High-flow nasal cannula therapy for hypoxemic respiratory failure in patients with COVID-19

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Abstract

Purpose

High-flow nasal cannula (HFNC) therapy in patients with hypoxemic respiratory failure due to COVID-19 is poorly understood and remains controversial.

Methods

We designed a prospective observational study of a large cohort of patients with COVID-19-related hypoxaemic respiratory failure at the Temporary COVID-19 Hospital in Mexico City. The primary outcome was the success rate of HFNC to prevent the progression to invasive mechanical ventilation (IMV). We also evaluated the risk factors associated with HFNC success or failure.

Results

This study included 378 patients who were admitted to the Temporary COVID-19 Hospital with a confirmed diagnosis of COVID-19 and hypoxemic respiratory failure. HFNC therapy effectively prevented IMV in 71.4% of patients ($n = 270$; 95% confidence interval [CI] 66.6–75.8%). Factors that were significantly different between patients who were only treated with HFNC therapy and those who progressed to IMV included age, the presence of hypertension, and the Charlson comorbidity index. Predictors of therapy failure included the CALL score at admission (adjusted hazard ratio [HR] 1.27; 95% CI 1.09–1.47; $p < 0.01$), Rox index at 1 hour (adjusted HR 0.82; 95% CI 0.7–0.96; $p = 0.02$), and no prior treatment with steroids (adjusted HR 0.34; 95% CI 0.19–0.62; $p < 0.0001$). Overall, therapy was significantly associated with a lower intensive care unit admission rate (7.0% vs 96.3%) and length of hospital stay (15.0 vs 26.5 days).

Conclusions

Treating patients with HFNC therapy at admission was effective and prevented the worsening of symptoms in some patients with COVID-19.

Introduction

A novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China in December 2019. Within 3 months of its emergence, SARS-CoV-2 was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 [1], with over 89.7 million confirmed cases and more than 1.9 million deaths reported globally by 12 January 2021 [2]. According to a report by the Chinese Centre for Disease Control and Prevention, 81% of cases present with mild respiratory illness, 14% present with severe respiratory illness requiring hospital care,

and 5% develop critical illness requiring treatment in an intensive care unit [3]. Clinical data suggest that viral pneumonia-induced acute respiratory distress syndrome is the most common clinical manifestation [4] among hospitalized patients, of which 14.8% develop an acute respiratory distress syndrome [5]. Although milder cases may be managed with non-invasive respiratory support, more severe cases require mechanical ventilation [6]. Furthermore, it has been speculated that hypoxia may play a role in virus replication, with oxygen therapy shown to disrupt some of the hypoxia-related molecular mechanisms (i.e., hypoxia-inducible factor 1α) that are implicated in the replication and metabolism of several different viruses [7].

Although several treatment guidelines have been published, there is still no consensus on high-flow nasal cannula (HFNC) therapy before endotracheal intubation in patients with severe SARS-CoV-2 pneumonia [8–11]. HFNC has emerged as an alternative non-invasive respiratory support option that can reduce the mortality rate as well as prevent or delay the need for intubation [12]. It has previously been reported that HFNC therapy reduces all-cause mortality at 90 days in patients with community-acquired pneumonia compared with standard oxygen therapy and non-invasive ventilation [13]. However, at present, there is limited evidence on the efficacy of HFNC in patients with severe SARS-CoV-2 pneumonia [14]. Furthermore, the risk of dispersion of SARS-CoV-2 through bio-aerosols and the risk of delayed intubation using HFNC is unknown. Based on the known usefulness of HFNC in patients with acute respiratory failure [15], it is crucial to determine the efficacy of this non-invasive respiratory support method to avoid the need for invasive mechanical ventilation (IMV) in patients with SARS-CoV-2.

The present study, which was performed at the Temporary COVID-19 Hospital located in the Citibanamex Exhibition Center in Mexico City, aimed to evaluate the efficacy of HFNC in patients with hypoxemic respiratory failure due to severe SARS-CoV-2 pneumonia to reduce the risk of requiring IMV. We also aimed to identify the risk factors of disease progression among patients with severe SARS-CoV-2 pneumonia and treated with HFNC.

Methods

Study design

This prospective observational study was conducted between 31 August 2020 and 2 October 2020 in accordance with the Declaration of Helsinki. The study protocol was approved by an independent Ethical Review Board at the National Autonomous University of Mexico (FM/DI/099/2020). All patients provided written informed consent prior to participation.

Patients

Patients aged ≥ 18 years who were admitted to the Temporary COVID-19 Hospital with a confirmed diagnosis of COVID-19 (as verified by a positive PCR test) and hypoxemic respiratory failure ($PaO_2 \leq 60$ mmHg) due to severe SARS-CoV-2 pneumonia were included. For HFNC use, a respiratory rate of > 24–30

breaths per minute, a PAFI ratio (PaO_2/FiO_2) of 100–200, and requiring a FiO_2 > 50% to achieve an oxygen saturation (SpO_2) of ≥ 92% was necessary.

Procedures

After admission, patients were initially evaluated for treatment with HFNC (**Online Resource 1**). In addition, patients were also retrospectively assessed for HFNC according to the Rox index (**Online Resource 2)**. The Rox index is a measure of hypoxemia severity that predicts the need for IMV [16, 17]. In this study, cut-off values of < 2.85, < 3.47, < 3.85, and < 4.88 after 2 hours, 6 hours, 12 hours, and 16 hours were considered failure of HFNC. A Rox index of ≥ 4.88 after 16 hours was considered HFNC success.

HFNC (Precision Flow Plus, Vapotherm, New Hampshire, USA) was started with an oxygen flow rate of 40 L/min and FiO_2 of 100%, humidified and heated to 34–37°C. Patients were instructed to maintain their mouth closed to avoid loss of gas flow. To mitigate aerosol dispersion and reduce the risk of viral transmission among patients and health-care workers, the use of N95 masks, ocular protection, surgical gown, and disposable gloves were mandatory.

Variables

We evaluated demographic and clinical characteristics, duration of symptoms prior to admission, duration of HFNC or IMV, length of hospital stay, Rox index measurements, respiratory and blood gas parameters at the start of HFNC and 16 hours after HFNC. The success of HFNC was defined as the non-progression from HFNC to IMV, with a CALL score cutoff of > 6 points used to stratify the risk of progression in patients with COVID-19 [18].

Statistical methods

A convenience sampling approach was used to select patients for inclusion in the study. Descriptive statistics were used for baseline demographic and clinical characteristics, with *n* (%) for categorical variables and median (interquartile range) for continuous variables. Wilcoxon rank-sum test was used to compare continuous data between patients who did or did not require IMV. Chi-square or Fisher's exact test was used to compare categorical data between the groups. Statistical significance was set at *p*-value < 0.05.

Survival analysis (Cox regression) was fitted to calculate adjusted hazard ratios and 95% confidence intervals (CIs) for IMV among patients treated with HFNC. Only patients with complete clinical data were included in the survival analysis. Data were analyzed from the start of HFNC until failure (the need of IMV) or censure (discharge date). STATA v.15 (Stata Corp., College Station, TX, USA) and R 1.3.1073 were used for statistical analyses.

Results

Patients

The characteristics of patients included in this study are summarized in Table 1. A total of 378 patients were included in this study and data were collected between 16 May 2020 and 9 November 2020. The median (interquartile range) age was 54.5 (46–64) years, and 66.7% were male. The proportions of patients with type 2 diabetes, hypertension, and obesity were 35.5%, 36.8%, and 47.6%, respectively.

Table 1
Patient characteristics

	Total *N* = 378	**HFNC only** *n* = 270	**HFNC + IMV** *n* = 108	***p*-value**
Age, years	54.5 (46–64)	53 (45–61)	60 (51–70)	< 0.0001
Sex				0.63
Female	126 (33.3)	92 (34.1)	34 (31.5)	-
Male	252 (66.7)	178 (65.9)	74 (68.5)	-
Diabetes	134 (35.5)	92 (34.1)	42 (38.9)	0.38
Uncontrolled[a]	71 (53.0)	44 (47.8)	27 (64.3)	0.08
Glucose, *n* = 348	128 (106–172)	124 (105.5–166.5)	135 (107.5–187)	0.26
Hypertension	139 (36.8)	90 (33.3)	49 (45.4)	0.03
Uncontrolled[b]	30 (7.9)	17 (6.3)	13 (12)	0.30
BMI (kg/m^2)				0.80
Normal (18.5–24.9)	43 (11.4)	31 (11.5)	12 (11.1)	-
Overweight (25.0–29.9)	140 (37.0)	101 (37.4)	39 (36.1)	-
Obesity (≥ 30)	180 (47.6)	124 (45.9)	56 (51.9)	-
Unknown	15 (4.0)	14 (5.2)	1 (0.9)	-
Charlson comorbidity index				< 0.0001
No comorbidities	162 (42.9)	130 (48.2)	32 (29.6)	-
Low-risk category (1–2)	178 (47.1)	121 (44.8)	57 (52.8)	-
High-risk category (≥ 3)	38 (10.1)	19 (7.0)	19 (17.6)	-

Data are presented as *n* (%) or median (interquartile range)

BMI, body mass index; HFNC, high-flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation

[a] Uncontrolled diabetes defined as glucose > 180 mg/dL

[b] Uncontrolled hypertension defined as a blood pressure of > 140/100 mmHg

	Total *N* = 378	HFNC only *n* = 270	HFNC + IMV *n* = 108	*p*-value
Duration of symptoms prior to admission, days	8 (5–11)	9 (6–12)	6 (4–8.5)	< 0.0001
≤ 5 days	109 (28.8)	59 (21.8)	50 (46.3)	< 0.0001
> 5 days	268 (70.9)	210 (77.8)	58 (53.7)	< 0.0001
Unknown	1 (0.3)	1 (0.4)	0 (0.0)	< 0.0001
Time from admission to HFNC, days	1.99 (2.4)	1.8 (2.3)	2.5 (2.6)	0.02
Duration of HFNC, (days)	11 (4–16)	13 (10–18)	2 (1–3)	< 0.0001
Steroid treatment at hospitalization	270 (71.4)	211 (78.2)	59 (54.6)	< 0.0001
ICU admission	123 (32.5)	19 (7.0)	104 (96.3)	< 0.0001
ICU duration, days	10 (5–19)	3 (2–3)	13 (7–20)	< 0.0001
Hospital duration, days	18 (12–25)	15 (11–20)	26.5 (20–36)	< 0.0001
Laboratory results at admission and when HFNC was started				
Creatinine (mg/dL), n **= 353**				
At admission	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.9 (0.8–1.2)	0.002
At HFNC start	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.6–1.2)	0.85
FiO_2 (mmHg), n **= 348**				
At admission	35 (24–56)	35 (24–53)	32 (24–60)	0.82
At HFNC start	45 (32–75)	40 (30–60)	63 (34–94)	< 0.0001

Data are presented as *n* (%) or median (interquartile range)

BMI, body mass index; HFNC, high-flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation

[a] Uncontrolled diabetes defined as glucose > 180 mg/dL

[b] Uncontrolled hypertension defined as a blood pressure of > 140/100 mmHg

	Total *N* = 378	HFNC only *n* = 270	HFNC + IMV *n* = 108	*p*-value
Lymphocyte (%), n = **362**				
At admission	11.7 (6.9–18.6)	12.4 (7.7–18.6)	10.6 (6.3–17.4)	0.06
At HFNC start	11.5 (7.4–19.1)	12.5 (8.0–20.7)	8.8 (5.5–16.1)	< 0.0001
D-dimer (ng/mL), n = **357**				
At admission	550 (380–890)	555 (390–940)	550 (360–790)	0.32
At HFNC start	580 (370–970)	540 (350–860)	735 (490–1145)	< 0.0001
Ferritin (µg/L), n = **279**				
At admission	466.6 (227.3–836.8)	466.6 (229.2–770.6)	467.8 (219.8–961.7)	0.69
At HFNC start	457.4 (249.9–780.7)	438.4 (230.5–714.1)	556.4 (305.2–971.7)	0.03
Data are presented as *n* (%) or median (interquartile range)				
BMI, body mass index; HFNC, high-flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation				
[a] Uncontrolled diabetes defined as glucose > 180 mg/dL				
[b] Uncontrolled hypertension defined as a blood pressure of > 140/100 mmHg				

Outcomes

A flow chart of the outcomes of 378 patients with hypoxemic respiratory failure who were treated with HFNC is shown in Fig. 1. The HFNC success rate, defined as patients who did not require IMV, was 71.4% (*n* = 270; 95% CI 66.6–75.8) compared with 28.6% (*n* = 108; 95% CI 24.2–33.4) of patients who required IMV. Of the 270 patients who were successfully treated with HFNC, 262 patients (97.0%) were discharged, seven patients (2.6%) were referred, and one patient (0.4%) died. Among those 108 patients who required IMV, 61.1% (*n* = 66; 95% CI 51.5–69.9) were successfully extubated. Of those 66 patients who required IMV and were successfully extubated, 64 patients (97.0%) were discharged and one patient (1.5%) died. Furthermore, the proportion of patients with HFNC success increased over time from when HFNC treatment was started (Fig. 2). The median (interquartile range) number of days of HFNC administration was 13 (10–18) days in patients who had success compared with 2 (1–3) days in patients who then also required IMV.

When comparing patients who required IMV and those who did not require IMV, age and the presence of hypertension were significantly different ($p < 0.0001$ and $p = 0.03$, respectively). The Charlson comorbidity index categories also differed significantly between these two groups ($p < 0.0001$) (Table 1). Patients who received HNFC only were treated for a significantly longer period of time versus those who eventually required IMV (13 vs 2 days, respectively; $p < 0.0001$). The intensive care unit admission rate (7.0% vs 96.3%) and length of hospital stay (15 vs 26.5 days) were also significantly different between patients who did not require IMV and those who required IMV.

Laboratory results at admission and when HFNC was commenced are summarized in Table 1 **and Online Resource 3** in the online data supplement. Patients who required IMV had less favorable laboratory parameters versus those who did not require IMV. Of note, there were significant differences at admission and when commencing HFNC in absolute lymphocyte counts ($p < 0.01$ and $p < 0.0001$, respectively). Although markers of inflammation (median D-dimer and ferritin levels) were not significantly different between patients who only required HFNC and those who also required IMV at admission ($p = 0.32$ and $p = 0.69$, respectively), they were significantly different when commencing HFNC ($p < 0.01$ and $p = 0.03$, respectively).

Rox index values were significantly higher at each time point in patients who did not require IMV versus those who required IMV (Fig. 3). In patients with HFNC success, Rox index values increased from 5.98 at baseline to 6.41, 6.83, 7.02, 7.37, 7.87, and 8.20 after 1, 2, 4, 6, 12, and 16 hours, respectively. In contrast, in patients with HFNC failure, Rox index values remained low from 5.40 at baseline to 5.70, 5.88, 5.76, 5.93, 5.74, and 5.62 after 1, 2, 4, 6, 12, and 16 hours, respectively. When comparing Rox index values between 2 hours and 16 hours, the difference was significant in the HFNC only group, but not in the HFNC and IMV group ($p < 0.0001$ and $p = 0.91$, respectively).

The changes in arterial blood gas parameters from 2 hours after HFNC to 16 hours after HFNC are summarized in **Online Resource 4**. In patients with HFNC success, the median (interquartile range) SPFI ratio increased from 135.7 (115.3, 160.0) after 2 hours to 158.4 (127.2, 192.2) after 16 hours of HFNC. In patients with HFNC failure, the median (interquartile range) SPFI ratio decreased from 115.0 (98.0, 140.0) after 2 hours to 110.4 (96.5, 134.9) after 16 hours of HFNC. When comparing SPFI ratios between 2 hours and 16 hours, the difference was only significant in the HFNC only group and not in the HFNC and IMV group ($p < 0.0001$ and $p = 0.34$, respectively).

Finally, we show that the CALL score at admission (adjusted hazard ratio 1.27; 95% CI 1.09–1.47; $p < 0.01$), Rox index at 1 hour (adjusted hazard ratio 0.82; 95% CI 0.70–0.96; $p = 0.02$), and absence of treatment with steroids (adjusted hazard ratio 0.34; 95% CI 0.19–0.62; $p < 0.0001$) were all significant predictors of HFNC failure (Table 2).

Table 2
Predictors of HFNC failure ($n = 238$)

Variable	Adjusted HR (95% CI)	*p*-value
Age (per year increase)	1.003 (0.99–1.01)	0.53
Male vs female	0.73 (0.41–1.32)	0.28
CALL score (per 1-point increase)	1.27 (1.09–1.47)	< 0.01
No diabetes (vs uncontrolled)	0.81 (0.43–1.51)	0.50
Diabetes (vs uncontrolled)	0.46 (0.16–1.29)	0.14
Hypertension (vs no hypertension)	1.08 (0.47–2.50)	0.85
Overweight (vs normal weight)	1.05 (0.38–2.93)	0.92
Obesity (vs normal weight)	1.49 (0.55–4.01)	0.43
Rox index 1 hour (per 1-point increase)	0.82 (0.70–0.96)	0.02
Treatment with steroids (vs no treatment)	0.34 (0.19–0.62)	< 0.0001
Absolute lymphocytes (per unit increase)	0.99 (0.99–1.00)	0.24
D-dimer 550–1000 (vs normal levels)	1.23 (0.66–2.27)	0.51
D-dimer > 1000–1500 (vs normal levels)	1.52 (0.61–3.76)	0.37
D-dimer > 1500 (vs normal levels)	0.31 (0.09–1.09)	0.07
PAFI (per unit increase)	0.99 (0.99–1.00)	0.94
Lactate–mmol/L (per unit increase)	1.25 (0.80–1.97)	0.33
$PaCO_2$ (per unit increase)	1.04 (0.98–1.11)	0.18

CALL, comorbidity–age–lymphocyte–and LDH; CI, confidence interval; HFNC, high-flow nasal cannula; HR, hazard ratio; PAFI, ratio of PaO_2 over FiO_2

Supplementary material

Online Resource 1. Clinical protocol for the management of hypoxemic respiratory failure in the Temporary COVID-19 Hospital

Abbreviations: FiO_2, fractional inspired oxygen; HFNC, high-flow nasal cannula; ICU, intensive care unit; RR–respiratory rate; RX, radiography; NEWS, National Early Warning Score; PAFI, ratio of PaO_2 over FIO2; SpO_2, oxygen saturation

Online Resource 2. Algorithms for HFNC follow up and admission to the intensive care unit

Abbreviations: HFNC, high-flow nasal cannula; ICU, intensive care unit; SpO_2, oxygen saturation; FiO2, fractional inspired oxygen; PAFI, ratio of PaO_2 over FIO_2

Variable	Adjusted HR (95% CI)	*p*-value
Online Resource 3. Disease severity risk markers at admission and at start of HFNC		

Discussion

The present study is one of the largest observational prospective studies to evaluate the efficacy of HFNC use in patients with severe SARS-CoV-2 pneumonia. Our results showed that the HFNC success rate of 71.4% significantly prevented escalation to IMV in patients with hypoxemic respiratory failure due to COVID-19. CALL score at admission predicted a linear increase in the risk of IMV with an HR of 1.27 for every point increase. Rox index at 1 hour after starting HFNC predicted an 18% decrease in the risk of IMV for every point increase whereas steroid treatment predicted a 66% decrease in the risk of IMV compared with the absence of steroid treatment. Overall, the present findings are consistent with those reported in previous studies [14, 19–21]. However, direct comparisons cannot be made because of differences in the study design and definitions of HFNC success between the studies.

In a multicenter prospective observational study of 293 consecutive patients with severe COVID-19-related hypoxemic respiratory failure in South Africa, the HFNC success rate (defined as the proportion of patients successfully weaned from HFNC) was 47% (137/293 patients), which is substantially lower than the 71.4% we report in the present study [19]. It was also reported that the median duration of HFNC was significantly higher in those with HFNC success vs those with HFNC failure ($p < 0.001$). In a study of 28 consecutive patients with hypoxemic acute respiratory failure due to SARS-CoV-2 infection in Italy, the HFNC success rate (defined as a reversal of hypoxemia or $SpO_2 \geq 92\%$), was 67.8% (19/28 patients) [14]. However, it was reported that only 17.8% of patients subsequently required IMV (vs 28.6% in the present study), although the small number of patients ($n = 28$) in that study is likely to be a confounding factor. In a larger multicenter, retrospective cohort study conducted in Wuhan, HFNC failure (defined as upgrading respiratory support to positive pressure ventilation or death) was reported in 46.5% of patients. Among these patients, 13 (30.2%) subsequently required IMV, with failure of HFNC associated with a higher mortality rate [21]. Finally, in a small study of eight patients with severe and critical COVID-19 in China, it was reported that after 2 hours of HFNC therapy, the Rox index was ≥ 4.88 in 100% of patients and this remained above this cut-off for 12 hours [20]. It was concluded that even in severe and critical patients who were experiencing hypoxemic respiratory failure, HFNC was successful.

When investigating factors associated with HFNC failure, the present study found that the CALL score at admission was a significant predictor of HFNC failure. Conversely, Rox index at 1 hour (per 1-point increase) and prior treatment with steroids were significant predictors of HFNC success. Our findings are consistent with those of a previous study, which reported that a Rox index of 6 after HFNC commencement and the use of steroids were associated with HFNC success [19]. The potential effect of corticoids in reducing the number of patients requiring IMV has been reported previously; however, a clear consensus on their evidence-based benefit has yet to be reached [22]. Similar to the present study, the severity of hypoxemia and lower oxygen saturation at admission were reported to be factors associated

with HFNC failure in previous studies [14, 21]. Other factors, including C reactive protein level [14] and male sex [21], have also been previously associated with HFNC failure.

There are many potential advantages of HFNC use including efficacy, less training needed for health-care personnel, lower cost compared with IMV, and better outcomes in patients who are initially treated with HFNC, even if IMV is required subsequently. Furthermore, in hospitals with saturated critical care capacities, the early use of HFNC is likely to have a positive impact. Conversely, some of the potential barriers of HFNC use in low resource settings are that some training of health-care personnel is needed, HFNC requires the cooperation of the patient for adequate use, and, as with IMV, there are limitations in the chain of supply. Despite concerns being raised regarding a perceived high risk of dispersion of bio-aerosols via HFNC, the evidence suggests that the risk of dispersing SARS-CoV-2 viral particles with HFNC using a surgical mask is the same as that of standard oxygen masks [23]. Furthermore, two previous trials comparing HFNC with different masks in other disease states have reported that there was no obvious increase in aerosol dispersion with HFNC use [24, 25].

The present study has some limitations, including those inherent to the observational, single-center study design and the retrospective analysis of patients according to the management/treatment algorithms, which may have introduced bias.

Conclusions

In conclusion, the present study showed that IMV was avoided in 71.4% of patients with SARS-CoV-2 pneumonia and hypoxemic respiratory failure when treated with HFNC, thus reinforcing the benefits of the timely use of HFNC. HFNC might prevent the worsening of some patients with severe SARS-CoV-2 pneumonia, reduce the need for IMV, and reduce the length of stay in the hospital and the intensive care unit. CALl score, Rox index at 1 hour after starting HFNC, and presence/absence of steroid treatment were identified as predictors of HFNC outcome. These results should be validated in prospectively registered randomized controlled trials.

Declarations

Ethics approval and consent to participate

The study protocol was approved by an independent Ethical Review Board at the National Autonomous University of Mexico (FM/DI/099/2020). All patients provided written informed consent prior to participation.

Consent for publication

Not applicable.

Availability of supporting data

Data will be made available upon reasonable request to the corresponding author.

Competing interests

APC, ESL, MGN, RRVV, HHB, LMJ, MAA, LERG, LMC, RVB, RVAW, BSO, and MLRC are full-time employees of the Temporary COVID-19 Hospital. HGR, JLG, LAMJ, and RTC are full-time employees of the Carlos Slim Foundation in Mexico. The authors declare no other conflicts of interest or outside funding from any other organizations.

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Authors' contributions

APC, ESL, MGN, RRVV, HHB, MAA, LERG, RVB, RVAW, BSO, MLRC, and LMC conceived and designed the study. HGR, JLG, LMJ, LAMJ, and RTC conceived and designed the study; drafted the manuscript; acquired, analyzed, and interpreted the data; and revised the manuscript for important intellectual content. All authors read and approved of the final version to be published and agree to be accountable for all aspects of the work.

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References

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Date accessed: 15 October 2020.
2. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. Data last updated: 2021/1/12, 11:03am CEST. https://covid19.who.int/?gclid=CjwKCAjw5p_8BRBUEiwAPpJO61ify6kstmiCBQsoIfv-Lw9ODtHirmHfVmA-3rj38yt3BzTUiR_6qRoCNokQAvD_BwE. Date accessed: 12 January, 2021.
3. Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 323:1239–1242.
4. Torres Acosta MA, Singer BD (2020) Pathogenesis of COVID-19-induced ARDS: implications for an ageing population. Eur Respir J 56:2002049.

5. Sun P, Qie S, Liu Z, Ren J, Li K, Xi J (2020) Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. J Med Virol 92(6):612–617.
6. Marini JJ, Gattinoni L (2020) Management of COVID-19 Respiratory Distress. JAMA 323:2329–2330.
7. Shen C, Yue X, Wang J, Shi C, Li W (2020) Nocturnal oxygen therapy as an option for early COVID-19. Int J Infect Dis 98:176–179.
8. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al (2020) Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 46:854–887.
9. Cheung J C-H, Ho LT, Cheng JV, Cham EYK, Lam KN (2020) Staff safety during emergency airway management for COVID-19 in Hong Kong. Lancet Respir Med 8: e19.
10. Gómez CC, Rodríguez OP, Torné ML, Santaolalla CE, Jiménez JFM, Fernández JG, et al (2020) Clinical consensus recommendations regarding non-invasive respiratory support in the adult patient with acute respiratory failure secondary to SARS-CoV-2 infection. Arch Bronconeumol 56:11–18.
11. WHO Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected: interim guidance. 2020. https://apps.who.int/iris/rest/bitstreams/1266296/retrieve. Date accessed: 15 October 2020
12. Matthay MA, Aldrich JM, Gotts JE (2020) Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med 8:433–434.
13. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al (2015) High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 372:2185–2196.
14. Vianello A, Arcaro G, Molena B, Turato C, Sukthi A, Guarnieri G, et al (2020) High-flow nasal cannula oxygen therapy to treat patients with hypoxemic acute respiratory failure consequent to SARS-CoV-2 infection. Thorax 75:998–1000.
15. Ricard JD, Roca O, Lemiale V, Corley A, Braunlich J, Jones P, et al (2020) Use of nasal high flow oxygen during acute respiratory failure. Intensive Care Med 1–10.
16. Roca O, Messika J, Caralt B, García-de-Acilu M, Sztrymf B, Ricard JD, et al (2016) Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index. J Crit Care 35:200–205.
17. Roca O, Caralt B, Messika J, Samper M, Szretmf B, Hernández G, et al (2019) An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med 199:1368–1376.
18. Ji D, Zhang D, Xu J, Chen Z, Yang T, Zhao P, et al (2020) Prediction for progression risk in patients with COVID-19 pneumonia: The CALL score. Clin Infect Dis 71:1393–1399.
19. Calligaro GL, Lalla U, Audley G, Gina P, Miller MG, Mendelson M, et al (2020) The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study. EClinicalMedicine 28:100570.

20. Geng S, Mei Q, Zhu C, Yang T, Yang Y, Fang X, et al (2020) High flow nasal cannula is a good treatment option for COVID-19. Heart Lung 49:444–445.
21. Xia J, Zhang Y, Ni L, Chen L, Zhou C, Gao C, et al (2020) High-flow nasal oxygen in coronavirus disease 2019 patients with acute hpoxemic respiratory failure: a multicenter, retrospective cohort study. Crit Care Med 48:e1079-e1086.
22. Solinas C, Perra L, Aiello M, Migliori E, Petrosillo N (2020) A critical evaluation of glucocorticoids in the management of severe COVID-19. Cytokine Growth Factor Rev 54:8–23.
23. Li J, Fink JB, Ehrmann S (2020) High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. Eur Respir J 55:2000892.
24. Hui DS, Chow BK, Lo T, Tsang OTY, Ko FW, Ng SS, et al (2019) Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. Eur Respir J 53:1802339.
25. Leun CCH, Joynt GM, Gomersall CD, Wong WT, Lee A, King L, et al (2019) Comparison of high-flow nasal cannula versus oxygen face mask for environmental bacterial contamination in critically ill pneumonia patients: a randomized controlled crossover trial. J Hosp Infect 101:84–87.

Tables

Table 1 Patient characteristics

	Total $N = 378$	HFNC only $n = 270$	HFNC + IMV $n = 108$	p-value
Age, years	54.5 (46–64)	53 (45–61)	60 (51–70)	<0.0001
Sex				0.63
Female	126 (33.3)	92 (34.1)	34 (31.5)	-
Male	252 (66.7)	178 (65.9)	74 (68.5)	-
Diabetes	134 (35.5)	92 (34.1)	42 (38.9)	0.38
Uncontrolled[a]	71 (53.0)	44 (47.8)	27 (64.3)	0.08
Glucose, $n = 348$	128 (106–172)	124 (105.5–166.5)	135 (107.5–187)	0.26
Hypertension	139 (36.8)	90 (33.3)	49 (45.4)	0.03
Uncontrolled[b]	30 (7.9)	17 (6.3)	13 (12)	0.30
BMI (kg/m^2)				0.80
Normal (18.5–24.9)	43 (11.4)	31 (11.5)	12 (11.1)	-
Overweight (25.0–29.9)	140 (37.0)	101 (37.4)	39 (36.1)	-
Obesity (≥30)	180 (47.6)	124 (45.9)	56 (51.9)	-
Unknown	15 (4.0)	14 (5.2)	1 (0.9)	-
Charlson comorbidity index				<0.0001
No comorbidities	162 (42.9)	130 (48.2)	32 (29.6)	-
Low-risk category (1–2)	178 (47.1)	121 (44.8)	57 (52.8)	-
High-risk category (≥3)	38 (10.1)	19 (7.0)	19 (17.6)	-
Duration of symptoms prior to admission, days	8 (5–11)	9 (6–12)	6 (4–8.5)	<0.0001
≤5 days	109 (28.8)	59 (21.8)	50 (46.3)	<0.0001
>5 days	268 (70.9)	210 (77.8)	58 (53.7)	<0.0001
Unknown	1 (0.3)	1 (0.4)	0 (0.0)	<0.0001
Time from admission to HFNC, days	1.99 (2.4)	1.8 (2.3)	2.5 (2.6)	0.02
Duration of HFNC, (days)	11 (4–16)	13 (10–18)	2 (1–3)	<0.0001
Steroid treatment at hospitalization	270 (71.4)	211 (78.2)	59 (54.6)	<0.0001
ICU admission	123 (32.5)	19 (7.0)	104 (96.3)	<0.0001
ICU duration, days	10 (5–19)	3 (2–3)	13 (7–20)	<0.0001
Hospital duration, days	18 (12–25)	15 (11–20)	26.5 (20–36)	<0.0001
Laboratory results at admission and when HFNC was started				
Creatinine (mg/dL), $n = 353$				
At admission	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.9 (0.8–1.2)	0.002
At HFNC start	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.6–1.2)	0.85
FiO_2 (mmHg), $n = 348$				
At admission	35 (24–56)	35 (24–53)	32 (24–60)	0.82
At HFNC start	45 (32–75)	40 (30–60)	63 (34–94)	<0.0001
Lymphocyte (%), $n = 362$				
At admission	11.7 (6.9–18.6)	12.4 (7.7–18.6)	10.6 (6.3–17.4)	0.06
At HFNC start	11.5 (7.4–19.1)	12.5 (8.0–20.7)	8.8 (5.5–16.1)	<0.0001
D-dimer (ng/mL), $n = 357$				
At admission	550 (380–890)	555 (390–940)	550 (360–790)	0.32

At HFNC start	580 (370–970)	540 (350–860)	735 (490–1145)	<0.0001
Ferritin (µg/L), *n* = 279				
At admission	466.6 (227.3–836.8)	466.6 (229.2–770.6)	467.8 (219.8–961.7)	0.69
At HFNC start	457.4 (249.9–780.7)	438.4 (230.5–714.1)	556.4 (305.2–971.7)	0.03

Data are presented as *n* (%) or median (interquartile range)
BMI, body mass index; HFNC, high-flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation

[a] Uncontrolled diabetes defined as glucose >180 mg/dL

[b] Uncontrolled hypertension defined as a blood pressure of >140/100 mmHg

Table 2 Predictors of HFNC failure (*n* = 238)

Variable	Adjusted HR (95% CI)	*p*-value
Age (per year increase)	1.003 (0.99–1.01)	0.53
Male vs female	0.73 (0.41–1.32)	0.28
CALL score (per 1-point increase)	1.27 (1.09–1.47)	<0.01
No diabetes (vs uncontrolled)	0.81 (0.43–1.51)	0.50
Diabetes (vs uncontrolled)	0.46 (0.16–1.29)	0.14
Hypertension (vs no hypertension)	1.08 (0.47–2.50)	0.85
Overweight (vs normal weight)	1.05 (0.38–2.93)	0.92
Obesity (vs normal weight)	1.49 (0.55–4.01)	0.43
Rox index 1 hour (per 1-point increase)	0.82 (0.70–0.96)	0.02
Treatment with steroids (vs no treatment)	0.34 (0.19–0.62)	<0.0001
Absolute lymphocytes (per unit increase)	0.99 (0.99–1.00)	0.24
D-dimer 550–1000 (vs normal levels)	1.23 (0.66–2.27)	0.51
D-dimer >1000–1500 (vs normal levels)	1.52 (0.61–3.76)	0.37
D-dimer >1500 (vs normal levels)	0.31 (0.09–1.09)	0.07
PAFI (per unit increase)	0.99 (0.99–1.00)	0.94
Lactate–mmol/L (per unit increase)	1.25 (0.80–1.97)	0.33
$PaCO_2$ (per unit increase)	1.04 (0.98–1.11)	0.18

CALL, comorbidity–age–lymphocyte–and LDH; CI, confidence interval; HFNC, high-flow nasal cannula; HR, hazard ratio; PAFI, ratio of PaO_2 over FiO_2

Figures

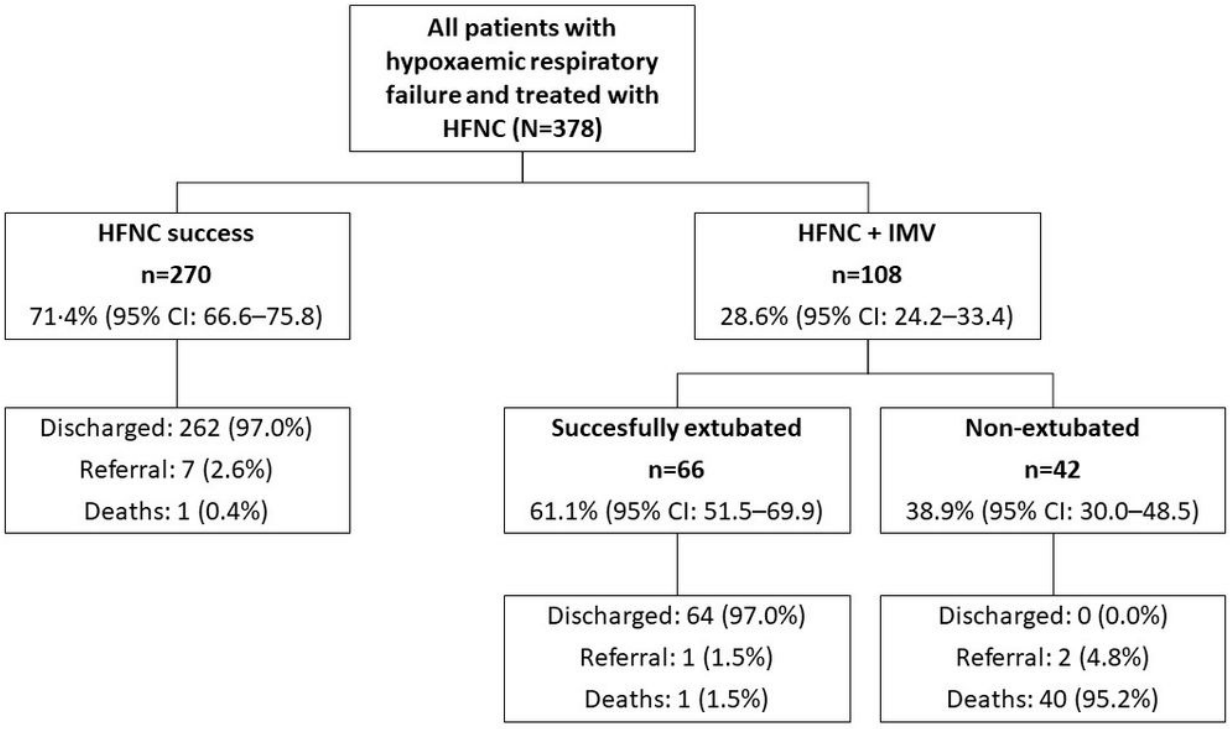
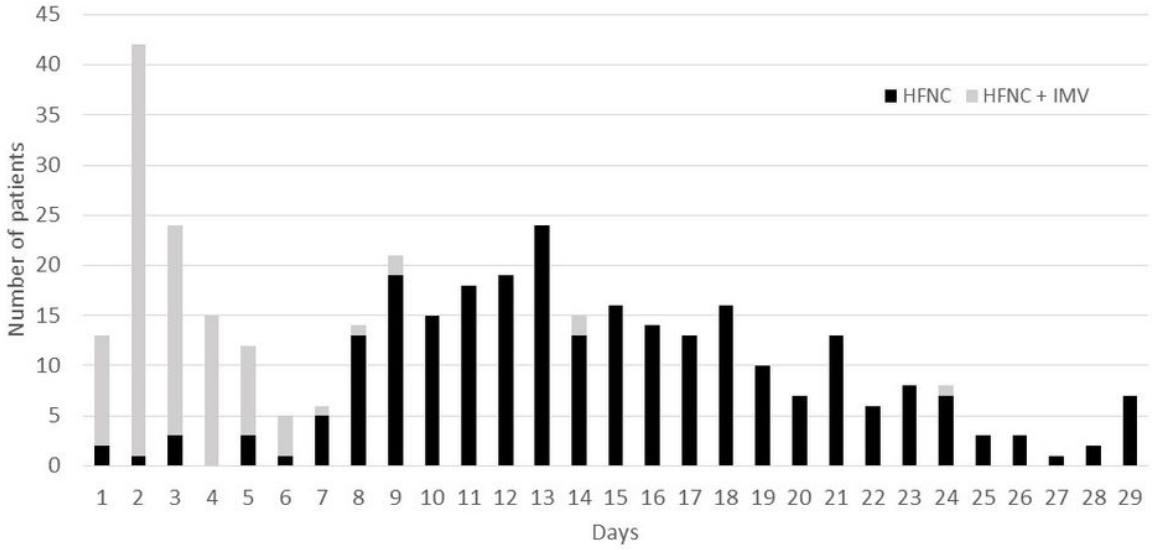


Figure 1

Flow chart of outcomes of patients treated with HFNC HFNC success was defined as the non-progression from HFNC to IMV. Abbreviations: HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation



	Median (IQR) days from start of HFNC
Only HFNC	13 (10–18)
HFNC + IMV	2 (1–3)
Total	**11 (4–16)**

1

Figure 2

Proportion of patients with HFNC success and failure over time *p-value <0.0001 Abbreviations: HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; IQR, interquartile range

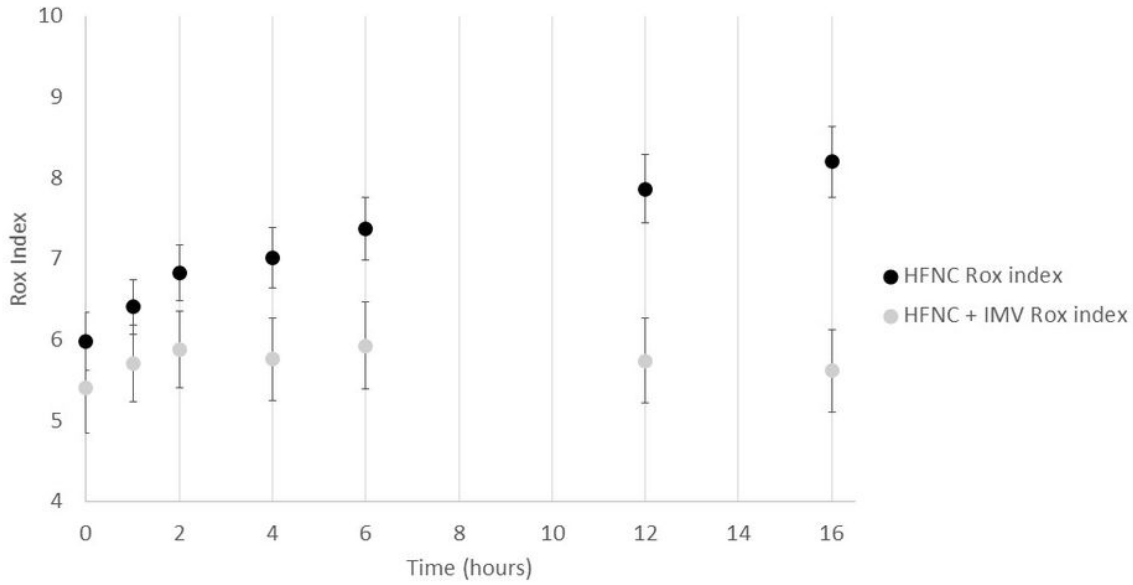


Figure 3

Rox index in patients with HFNC success and failure Rox index values at different time points in patients who did not require IMV (success of HFNC; black dots) versus those who required IMV (failure of HFNC; grey dots) among patients with hypoxemic respiratory failure who underwent treatment with HFNC. Abbreviations: HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation

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