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

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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 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 randomised controlled trials or cohort studies comparing HFNC with COT in patients with COVID-19 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 randomised controlled trials or cohort studies. Meta-analysis was conducted using RevMan V.5.4 computer software using a random effects model with a 95% CI. Heterogeneity was assessed using Cochran's Q test (χ^2) 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 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 (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 randomised controlled trials are necessary to validate our findings.

PROSPERO registration number CRD42022345713.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This meta-analysis was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
⇒ Cochrane Collaboration tool was used to assess the quality of randomised controlled trials (RCTs), and Newcastle-Ottawa Scale was used to evaluate the quality of cohort studies.
⇒ Subgroup analyses were performed to account for sources of heterogeneity.
⇒ Due to the limited number of relevant RCTs, our meta-analysis consisted mainly of cohort studies, which may still affect the accuracy of the results.
⇒ Significant differences between high-flow nasal cannula therapy and conventional oxygen therapy made blinding of participants and personnel difficult, so the performance bias of all included RCTs was all at high risk.

INTRODUCTION

The outbreak of COVID-19 has caused untold harm and challenges to people in >200 countries and territories worldwide. As of 26 June 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 hospitalisation.[2 3] It can progress to acute respiratory failure (ARF), which presents with severe hypoxaemia and dyspnoea, 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 optimisation.[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]

Non-invasive 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 patients with COVID-19-related 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 non-invasive 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.

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]

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: randomised controlled trials (RCTs) or cohort studies.
2. Population: patients aged over 16 years, 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 (eg, 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 judgement of the physician in charge. The secondary outcomes were 28-day ICU mortality, 28-day VFDs and ICU LOS. Twenty-eight-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 online supplemental 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 finalise 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, comorbidities, oxygenation index (OI) (PaO_2/FiO_2) before the start of oxygen therapy, sequential organ failure assessment score 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 email used to contact the authors is available in the online supplemental 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 V.5.4 software (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 judgements. In cases of disagreement, 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 V.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 Grading of Recommendations, Assessment, Development and Evaluations (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 Cochran's Q test (χ^2) 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 V.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 (M-H) method and expressed as OR with 95% CIs. 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 IQR were reported in the study, they were converted into the mean and SD using the formulas proposed by Luo *et al* and Wan *et al*.[27 28]

SUBGROUP ANALYSIS

Some subgroup analyses were pre-established. Owing to the higher gas flow rate of HFNC compared with COT, HFNC is more effective in targeting hypercapnic respiratory failure with CO_2 retention. However, its efficacy in AHRF 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 in patients with OI ≤200 mm Hg and OI >200 mm Hg before the start of oxygen therapy compared with 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

We used trail sequential analysis (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 AHRF.[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 V.0.9.5.10 beta.[30]

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.

RESULTS

Study identification and selection

We initially obtained 1363 records in accordance with the search strategy. After excluding 82 duplicate studies, 1281

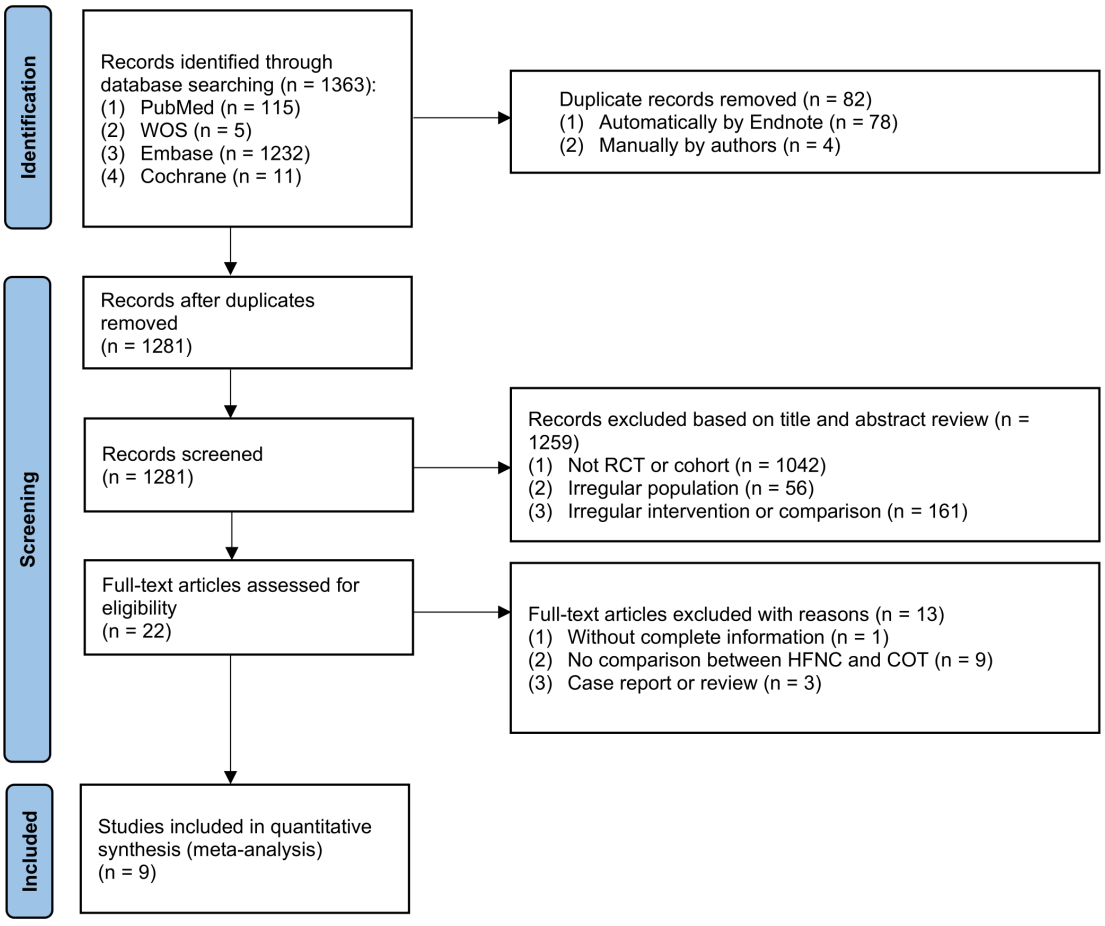

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of search strategy and included studies. COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; RCT, randomised controlled trial; WOS, Web of Science.

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: 1 lacked complete information, 9 did not compare HFNC with COT and 3 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

Tables 1 and 2 summarise 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 USA,[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 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 email 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 mm Hg 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 of summary bias in individual studies is shown in online supplemental figures S1 and S2. The quality of the cohort studies was assessed using NOS. The overall quality of all the included cohort

Table 1 Study characteristics of the included studies

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

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

studies was good, with all studies scoring 8. The results of the quality assessment are shown in online supplemental table S3.

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

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 *et al*[31]	29.0±6.05/28.8±5.3	37/19	24/19	NR	NR	NR	①②③④
Schmidt *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[13]	NR	7/4	3/3	NR	224.3±12.6/213.7±4.6	NR	④
Wendel-Garcia *et al*[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 *et al*[38]	28.4±3.7/28.0±4.5	NR	91/114	32/40	NR	NR	① ④

①: intubation rate; ②: mortality; ③: ventilator-free days; ④: ICU length of stay.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; COT, conventional oxygen therapy; DM, diabetes mellitus; HFNC, high-flow nasal cannula; HT, hypertension; ICU, intensive care unit; NR, not reported; OI, oxygenation index; SOFA, sequential organ function assessment.

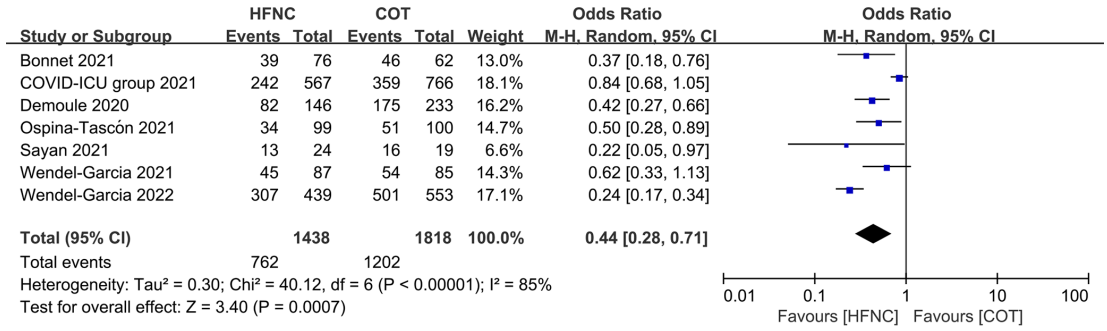

Figure 2 Forest plot for intubation rate. COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; M-H, Mantel-Haenszel.

patients treated with HFNC had a statistically significantly lower rate of intubation compared with 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 (online supplemental table S4). Funnel plots were visually inspected and did not show any evidence of publication bias (online supplemental 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 (online supplemental figure S4). However, more RCTs are needed because the study included mostly cohort studies.

Secondary outcomes

Twenty-eight-day ICU mortality

Six studies involving 2183 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 (online supplemental table S3).

Twenty-eight-day ventilator-free days

Four studies involving 471 patients evaluated the 28-day VFDs.[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 VFDs was thought to be moderate (online supplemental 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 (online supplemental 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) (online supplemental figure S5). For 28-day ICU mortality, subgroup analysis revealed that HFNC was favoured over COT (OR 0.49, 95% CI 0.34 to 0.71, p=0.0002; M-H random; I^2=0%, p=0.43) (online supplemental 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) (online supplemental 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) (online supplemental figure S8).

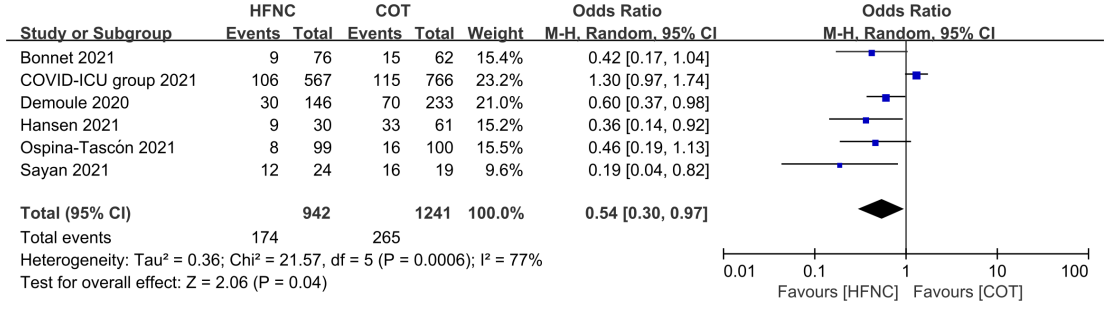

Figure 3 Forest plot for mortality. COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; M-H, Mantel-Haenszel.

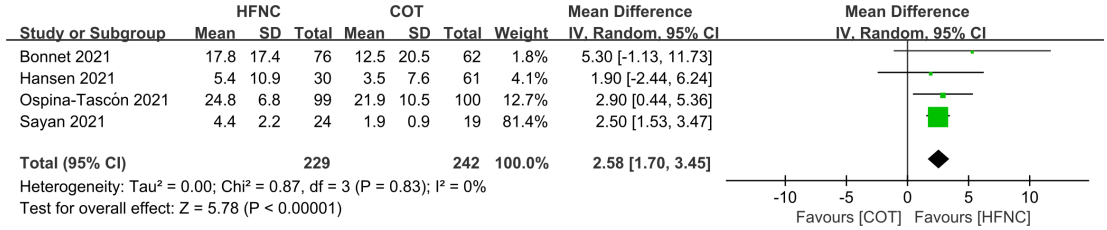

Figure 4 Forest plot for VFDs. COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; VFDs, ventilator-free days.

Initial oxygenation index

Six trials included patients with an OI ≤200 mm Hg. Five studies, including 2126 patients, reported the intubation rate in patients with an initial OI ≤200 mm Hg. The results of the subgroup analysis showed a statistically significant reduction in the intubation rate in patients with OI ≤200 mm Hg treated with HFNC compared with 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) (online supplemental 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) (online supplemental figure S10). Three studies reported VFDs in patients with an initial OI ≤200 mm Hg: 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) (online supplemental figure S11). In addition, HFNC did not reduce ICU LOS compared with COT (MD 1.52, 95% CI −0.86 to 3.89, p=0.21; M-H random; I^2=76%, p=0.002) (online supplemental 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) (online supplemental figure S13).

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 mm Hg, 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 with 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 multicentre RCT conducted in France by Frat *et al*, the leading cause of ARF 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 mm Hg 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.

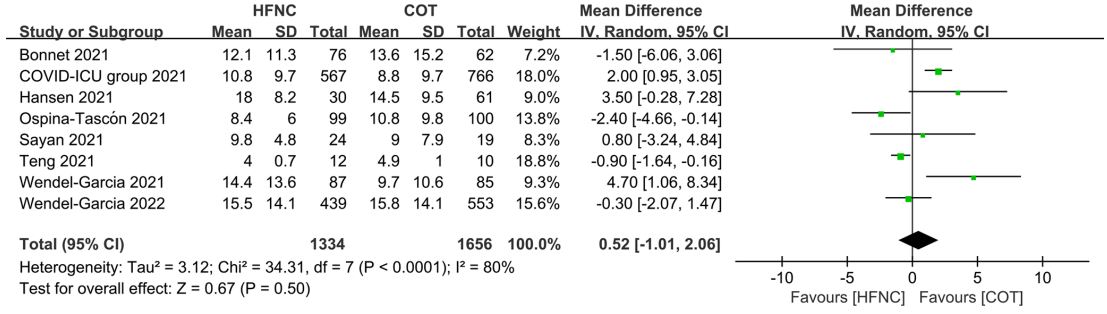

Figure 5 Forest plot for ICU LOS. COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; ICU, intensive care unit; LOS, length of stay.

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 chronic obstructive pulmonary disease (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, 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 centres; (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, non-invasive 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 ARF caused by COPD. Compared with HFNC, NIV should theoretically improve pulmonary oxygenation and gas exchange in ARF because it provides a higher positive end-expiratory pressure.[43] However, not all patients can tolerate NIV owing to adverse events, such as claustrophobia, facial pressure ulcers and eye irritation.[44 45] In an RCT that included 1273 patients, the authors compared the effects of HFNC, COT and continuous positive airway pressure (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, dyspnoea 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 dyspnoea 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 RCTs. 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 (eg, 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 emphasise 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 included documented treatments for COVID-19. We attempted to contact the primary authors by email 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.

CONCLUSION

Overall, HFNC reduced intubation rate and 28-day ICU mortality in patients with ARF due to COVID-19 and improved 28-day VFDs compared with COT. However, it did not reduce the ICU LOS. To validate our finding, large-scale RCTs are necessary.

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. YL is responsible for the overall content as guarantor. All authors read and approved of the final manuscript for publication.

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Competing interests None declared.

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 Not applicable.

Ethics approval As this study did not directly involve human subjects, and only used data from published articles, institutional review board approval was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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

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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

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

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

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

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)	86 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

Figure S1 Risk of bias graph

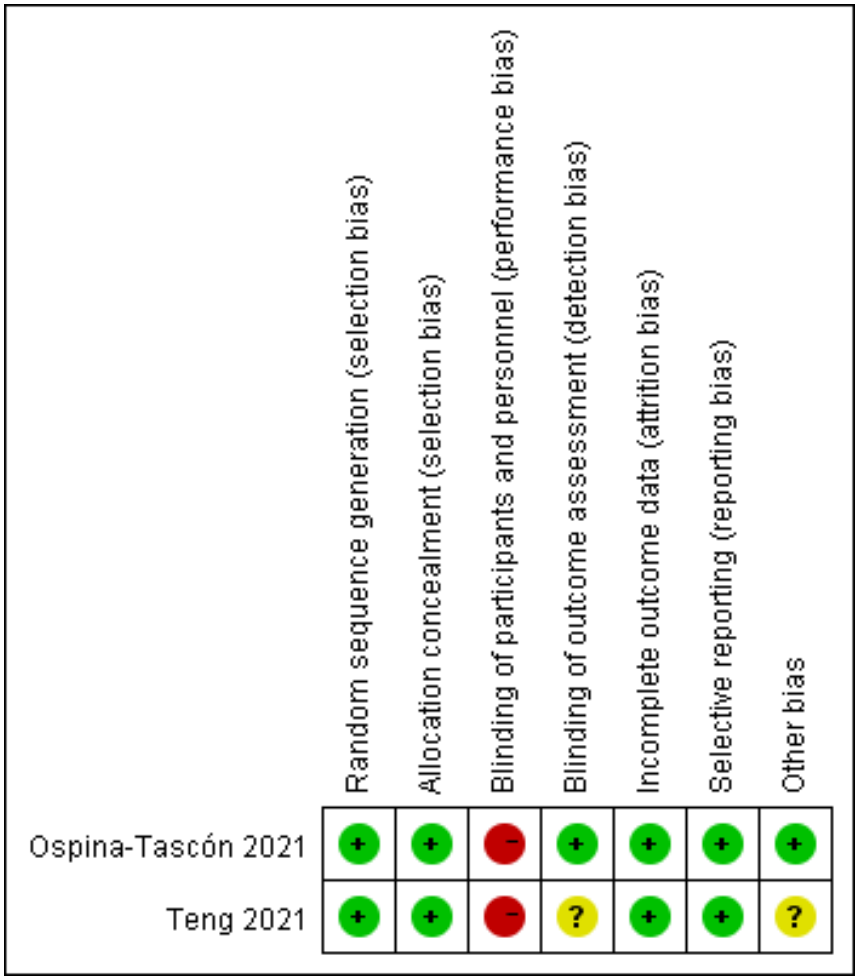

Figure S2 Risk of bias summary

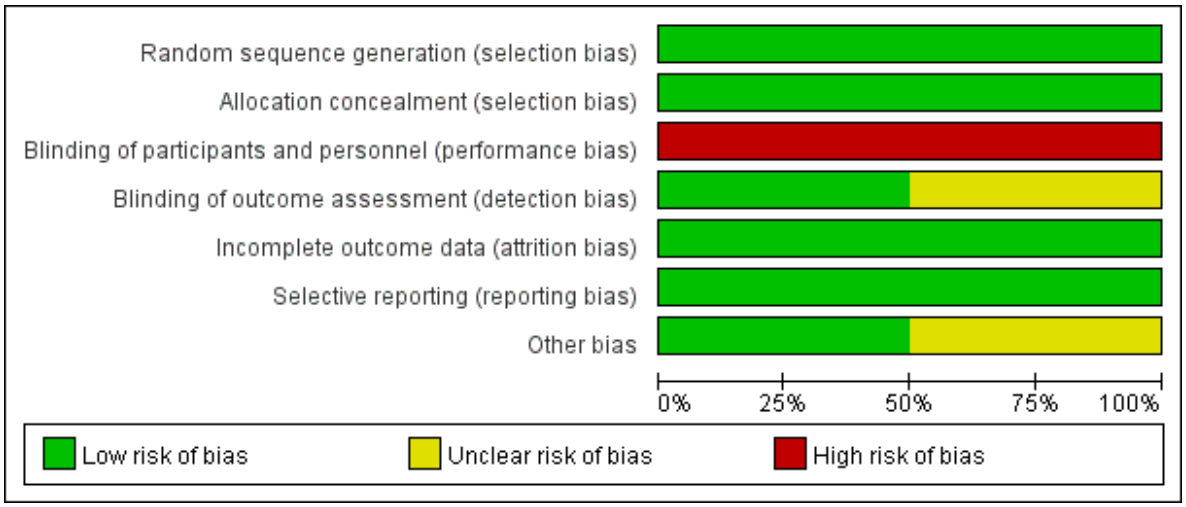

Figure S3 Funnel plot for intubation rate

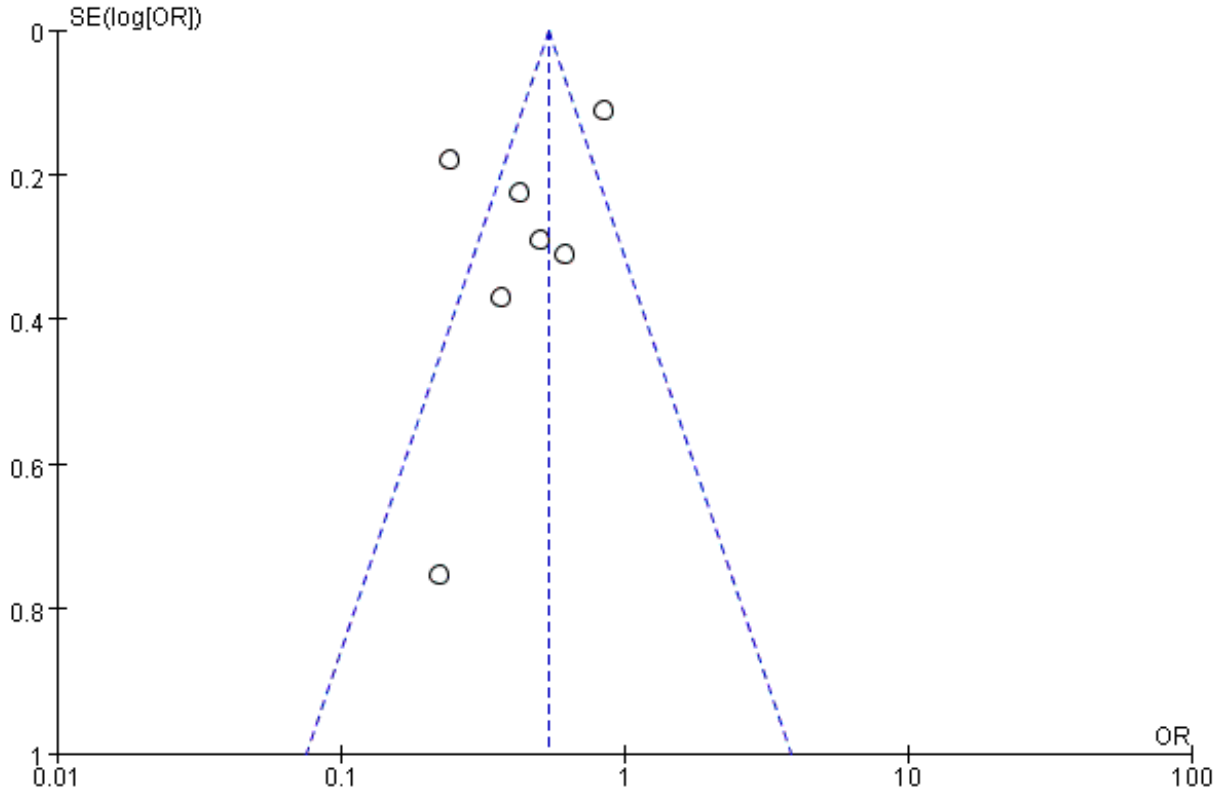

Figure S4 Trial sequential analysis of weaning success

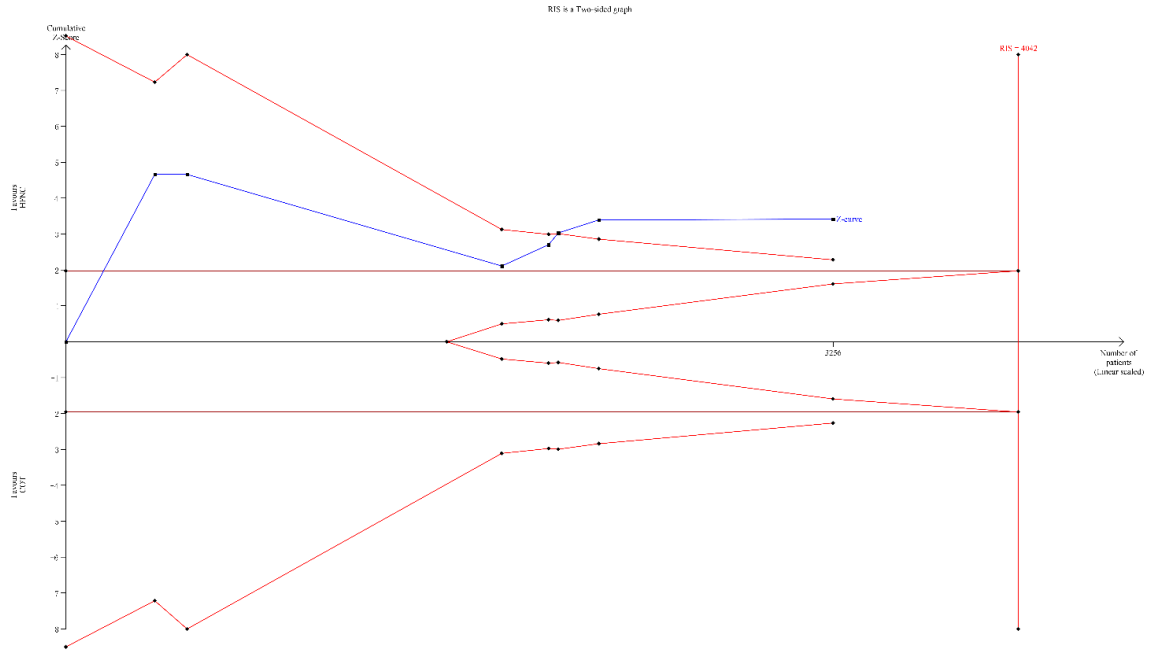

Figure S5 Subgroup analysis of intubation rate between the two groups with regard to type of ARF

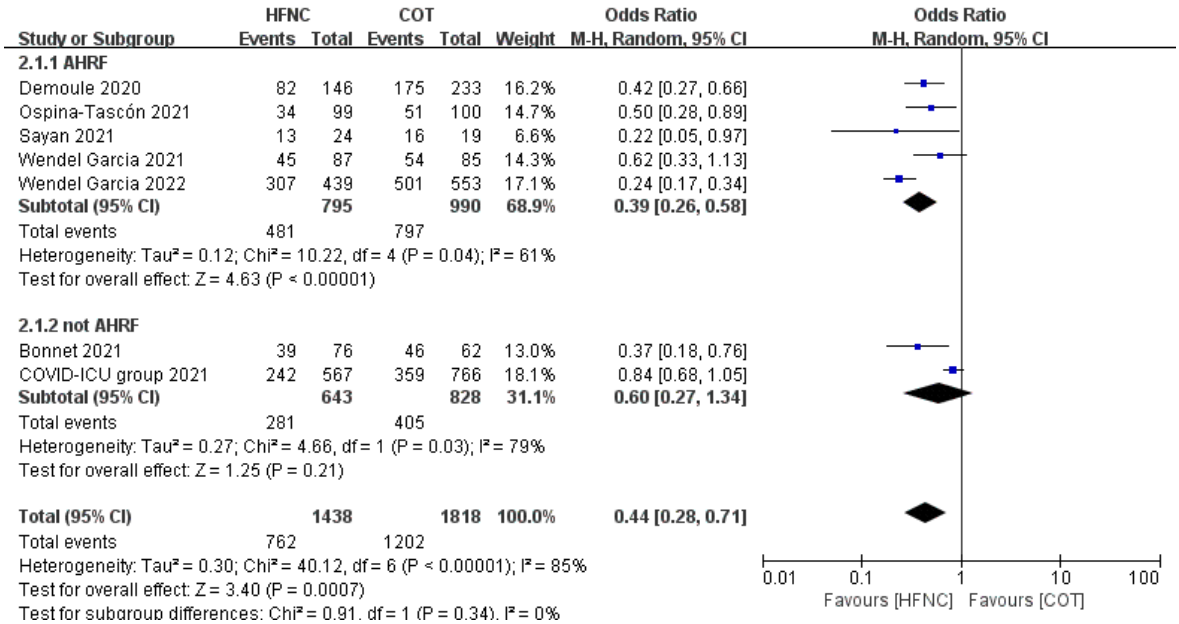

Figure S6 Subgroup analysis of mortality between the two groups with regard to type of ARF

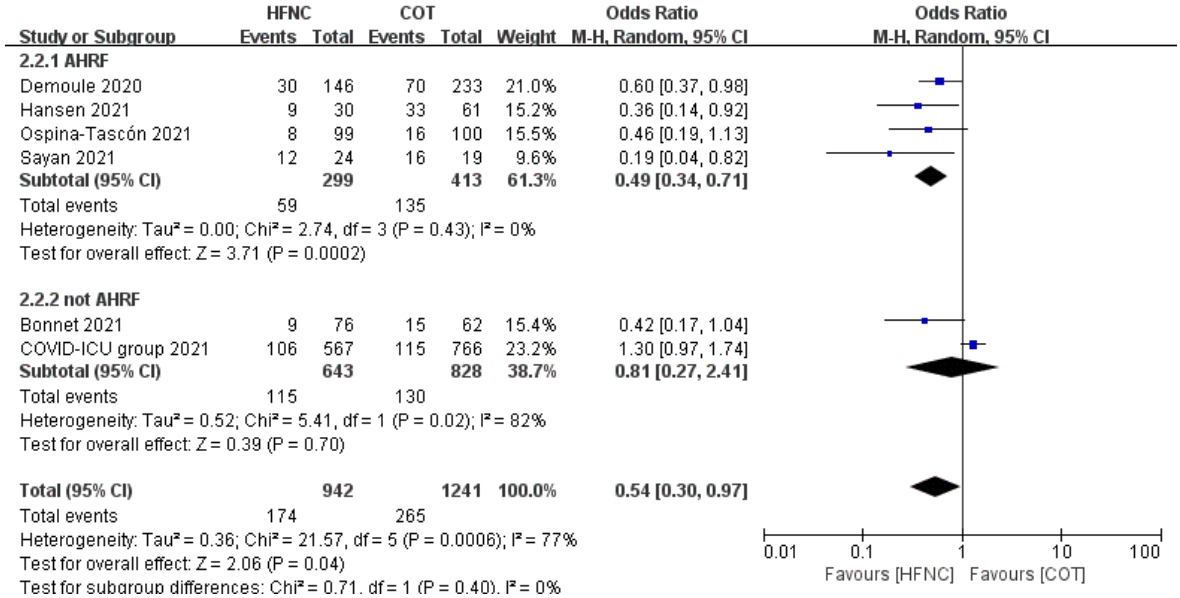

Figure S7 Subgroup analysis of VFDs between the two groups with regard to type of ARF

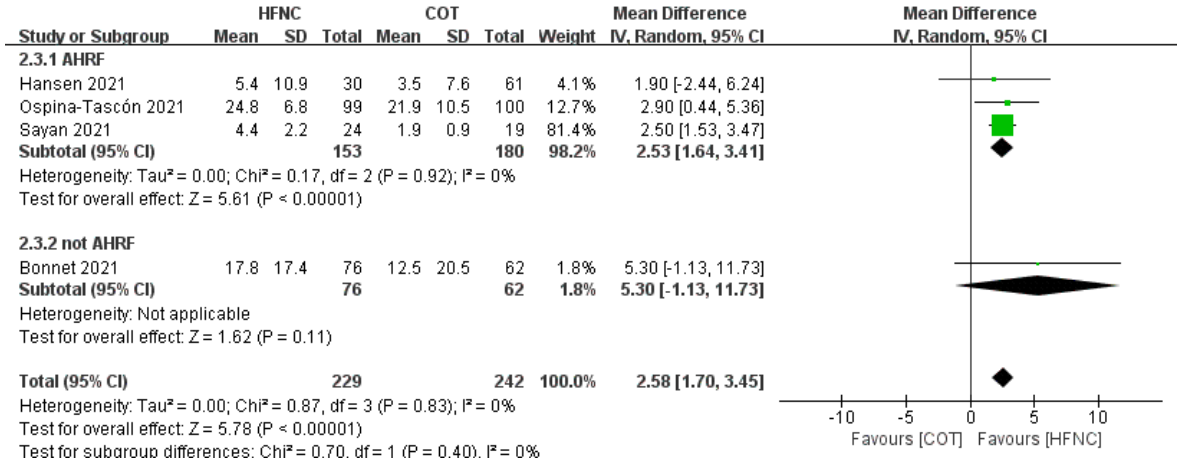

Figure S8 Subgroup analysis of LOS between the two groups with regard to type of ARF

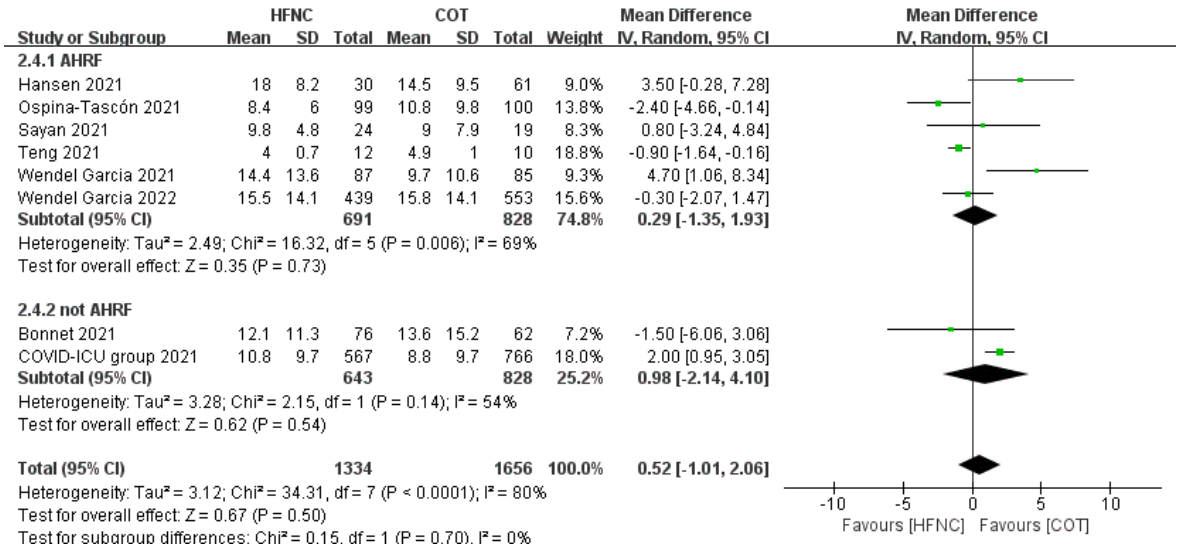

Figure S9 Subgroup analysis of intubation rate between the two groups with regard to OI

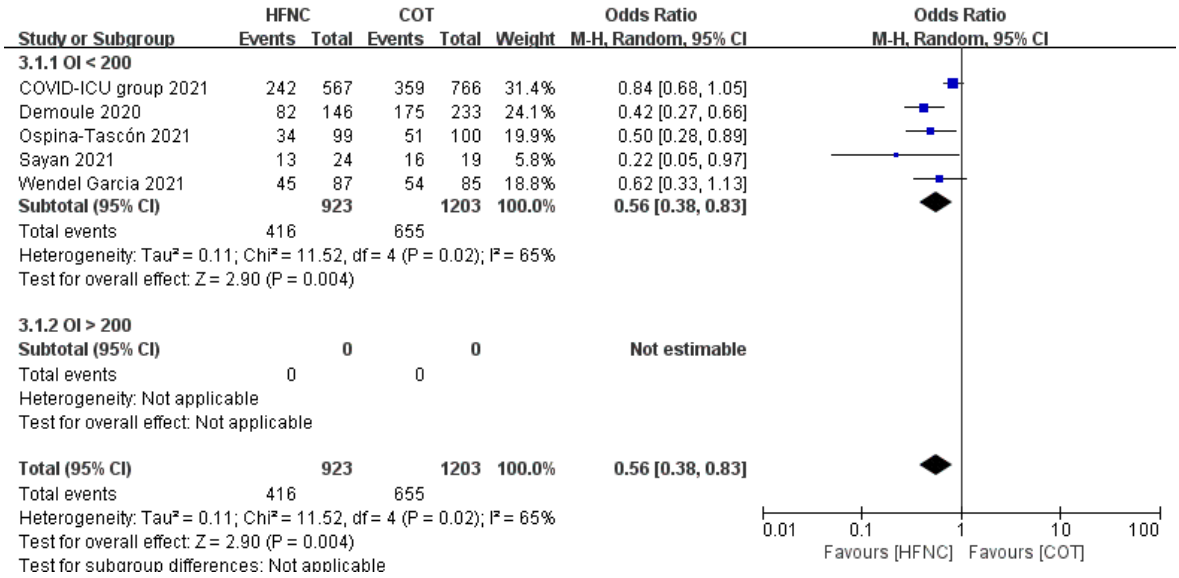

Figure S10 Subgroup analysis of mortality between the two groups with regard to OI

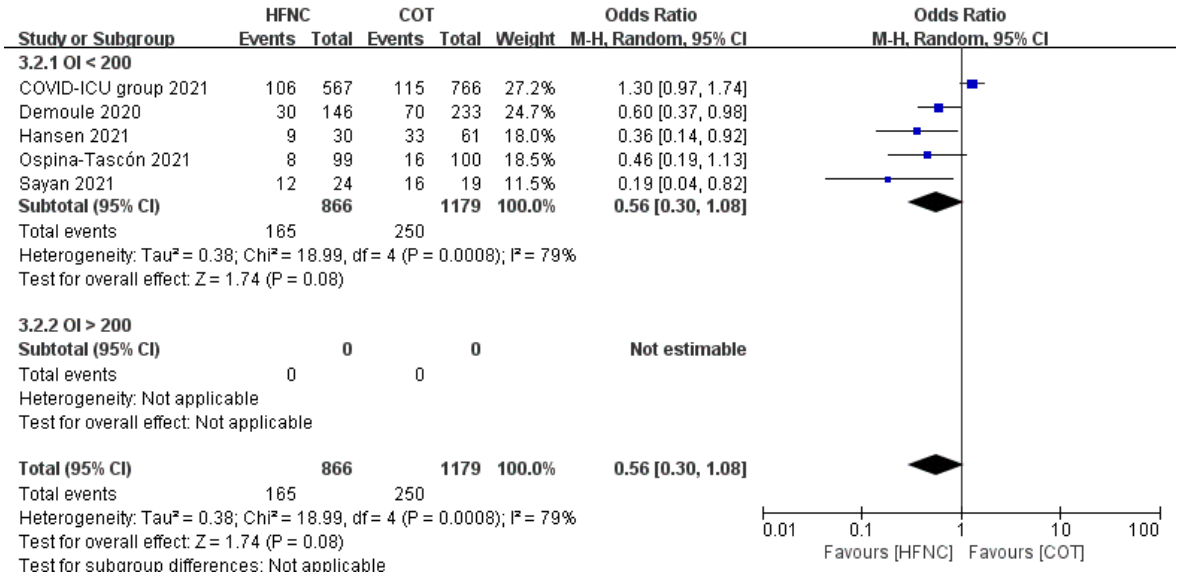

Figure S11 Subgroup analysis of VFDs between the two groups with regard to OI

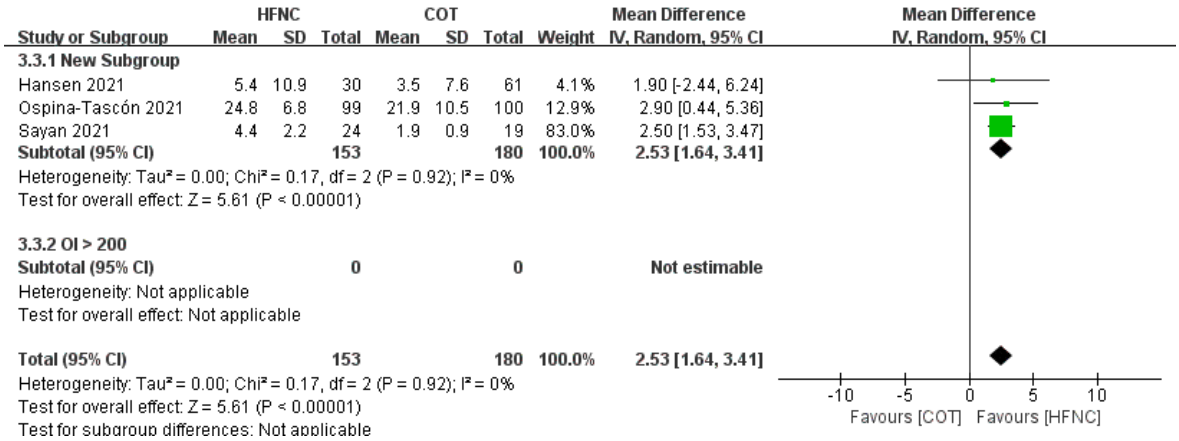

Figure S12 Subgroup analysis of LOS between the two groups with regard to OI

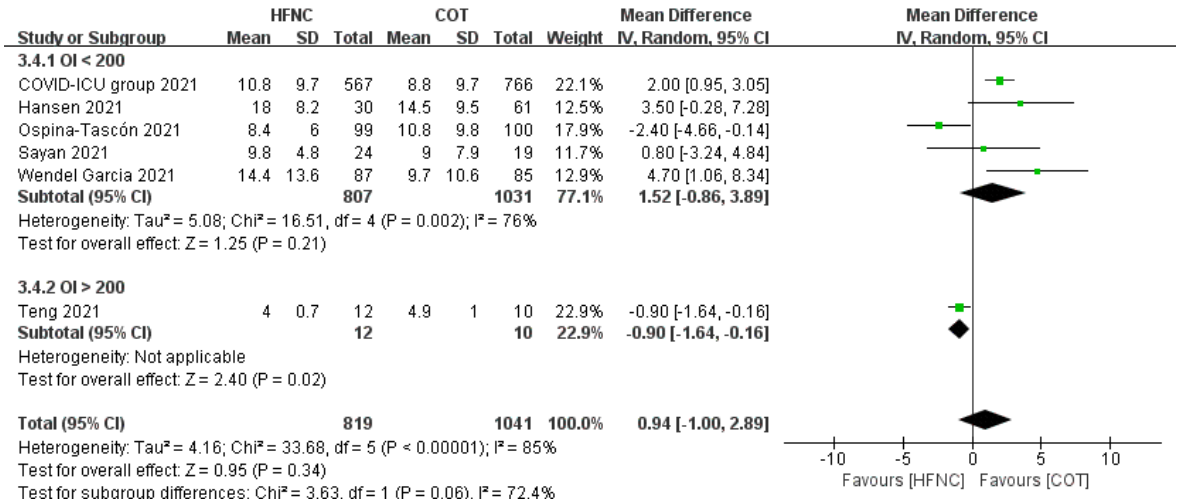

Figure S13 Subgroup analysis of IR between the two groups with regard to type of research