently, it's particularly important to select a ventilation support therapy for patients with COVID-19.

Traditionally, the treatment of ARF has focused mainly on invasive mechanical ventilation (IMV) and its optimization.[4] However, IMV represents a risk factor for the development of ventilator-associated pneumonia (VAP).[5] Approximately 16% of the patients infected with COVID-19 showed severe ARF,[6] and 4-12% needed invasive respiratory support.[3, 7] Early observational studies during the COVID-19 pandemic reported a very high mortality in patients subjected to IMV.[8] Some investigators warned about early intubation and mechanical ventilation.[9]

Noninvasive respiratory support techniques could prevent adverse events associated with intubation and mechanical ventilation. Most patients usually receive oxygen therapy through a nasal cannula, simple or venturi face mask, called conventional oxygen therapy (COT) or standard oxygen therapy.[2] At the onset of the COVID-19 pandemic, most clinicians used COT or early IMV to treat COVID-19 patients with ARDS, as recommended by international guidelines.[10] However, COT may be difficult to perform in situations where high inspiratory flow is necessary.[11]

High-flow nasal cannula oxygen (HFNC) is a relatively new and increasingly used therapy in adults with ARF.[12] This non-invasive technic delivers warmed, humidified oxygen with a fraction of inspired oxygen (FiO_2) up to 1.0 and a maximum flow rate of 60 L/min.[13] HFNC may reduce the need for endotracheal intubation and the risk of treatment escalation in patients with ARF,[14, 15] but with no significant effect on mortality.[15, 16] Although international guidelines and early observational studies recommended HFNC for the initial treatment of severe patients with COVID-19, there is limited evidence to support this view.[17]

Therefore, we conducted a meta-analysis to investigate the effect of HFNC on intubation rate, 28-day intensive care unit (ICU) mortality, and its effect on 28-day ventilator-free days (VFDs) and ICU length of stay (ICU LOS) versus COT in adult patients with ARF by COVID-19.

For peer review only

For peer review only

METHODS

Protocol and registration

We conducted a systematic review in accordance with the methods recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

As this paper did not directly involve human subjects, while only using data from published articles, institutional review board approval was not required. The protocol used in this study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022345713).

Eligibility criteria

The included studies had to meet the following criteria:

1. Type of study: randomized controlled trials (RCTs) or cohort studies;
2. Population: patients over 16-year-old with ARF by COVID-19;
3. Intervention: HFNC compared with COT;

Characteristics for excluded studies: case reports or case series, guidelines, expert consensus, animal studies, protocol, reviews, meta-analysis, conference abstract, studies conducted on children or pregnant women, unrelated studies (e.g., HFNC or COT not used in patients), studies involving repeated experiments (commentary articles on specific studies or secondary analyses of experimental data), and studies not in English language.

The primary outcome was intubation rate. Decisions regarding intubation of the trachea were based on clinical grounds and judgment of the physician in charge. The secondary outcomes were 28-day ICU mortality, 28-day ventilator-free days (VFDs), and ICU length of stay (ICU LOS). 28-day VFDs was defined as the cumulative time in the first 28 days after starting HFNC or COT without the need for invasive mechanical ventilation.

Search strategy

Literature search was carried out with multiple electronic databases, such as PubMed, Web of Science, Cochrane Library, and Embase to identify articles published up to June 2022. We restricted the articles to those published in English. The details of the search strategies used for each database were presented in the **Supplemental file: Table S1**. We also checked the references of related journals to make sure we didn't skip any studies. The literature review was conducted independently by two authors (YL and CL). Disparities in

For peer review only

the literature review were resolved by a third author (WC).

Study selection and data extraction

We merged the search results and then removed duplicate records of the same study. Two reviewers (YL and CL) independently reviewed the titles and abstracts of the remaining studies after excluding duplicates to initially identify potentially eligible studies. A full-text review of the remaining literatures was conducted to finalize the studies for inclusion. Two investigators (YL and CL) independently extracted the data from the selected qualified articles. The conflicts between two reviewers were resolved by a third reviewer (WC). The data extracted included the study ID (the first author's name and publication year), region, study type, setting, type of ARF (acute hypoxic respiratory failure (AHRF) or not), control therapy, sample size, age, gender, body mass Index (BMI), comorbidities, oxygenation index (OI) (PaO2/FiO2) before the start of oxygen therapy, sequential organ failure assessment score (SOFA), and primary and secondary outcomes.

Risk of bias assessment

Two reviewers assessed the risk of bias of included trials independently with any discrepancies resolved through discussion with a third reviewer (WC). Cochrane collaboration tool in RevMan 5.4 software (Review Manager, Version 5.4, The Cochrane Collaboration, 2014) was used to assess the quality of RCTs,[19] which considers seven different domains: adequacy of sequence generation; allocation sequence concealment; blinding of participants and caregivers; blinding for outcome assessment; incomplete outcome data; selective outcome reporting; and the presence of other potential sources of bias not accounted for in the other six domains. Based on the method of the trials, each was graded as "yes", "no" or "unclear", to reflect a high, low risk or uncertain risk of bias, respectively. Meanwhile, Newcastle-Ottawa scale (NOS) was used to evaluate the quality of cohort studies based on the selection of the study groups, comparability of study groups, and ascertainment of exposure/outcome.[20, 21] Studies with total scores of ≥6 were considered to have a low risk of bias. Two reviewers (YL and CL) made judgments independently. In cases of disagreement, resolution was attempted by discussion.

Assessment of publication bias

Funnel plots were used to assess the possibility of publication bias and were implemented in RevMan 5.4 software. The Egger's regression test was used to measure funnel plot asymmetry.[22, 23]

For peer review only

Grading the quality of the evidence

We used the methodology of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group to assess the overall quality of the evidence for the primary and secondary outcomes in the following domains: risk of bias, inconsistency, indirection, imprecision and publication bias. Overall certainty of evidence was shown as high, moderate, low, or very low quality.[24]

Assessment of heterogeneity

Heterogeneity of included studies were assessed using Cochrane's Q Test (chi-square) of homogeneity and Higgins I^2 statistics.[25, 26] I^2 describes the percentage of effective variability and the corresponding P-value calculates the estimate of effective variability due to heterogeneity rather than sampling error. I^2 values of 25% to 50% indicate low heterogeneity, 50% to 75% indicates moderate heterogeneity, and more than 75% indicates high heterogeneity.[25] To confirm the robustness of our results, sensitivity analysis using leave-one-out meta-analysis was performed to see if it had a significant influence on the meta-analysis result.

Statistical analysis

RevMan 5.4 computer software was used for all data analysis in this study. For dichotomous variables, the estimated effects were pooled with Mantel–Haenszel method and expressed with the odds ratio (OR) with 95% confidence interval (CI). For the continuous variables, the estimated effects were pooled with the inverse variance method and expressed with the mean difference (MD) with 95% CI. The analysis was performed using a random effects model. A *P*-value <0.05 was considered statistically significant. If the median and interquartile range (IQR) were reported in the study, it can be converted into the mean and standard deviation through formulas proposed by Luo and Wan.[27, 28]

Subgroup analysis

We performed a subgroup analysis according to the type of ARF (AHRF or not) to explore the efficacy of HFNC in patients with AHRF due to COVID-19. Secondly, we assessed the efficacy of HFNC applied to patients with an OI below 200 mmHg and higher than 200 mmHg before the start of oxygen therapy compared to COT.

TSA

For peer review only

We used TSA to identify the risk of both type 1 and type 2 error due to sparse data and repetitive testing of accumulating data for primary outcome in our meta-analysis.[29] The findings were represented by the cumulative Z-curves. When the cumulative Z-curves surpassed the futility boundary, the level of evidence was adequate and further trials would be judged as futile. The level of evidence was judged as adequate and conclusive, if the Z-curves surpassed the conventional and trial sequential significance boundaries. On the contrary, when Z-curves did not cross any boundaries or only surpassed the conventional boundary, the level of evidence was inadequate and more trials were required to clarify the conclusion. A two-sided trial sequential monitoring boundary type was used in our TSA. We defined a statistical significance level of 5%, a power of 80%, a control event rate of 66%, and a relative risk reduction of 20%. TSA was performed using TSA version 0.9.5.10 beta.[30]

Patient and public involvement

Patients and the public were not directly involved in this study.

For peer review only

RESULTS

Study identification and selection

We initially obtained 1363 records in accordance with the search strategy. After excluding 82 duplicate studies, 1281 items remained. 1259 articles were excluded through initial screening by title and abstract because they did not match our study topic. After full text review of 22 potentially eligible studies, 13 articles were excluded based on the following reasons: 1 lacked complete information, 9 did not compare HFNC with COT, and 3 were case report or review. Eventually, a total of 9 studies were eligible and included in this meta-analysis. A PRISMA flow diagram of the selection of studies is shown in **Figure 1.**

Study characteristics

Table 1 and **Table 2** summarized the study characteristics and patient characteristics of the included studies. All included studies were published by June 2022. A total of nine studies were included, two studies conducted in France,[31, 32] one study was multinational,[33] one study from the United States,[34] one from Colombia,[35] one from Turkey,[36] one from China,[13] one from Switzerland and one from Spain.[37, 38] Regarding study design, two were RCTs,[13, 35] and the remaining seven were prospective or retrospective cohort studies.[31-34, 36-38] Seven studies were conducted in ICU,[13, 31-33, 36-38] one study was conducted in ICU, emergency department (ED) and ward,[35] and one was not reported.[34] A total of 3370 subjects (1480 received HFNC, 1890 received COT) were included, of which 71.8% were male. Seven studies specified the included patients as AHRF due to COVID-19,[13, 32, 34-38] and two other studies did not specify the type of ARF. Six studies included patients with an OI below 200 mmHg before the start of oxygen therapy.[32-37]

Risk of bias assessment

Two RCTs were evaluated for quality using the Cochrane collaboration tool and most domains were assessed as low risk of bias (random sequence generation, allocation concealment, incomplete outcome data, and selective reporting).[13, 35] However, due to the apparent differences between HFNC and COT, blinding of subjects and personnel was difficult to achieve, performance bias was considered high risk for all included RCTs. Teng et al. did not specify whether they were blinded to outcome assessment.[13] The risk of summary bias in individual studies is shown in **Supplemental file: Figure S1, Figure S2**. The quality of the cohort studies was assessed using the Newcastle-Ottawa scale. The overall quality of all included cohort studies was

For peer review only

good, with all studies scoring 8. The results of the quality assessment were shown in **Supplemental file: Table S2**.

Table 1: Study characteristics of the included studies

Study	Region	Study type	Setting	ARF	Control	Sample size	Age (HFNC/COT)	Male, n (%)
Bonnet, 2021 [31]	France	RC	ICU	NR	FM	76/62	59.6±11.3/59.3±12.1	112 (81)
COVID-ICU group, 2021 [33]	Multicentric	RC	ICU	NR	NR	567/766	63.6±12.6/61.4±12.6	981 (74)
Demoule, 2020 [32]	France	RC	ICU	AHRF	NR	146/233	60±10.5/61.6±11.9	291 (77)
Hansen, 2021 [34]	American	PC	NR	AHRF	FM/NC	30/62	68.6±12.5/68.3±11.9	58 (63)
Ospina-Tascón,2021 [35]	Colombia	RCT	ICU, ED and Ward	AHRF	FM/NP	99/100	59.6±14.3/58.3±13.5	134 (67)
Sayan, 2021 [36]	Turkey	RC	ICU	AHRF	FM	24/19	63.3±12.1/69.5±12.3	30 (70)
Teng, 2021 [13]	China	RCT	ICU	AHRF	FM/NC	12/10	56.6±3.0/53.5±5.5	15 (68)
Wendel Garcia, 2021 [37]	Switzerland	PC	ICU	AHRF	NR	87/85	64.1±14.3/62.6±14.3	128 (74)
Wendel Garcia, 2022 [38]	Spain	RC	ICU	AHRF	FM	439/553	62.0±11.9/62.6±11.9	671 (68)

ARF: acute respiratory failure, HFNC: high flow nasal cannula, COT: conventional oxygen therapy, NR: not reported, RC: retrospective cohort, RCT: randomized controlled trial, ICU: intensive care unit, ED: emergency department, AHRF: acute hypoxic respiratory failure, FM: face mask. NC: nasal cannula, NP: nasal prong

Assessment of heterogeneity

Heterogeneity in the results of three outcomes was high (intubation rate, mortality and VFDs). Sensitivity analysis by leave-one-out revealed that the study by COVID-ICU group had a high impact on the heterogeneity of the results.[33] Heterogeneity decreased significantly if this study was excluded (intubation rate: 85%-51%; mortality: 77%-0%; ICU LOS: 80%-64%).

Primary outcome

Seven studies including 3256 patients reported intubation rates.[31-33, 35-38] In these seven studies, we found that patients treated with HFNC had a statistically significant lower rate of intubation compared to those undergoing COT (OR = 0.44, 95% CI 0.28 to 0.71, P = 0.0007; M-H random), and the heterogeneity was high with I^2 = 85% (P < 0.00001) (**Figure 2**).

The quality of evidence on intubation rate was thought to be low, due to inconsistency associated with high heterogeneity (**Supplemental file: Table S3**). Funnel plots were visually inspected and did not demonstrate evidence of publication bias (**Supplemental file: Figure S3**). TSA suggested that although the cumulative Z-curve did not reach the required information size (RIS), it surpassed both the conventional and TSA boundaries, indicating that a positive conclusion had been obtained before the RIS had been reached, and TSA supported the results of the meta-analysis **(Supplemental file: Figure S4)**. However, more RCTs were still needed because the study included mostly cohort studies.

Table 2: Subject characteristics and outcomes of the included studies in the meta-analysis

Study	BMI (HFNC/COT)	Comorbidities (HFNC/COT)			OI (HFNC/COT)	SOFA (HFNC/COT)	Outcomes			
		HT	DM	COPD			IR	M	VFD	ILOS
Bonnet, 2021 [31]	29.0±6.05/28.8±5.3	37/19	24/19	NR	NR	NR	Y	Y	Y	Y
COVID-ICU group, 2021 [33]	28.0±4.5/28.4±5.2	263/331	145/206	NR	105.1±42.4/154.0±96.6	3.0±1.5/2.7±1.5	Y	Y	_	Y
Demoule, 2020 [32]	27.4±3.7/28.3±5.2	67/121	42/72	7/13	134.1±77.1/141.2±73.1	4.0±1.5/6±4.5	Y	Y	_	_
Hansen, 2021 [34]	32.2±8.1/31.4±9.8	16/45	9/27	6/6	152.0±62.0/153.0±67.0	6.6±2.2/7.7±3.0	_	Y	Y	Y
Ospina-Tascón,2021 [35]	29.1±4.4/29.6±5.2	35/44	18/20	3/1	107.2±35.4/110.6±42.1	3.6±0.8/3.6±0.8	Y	Y	Y	Y
Sayan, 2021 [36]	26.5±2.6/26.5±3.2	6/12	3/5	2/0	170.7±19.1/183.9±40.3	NR	Y	Y	Y	Y
Teng, 2021 [13]	NR	7/4	3/3	NR	224.3±12.6/213.7±4.6	NR	_	_	_	Y
Wendel Garcia, 2021 [37]	28.1±5.3/28.7±4.5	NR	26/23	10/14	124.6±67.9/127.9±14.5	5.3±3.0/5.9±2.3	Y	_	_	Y
Wendel Garcia, 2022 [38]	28.4±3.7/28.0±4.5	NR	91/114	32/40	NR	NR	Y	_	_	Y

BMI: body mass index, HT: hypertension, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, OI: oxygenation index, SOFA: sequential organ function assessment, IR: intubation rate, M: mortality, VFD: ventilator free days, ILOS: ICU stay of length

Secondary outcomes

28-day ICU mortality

Six studies about 2183 patients reported the mortality.[31-36] Overall, HFNC was associated with lower mortality compared to COT (OR = 0.54, 95% CI 0.30 to 0.97, P = 0.04; M-H random; I^2 = 77%, P = 0.0006) (**Figure 3**). The quality of evidence on mortality was thought to be moderate (**Supplemental file: Table S3**).

28-day ventilator-free days

Four studies involving 471 patients evaluated the 28-day ventilator-free days.[31, 34-36] Patients undergoing HFNC had a greater VFDs compared with patients undergoing COT (MD = 2.58, 95% CI 1.70 to 3.45, P < 0.00001; M-H random; I^2 = 0%, P = 0.83) (**Figure 4**). The quality of evidence on 28-day ventilator-free days was thought to be moderate (**Supplemental file: Table S3**).

ICU length of stay

For the 8 studies recruiting 2990 patients,[13, 31, 33-38] HFNC had no effect on ICU LOS compared to COT (MD = 0.52, 95% CI -1.01 to 2.06, P = 0.50; M-H random; I^2 = 80%, P < 0.0001) (**Figure 5**). The quality of evidence on ICU LOS was thought to be very low, due to inconsistency and imprecision (**Supplemental file: Table S3**).

Subgroup analysis

Type of ARF

Subgroup analysis showed that seven trials included patients with AHRF. In five studies including 1785 patients with AHRF due to COVID-19, the HFNC group had a lower intubation rate than the COT group (OR = 0.39, 95% CI 0.26 to 0.58, P < 0.00001; M-H random), with moderate heterogeneity (I^2 = 61%, P = 0.04) (**Supplemental file: Figure S5**). In 28-day ICU mortality, subgroup analysis revealed favored HFNC over COT (OR = 0.49, 95% CI 0.34 to 0.71, P = 0.0002; M-H random; I^2 = 0%, P = 0.43) (**Supplemental file: Figure S6**). Three studies reported VFDs in patients with AHRF, HFNC group had a greater VFDs compared with COT group (MD = 2.53, 95% CI 1.64 to 3.41, P < 0.00001; M-H random; I^2 = 0%, P = 0.92) (**Supplemental file: Figure S7**). However, there was no significant difference between HFNC and COT in ICU LOS (MD = 0.29, 95% CI 1.35 to 1.93, P = 0.73; M-H random; I^2 = 69%, P = 0.006) (**Supplemental file: Figure S8**).

Initial oxygenation index

Six trials included patients with an OI below 200 mmHg. Five studies, including 2126 patients, reported intubation rate in patients with an initial OI below 200 mmHg. The results of the subgroup analysis showed a statistically significant reduction in intubation rate in patients with OI below 200 mmHg treated with HFNC compared to those treated with COT (OR = 0.56, 95% CI 0.38 to 0.83, P = 0.004; M-H random; I^2 = 65%, P =

For peer review only

0.02) (**Supplemental file: Figure S9**). However, there was no significant difference in 28-day ICU mortality between the HFNC and COT groups (OR = 0.56, 95% CI 0.30 to 1.08, P = 0.08; M-H random; I^2 = 79%, P = 0.0008) (Supplemental file: Figure S10). Three studies reported VFDs in patients with an initial OI below 200 mmHg, HFNC group had a greater VFDs compared with COT group (MD = 2.53, 95% CI 1.64 to 3.41, P < 0.00001; M-H random; I^2 = 0%, P = 0.92) (**Supplemental file: Figure S11**). And HFNC also did not reduce the ICU LOS compared to COT (MD = 1.52, 95% CI -0.86 to 3.89, P = 0.21; M-H random; I^2 = 76%, P = 0.002) (**Supplemental file: Figure S12**).

For peer review only

DISCUSSION

A total of nine studies were included in our study, to evaluate the efficacy of HFNC as initial oxygen therapy for patients with ARF due to COVID-19. In this analysis, compared with COT, HFNC reduced intubation rates and 28-day ICU mortality in patients with ARF due to COVID-19 infection, and also improved 28-day VFDs. However, HFNC did not significantly reduce the ICU LOS of patients. In a subgroup analysis of patients with AHRF caused by COVID-19, our meta-analysis showed the same results. HFNC significantly outperformed COT in reducing intubation rates and 28-day ICU mortality, as well as improving the number of 28-day VFDs. In patients with an initial OI below 200 mmHg, although HFNC was associated with lower intubation rates and extended 28-day VFDs, there was no significant difference in 28-day ICU mortality and ICU LOS between HFNC and COT.

Our meta-analysis discovered that HFNC significantly reduced intubation rates compared to COT. Similar results have been observed in other studies. Studies by Ni et al. and Zhao et al.,[39, 40] comparing the efficacy of HFNC and COT in patients with ARF, showed that HFNC was associated with a lower rate of endotracheal intubation. In another study, Rochwerg et al. found that HFNC reduced the rate of intubation in patients with AHRF compared to COT.[15] In a multicenter RCT conducted in France by Frat et al., the leading cause of acute respiratory failure was community-acquired pneumonia (64% of patients were diagnosed with community-acquired pneumonia).[14] They noticed that in the subgroup of patients with OI of 200 mmHg or less, the intubation rate was significantly lower in the HFNC group than in the COT group. These results were similar to the results of our subgroup analysis.

Our study also indicated that HFNC was superior to COT in reducing 28-day ICU mortality and extending the 28-day VFDs, although no significant effect of HFNC in reducing mortality was found in the studies of Ni et al. and Rochwerg et al.[15, 39] However, this could be explained by the complex causes of respiratory failure, as they did not specify the cause of the patient's respiratory failure. In another RCT, HFNC reduced ICU mortality and mortality at day 90, and VFDs were significantly higher in the HFNC group than in the control group.[14] Also in our study, the number of comorbidities (hypertension, diabetes mellitus and COPD) were higher among patients undergoing COT group, which could explain the higher mortality in the COT group.

In terms of ICU LOS, our meta-analysis also indicated that HFNC could not further decrease ICU LOS in adults, similar to the results reported in our subgroup analysis. Numerous factors, especially the concomitant complications such as acute kidney dysfunction and cardiac impairment, may contribute to ICU LOS besides respiratory status itself.[41, 42] In addition, many non-disease factors have significant contribution to ICU LOS.

For peer review only

It is undeniable that medical resources as well as expenditures are tightly related to the disease outcomes, such as bed availability in general wards and insurance status, which to some extent may offset the positive effects of HFNC.

Sensitivity analysis indicated a significant effect on heterogeneity by COVID-ICU group.[33] Several reasons may contribute to its apparent effect on heterogeneity: (1) the study included patients from multiple countries and there may be differences between study centers; (2) the study did not specify the type of ARF, whereas most other studies explicitly included patients with AHRF; (3) the study included patients aged >16 years, while all other studies included patients over 18 years; (4) this study included the largest number of patients, which had a large impact on outcome indicators.

According to our study, HFNC improved intubation rate, 28-day ICU mortality and 28-day VFDs in patients with ARF caused by COVID-19. A study by Sztrymf et al. revealed that HFNC significantly reduced the respiratory rate, heart rate, dyspnea score, supraclavicular retraction and thoracoabdominal asynchrony, and increased pulse oximetry.[43] HFNC is superior to COT, probably due to several reasons. (1) Heated and humidified gas may protect mucosal function and promote secretion clearance, thereby reducing the risk of pulmonary atelectasis.[44, 45] (2) There was a positive linear relationship between flow and airway pressure during HFNC, producing a low-level positive airway pressure effect.[46] This low-level positive airway pressure effect could somewhat reduce anatomical dead space and improve ventilation-perfusion mismatch.[41, 47] (3) Through more adequately matching the patient's respiratory flow demands to reduce the inspiratory resistance associated with the nasopharynx and decrease the risk of patient self-inflicted lung injury.[41, 48] (4) HFNC can deliver predictable and stable FiO_2.[49] (5) HFNC ensures adequate ventilation and sufficient oxygenation through continuous high flow oxygen accompanied by higher tidal volumes and reduced inspiratory resistance.[50-52] (6) HFNC could reduce the intensity of respiratory discomfort and improve the dyspnea score in the patients with ARF.[14]

Strengths and limitations

This meta-analysis was the first to assess the efficacy of HFNC compared to COT in patients with ARF due to COVID-19. An extensive search strategy was developed and all reviews were conducted by at least two reviewers. The quality of the enrolled studies was assessed using appropriate methods, and the methodology of the GRADE Working Group was used to evaluate the overall quality of the evidence for outcomes. Subgroup analysis was also performed to interpret the origin of heterogeneity. TSA was applied to identify the risk of

both type 1 and type 2 error due to sparse data and repetitive testing of accumulating data.

There are several limitations to our meta-analysis. First, despite an extensive literature search, our meta-analysis consisted mainly of cohort studies due to the limited number of relevant randomized controlled trials. Although the quality assessment was passed and the TSA suggested that no further testing was required, it may still affect the accuracy of the results. Therefore, further large-scale RCTs are warranted to confirm our findings. Second, significant differences between HFNC and COT made blinding of participants and personnel difficult, so the performance bias of all included RCTs was all at high risk. Third, despite the random effects model used in our analysis, moderate to high heterogeneity was observed in the results. This may be due to different patient characteristics (such as comorbidities), inconsistent oxygen therapy measures (duration of oxygen therapy, initial flow rate, and oxygen concentration), inconsistent severity of patient ARF, therapeutic measures other than oxygen therapy (e.g., medications), and different follow-up duration. Meanwhile, the definition of outcomes may vary from study to study, such as the choice of timing of intubation, which can also increase heterogeneity. Subgroup analysis and sensitivity analysis partially explained the source of heterogeneity.

For peer review only

CONCLUSION

Overall, HFNC reduced intubation rate and 28-day ICU mortality in patients with ARF due to COVID-19 and improved 28-day ventilator-free days compared with COT. However, it did not reduce the ICU length of stay. To validate our finding, large-scale randomized controlled trials are necessary.

For peer review only

Contributors YL and LL contributed to the conception and design of the study. YL, CL and WC made substantial contributions to literature search, data collection, statistical analysis and the original drafting and revising of the manuscript. LL provided daily assistance and professional comments on the manuscript. All authors read and approved of the final manuscript for publication.

Funding: This work was funded by National Natural Science Foundation of China [Grant numbers 81870066, 81930058], Clinical Science and Technology Specific Projects of Jiangsu Province (Grant number. BE2020786).

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication: Patient consent was not required as the data were obtained from previously published papers in the public domain.

Ethics approval: Ethical approval was not required as the data were obtained from previously published papers in the public domain.

Data availability statement: The access policy and procedures are available at https://datadryad.org/stash/share/_mR-3750nia5YWsl4MAd8j8k0Bg8gMJQ6TzpH91oWxI

For peer review only

REFERENCE

1 Geneva World Health Organization. COVID-19 Weekly Epidemiological Update Edition 98. Available from: www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---29-june-2022 accessed 06/30 2022.

2 Huang C, Wang Y, Li X*, et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;10223:497-506.

3 Wang D, Hu B, Hu C*, et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama* 2020;11:1061-69.

4 Curley GF, Laffey JG, Zhang H*, et al.* Biotrauma and Ventilator-Induced Lung Injury: Clinical Implications. *Chest* 2016;5:1109-17.

5 Oliveira J, Zagalo C, Cavaco-Silva P. Prevention of ventilator-associated pneumonia. *Rev Port Pneumol* 2014;3:152-61.

6 Guan WJ, Zhong NS. Clinical Characteristics of Covid-19 in China. Reply. *N Engl J Med* 2020;19:1861-62.

7 Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *Jama* 2020;13:1239-42.

8 Richardson S, Hirsch JS, Narasimhan M*, et al.* Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama* 2020;20:2052-59.

9 Tobin MJ. Basing Respiratory Management of COVID-19 on Physiological Principles. *Am J Respir Crit Care Med* 2020;11:1319-20.

10 Geneva World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Available from: www.who.int/publications/i/item/10665-

For peer review only

332299 accessed 06/30 2022.

11 Confalonieri M, Potena A, Carbone G, *et al.* Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med* 1999;5 Pt 1:1585-91.

12 Nishimura M. High-flow nasal cannula oxygen therapy in adults. *J Intensive Care* 2015;1:15.

13 Teng XB, Shen Y, Han MF, *et al.* The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. *European journal of clinical investigation* 2021;3:e13435.

14 Frat JP, Thille AW, Mercat A, *et al.* High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;23:2185-96.

15 Rochwerg B, Granton D, Wang DX, *et al.* High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. *Intensive Care Med* 2019;5:563-72.

16 Azoulay E, Lemiale V, Mokart D, *et al.* Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure: The HIGH Randomized Clinical Trial. *Jama* 2018;20:2099-107.

17 Alhazzani W, Møller MH, Arabi YM, *et al.* Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020;5:854-87.

18 Stewart LA, Clarke M, Rovers M, *et al.* Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *Jama* 2015;16:1657-65.

19 Higgins JP, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011:d5928.

20 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of

For peer review only

nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;9:603-5.

21 Wells GA SB OCD, Peterson J, Welch V , Losos M, et al. NewCastle-Ottawa Quality Assessment Scale. 2013

22 Egger M, Davey Smith G, Schneider M*, et al.* Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997;7109:629-34.

23 Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics* 2018;3:785-94.

24 Guyatt GH, Oxman AD, Kunz R*, et al.* Going from evidence to recommendations. *Bmj* 2008;7652:1049-51.

25 Higgins JP, Thompson SG, Deeks JJ*, et al.* Measuring inconsistency in meta-analyses. *Bmj* 2003;7414:557-60.

26 Pereira TV, Patsopoulos NA, Salanti G*, et al.* Critical interpretation of Cochran's Q test depends on power and prior assumptions about heterogeneity. *Res Synth Methods* 2010;2:149-61.

27 Luo D, Wan X, Liu J*, et al.* Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;6:1785-805.

28 Wan X, Wang W, Liu J*, et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014:135.

29 Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol* 2017;1:39.

30 Thorlund K EJ, Wetterslev J, Brok J, Imberger G, Gluud , C. User manual for trial sequential analysis (TSA) *Copenhagen: Copenhagen Trial Unit, Centre for Clinical Intervention Research; 2011 [cited 2021 Dec 10]*

31 Bonnet N, Martin O, Boubaya M*, et al.* High flow nasal oxygen therapy to avoid invasive mechanical ventilation in SARS-CoV-2 pneumonia: a retrospective study. *Annals of Intensive Care* 2021;1

For peer review only

32 Demoule A, Baron AV, Darmon M, *et al.* High-Flow Nasal Cannula in Critically Ill Patients with Severe COVID-19. *American Journal of Respiratory and Critical Care Medicine* 2020;7:1039-42.

33 Schmidt M, Demoule A, Hajage D, *et al.* Benefits and risks of noninvasive oxygenation strategy in COVID-19: a multicenter, prospective cohort study (COVID-ICU) in 137 hospitals. *Critical Care* 2021;1

34 Hansen CK, Stempek S, Liesching T, *et al.* Characteristics and outcomes of patients receiving high flow nasal cannula therapy prior to mechanical ventilation in COVID-19 respiratory failure: A prospective observational study. *Int J Crit Illn Inj Sci* 2021;2:56-60.

35 Ospina-Tascón GA, Calderón-Tapia LE, García AF, *et al.* Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: a Randomized Clinical Trial. *JAMA* 2021;21:2161-71.

36 Sayan İ, Altınay M, Çınar AS, *et al.* Impact of HFNC application on mortality and intensive care length of stay in acute respiratory failure secondary to COVID-19 pneumonia. *Heart Lung* 2021;3:425-29.

37 Wendel Garcia PD, Aguirre-Bermeo H, Buehler PK, *et al.* Implications of early respiratory support strategies on disease progression in critical COVID-19: a matched subanalysis of the prospective RISC-19-ICU cohort. *Critical Care* 2021;1

38 Wendel-Garcia PD, Mas A, González-Isern C, *et al.* Non-invasive oxygenation support in acutely hypoxemic COVID-19 patients admitted to the ICU: a multicenter observational retrospective study. *Critical Care* 2022;1

39 Ni YN, Luo J, Yu H, *et al.* Can High-flow Nasal Cannula Reduce the Rate of Endotracheal Intubation in Adult Patients With Acute Respiratory Failure Compared With Conventional Oxygen Therapy and Noninvasive Positive Pressure Ventilation?: A Systematic Review and Meta-analysis. *Chest* 2017;4:764-75.

For peer review only

40 Zhao H, Wang H, Sun F, *et al.* High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: a systematic review and meta-analysis. *Crit Care* 2017;1:184.

41 Dysart K, Miller TL, Wolfson MR, *et al.* Research in high flow therapy: mechanisms of action. *Respir Med* 2009;10:1400-5.

42 Marshall JC, Cook DJ, Christou NV, *et al.* Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995;10:1638-52.

43 Sztrymf B, Messika J, Bertrand F, *et al.* Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. *Intensive Care Med* 2011;11:1780-6.

44 Kernick J, Magarey J. What is the evidence for the use of high flow nasal cannula oxygen in adult patients admitted to critical care units? A systematic review. *Aust Crit Care* 2010;2:53-70.

45 Li G, Cook DJ, Thabane L, *et al.* Risk factors for mortality in patients admitted to intensive care units with pneumonia. *Respir Res* 2016;1:80.

46 Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during nasal high-flow oxygen therapy. *Respir Care* 2011;8:1151-5.

47 Ritchie JE, Williams AB, Gerard C, *et al.* Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. *Anaesth Intensive Care* 2011;6:1103-10.

48 Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. *Am J Respir Crit Care Med* 2017;4:438-42.

49 Wagstaff TA, Soni N. Performance of six types of oxygen delivery devices at varying respiratory rates. *Anaesthesia* 2007;5:492-503.

For peer review only

50 Frizzola M, Miller TL, Rodriguez ME*, et al.* High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. *Pediatr Pulmonol* 2011;1:67-74.

51 Jones PG, Kamona S, Doran O*, et al.* Randomized Controlled Trial of Humidified High-Flow Nasal Oxygen for Acute Respiratory Distress in the Emergency Department: The HOT-ER Study. *Respir Care* 2016;3:291-9.

52 Mündel T, Feng S, Tatkov S*, et al.* Mechanisms of nasal high flow on ventilation during wakefulness and sleep. *J Appl Physiol (1985)* 2013;8:1058-65.

For peer review only

Figure 1 PRISMA flow diagram of search strategy and included studies.

Figure 2 Forest plot for intubation rate.

HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; CI, confidence interval.

Figure 3 Forest plot for mortality.

HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; CI, confidence interval.

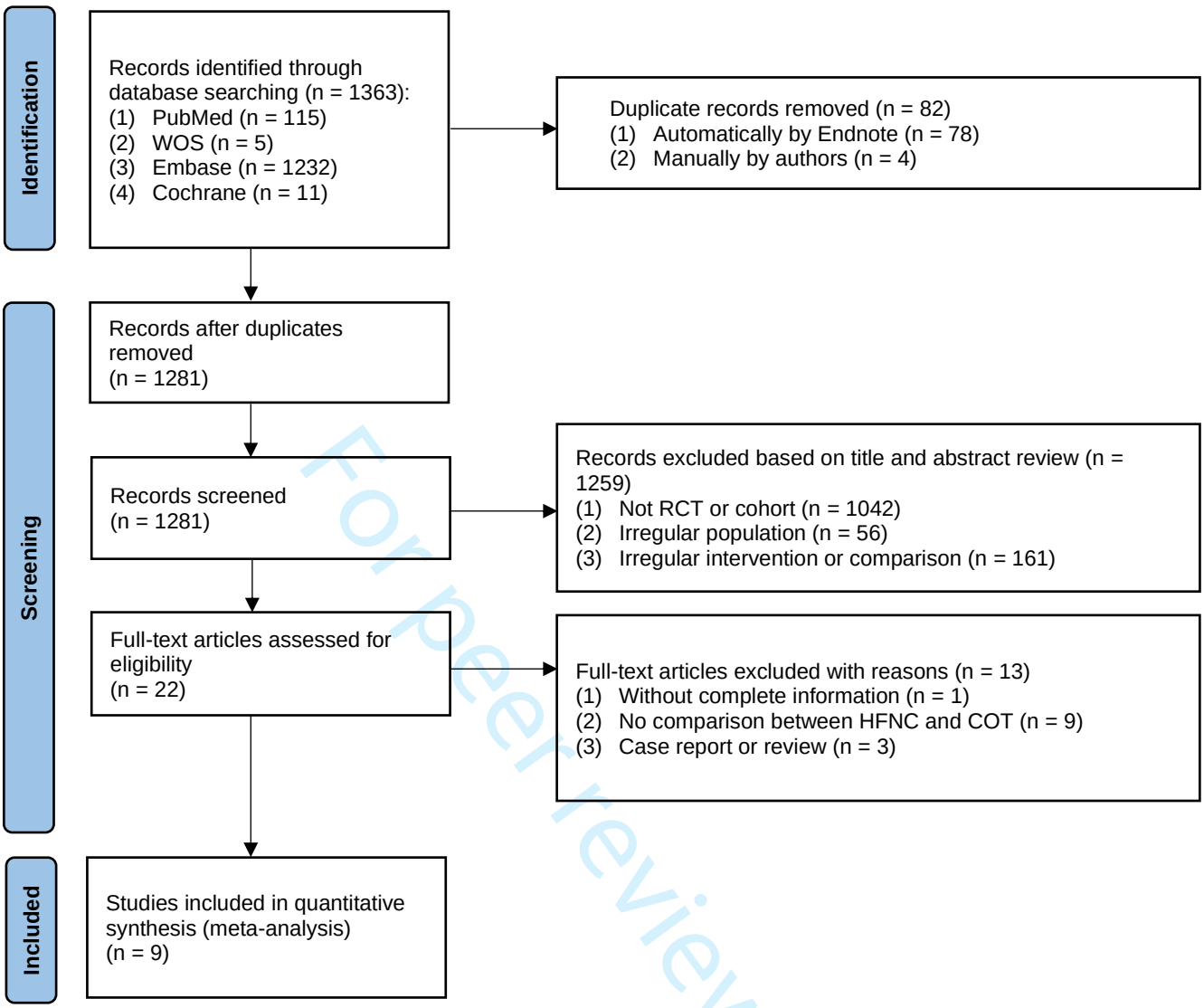
Figure 4 Forest plot for VFDs.

HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; CI, confidence interval; VFDs, ventilator free days.

Figure 5 Forest plot for ICU LOS.

HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; CI, confidence interval; ICU, intensive care unit; LOS, length of stay.

For peer review only

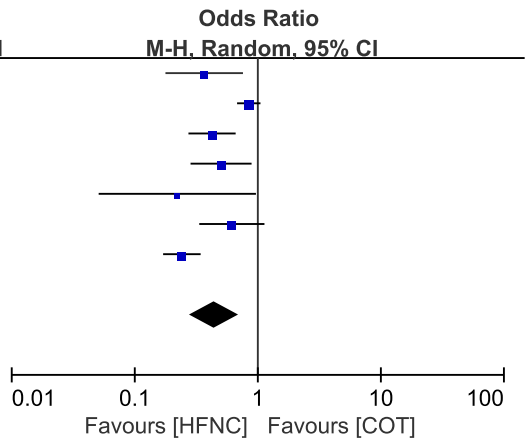


For peer review only

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bonnet 2021	39	76	46	62	13.0%	0.37 [0.18, 0.76]
COVID-ICU group 2021	242	567	359	766	18.1%	0.84 [0.68, 1.05]
Demoule 2020	82	146	175	233	16.2%	0.42 [0.27, 0.66]
Ospina-Tascón 2021	34	99	51	100	14.7%	0.50 [0.28, 0.89]
Sayan 2021	13	24	16	19	6.6%	0.22 [0.05, 0.97]
Wendel Garcia 2021	45	87	54	85	14.3%	0.62 [0.33, 1.13]
Wendel Garcia 2022	307	439	501	553	17.1%	0.24 [0.17, 0.34]
Total (95% CI)		**1438**		**1818**	**100.0%**	**0.44 [0.28, 0.71]**
Total events	762		1202			

Heterogeneity: Tau² = 0.30; Chi² = 40.12, df = 6 (P < 0.00001); I² = 85%

Test for overall effect: Z = 3.40 (P = 0.0007)

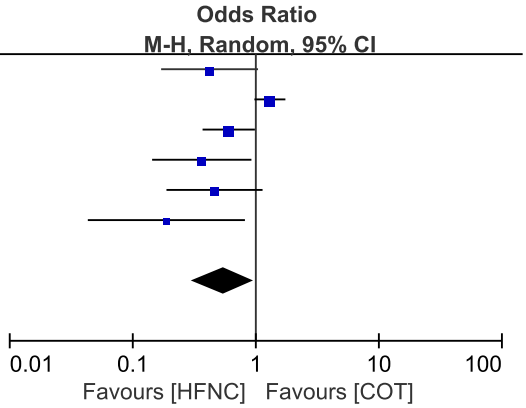


For peer review only

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bonnet 2021	9	76	15	62	15.4%	0.42 [0.17, 1.04]
COVID-ICU group 2021	106	567	115	766	23.2%	1.30 [0.97, 1.74]
Demoule 2020	30	146	70	233	21.0%	0.60 [0.37, 0.98]
Hansen 2021	9	30	33	61	15.2%	0.36 [0.14, 0.92]
Ospina-Tascón 2021	8	99	16	100	15.5%	0.46 [0.19, 1.13]
Sayan 2021	12	24	16	19	9.6%	0.19 [0.04, 0.82]
Total (95% CI)		**942**		**1241**	**100.0%**	**0.54 [0.30, 0.97]**
Total events	174		265			

Heterogeneity: Tau² = 0.36; Chi² = 21.57, df = 5 (P = 0.0006); I² = 77%

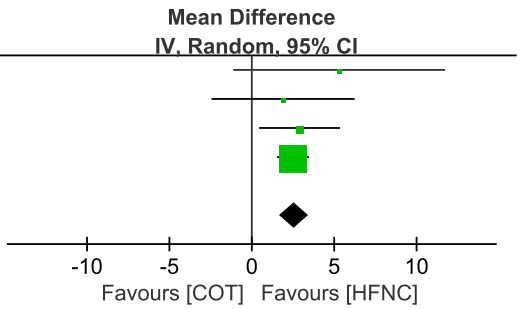
Test for overall effect: Z = 2.06 (P = 0.04)



For peer review only

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI
Bonnet 2021	17.8	17.4	76	12.5	20.5	62	1.8%	5.30 [-1.13, 11.73]
Hansen 2021	5.4	10.9	30	3.5	7.6	61	4.1%	1.90 [-2.44, 6.24]
Ospina-Tascón 2021	24.8	6.8	99	21.9	10.5	100	12.7%	2.90 [0.44, 5.36]
Sayan 2021	4.4	2.2	24	1.9	0.9	19	81.4%	2.50 [1.53, 3.47]
Total (95% CI)			**229**			**242**	**100.0%**	**2.58 [1.70, 3.45]**

Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 5.78 (P < 0.00001)

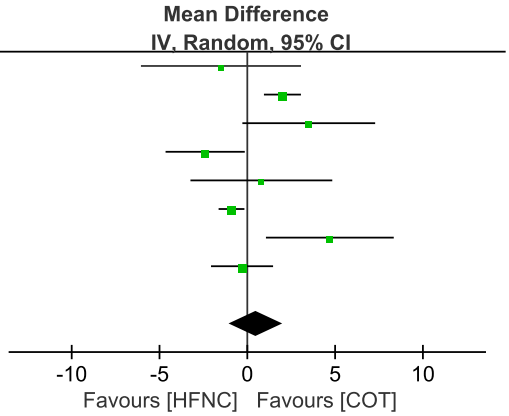


For peer review only

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI
Bonnet 2021	12.1	11.3	76	13.6	15.2	62	7.2%	-1.50 [-6.06, 3.06]
COVID-ICU group 2021	10.8	9.7	567	8.8	9.7	766	18.0%	2.00 [0.95, 3.05]
Hansen 2021	18	8.2	30	14.5	9.5	61	9.0%	3.50 [-0.28, 7.28]
Ospina-Tascón 2021	8.4	6	99	10.8	9.8	100	13.8%	-2.40 [-4.66, -0.14]
Sayan 2021	9.8	4.8	24	9	7.9	19	8.3%	0.80 [-3.24, 4.84]
Teng 2021	4	0.7	12	4.9	1	10	18.8%	-0.90 [-1.64, -0.16]
Wendel Garcia 2021	14.4	13.6	87	9.7	10.6	85	9.3%	4.70 [1.06, 8.34]
Wendel Garcia 2022	15.5	14.1	439	15.8	14.1	553	15.6%	-0.30 [-2.07, 1.47]
Total (95% CI)			**1334**			**1656**	**100.0%**	**0.52 [-1.01, 2.06]**

Heterogeneity: Tau² = 3.12; Chi² = 34.31, df = 7 (P < 0.0001); I² = 80%

Test for overall effect: Z = 0.67 (P = 0.50)



For peer review only

Table S1 – Search strategy

Database: PubMed

((("Cannula"[Mesh]) OR ((((((Cannula[Title/Abstract]) OR (Cannulae[Title/Abstract])) OR (Nasal Cannula[Title/Abstract])) OR (Cannula, Nasal[Title/Abstract])) OR (Nasal Cannulae[Title/Abstract])) OR (Cannulae, Nasal[Title/Abstract]))) AND (("COVID-19"[Mesh]) OR ((((((((((((((((((((((((((((((((((((((COVID-19[Title/Abstract]) OR (COVID 19[Title/Abstract])) OR (SARS-CoV-2 Infection[Title/Abstract])) OR (Infection, SARS-CoV-2[Title/Abstract])) OR (SARS CoV 2 Infection[Title/Abstract])) OR (SARS-CoV-2 Infections[Title/Abstract])) OR (2019 Novel Coronavirus Disease[Title/Abstract])) OR (2019 Novel Coronavirus Infection[Title/Abstract])) OR (2019-nCoV Disease[Title/Abstract])) OR (2019 nCoV Disease[Title/Abstract])) OR (2019-nCoV Diseases[Title/Abstract])) OR (Disease, 2019-nCoV[Title/Abstract])) OR (COVID-19 Virus Infection[Title/Abstract])) OR (COVID 19 Virus Infection[Title/Abstract])) OR (COVID-19 Virus Infections[Title/Abstract])) OR (Infection, COVID-19 Virus[Title/Abstract])) OR (Virus Infection, COVID-19[Title/Abstract])) OR (Coronavirus Disease 2019[Title/Abstract])) OR (Disease 2019, Coronavirus[Title/Abstract])) OR (Coronavirus Disease-19[Title/Abstract])) OR (Coronavirus Disease 19[Title/Abstract])) OR (Severe Acute Respiratory Syndrome Coronavirus 2 Infection[Title/Abstract])) OR (SARS Coronavirus 2 Infection[Title/Abstract])) OR (COVID-19 Virus Disease[Title/Abstract])) OR (COVID 19 Virus Disease[Title/Abstract])) OR (COVID-19 Virus Diseases[Title/Abstract])) OR (Disease, COVID-19 Virus[Title/Abstract])) OR (Virus Disease, COVID-19[Title/Abstract])) OR (2019-nCoV Infection[Title/Abstract])) OR (2019 nCoV Infection[Title/Abstract])) OR (2019-nCoV Infections[Title/Abstract])) OR (Infection, 2019-nCoV[Title/Abstract])) OR (COVID19[Title/Abstract])) OR (COVID-19 Pandemic[Title/Abstract])) OR (COVID 19 Pandemic[Title/Abstract])) OR (Pandemic, COVID-19[Title/Abstract])) OR (COVID-19 Pandemics[Title/Abstract])))) AND (("Oxygen Inhalation Therapy"[Mesh]) OR ((((((Oxygen Inhalation Therapy[Title/Abstract]) OR (Inhalation Therapy, Oxygen[Title/Abstract])) OR (Inhalation Therapies, Oxygen[Title/Abstract])) OR (Oxygen Inhalation Therapies[Title/Abstract])) OR (Therapies, Oxygen Inhalation[Title/Abstract])) OR (Therapy, Oxygen Inhalation[Title/Abstract])))

Database: Embase

#17. #12 AND #15 AND #16

#16. #3 OR #6 OR #9

#15. #13 OR #14

#14. 'oxygen therapy':ab,ti OR 'o2 administration':ab,ti OR 'o2 therapy':ab,ti OR 'oxygen administration':ab,ti OR 'oxygen inhalation therapy':ab,ti OR 'oxygen insufflation':ab,ti OR 'oxygen treatment':ab,ti

#13. 'oxygen therapy'/exp

#12. #10 OR #11

#11. 'coronavirus disease 2019':ab,ti OR '2019 novelcoronavirus disease':ab,ti OR '2019 novel coronavirus epidemic':ab,ti OR '2019 novel coronavirus infection':ab,ti OR '2019-ncov disease':ab,ti OR '2019-ncov infection':ab,ti OR 'coronavirus disease 2':ab,ti OR 'coronavirus disease 2010':ab,ti OR 'coronavirus disease 2019 pneumonia':ab,ti OR 'coronavirus disease-19':ab,ti OR 'coronavirus infection 2019':ab,ti OR covid:ab,ti OR 'covid 19 induced pneumonia':ab,ti OR 'covid 2019':ab,ti OR 'covid 10':ab,ti OR 'covid 19':ab,ti OR 'covid-19 induced pneumonia':ab,ti OR 'covid-19 pneumonia':ab,ti OR covid19:ab,ti OR 'ncov 2019 disease':ab,ti OR 'ncov 2019 infection':ab,ti OR 'new coronavirus pneumonia':ab,ti OR 'novel coronavirus 2019 disease':ab,ti

For peer review only

OR 'novel coronavirus 2019 infection':ab,ti OR 'novel coronavirus disease 2019':ab,ti OR 'novel coronavirus infected pneumonia':ab,ti OR 'novel coronavirus infection 2019':ab,ti OR 'novel coronavirus pneumonia':ab,ti OR 'paucisymptomatic coronavirus disease 2019':ab,ti OR 'sars coronavirus 2 infection':ab,ti OR 'sars coronavirus 2 pneumonia':ab,ti OR 'sars-cov-2 disease':ab,ti OR 'sars-cov-2 infection':ab,ti OR 'sars-cov-2 pneumonia':ab,ti OR 'sars-cov2 disease':ab,ti OR 'sars-cov2 infection':ab,ti OR 'sarscov2 disease':ab,ti OR 'sarscov2 infection':ab,ti OR 'severe acute respiratory syndrome 2':ab,ti OR 'severe acute respiratory syndrome 2 pneumonia':ab,ti OR 'severe acute respiratory syndrome coronavirus 2 infection':ab,ti OR 'severe acute respiratory syndrome coronavirus 2019 infection':ab,ti OR 'severe acute respiratory syndrome cov-2 infection':ab,ti OR 'wuhan coronavirus disease':ab,ti OR 'wuhan coronavirus infection':ab,ti

#10. 'coronavirus disease 2019'/exp

#9. #7 OR #8

#8. (((('high flow nasal cannula therapy':ab,ti OR 'hfoxygen therapy':ab,ti OR hfnc:ab,ti) AND 'high flow nasal cannula':ab,ti OR 'hfnc assisted ventilation':ab,ti OR 'hfnc therapy':ab,ti OR 'hfnc ventilation':ab,ti OR hfnct:ab,ti) AND 'high flow nasal cannula therapy':ab,ti OR 'high flow nasal cannula':ab,ti OR 'high flow nasal cannula respiratory support':ab,ti OR 'high flow nasal canula':ab,ti OR 'high flow nasal prong therapy':ab,ti OR 'high flow nasal therapy':ab,ti OR 'high flow oxygenation therapy':ab,ti OR 'high flow':ab,ti) AND hf:ab,ti AND 'oxygen therapy':ab,ti OR 'high-flow oxygen therapy':ab,ti OR 'high-flow oxygen treatment':ab,ti OR 'highflow nasal cannula':ab,ti OR 'highflow nasal cannula therapy':ab,ti OR 'nasal high flow':ab,ti

#7. 'high flow nasal cannula therapy'/exp

#6. #4 OR #5

#5. 'oxygen nasal cannula':ab,ti OR 'acucarehfnc':ab,ti OR 'basic nasal oxygen cannula':ab,ti OR 'basic nasal oxygen delivery catheter':ab,ti OR 'basic oxygen nasal cannula':ab,ti OR 'carbon dioxide sampling cannula':ab,ti OR 'carbon dioxide sampling nasal oxygen cannula':ab,ti OR 'carbon-dioxide-sampling nasal oxygen cannula':ab,ti OR 'cpap nasal oxygen cannula':ab,ti OR 'dispo med':ab,ti OR 'kentron capnography':ab,ti OR 'nasal oxygen cannulae':ab,ti OR 'nasal oxygen delivery catheter':ab,ti OR 'niv linemicrostream':ab,ti OR 'oxygen delivery nasal catheter':ab,ti

#4. 'oxygen nasal cannula'/exp

#3. #1 OR #2

#2. 'nasal cannula':ab,ti OR filterline:ab,ti OR'nasal canula':ab,ti OR 'nasal tube':ab,ti OR 'nose cannula':ab,ti OR 'nose tube':ab,ti OR 'optiflow nasal cannula':ab,ti OR 'pro-flow nasal cannula':ab,ti OR 'smart capnoline':ab,ti

Database: Web of Science

#1 TS=(Cannula) 20941

#2 AB=(Cannula OR Cannulae OR (Nasal Cannula) OR (Cannula, Nasal) OR (Nasal Cannulae) OR (Cannulae, Nasal)) 16968

#3 #1 OR #2 20941

#4 TS=(COVID-19) 272414

#5 AB=((COVID-19) OR (COVID 19) OR (SARS-CoV-2 Infection) OR (Infection, SARS-CoV-2) OR (SARS CoV 2 Infection) OR (SARS-CoV-2 Infections) OR (2019 Novel Coronavirus Disease) OR (2019 Novel Coronavirus Infection) OR (2019-nCoV Disease) OR (2019 nCoV Disease) OR (2019-nCoV Diseases) OR (Disease, 2019-nCoV) OR (COVID-19 Virus Infection) OR (COVID 19 Virus Infection) OR (COVID-19 Virus Infections) OR (Infection, COVID-19 Virus) OR (Virus Infection, COVID-19) OR (Coronavirus Disease 2019) OR (Disease 2019, Coronavirus) OR (Coronavirus Disease-19) OR (Coronavirus Disease 19) OR (Severe

For peer review only

Acute Respiratory Syndrome Coronavirus 2 Infection) OR (SARS Coronavirus 2 Infection) OR (COVID-19 Virus Disease) OR (COVID 19 Virus Disease) OR (COVID-19 Virus Diseases) OR (Disease, COVID-19 Virus) OR (Virus Disease, COVID-19) OR (2019-nCoV Infection) OR (2019 nCoV Infection) OR (2019-nCoV Infections) OR (Infection, 2019-nCoV) OR (COVID19) OR (COVID-19 Pandemic) OR (COVID 19 Pandemic) OR (Pandemic, COVID-19) OR (COVID-19 Pandemics)) 198041

#6 #4 OR #5 278439

#7 TS=(Oxygen Inhalation Therapy) 1367

#8 AB=((Oxygen Inhalation Therapy) OR (Inhalation Therapy, Oxygen) OR (Inhalation Therapies, Oxygen) OR (Oxygen Inhalation Therapies) OR (Therapies, Oxygen Inhalation) OR (Therapy, Oxygen Inhalation)) 613

#9 #7 OR #8 1367

#10 #3 AND #6 AND #9 5

Database: Cochrane Library

#1 MeSH descriptor: [Cannula] explode all trees

#2 (Cannula or Cannulae or Nasal Cannula or Cannula, Nasal or Nasal Cannulae or Cannulae, Nasal):ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [COVID-19] explode all trees

#5 (COVID-19 or COVID 19 or SARS-CoV-2 Infection or Infection, SARS-CoV-2 or SARS CoV 2 Infection or SARS-CoV-2 Infections or 2019 Novel Coronavirus Disease or 2019 Novel Coronavirus Infection or 2019 nCoV Disease or COVID-19 Virus Infection or COVID 19 Virus Infection or COVID-19 Virus Infections or Infection, COVID-19 Virus or Virus Infection, COVID-19 or Coronavirus Disease 2019 or Disease 2019, Coronavirus or Coronavirus Disease-19 or Coronavirus Disease 19 or Severe Acute Respiratory Syndrome Coronavirus 2 Infection or SARS Coronavirus 2 Infection or COVID-19 Virus Disease or COVID 19 Virus Disease or COVID-19 Virus Diseases or Disease, COVID-19 Virus or Virus Disease, COVID-19 or 2019 nCoV Infection or COVID19 or COVID-19 Pandemic or COVID 19 Pandemic or Pandemic, COVID-19 or COVID-19 Pandemics):ti,ab,kw (Word variations have been searched)

#6 #4 or #5

#7 MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees

#8 (Oxygen Inhalation Therapy or Inhalation Therapy, Oxygen or Inhalation Therapies, Oxygen or Oxygen Inhalation Therapies or Therapies, Oxygen Inhalation or Therapy, Oxygen Inhalation):ti,ab,kw (Word variations have been searched)

#9 #7 or #8

#10 #3 and #6 and #9

Table S2 Methodological quality (cohort studies)

Study	Selection				Comparability	Outcome			Overall quality assessment
	Representativeof exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of cohorts based on design and analysis	Assessment of outcome	Timing of follow-up	Adequate follow-up	
Bonnet, 2021	★	★	★	★	★	★	★	★	8
COVID-ICU group, 2021	★	★	★	★	★	★	★	★	8
Demoule, 2020	★	★	★	★	★	★	★	★	8
Hansen, 2021	★	★	★	★	★	★	★	★	8
Sayan, 2021	★	★	★	★	★	★	★	★	8
Wendel Garcia, 2021	★	★	★	★	★	★	★	★	8
Wendel Garcia, 2022	★	★	★	★	★	★	★	★	8

Peer review only

Table S3 GRADE evidence profile for the studies in the meta-analysis

Outcomes	No. of studies	Study design	Quality assessment					No. of patients		Effect		Evidence quality	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	HFNC	COT	Relative (95% CI)	Absolute (95% CI)		
IR	7	1 RCT, 6 Cohort	Not serious	Serious [a]	Not serious	Not serious	NA [b]	762/1438	1202/1818	OR 0.44 (0.28, 0.71)	199 fewer per 1,000 (from 80 fewer to 308 fewer)	Low	CRITICAL
M	6	1RCT, 5 Cohort	Not serious	Not serious	Not serious	Not serious	NA [b]	174/942	265/1241	OR 0.54 (0.30, 0.97)	76 fewer per 1,000 (from 5 fewer to 138 fewer)	Moderate	CRITICAL
VFD	4	1 RCT, 3 Cohort	Not serious	Not serious	Not serious	Not serious	NA [b]	229	242	_	MD 2.58 higher (1.7 to 3.45 higher)	Moderate	IMPORTANT
LOS	8	2 RCT, 6 Cohort	Not serious	Serious [c]	Not serious	Serious [d]	NA [b]	1334	1656	_	MD 0.52 higher (1.01 lower to 2.06 higher)	Very low	IMPORTANT

HFNC: high flow nasal cannula, COT: conventional oxygen therapy, CI: confidence interval, OR: odds ratio, MD: mean difference

NA: not applicable

a. I2=85%, the heterogeneity was high

b. Publication bias could not be determined as the number of studies was less than 10

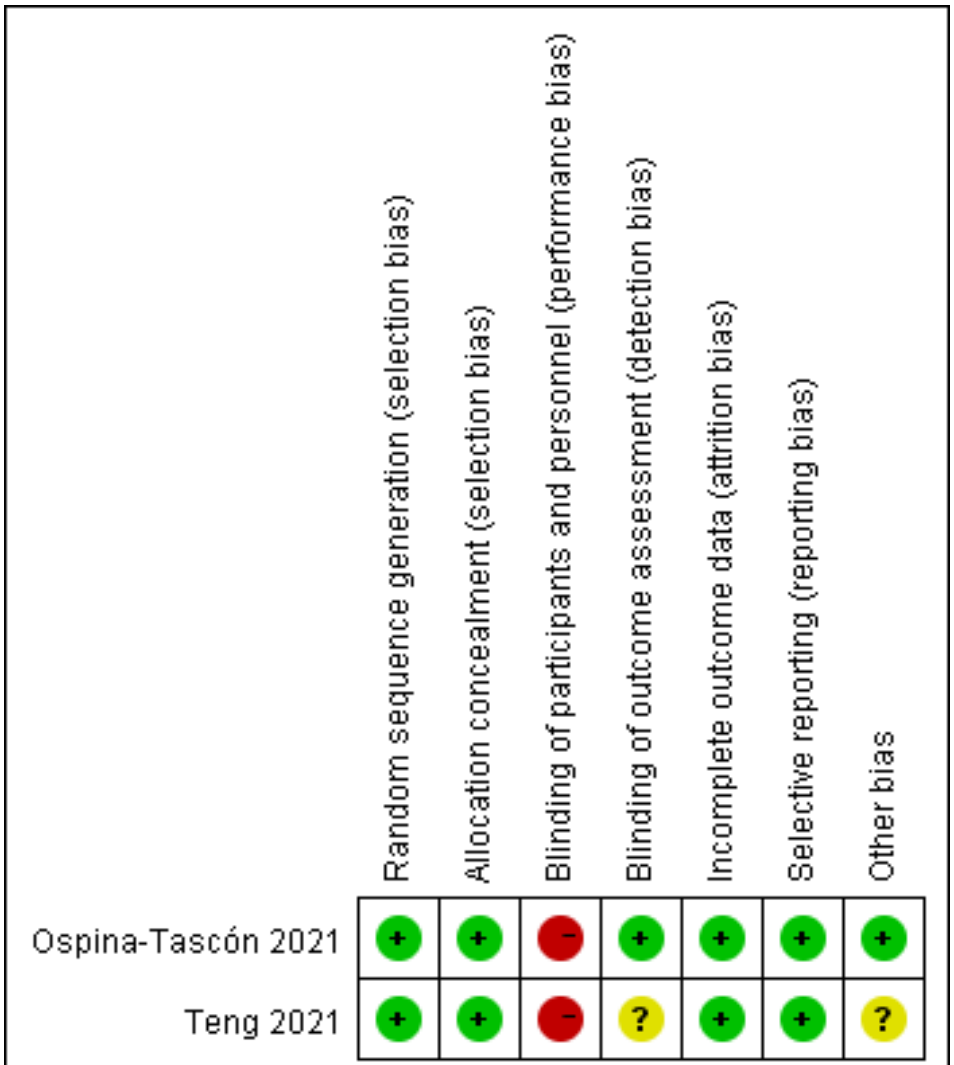
c. I2=80%, the heterogeneity was high

d. Wide confidence interval including benefits and harms

For peer review only

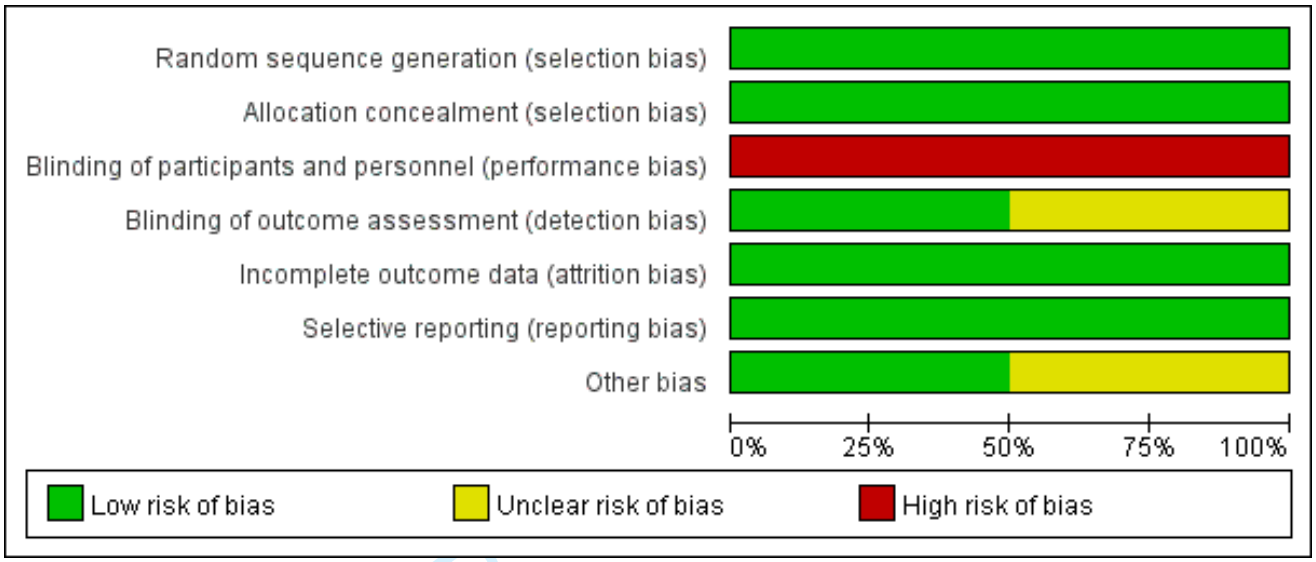
http://bmjopen.bmj.com/bmjopen-2022-067879 on 30 March 2023. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

Figure S1 Risk of bias graph



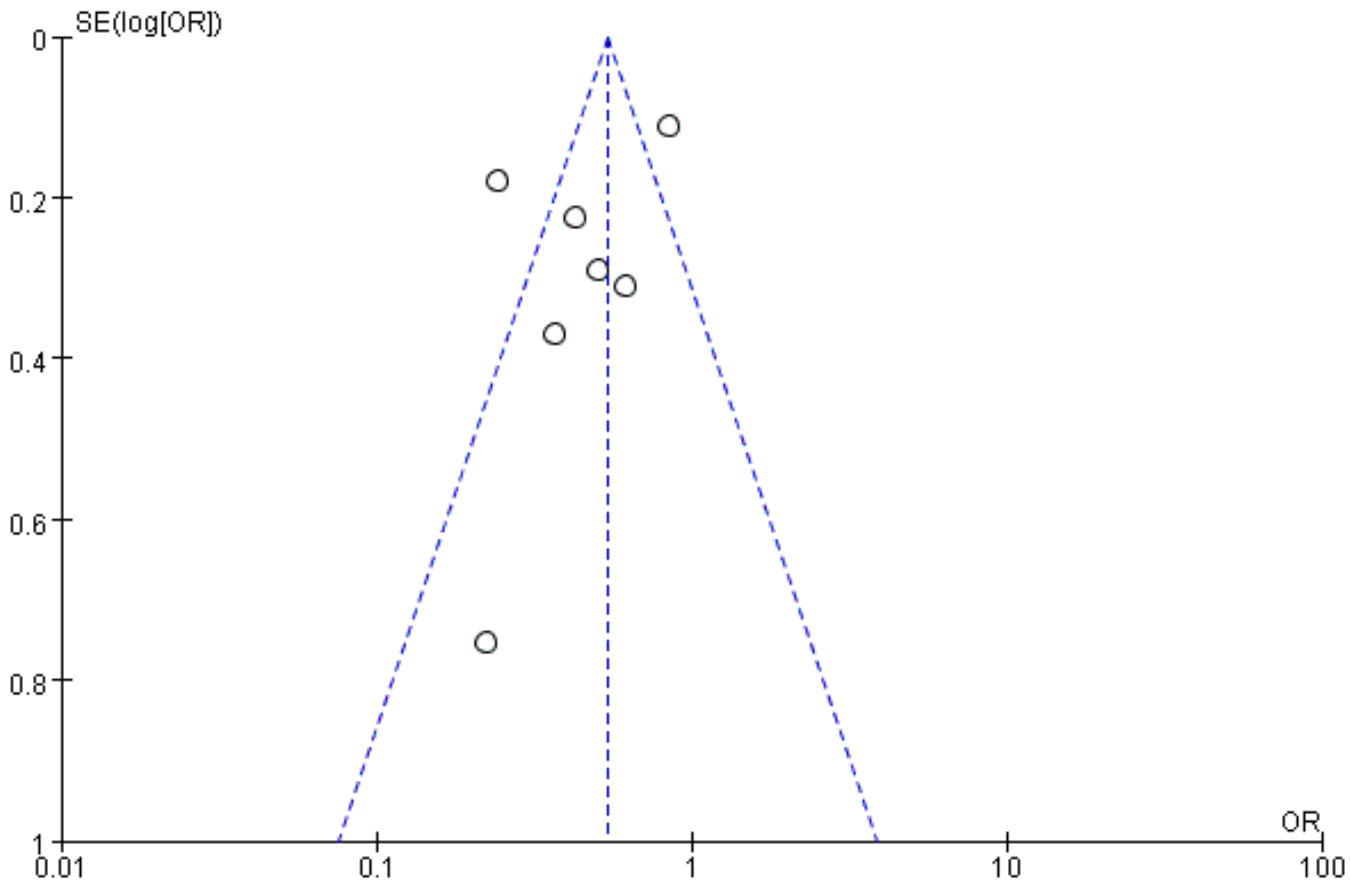
For peer review only

Figure S2 Risk of bias summary



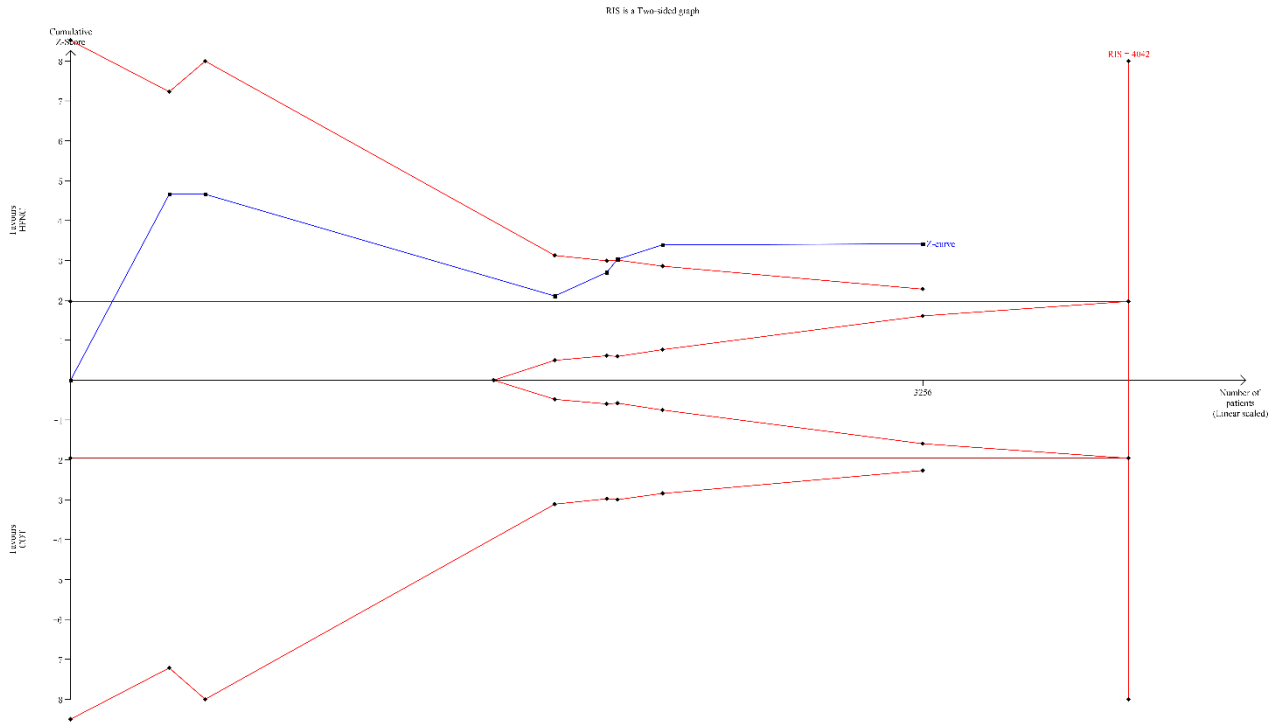
peer review only

Figure S3 Funnel plot for intubation rate



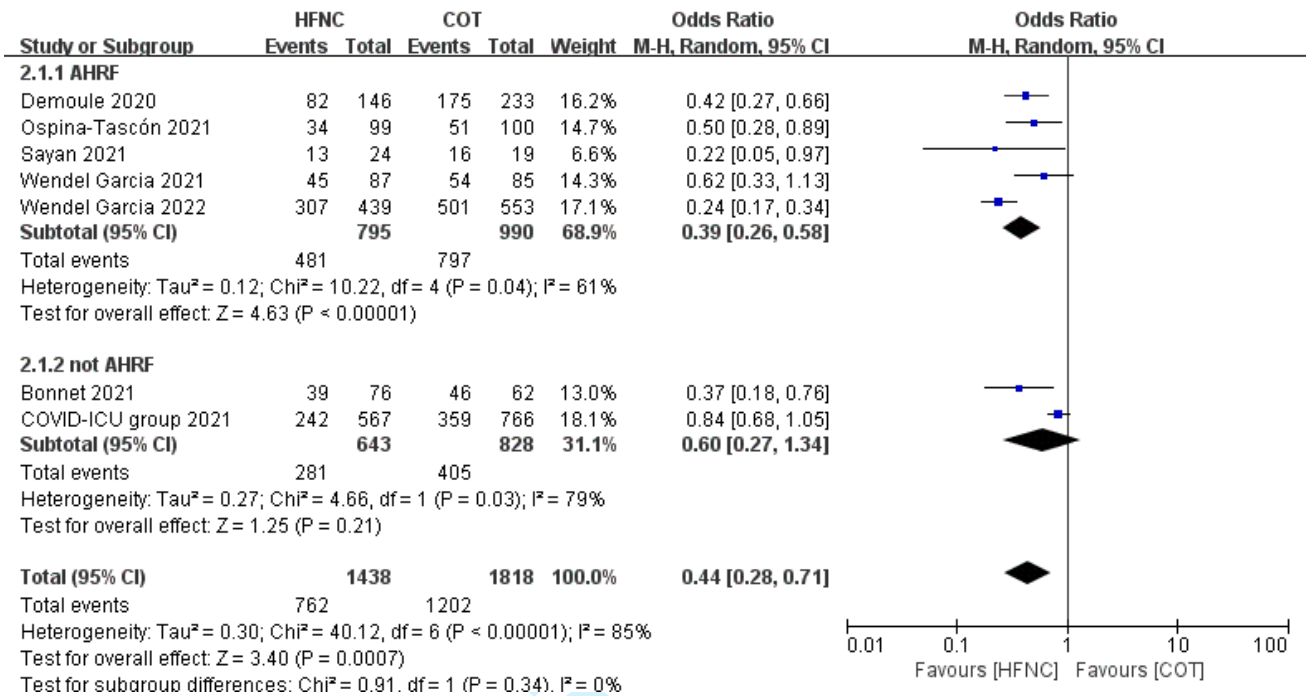
For peer review only

Figure S4 Trial sequential analysis of weaning success



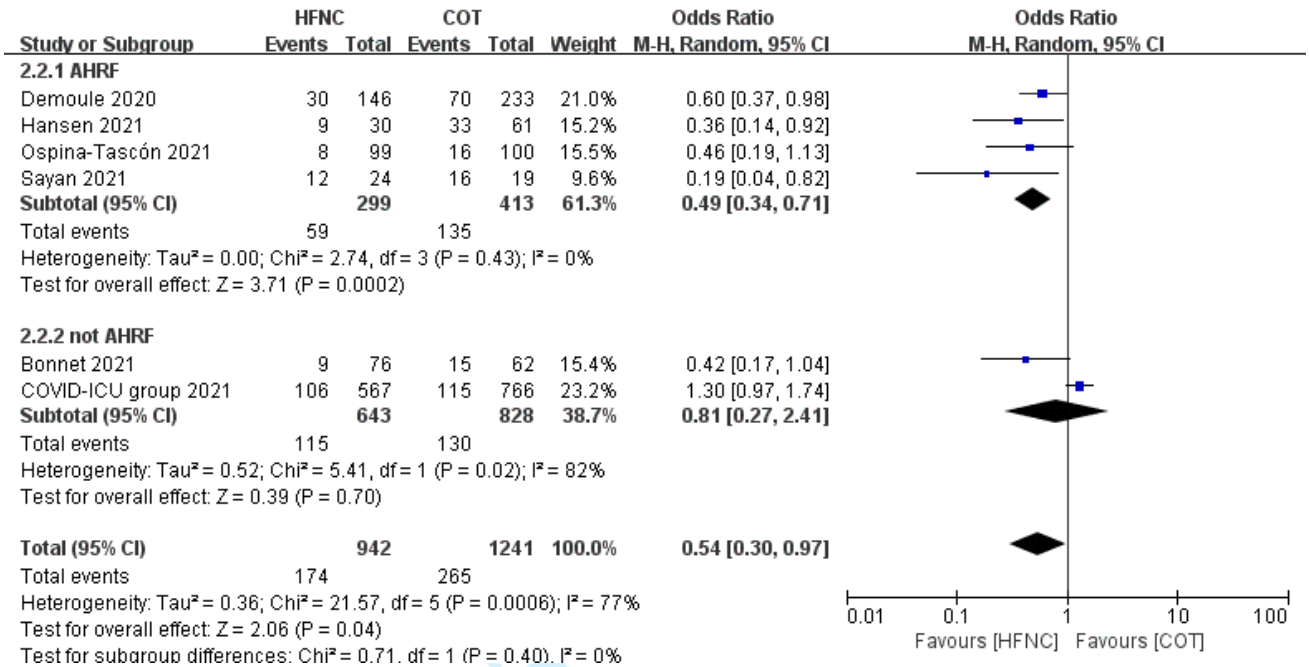
For peer review only

Figure S5 Subgroup analysis of intubation rate between the two groups with regard to type of ARF



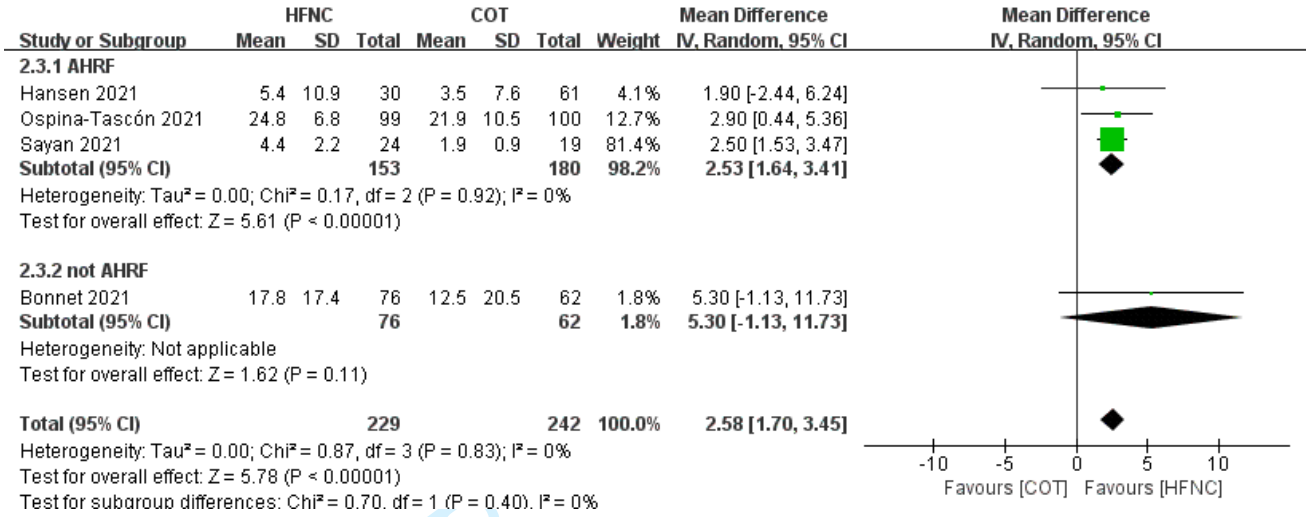
For peer review only

Figure S6 Subgroup analysis of mortality between the two groups with regard to type of ARF



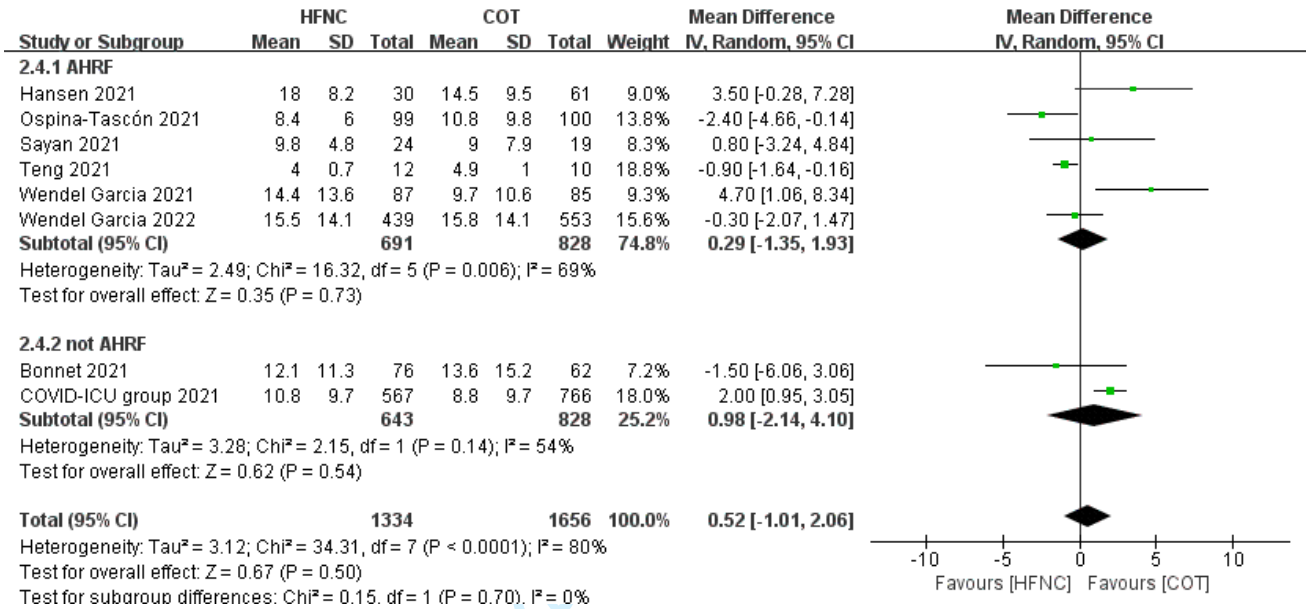
For peer review only

Figure S7 Subgroup analysis of VFDs between the two groups with regard to type of ARF



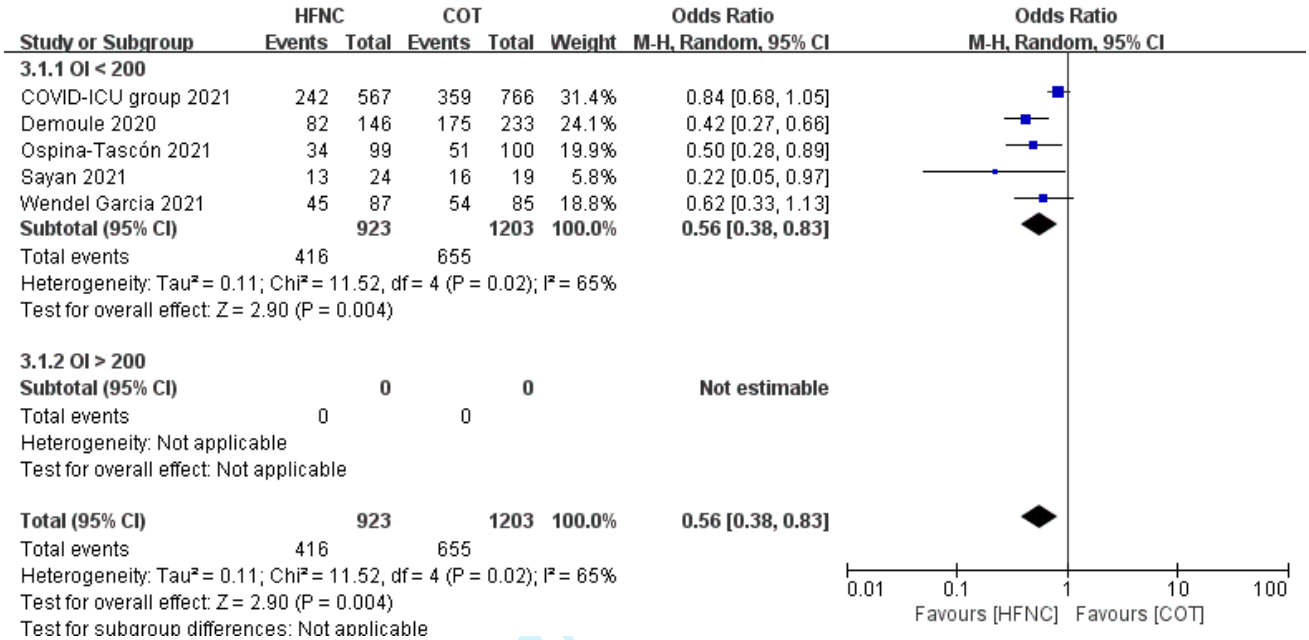
peer review only

Figure S8 Subgroup analysis of LOS between the two groups with regard to type of ARF



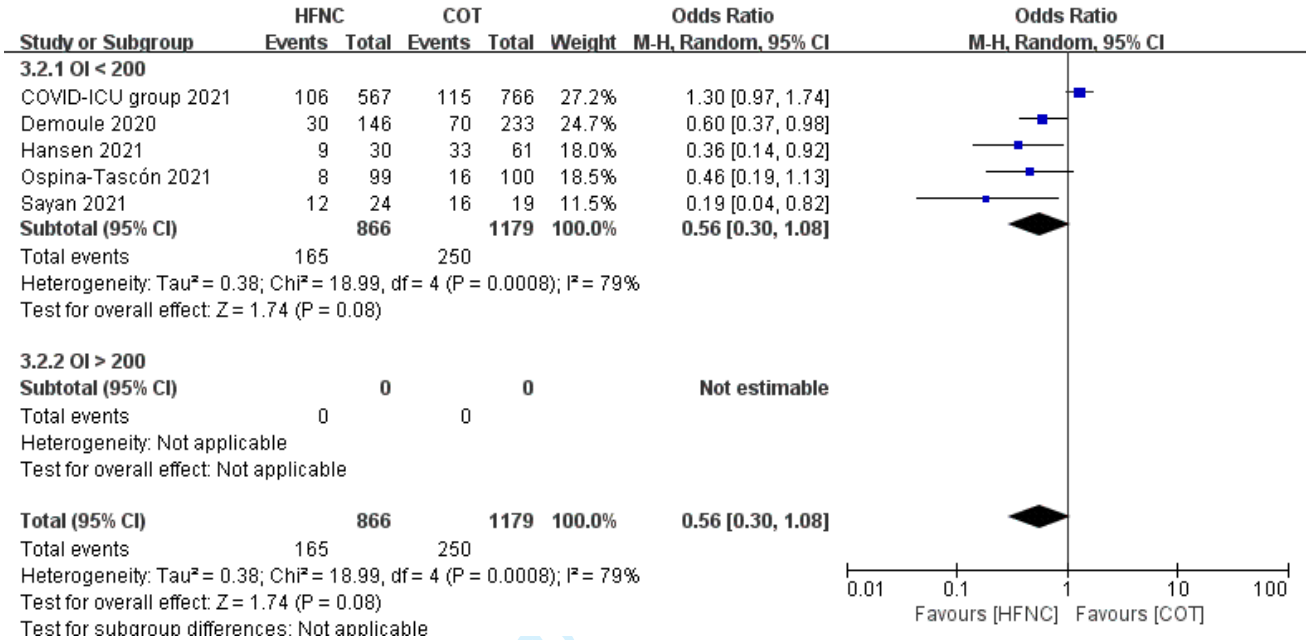
For peer review only

Figure S9 Subgroup analysis of intubation rate between the two groups with regard to OI



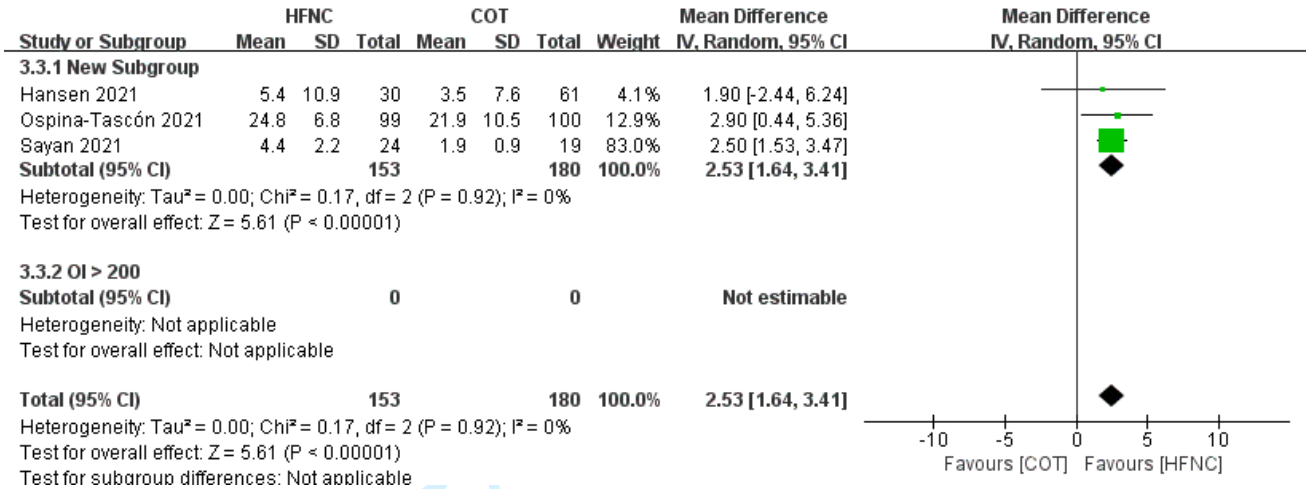
er review only

Figure S10 Subgroup analysis of mortality between the two groups with regard to OI



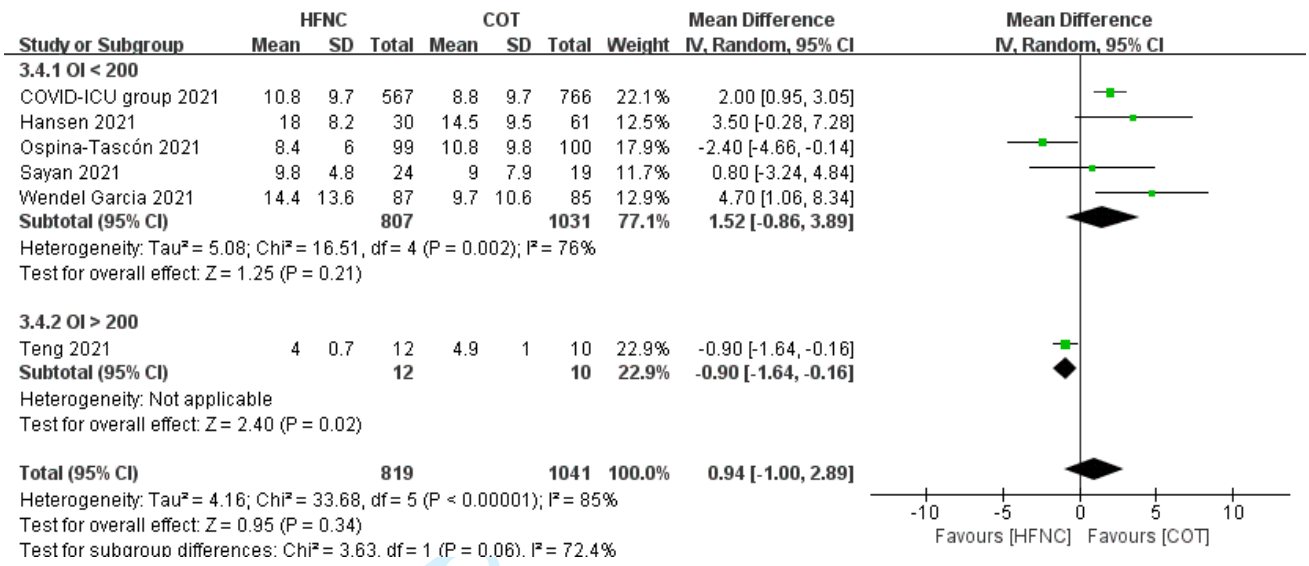
For peer review only

Figure S11 Subgroup analysis of VFDs between the two groups with regard to OI



peer review only

Figure S12 Subgroup analysis of LOS between the two groups with regard to OI



peer review only

BMJ Open

High-flow nasal cannula reduces intubation rate in COVID-19 patients with acute respiratory failure: a meta-analysis and systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067879.R1
Article Type:	Original research
Date Submitted by the Author:	22-Feb-2023
Complete List of Authors:	Li, Yang; Southeast University, Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine LI, Cong; Southeast University, Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine Chang, Wei; Southeast University, Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine Liu, Ling; Southeast University, Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Emergency medicine, Intensive care, Evidence based practice
Keywords:	COVID-19, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Respiratory infections < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2022-067879 on 30 March 2023. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

High-flow nasal cannula reduces intubation rate in COVID-19 patients with acute respiratory failure: a meta-analysis and systematic review

Yang Li,[1] Cong LI,[1] Wei Chang,[1] Ling Liu[1]

Author affiliations

1 Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, Jiangsu, China

***Corresponding author**

Ling Liu

Address: NO.87 Dingjiaqiao, Nanjing 210009, China.

E-mail: liulingdoctor@126.com.

Phone: 86-13851435472.

E-mail Adress

Yang Li: liyang2022@seu.edu.cn; Cong Li: congcongli2020@163.com; Wei Chang: ewei_0181@126.com; Ling Liu: liulingdoctor@126.com.

Keywords COVID-19 acute respiratory failure; high-flow nasal cannula; conventional oxygen therapy; meta-analysis

Word count 4572

For peer review only

ABSTRACT

Objective This study aimed to investigate the effect of high-flow nasal cannula therapy (HFNC) versus conventional oxygen therapy (COT) on intubation rate, 28-day intensive care unit (ICU) mortality, 28-day ventilator-free days (VFDs) and ICU length of stay (ICU LOS) in adult patients with acute respiratory failure (ARF) associated with novel coronavirus disease 2019 (COVID-19).

Design Systematic review and meta-analysis.

Data sources PubMed, Web of Science, Cochrane Library, and Embase up to June 2022.

Eligibility criteria for selecting studies Only randomized controlled trials or cohort studies comparing HFNC with COT in COVID-19 patients were included up to June 2022. Studies conducted on children or pregnant women, and those not published in English were excluded.

Data extraction and synthesis Two reviewers independently screened the titles, abstracts and full texts. Relevant information was extracted and curated in the tables. The Cochrane collaboration tool and Newcastle-Ottawa scale were used to assess the quality of randomized controlled trials or cohort studies. Meta-analysis was conducted using RevMan 5.4 computer software using a random effects model with a 95% confidence interval (CI). Heterogeneity was assessed using Cochran's Q test (chi-square) and Higgins I^2 statistics, with subgroup analyses to account for sources of heterogeneity.

Results Nine studies involving 3370 (1480 received HFNC) were included. HFNC reduced the intubation rate compared to COT (odds ratio [OR] = 0.44, 95% CI 0.28 to 0.71, P = 0.0007), decreased 28-day ICU mortality (OR = 0.54, 95% CI 0.30 to 0.97, P = 0.04), and improved 28-day VFDs (mean difference [MD] = 2.58, 95% CI 1.70 to 3.45, P < 0.00001). However, HFNC had no effect on ICU LOS versus COT (MD = 0.52, 95% CI -1.01 to 2.06, P = 0.50).

Conclusions Our study indicates that HFNC may reduce intubation rate and 28-day ICU mortality, and improve 28-day VFDs in patients with ARF due to COVID-19 compared with COT. Large-scale randomized controlled trials are necessary to validate our findings.

PROSPERO registration number CRD42022345713.

Keywords COVID-19; acute respiratory failure; high-flow nasal cannula; conventional oxygen therapy; meta-analysis

For peer review only

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This meta-analysis was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
2. Cochrane collaboration tool was used to assess the quality of randomized controlled trials, and Newcastle-Ottawa scale was used to evaluate the quality of cohort studies.
3. Subgroup analyses were performed to account for sources of heterogeneity.
4. Due to the limited number of relevant randomized controlled trials, our meta-analysis consisted mainly of cohort studies, which may still affect the accuracy of the results.
5. Significant differences between HFNC and COT made blinding of participants and personnel difficult, so the performance bias of all included RCTs was all at high risk.

For peer review only

INTRODUCTION

The outbreak of the novel coronavirus disease 2019 (COVID-19) has caused untold harm and challenges to people in more than 200 countries and territories worldwide. As of June 26 2022, over 541 million confirmed cases and over 6.3 million deaths had been reported globally.[1] Acute respiratory distress syndrome (ARDS) is a major complication of COVID-19 during hospitalization.[2, 3] **It** can progress to acute respiratory failure (ARF), which presents with severe hypoxemia and dyspnea, and is associated with higher mortality. Consequently, it is particularly important to select a ventilation support therapy for patients with COVID-19.

Traditionally, ARF treatment has focused mainly on invasive mechanical ventilation (IMV) and its optimization.[4] However, IMV is a risk factor for ventilator-associated pneumonia (VAP).[5] Approximately 16% of patients infected with COVID-19 experienced severe ARF,[6] and 4-12% needed invasive respiratory support.[3, 7] Early observational studies during the COVID-19 pandemic reported a very high mortality rate in patients subjected to IMV,[8] and some investigators have warned on the need for early intubation and mechanical ventilation.[9]

Noninvasive respiratory support techniques can prevent adverse events associated with intubation and mechanical ventilation. Most patients usually receive oxygen therapy through a nasal cannula, simple or venturi face mask, called conventional oxygen therapy (COT) or standard oxygen therapy.[2] At the onset of the COVID-19 pandemic, most clinicians use COT or early IMV to treat COVID-19 patients with ARDS, as recommended by the international guidelines.[10] However, the COT may be difficult to perform in situations where high inspiratory flow is necessary.[11]

High-flow nasal cannula oxygen (HFNC) is a relatively new and increasingly used therapy for adults with ARF.[12] This noninvasive technique delivers warmed, humidified oxygen with a fraction of inspired oxygen (FiO_2) of up to 1.0 and a maximum flow rate of 60 L/min.[13] HFNC may reduce the need for endotracheal intubation and the risk of treatment escalation in patients with ARF,[14, 15] but with no significant effect on mortality.[15, 16] Although international guidelines and early observational studies recommend HFNC as the initial treatment for patients with severe COVID-19, there is limited evidence to support this view.[17]

Therefore, we conducted a meta-analysis to investigate the effect of HFNC on intubation rate and 28-day intensive care unit (ICU) mortality, and its effect on 28-day ventilator-free days (VFDs) and ICU length of stay (ICU LOS) versus COT in adult patients with ARF resulting from COVID-19.

For peer review only

METHODS

Protocol and registration

We conducted a systematic review in accordance with the methods recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

As this study did not directly involve human subjects, and only used data from published articles, institutional review board approval was not required. The protocol used in this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022345713).

Eligibility criteria

The included studies had to meet the following criteria:

1. Type of study: randomized controlled trials (RCTs) or cohort studies
2. Population: patients aged over 16years, with ARF by COVID-19
3. Intervention: HFNC compared with COT

Characteristics of the excluded studies: case reports or case series, guidelines, expert consensus, animal studies, protocol, reviews, meta-analysis, conference abstract, studies conducted on children or pregnant women, unrelated studies (e.g., HFNC or COT not used in patients), studies involving repeated experiments (commentary articles on specific studies or secondary analyses of experimental data), and studies not published in English.

The primary outcome was the intubation rate. Decisions regarding tracheal intubation were based on the clinical grounds and judgment of the physician in charge. The secondary outcomes were 28-day ICU mortality, 28-day ventilator-free days (VFDs), and ICU length of stay (ICU LOS). 28-day VFDs was defined as the cumulative time in the first 28 days after starting HFNC or COT without the need for invasive mechanical ventilation.

Search strategy

A literature search was carried out using multiple electronic databases, such as PubMed, Web of Science, Cochrane Library, and Embase to identify articles published up to June 2022. We restricted the articles to those published in English. Details of the search strategies used for each database are presented in the **Supplemental file: Table S1**. We also checked the references of the related journals to ensure that we did not skip any studies. The literature review was conducted independently by two authors (YL and CL). Disparities

in the literature review were resolved by a third author (WC).

Study selection and data extraction

The search results were merged, and duplicate records were removed from the same study. Two reviewers (YL and CL) independently reviewed the titles and abstracts of the remaining studies, after excluding duplicates, to identify potentially eligible studies. A full-text review of the remaining literatures was conducted to finalize the studies for inclusion. Two investigators (YL and CL) independently extracted data from the selected qualified articles. Conflicts between the two reviewers were resolved by a third reviewer (WC). The extracted data included the study ID (the first author's name and publication year), region, study type, setting, type of ARF (acute hypoxic respiratory failure [AHRF] or not), control therapy, sample size, age, sex, body mass index (BMI), comorbidities, oxygenation index (OI) (PaO2/FiO2) before the start of oxygen therapy, sequential organ failure assessment score (SOFA), and primary and secondary outcomes. Data on therapies for COVID-19 pneumonia including the use of steroids, hydroxychloroquine, tocilizumab, convalescent plasma and Paxlovid were also extracted. For any missing data or information, the corresponding authors were contacted by email to request full original data. The e-mail used to contact the authors is available in the **Supplemental file：Table S2**.

Risk of bias assessment

Two reviewers independently assessed the risk of bias of the included trials, with any discrepancies resolved through discussion with a third reviewer (WC). The Cochrane Collaboration tool in RevMan 5.4 software (Review Manager, Version 5.4, The Cochrane Collaboration, 2014) was used to assess the quality of the RCTs,[19] which considers seven different domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the other six domains. Based on the method of the trials, each was graded as "yes," "no" or "unclear," to reflect a high, low risk or uncertain risk of bias, respectively. The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of cohort studies based on the selection of the study groups, comparability of study groups, and ascertainment of exposure/outcome.[20, 21] Studies with total scores of ≥6 were considered to have a low risk of bias. Two reviewers (YL and CL) independently made these judgments. In cases of disagreement,

For peer review only

resolution was attempted through a discussion.

Assessment of publication bias

Funnel plots were used to assess the possibility of publication bias and were implemented using RevMan 5.4 software. Egger's regression test was used to measure the funnel plot asymmetry.[22, 23]

Grading the quality of the evidence

We used the methodology of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group to assess the overall quality of the evidence for the primary and secondary outcomes in the following domains: risk of bias, inconsistency, indirection, imprecision and publication bias. The overall quality of the certainty of evidence was high, moderate, low, or very low quality.[24]

Assessment of heterogeneity

The heterogeneity of the included studies was assessed using Cochrane's Q Test (chi-square) of homogeneity and Higgins I^2 statistics.[25, 26] I^2 describes the percentage of effective variability and the corresponding P-value calculates the estimate of effective variability due to heterogeneity rather than sampling error. I^2 values of 25- 50% indicated low heterogeneity, 50-75% indicated moderate heterogeneity, and >75% indicated high heterogeneity.[25] To confirm the robustness of our results, a sensitivity analysis using leave-one-out meta-analysis was performed to determine whether it had a significant influence on the meta-analysis results.

Statistical analysis

RevMan 5.4 computer software was used for all data analysis in this study. For dichotomous variables, the estimated effects were pooled using the Mantel–Haenszel method and expressed as odds ratio (OR) with 95% confidence intervals (CI). For continuous variables, the estimated effects were pooled using the inverse variance method and expressed as the mean difference (MD) with 95% CI. The analysis was performed using a random-effects model. A *P*-value <0.05 was considered statistically significant. If the median and interquartile range (IQR) were reported in the study, they were converted into the mean and standard deviation using the formulas proposed by Luo and Wan.[27, 28]

Subgroup analysis

Some subgroup analyses were pre-established. Owing to the higher gas flow rate of HFNC compared to COT, HFNC is more effective in targeting hypercapnic respiratory failure with CO2 retention. However, its efficacy in acute hypoxic respiratory failure due to COVID-19 has not been confirmed. Therefore, we compared HFNC with COT in patients with AHRF. We performed a subgroup analysis according to the type of ARF (AHRF or not) to explore the efficacy of HFNC therapy in patients with AHRF due to COVID-19. The effect of HFNC may also be different for patients with different severities of respiratory failure; therefore, we assessed the efficacy of HFNC inpatients with OI $\leq$ 200 mmHg and OI > 200 mmHg before the start of oxygen therapy compared to COT. Owing to the small number of RCTs related to our study topic, we included both cohort studies and pooled them to derive the results. We performed a subgroup analysis between RCTs and cohort studies to evaluate whether there were differences in the results.

Trail sequential analysis (TSA)

We used TSA to identify the risk of both type 1 and type 2 error due to sparse data and repetitive testing of accumulated data for the primary outcome in our meta-analysis.[29] The findings are represented by the cumulative Z-curves. When the cumulative Z-curves surpassed the futility boundary, the level of evidence was adequate and further trials were judged as futile. If the Z-curves surpassed the conventional and trial sequential significance boundaries, the level of evidence was judged adequate and conclusive. In contrast, when the Z-curves did not cross any boundaries or only surpassed the conventional boundary, the level of evidence was inadequate, and more trials were required to clarify the conclusion. A two-sided trial sequential monitoring boundary was used in the TSA. We defined a statistical significance level of 5%, power of 80%, control event rate of 66%, and a relative risk reduction of 20%. A 20% relative risk reduction was determined based on an RCT comparing HFNC and COT applied to acute hypoxic respiratory failure.[14] The 66% control event rate was calculated by pooling the incidence of intubation in the control group based on all included studies. TSA was performed using TSA version 0.9.5.10 beta.[30]

Patient and public involvement

Patients and the public were not directly involved in this study.

For peer review only

RESULTS

Study identification and selection

We initially obtained 1363 records in accordance with the search strategy. After excluding 82 duplicate studies, 1281 items remained. 1259 articles were excluded through initial screening by title and abstract because they did not match our study topic. After a full-text review of 22 potentially eligible studies, 13 articles were excluded for the following reasons: one lacked complete information, nine did not compare HFNC with COT, and three were case reports or reviews. Eventually, nine studies were eligible and included in this meta-analysis. A PRISMA flow diagram for the selection of studies is shown in **Figure 1.**

Study characteristics

Table 1 and **Table 2** summarize the study and patient characteristics of the included studies. All included studies were published by June 2022. A total of nine studies were included: two conducted in France,[31, 32] one multinational,[33] one from the United States,[34] one from Colombia,[35] one from Turkey,[36] one from China,[13] one from Switzerland and one from Spain.[37, 38] Regarding study design, two were RCTs[13, 35] and the remaining seven were prospective or retrospective cohort studies.[31-34, 36-38] Seven studies were conducted in ICU,[13, 31-33, 36-38] one study was conducted in ICU, emergency department (ED) and ward,[35] and one was not reported.[34] A total of 3370 subjects (1480 received HFNC, 1890 received COT) were included, of which 71.8% were male. Only one of the nine studies documented treatments for COVID-19, including the use of steroids, hydroxychloroquine, tocilizumab, and convalescent plasma. We attempted to contact the primary authors by e-mail to obtain more information and details about the treatment, but did not receive any replies. Seven studies specified the included patients as AHRF due to COVID-19,[13, 32, 34-38] and two other studies did not specify the type of ARF. Six studies included patients with an OI < 200 mmHg before the start of oxygen therapy.[32-37]

Risk of bias assessment

Two RCTs were evaluated for quality using the Cochrane collaboration tool and most domains were assessed to have a low risk of bias (random sequence generation, allocation concealment, incomplete outcome data, and selective reporting).[13, 35] However, because of the apparent differences between HFNC and COT, blinding of subjects and personnel was difficult to achieve, and performance bias was considered high risk for all included RCTs. Teng et al. did not specify whether they were blinded to outcome assessment.[13] The risk

For peer review only

of summary bias in individual studies is shown in **Supplemental file: Figure S1, Figure S2**. The quality of the cohort studies was assessed using the Newcastle-Ottawa scale. The overall quality of all the included cohort studies was good, with all studies scoring 8. The results of the quality assessment are shown in **Supplemental file: Table S3**.

Table 1: Study characteristics of the included studies

Study	Region	Study type	Setting	ARF	Control	Sample size	Age (HFNC/COT)	Male, n (%)
Bonnet, 2021 [31]	France	RC	ICU	NR	FM	76/62	59.6±11.3/59.3±12.1	112 (81)
COVID-ICU group, 2021 [33]	Multicentric	RC	ICU	NR	NR	567/766	63.6±12.6/61.4±12.6	981 (74)
Demoule, 2020 [32]	France	RC	ICU	AHRF	NR	146/233	60±10.5/61.6±11.9	291 (77)
Hansen, 2021 [34]	American	PC	NR	AHRF	FM/NC	30/62	68.6±12.5/68.3±11.9	58 (63)
Ospina-Tascón,2021 [35]	Colombia	RCT	ICU, ED and Ward	AHRF	FM/NP	99/100	59.6±14.3/58.3±13.5	134 (67)
Sayan, 2021 [36]	Turkey	RC	ICU	AHRF	FM	24/19	63.3±12.1/69.5±12.3	30 (70)
Teng, 2021 [13]	China	RCT	ICU	AHRF	FM/NC	12/10	56.6±3.0/53.5±5.5	15 (68)
Wendel Garcia, 2021 [37]	Switzerland	PC	ICU	AHRF	NR	87/85	64.1±14.3/62.6±14.3	128 (74)
Wendel Garcia, 2022 [38]	Spain	RC	ICU	AHRF	FM	439/553	62.0±11.9/62.6±11.9	671 (68)

ARF: acute respiratory failure, HFNC: high flow nasal cannula, COT: conventional oxygen therapy, NR: not reported, RC: retrospective cohort, RCT: randomized controlled trial, ICU: intensive care unit, ED: emergency department, AHRF: acute hypoxic respiratory failure, FM: face mask. NC: nasal cannula, NP: nasal prong

Assessment of heterogeneity

Heterogeneity in the results of the three outcomes (intubation rate, mortality and VFDs) was high. Sensitivity analysis by leave-one-out method revealed that the study by the COVID-ICU group had a high impact on the heterogeneity of the results.[33] Heterogeneity decreased significantly if this study was excluded (intubation rate: 85%-51%; mortality: 77%-0%; ICU LOS: 80%-64%).

Primary outcome

Seven studies including 3256 patients reported intubation rates.[31-33, 35-38] In these seven studies, we found that patients treated with HFNC had a statistically significantly lower rate of intubation compared to

those undergoing COT (OR = 0.44, 95% CI 0.28 to 0.71, P = 0.0007; M-H random), and the heterogeneity was high with I^2 = 85% (P < 0.00001) (**Figure 2**).

The quality of evidence on intubation rate was thought to be low because of the inconsistency associated with the high heterogeneity (**Supplemental file: Table S4**). Funnel plots were visually inspected and did not show any evidence of publication bias (**Supplemental file: Figure S3**). TSA suggested that although the cumulative Z-curve did not reach the required information size (RIS), it surpassed both the conventional and TSA boundaries, indicating that a positive conclusion had been obtained before the RIS was reached, and TSA supported the results of the meta-analysis **(Supplemental file: Figure S4)**. However, more RCTs are needed because the study included mostly cohort studies.

Table 2: Subject characteristics and outcomes of the included studies in the meta-analysis

Study	BMI (HFNC/COT)	Comorbidities (HFNC/COT)			OI (HFNC/COT)	SOFA (HFNC/COT)	Outcomes
		HT	DM	COPD			
Bonnet, 2021 [31]	29.0±6.05/28.8±5.3	37/19	24/19	NR	NR	NR	①②③④
COVID-ICU group, 2021 [33]	28.0±4.5/28.4±5.2	263/331	145/206	NR	105.1±42.4/154.0±96.6	3.0±1.5/2.7±1.5	①②④
Demoule, 2020 [32]	27.4±3.7/28.3±5.2	67/121	42/72	7/13	134.1±77.1/141.2±73.1	4.0±1.5/6±4.5	①②
Hansen, 2021 [34]	32.2±8.1/31.4±9.8	16/45	9/27	6/6	152.0±62.0/153.0±67.0	6.6±2.2/7.7±3.0	②③④
Ospina-Tascón, 2021 [35]	29.1±4.4/29.6±5.2	35/44	18/20	3/1	107.2±35.4/110.6±42.1	3.6±0.8/3.6±0.8	①②③④
Sayan, 2021 [36]	26.5±2.6/26.5±3.2	6/12	3/5	2/0	170.7±19.1/183.9±40.3	NR	①②③④
Teng, 2021 [13]	NR	7/4	3/3	NR	224.3±12.6/213.7±4.6	NR	④
Wendel Garcia, 2021 [37]	28.1±5.3/28.7±4.5	NR	26/23	10/14	124.6±67.9/127.9±14.5	5.3±3.0/5.9±2.3	①④
Wendel Garcia, 2022 [38]	28.4±3.7/28.0±4.5	NR	91/114	32/40	NR	NR	①④

BMI: body mass index, HT: hypertension, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, OI: oxygenation index, SOFA: sequential organ function assessment, IR: intubation rate, M: mortality, VFD: ventilator free days, ILOS: ICU stay of length, ①: intubation rate, ②: mortality, ③: ventilator-free days, ④: ICU length of stay

Secondary outcomes

28-day ICU mortality

Six studies involving2183 patients reported mortality.[31-36] Overall, HFNC was associated with lower mortality than COT (OR = 0.54, 95% CI 0.30 to 0.97, P = 0.04; M-H random; I^2 = 77%, P = 0.0006) (**Figure 3**). The quality of evidence on mortality was considered moderate (**Supplemental file: Table S3**).

28-day ventilator-free days

Four studies involving 471 patients evaluated the 28-day ventilator-free days.[31, 34-36] Patients undergoing HFNC had greater VFDs than those undergoing COT (MD = 2.58, 95% CI 1.70 to 3.45, P < 0.00001; M-H random; I^2 = 0%, P = 0.83) (**Figure 4**). The quality of evidence on the 28-day ventilator-free days was thought to be moderate (**Supplemental file: Table S3**).

ICU length of stay

For the eight studies recruiting 2990 patients,[13, 31, 33-38] HFNC had no effect on ICU LOS compared with COT (MD = 0.52, 95% CI -1.01 to 2.06, P = 0.50; M-H random; I^2 = 80%, P < 0.0001) (**Figure 5**). The quality of evidence on ICU LOS was thought to be very low owing to inconsistency and imprecision (**Supplemental file: Table S3**).

Subgroup analysis

Type of ARF

Subgroup analysis showed that seven trials included patients with AHRF. In five studies including 1785 patients with AHRF due to COVID-19, the HFNC group had a lower intubation rate than the COT group (OR = 0.39, 95% CI 0.26 to 0.58, P < 0.00001; M-H random), with moderate heterogeneity (I^2 = 61%, P = 0.04) (**Supplemental file: Figure S5**). For28-day ICU mortality, subgroup analysis revealed that HFNC was favored over COT (OR = 0.49, 95% CI 0.34 to 0.71, P = 0.0002; M-H random; I^2 = 0%, P = 0.43) (**Supplemental file: Figure S6**). Three studies reported VFDs in patients with AHRF: the HFNC group had greater VFDs than the COT group (MD = 2.53, 95% CI 1.64 to 3.41, P < 0.00001; M-H random; I^2 = 0%, P = 0.92) (**Supplemental file: Figure S7**). However, there was no significant difference between HFNC and COT in terms of ICU LOS (MD = 0.29, 95% CI 1.35 to 1.93, P = 0.73; M-H random; I^2 = 69%, P = 0.006) (**Supplemental file: Figure S8**).

Initial oxygenation index

Six trials included patients with an OI ≤ 200 mmHg. Five studies, including 2126 patients, reported the intubation rate in patients with an initial OI ≤ 200 mmHg. The results of the subgroup analysis showed a statistically significant reduction in the intubation rate in patients with OI ≤ 200 mmHg treated with HFNC

compared to those treated with COT (OR = 0.56, 95% CI 0.38 to 0.83, P = 0.004; M-H random; I^2 = 65%, P = 0.02) (**Supplemental file: Figure S9**). However, there was no significant difference in the 28-day ICU mortality between the HFNC and COT groups (OR = 0.56, 95% CI 0.30 to 1.08, P = 0.08; M-H random; I^2 = 79%, P = 0.0008) (Supplemental file: Figure S10). Three studies reported VFDs in patients with an initial OI ≤ 200 mmHg: the HFNC group had greater VFDs than the COT group (MD = 2.53, 95% CI 1.64 to 3.41, P < 0.00001; M-H random; I^2 = 0%, P = 0.92) (**Supplemental file: Figure S11**). In addition, HFNC did not reduce ICU LOS compared to COT (MD = 1.52, 95% CI -0.86 to 3.89, P = 0.21; M-H random; I^2 = 76%, P = 0.002) (**Supplemental file: Figure S12**).

Type of research

Two studies were RCTs, and the remaining seven were prospective or retrospective cohort studies. Similar results were demonstrated for intubation rate between the RCT and cohort study groups. In the RCT group, patients in the HFNC group had a lower intubation rate than those in the COT group (OR = 0.50, 95% CI 0.28 to 0.89). Similar results were found in the cohort study group (OR = 0.43, 95% CI 0.258 to 0.74, P = 0.002; M-H random; I^2 = 88%, P < 0.00001) (**Supplemental file: Figure S13**).

For peer review only

DISCUSSION

Nine studies were included in our study, to evaluate the efficacy of HFNC as an initial oxygen therapy for patients with ARF due to COVID-19. In this analysis, compared with COT, HFNC reduced intubation rates and 28-day ICU mortality in patients with ARF due to COVID-19 infection and improved 28-day VFDs. However, HFNC did not significantly reduce ICU LOS in patients. In a subgroup analysis of patients with AHRF caused by COVID-19, our meta-analysis showed similar results. HFNC significantly outperformed COT in reducing intubation rates and 28-day ICU mortality, as well as improving the number of 28-day VFDs. In patients with an initial OI < 200 mmHg, although HFNC was associated with lower intubation rates and extended 28-day VFDs, there was no significant difference in 28-day ICU mortality and ICU LOS between HFNC and COT.

Our meta-analysis revealed that HFNC significantly reduced intubation rates compared to COT. Similar results have also been reported in other studies. Studies by Ni et al. and Zhao et al.,[39, 40] which compared the efficacy of HFNC and COT in patients with ARF, showed that HFNC was associated with a lower rate of endotracheal intubation. In another study, Rochwerg et al. found that HFNC reduced the rate of intubation in patients with AHRF compared with COT.[15] In a multicenter RCT conducted in France by Frat et al., the leading cause of acute respiratory failure was community-acquired pneumonia (64% of the patients were diagnosed with community-acquired pneumonia).[14] They noticed that in the subgroup of patients with an OI of 200 mmHg or less, the intubation rate was significantly lower in the HFNC group than in the COT group. These results were similar to those of our subgroup analysis.

Our study also indicated that HFNC was superior to COT in reducing 28-day ICU mortality and extending the 28-day VFDs, although no significant effect of HFNC in reducing mortality was found in the studies by Ni et al. and Rochwerg et al.[15, 39] However, this could be explained by the complex causes of respiratory failure, as the cause of the patient's respiratory failure was not specified. In another RCT, HFNC reduced ICU mortality and mortality on day 90, and VFDs were significantly higher in the HFNC group than in the control group.[14] In our study, the number of comorbidities (hypertension, diabetes mellitus and COPD) was higher among the patients in the COT group, which could explain the higher mortality in the COT group.

In terms of ICU LOS, our meta-analysis also indicated that HFNC did not further decrease ICU LOS in adults, similar to the results reported in our subgroup analysis. Numerous factors, especially concomitant complications such as acute kidney dysfunction and cardiac impairment, may contribute to ICU LOS in addition to the respiratory status itself.[41, 42] In addition, many non-disease factors significantly contributed to the ICU LOS. It is undeniable that medical resources and expenditures are closely related to disease outcomes,

For peer review only

such as bed availability in general wards and insurance status, which may offset the positive effects of HFNC to some extent.

The sensitivity analysis indicated a significant effect on heterogeneity in the COVID-ICU group.[33] Several reasons may contribute to its apparent effect on heterogeneity: (1) the study included patients from multiple countries and there may be differences between study centers; (2) the study did not specify the type of ARF, whereas most other studies explicitly included patients with AHRF; (3) the study included patients aged >16 years, while all other studies included patients over 18 years of age; (4) the study included the largest number of patients, which had a large impact on outcome indicators.

In addition to HFNC, noninvasive ventilation (NIV) is widely used in patients with COVID-19 pneumonia to avoid the need for tracheal intubation and mechanical ventilation if conventional oxygen therapy fails. NIV is the first-line treatment for hypercapnic acute respiratory failure caused by COPD. Compared to HFNC, NIV should theoretically improve pulmonary oxygenation and gas exchange in ARF because it provides a higher positive end-expiratory pressure (PEEP).[43] However, not all patients can tolerate NIV owing to adverse events, such as claustrophobia, facial pressure ulcers, and eye irritation.[44, 45] In a randomized controlled trial that included 1273 patients, the authors compared the effects of HFNC, COT, and CPAP on the 30-day intubation rate and 30-day mortality in patients with COVID-19-related AHRF.[46] The results showed a significant decrease in intubation rate in the CPAP group compared with that in the COT group, but there was no significant difference in mortality. Among patients requiring tracheal intubation, there was a statistically significant increase in the median time to tracheal intubation in the CPAP group. In contrast, HFNC had no significant effect on intubation rate or mortality compared with COT. The lower tracheal intubation rate in the CPAP group may be due to the greater willingness of clinicians and patients to delay tracheal intubation. A meta-analysis comparing HFNC and NIV in patients with COVID-19 pneumonia showed no significant differences between the two groups in terms of intubation rate, mortality, and length of hospital stay.[47]

According to our study, HFNC improved the intubation rate, 28-day ICU mortality and 28-day VFDs in patients with ARF caused by COVID-19. A study by Sztrymf et al. revealed that HFNC significantly reduced the respiratory rate, heart rate, dyspnea score, supraclavicular retraction and thoracoabdominal asynchrony, and increased pulse oximetry.[48] HFNC is superior to COT, probably for several reasons: (1) Heated and humidified gas may protect mucosal function and promote secretion clearance, thereby reducing the risk of pulmonary atelectasis.[49, 50] (2) There was a positive linear relationship between the flow and airway pressure during HFNC, producing a low-level positive airway pressure effect.[51] This low-level positive

airway pressure effect could somewhat reduce anatomical dead space and improve ventilation-perfusion mismatch.[41, 52] (3) There is more adequately matching of the patient's respiratory flow demands to reduce the inspiratory resistance associated with the nasopharynx and decrease the risk of patient self-inflicted lung injury.[41, 53] (4) HFNC can deliver predictable and stable FiO_2.[54] (5) HFNC ensures adequate ventilation and oxygenation through continuous high flow oxygen accompanied by higher tidal volumes and reduced inspiratory resistance.[55-57] (6) HFNC can reduce the intensity of respiratory discomfort and improve the dyspnea score in patients with ARF.[14]

Strengths and limitations

This meta-analysis was the first to assess the efficacy of HFNC compared with COT in patients with ARF due to COVID-19. An extensive search strategy was developed and all reviews were conducted by at least two reviewers. The quality of the enrolled studies was assessed using appropriate methods, and the methodology of the GRADE Working Group was used to evaluate the overall quality of evidence for outcomes. Subgroup analysis was performed to determine the origin of the heterogeneity. TSA was applied to identify the risk of both type 1 and type 2 error due to sparse data and repetitive testing of accumulated data.

Our meta-analysis has several limitations. First, despite an extensive literature search, our meta-analysis consisted mainly of cohort studies because of the limited number of relevant randomized controlled trials. Although the quality assessment was passed and TSA suggested that no further testing was required, it may still affect the accuracy of the results. Therefore, further large-scale RCTs are required to confirm our findings. Second, significant differences between HFNC and COT made blinding of participants and personnel difficult, so the performance bias of all included RCTs was at high risk. Third, despite the random effects model used in our analysis, moderate-to-high heterogeneity was observed in the results. This may be due to different patient characteristics (such as comorbidities), inconsistent oxygen therapy measures (duration of oxygen therapy, initial flow rate, and oxygen concentration), inconsistent severity of patient ARF, therapeutic measures other than oxygen therapy (e.g., medications), and different follow-up durations. Meanwhile, the definition of outcomes may vary from study to study, such as the choice of intubation timing, which can also increase heterogeneity. The subgroup and sensitivity analyses partially explained the sources of heterogeneity. Finally, targeted treatment of COVID-19 has a considerable impact on prognosis. Therefore, it is important to emphasize the therapies for patients with COVID-19 in the preliminary study. The different treatments used in different studies may help explain part of the source of heterogeneity. However, only one of the nine studies

For peer review only

included documented treatments for COVID-19. We attempted to contact the primary authors by e-mail to obtain more information and details about the treatment, but did not receive any replies. This makes it difficult to exclude heterogeneity due to differences in targeted treatment for COVID-19 pneumonia.

For peer review only

CONCLUSION

Overall, HFNC reduced intubation rate and 28-day ICU mortality in patients with ARF due to COVID-19 and improved 28-day ventilator-free days compared with COT. However, it did not reduce the ICU length of stay. To validate our finding, large-scale randomized controlled trials are necessary.

For peer review only

Contributors YL and LL contributed to the conception and design of the study. YL, CL and WC made substantial contributions to literature search, data collection, statistical analysis and the original drafting and revising of the manuscript. LL provided daily assistance and professional comments on the manuscript. All authors read and approved of the final manuscript for publication.

Funding: This work was funded by National Natural Science Foundation of China [Grant numbers 81870066, 81930058], Clinical Science and Technology Specific Projects of Jiangsu Province (Grant number. BE2020786).

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication: Patient consent was not required as the data were obtained from previously published papers in the public domain.

Ethics approval: Ethical approval was not required as the data were obtained from previously published papers in the public domain.

Data availability statement: The access policy and procedures are available at https://datadryad.org/stash/share/_mR-3750nia5YWsl4MAd8j8k0Bg8gMJQ6TzpH91oWxI

For peer review only

REFERENCE

1 Organization GWH. COVID-19 Weekly Epidemiological Update Edition 98 2022 [updated 2022/06/29. Available from: www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---29-june-2022 accessed 06/30 2022.

2 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497-506. doi: 10.1016/s0140-6736(20)30183-5 [published Online First: 2020/01/28]

3 Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama* 2020;323(11):1061-69. doi: 10.1001/jama.2020.1585 [published Online First: 2020/02/08]

4 Curley GF, Laffey JG, Zhang H, et al. Biotrauma and Ventilator-Induced Lung Injury: Clinical Implications. *Chest* 2016;150(5):1109-17. doi: 10.1016/j.chest.2016.07.019 [published Online First: 2016/08/02]

5 Oliveira J, Zagalo C, Cavaco-Silva P. Prevention of ventilator-associated pneumonia. *Rev Port Pneumol* 2014;20(3):152-61. doi: 10.1016/j.rppneu.2014.01.002 [published Online First: 2014/03/29]

6 Guan WJ, Zhong NS. Clinical Characteristics of Covid-19 in China. Reply. *N Engl J Med* 2020;382(19):1861-62. doi: 10.1056/NEJMc2005203 [published Online First: 2020/03/29]

7 Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *Jama* 2020;323(13):1239-42. doi: 10.1001/jama.2020.2648 [published Online First: 2020/02/25]

8 Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama*

For peer review only

2020;323(20):2052-59. doi: 10.1001/jama.2020.6775 [published Online First: 2020/04/23]

9 Tobin MJ. Basing Respiratory Management of COVID-19 on Physiological Principles. *Am J Respir Crit Care Med* 2020;201(11):1319-20. doi: 10.1164/rccm.202004-1076ED [published Online First: 2020/04/14]

10 Organization GWH. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected 2020 [2020/01/12:[Available from: www.who.int/publications/i/item/10665-332299 accessed 06/30 2022.

11 Confalonieri M, Potena A, Carbone G, et al. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1585-91. doi: 10.1164/ajrccm.160.5.9903015 [published Online First: 1999/11/11]

12 Nishimura M. High-flow nasal cannula oxygen therapy in adults. *J Intensive Care* 2015;3(1):15. doi: 10.1186/s40560-015-0084-5 [published Online First: 2015/04/14]

13 Teng XB, Shen Y, Han MF, et al. The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. *European journal of clinical investigation* 2021;51(3):e13435. doi: 10.1111/eci.13435

14 Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372(23):2185-96. doi: 10.1056/NEJMoa1503326 [published Online First: 2015/05/20]

15 Rochwerg B, Granton D, Wang DX, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. *Intensive Care Med* 2019;45(5):563-72. doi: 10.1007/s00134-019-05590-5 [published Online First: 2019/03/20]

16 Azoulay E, Lemiale V, Mokart D, et al. Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day

For peer review only

Mortality in Immunocompromised Patients With Acute Respiratory Failure: The HIGH Randomized Clinical Trial. *Jama* 2018;320(20):2099-107. doi: 10.1001/jama.2018.14282 [published Online First: 2018/10/26]

17 Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020;46(5):854-87. doi: 10.1007/s00134-020-06022-5 [published Online First: 2020/03/31]

18 Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *Jama* 2015;313(16):1657-65. doi: 10.1001/jama.2015.3656 [published Online First: 2015/04/29]

19 Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928. doi: 10.1136/bmj.d5928 [published Online First: 2011/10/20]

20 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25(9):603-5. doi: 10.1007/s10654-010-9491-z [published Online First: 2010/07/24]

21 Wells GA SB OCD, Peterson J, Welch V , Losos M, et al. NewCastle-Ottawa Quality Assessment Scale. 2013

22 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629 [published Online First: 1997/10/06]

23 Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics* 2018;74(3):785-94. doi: 10.1111/biom.12817 [published Online First: 2017/11/16]

24 Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *Bmj* 2008;336(7652):1049-51. doi: 10.1136/bmj.39493.646875.AE [published Online First: 2008/05/10]

For peer review only

25 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *Bmj* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557 [published Online First: 2003/09/06]

26 Pereira TV, Patsopoulos NA, Salanti G, et al. Critical interpretation of Cochran's Q test depends on power and prior assumptions about heterogeneity. *Res Synth Methods* 2010;1(2):149-61. doi: 10.1002/jrsm.13 [published Online First: 2010/04/01]

27 Luo D, Wan X, Liu J, et al. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;27(6):1785-805. doi: 10.1177/0962280216669183 [published Online First: 2016/09/30]

28 Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. doi: 10.1186/1471-2288-14-135 [published Online First: 2014/12/20]

29 Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol* 2017;17(1):39. doi: 10.1186/s12874-017-0315-7 [published Online First: 2017/03/08]

30 Thorlund K EJ, Wetterslev J, Brok J, Imberger G, Gluud , C. User manual for trial sequential analysis (TSA) *Copenhagen: Copenhagen Trial Unit, Centre for Clinical In-*

tervention Research; 2011 [cited 2021 Dec 10]

31 Bonnet N, Martin O, Boubaya M, et al. High flow nasal oxygen therapy to avoid invasive mechanical ventilation in SARS-CoV-2 pneumonia: a retrospective study. *Annals of Intensive Care* 2021;11(1) doi: 10.1186/s13613-021-00825-5

32 Demoule A, Baron AV, Darmon M, et al. High-Flow Nasal Cannula in Critically Ill Patients with Severe COVID-19. *American Journal of Respiratory and Critical Care Medicine* 2020;202(7):1039-42. doi:

For peer review only

10.1164/rccm.202005-2007LE

33 Schmidt M, Demoule A, Hajage D, et al. Benefits and risks of noninvasive oxygenation strategy in COVID-19: a multicenter, prospective cohort study (COVID-ICU) in 137 hospitals. *Critical Care* 2021;25(1) doi: 10.1186/s13054-021-03784-2

34 Hansen CK, Stempek S, Liesching T, et al. Characteristics and outcomes of patients receiving high flow nasal cannula therapy prior to mechanical ventilation in COVID-19 respiratory failure: A prospective observational study. *Int J Crit Illn Inj Sci* 2021;11(2):56-60. doi: 10.4103/ijciis.Ijciis_181_20 [published Online First: 2021/08/17]

35 Ospina-Tascón GA, Calderón-Tapia LE, García AF, et al. Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: a Randomized Clinical Trial. *JAMA* 2021;326(21):2161 - 71. doi: 10.1001/jama.2021.20714

36 Sayan İ, Altınay M, Çınar AS, et al. Impact of HFNC application on mortality and intensive care length of stay in acute respiratory failure secondary to COVID-19 pneumonia. *Heart Lung* 2021;50(3):425-29. doi: 10.1016/j.hrtlng.2021.02.009 [published Online First: 2021/02/24]

37 Wendel Garcia PD, Aguirre-Bermeo H, Buehler PK, et al. Implications of early respiratory support strategies on disease progression in critical COVID-19: a matched subanalysis of the prospective RISC-19-ICU cohort. *Critical Care* 2021;25(1) doi: 10.1186/s13054-021-03580-y

38 Wendel-Garcia PD, Mas A, González-Isern C, et al. Non-invasive oxygenation support in acutely hypoxemic COVID-19 patients admitted to the ICU: a multicenter observational retrospective study. *Critical Care* 2022;26(1) doi: 10.1186/s13054-022-03905-5

39 Ni YN, Luo J, Yu H, et al. Can High-flow Nasal Cannula Reduce the Rate of Endotracheal Intubation in

For peer review only

Adult Patients With Acute Respiratory Failure Compared With Conventional Oxygen Therapy and Noninvasive Positive Pressure Ventilation?: A Systematic Review and Meta-analysis. *Chest* 2017;151(4):764-75. doi: 10.1016/j.chest.2017.01.004 [published Online First: 2017/01/17]

40 Zhao H, Wang H, Sun F, et al. High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: a systematic review and meta-analysis. *Crit Care* 2017;21(1):184. doi: 10.1186/s13054-017-1760-8 [published Online First: 2017/07/14]

41 Dysart K, Miller TL, Wolfson MR, et al. Research in high flow therapy: mechanisms of action. *Respir Med* 2009;103(10):1400-5. doi: 10.1016/j.rmed.2009.04.007 [published Online First: 2009/05/27]

42 Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995;23(10):1638-52. doi: 10.1097/00003246-199510000-00007 [published Online First: 1995/10/01]

43 Pelosi P, Jaber S. Noninvasive respiratory support in the perioperative period. *Curr Opin Anaesthesiol* 2010;23(2):233-8. doi: 10.1097/ACO.0b013e328335daec [published Online First: 2009/12/19]

44 Alqahtani JS, Worsley P, Voegeli D. Effect of Humidified Noninvasive Ventilation on the Development of Facial Skin Breakdown. *Respir Care* 2018;63(9):1102-10. doi: 10.4187/respcare.06087 [published Online First: 2018/09/01]

45 Bräunlich J, Köhler M, Wirtz H. Nasal highflow improves ventilation in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11:1077-85. doi: 10.2147/copd.S104616 [published Online First: 2016/06/17]

46 Perkins GD, Ji C, Connolly BA, et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. *Jama* 2022;327(6):546-58. doi: 10.1001/jama.2022.0028 [published Online

For peer review only

First: 2022/01/25]

47 Beran A, Srour O, Malhas S-E, et al. High-Flow Nasal Cannula Versus Noninvasive Ventilation in Patients With COVID-19. *Respiratory Care* 2022;67(9):1177-89. doi: 10.4187/respcare.09987

48 Sztrymf B, Messika J, Bertrand F, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. *Intensive Care Med* 2011;37(11):1780-6. doi: 10.1007/s00134-011-2354-6 [published Online First: 2011/09/29]

49 Kernick J, Magarey J. What is the evidence for the use of high flow nasal cannula oxygen in adult patients admitted to critical care units? A systematic review. *Aust Crit Care* 2010;23(2):53-70. doi: 10.1016/j.aucc.2010.01.001 [published Online First: 2010/03/09]

50 Li G, Cook DJ, Thabane L, et al. Risk factors for mortality in patients admitted to intensive care units with pneumonia. *Respir Res* 2016;17(1):80. doi: 10.1186/s12931-016-0397-5 [published Online First: 2016/07/13]

51 Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during nasal high-flow oxygen therapy. *Respir Care* 2011;56(8):1151-5. doi: 10.4187/respcare.01106 [published Online First: 2011/04/19]

52 Ritchie JE, Williams AB, Gerard C, et al. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. *Anaesth Intensive Care* 2011;39(6):1103-10. doi: 10.1177/0310057x1103900620 [published Online First: 2011/12/15]

53 Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. *Am J Respir Crit Care Med* 2017;195(4):438-42. doi: 10.1164/rccm.201605-1081CP [published Online First: 2016/09/15]

54 Wagstaff TA, Soni N. Performance of six types of oxygen delivery devices at varying respiratory rates.

For peer review only

Anaesthesia 2007;62(5):492-503. doi: 10.1111/j.1365-2044.2007.05026.x [published Online First: 2007/04/24]

55 Frizzola M, Miller TL, Rodriguez ME, et al. High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. *Pediatr Pulmonol* 2011;46(1):67-74. doi: 10.1002/ppul.21326 [published Online First: 2010/12/21]

56 Jones PG, Kamona S, Doran O, et al. Randomized Controlled Trial of Humidified High-Flow Nasal Oxygen for Acute Respiratory Distress in the Emergency Department: The HOT-ER Study. *Respir Care* 2016;61(3):291-9. doi: 10.4187/respcare.04252 [published Online First: 2015/11/19]

57 Mündel T, Feng S, Tatkov S, et al. Mechanisms of nasal high flow on ventilation during wakefulness and sleep. *J Appl Physiol (1985)* 2013;114(8):1058-65. doi: 10.1152/japplphysiol.01308.2012 [published Online First: 2013/02/16]

For peer review only

Figure 1 PRISMA flow diagram of search strategy and included studies.

Figure 2 Forest plot for intubation rate.

HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; CI, confidence interval.

Figure 3 Forest plot for mortality.

HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; CI, confidence interval.

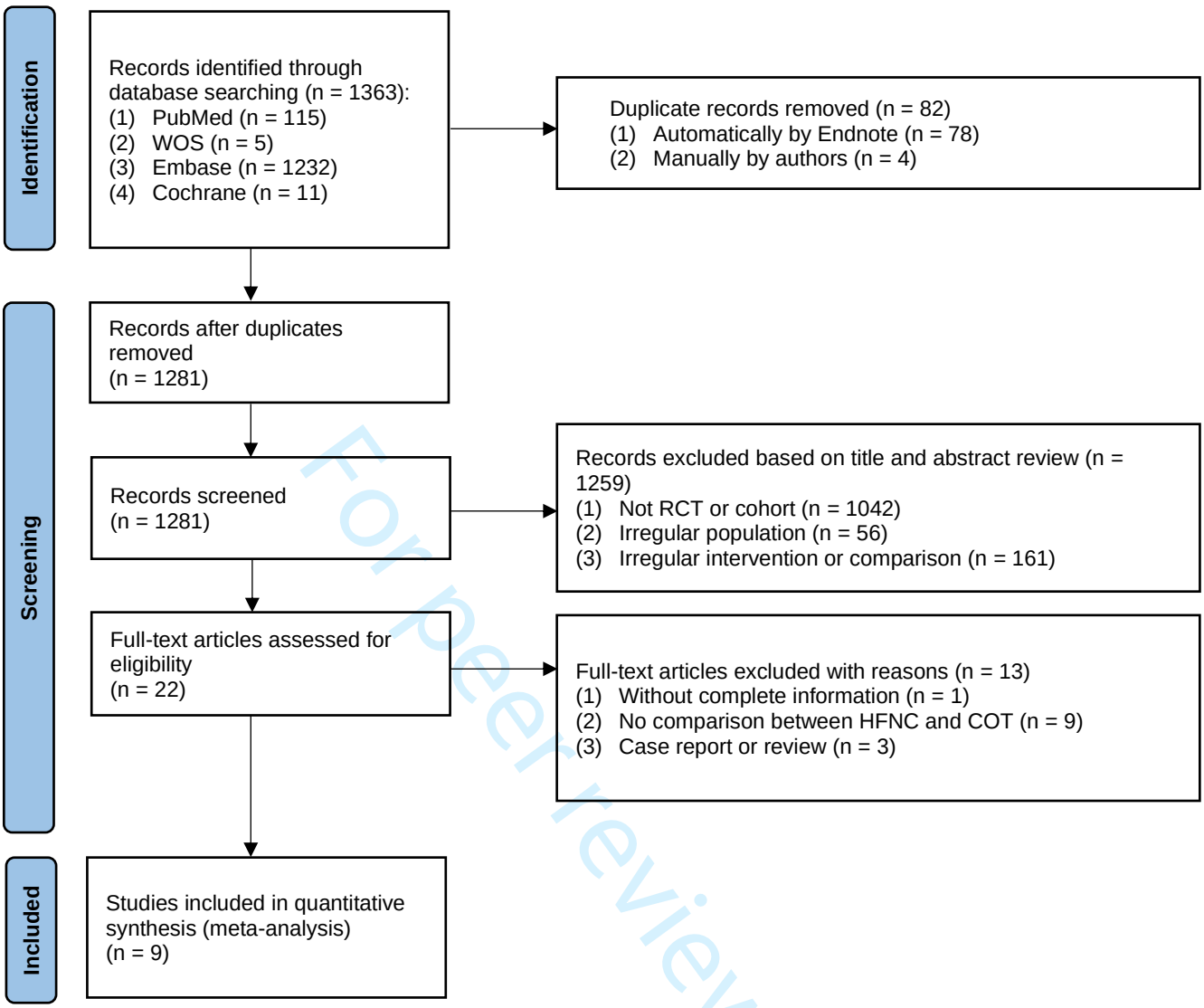
Figure 4 Forest plot for VFDs.

HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; CI, confidence interval; VFDs, ventilator free days.

Figure 5 Forest plot for ICU LOS.

HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; CI, confidence interval; ICU, intensive care unit; LOS, length of stay.

For peer review only

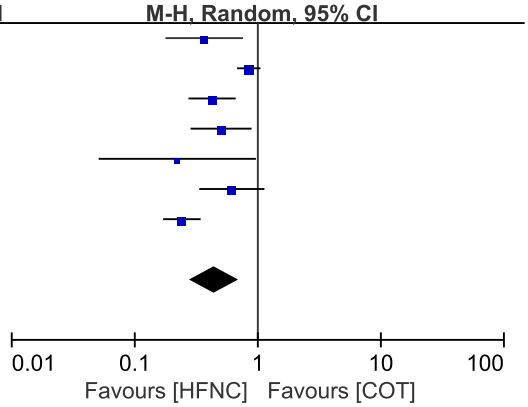


For peer review only

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bonnet 2021	39	76	46	62	13.0%	0.37 [0.18, 0.76]
COVID-ICU group 2021	242	567	359	766	18.1%	0.84 [0.68, 1.05]
Demoule 2020	82	146	175	233	16.2%	0.42 [0.27, 0.66]
Ospina-Tascón 2021	34	99	51	100	14.7%	0.50 [0.28, 0.89]
Sayan 2021	13	24	16	19	6.6%	0.22 [0.05, 0.97]
Wendel Garcia 2021	45	87	54	85	14.3%	0.62 [0.33, 1.13]
Wendel Garcia 2022	307	439	501	553	17.1%	0.24 [0.17, 0.34]
Total (95% CI)		**1438**		**1818**	**100.0%**	**0.44 [0.28, 0.71]**
Total events	762		1202			

Heterogeneity: Tau² = 0.30; Chi² = 40.12, df = 6 (P < 0.00001); I² = 85%

Test for overall effect: Z = 3.40 (P = 0.0007)

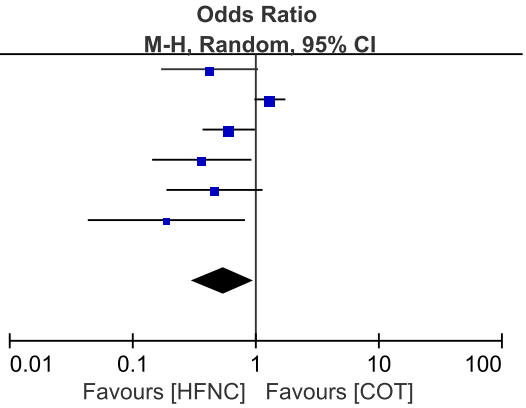


For peer review only

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bonnet 2021	9	76	15	62	15.4%	0.42 [0.17, 1.04]
COVID-ICU group 2021	106	567	115	766	23.2%	1.30 [0.97, 1.74]
Demoule 2020	30	146	70	233	21.0%	0.60 [0.37, 0.98]
Hansen 2021	9	30	33	61	15.2%	0.36 [0.14, 0.92]
Ospina-Tascón 2021	8	99	16	100	15.5%	0.46 [0.19, 1.13]
Sayan 2021	12	24	16	19	9.6%	0.19 [0.04, 0.82]
Total (95% CI)		**942**		**1241**	**100.0%**	**0.54 [0.30, 0.97]**
Total events	174		265			

Heterogeneity: Tau² = 0.36; Chi² = 21.57, df = 5 (P = 0.0006); I² = 77%

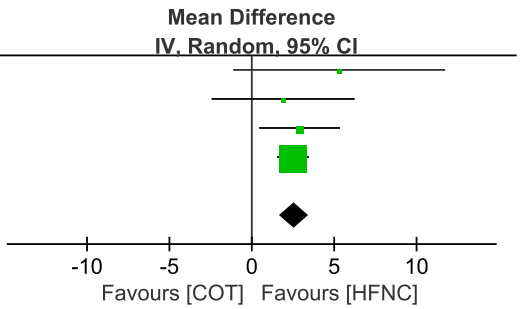
Test for overall effect: Z = 2.06 (P = 0.04)



For peer review only

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI
Bonnet 2021	17.8	17.4	76	12.5	20.5	62	1.8%	5.30 [-1.13, 11.73]
Hansen 2021	5.4	10.9	30	3.5	7.6	61	4.1%	1.90 [-2.44, 6.24]
Ospina-Tascón 2021	24.8	6.8	99	21.9	10.5	100	12.7%	2.90 [0.44, 5.36]
Sayan 2021	4.4	2.2	24	1.9	0.9	19	81.4%	2.50 [1.53, 3.47]
Total (95% CI)			**229**			**242**	**100.0%**	**2.58 [1.70, 3.45]**

Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 5.78 (P < 0.00001)

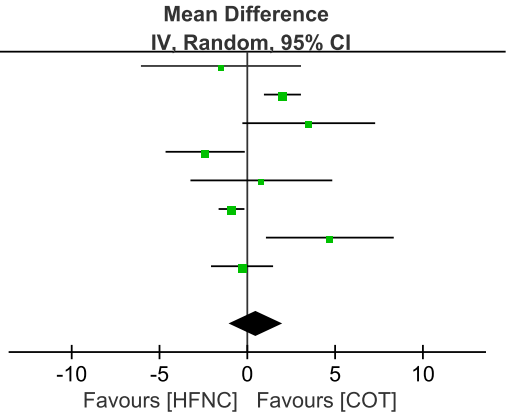


For peer review only

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI
Bonnet 2021	12.1	11.3	76	13.6	15.2	62	7.2%	-1.50 [-6.06, 3.06]
COVID-ICU group 2021	10.8	9.7	567	8.8	9.7	766	18.0%	2.00 [0.95, 3.05]
Hansen 2021	18	8.2	30	14.5	9.5	61	9.0%	3.50 [-0.28, 7.28]
Ospina-Tascón 2021	8.4	6	99	10.8	9.8	100	13.8%	-2.40 [-4.66, -0.14]
Sayan 2021	9.8	4.8	24	9	7.9	19	8.3%	0.80 [-3.24, 4.84]
Teng 2021	4	0.7	12	4.9	1	10	18.8%	-0.90 [-1.64, -0.16]
Wendel Garcia 2021	14.4	13.6	87	9.7	10.6	85	9.3%	4.70 [1.06, 8.34]
Wendel Garcia 2022	15.5	14.1	439	15.8	14.1	553	15.6%	-0.30 [-2.07, 1.47]
Total (95% CI)			**1334**			**1656**	**100.0%**	**0.52 [-1.01, 2.06]**

Heterogeneity: Tau² = 3.12; Chi² = 34.31, df = 7 (P < 0.0001); I² = 80%

Test for overall effect: Z = 0.67 (P = 0.50)



For peer review only

Table S1 – Search strategy

Database: PubMed

((("Cannula"[Mesh]) OR ((((((Cannula[Title/Abstract]) OR (Cannulae[Title/Abstract])) OR (Nasal Cannula[Title/Abstract])) OR (Cannula, Nasal[Title/Abstract])) OR (Nasal Cannulae[Title/Abstract])) OR (Cannulae, Nasal[Title/Abstract]))) AND (("COVID-19"[Mesh]) OR ((((((((((((((((((((((((((((((((((((((COVID-19[Title/Abstract]) OR (COVID 19[Title/Abstract])) OR (SARS-CoV-2 Infection[Title/Abstract])) OR (Infection, SARS-CoV-2[Title/Abstract])) OR (SARS CoV 2 Infection[Title/Abstract])) OR (SARS-CoV-2 Infections[Title/Abstract])) OR (2019 Novel Coronavirus Disease[Title/Abstract])) OR (2019 Novel Coronavirus Infection[Title/Abstract])) OR (2019-nCoV Disease[Title/Abstract])) OR (2019 nCoV Disease[Title/Abstract])) OR (2019-nCoV Diseases[Title/Abstract])) OR (Disease, 2019-nCoV[Title/Abstract])) OR (COVID-19 Virus Infection[Title/Abstract])) OR (COVID 19 Virus Infection[Title/Abstract])) OR (COVID-19 Virus Infections[Title/Abstract])) OR (Infection, COVID-19 Virus[Title/Abstract])) OR (Virus Infection, COVID-19[Title/Abstract])) OR (Coronavirus Disease 2019[Title/Abstract])) OR (Disease 2019, Coronavirus[Title/Abstract])) OR (Coronavirus Disease-19[Title/Abstract])) OR (Coronavirus Disease 19[Title/Abstract])) OR (Severe Acute Respiratory Syndrome Coronavirus 2 Infection[Title/Abstract])) OR (SARS Coronavirus 2 Infection[Title/Abstract])) OR (COVID-19 Virus Disease[Title/Abstract])) OR (COVID 19 Virus Disease[Title/Abstract])) OR (COVID-19 Virus Diseases[Title/Abstract])) OR (Disease, COVID-19 Virus[Title/Abstract])) OR (Virus Disease, COVID-19[Title/Abstract])) OR (2019-nCoV Infection[Title/Abstract])) OR (2019 nCoV Infection[Title/Abstract])) OR (2019-nCoV Infections[Title/Abstract])) OR (Infection, 2019-nCoV[Title/Abstract])) OR (COVID19[Title/Abstract])) OR (COVID-19 Pandemic[Title/Abstract])) OR (COVID 19 Pandemic[Title/Abstract])) OR (Pandemic, COVID-19[Title/Abstract])) OR (COVID-19 Pandemics[Title/Abstract])))) AND (("Oxygen Inhalation Therapy"[Mesh]) OR ((((((Oxygen Inhalation Therapy[Title/Abstract]) OR (Inhalation Therapy, Oxygen[Title/Abstract])) OR (Inhalation Therapies, Oxygen[Title/Abstract])) OR (Oxygen Inhalation Therapies[Title/Abstract])) OR (Therapies, Oxygen Inhalation[Title/Abstract])) OR (Therapy, Oxygen Inhalation[Title/Abstract])))

Database: Embase

#17. #12 AND #15 AND #16
#16. #3 OR #6 OR #9
#15. #13 OR #14
#14. 'oxygen therapy':ab,ti OR 'o2 administration':ab,ti OR 'o2 therapy':ab,ti OR 'oxygen administration':ab,ti OR 'oxygen inhalation therapy':ab,ti OR 'oxygen insufflation':ab,ti OR 'oxygen treatment':ab,ti
#13. 'oxygen therapy'/exp
#12. #10 OR #11
#11. 'coronavirus disease 2019':ab,ti OR '2019 novelcoronavirus disease':ab,ti OR '2019 novel coronavirus epidemic':ab,ti OR '2019 novel coronavirus infection':ab,ti OR '2019-ncov disease':ab,ti OR '2019-ncov infection':ab,ti OR 'coronavirus disease 2':ab,ti OR 'coronavirus disease 2010':ab,ti OR 'coronavirus disease 2019 pneumonia':ab,ti OR 'coronavirus disease-19':ab,ti OR 'coronavirus infection 2019':ab,ti OR covid:ab,ti OR 'covid 19 induced pneumonia':ab,ti OR 'covid 2019':ab,ti OR 'covid 10':ab,ti OR 'covid 19':ab,ti OR 'covid-19 induced pneumonia':ab,ti OR 'covid-19 pneumonia':ab,ti OR covid19:ab,ti OR 'ncov 2019 disease':ab,ti OR 'ncov 2019 infection':ab,ti OR 'new coronavirus pneumonia':ab,ti OR 'novel coronavirus 2019 disease':ab,ti

For peer review only

OR 'novel coronavirus 2019 infection':ab,ti OR 'novel coronavirus disease 2019':ab,ti OR 'novel coronavirus infected pneumonia':ab,ti OR 'novel coronavirus infection 2019':ab,ti OR 'novel coronavirus pneumonia':ab,ti OR 'paucisymptomatic coronavirus disease 2019':ab,ti OR 'sars coronavirus 2 infection':ab,ti OR 'sars coronavirus 2 pneumonia':ab,ti OR 'sars-cov-2 disease':ab,ti OR 'sars-cov-2 infection':ab,ti OR 'sars-cov-2 pneumonia':ab,ti OR 'sars-cov2 disease':ab,ti OR 'sars-cov2 infection':ab,ti OR 'sarscov2 disease':ab,ti OR 'sarscov2 infection':ab,ti OR 'severe acute respiratory syndrome 2':ab,ti OR 'severe acute respiratory syndrome 2 pneumonia':ab,ti OR 'severe acute respiratory syndrome coronavirus 2 infection':ab,ti OR 'severe acute respiratory syndrome coronavirus 2019 infection':ab,ti OR 'severe acute respiratory syndrome cov-2 infection':ab,ti OR 'wuhan coronavirus disease':ab,ti OR 'wuhan coronavirus infection':ab,ti

#10. 'coronavirus disease 2019'/exp

#9. #7 OR #8

#8. (((('high flow nasal cannula therapy':ab,ti OR 'hfoxygen therapy':ab,ti OR hfnc:ab,ti) AND 'high flow nasal cannula':ab,ti OR 'hfnc assisted ventilation':ab,ti OR 'hfnc therapy':ab,ti OR 'hfnc ventilation':ab,ti OR hfnct:ab,ti) AND 'high flow nasal cannula therapy':ab,ti OR 'high flow nasal cannula':ab,ti OR 'high flow nasal cannula respiratory support':ab,ti OR 'high flow nasal canula':ab,ti OR 'high flow nasal prong therapy':ab,ti OR 'high flow nasal therapy':ab,ti OR 'high flow oxygenation therapy':ab,ti OR 'high flow':ab,ti) AND hf:ab,ti AND 'oxygen therapy':ab,ti OR 'high-flow oxygen therapy':ab,ti OR 'high-flow oxygen treatment':ab,ti OR 'highflow nasal cannula':ab,ti OR 'highflow nasal cannula therapy':ab,ti OR 'nasal high flow':ab,ti

#7. 'high flow nasal cannula therapy'/exp

#6. #4 OR #5

#5. 'oxygen nasal cannula':ab,ti OR 'acucarehfnc':ab,ti OR 'basic nasal oxygen cannula':ab,ti OR 'basic nasal oxygen delivery catheter':ab,ti OR 'basic oxygen nasal cannula':ab,ti OR 'carbon dioxide sampling cannula':ab,ti OR 'carbon dioxide sampling nasal oxygen cannula':ab,ti OR 'carbon-dioxide-sampling nasal oxygen cannula':ab,ti OR 'cpap nasal oxygen cannula':ab,ti OR 'dispo med':ab,ti OR 'kentron capnography':ab,ti OR 'nasal oxygen cannulae':ab,ti OR 'nasal oxygen delivery catheter':ab,ti OR 'niv linemicrostream':ab,ti OR 'oxygen delivery nasal catheter':ab,ti

#4. 'oxygen nasal cannula'/exp

#3. #1 OR #2

#2. 'nasal cannula':ab,ti OR filterline:ab,ti OR'nasal canula':ab,ti OR 'nasal tube':ab,ti OR 'nose cannula':ab,ti OR 'nose tube':ab,ti OR 'optiflow nasal cannula':ab,ti OR 'pro-flow nasal cannula':ab,ti OR 'smart capnoline':ab,ti

Database: Web of Science

#1 TS=(Cannula) 20941

#2 AB=(Cannula OR Cannulae OR (Nasal Cannula) OR (Cannula, Nasal) OR (Nasal Cannulae) OR (Cannulae, Nasal)) 16968

#3 #1 OR #2 20941

#4 TS=(COVID-19) 272414

#5 AB=((COVID-19) OR (COVID 19) OR (SARS-CoV-2 Infection) OR (Infection, SARS-CoV-2) OR (SARS CoV 2 Infection) OR (SARS-CoV-2 Infections) OR (2019 Novel Coronavirus Disease) OR (2019 Novel Coronavirus Infection) OR (2019-nCoV Disease) OR (2019 nCoV Disease) OR (2019-nCoV Diseases) OR (Disease, 2019-nCoV) OR (COVID-19 Virus Infection) OR (COVID 19 Virus Infection) OR (COVID-19 Virus Infections) OR (Infection, COVID-19 Virus) OR (Virus Infection, COVID-19) OR (Coronavirus Disease 2019) OR (Disease 2019, Coronavirus) OR (Coronavirus Disease-19) OR (Coronavirus Disease 19) OR (Severe

For peer review only

Acute Respiratory Syndrome Coronavirus 2 Infection) OR (SARS Coronavirus 2 Infection) OR (COVID-19 Virus Disease) OR (COVID 19 Virus Disease) OR (COVID-19 Virus Diseases) OR (Disease, COVID-19 Virus) OR (Virus Disease, COVID-19) OR (2019-nCoV Infection) OR (2019 nCoV Infection) OR (2019-nCoV Infections) OR (Infection, 2019-nCoV) OR (COVID19) OR (COVID-19 Pandemic) OR (COVID 19 Pandemic) OR (Pandemic, COVID-19) OR (COVID-19 Pandemics)) 198041

#6 #4 OR #5 278439

#7 TS=(Oxygen Inhalation Therapy) 1367

#8 AB=((Oxygen Inhalation Therapy) OR (Inhalation Therapy, Oxygen) OR (Inhalation Therapies, Oxygen) OR (Oxygen Inhalation Therapies) OR (Therapies, Oxygen Inhalation) OR (Therapy, Oxygen Inhalation)) 613

#9 #7 OR #8 1367

#10 #3 AND #6 AND #9 5

Database: Cochrane Library

#1 MeSH descriptor: [Cannula] explode all trees

#2 (Cannula or Cannulae or Nasal Cannula or Cannula, Nasal or Nasal Cannulae or Cannulae, Nasal):ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [COVID-19] explode all trees

#5 (COVID-19 or COVID 19 or SARS-CoV-2 Infection or Infection, SARS-CoV-2 or SARS CoV 2 Infection or SARS-CoV-2 Infections or 2019 Novel Coronavirus Disease or 2019 Novel Coronavirus Infection or 2019 nCoV Disease or COVID-19 Virus Infection or COVID 19 Virus Infection or COVID-19 Virus Infections or Infection, COVID-19 Virus or Virus Infection, COVID-19 or Coronavirus Disease 2019 or Disease 2019, Coronavirus or Coronavirus Disease-19 or Coronavirus Disease 19 or Severe Acute Respiratory Syndrome Coronavirus 2 Infection or SARS Coronavirus 2 Infection or COVID-19 Virus Disease or COVID 19 Virus Disease or COVID-19 Virus Diseases or Disease, COVID-19 Virus or Virus Disease, COVID-19 or 2019 nCoV Infection or COVID19 or COVID-19 Pandemic or COVID 19 Pandemic or Pandemic, COVID-19 or COVID-19 Pandemics):ti,ab,kw (Word variations have been searched)

#6 #4 or #5

#7 MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees

#8 (Oxygen Inhalation Therapy or Inhalation Therapy, Oxygen or Inhalation Therapies, Oxygen or Oxygen Inhalation Therapies or Therapies, Oxygen Inhalation or Therapy, Oxygen Inhalation):ti,ab,kw (Word variations have been searched)

#9 #7 or #8

#10 #3 and #6 and #9

Table S2 Methodological quality (cohort studies)

Dear Dr./Prof. ***,

Hope this e-mail finds you well.

My name is Yang Li and I'm a researcher from Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, China.

Recently our group are performing a systematic review and meta-analysis to investigate the effect of high-flow nasal cannula therapy (HFNC) versus conventional oxygen therapy (COT) on intubation rate, 28-day ICU mortality, 28-day ventilator-free days (VFDs) and ICU length of stay (ICU LOS) in adult patients with acute respiratory failure (ARF) by COVID-19. Your paper entitled "***" is of significant importance in this topic. Of course, your excellent work will be included into the meta-analysis. However, some important information and data have not been reported in the paper. We would appreciate it if you could provide us the following data: ___. By the way, on behalf of our group, we will add your contribution in the acknowledgement part of the article. We believe that this paper will result in a good publication.

Your help is of great importance, and the results of the meta-analysis may be useful for future studies.

We are looking forward to hearing from you.

Kindest regards

For peer review only

Table S3 Methodological quality (cohort studies)

Study	Selection				Comparability	Outcome			Overall quality assessment
	Representativeof exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of cohorts based on design and analysis	Assessment of outcome	Timing of follow-up	Adequate follow-up	
Bonnet, 2021	★	★	★	★	★	★	★	★	8
COVID-ICU group, 2021	★	★	★	★	★	★	★	★	8
Demoule, 2020	★	★	★	★	★	★	★	★	8
Hansen, 2021	★	★	★	★	★	★	★	★	8
Sayan, 2021	★	★	★	★	★	★	★	★	8
Wendel Garcia, 2021	★	★	★	★	★	★	★	★	8
Wendel Garcia, 2022	★	★	★	★	★	★	★	★	8

For peer review only

Table S4 GRADE evidence profile for the studies in the meta-analysis

Outcomes	No. of studies	Study design	Quality assessment					No. of patients		Effect		Evidence quality	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	HFNC	COT	Relative (95% CI)	Absolute (95% CI)		
IR	7	1 RCT, 6 Cohort	Not serious	Serious [a]	Not serious	Not serious	NA [b]	762/1438	1202/1818	OR 0.44 (0.28, 0.71)	199 fewer per 1,000 (from 80 fewer to 308 fewer)	Low	CRITICAL
M	6	1RCT, 5 Cohort	Not serious	Not serious	Not serious	Not serious	NA [b]	174/942	265/1241	OR 0.54 (0.30, 0.97)	76 fewer per 1,000 (from 5 fewer to 138 fewer)	Moderate	CRITICAL
VFD	4	1 RCT, 3 Cohort	Not serious	Not serious	Not serious	Not serious	NA [b]	229	242	_	MD 2.58 higher (1.7 to 3.45 higher)	Moderate	IMPORTANT
LOS	8	2 RCT, 6 Cohort	Not serious	Serious [c]	Not serious	Serious [d]	NA [b]	1334	1656	_	MD 0.52 higher (1.01 lower to 2.06 higher)	Very low	IMPORTANT

HFNC: high flow nasal cannula, COT: conventional oxygen therapy, CI: confidence interval, OR: odds ratio, MD: mean difference

NA: not applicable

a. I2=85%, the heterogeneity was high

b. Publication bias could not be determined as the number of studies was less than 10

c. I2=80%, the heterogeneity was high

d. Wide confidence interval including benefits and harms

For peer review only

http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

bmjopen-2022-067879 on 30 March 2023. Downloaded from

Figure S1 Risk of bias graph

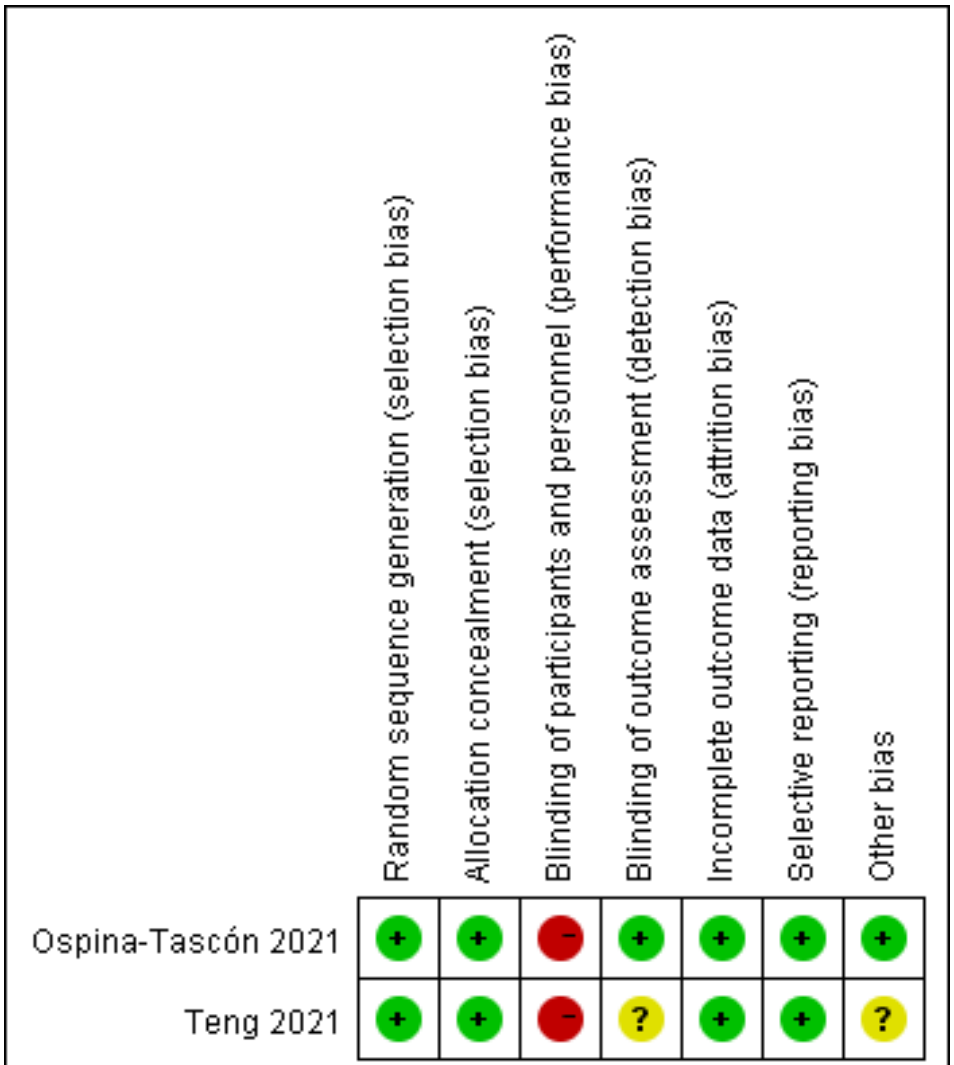
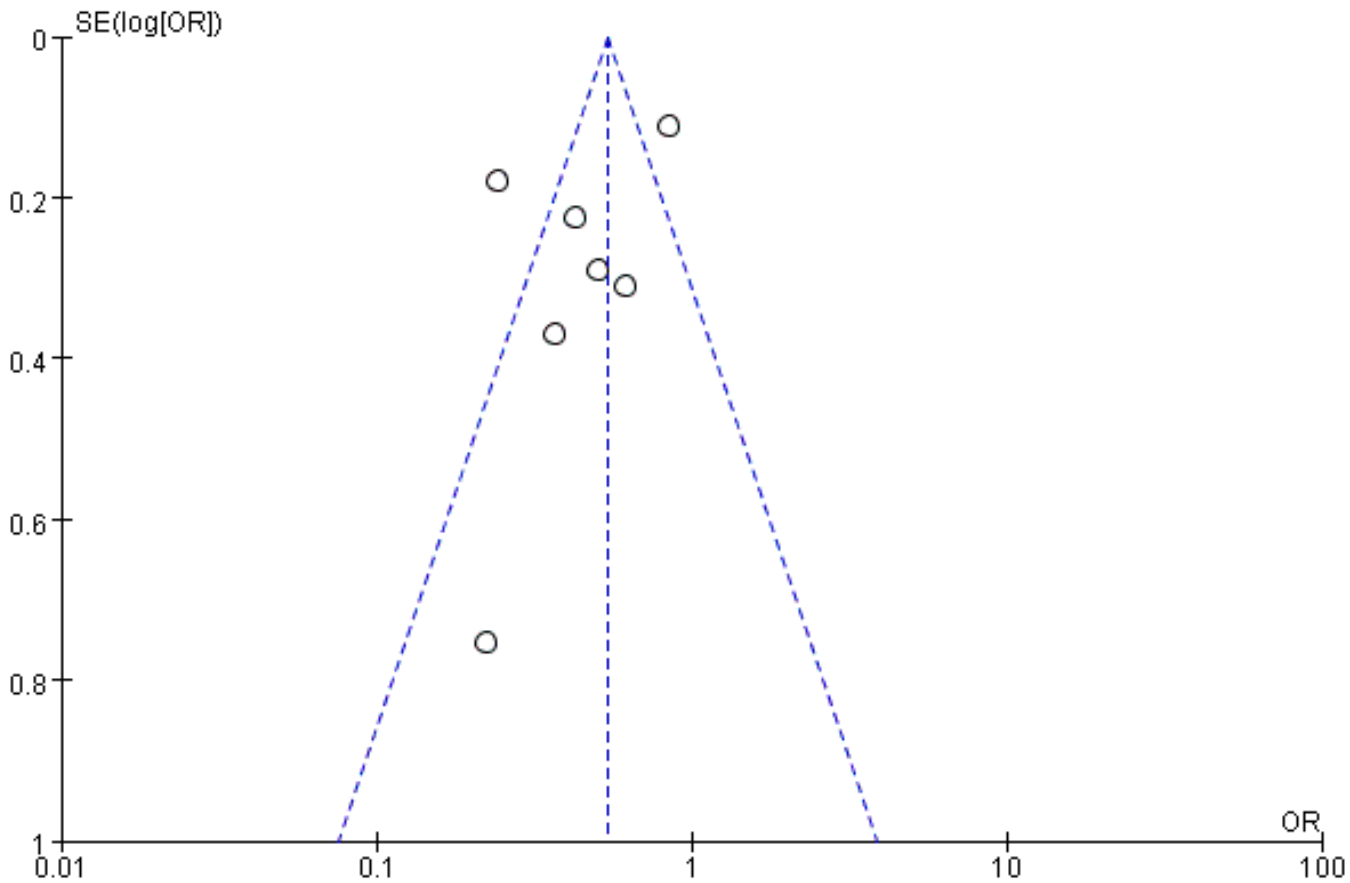


Figure S2 Risk of bias summary

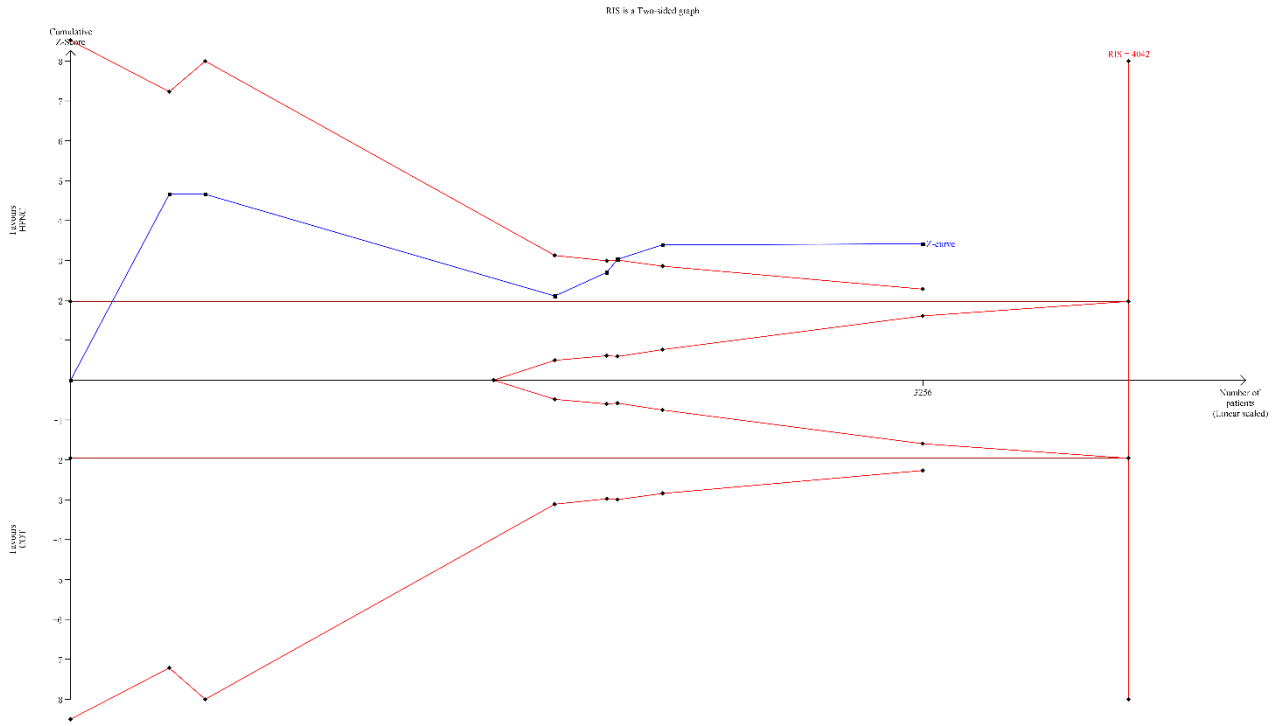
peer review only

Figure S3 Funnel plot for intubation rate



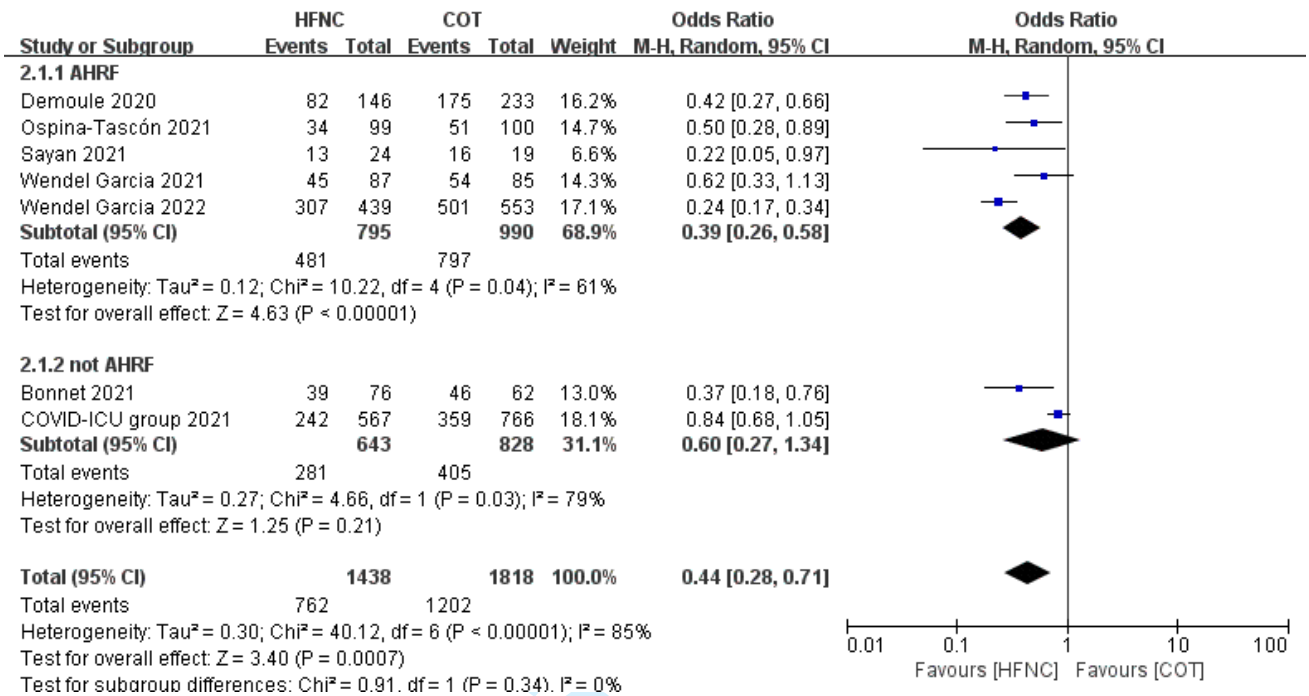
iew only

Figure S4 Trial sequential analysis of weaning success



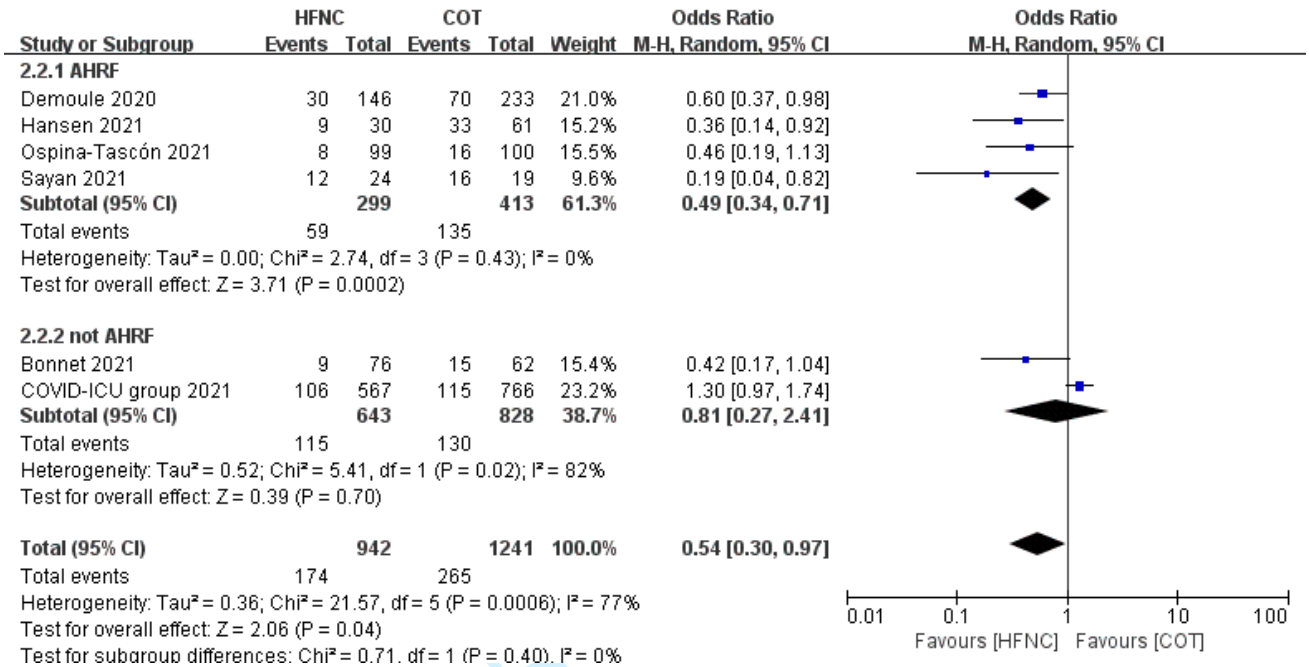
For peer review only

Figure S5 Subgroup analysis of intubation rate between the two groups with regard to type of ARF



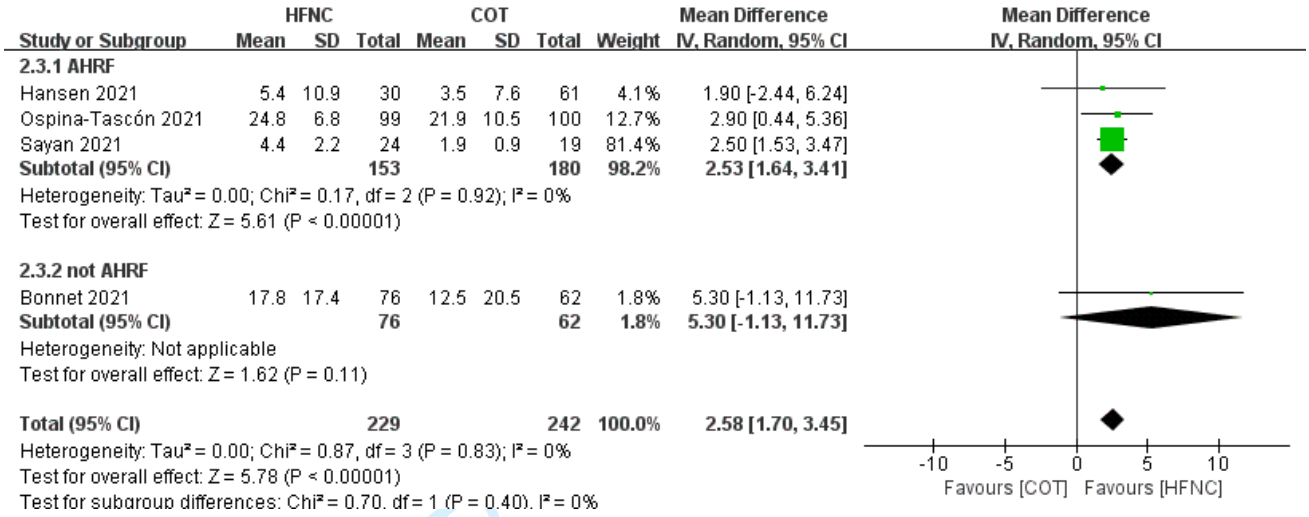
For peer review only

Figure S6 Subgroup analysis of mortality between the two groups with regard to type of ARF



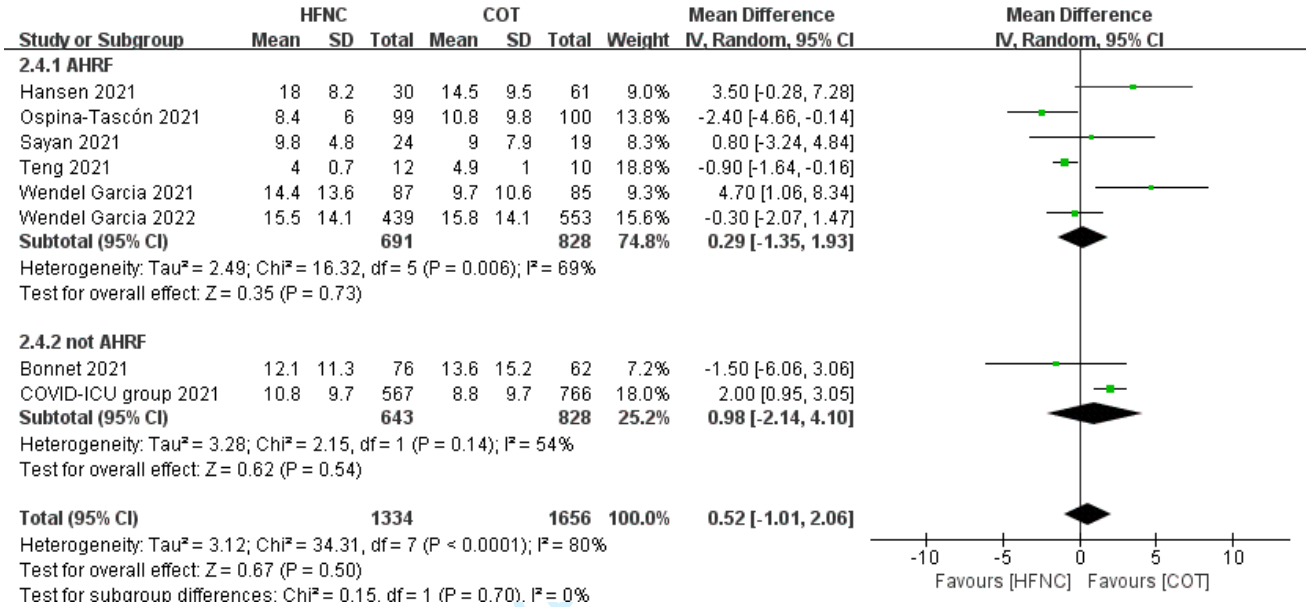
For peer review only

Figure S7 Subgroup analysis of VFDs between the two groups with regard to type of ARF



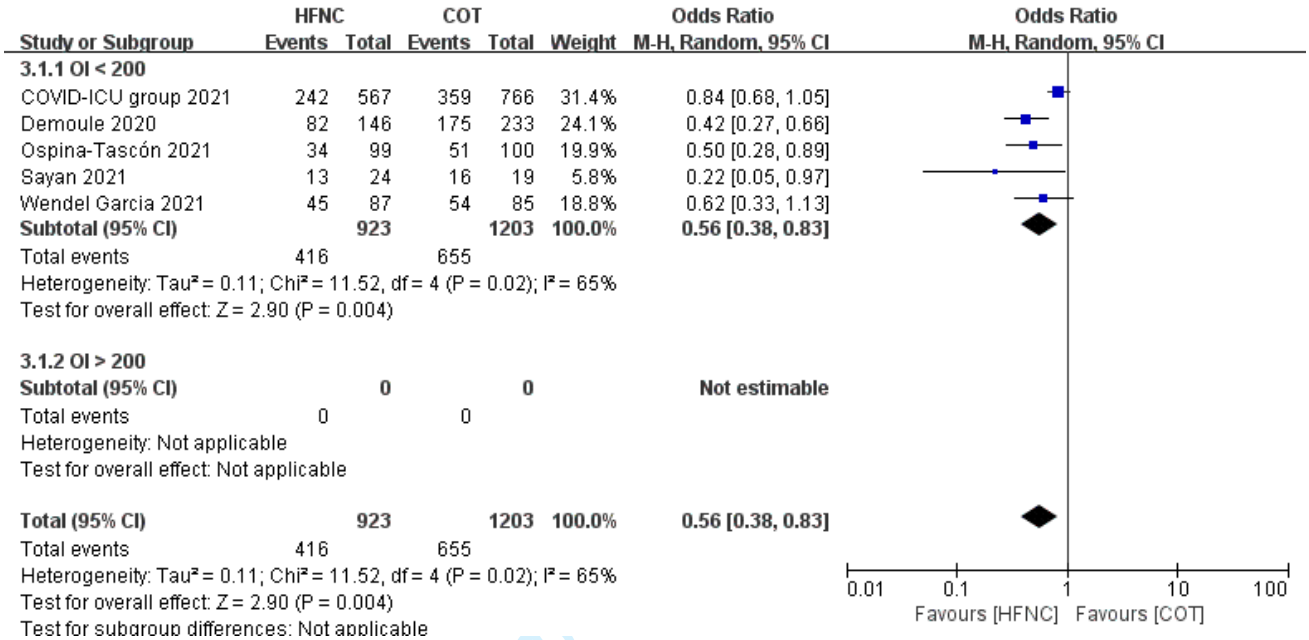
peer review only

Figure S8 Subgroup analysis of LOS between the two groups with regard to type of ARF



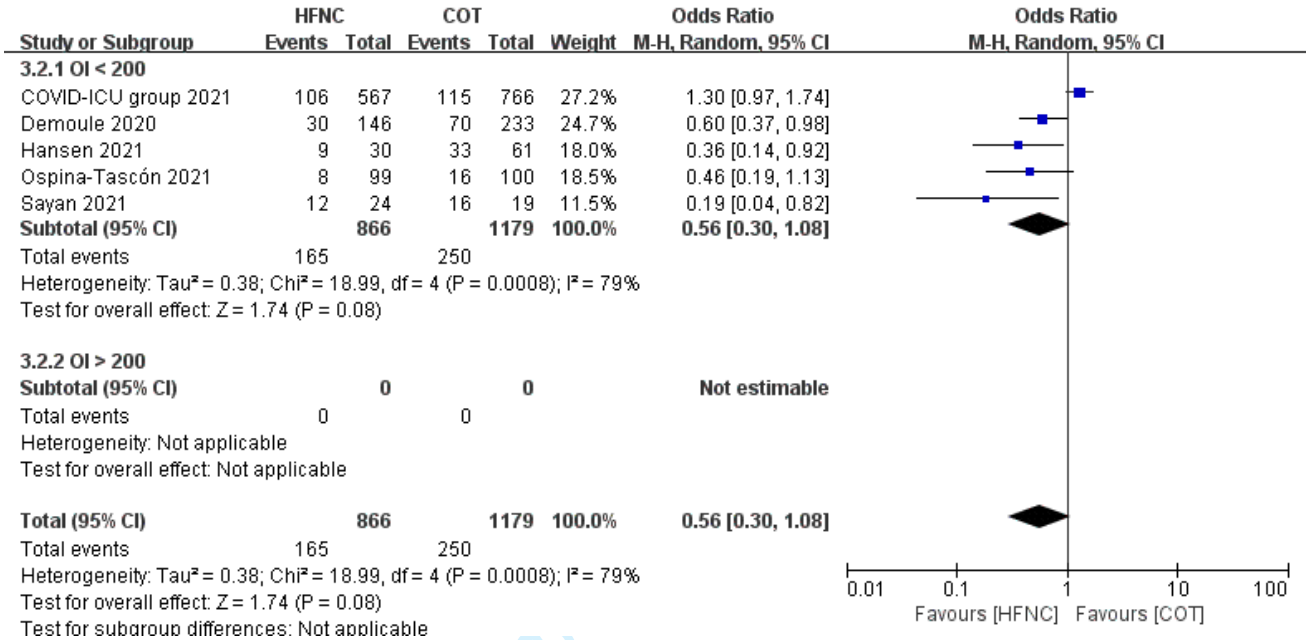
For peer review only

Figure S9 Subgroup analysis of intubation rate between the two groups with regard to OI



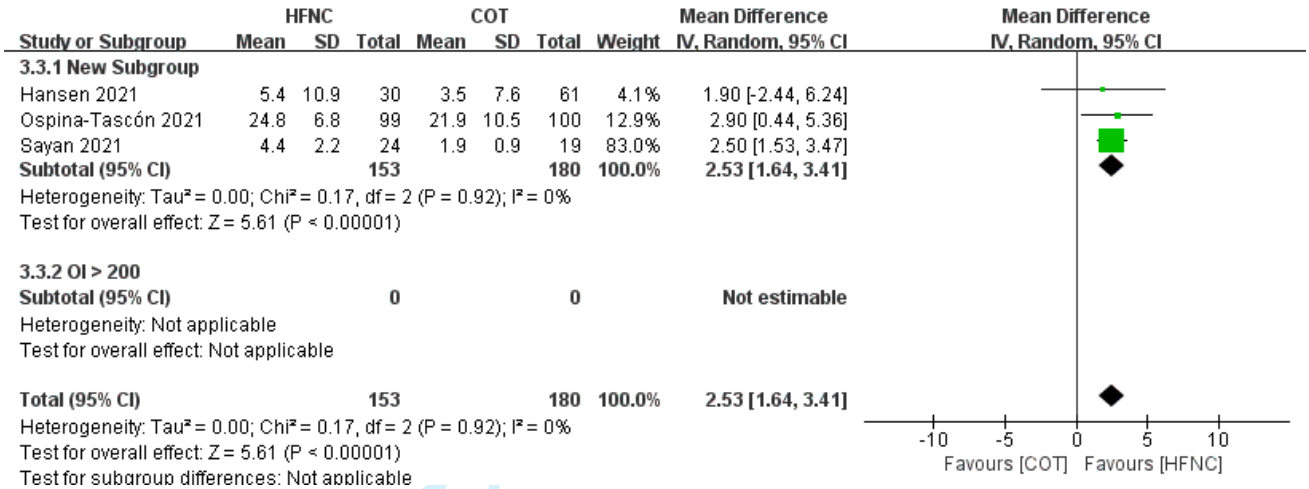
er review only

Figure S10 Subgroup analysis of mortality between the two groups with regard to OI



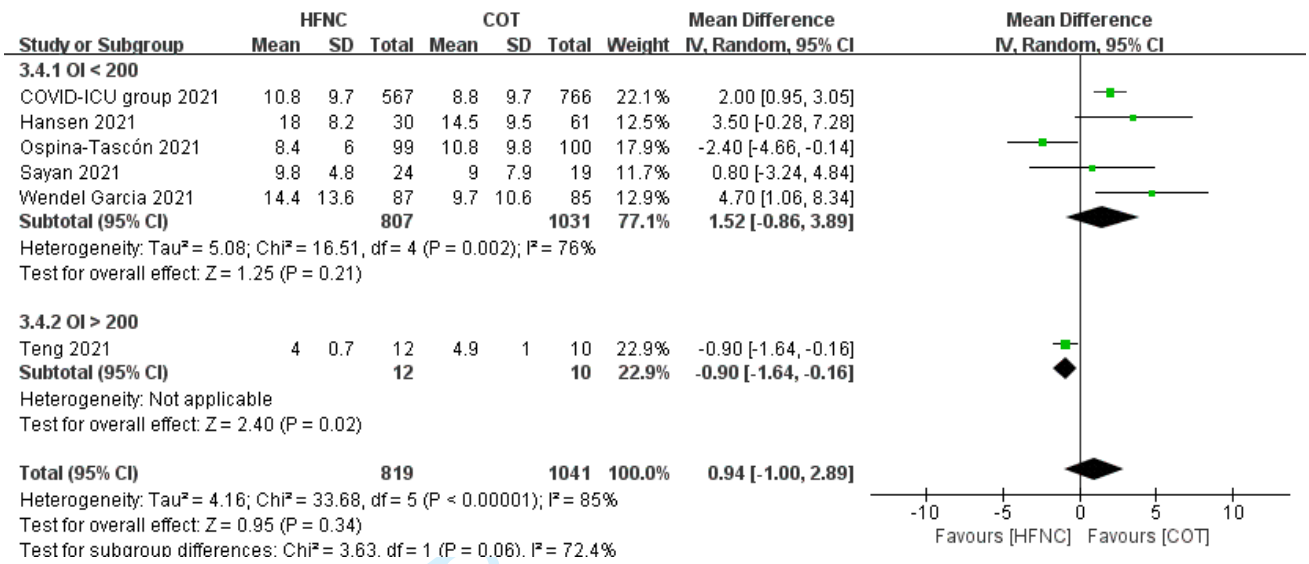
For peer review only

Figure S11 Subgroup analysis of VFDs between the two groups with regard to OI



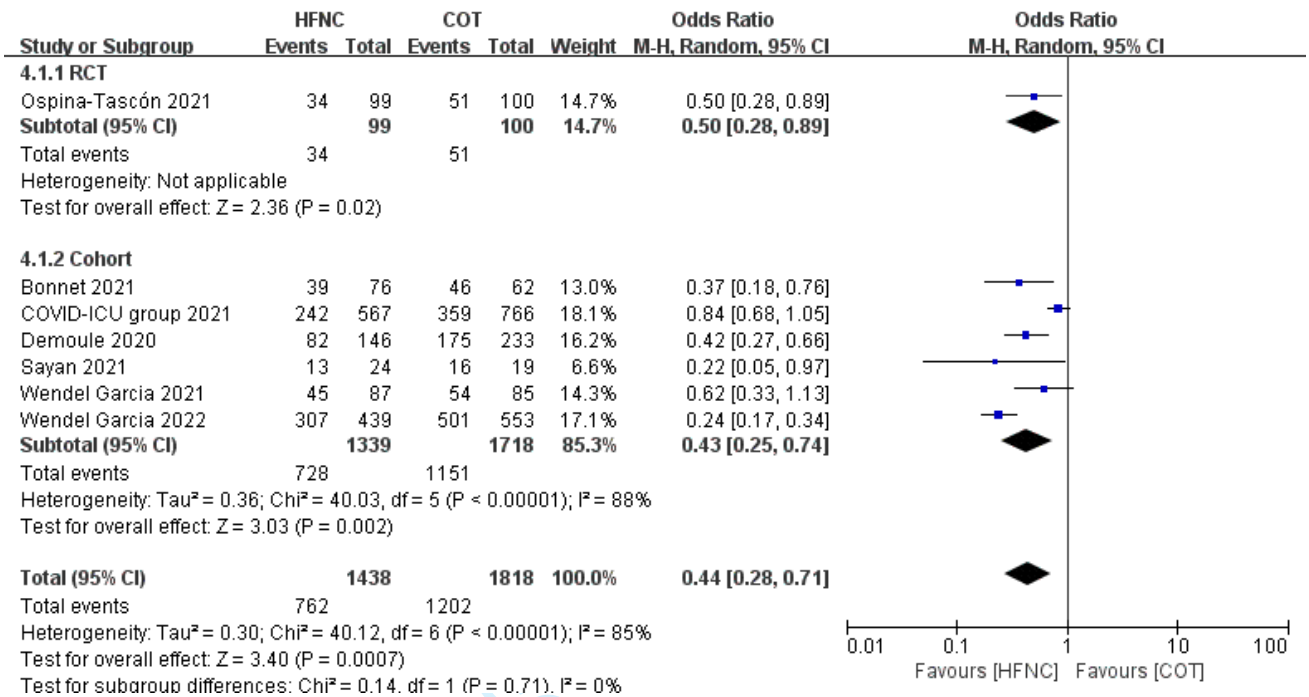
peer review only

Figure S12 Subgroup analysis of LOS between the two groups with regard to OI



peer review only

Figure S13 Subgroup analysis of IR between the two groups with regard to type of research



For peer review only

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-067879 on 30 March 2023. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7,8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10, 11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10, 11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, 11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12,13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14,15,16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16,17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1136/bmjopen-2022-067879 on 30 March 2023. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.