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Non-rebreather mask and low-flow nasal cannula vs high-flow nasal cannula in severe COVID–19 pneumonia in the emergency department

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ABSTRACT

Background: To assess the effectiveness of non-rebreather mask combined with low-flow nasal cannula (NRB + NC) compared to high-flow nasal cannula (HFNC) in improving oxygenation in patients with COVID-19-related hypoxemic respiratory failure (HRF).

Methods: This retrospective study was conducted in emergency departments of two tertiary hospitals from June 1 to August 31, 2021. Consecutive patients aged >18 years admitted for COVID-19-related HRF (World Health Organization criteria: confirmed COVID-19 pneumonia with respiratory rate > 30 breaths/min, severe respiratory distress, or peripheral oxygen saturation < 90% on room air) requiring NRB + NC or HFNC were screened for enrollment. Primary outcome was improvement of partial pressure arterial oxygen (PaO₂) at two hours. Secondary outcomes were intubation rate, ventilator-free days, hospital length of stay, and 28-day mortality. Data were analyzed using linear regression with inverse probability of treatment weighting (IPTW) based on propensity score. **Results:** Among the 110 patients recruited, 52 (47.3%) were treated with NRB + NC, and 58 (52.7%) with HFNC. There were significant improvements in patients' PaO₂, PaO₂/F_{IO₂} ratio, and respiratory rate two hours after the initiation of NRB + NC and HFNC. Comparing the two groups, after IPTW adjustment, there were no statistically significant differences in PaO₂ improvement (adjusted mean ratio [MR] 2.81; 95% CI -5.82 to 11.43; *p* = .524), intubation rate (adjusted OR 1.76; 95% CI 0.44 to 6.92; *p* = .423), ventilator-free days (adjusted MR 0.00; 95% CI -8.84 to 8.85; *p* = .999), hospital length of stay (adjusted MR 3.04; 95% CI -2.62 to 8.69; *p* = .293), and 28-day mortality (adjusted OR 0.68; 95% CI 0.15 to 2.98; *p* = .608).

Conclusion: HFNC may be beneficial in COVID-19 HRF. NRB + NC is a viable alternative, especially in resource-limited settings, given similar improvement in oxygenation at two hours, and no significant differences in long-term outcomes. The effectiveness of NRB + NC needs to be investigated by a powered randomized controlled trial.

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1. Introduction

More than 460 million people have been infected with coronavirus disease 2019 (COVID-19), killing 6 million during the global pandemic [1]. Early in the pandemic, many hospitals received

COVID-19 patients with hypoxemic respiratory failure (HRF) requiring supplemental oxygen and ventilator support [2,3]. In a study of 5700 patients with COVID-19 hospitalized in the United States between March and April 2020, 27.8% received supplemental oxygen, 14.2% admitted in the intensive care unit (ICU), and 12.2% required endotracheal intubation and mechanical ventilation [4]. ICUs have been overwhelmed and high mortality was observed in COVID-19 patients requiring invasive ventilation [4]. The initial respiratory treatment modalities for these patients are widely debated, and different strategies including non-invasive oxygen therapy have yielded variable outcomes [5,6].

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Non-invasive respiratory support such as high-flow nasal cannula (HFNC) is an attractive strategy for avoiding invasive ventilation. HFNC is simple to use and has physiological benefits [7–10]. In previous studies, HFNC reduced the need for endotracheal intubation in HRF due to chronic obstructive pulmonary disease, cardiogenic pulmonary oedema, community-acquired pneumonia, and COVID-19 [7,10–13]. However, there were no differences in mortality rates, ICU admission, or length of stay [7]. Many low- and middle-income countries are struggling with scarcity of healthcare resources, particularly oxygen supply amid a devastating COVID-19 surge [14]. HFNC devices are dependent on the wall oxygen system and consume 5 to 10 times the amount of oxygen that a mechanical ventilator does [15]. However, the oxygen pipes and vaporizers in many older hospitals are unable to accommodate the higher flow needs due to building structural limitations. Conventional oxygen therapy (COT) can be delivered using portable oxygen cylinders to lessen the demand for wall oxygen [15].

Current trials do not provide definitive evidence to recommend the use of HFNC in COVID-19 with HRF [16–18]. In resource-limited settings, particularly in the emergency department (ED), COT may offer a viable option for treating severe COVID-19 infection [8,19]. Problems arise in patients with severe HRF who require higher concentrations of oxygen that are not met by non-rebreather mask (NRB) alone. Previous reports in India have demonstrated an improvement in oxygenation with the usage of combined NRB and low-flow nasal cannula (NRB + NC) therapy for COVID-19-related HRF [20]. A retrospective study of 54 ICU patients found that NRB + NC yielded comparable results to HFNC in terms of mortality, intubation rate, and length of ICU and hospital stay [21]. However, this study recruited a small sample size in an ICU setting. It is uncertain if the results of this study would be applicable in the ED.

This retrospective, bicenter, observational study was conducted in COVID-19-related HRF patients to compare arterial oxygenation, intubation rate, invasive ventilation-free days, hospital length of stay, and 28-day mortality between NRB + NC and HFNC treatment groups.

2. Methods

2.1. Study design and setting

This retrospective, observational study was conducted in the ED of two tertiary hospitals in Malaysia. The Medical Research Ethics and the National Medical Research Register approved the study protocol (MREC ID: 2021819–10491, NMRR ID: 21–02094-TYT) and waived the requirement for informed consent. This study was conducted in accordance with Declaration of Helsinki.

2.2. Selection of participants

All consecutive adult patients admitted in the ED between June 1 to August 31, 2021 for severe COVID-19 pneumonia were screened for enrollment. Severe COVID-19 pneumonia was based on the World Health Organization (WHO) criteria: clinical signs of pneumonia (fever, cough, dyspnea) plus one of the following; respiratory rate > 30 breaths/min, severe respiratory distress, or peripheral oxygen saturation (SpO_2) < 90% on room air [22]. Other inclusion criteria were patients aged 18 years and older requiring NRB + NC or HFNC. COVID-19 infection was confirmed via reverse transcriptase-polymerase chain reaction (RT-PCR) assay.

Patients were excluded if emergent invasive ventilation was required upon presentation or within two hours of initiation of oxygen therapy. Other exclusion criteria were cross-treatment between NRB + NC and HFNC in ED, acute exacerbation of chronic pulmonary diseases, moderate to severe heart failure (New York Heart Association class ≥ 3 or left ventricular ejection fraction <40%), end-stage renal disease, and pregnancy.

2.3. Measurements

Data extracted from patients' medical records were age, gender, comorbidities, vaccination status, vital signs, chest radiograph findings, arterial blood gas (ABG), lactate, C-reactive protein, ferritin, D-dimer, and treatment provided. The decision to initiate oxygen therapy was at the discretion of the attending physician and based on the availability of the HFNC device and the oxygen capacity in the ED. In the NRB + NC group, patients received oxygen via 15 L/min of non-rebreather mask and 5 L/min of nasal cannula with fraction of inspired oxygen (F_{IO_2}) determined as 1.0. In the HFNC group, patients received oxygen via AIRVO 2 Optiflow (Fisher Paykel, New Zealand) with the flow rate and F_{IO_2} determined by the treating physician. The need for invasive ventilation was determined two hours after the initiation of oxygen therapy based on clinical parameters and ratio of oxygen saturation ($\text{SpO}_2/\text{F}_{\text{IO}_2}$) to respiratory rate (ROX) as per standard institutional protocol. Partial pressure of arterial oxygen (PaO_2) to F_{IO_2} ratio (PFR), Sequential Organ Failure Assessment (SOFA), ROX, and APACHE II scores were calculated from the recorded parameters.

Treatment included prone positioning and concomitant medical therapies such as steroids and other immunomodulatory agents, antibiotics, antiviral agents, and vasopressors as determined by the treating physicians. Patients were followed-up for 28 days.

Data were collected retrospectively from the respective hospital's medical records. The International Classification of Disease (ICD-10-CM) code U07.1 was used to extract patient records for "Confirmed COVID-19 virus identified". Data abstraction was performed by two experienced medical doctors who had undergone training on the study protocol to minimize inter-rater variability. The data abstractors were not blinded to the study objectives and hypotheses. Patients' clinical and biochemical characteristics were recorded on the data-abstraction forms. Three certified emergency physicians (KPY, AMNA, and AB) validated that all participants included in the study fulfilled the definition for severe COVID-19 pneumonia according to the WHO criteria.

2.4. Outcomes

The primary outcome of the study was the improvement of PaO_2 after receiving NRB + NC or HFNC at two hours. Secondary outcomes were intubation rate, ventilator-free days, length of hospital stay, 28-day mortality, improvement in SpO_2 , PFR, and respiratory rate, and number of days to intubation or to de-escalation of oxygen therapy. Ventilator-free days was defined as the number of days the patients were liberated from mechanical ventilation. If a patient died within the 28 days, the ventilator-free days was documented as 0.

The sample size was calculated using G*power version 3.1.9.4 with an effect size of 0.5 and α -error probability of 0.05. The effect size of 0.5 was used since there were no previous comparable studies. For a study power of 0.80, the total sample size required was 102 including a dropout rate of 10%.

2.5. Statistical analysis

The results were analyzed using Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp, Armonk, NY) and R Project for Statistical Computing (version 4.0.4). Descriptive statistics were expressed as frequencies (percentages), mean (standard deviation), or median (interquartile range). Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test when appropriate. Test of normality was determined with the Shapiro-Wilk test for continuous variables. Normally distributed continuous data were analyzed using Student's *t*-test and reported as mean differences and mean ratio (MR), whereas non-parametric data was analyzed with Mann-Whitney *U* test and reported as odds ratio (OR). The Paired Samples *t*-test and Wilcoxon Signed-Rank Test were used to calculate the

differences in physiological variables at baseline and two hours of administration of oxygen therapy.

In the sensitivity analysis, heterogeneity in the NRB + NC and HFNC groups were adjusted with propensity score using inverse probability of treatment weighting (IPTW) due to the small cohort in both groups. The data between NRB + NC and HFNC groups were heterogeneous in vaccination status, heart rate, respiratory rate, SpO₂, pH, partial pressure of carbon dioxide (PaCO₂), bicarbonate (HCO₃⁻), serum lactate, SOFA, and APACHE II scores, and thus were selected as covariates for the IPTW. The IPTW method creates a pseudo-population where the weighted data can mitigate the covariate bias. Average treatment effects were calculated using 1/propensity score for NRB + NC group and inverse of (1-propensity score) for HFNC group [23]. Generalized linear model and regression analyses were used to analyze the adjusted outcomes. The survival analysis and cumulative intubation rates were plotted as IPTW-adjusted Kaplan-Meier curves using Cox proportional hazards regression model. The findings were considered statistically significant if the *p* < .05.

3. Results

3.1. Characteristics of study subjects

Out of the 531 severe COVID-19 pneumonia patients admitted to the 2 participating EDs between June 1 and August 31, 2021, 110 met the inclusion criteria and were included in the analysis (Fig. 1). Fifty-two patients (47.3%) were in the NRB + NC group, and 58 (52.7%) were in the HFNC group. No patients were lost to follow-up and no missing data was reported. There was no crossover of patients between the two treatment arms. In the HFNC group, the mean initial flow rate and F_{IO2} were 58.3 L/min (95% CI 57.3 to 59.3 L/min) and 0.58 (95% CI 0.57 to 0.59). Mean ROX indices at two hours for NRB + NC and HFNC were 2.73 (95% CI 2.11 to 4.08) and 6.21 (95% CI 4.04 to 8.44), respectively. Two patients from each group had a do-not-intubate (DNI) order. Baseline characteristics of the patients are summarized in Table 1. The physiologic variables at baseline and two hours of application of oxygen therapy are shown in Table 2 and Fig. 2.

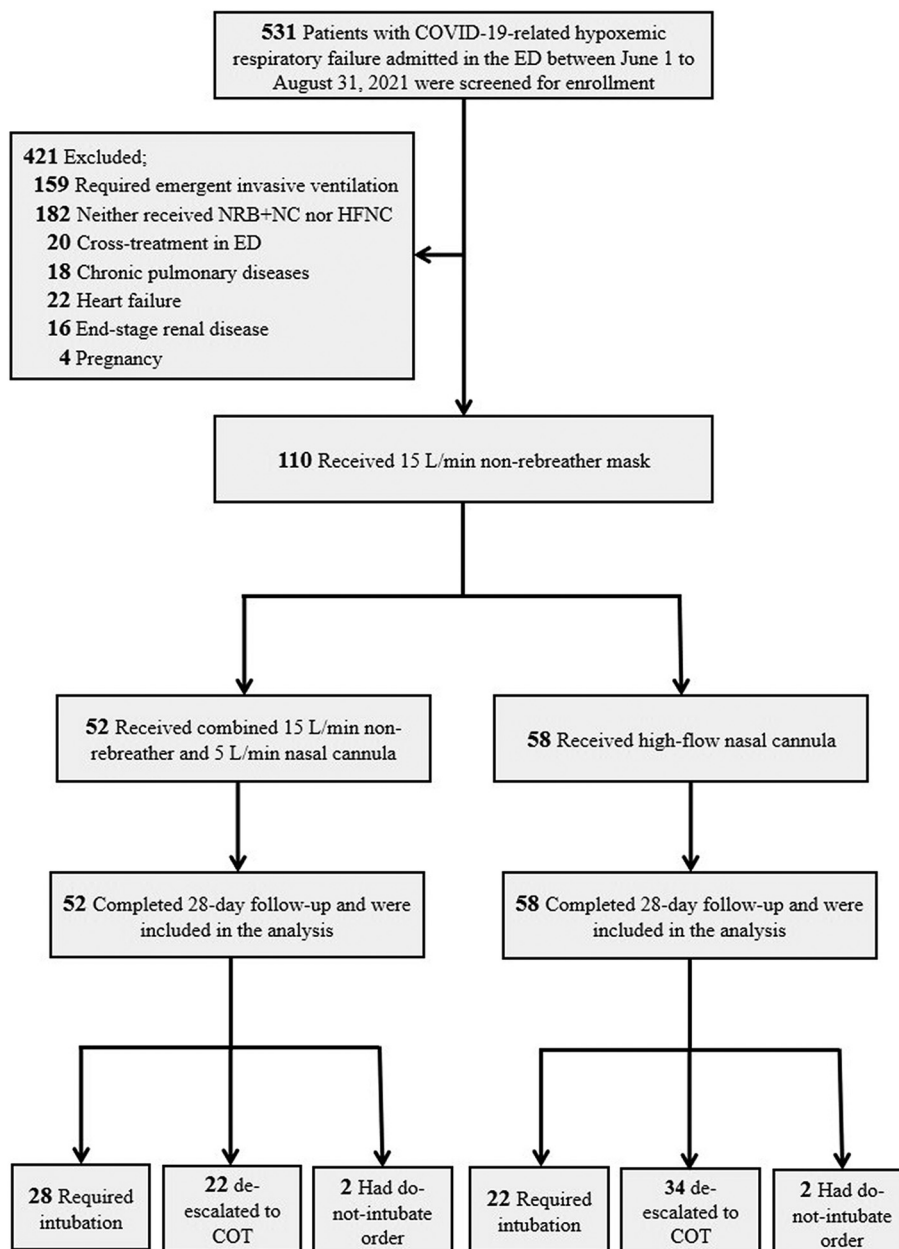


Fig. 1. Selection of study participants.

Table 1
Baseline characteristics of patients, according to study group.

Characteristic	No. (percentage, %)		p-value ^a
	Non-rebreather mask and low-flow nasal cannula (n = 52)	High-flow nasal cannula (n = 58)	
Age, median (IQR), years	48 (36–60)	53 (41–63)	0.237
Sex			0.822
Male	33 (63.5)	38 (65.5)	
Female	19 (36.5)	20 (34.5)	
Relevant comorbidities			
Type 2 diabetes	19 (36.5)	16 (27.6)	0.314
Hypertension	29 (55.8)	26 (44.8)	0.252
Dyslipidaemia	28 (53.8)	9 (15.5)	<0.001
Obesity	1 (1.9)	4 (6.9)	0.211
Ischaemic Heart Disease	1 (1.9)	4 (6.9)	0.211
Congestive Cardiac Failure	1 (1.9)	0	0.289
Chronic Kidney Disease	1 (1.9)	0	0.289
Cerebrovascular disease	0	2 (3.4)	0.177
Bronchial asthma	0	4 (6.9)	0.054
History of cancer			0.938
Breast cancer	1 (1.9)	1 (1.7)	
Vaccination status			<0.001
Unvaccinated	28 (53.8)	51 (87.9)	
^d Partially vaccinated	22 (42.3)	6 (10.3)	
Pfizer-BioNTech	7 (13.4)	1 (1.7)	
Sinovac	15 (28.9)	5 (8.6)	
^e Completely vaccinated	2 (3.8)	1 (1.7)	
Pfizer-BioNTech	1 (1.9)	0	
Sinovac	1 (1.9)	1 (1.7)	
Blood pressure, median (IQR) mmHg			
Systolic	127 (88–139)	129 (111–135)	0.567
Diastolic	74 (55–82)	77 (68–82)	0.086
Mean arterial pressure	92 (65–101)	94 (83–98)	0.244
Heart rate, mean (SD) beats/min	106 (12)	98 (17)	0.004
Respiratory rate, median (IQR) breaths/min	38 (37–39)	30 (28–36)	<0.001
Temperature, median (IQR), °C	38.0 (37.8–39.0)	37.0	<0.001
Oxygen saturation on non-rebreather 15 L/min, SpO ₂ median (IQR) SpO ₂	82 (80–84)	92 (87–95)	<0.001
Glasgow Coma Scale (GCS)	15	15	0.098
Arterial blood gases on non-rebreather 15 L/min, median (IQR)			
pH	7.30 (7.26–7.36)	7.48 (7.45–7.51)	<0.001
PaO ₂ , mm Hg	65.7 (61.0–72.4)	64.5 (54.7–72.8)	0.580
PaCO ₂ , mm Hg	31.7 (28.9–36.6)	28.9 (26.1–31.8)	0.001
HCO ₃ ⁻ , mmol/L	16.9 (15.4–18.7)	23.8 (21.6–25.5)	<0.001
Base deficit, mmol/L	2.7 (1.7–3.6)	1.7 (0.6–3.7)	0.165
PaO ₂ / F _{IO2} ratio	66 (61–72)	69 (58–83)	0.188
Serum lactate, median (IQR) mmol/L	3.00 (2.63–3.48)	1.49 (1.17–2.11)	<0.001
C-reactive protein, median (IQR) mg/L	206.5 (167.0–312.5)	130.1 (95.7–165.1)	<0.001
Serum ferritin, median (IQR), µg/L	467 (339–736)	1075 (637–2495)	<0.001
Positive D-dimer (qualitative)	16 (30.8)	11 (19.0)	0.185
^b SOFA score, median (IQR)	3 (2–6)	2 (2–3)	0.001
^c APACHE II score, median (IQR)	17 (13–22)	11 (8–13)	<0.001
A-a gradient, median (IQR)	608 (598–613)	608 (594–616)	0.722
Bilateral infiltrates on chest x-ray	52 (100)	58 (100)	
Concomitant medications			
Steroids	52 (100)	58 (100)	
Anti-coagulants	52 (100)	58 (100)	
Antibiotics	51 (98.1)	47 (81.0)	0.005
Favipiravir	8 (15.4)	12 (20.7)	0.621
Tocilizumab	3 (5.8)	15 (25.9)	0.002
Baricitinib	2 (3.8)	7 (12.1)	0.002
Prone position	46 (88.5)	12 (20.7)	<0.001
Vasopressor / inotropic support			<0.001
Single (Noradrenaline)	20 (38.5)	5 (8.6)	

Abbreviations: F_{IO2}, fraction of inspired oxygen; IQR, interquartile range; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of arterial oxygen; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SpO₂, peripheral arterial oxygenation.

^a For qualitative variables, p-values refer to the Chi-square test or Fisher exact test, whereas for quantitative variables, p-values tabulated from the student's t-test or Mann-Whitney U test.

^b SOFA score was calculated from 6 variables at enrollment. Scores range from 0 to 24, with higher scores indicating more severe disease.

^c APACHE II score was calculated from 12 variables at enrollment. Scores range from 0 to 71, with higher scores indicating more severe disease and higher mortality.

^d Patients who received a COVID-19 vaccine injection or received two injections but <14 days from date of ED admission.

^e Patients who received two injections with at least 14 days from date of admission.

3.2. Main results

3.2.1. Primary outcome

The median improvement of PaO₂ at two hours after application of oxygen therapy was 13.0 mmHg (IQR 7,18) in the

NRB + NC group and 4.0 mmHg (IQR -6.4, 17.0) in the HFNC group (*p* = .009). The mean difference and MR between the NRB + NC and HFNC groups were 6.0 mmHg (95% CI 0 to 12.0) and 5.61 mmHg (95% CI -0.59 to 11.81), respectively (Table 3).

Table 2
Physiologic variables at baseline and two hours of application of oxygen therapy, according to study group.

Variable	Non-breather mask and low-flow nasal cannula			High-flow nasal cannula		
	Baseline	Two hours	p-value	Baseline	Two hours	p-value
Oxygen saturation, median (IQR), SpO ₂ (%) ^a	82 (80–84)	90 (88–94)	<0.001	92 (87–95)	93 (89–95)	0.164
Respiratory rate, median (IQR) breaths/min ^a	38 (37–39)	35 (32–36)	<0.001	30 (28–36)	25 (23–30)	<0.001
Heart rate, mean (SD) beats/min ^b	106 (12)	98 (9)	<0.001	98 (17)	89 (14)	<0.001
Systolic blood pressure, median (IQR), mm Hg ^a	127 (88–139)	125(120–131)	0.096	129 (111–135)	127 (115–138)	0.353
Diastolic blood pressure, median (IQR), mm Hg ^a	74 (55–82)	75 (68–82)	0.019	77 (68–82)	71 (60–78)	0.001
Mean arterial pressure, median (IQR), mm Hg ^a	92 (65–101)	91 (86–98)	0.020	94 (83–98)	88 (82–98)	0.071
Arterial pH, median (IQR) ^a	7.30 (7.26–7.36)	7.32 (7.28–7.35)	0.639	7.48 (7.45–7.51)	7.45 (7.41–7.48)	0.000
PaO ₂ , median (IQR), mm Hg ^a	65.7 (61.0–72.4)	80.2 (72.2–84.0)	<0.001	64.5 (54.7–72.8)	69.1 (57.6–80.2)	0.041
PaCO ₂ , median (IQR) mm Hg ^a	31.7 (28.9–36.6)	34.0 (30.3–38.0)	0.128	28.9 (26.1–31.8)	32.6 (29.0–35.8)	<0.001
HCO ₃ ⁻ , median (IQR), mmol/L ^a	16.9 (15.4–18.7)	17.8 (15.3–20.0)	0.415	23.8 (21.6–25.5)	23.6 (21.4–26.1)	0.354
PaO ₂ / F _{IO2} ratio (PFR), median (IQR) ^a	66 (61–72)	80 (72–84)	<0.001	69 (58–83)	118 (105–141)	<0.001
Serum lactate, median (IQR) mmol/L ^a	3.00 (2.63–3.48)	2.35 (1.70–3.08)	<0.001	1.49 (1.17–2.11)	1.20 (1.10–1.58)	<0.001

Abbreviations: HCO₃⁻, bicarbonate; IQR, interquartile range; PaO₂, partial pressure of arterial oxygen; PaCO₂, partial pressure of carbon dioxide; SD, standard deviation; SpO₂, peripheral arterial oxygenation.

^a Wilcoxon Signed-Rank Test.
^b Paired-Samples t-Test.

3.2.2. Secondary outcomes

The mean improvement of SpO₂ at two hours in the NRB + NC group vs HFNC group were 8% vs 1% (mean difference 6%; 95% CI 4 to 8; p ≤ 0.001). The median improvement of PFR at two hours in the NRB + NC group vs HFNC group were 13 vs 49 (mean difference - 36; 95% CI -47 to -25; p ≤ 0.001). The reduction of respiratory rate in the NRB + NC group vs HFNC group were 3 vs 5 breaths/min (mean difference - 2; 95% CI -4 to 0; p = .038).

The rates of endotracheal intubation within 28 days in the NRB + NC and HFNC groups were 53.8% vs 37.9% (OR 1.91; 95% CI 0.89 to 4.09; p = .094). The median days to intubation in the NRB + NC and HFNC groups were 0 vs 3 days (mean difference - 4; 95% CI -7 to -1; p ≤ 0.001). The median ventilator-free days in the NRB + NC group compared to the HFNC group were 23 vs 28 days (mean difference - 2; 95% CI -6 to 3; p = .145).

The median length of hospital stay in the NRB + NC and HFNC groups were 16 vs 13 days (mean difference 0; 95% CI -3 to 3; p = .561). The 28-day mortality rates in the NRBC+NC vs HFNC groups were 28.8% vs 27.6% (OR 1.06; 95% CI 0.46 to 2.44; p = .883) (Table 3).

3.2.3. Sensitivity analyses

Fig. 3 shows the covariates before and after IPTW adjustment. After the adjustment, there were no differences between NRB + NC and HFNC groups in improvement of PaO₂ (adjusted MR 2.81; 95% CI -5.82 to 11.43; p = .524), requirement for intubation (adjusted OR 1.76; 95% CI 0.44 to 6.92; p = .423), ventilator-free days (adjusted MR 0.00; 95% CI -8.84 to 8.85; p = .999), hospital length of stay (adjusted MR 3.04; 95% CI -2.62 to 8.69; p = .293), and 28-day mortality (adjusted OR 0.68; 95% CI 0.15 to 2.98; p = .608).

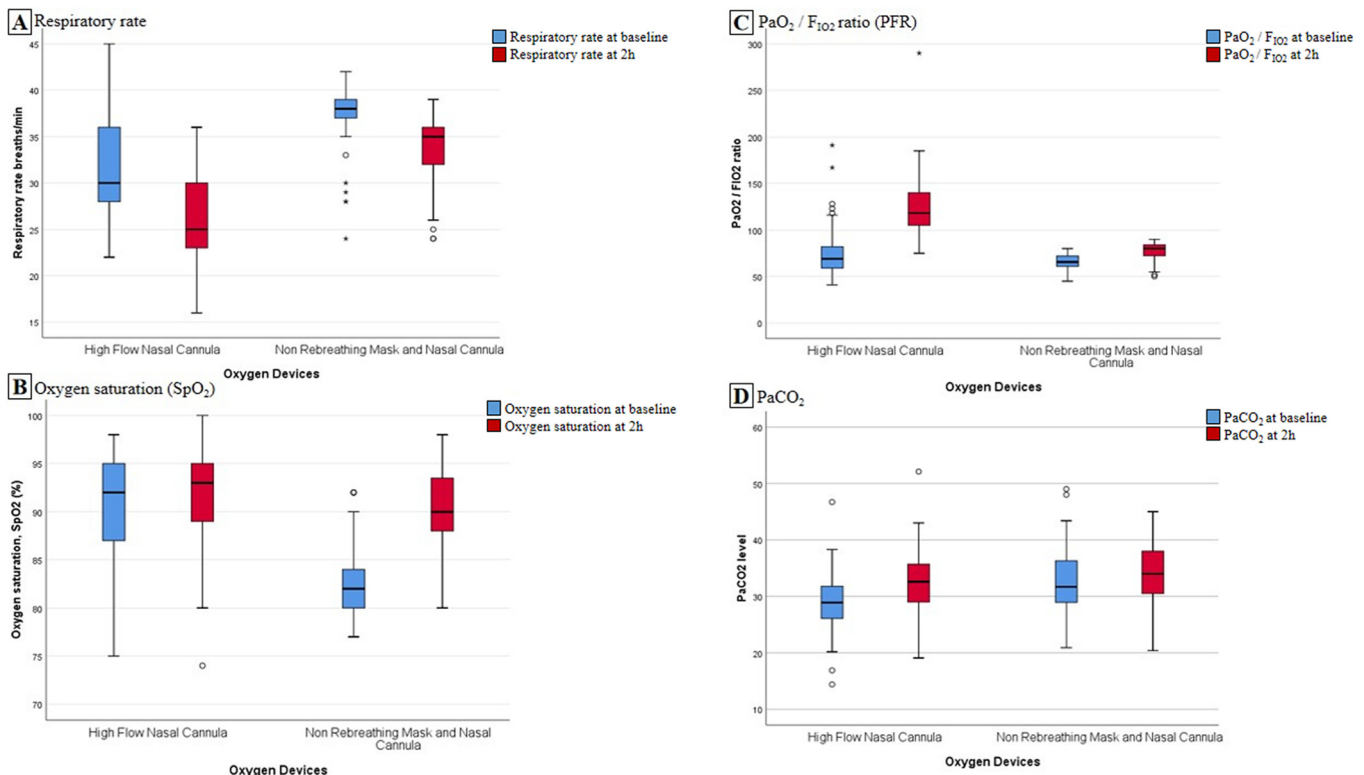


Fig. 2. Physiologic variables at baseline and two hours of application of oxygen therapy.

Table 3
Primary and secondary outcomes, according to study group.

Outcomes	No (%)		Unweighted		ATE weighted		
	Non-rebreather mask and low-flow nasal cannula	High-flow nasal cannula	Absolute / mean difference	Odds ratio / mean ratio (95% CI)	p-value	Adjusted odds ratio / mean ratio (95% CI)	Adjusted p-value
Primary Outcome							
Partial pressure of arterial oxygen at 2 h, PaO ₂ median (IQR) mm Hg ^a	80.2 (72.0 to 84.0)	69.1 (57.6 to 80.2)	6.0 (0 to 12.0)	1.11 (1.03 to 1.19)	0.001	1.09 (0.93 to 1.27)	0.311
Improvement in partial pressure of arterial oxygen at 2 h, PaO ₂ median (IQR) mm Hg ^a	13.0 (7.0 to 18.0)	4.0 (-6.4 to 17.0)	6.0 (0 to 12.0)	5.61 (-0.59 to 11.81)	0.009	2.81 (-5.82 to 11.43)	0.524
Secondary Outcomes							
Oxygen saturation at 2 h, SpO ₂ median (IQR) % ^a	90 (88 to 94)	93 (89 to 95)	-1 (-3 to 0)	-1.38 (-3.13 to 0.38)	0.025	2.40 (-1.27 to 6.08)	0.200
Improvement in oxygen saturation at 2 h, SpO ₂ mean (SD), % ^a	8 (4)	1 (6)	6 (4 to 8)	6.18 (4.21 to 8.14)	<0.001	4.80 (-0.04 to 9.63)	0.052
PaO ₂ / F _{IO2} at 2 h, median (IQR) ^a	80 (72 to 84)	118 (105 to 141)	-46 (-56 to -37)	0.64 (0.59 to 0.69)	<0.001	0.64 (0.54 to 0.75)	<0.001
Improvement in PaO ₂ / F _{IO2} at 2 h, median (IQR) ^a	13 (7 to 18)	49 (30 to 68)	-36 (-47 to -25)	-36.08 (-46.79 to -25.38)	<0.001	-42.09 (-56.98 to -27.20)	<0.001
Respiratory rate at 2 h, median (IQR) breaths/min ^a	35 (32 to 36)	25 (23 to 30)	7 (5 to 9)	7.31 (5.73 to 8.89)	<0.001	3.50 (0.98 to 6.03)	0.006
Reduction in respiratory rate at 2 h, median (IQR) breaths/min ^a	3 (2 to 5)	5 (1 to 9)	-2 (-4 to 0)	-1.85 (-3.64 to 0.06)	0.038	-1.35 (-2.78 to 0.09)	0.066
Intubation within 28 days from enrollment ^b	28 (53.8)	22 (37.9)	-4 (-7 to -1)	1.91 (0.89 to 4.09)	0.094	1.76 (0.44 to 6.92)	0.423
Days to intubation, median (IQR) ^c	0 (0 to 1)	3 (1 to 6)	-4 (-7 to -1)	-0.41 (-0.63 to -0.25)	<0.001	0.60 (0.32 to 1.12)	0.110
Invasive ventilation-free days within 28d, median (IQR) ^a	23 (0 to 28)	28 (0 to 28)	-2 (-6 to 3)	-1.51 (-6.12 to 3.09)	0.145	0.00 (-8.84 to 8.85)	0.999
Days to de-escalation to lower respiratory support (e.g. nasal cannula, simple face mask), median (IQR) ^b	4 (3 to 4)	5 (3 to 7)	-2 (-5 to 0)	-0.37 (-0.58 to -0.23)	<0.001	0.54 (0.29 to 1.00)	0.049
Mortality within 28d ^b	15 (28.8)	16 (27.6)	0 (-3 to 3)	1.06 (0.46 to 2.44)	0.883	0.68 (0.15 to 2.98)	0.608
Hospital length of stay, median (IQR) days ^a	16 (8 to 19)	13 (10 to 19)	0 (-3 to 3)	-0.32 (-3.23 to 2.59)	0.561	3.04 (-2.62 to 8.69)	0.293

Abbreviations: ATE, Average treatment effects; F_{IO2}, fraction of inspired oxygen; IQR, interquartile range; PaO₂, partial pressure of arterial oxygen; SpO₂, peripheral arterial oxygenation.

^a Linear regression analysis.

^b Logistic regression analysis.

^c Poisson regression analysis.

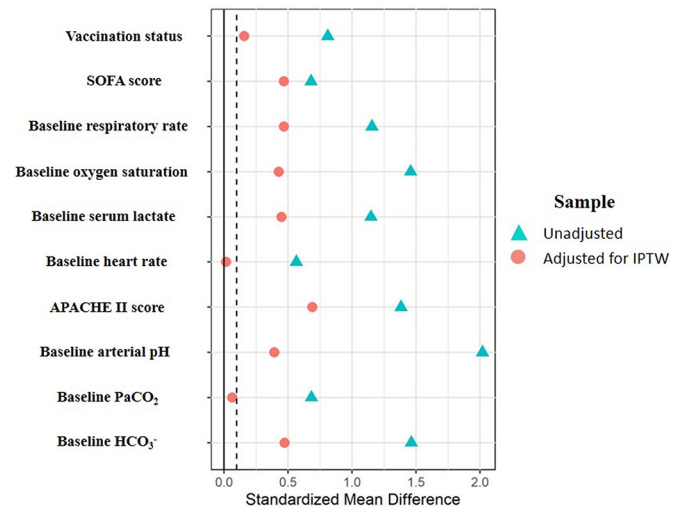


Fig. 3. Standardized mean differences of covariates for IPTW adjustment.

However, there were differences in the outcomes observed between NRB + NC and HFNC groups in PFR improvement (13 vs 49; adjusted MR -42.09; 95% CI -56.98 to -27.20; $p \leq 0.001$), respiratory rate at two hour (35 vs 25 breaths/min; adjusted MR 3.50; 95% CI 0.98 to 6.03; $p = .006$), and duration to de-escalate to lower respiratory support, such as simple face mask or NC (4 vs 5 days; adjusted MR 0.54; 95% CI 0.29 to 1.00; $p = .049$).

4. Discussion

In this retrospective study of COVID-19 patients with HRF presenting to the ED, both NRB + NC and HFNC groups demonstrated significant improvements in PaO₂ at two hours. The NRB + NC group had a greater two-hour median difference in PaO₂ improvement compared to the HFNC group (13 vs 4 mmHg; p -value = .009), but this difference was not statistically significant after IPTW adjustment (adjusted MR 2.81; p -value = .524). In contrast, SpO₂ improvement was significantly different between the two groups. This could be explained by the NRB + NC group having lower SpO₂ at baseline, attributable to a greater proportion of severely ill patients compared to the HFNC group (APACHE II score 17 vs 11; p -value = .001). Moreover, more patients in the NRB + NC group required proning compared to the HFNC group (46 vs 12; p -value = .001) to achieve a similar targeted SpO₂.

The findings of this study corroborate previous trials that observed significant improvements in PFR and reduction in respiratory rate after initiating HFNC [13]. A systematic review found that HFNC significantly improves PFR and respiratory rate [13]. HFNC reduces oxygen dilution, allows a more reliable F_{IO2}, eliminates physiological dead space, and generates positive end expiratory pressure (PEEP) [24]. Nonetheless, improvement of PFR and respiratory rate were also seen in the NRB + NC group. The use of a low-flow NC in combination with NRB reduces air mixing and increases F_{IO2} closer to 1.0, which cannot be achieved by NRB alone [13,20,21].

Early observational studies demonstrated high mortality rates in COVID-19 patients with HRF requiring invasive ventilation [4,6]. The usage of non-invasive respiratory support avoids ventilator-induced lung injury and the complications related to prolonged sedation and neuromuscular paralysis [25]. Evidence for HFNC as an effective treatment for HRF is drawn from studies on populations other than COVID-19 pneumonia [7,11-13].

Despite the presumed physiological benefits of HFNC use over COT, there is no evidence that it reduces mortality. A meta-analysis by Rochwerger et al. of 9 trials involving 2093 patients with HRF of various

aetiologies, found no difference in mortality in patients treated with HFNC compared to COT (relative risk 0.94; 95% CI 0.67 to 1.31) [7]. Similarly, other recent trials did not demonstrate the mortality benefits of HFNC over COT [16–18]. This suggests that neither HFNC nor COT have a direct effect on the disease process and impacting mortality, but both have similar efficacy in terms of improving oxygenation and preventing intubation in a greater proportion of patients. Early relief of respiratory effort could theoretically reduce patients' self-inflicted lung injury and result in improved clinical outcomes [17]. However, COVID-19 is a unique disease from other causes of HRF, with complex manifestations of dysregulated immuno-inflammatory response, thrombotic, parenchymal, and endotheliopathy derangements [26]. Various factors and treatments may influence long-term outcomes of patients.

In COVID-19-related HRF, current trials have shown inconsistent evidence in the role of HFNC in avoiding intubation [16–18]. In the HifLo-Covid trial, the use of HFNC reduced the rate of endotracheal intubation compared with COT (34.3% vs 51.0%) [17]. However, the RECOVERY-RS trial contradicted this finding [18]. The RECOVERY-RS trial randomized 1273 COVID-19 patients to continuous positive airway pressure (CPAP), HFNC, or COT, and found reduced rate of endotracheal intubation in CPAP compared to COT (36.3% vs 44.4%), but no significant difference between HFNC and COT (44.3% vs 45.1%) [18].

In this study, patients in the NRB + NC group were more severely ill at baseline with more dyspnea, hypoxia, and acidosis. They also had a greater vasopressor requirement than patients in the HFNC group. Consequently, the cumulative intubation rates over 28 days showed that patients in the NRB + NC group were more likely to require early intubation, with the majority requiring it within a day (Log rank $p = .02$) (Fig. 4). This correlated with the low ROX index after two hours of initiating NRB + NC therapy. Although the patients treated with NRB + NC appeared to have a lower survival rate than those treated with HFNC, this was not statistically significant (Log rank $p = .503$) (Fig. 5). The curves imply that a considerable number of patients in the NRB + NC died early in the course of the disease within 8 days, before reaching a plateau at day 10 and nearly converges with the HFNC curve at day 24.

The HFNC group did not show a statistically significant difference in intubation rate compared to the NRB + NC group. Comparatively, the rates of intubation in recent COVID-19-related HRF trials were 34% and 44% [17,18]. In this study, patients in the HFNC group had more

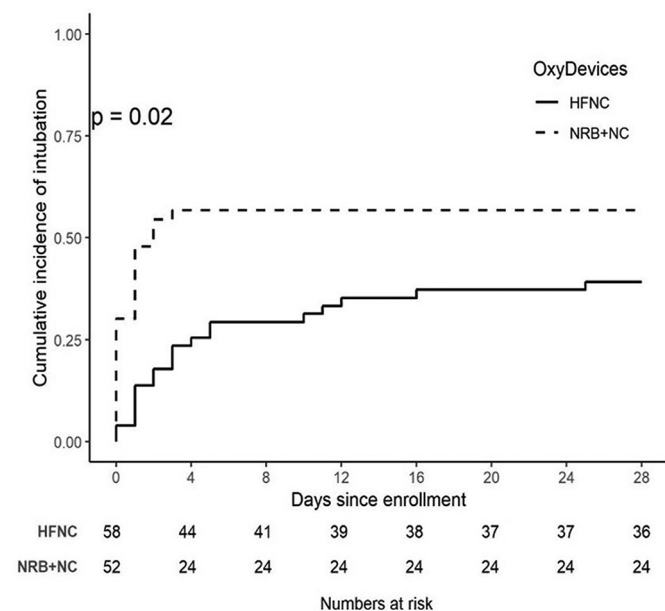


Fig. 4. Cumulative incidence of intubation over 28 days using IPTW-adjusted Kaplan-Meier plots.

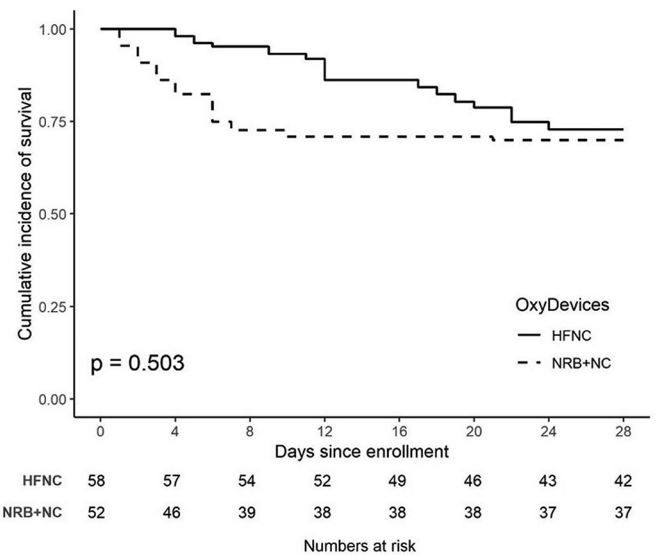


Fig. 5. Cumulative Incidence of Survival over 28 days using IPTW-adjusted Kaplan-Meier plots.

ventilator-free days compared to those in the NRB + NC group. Despite the patients in the NRB + NC group being more critically ill at baseline, the difference in ventilator-free days was not statistically significant compared to the HFNC group.

It was observed in this study that patients on HFNC took longer to de-escalate to COT. This was likely due to a greater inclination among physicians to maintain HFNC use until the required F_{IO_2} was within 0.30. This corresponds with experts' recommendation that F_{IO_2} should be <0.4 before weaning off HFNC [27,28]. However, the ideal weaning strategy of HFNC is not yet established. The current SLOWH trial is investigating different HFNC weaning protocols among patients with various causes of HRF [29].

Successful avoidance of intubation could optimize resource allocation in the ED, especially in the context of the COVID-19 pandemic. In settings where access to HFNC is available, using HFNC is reasonable, but NRB + NC may be a viable alternative. This study was conducted in a developing country with significant resource limitations, especially in regards to the availability of oxygen canisters and HFNC devices that were further exacerbated by the massive caseload of COVID-19 pandemic. HFNC may consume more oxygen than NRB + NC, and invasive ventilation is cumulatively more resource-intensive than non-invasive ventilation or COT. Therefore, this necessitated the use of the readily available NRB + NC which was deemed an efficient alternative to the more resource-intensive HFNC.

This study has several limitations. Firstly, this was a retrospective observational study with a possibility of selection bias. Secondly, despite sensitivity analysis through IPTW, optimal matching could not be achieved due to the heterogeneity of the patients' baseline characteristics in the two treatment groups. Potentially significant covariates which were not matched were vasopressor use and prone position. However, there was no difference in the baseline blood pressure and there is insufficient evidence regarding the benefits of awake prone positioning in the management of nonintubated COVID-19 patients with HRF [30]. Thirdly, given the use of oxygen therapy with varying F_{IO_2} , PFR may be a more accurate reflection of improvement in oxygenation, especially in the setting of a right-to-left shunt due to ventilation-perfusion mismatch. Lastly, because of its retrospective nature, there may have been some variability in the exact timing of ABG sampling, although local protocol requiring ROX score to be obtained two hours after therapy is initiated may reduce this error if adhered to. Further multi-centered randomized controlled trials are required to assess the efficacy and safety of NRB + NC in severe COVID-19 infection.

5. Conclusions

In summary, HFNC may be beneficial in COVID-19 HRF. NRB + NC is a viable alternative, especially in resource-limited settings, given similar improvement in oxygenation at two hours, and no significant differences in long-term outcomes. The effectiveness of NRB + NC needs to be investigated by a powered randomized controlled trial.

CRediT authorship contribution statement

Muhammad Khidir Mohd Kamil: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Khadijah Poh Yuen Yoong:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Abdul Muhaimin Noor Azhar:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Aida Bustam:** Writing – review & editing, Supervision, Software, Methodology, Conceptualization. **Ahmad Hariz Abdullah:** Data curation. **Mohd Hafyuzuddin Md Yusuf:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Aliyah Zambri:** Writing – review & editing. **Ahmad Zulkarnain Ahmad Zahedi:** Supervision, Methodology, Conceptualization. **Hidayah Shafie:** Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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