High-flow Nasal Cannula Oxygen Therapy as Initial Respiratory Management for Severe COVID-19-induced Respiratory Failure: a Single-center Observational Study

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Research Article

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Abstract

Background: The efficacy and safety of high-flow nasal cannula (HFNC) oxygen therapy in severe respiratory failure, especially induced by COVID-19, has not been fully elucidated. We aimed to examine the usefulness of HFNC compared to invasive mechanical ventilation (IMV) as initial respiratory management for severe COVID-19-induced respiratory failure.

Methods: In this retrospective observational study, we enrolled and categorized the patients with COVID-19-induced severe respiratory failure who were intolerant of conventional oxygen therapy into two groups: 1) patients who initially received HFNC (HFNC group) and 2) patients who initially underwent IMV (IMV group). The primary outcome was in-hospital mortality. The secondary outcomes were ventilator-free days within 28 days, intensive care unit (ICU)-free days within 28 days, and respiratory failure days defined as the length from day 1 to achieving successful weaning from both HFNC and IMV.

Results: We analyzed 182 patients (HFNC group, n=81; IMV group, n=101). There was no difference in in-hospital mortality between the two groups (19% in the HFNC group vs. 25% in the IMV group, p=0.37). Initial use of HFNC was not associated with mortality in the univariate analysis (OR, 0.69; CI, 0.34–1.42; p=0.31) and inverse probability of treatment weighting analysis using propensity scoring (OR, 1.01; CI, 0.37–2.77; p=0.984). Ventilator-free days within 28 days were significantly longer in the HFNC group than those in the IMV group (median, 22 days [interquartile range (IQR), 2–28 days] vs. median, 14 days [IQR, 0–20 days], p<0.001). ICU-free days within 28 days were significantly longer in the HFNC group than those in the IMV group (median, 23 days [IQR, 0–28 days] vs. median, 15 days [IQR, 0–20 days], p<0.001). Respiratory failure days were relatively shorter in the HFNC group, but the difference was not statistically significant (p=0.071).

Conclusions: Among patients with severe COVID-19-induced respiratory failure, HFNC compared to IMV resulted in a statistically significant increase in ventilator-free and ICU-free days within 28 days without increasing in-hospital mortality. This study showed the potential for HFNC to be an effective alternative to IMV as initial respiratory management for severe COVID-19-induced respiratory failure.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), has expanded rapidly around the world since December 2019. COVID-19 mainly affects the respiratory system with some patients rapidly progressing to severe interstitial pneumonia and acute respiratory distress syndrome [1]. As of December 5, 2021, more than 265.7 million confirmed infections with approximately 5.3 million deaths were reported around the world [2]. Some reports showed that mechanical ventilation management was required in about 49–88% of critically ill patients [3–5], whose mortality rate ranged widely from 28–88% [4–6]. In the early phase of the COVID-19 pandemic in 2020, several clinical guidelines recommended early intubation to protect healthcare workers from aerosols containing SARS-CoV-2 [7–10]. However, along with the global spread of COVID-19, ventilator shortage

was reported to be a serious bottleneck in some regions [11]. Actually, the clinical guidelines for COVID-19 in Italy proposed directing crucial resources, such as intensive care beds and ventilators, to only limited patients who could receive maximal benefit from the treatments [12]. Therefore, establishment of an alternative and effective respiratory treatment strategy is required for critically ill patients who cannot be adequately treated with standard oxygen therapy.

High-flow nasal cannula (HFNC) oxygen therapy was reported to reduce mortality in hypoxemic acute respiratory failure compared with standard oxygen therapy or noninvasive ventilation [13]. Besides, a recent meta-analysis reported that HFNC for patients with severe respiratory failure reduced the need for intubation [14]. In this context, HFNC is expected to be an alternative to invasive mechanical ventilation (IMV) as initial respiratory management for COVID-19 due to limited medical resources. However, failure of HFNC is reported to possibly increase mortality through missing of the best timing for intubation [15], and thus clinical evidence of the efficacy and safety of HFNC for COVID-19 needs to be sufficiently elucidated. To date, there is still limited evidence of the usefulness of HFNC for the treatment of COVID-19.

The purpose of this study was to examine the usefulness of HFNC as initial respiratory management for severe COVID-19-induced respiratory failure.

Methods

Study design, setting, and participants

This was a single-center, retrospective, observational study conducted at a tertiary care hospital in Japan from 1 March 2020 to 30 April 2021, for patients with COVID-19-induced acute respiratory failure. Patients included in the analysis were 20 years of age or older, were intolerant of conventional oxygen therapy, and needed HFNC or IMV via orotracheal intubation. Noninvasive ventilation was avoided due to concerns regarding aerosolization of the SARS-CoV-2 virus. Exclusion criteria included the initiation of HFNC or IMV before transfer to our hospital, disturbance of consciousness (Glasgow Coma Scale score <8), septic shock, do-not-intubate order, out-of-hospital cardiac arrest, and cases in which introduction of HFNC was inappropriate.

This study followed the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board for Clinical Research of Osaka General Medical Center (IRB No. S202004004). The board waived the requirement for informed consent because of the anonymous and retrospective nature of the study design.

Patient categorization

To evaluate the impact of the initial use of HFNC on the study outcomes, we categorized the study patients into two groups: 1) patients who initially received HFNC (HFNC group) and 2) patients who initially underwent IMV (IMV group) as the initial respiratory management when they became intolerant of

conventional oxygen therapy. As a subgroup analysis, we further divided the HFNC group into two additional groups: 1) patients who received only HFNC oxygen therapy (HFNC group) and 2) patients who were secondarily intubated after initiation of HFNC (HFNC to IMV group).

Definitions

The diagnosis of COVID-19 was performed according to World Health Organization interim guidance (World Health Organization, 2021) and confirmed RNA detection of the SARS-CoV-2 by polymerase chain reaction testing of a nasopharyngeal sample in a clinical laboratory of the Osaka General Medical Center. We defined “day 1” in this study as the first day when the study patients became intolerant to conventional oxygen therapy and required HFNC or IMV. Conventional oxygen therapy was performed with up to 15 L/min of oxygen flow via nasal cannula, face mask, or non-rebreathing reservoir mask in patients with a respiratory rate of up to 30 rpm and with tolerable respiratory distress.

Treatment

The decision to intubate or use HFNC for patients with COVID-19-induced respiratory failure was at the discretion of the attending physicians. The system used for HFNC was the Airvo™ 2 (Fisher & Paykel Healthcare, Auckland, New Zealand). HFNC treatment was initiated with high flows of 40–60 L/min and adjustment of FiO_2 to maintain SpO_2 >93%. If the patient’s respiratory distress and oxygenation progressively deteriorated during HFNC, intubation for IMV was performed based on the decision of the attending physicians. IMV was initiated with lung-protective mechanical ventilation. Patients were ventilated as much as possible with a tidal volume of 4–8 mL/kg predicted bodyweight, with a plateau pressure of <30 cm H_2O [16]. Depending on the patient’s respiratory condition, continuous neuromuscular blocking agents were used and prone position therapy was performed.

Data collection

Data were extracted retrospectively from the electronic medical records. Extracted data included demographic characteristics, comorbidities, respiratory parameters, severity score such as the Sequential Organ Failure Assessment (SOFA), and treatments received at or after enrollment. To calculate the PaO_2/FiO_2 ratio, we estimated the FiO_2 as follows: FiO_2 (%) = 21 + 4 * flow (L/min) [17].

Study outcomes

The primary outcome was in-hospital mortality. Secondary outcomes were ventilator-free days within 28 days, defined as the days alive without mechanical ventilation from day 1 to day 28; ICU-free days within 28 days, defined as the days alive outside the intensive care unit (ICU) from day 1 to day 28; and respiratory failure days, defined as the length from day 1 to achievement of successful weaning from both HFNC and IMV. Patients discharged or transferred from the hospital without a ventilator before 28 days were considered alive and free from mechanical ventilation and the ICU at 28 days. Patients transferred from the hospital with a ventilator before 28 days were considered alive and free from the ICU and to have no ventilator-free days after transfer. Non-survivors at day 28 were considered to have no

ventilator-free days and no ICU-free days. Patients with HFNC were admitted to the general ward and free from the ICU.

Statistical analysis

We summarize the patient's baseline characteristics and results using numbers and percentages for categorical variables and medians and interquartile ranges for continuous variables. The Mann-Whitney U test was used to analyze continuous variables, and Fisher's exact test was used for categorical variables. Kaplan-Meier curves were constructed to evaluate mortality and respiratory failure days. A log rank test was conducted for mortality, and the Gehan-Breslow-Wilcoxon test was conducted for the respiratory failure days to compare the Kaplan-Meier curves between two groups.

To evaluate the association between in-hospital mortality and the variables, we performed univariate and multivariate logistic regression analysis with in-hospital mortality as the dependent variable. The impact of the initial use of HFNC on in-hospital mortality was estimated using an inverse probability of treatment weighting (IPTW) logistic regression analysis with propensity scoring to adjust the baseline imbalances between the HFNC and IMV patients. The propensity score for the initial use of HFNC was determined using a logistic regression with the following covariates as independent variables: patient age, sex, body mass index (BMI), pre-existing comorbidities (chronic respiratory failure, chronic heart failure, diabetes mellitus, and chronic kidney diseases), respiratory rate, Glasgow Coma Scale score, and oxygen flow just before the induction of HFNC or IMV. To enhance the robustness of the result, multivariable logistic regression analysis including the propensity score as a covariable was also conducted. Selected variables were those considered clinically relevant. We measured the odds ratio (OR) and 95% confidence interval (CI) for selected variables. $P<0.05$ was considered to indicate statistical significance. Data were analyzed by R statistical software, version 4.0.3.

Results

Study population

The study flow diagram is shown in Figure 1. From 1 March 2020 to 30 April 2021, 522 patients were admitted to our hospital with the diagnosis of COVID-19. Among them, 303 patients were intolerant of conventional oxygen therapy and fulfilled our inclusion criteria. After excluding 121 patients who met the exclusion criteria, we analyzed 81 patients who initially received HFNC (HFNC group) and 101 patients who initially received IMV (IMV group).

Baseline characteristics, comorbidities, respiratory parameters, duration from symptoms to enrollment, SOFA score, and therapeutic interventions in the two groups are shown in Table 1. Age, sex, BMI, and comorbidities were similar between the two groups. The duration from symptoms to enrollment was significantly longer in the HFNC group than that in the IMV group (median, 9 days [interquartile range (IQR), 7–11 days] vs. median, 7 days [IQR, 5–10 days], p=0.010). SOFA score (median, 4 [IQR, 3–4] vs. median, 4 [IQR, 4–6], p=0.001), PaO_2/FiO_2 ratio (median, 131 [IQR, 115–148] vs. median, 99 [IQR, 82–

148], p<0.001), oxygen flow rate (median, 9 L/min [IQR, 8–10 L/min] vs. median, 10 L/min [IQR, 10–15 L/min], p<0.001), and respiratory rate (median, 25 rpm [IQR, 22–29 rpm] vs. median, 27 rpm [IQR, 23–32 rpm], p=0.014) were significantly lower in in the HFNC group than those in the IMV group. Regarding therapeutic interventions, there was no significant difference between the two groups in treatments such as the use of corticosteroids, favipiravir, veno-venous extracorporeal membrane oxygenation, and tracheostomy. The frequency of the use of remdesivir was significantly higher in the HFNC group versus the IMV group (40% vs. 7%, p<0.001). The intubation rate was 53% in the HFNC group.

Table 1
Clinical characteristics and therapeutic interventions in the HFNC and IMV groups

	HFNC (n=81)	IMV (n=101)	p Value
Age, years	72 [63, 78]	69 [62, 77]	0.368
Male	58 (72)	69 (68)	0.746
Body mass index, kg/m^2	25 [22, 28]	25 [23, 29]	0.907
Comorbid diseases			
Hypertension	46 (57)	53 (53)	0.653
Diabetes mellitus	33 (41)	38 (38)	0.760
Chronic kidney disease	8 (9.9)	15 (15)	0.374
End-stage renal disease	2 (2.5)	6 (5.9)	0.302
Chronic heart disease	9 (11)	11 (11)	1.000
Chronic respiratory disease	16 (20)	14 (14)	0.319
COPD	13 (16)	9 (8.9)	0.172
Liver disease	2 (2.5)	0 (0.0)	0.197
Malignancy	3 (3.7)	8 (7.9)	0.350
Duration from symptoms, days	9 [7, 11]	7 [5, 10]	0.010
SOFA score	4 [3, 4]	4 [4, 6]	0.001
Glasgow Coma Scale, score	15 [15, 15]	15 [15, 15]	0.001
PaO_2/FiO_2 ratio	131 [115, 148]	99 [82, 148]	<0.001
Oxygen flow rate, L/min	9 [8, 10]	10 [10, 15]	<0.001
Respiratory rate, rpm	25 [22, 29]	27 [23, 32]	0.014
Therapeutic interventions			
Corticosteroids	81 (100)	99 (98)	0.503
Remdesivir	32 (40)	7 (6.9)	<0.001
Favipiravir	35 (43)	52 (52)	0.298
Intubation	43 (53)	101 (100)	<0.001
Tracheostomy	26 (32)	49 (49)	0.034

	HFNC (n=81)	IMV (n=101)	p Value
VV-ECMO	6 (7.4)	11 (11)	0.456

HFNC high-flow nasal cannula, *IMV* invasive mechanical ventilation, *COPD* chronic obstructive pulmonary disease, *SOFA* Sequential Organ Failure Assessment, *VV-ECMO* veno-venous extracorporeal membrane oxygenation

Continuous variables are expressed as median [interquartile range] and categorical variables as absolute value (%)

Effect on primary and secondary outcomes

In-hospital mortality tended to be lower in the HFNC group compared to that in the IMV group, but the difference was not statistically significant (19% in the HFNC group vs. 25% in the IMV group, p=0.37, Table 2). The Kaplan-Meier survival curves were not significantly different between the groups (p=0.374, log rank test, Figure 2). Similarly, the univariate analysis showed that initial use of HFNC was associated with relatively lower mortality, which was not statistically significant (OR, 0.69; CI, 0.34–1.42; p=0.31, Figure 3). After adjusting the baseline imbalances by IPTW, initial use of HFNC was not associated with either an increase or decrease in mortality compared to the initial use of IMV (OR, 1.01; CI, 0.37–2.77; p=0.984, Figure 3). This association was confirmed not to be materially affected by the other models: a multivariable logistic regression analysis adjusted by propensity score for a confounder showed no significant association between the initial use of HFNC and mortality (OR, 0.97; CI, 0.39–2.43; p=0.945, Figure 3).

Table 2
Primary and secondary outcomes

	HFNC (n=81)	IMV (n=101)	p Value
Primary outcome			
In-hospital mortality	15 (19)	25 (25)	0.370
Secondary outcomes			
Ventilator-free days within 28 days	22 [2, 28]	14 [0, 20]	<0.001
ICU-free days within 28 days	23 [0, 28]	15 [0, 20]	<0.001

HFNC high-flow nasal cannula, *IMV* invasive mechanical ventilation, *ICU* intensive care unit, Continuous variables are expressed as median [interquartile range] and categorical variables as absolute value (%)

Ventilator-free days within 28 days were significantly longer in the HFNC group than those in the IMV group (median, 22 days [IQR, 2–28 days] vs. median, 14 days [IQR, 0–20 days], p<0.001, Table 2). ICU-free days within 28 days were significantly longer in the HFNC group than those in the IMV group (median, 23 days [IQR, 0–28 days] vs. median, 15 days [IQR, 0–20 days], p<0.001, Table 2). Respiratory failure days were relatively shorter in the HFNC group, but the difference was not statistically significant (p=0.071, Gehan-Breslow-Wilcoxon test, Figure 2).

Subgroup analysis of the patients intubated and receiving IMV in both groups

Among the 81 patients in the HFNC group, 43 patients (53%) were secondarily intubated after the initiation of HFNC and categorized into the HFNC to IMV group. Baseline characteristics, therapeutic interventions, and outcomes in the subgroups are shown in **Table S1**. Sex, age, and BMI were not significantly different between the groups. The prevalence of chronic obstructive pulmonary disease (COPD) was significantly different between the groups; the HFNC to IMV group had a higher ratio of COPD compared to those in the other two groups.

The Kaplan-Meier survival curves are shown in **Figure S1**. The in-hospital mortality in the HFNC to IMV group was 30% (13 of 43 patients) and higher than that in the other two groups. Both the ventilator-free days and ICU-free days were significantly different between groups and were remarkably shorter in the HFNC to IMV group. The Kaplan-Meier curves for the lengths of respiratory failure days also showed them to be remarkably longer in the HFNC to IMV group (**Figure S1**).

Discussion

The present study showed no significant difference in mortality between HFNC and IMV as initial management for acute respiratory failure induced by COVID-19. However, HFNC was associated with statistically significantly longer ventilator-free days and ICU-free days, possibly due to the avoidance of intubation. In contrast, patients secondarily intubated after the initiation of HFNC had relatively poor outcomes even compared to those in the IMV group.

Usefulness of HFNC

A previous prospective cohort study on COVID-19 that used propensity score matching reported that compared to early initiation of IMV, the initial use of HFNC led to an increase in ventilator-free days and a reduction in the ICU length of stay without an increase in mortality [18], which were consistent with the results of the present study. Compared with the previous study, patients in the present study were about 10 years older, which suggested the efficacy of HFNC for elderly patients as well. The present study also showed the utility of HFNC in regard to the avoidance of intubation, which was avoided in 37 of 81 patients (46%) in the HFNC group even though they had been intolerant of conventional oxygen therapy. This result agreed with that of a number of previous studies, which reported that HFNC could prevent the need for intubation in approximately 48–60% patients [19–22].

Regarding the pathophysiological mechanisms in ICU patients, there are several benefits in initiating HFNC ahead of IMV. For instance, IMV may result in various complications due to sedatives and long mechanical ventilation management, such as ventilator-induced lung injury [23], ventilator-associated pneumonia [24], ICU-acquired weakness [25], delirium [26], and disuse syndrome. Initiating HFNC first may allow these complications to be avoided and may shorten the treatment period by avoiding possibly unnecessary IMV.

In addition, initiating HFNC first can preserve ventilators, which might be in short supply owing to the explosive spread of COVID-19, and reduce the burden on medical staff who care for patients. Currently, several SARS-CoV-2 variants have been reported to become common, cause more severe infections, and spread faster than the earlier forms of SARS-CoV-2 [27–29], possibly leading to a rapid increase in the demand for ventilators in the near future. Therefore, the appropriate use of HFNC may not only reduce the lack of medical resources but also save the lives of many patients who are difficult to treat due to the lack of ventilator.

Concerns about HFNC

Although several scientific societies recommend the use of HFNC as non-invasive respiratory therapy for COVID-19 [30–33], some groups have warned against non-invasive respiratory support therapy and claimed that early intubation prevents the progression of lung injury and dispersion of aerosols [34, 35].

Regarding the dispersion of aerosols, a high-fidelity human model study showed that even at the highest flow setting of 60 L/min with HFNC, exhaled air dispersion was 17 cm in a healthy lung scenario and only 4.8 cm in a severely diseased lung scenario [36]. A computational fluid dynamic simulation study also found that a properly fitted mask might reduce the velocity of exhaled gas flow and capture particles during HFNC [37]. Therefore, we considered that the dispersion of aerosols might be relatively low during HFNC and could be reduced. Nevertheless, the risk of infection from aerosols is unknown in practice, and thus, personal protective equipment, high-filtration fit-tested respirators (N95, FFP2, etc.), and environmental precautions are required for healthcare workers.

Regarding progression of lung injury, HFNC may possibly result in missing the optimal time to introduce IMV and may even worsen the prognosis due to the high trans-pulmonary pressures associated with excessive spontaneous inspiratory effort, so-called patient self-inflicted lung injury [38]. Actually, subgroup analysis in the present study showed higher mortality in patients secondarily intubated after the initiation of HFNC, even compared to the IMV group, although it was possible that the more critically ill patients who could not have avoided intubation were intubated. Therefore, although using HFNC first did not worsen the overall prognosis in the present study, it was thought to be necessary to intubate at the appropriate time. The ROX index (SpO_2/FiO_2/respiratory rate) and SOFA score were reported to be helpful predictors of intubation after HFNC [20, 22, 39]. Accordingly, we considered that by carefully monitoring the patient's respiratory effort and parameters, including these predictors, and then transitioning to intubation without delay, HFNC could be more useful as an initial respiratory management for severe COVID-19-induced respiratory failure.

Limitations

Our study has several limitations. First, it was a retrospective observational study. Although we performed analyses using propensity scoring to eliminate the effects of the baseline imbalances as much as possible, the effects of unadjusted and unmeasured confounding factors could not be completely excluded. Second, some patients were transferred to other hospitals after acute treatment, and their long-term prognosis is unknown. Third, although the rate of intubation avoidance was generally consistent with the studies mentioned above [20–23], the present study results may not be generalizable to other situations because the criteria for HFNC and intubation have not been uniformly defined.

Conclusions

Our study showed that HFNC significantly increased ventilator-free days and ICU-free days, possibly due to the avoidance of intubation without increasing in-hospital mortality for severe COVID-19-induced respiratory failure. Although an appropriate transition to intubation with careful respiratory monitoring is required, HFNC may be useful as initial respiratory management in patients with severe COVID-19-induced respiratory failure.

Abbreviations

BMI: Body mass index; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; GCS: Glasgow Coma Scale; HFNC: High-flow nasal cannula; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; IPTW: Inverse probability of treatment weighting; IQR: Interquartile range; OR: Odds ratio; ROX index: SpO_2/FiO_2/respiratory rate; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SOFA: Sequential Organ Failure Assessment; VV-ECMO: Veno-venous extracorporeal membrane oxygenation

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board for Clinical Research of Osaka General Medical center (IRB No. S202004004). The board waived the requirement for informed consent because of the anonymous nature of the data and because no information on individual patients, hospitals, or treating physicians was obtained.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

T. Nakai conceived and designed this study; contributed to acquisition, shaping data, analyses, and interpretation of the results; and was responsible for drafting, editing, and submission of the manuscript. Y. Umemura contributed to the study design; acquisition, analysis, and interpretation of the data; and drafting of the manuscript. Y. Mitsuyama supported analysis and interpretation of the results. T. Nishida, A. Watanabe and S. Fujimi contributed to interpretation of the data and critical appraisal of the manuscript. All of the authors reviewed, discussed, and approved the final manuscript.

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Figures

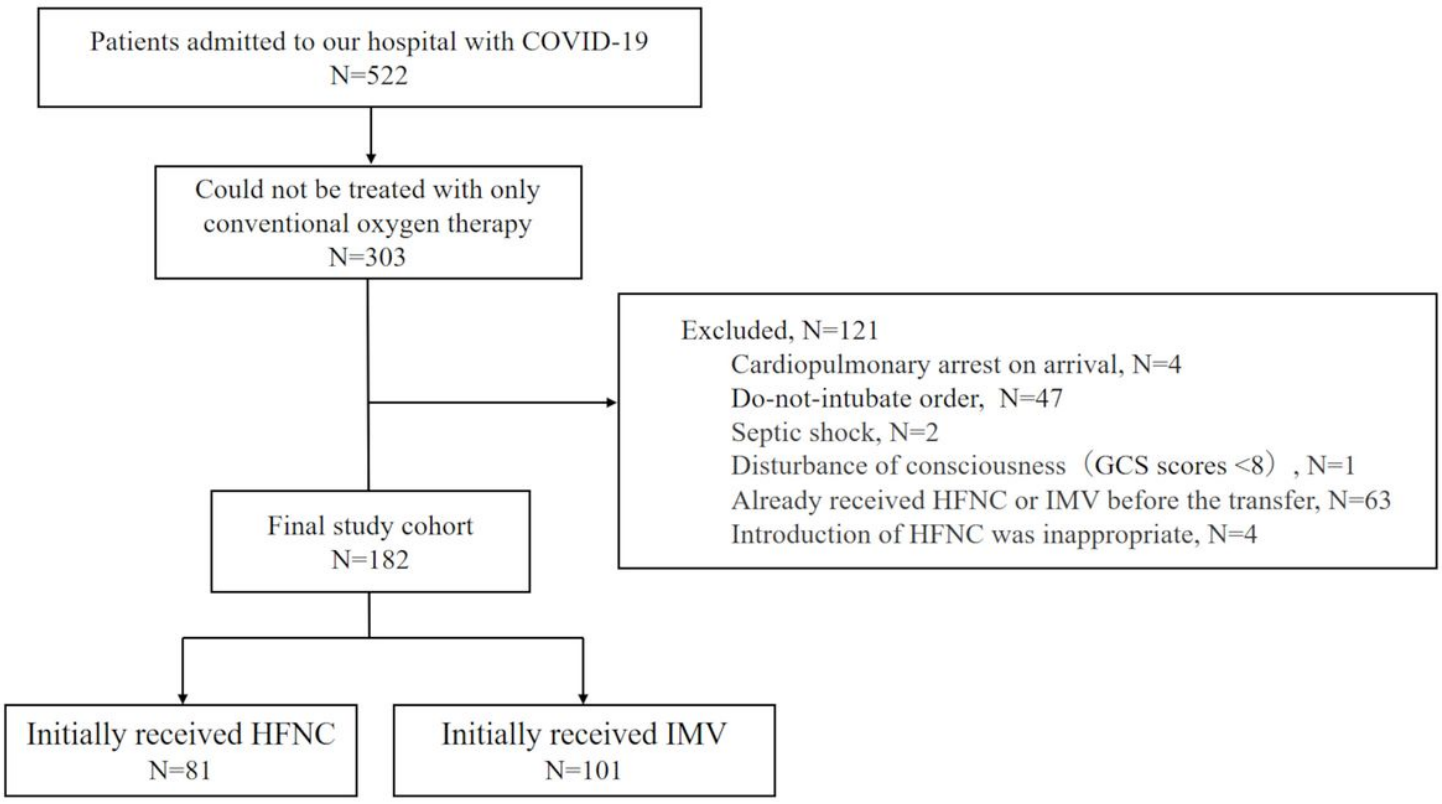

Figure 1

Flowchart of the study. *GCS* Glasgow Coma Scale, *HFNC* high-flow nasal cannula, IMV invasive mechanical ventilation

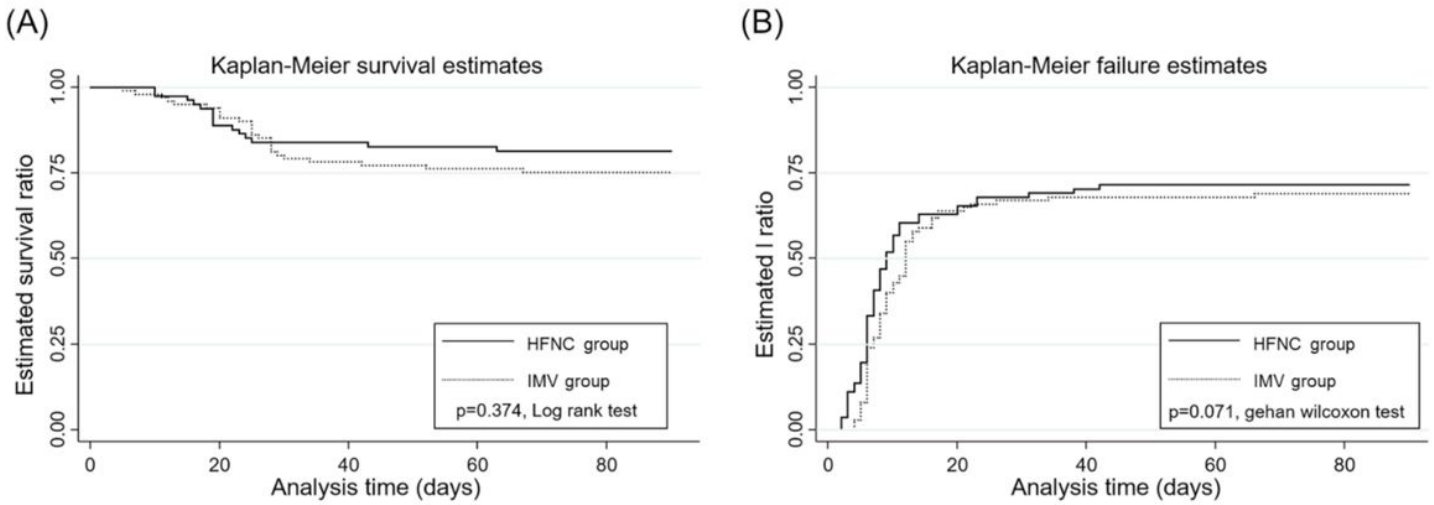

Figure 2

Kaplan-Meier curves of the probability of (A) survival and (B) status of respiratory failure. *HFNC* high-flow nasal cannula, *IMV* invasive mechanical ventilation

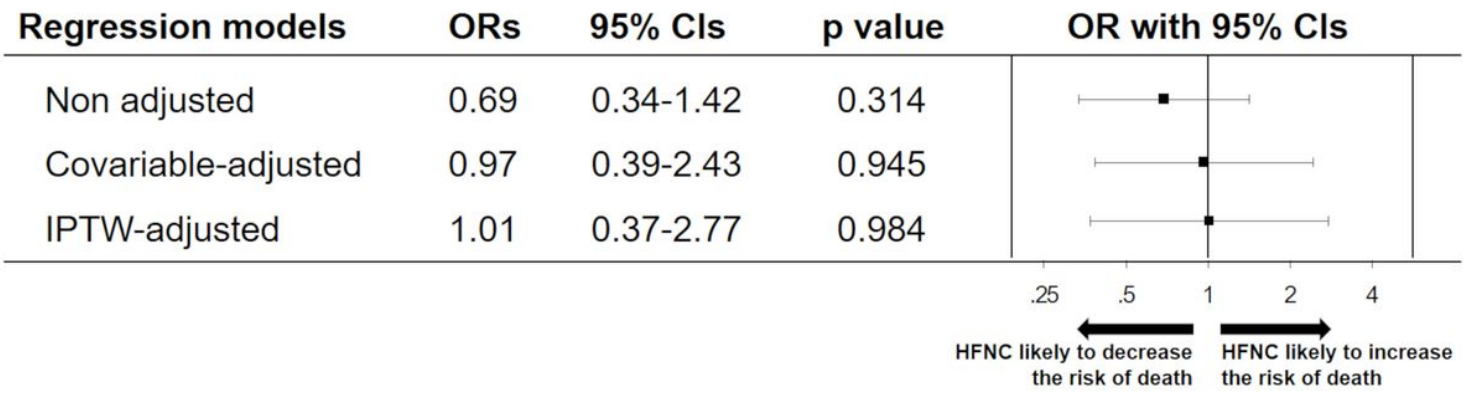

Figure 3

Forest plots of the association between HFNC use and in-hospital mortality. *CI* confidence interval, *HFNC* high-flow nasal cannula, *IPTW* inverse probability of treatment weighting, *OR* odds ratio

Supplementary Files

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