High-Flow Nasal Cannula Versus Noninvasive Ventilation in Patients With COVID-19

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BACKGROUND: High-flow nasal cannula (HFNC) oxygen and noninvasive ventilation (NIV) have been widely used in patients with acute hypoxic respiratory failure (AHRF) due to COVID-19. However, the impact of HFNC versus NIV on clinical outcomes of COVID-19 is uncertain. Therefore, we performed this meta-analysis to evaluate the effect of HFNC versus NIV in COVID-19-related AHRF. METHODS: Several electronic databases were searched through February 10, 2022, for eligible studies comparing HFNC and NIV in COVID-19-related AHRF. Our primary outcome was intubation. The secondary outcomes were mortality, hospital length of stay (LOS), and P_{aO_2}/F_{IO_2} changes. Pooled risk ratio (RR) and mean difference (MD) with the corresponding 95% CI were obtained using a random-effect model. Prediction intervals were calculated to indicate the variance in outcomes that would be expected if new studies were conducted in the future. RESULTS: Nineteen studies involving 3,606 subjects (1,880 received HFNC and 1,726 received NIV) were included. There were no differences in intubation (RR 1.01 [95% CI 0.85–1.20], $P = .89$) or LOS (MD 0.38 d [95% CI −0.61 to 1.37], $P = .45$) between groups, with consistent results on the subgroup of randomized controlled trials (RCTs). Mortality was lower in NIV (RR 0.81 [95% CI 0.66–0.98], $P = .03$). However, the prediction interval was 0.41–1.59, and subgroup analysis of RCTs showed no difference in mortality between groups. There was a greater improvement in P_{aO_2}/F_{IO_2} with NIV (MD 22.80 [95% CI 5.30–40.31], $P = .01$). CONCLUSIONS: Our study showed that despite the greater improvement in P_{aO_2}/F_{IO_2} with NIV, intubation rates and LOS were similar between HFNC and NIV. Although mortality was lower with HFNC than NIV, the prediction interval included the null value, and there was no difference in mortality between HFNC and NIV on a subgroup of RCTs. Future large-scale RCTs are necessary to support our findings. [Respir Care 2022;67 (9):1177–1189. © 2022 Daedalus Enterprises]

Introduction

COVID-19, caused by SARS-CoV-2 infection, was first discovered in China in December 2019.[1] COVID-19 has become a worldwide pandemic leading to significant morbidity and mortality.[1,2] Acute hypoxic respiratory failure (AHRF) due to viral pneumonitis is the most common organ failure and the most common cause of admission to the ICU and mortality among patients with COVID-19.[3]

During this COVID-19 pandemic, noninvasive respiratory support (NIRS), such as high-flow nasal cannula oxygen (HFNC) and noninvasive ventilation (NIV), has gained popularity among patients with AHRF secondary to COVID-19.[4] These NIRS modalities might help avoid the need for intubation and invasive mechanical ventilation and its associated risks.[4] NIRS includes CPAP and bi-level positive airway pressure (BPAP).[5] NIV has been widely used in AHRF due to non–COVID-19 causes, and it effectively decreased the intubation rate in COPD exacerbation.[6] HFNC is a relatively new NIRS used in managing AHRF, and due to its simplicity, it has been recently utilized increasingly in patients with AHRF and COVID-19.[7] HFNC delivers warmed humidified oxygen through nasal cannula at high flows up to 60 L/min.[7]

Several studies compared HFNC versus NIV to determine their effect on clinical outcomes in subjects with COVID-19. In July 2020, Duan et al[8] published the first study comparing HFNC versus NIV, which showed com-

parable rates of intubation and mortality between the 2 groups. Since then, many studies have compared these modalities, with conflicting findings.[7,9,10] Although a few studies[7,8,11] revealed that HFNC and NIV were associated with similar clinical outcomes, Gaulton et al[10] found that subjects who received NIV had a lower intubation rate than HFNC. On the contrary, Nair et al[9] showed that HFNC was associated with a lower intubation rate than NIV. Due to the uncertainty regarding the impact of various NIRS on patients with COVID-19, we performed this meta-analysis to compare the effect of HFNC versus NIV on clinical outcomes of subjects with AHRF associated with COVID-19.

Methods

Data Sources and Search Strategy

We performed a comprehensive search for published studies indexed in PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and preprint servers (medRxiv and Research Square) from inception to February 10, 2022. We also performed a manual search for additional relevant studies using references of the included articles. The following search terms were used: ("high-flow nasal cannula" or "HFNC"), ("noninvasive ventilation" or "NIV" or "CPAP" or "positive-pressure ventilation" or "BiPAP"), and ("COVID" or "COVID-19"). The search was not limited by language, study design, or country of origin. Supplementary Table 1 (see related supplementary materials at http://www.rcjournal.com) describes the full search term used in each database searched.

Eligibility Criteria

All studies that performed a direct comparison of first-line use of HFNC or NIV (either BPAP or CPAP) in subjects with AHRF associated with COVID-19 and reported the following clinical outcomes, intubation, mortality, or hospital length of stay (LOS), were eligible for inclusion. We note that CPAP does not provide ventilatory support but is an important NIRS adjunct, whereas BPAP does provide ventilatory support. The inclusion of CPAP within NIV as part of the studies included in this analysis results in some mixing of oxygenation and ventilatory support in the data. We excluded single-arm studies, case reports, case series, and reviews.

Data Extraction

The following data were extracted from the studies: first author name, publication year, country of origin, study design, sample size, sex of subjects, mean age, and baseline patient characteristics. Outcome measures in both groups (HFNC and NIV) were retrieved, including intubation, mortality, LOS, and the change in oxygenation in the form of partial arterial pressure of oxygen to the P_{aO_2}/F_{IO_2}. We contacted the corresponding authors of studies for missing or unclear data. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines to select the final studies.[12] Two investigators (AB and OS) independently performed the search and short-listed the studies for final review. Discrepancies were resolved by a third reviewer (KS).

Outcomes of Interest

The primary outcome of our study was the intubation rate between HFNC and NIV. The secondary outcomes were mortality, LOS, and the change in P_{aO_2}/F_{IO_2} between HFNC and NIV.

Statistical Analysis

We performed a meta-analysis of the included studies using ReviewManager 5.3 (Cochrane, England, United Kingdom) and Comprehensive Meta-Analysis (Biostat, Englewood, New Jersey). The median and interquartile range were converted to mean and SD where applicable.[13] The random-effects model was used to calculate the pooled risk ratio (RR) and mean difference (MD) with the corresponding 95% CI for proportional and continuous variables, respectively. A P value $< .05$ was considered statistically significant. Where the mean and SD of the change from baseline to end point were not reported in the original studies for P_{aO_2}/F_{IO_2}, an imputed value, Corr, for the correlation coefficient (r) was used to calculate them.[14] We performed a sensitivity analysis using r of 0.4, 0.5, and 0.6 for our meta-analyses; and the results did not significantly change, indicating that our analyses were robust to this assumption.[14] We used r of 0.5 in our meta-analysis.[15] The heterogeneity of the effect size estimates across the studies was quantified using the Q statistic and I^2 ($P < .10$ was considered significant). A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and 76–100% high heterogeneity.[16]

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The authors have disclosed no conflicts of interest.

Supplementary material related to this paper is available at http://www.rcjournal.com.

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DOI: 10.4187/respcare.09987

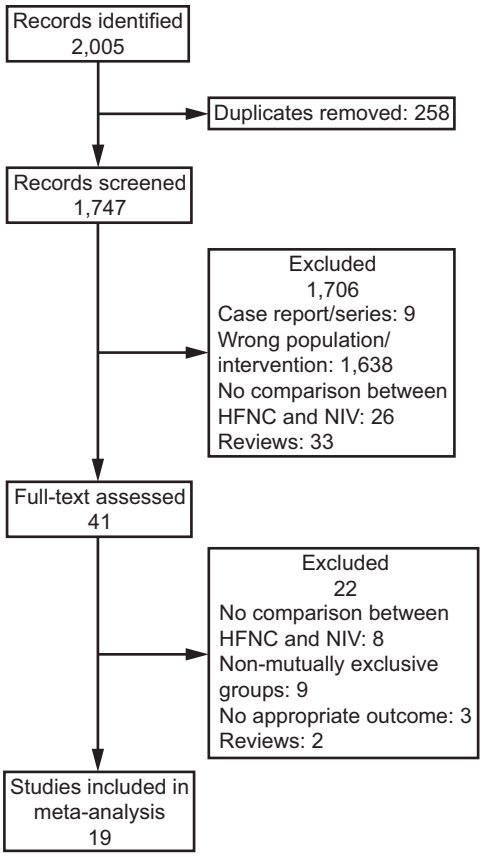

Fig. 1. Flow chart. HFNC = high-flow nasal cannula; NIV = noninvasive ventilation.

In addition, we also provided the 95% prediction intervals for outcomes reported by more than 10 studies, which indicate the variance in outcomes that would be expected if future studies were conducted.[17,18] Calculating prediction intervals was helpful for assessing whether the variation across studies was clinically important.

Sensitivity and Subgroup Analyses

We performed subgroup analysis based on the type of NIV (BPAP or CPAP) and method of NIV delivery (helmet or mask) if at least 3 studies reported the outcome. We also performed subgroup analysis based on the study design (randomized controlled trials [RCTs] vs observational studies). To confirm the robustness of our results, sensitivity analysis for intubation and mortality using leave-one-out meta-analysis was performed to see if it had a significant influence on the meta-analysis result (ie, jack-knife sensitivity analysis).

Bias Assessment

The Jadad composite scale was used to assess the methodological quality of the clinical trials based on randomization, blinding, and withdrawals.[19] The scale ranged from 0–5 points.[19] Studies with a total score of ≥ 3 were considered to have a low risk of bias. The Newcastle-Ottawa quality assessment scale was used to assess the quality of the observational studies based on the selection of the study groups, comparability of study groups, and ascertainment of exposure/outcome.[20] Studies with total scores of ≥ 6 were considered to have a low risk of bias. For outcomes reported by 10 or more studies, publication bias was assessed qualitatively by visual inspection of the funnel plot and quantitively by Egger regression analysis. Two authors (AB and MM) independently assessed each study for bias. Discrepancies were resolved by a third reviewer (HA).

Results

Study Selection

Our search strategy retrieved a total of 2,005 studies. Among these, 41 were eligible for systematic review. Subsequently, we excluded 22 studies because of single-arm studies reporting either HFNC or NIV only, lack of appropriate outcome, or presence of non–mutually exclusive groups. Eventually, 19 studies[7-11,21-34] met our inclusion criteria and were included in the meta-analysis. Figure 1 shows the PRISMA flow chart that illustrates how the final studies were selected.

Study and Subjects' Characteristics

Tables 1 and 2 show the study and subject characteristics of the studies included in the meta-analysis. All the included studies were published between July 2020–February 2022 and included hypoxic subjects with COVID-19. Based on country of origin, 3 studies originated from Italy, 4 studies from the United Kingdom, 2 studies from China, 2 studies from the United States, 2 studies were multinational, one study from Brazil, one from Egypt, one from India, one from Morocco, one from Portugal, and one from Saudi Arabia. Regarding the design of studies, 3 were RCTs,[9,21,33] and 16 were observational cohort studies[7,8,10,11,22-32,34] (13 of these were retrospective, and 3 were prospective).

A total of 3,606 subjects (1,880 received HFNC and 1,726 received NIV) were included, with males representing 66.5% of the total subjects. Six studies applied BPAP, whereas 6 studies applied CPAP, and 4 reported applying both BPAP and CPAP, and 3 studies did not report whether they applied BPAP or CPAP. The assessment of the risk of bias is shown in Supplementary Table 2 (see related supplementary materials at http://www.rcjournal.com). Among the observational studies, all studies scored ≥ 6 on the Newcastle-Ottawa quality assessment scale except one,[11] which scored < 6, and all 3 RCTs scored ≥ 3 (Supplementary Table 2).

Table 1. Study Characteristics of the Included Studies

Study, Year	Study Design	Country	Total (HFNC/NIV)	Male	Age, y	Subject Location and APP (HFNC/NIV)	Type of NIV (Method of Delivery)	HFNC/NIV Duration	Follow-Up Duration
Alharthy, 2020	RC	Saudi Arabia	30 (15/15)	25 (83.3)	46.3 ± 15	ICU (15/6)	CPAP (helmet)	9 (7–11)/ 8 (6–11)	NR
Alkouh, 2022	RC	Morocco	233 (162/71)	166 (71.2)	65.8 ± 13.5	ICU (NR)	NR	NR	NR
Costa, 2022	RC	Brazil	37 (23/14)	26 (70.3)	68.8 ± 18.5	ICU and ward (NR)	BPAP (mask)	NR	NR
Duan, 2020	RC	China	36 (23/13)	24 (66.7)	59.6 ± 15.6	ICU and ward (NR)	BPAP (mask)	3.6 (1.6–8.4)/ 6.8 (4.5–10.0)	NR
Franco, 2020	RC	Italy	670 (163/507)	464 (69.3)	68.3 ± 13.3	Ward (NR)	BPAP and CPAP (mask and helmet)	NR	30 d
Gaulton, 2020	RC	USA	59 (42/17)	28 (47.5)	60 ± 15	ICU (NR)	CPAP (helmet)	NR	NR
Ghani, 2021	PC	United Kingdom	130 (35/95)	89 (68.5)	60 (median)	Ward (NR)	CPAP (mask)	NR	NR
Grieco, 2021	RCT	Italy	109 (55/54)	88 (80.7)	63.6 ± 11.1	ICU (NR)	BPAP (helmet)	NR	60 d
Menga, 2021	PC	Italy	85 (24/61)	NR	NR	ICU (NR)	BPAP (mask and helmet)	NR	NR
Nadeem, 2021	RC	United Kingdom	100 (44/56)	61 (61)	76.5	Ward (NR)	BPAP and CPAP (NR)	NR	NR
Nair, 2021	RCT	India	109 (55/54)	79 (72.5)	56.4 ± 12.9	ICU (NR)	BPAP (mask and helmet)	NR	NR
Pearson, 2021	RC	USA	62 (31/31)	38 (61.3)	64.5 ± 15.9	ICU (NR)	CPAP (helmet)	NR	NR
Perkins, 2021	RCT	United Kingdom	798 (418/380)	532 (66.7)	57.2 ± 12.8	ICU and ward (243/ 207)	CPAP (mask)	3.7 ± 4.1/ 3.5 ± 4.6	30 d
Rodrigues Santos, 2022	RC	Portugal	190 (139/51)	130 (68.4)	66.7 ± 11.8	Ward (47/18)	BPAP and CPAP (mask)	15.4 ± 13.6/ 14.7 ± 11.3	NR
Shoukri, 2021	RC	Egypt	63 (37/26)	40 (63.5)	66.44 ± 8.86	ICU (NR)	BPAP (mask)	5.53 ± 1.11/ 5.86 ± 1.10	NR
Sykes, 2021	PC	United Kingdom	140 (71/69)	89 (63.7)	71.2 ± 11.1	Ward (NR)	CPAP (mask)	3 (1–14)/ 3 (1–24)	NR
Wendel-Garcia, 2021	RC	Multi-centric	174 (87/87)	127 (73)	64.9 ± 15.4	ICU (NR)	BPAP and CPAP (NR)	NR	NR
Wendel-Garcia, 2022	RC	Multi-centric	540 (439/101)	365 (67.6)	61.9 ± 11.9	ICU (NR)	BPAP and CPAP (NR)	NR	90 d
Zhao,2021	RC	China	41 (17/24)	28 (68.3)	66.6 ± 12.3	NR (NR)	NR	NR	NR

Data are presented as *n* or *n* (%) or median (interquartile range) or mean ± SD.
HFNC= high-flow nasal cannula
NIV= noninvasive ventilation
APP = awake prone positioning
RC = retrospective cohort
NR = not reported
BPAP = bi-level positive airway pressure
PC = prospective cohort
RCT = randomized controlled trial

Table 2 . Subject Characteristics and Outcomes of the Included Studies in the Meta-Analysis

Study, Year	BMI, kg/m^2 (HFNC/NIV)	SOFA Score (HFNC/NIV)	P_{aCO_2}, mm Hg (HFNC/NIV)	DM (HFNC/NIV)	COPD (HFNC/NIV)	Mortality (HFNC/NIV)	Intubation (HFNC/NIV)	LOS, d (HFNC/NIV)	P_{aO_2}/F_{IO_2} (Baseline/Post Treatment)	
									HFNC	NIV
Alharthy, 2020	24 (20–29)/ 24 (20–29)	9 (8–10)/ 9 (8–10)	NR	7/5	NR	NR	2/3	NR	213 (199–241)/ 380 (352–421)	211 (198–235)/ 377 (344–422)
Alkouh, 2022	27.6 ± 4.7/ 27.5 ± 4.9	NR	NR	50/19	NR	79/34	80/33	NR	NR	NR
Costa, 2022	29 ± 5.5/ 32 ± 5	4.0 (0.7–2.0)/ 5 (2.2–10.0)	NR	9/5	4/5	5/5	16/8	23.0 (14.7–32.5)/ 20.5 (12.0–35.0)	NR	NR
Duan, 2020	NR	4 ± 2/4 ± 1	36 ± 5/35 ± 4	4/0	1/0	1/1	4/2	NR	196 ± 48/224 ± 92	165 ± 48/202 ± 65
Franco, 2020	NR	2.5 ± 0.9/ 3.5 (1.8)	NR	32/93	9/37	26/154	47/131	19.2 ± 13.3/ 20.4 ± 13.2	166 ± 65/NR	146.5 ± 82.6/ NR
Gaulton, 2020	36 ± 9.0/ 34.8 ± 7.8	NR	NR	13/8	NR	8/1	22/3	NR	NR	NR
Ghani, 2021	NR	NR	NR	NR	NR	12/54	6/44	NR	NR	NR
Grieco, 2021	28 (26–31)/ 27 (26–30)	2 (2–3)/ 2 (2–3)	34 (32–37)/ 34 (31–37)	10/13	NR	14/13	28/16	26.6 ± 23.6/ 21.7 ± 12.2	102.0 ± 33.5/ 138 ± 46	104.3 ± 32.0/ 188 ± 73
Menga, 2021	NR	NR	32 (28–35) in both groups	NR	NR	NR	15/37	NR	NR	NR
Nadeem, 2021	NR	NR	NR	NR	NR	35/37	NR	NR	NR	NR
Nair, 2021	NR	NR	34 (26.3–38.5)/ 32 (26.0–43.3)	17/16	NR	16/25	15/25	9.7 ± 4.6/ 9.0 ± 4.6	112.5 ± 36.0/ 134.7 ± 78.8	115.50 ± 42.04/ 157.60 ± 82.60
Pearson, 2021	29.1 (23.5–38.6)/ 32.0 (27.6–38.8)	NR	NR	14/18	9/4	18/15	15/17	NR	NR	NR
Perkins, 2022	NR	NR	33 (30–36)/ 33 (30.0–36.8)	98/86	NR	86/72	169/126	18.3 ± 20.0/ 16.4 ± 17.5	186.3 ± 97.5/NR	182.8 ± 94.7/NR
Rodrigues Santos, 2022	28.2 ± 5.7/ 28.2 ± 5.7	NR	NR	47/18	8/4	38/31	23/8	15.4 ± 13.6	14.7 ± 11.3	NR/NR
Shoukri, 2021	NR	3.02 ± 0.94/ 2.69 ± 0.77	34.67 ± 3.69/ 35.03 ± 3.99	12/9	3/3	1/1	4/3	NR	191.08 ± 37.83/ 225.67 ± 44.33	190.38 ± 42.47/ 241.53 ± 44.43
Sykes, 2021	NR	NR	NR	19/21	16/20	44/40	NR	NR	75.9 ± 40.3/NR	77.3 ± 38.2/NR
Wendel-Garcia, 2021	27 (25–32)/ 26 (24–29)	6 (3–7)/ 6 (4–7)	NR	26/17	10/7	17/32	45/43	13 (6–24)/ 17 (8–26)	126 (79–169)/NR	135 (97–168)/ NR
Wendel-Garcia, 2022	28 (26–31)/ 28 (26–31)	NR	NR	91/21	32/7	106/37	307/89	13 (7–26)/13 (8–24)	NR	NR
Zhao, 2021	NR	NR	NR	NR	NR	9/14	12/16	NR	NR	NR

Data are presented as *n* or *n* (%) or median (interquartile range) or mean ± SD.
BMI = body mass index
HFNC = high-flow nasal cannula
NIV= noninvasive ventilation
SOFA = sequential organ function assessment
DM = diabetes mellitus
LOS = length of stay
NR = not reported

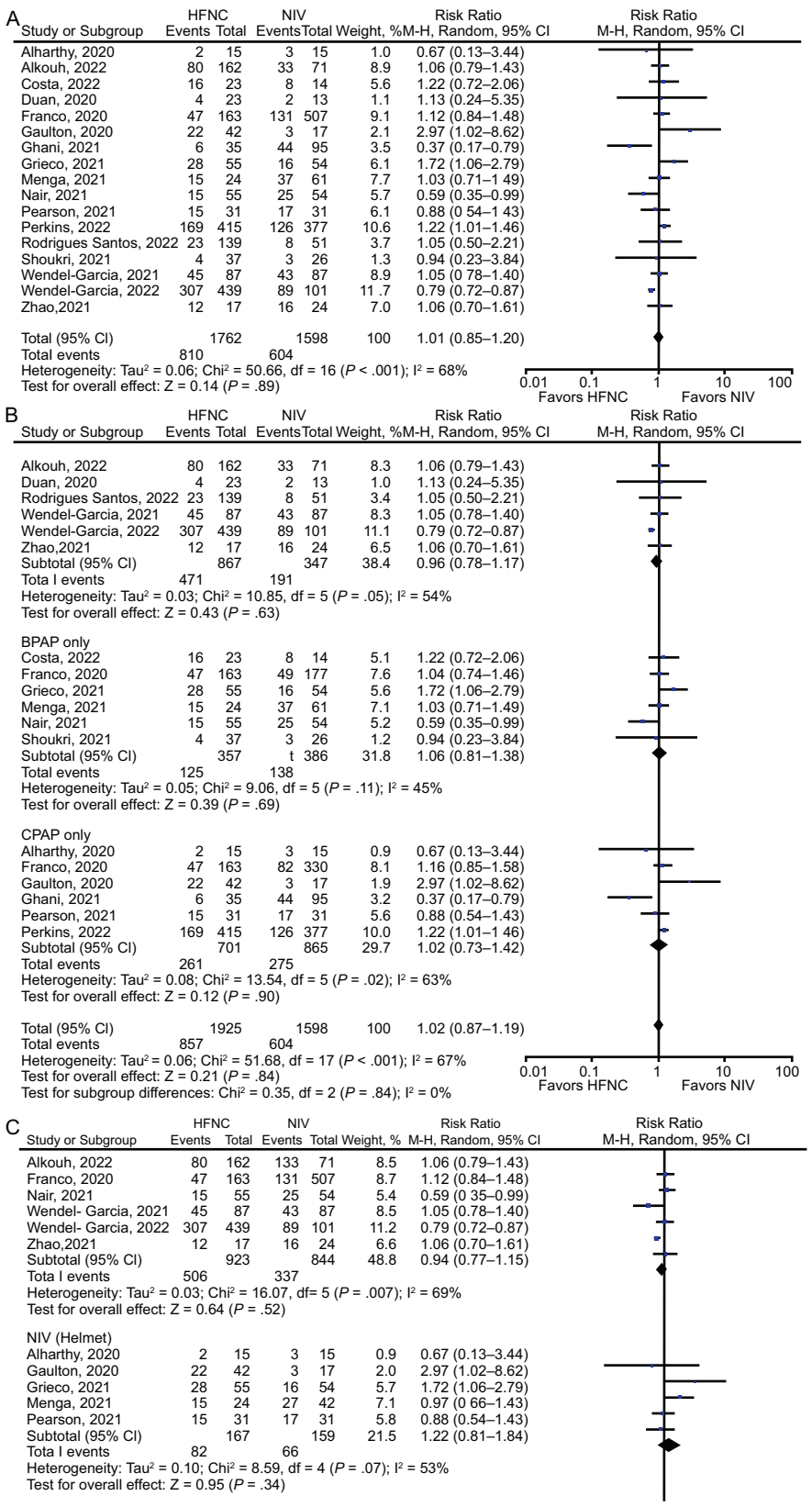

Fig. 2. A: Forest plot comparing high-flow nasal cannula and noninvasive ventilation regarding the intubation rate. B: Subgroup analysis based on the type of support (CPAP vs BPAP) for the intubation rate. C: Subgroup analysis based on the noninvasive ventilation interface (helmet vs mask).

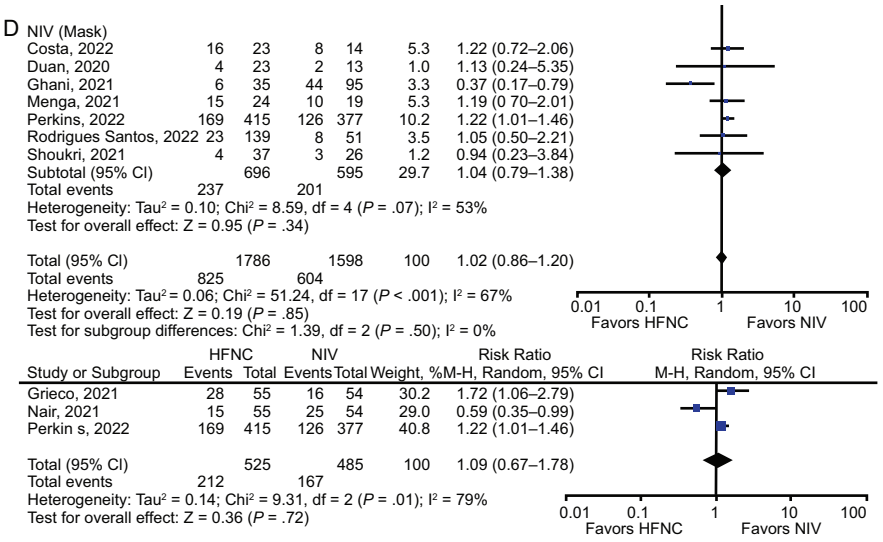

Fig. 2. *Continued*. D: Subgroup analysis of randomized controlled trials for the intubation rate. HFNC = high-flow nasal cannula; NIV = noninvasive ventilation; M-H = Mantel-Haenszel; BPAP = bi-level positive airway pressure.

Outcomes of Interest

Intubation. Table 2 summarizes the outcomes of the individual studies included in the meta-analysis. Across the 17[7-11,21-23,25-28,30-34] studies that reported the intubation rate, 46% of subjects who received HFNC required intubation compared to 37.8% in subjects who received NIV. The intubation rate was similar between HFNC and NIV groups (RR 1.01 [95% CI 0.85–1.20], $P = .89$; $I^2 = 68\%$) (Fig. 2A). The 95% prediction interval was estimated to be 0.58–1.76. The results remained consistent on subgroup analysis of BPAP (RR 1.06 [95% CI 0.81–1.38] $P = .69$; $I^2 = 45\%$) and CPAP (RR 1.02 [95% CI 0.73–1.42], $P = .90$; $I^2 = 63\%$) (Fig. 2B). Consistent results were obtained on subgroup analysis based on the method of NIV delivery (mask or helmet) (Fig. 2C).

The results were consistent on subgroup of RCTs (RR 1.09 [95% CI 0.67–1.78], $P = .72$; $I^2 = 79\%$) (Fig. 2D). No significant difference in rates of intubation was observed on subgroup analysis for peer-reviewed studies (RR 1.06 [95% CI 0.89–1.28], $P = .51$; $I^2 = 71\%$) and high-quality studies (RR 1.01 [95% CI 0.84–1.21], $P = .91$; $I^2 = 70\%$). A leave-one-out sensitivity analysis showed consistent results. However, sensitivity analysis on excluding the study by Wendel-Garcia et al[32] resulted in $I^2 = 34\%$ without significant change in overall intubation rate (Supplementary Fig. 1, see related supplementary materials at http://www.rcjournal.com).

Mortality

Seventeen studies[7-10,21,23-34] reported the mortality rate. The mortality rate was 28.2% in the HFNC group compared to 34.6% in the NIV group. Overall, HFNC was associated with lower mortality compared to NIV (RR 0.81 [95% CI 0.66–0.98], $P = .03$; $I^2 = 68\%$) (Fig. 3A); however, 95% prediction interval was estimated to be 0.41–1.59. Subgroup analysis of peer-reviewed studies revealed favored HFNC over NIV in mortality (RR 0.80 [95% CI 0.65–0.99], $P = .04$; $I^2 = 69\%$) (Fig. 3B). However, 95% prediction interval was estimated to be 0.39–1.65. Furthermore, subgroup analysis of RCTs revealed no significant difference between HFNC and NIV in mortality (0.92 [95% CI 0.65–1.29], $P = .62$; $I^2 = 42\%$) (Fig. 3C). On subgroup analysis based on the type of NIV, HFNC and CPAP were comparable in mortality (RR 0.89 [95% CI 0.65–1.21], $P = .46$; $I^2 = 69\%$) (Fig. 3D); however, HFNC was associated with a lower mortality compared to BPAP (RR 0.63 [95% CI 0.48–0.84], $P = .001$; $I^2 = 0\%$) (Fig. 3D). Nonetheless, the subgroup difference between the types of NIV (BPAP and CPAP) was not statistically significant ($P = .28$) (Fig. 3D). Furthermore, subgroup of RCTs comparing HFNC and BPAP showed no difference in mortality (RR 0.78 [95% CI 0.47–1.29], $P = .33$; $I^2 = 35\%$) (Fig. 3C).

Subgroup analysis based on the method of NIV delivery (mask or helmet) demonstrated no significant difference in mortality between HFNC and NIV. A leave-one-out sensitivity analysis showed inconsistent findings in mortality between the 2 groups. (Removal of either one of these studies[9,23,26,30,32] moved the overall effect to be nonsignificant between HFNC and NIV (Supplementary Fig. 2, Supplementary Fig. 2, see related supplementary materials at http://www.rcjournal.com).

Hospital Length of Stay

Eight studies[9,21,23,27,30-34] reported the LOS. There was no significant difference with regard to the LOS (MD 0.38 d

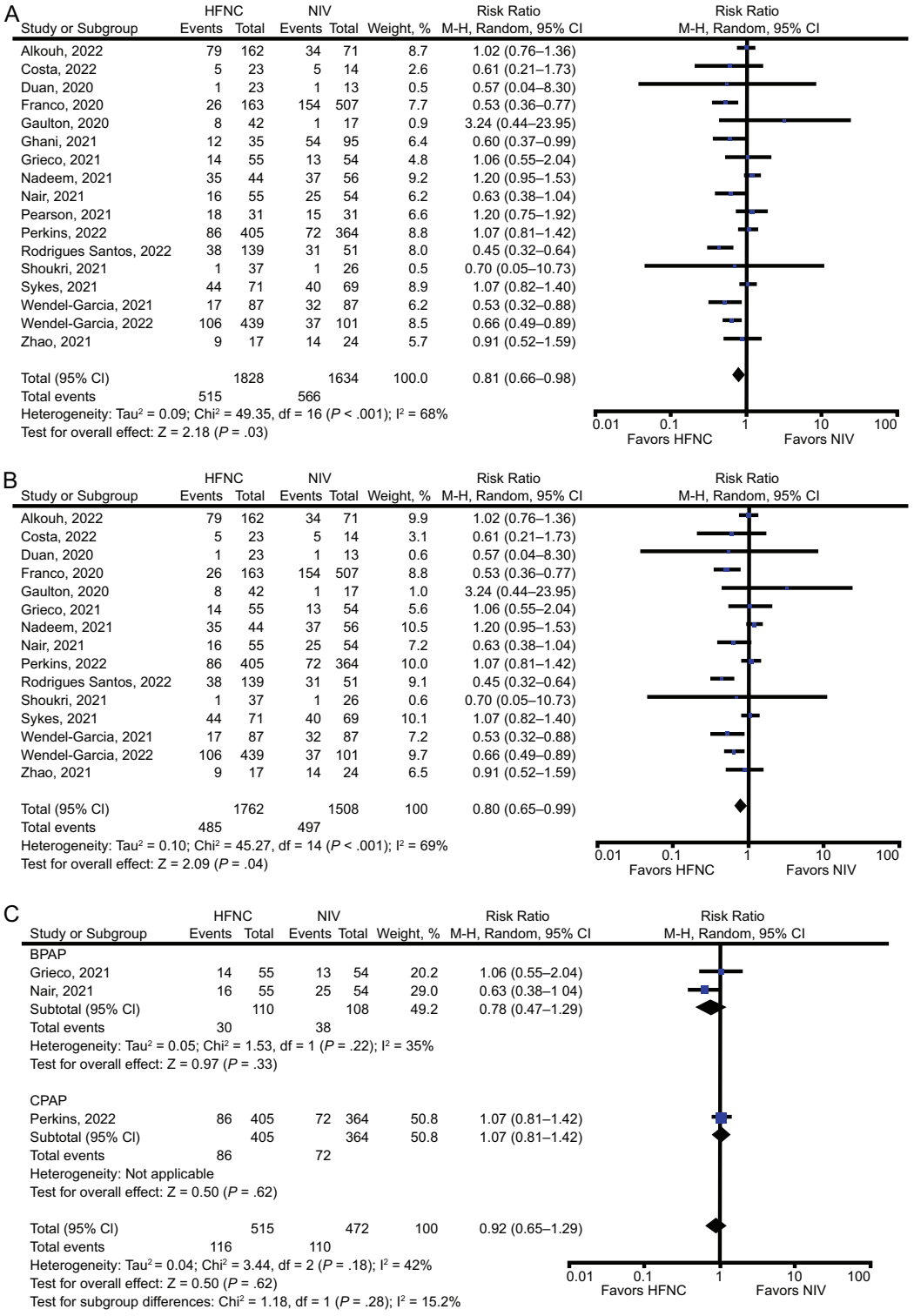

Fig. 3. A: Forest plot comparing high-flow nasal cannula and noninvasive ventilation regarding mortality. B: Subgroup analysis of peer-reviewed studies for mortality. C: Subgroup analysis of randomized controlled trials for mortality with subgroup based on the type of support used (BPAP vs CPAP).

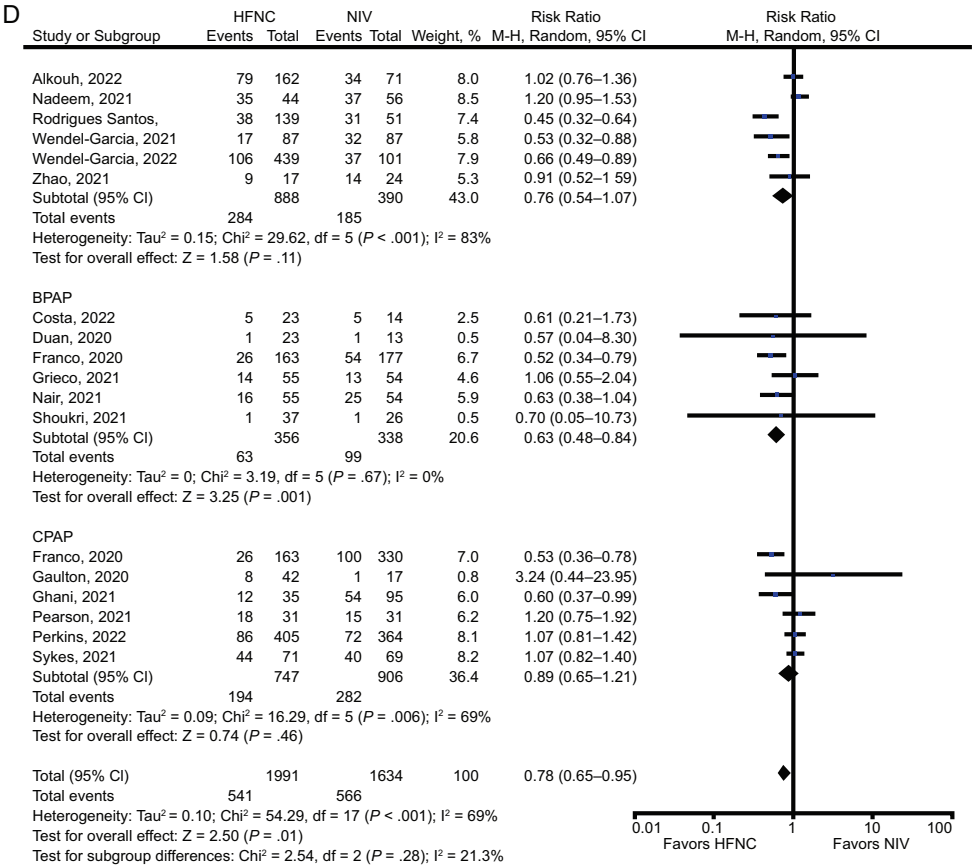

Fig. 3. *Continued*. D: Subgroup analysis based on the type of ventilation (CPAP vs BPAP) for mortality. HFNC = high-flow nasal cannula; NIV = noninvasive ventilation; M-H = Mantel-Haenszel; BPAP = bi-level positive airway pressure.

[95% CI −0.61 to 1.37], $P = .45$; $I^2 = 0\%$) (Fig. 4A). Subgroup of RCTs showed consistent results (MD 1.16 [95% CI −0.26 to 2.57], $P = .11$; $I^2 = 0\%$) (Fig. 4B).

Changes in P_{aO_2}/F_{IO_2}

Five studies[7-9,21,22] reported the changes in oxygenation before and after NIRS therapy in the form of P_{aO_2}/F_{IO_2}. NIV was associated with a greater improvement in P_{aO_2}/F_{IO_2} compared to HFNC (MD 22.80 [95% CI 5.30–40.31], $P = .01$; $I^2 = 48.1\%$) (Fig. 5A). Subgroup of RCTs demonstrated consistent findings (MD 35.09 [95% CI 7.88–62.31], $P = .01$; $I^2 = 63.5\%$) (Fig. 5B).

Quality and Publication Bias Assessment

Quality assessment scores of the RCTs and observational studies are summarized in Supplementary Table 2 (see related supplementary materials at http://www.rcjournal.com). There was a low risk of bias for 18 studies,[7-10,21-34] whereas the risk of bias for one study was high.[11] The funnel plots for intubation and mortality appeared symmetric by visual inspection (Supplementary Fig. 3, see related supplementary materials at http://www.rcjournal.com), and Egger regression analysis did not show evidence of publication bias ($P = .19$ and $P = .45$ for the intubation and mortality rates, respectively).

Discussion

Our meta-analysis shows no significant difference in the intubation rate and LOS between HFNC and NIV despite greater improvement of P_{aO_2}/F_{IO_2} with NIV. Although mortality was lower overall in HFNC than in NIV (especially BPAP), subgroup analysis of RCTs revealed no significant difference in mortality between HFNC and NIV.

In the current prolonged COVID-19 pandemic era, many patients with COVID-19 develop AHRF with increasing demand for respiratory support with intubation and mechanical ventilation. However, there is a shortage of human and medical resources; and the mortality rates are high among intubated patients with COVID-19, which were as high as 67% in early reports.[35] Therefore, NIRSs, such as HFNC and NIV, have been widely implemented to avoid the need for endotracheal intubation and invasive mechanical ventilation among patients with AHRF due to COVID-19 failing on conventional oxygen therapy.

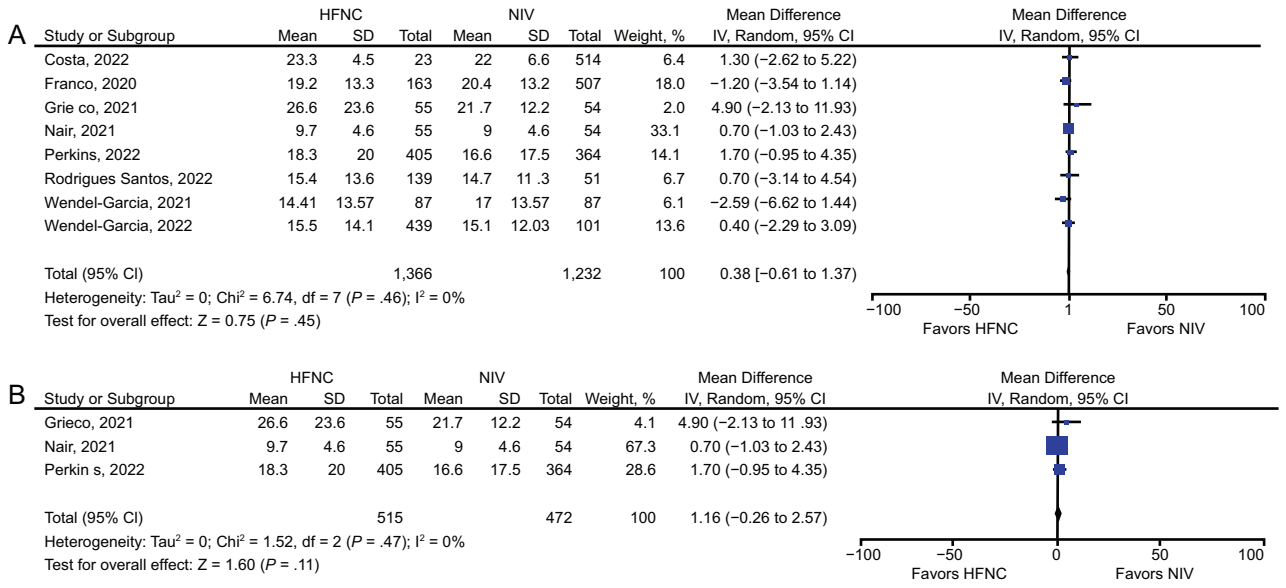

Fig. 4. A: Forest plot comparing high-flow nasal cannula and noninvasive ventilation regarding hospital stay. B: Subgroup analysis of randomized controlled trials for hospital stay. HFNC = high-flow nasal cannula; NIV = noninvasive ventilation; IV = weighted mean difference.

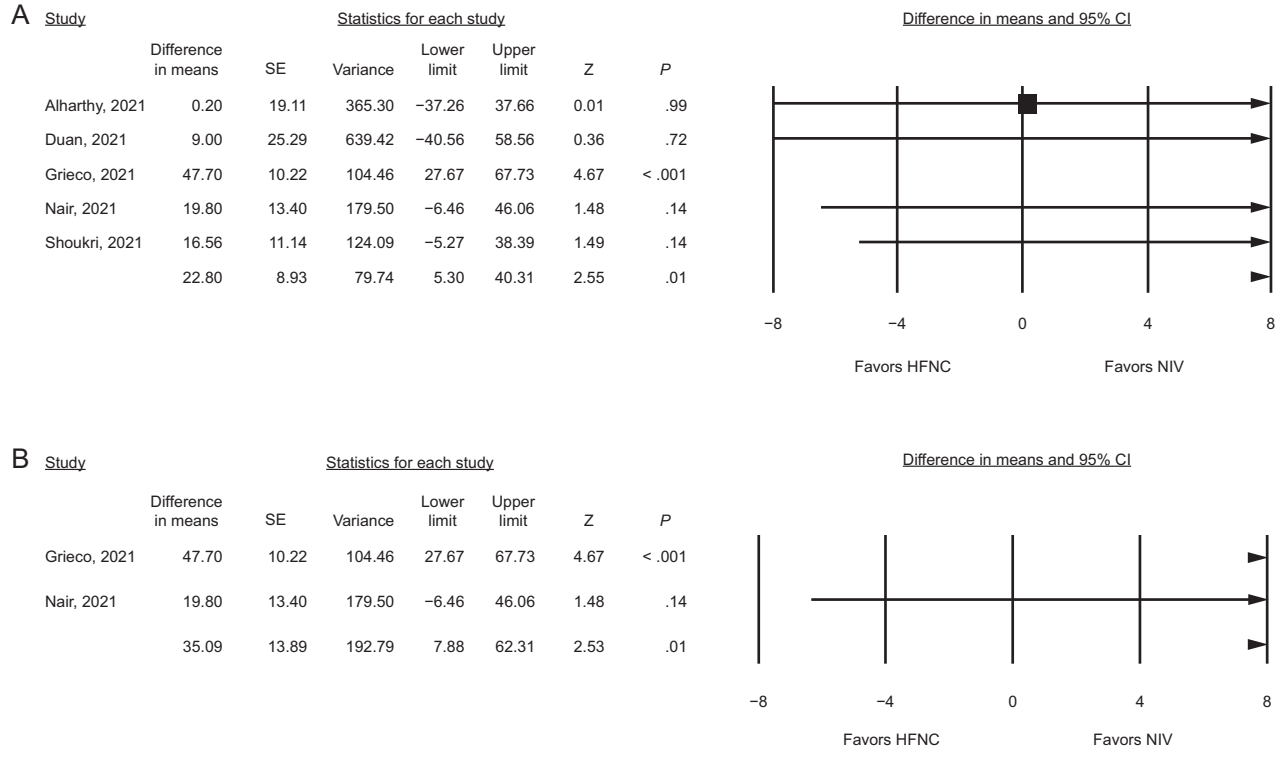

Fig. 5. A: Forest plot comparing high-flow nasal cannula and noninvasive ventilation regarding the change in P_{aO_2}/F_{IO_2}. B: Subgroup analysis of randomized controlled trials for the change in P_{aO_2}/F_{IO_2}. HFNC = high-flow nasal cannula; NIV = noninvasive ventilation; SE = standard error.

NIV is the first-line NIRS to treat patients with hypercapnic AHRF due to COPD.[36] However, the use of NIV for non–hypercapnic AHRF without prior chronic respiratory disease (de novo AHRF) as in COVID-19 remains debatable.[37] NIV should theoretically improve lung oxygenation and gas exchange in AHRF compared to HFNC because it provides a higher PEEP.[38] However, not all patients can tolerate NIV due to adverse events, such as claustrophobia, facial pressure ulcers, and eye irritation.[39,40] Given the high rates of intolerability, especially with mask NIV, HFNC is

becoming the first-line NIRS in patients with COVID-19 failing on conventional oxygen therapy in many hospital settings and has been recommended in the Surviving Sepsis Campaign guidelines on COVID-19.[41] The Surviving Sepsis Campaign guidelines[41] recommended using HFNC over NIV as the first-line NIRS based on indirect data in an RCT comparing HFNC with NIV in subjects with non–hypercapnic AHRF unrelated to COVID-19.[42] That RCT showed that HFNC was associated with a lower mortality rate at 90 d (hazard ratio 2.50 [95% CI 1.31–4.78]) but did not significantly decrease the intubation rate (40% intubation rate in HFNC group vs 50% in NIV group, $P = .18$).[42] Another meta-analysis by Ni et al[43] comparing HFNC with NIV demonstrated that HFNC decreased the intubation rate among subjects with AHRF not related to COVID-19 without significantly improving mortality or ICU length of stay.

Due to the lack of clear evidence, few studies have recently evaluated the effectiveness of HFNC in comparison to NIV on the clinical outcomes of subjects with COVID-19-related AHRF.[8-11] However, the findings of these studies were conflicting. A study by Franco et al[23] showed comparable rates of intubation and mortality between HFNC and NIV. On the other hand, in some studies[9,21] HFNC was favored over NIV regarding intubation rate, whereas others[10,11] favored NIV over HFNC regarding intubation rate. Given the contradicting results of the studies in the literature, we conducted this meta-analysis to provide the first comprehensive evaluation and comparison of HFNC and NIV to address critical knowledge gaps in the management of COVID-19.

In this meta-analysis, we found greater improvement in P_{aO_2}/F_{IO_2} with NIV compared to HFNC, which is similar to the findings of Grieco et al,[11] who found a higher mean P_{aO_2}/F_{IO_2} in the NIV group compared to the HFNC group with an MD of 50 (95% CI 39–61). However, there was no significant difference between the 2 groups in the intubation rate. Our overall study results were in line with the study by Franco et al,[23] which revealed a comparable intubation rate between HFNC and NIV groups (28.8%, 25.8%, respectively). We believe that despite the improvement in P_{aO_2}/F_{IO_2} being statistically significant, the level of improvement in P_{aO_2}/F_{IO_2} was relatively trivial clinically (MD of 22.8 in favor of NIV), which might not be enough to translate into improvement in the clinical outcomes in these patients. In addition, our study results were consistent with Franco et al,[23] which showed no difference in LOS (mean 19.2 ± 13.3 d and 20.4 ± 13.2 d) between HFNC and NIV groups, respectively. Subgroup analysis based on the type of NIV interface (helmet vs mask) showed similar intubation rates between HFNC and NIV.

On overall analysis, HFNC was associated with lower mortality than NIV (especially with BPAP), but 95% prediction interval included the null value, and subgroup difference between the type of NIV was not statistically significant. In addition, when subgroup analysis is restricted to RCTs, there was no significant difference in mortality between HFNC and NIV, including BPAP. Notably, the reduction in mortality with HFNC compared to NIV was driven by observational studies,[31,32] which are more vulnerable to methodological problems such as selection and confounding biases. This difference in mortality between HFNC and NIV (including BPAP) could be attributed to BPAP being applied to sicker patients compared to HFNC. Some observational studies that showed lower crude mortality rate in the HFNC found that the difference in mortality between groups disappeared after adjusting for confounders such as age, baseline P_{aO_2}/F_{IO_2}, and the number of comorbidities,[23,30] which support our study findings. Therefore, more RCTs with controlling for these confounders needed to evaluate the impact of NIRS on clinical outcomes of patients with COVID-19. In addition, the majority of the studies did not report the details of awake prone positioning between the 2 groups, which could also have influenced the mortality outcome in favor of HFNC.[23] The HFNC group could tolerate and implement awake prone positioning better than the NIV group. A recent meta-analysis has shown that awake prone positioning reduced mortality without significant change in intubation or LOS.[44] For instance, in an RCT by Grieco et al,[21] the use of awake prone positioning was not standardized, and awake prone positioning was implemented more frequently in subjects in the HFNC group. Lastly, the higher mortality rate in the NIV group, especially with BPAP, could be attributed partly to the increased risk of volutrauma in the NIV group due to higher tidal volume.[45]

Our results regarding intubation and mortality were in line with the findings of single-arm studies. Demoule et al[46] showed that 25% of subjects who used HFNC required intubation and 56% died. Kofod et al[47] showed a 43% intubation rate and 29% mortality among subjects who received CPAP. However, there is a need for future RCTs for better evaluation of such an important topic. There are several registered clinical trials still in the recruitment stage evaluating the effect of HFNC versus NIV on the clinical outcomes of COVID-19, such as the RCT by Tverring et al[48] (NCT04395807) and NCT04715243. These trials are expected to provide more solid evidence regarding the role of HFNC and NIV among subjects with AHRF and COVID-19. However, it will be difficult to include subjects with a history of COPD or chronic hypercapnic respiratory failure as this will violate the concept of equipoise since NIV is the NIRS of choice in these patients.[36,49] For instance, Tverring et al[48] will exclude patients with underlying COPD stage III/IV.

Several limitations of this study should be acknowledged. First, the meta-analysis included mainly observational studies, which are vulnerable to confounding and selection biases. Therefore, further large-scale RCTs are warranted to confirm our findings. Second, even though the random-

effects model was used in our analysis, there was moderate-to-high heterogeneity noted in the measurement of our outcomes, such as intubation and mortality. This might be driven by differences in patient characteristics (such as the presence of COPD) and COVID-19 severity, inconsistent follow-up duration, and the variations in the concomitant drugs used for COVID-19 in the included studies. Subsequent subgroup/sensitivity analyses and calculation of prediction intervals were performed to help explain the significant heterogeneity in the outcomes of intubation and mortality. Third, the lack of patient-level data did not allow to control for the presence of COPD/chronic respiratory failure among the subjects in the included studies, which might introduce potential bias since it is well known that NIV is the standard-of-care NIRS in patients with hypercapnic AHRF due to COPD.[36] Only one trial by Nair et al[9] excluded patients with COPD or chronic respiratory failure. However, the rest of the studies did not control for the presence of COPD in the included subjects. Therefore, our findings cannot be generalized to patients with COPD or chronic respiratory failure. Fourth, we completed the analysis before pre-registration without PROSPERO registration number, which should be avoided in our future meta-analysis. Finally, we were unable to evaluate the proportion of subjects performing awake prone positioning sessions in each group in most studies due to limited reported data. We also could not evaluate the tolerability and complications of NIV versus HFNC.

Despite the limitations, our study has significant strengths. First, we included a total of 19 studies with > 3,600 subjects with COVID-19. To our knowledge, this is the first meta-analysis comparing the effect of HFNC versus NIV on clinical outcomes in subjects with COVID-19. The results were consistent for intubation on sensitivity analysis and subgroup analysis based on the study design (RCTs vs observational studies) and the method of NIV delivery (helmet vs mask). Furthermore, most of the included studies were of high quality based on quality assessment. Finally, we provided prediction intervals for mortality and intubation, which further accounts the uncertainty for the effect that would be expected in a new study addressing the same association.

Conclusions

In summary, our study showed that despite greater improvement in P_{aO_2}/F_{IO_2} with NIV, intubation rates and hospital LOS were similar between HFNC and NIV. Although mortality was lower with HFNC than NIV, the prediction interval included the null value, and there was no difference in mortality between HFNC and NIV on a subgroup of RCTs. Future large-scale RCTs are necessary to support our findings.

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