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Retrospective analysis of high flow nasal therapy in COVID-19-related moderate-to-severe hypoxaemic respiratory failure

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ABSTRACT

Invasive mechanical has been associated with high mortality in COVID-19. Alternative therapy of high flow nasal therapy (HFNT) has been greatly debated around the world for use in COVID-19 pandemic due to concern for increased healthcare worker transmission.This was a retrospective analysis of consecutive patients admitted to Temple University Hospital in Philadelphia, Pennsylvania, from 10 March 2020 to 24 April 2020 with moderate-to-severe respiratory failure treated with HFNT. Primary outcome was prevention of intubation. Of the 445 patients with COVID-19, 104 met our inclusion criteria. The average age was 60.66 (+13.50) years, 49 (47.12 %) were female, 53 (50.96%) were African-American, 23 (22.12%) Hispanic. Forty-three patients (43.43%) were smokers. Saturation to fraction ratio and chest X-ray scores had a statistically significant improvement from day 1 to day 7. 67 of 104 (64.42%) were able to avoid invasive mechanical ventilation in our cohort. Incidence of hospital-associated/ventilator-associated pneumonia was 2.9%. Overall, mortality was 14.44% (n=15) in our cohort with 13 (34.4%) in the progressed to intubation group and 2 (2.9%) in the non-intubation group. Mortality and incidence of pneumonia was statistically higher in the progressed to intubation group.

Conclusion HFNT use is associated with a reduction in the rate of invasive mechanical ventilation and overall mortality in patients with COVID-19 infection.

INTRODUCTION

In December 2019, a cluster of acute respiratory illnesses occurred in Hubei province, China, now known to be caused by a novel coronavirus, also known as SARS-CoV-2. It has spread globally since with more than 2 million cases reported as of April 2020.[1 2] Severe hypoxaemic respiratory failure is by far the most common reason for admission to intensive care units (ICUs) due to COVID-19. In a report from Lombardi, Italy, of 1591 critically ill patients with COVID-19, 99% required respiratory support of at least supplemental oxygen and 88% (or 1150 patients) required invasive mechanical ventilation (IMV).[3] Another retrospective review of Wuhan hospitalised patients, including patients without COVID-19, showed 52% required respiratory support, of which 55% needed mechanical ventilation.[4] Mortality of patients with COVID-19 on IMV has been reported to in the range of 61%–96% in Italy, China and New York.[3–5]

High flow nasal therapy (HFNT) is a non-invasive oxygen delivery system that allows for administration of humidified air-oxygen blends as high as 60 L/min and a titratable fraction of inspired oxygen as high as 100%. HFNT has shown effectiveness in other severe viral respiratory illnesses like influenza A and H1N1.[6] Use of HFNT has led to lower progression to invasive ventilation compared with other forms of non-invasive oxygen therapy.[7–9] By decreasing the incidence of invasive ventilation, HFNT has the potential advantage of theoretically decreasing the incidence of ventilator-associated pneumonia (VAP), as well as reduction in hospital resources which can be critical during times of increasing strain on the healthcare system. When compared with non-invasive ventilation (NIV), the use of HFNT is associated with similar rates of reintubation due to postextubation respiratory failure.[10] However, no short-term mortality benefit has been reported using HFNT to treat acute hypoxaemic respiratory failure.[7 11 12]

The Surviving Sepsis Guidelines for COVID-19 recommends using HFNT in patients with acute hypoxaemic respiratory failure due to COVID-19.[13] However, others recommend against using HFNT fearing

Figure 1 Radiographic Assessment of Lung Edema Score (RALES) grading system for chest X-ray.

that it will create aerosolisation of the COVID-19 virus and increase transmission to healthcare providers.[14–16] In the few case series that report HFNT use in patients with COVID-19, its usage has ranged from 4.8% to 63.5%.[17–20] In a recent report of patients who succumbed to COVID-19 in China, 34.5% were placed on HFNT alone; the authors postulated that use of HFNT may have contributed to a delay in intubation thereby increasing mortality.[21]

Herein, we present a retrospective analysis of the outcomes of patients with COVID-19 with moderate-to-severe hypoxaemic respiratory failure receiving HFNT at our centre.

METHODS
Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Design
This was a retrospective analysis of consecutive patients admitted to Temple University Hospital in Philadelphia, Pennsylvania, from 10 March 2020 to 24 April 2020, for moderate-to-severe hypoxaemia due to highly suspected or proven COVID-19 infection. Patients who presented to our hospital with fever or acute respiratory symptoms of unknown aetiology were screened for COVID-19 infection. Patients included in analysis were those that tested positive for COVID-19 using nasopharyngeal real-time reverse transcriptase PCR (RT-PCR) or patients with high clinical suspicion and findings suggestive of COVID-19 based on high-resolution CT of the chest (typical peripheral nodular or ground glass opacities without alternative cause[22 23] with typical inflammatory biomarker profile).

Data including demographics, age, sex, comorbidities, body mass index (BMI), smoking status (current smoker, non-smoker), admission laboratory data including complete blood count with differential, ferritin, lactate dehydrogenase (LDH), D-dimer and C reactive protein (CRP), treatments offered were collected for all of these patients. We also collected oxygen saturation to fraction of inspired oxygen ratio (SF ratio) on day of HFNT initiation, at day 7 after HFNT initiation or at discharge, whichever came earlier. SF was used as a surrogate for partial pressure of oxygen/fraction of inspired oxygen (PF ratio) as they have been correlated well in clinical trials.[24]

Radiology
Chest X-rays (CXRs) were graded by senior pulmonary and critical care fellows according to the Radiographic Assessment of Lung Edema Score (RALES) grading system grading system (figure 1) previously studied in acute respiratory distress syndrome (ARDS) and organ donors.[25] CXRs were graded on the day of initiation of HFNT and earlier of discharge day or day 7.

Respiratory therapy
All patients included in the analysis had moderate-to-severe hypoxaemic respiratory failure and were on oxygen delivery via HFNT during the hospital course. Moderate-to-severe hypoxaemic respiratory failure was defined as any patient requiring >15 L/min of oxygen via nasal cannula. Receipt of any other form of respiratory support initially was considered as exclusion criteria for the study. As an institutional policy, HFNT was preferred over NIV/IMV and was maintained indefinitely if oxygenation, ventilation and work of breathing parameters were acceptable. The decision to switch to NIV or IMV was at the discretion of the clinical care team. HFNT was provided with a humidified air-oxygen blend usually starting at 35 L/min with immediate titration to 20–60 L/min per patient comfort; the fraction of inspired oxygen (FiO_2) was adjusted to maintain oxygen saturations>94%; further adjustments were made based on patients' tolerance and goals of oxygenation. The initial temperature for the high flow setup was 37°C and was titrated between 34°C and 37°C for patient comfort. Data on initial oxygenation support were collected which included the

flow of air-oxygen blend in litres per minute and fractional percentage of inspired oxygen.

Outcomes

Our primary outcome was the prevention of IMV (%) with use of HFNT. Our secondary outcomes were mortality, change in SF ratio, change in RALES of CXR, hospital length of stay (LOS) and hospital-acquired/ventilator-acquired pneumonia. Hospital-acquired and ventilator-acquired pneumonia was defined based on the presence of sputum positivity and treatment with antibiotics. Changes in SF ratio were calculated by difference between SF ratio at day 7 or discharge (whichever was earlier) versus day 1.

HFNT patients were divided into two groups: 1) progression to IMV (ie, intubation group) and 2) continued HFNT support (ie, non-intubation group). Patients who required NIV are reported in the non-intubation group. Comparison was made between demographics, baseline laboratory values and outcomes within the two groups. Improvements/worsening in oxygenation at day 7 and change in clinical parameters of heart rate and respiratory rate were also analysed.

We constructed a prediction model for intubation for our cohort. All comorbidities, demographics, clinical and laboratory data were used to investigate parameters that could predict need for intubation. A cumulative comorbidity score (1 point allocated for each of the five comorbidities reported) and cumulative inflammatory laboratory marker score (1 point for each abnormal lab) were tested as predictors of intubation.

Statistical methods

Continuous variables are presented as means ($\pm$SD), and categorical variables as numbers and frequency (percentages). Continuous variables were compared with the use of the two-sample t-test or paired t-test for categorical variables with the use of the Pearson's χ^2 test. Laboratory data were non-parametric and compared using Wilcoxon rank-sum test. Kaplan-Meier analysis was estimated for survival and compared by log-rank test.

To build a predictive model of the intubation, multivariable logistic regression was performed to determine the adjusted associations of the variables with intubation. The initial model included all the variables associated with intubation in univariate analyses for p<0.1. The final model that optimised the balance of the fewest variables with good predictive performance. Assessment of model performance was based on discrimination and calibration. Discrimination was evaluated using the C-statistic, which represents the area under the receiver operating characteristic (ROC) curve, where higher values represent better discrimination. Calibration was assessed by the Hosmer-Lemeshow test, where a p value >0.05 indicates adequate calibration.

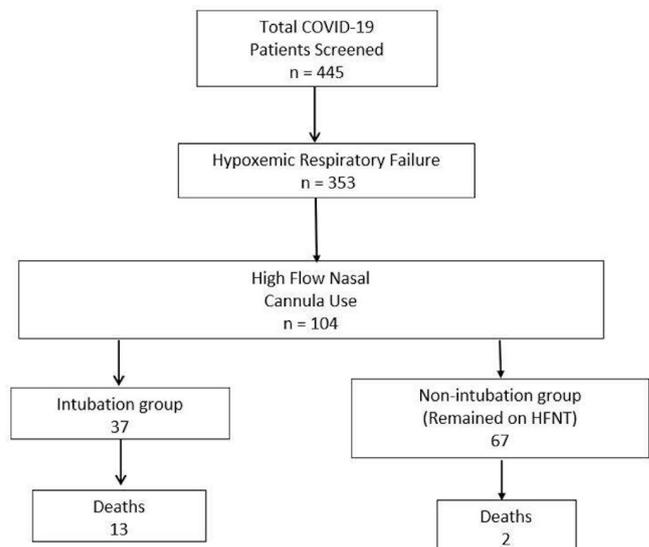All statistical tests were two-tailed, and p values <0.05 were considered to indicate statistical significance. All

Figure 2 Flow chart demonstrating screening for our patients. HFNT, high flow nasal therapy.

statistical analyses were performed with the use of Stata V.14.0 (StataCorp, College Station, Texas, USA).

RESULTS

Patient population

Eight hundred ninety-four patients admitted to Temple University Hospital between 10 March 2020 and 24 April 2020 who had suspected COVID-19 infection were retrospectively screened for our study. Four hundred forty-five patients had tested positive for COVID-19 by nasopharyngeal RT-PCR or were treated for high clinical suspicion based on typical CT imaging and inflammatory biomarker profile.

Of the 445 patients, 353 patients had hypoxaemic respiratory failure requiring some form of oxygen therapy. The level of oxygen ranged from 2 L/min of oxygen via simple nasal cannula to requiring IMV and 100% oxygen. One hundred four (23.3% of all COVID-19-positive patients) met our inclusion criteria of having moderate-to-severe COVID-19-related hypoxaemic respiratory failure and were treated with HFNT (figure 2). The reported hypoxaemia was moderate-to-severe with mean SF ratio of 121.9 (range 79–225). Higher CXR RALES were associated with more severe SF ratios.

The average age was 60.66 ($\pm$13.50) years, 49 (47.12 %) were female, 53 (50.96%) were African-American, 23 (22.12%) Hispanic. Forty-three patients (43.43%) were smokers. The major comorbidities reported (in descending incidence) were hypertension, diabetes, lung disease, heart disease and chronic kidney disease (CKD) (table 1). Nine (9.78%) patients were also on haemodialysis. Baseline SF ratios were severely low at 121.9, corresponding to a PF ratio of ~100. Elevated inflammatory markers (ie, ferritin, CRP, D-dimer, fibrinogen, LDH, interleukin (IL)-6), creatinine along with transaminitis and lymphopenia were observed in all patients. In

Table 1 Demographics data including laboratory and clinical parameters

Demographics	n=104
Age (years, mean±SD)	60.66 (±13.50)
Sex (F) n (%)	49 (47.12 %)
BMI* kg/m^2 (mean±SD)	32.14 (±7.80)
Comorbidities n (%)	
Hypertension	46 (45.10%)
Diabetes	35 (34.65%)
Lung Dx	31 (30.69%)
Heart Dx	23 (22.55%)
CKD	15 (16.3%), 9 (9.78%) on HD
Race	
African-American	53 (50.96%)
Hispanic	23 (22.12%)
Caucasian	9 (8.65%)
Other	4 (3.85%)
Unknown	15 (14.42%)
Smoking n (%)	
No	51 (51.52%)
Yes	43 (43.43%)
Initial vitals	
Heart rate (mean±SD) bpm	98.0 (±20.17)
Respiratory rate (mean±SD) bts/min	22.03 (±5.47)
Temperature (mean±SD) °F	99.4 (±2.18)
Pulse oximetry (mean±SD) %	89.9 (±10.09)
Laboratory abnormalities mean (±SD)	
Ferritin (ng/mL)	1216.0 (±2790.6)
CRP* (mg/dL)	11.77 (±8.38)
LDH* (U/L)	452.06 (±292.36)
D-dimer (ng/mL)	5659.6 (±17267.49)
Fibrinogen (mg/dL)	490.23 (±178.44)
Lymphocyte count (K/mm^3)	1.02 (±0.54)
IL-6 (pg/mL)	82.5 (±149.54)
AST (U/L)	56.8 (±74.90)
ALT (U/L)	38.6 (±31.93)
Platelets (K/mm^3)	221.7 (±106.19)
Triglycerides (mg/dL)	186.7 (±253.78)
BUN (mg/dL)	28.4 (±24.07)
Creatinine (mg/dL)	2.61 (±3.95)
Treatments	
Remdesivir	9 (9.68%)
Sarilumab	40 (39.22%)
Anakinra	12 (11.76%)
Tocilizumab	6 (5.88%)

Continued

Table 1 Continued

Demographics	n=104
Etoposide	1 (0.97%)
IVIG	19 (18.63%)
Pulse steroids	66 (64.71%)
Hydroxychloroquine	22 (21.57%)
Azithromycin	59 (57.2%)
Antibiotics	76 (73.08%)

ALT, alanine transaminase; AST, aspartate transaminase; bpm, beats per min; bts/min, breaths per min; BUN, blood urea nitrogen; CKD, chronic kidney disease; CRP, C reactive protein; Dx, diagnosis; F, Fahrenheit; HD, haemodialysis; IL-6, interleukin 6; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase.

terms of treatments, azithromycin (57.2%) and steroids (64.71%) were the most frequently used therapies. Immunomodulators like sarilumab, anakinra, intravenous immunoglobulin (IVIG) and tocilizumab were the next most used therapies.

HFNT details

One hundred four (23.3%) of 445 COVID-19-positive patients required HFNT support. Initial HFNT settings were 31.8 (±9.17) L/min of flow, while fractional of inspired oxygen (FiO$_2$) was 90% (±16.7, range: 30%–100%). The average use of HFNT for our population was 4.58 days (±3.28). The minimum settings on HFNT were 10 L flow and FiO$_2$ of 30%, while the maximum settings were 60 L and FiO$_2$ of 100%. Forty-five (43.2%) of patients receiving HFNT progressed to IMV or NIV. The incidence of hospital-associated pneumonia on HFNT was 2.94%. Two patients were excluded from analysis due to short follow-up.

Use of high flow for liberation from mechanical ventilation (IMV+NIV)

Eleven of the IMV patients were successfully extubated to high flow with no re-intubations in this subgroup. Six of the eight patients on NIV were successfully liberated from NIV with the use of HFNT.

Outcomes

The SF ratio significantly improved from 123.5 (±42.25) to 234.5 (±120.79) from day 1 to day 7. CXR score improved from 18.17 (±7.87) to 16.13 (±8.79) (p=0.033), heart rate decreased from 88.2 (±17.13) to 75.7 (±23.13) (p=0.0004) and respiratory rate improved from 29.71 (±18.99) to 26.38 (±16.93) (p=0.0001) (table 2). Sixty seven of 104 (64.42%) were able to avoid IMV in our cohort. Overall, 45 patients required mechanical ventilation, of which 37 (35.58%) required IMV and 8 patients (7.69 %) required NIV.

Overall, mortality was 14.44% (n=15) in our cohort with 13 (34.4%) in the intubation group and 2 (2.9%)

Table 2 Outcomes of patients treated with HFNT

Outcomes	Total (n=104)		P value
Prevention of intubation	67 (64.42%)		
Intubation rate	37 (35.58%)		
Mortality	14.44% (n=15)		
Hospital LOS	10.96 days (±6.04)		
ICU LOS	6.55 days (±5.31)		
HAP/VAP incidence	3 (2.94%)		
	Day 0	Day 7–10	
SF ratio	123.5 (±42.25)	234.5 (±120.79)	<0.0001
CXR RALES	18.17 (±7.87)	16.13 (±8.79)	0.033
Heart rate (bpm)	88.2 (±17.13)	75.7 (±23.13)	0.0004
Respiratory rate (breaths/min)	29.71 (±18.99)	26.38 (±16.93)	0.0001

CXR, chest X-ray; HAP, hospital-associated pneumonia; ICU, intensive care unit; LOS, length of stay; RALES, Radiographic Assessment of Lung Edema Score; SF ratio, saturation to fraction ratio; VAP, ventilator-associated pneumonia.

in the non-intubation group. Both the deaths in the non-intubation group were patients transitioned to comfort-directed care. Lastly, 10 of the 13 deaths were related to non-pulmonary organ failure and complications.

As of this writing, 48 patients from the HFNT group were discharged from the hospital with LOS 10.9 days (±6.04). ICU LOS for the 38 patients discharged from ICU was 6.55 days (±5.31). ICU LOS was higher for the intubation group (10.45 days±6.12 vs 4.05 ± 2.64 days, p=0.0008).

Intubation versus non-intubation (continued HFNT) group

The average duration of high flow use was higher in the non-intubation group (5.38±3.31 days vs 3.11±2.70 days, p=0.0023). There were no statistically significant differences between the intubation and non-intubation groups in terms of demographics (age, sex, BMI, most comorbidities, smoking). Hypertension and smoking prevalence were higher in the intubation group. Among laboratory markers, ferritin, LDH and fibrinogen was higher in the non-intubation group while triglycerides, IL-6, aspartate transaminase, D-dimer blood urea nitrogen and creatinine were higher in the intubation group (table 3). SF ratios were significantly different between the two groups at baseline, with the intubation group having much lower SF ratios compared with those who remained on HFNT (111.03±34.09 vs 127.9+43.47, p=004). There was greater improvement in SF ratio and CXR score (figure 3) in the non-intubation group (table 4). Patients in the intubation group had higher tocilizumab use, whereas anakinra, IVIG and antibiotics were more common in the non-intubation group.

Mortality and incidence of ventilator-associated pneumonia/hospital-acquired pneumonia was statistically higher in the intubation groups. Figure 4 shows better survival for the non-intubation group compared with the intubation group.
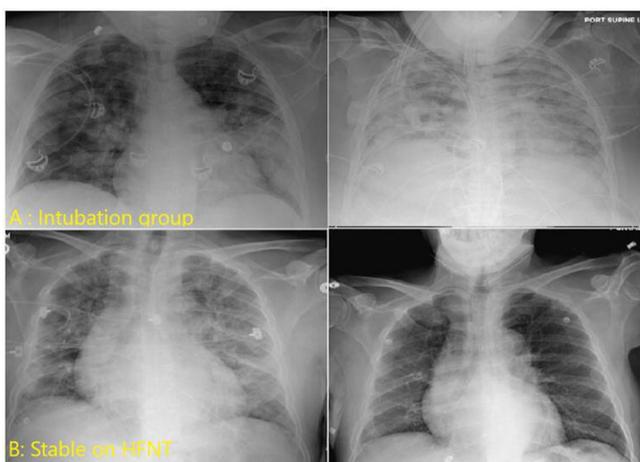

Figure 3 Progression of chest imaging for patients on high flow nasal therapy (HFNT). (A) Worsening bilateral infiltrates in intubation group. (B) Non-intubation group, improved infiltrates.

Prediction model

In the univariate analysis, history of hypertension, CKD or having a composite comorbidity score of 1 or greater was predictive of progression to intubation. In terms of laboratory markers, elevated triglycerides (>300 mg/dL) and lower fibrinogen (≤450) were predictive in univariate analysis. SF ratio <100 (OR=2.3) was also a significant predictor in univariate analysis. In the multivariate analysis, only SF ratio (<100), history of CKD and fibrinogen (<450 mg/dL) were predictive of intubation (table 5). Figure 5 shows the ROC curve for our prediction model (ROC=0.7229).

DISCUSSION

In this retrospective review of patients with COVID-19 and acute hypoxaemic respiratory failure, we found that 104 patients (23.3%) were treated initially with HFNT,

Table 3 Comparing demographics data between intubation and non-progression groups

Demographics	Intubation (n=37)	Non-intubation (n=67)	P value
Age (years, mean±SD)	63.9 (±11.67)	58.9 (±14.17)	0.06
Sex (F) n (%)	16 (43.24 %)	33 (49.25 %)	0.55
BMI kg/m^2 (mean±SD)	31.0 (±6.74)	32.8 (±8.33)	0.27
Comorbidities n (%)			
Diabetes	12 (33.33%)	23 (35.38%)	0.84
Hypertension	21 (56.76%)	25 (38.46%)	0.07
Lung Dx	14 (38.89%)	17 (26.15%)	0.18
Heart Dx	10 (27.03%)	13 (20.00%)	0.41
CKD	7 (21.21%)	8 (13.56%)	0.34
Chronic haemodialysis	4 (12.12%)	5 (8.47%)	0.57
Race			
African-American	18 (48.65%)	35 (52.24%)	0.192
Hispanic	8 (21.62%)	15 (22.62%)	
Caucasian	6 (16.22%)	3 (4.48%)	
Other	0	4 (5.97%)	
Unknown	5 (13.51%)	10 (14.93%)	
Smoking* n (%)			
No	15 (41.67%)	36 (57.14%)	0.19
Yes	18 (50.00%)	25 (39.68%)	
Initial vitals			
HR (mean±SD)	97.32 (±21.98)	98.3 (±19.24)	0.80
RR (mean±SD)	21.49 (±6.11)	22.3 (±5.09)	0.45
Temperature (mean±SD)	99.2 (±2.54)	99.6 (±1.95)	0.36
Pulse oximetry (mean±SD)	89.2 (±12.30)	90.4 (±8.67)	0.58
Laboratory abnormalities			
Mean (±SD)			
Ferritin (ng/mL)	1078.2 (±1720.37)	1290.5 (±3236.69)	0.59
CRP (mg/dL)	12.51 (±10.02)	11.35 (±7.38)	0.90
LDH (U/L)	444.51 (±322.57)	463.4 (±244.33)	0.58
D-dimer (ng/mL)	9241.76 (±24519.18)	3604.36 (±10938.11)	0.36
Fibrinogen (mg/dL)	430.9 (±205.05)	523.64 (±153.66)	0.009
Abs Lymph Ct (K/mm^3)*	1.05 (±0.43)	1.00 (±0.50)	0.39
IL-6 (pg/mL)	130.9 (±210.15)	42.6 (±48.07)	0.12
AST (U/L)	69.2 (±112.06)	48.6 (±32.45)	0.90
ALT (U/L)	39.78 (±43.54)	37.85 (±22.89)	0.51
Platelets (K/mm^3)	215.2 (±115.74)	225.5 (±101.02)	0.60
Triglycerides (mg/dL)	293.96 (±454.58)	145.26 (±75.86)	0.52
BUN (mg/dL)	31.95 (±21.86)	26.32 (±25.24)	0.08
Creatinine (mg/dL)	2.88 (±3.58)	2.46 (±4.15)	0.09
Treatments	5 (13.89%)	4 (7.02%)	0.27
Remdesivir trial*	12 (33.33%)	28 (42.42%)	0.36
Sarilumab trial†	0	12 (18.18%)	0.006
Anakinra	5 (13.89%%)	1 (1.52%)	0.011
Tocilizumab	1 (2.70%)	0	0.18
Etoposide	11 (30.56%)	8 (12.12%)	0.02

Table 3 Continued

Demographics	Intubation (n=37)	Non-intubation (n=67)	P value
IVIG	26 (72.22%)	40 (60.61%)	0.24
Pulse steroids	6 (16.67%)	16 (24.24%)	0.37
Hydroxychloroquine	12 (41.38%)	22 (61.1%)	0.30
Azithromycin	24 (64.86%)	15 (22.39%)	0.16
Antibiotics			

*Smoking—current vs former/non-smokers. NCT04292899 and NCT04292899.
†NCT04315298.
Abs Lymph Ct, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea Nitrogen; CKD, chronic kidney disease; CRP, C reactive protein; Dx, diagnosis; HD, haemodialysis; IL-6, interleukin 6; LDH, lactate dehydrogenase.

of which 64.4% remained on HFNT and were able to avoid escalation to non-invasive and IMV. The 67 non-intubation patients (continued HFNT therapy) had a significant improvement in oxygenation and reduction in incidence of hospital-acquired pneumonia compared with those who progressed to intubation. While the survival advantage cannot be attributed to HFNT based on our study's retrospective design, use of HFNT did not result in worsened outcomes either. The majority of the patient mortality was attributed to the high burden of comorbidities (metastatic cancer, underlying renal and cardiac conditions, obesity, smoking and bacteraemia), rather than progression of respiratory failure on HFNT (table 5).

In similar patients in Italy and China, the intubation rate has been reported between 70% and 90%.[3][20] In addition, our group also had a very high burden of comorbid disease, including underlying lung disease and tobacco use. Among our cohort of patients, 30.69% of patients had underlying lung disease and 43.43% were current smokers. In comparison, early case series reports from China only describe 1.1%–3.1% of patients with chronic obstructive pulmonary disease (COPD),[1][4][22] whereas case series from the Lombardy region of Italy reports 4% of patients with COPD.[3] Bhatraju et al reported only one patient with COPD in their recent case series of 21 patients from the Seattle region.[23] The rate of smokers in these studies was also low compared with our group's prevalence of 43.43%. There was no statistically significant difference in our group between those with and without underlying lung disease with regard to progression to IMV. In addition, hypertension and CKD were also shown to be predictive of intubation in our univariate analysis, with CKD also a predictor in multivariate analysis. Chronic uraemia in presence of hypertension leads to chronic left ventricular hypertrophy and other structural changes to the myocardium leaving the patients vulnerable to very small amounts of fluid shifts, subsequently leading to pulmonary oedema.[24] CKD has also previously been shown to have worse outcomes including mortality in patients diagnosed with pneumonia.[25] A fibrinogen level of <450 mg/dL was found to be predictive of intubation in both univariate and multivariate analysis. Fibrinogen is an acute phase reactant and it is possible that patients who present with a fibrinogen <450 mg/dL may be presenting in a later stage of disease and less amenable to antiviral or anti-inflammatory therapies during support with HFNT.

Prevention of avoidable IMV with HFNT is significant as by nature it avoids incidence of ventilator-associated pneumonia, reduces the need to use medications such as sedatives in which shortages are being reported in the current public health crisis.[26][27] The reported mortality in patients requiring IMV in COVID-19 is 90%.[3][4][20] Our study shows mortality to be much lower when IMV can be avoided. In addition, HFNT can also decrease utilisation of ventilators, sedatives in the setting of a global pandemic; thus, representing a viable alternative to IMV.

Gattinoni et al have previously reported high respiratory compliance despite a large shunt fraction,[28] proposing that patients with COVID-19 fall into two groups. The 'type L' or 'non-ARDS type 1' phenotype have low elastance/high compliance and possible loss of hypoxic vasoconstriction mechanisms and often present
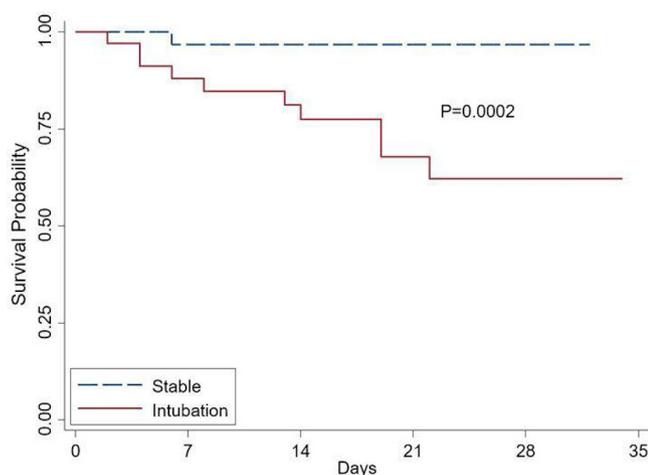

Figure 4 Kaplan-Meier estimate of survival of high flow nasal therapy (HFNT) patients, comparing intubation with non-intubation (continued HFNT) groups.

Table 4 Comparing outcomes between intubation and non-intubation groups

Outcomes	Intubation	Non-intubation	P value
Mortality	13 (35.1%)	2 (2.9%)	0.0018
Hospital LOS (days)	13.67 (±7.97)	9.7 (±4.6)	0.03
ICU LOS (days)	10.45 (±6.12)	4.05 (±2.64)	0.0008
HAP/VAP incidence	3 (8.57%)	0	0.017
Change in SF ratio	40.5 (±67.90)	141.4 (±117.14)	0.0001
Change in CXR RALES	−0.13 (±11.18)	−3.2 (±8.50)	0.09
Change in HR (beats/min)	−7.65 (±20.69)	−7.95 (±19.19)	0.94
Change in RR (breaths/min)	−2.32 (±9.32)	−4.4 (±8.39)	0.27

HAP/VAP incidence was defined as number of patients with positive sputum cultures (expectorated or aspirate) that required treatment.
Change in SF ratio=SF ratio at day 7–10–SF ratio at day 0.
CXR, chest X-ray; HAP, hospital-acquired pneumonia; HR, heart rate; ICU, intensive care unit; LOS, length of stay; RALES, Radiographic Assessment of Lung Edema Score; RR, respiratory rate; SF ratio, saturation to fraction ratio; VAP, ventilator-associated pneumonia.

with profound hypoxaemia due to ventilation/perfusion mismatch. The 'type H' or 'ARDS type 2' phenotype has increased pulmonary oedema and progression to consolidation and requires traditional management strategies of higher positive end-expiratory pressure (PEEP) and lower tidal volumes.[29] We have experienced similar patient subgroups in our practice. As HFNT only provides a modest PEEP effect (ie, 3–5 cmH$_2$O at flow rates of 30–50 L/min with mouth closed),[30] patients with predominant type L physiology who do not require the higher positive pressure benefit from the oxygenation support that HFNC can provide non-invasively. HFNT can lead to a high oxygen reservoir by reducing anatomical dead space in the nasopharynx.[31] Furthermore, IMV using high tidal volume (which is often employed in type L patients) has shown to have inflammatory cytokine release in patients with ARDS, including IL-6, both in critically ill humans[32 33] and murine models[34 35]; IL-6 in particular is one of the pathological mechanisms for lung injury in COVID-19.[36 37] Lastly, patient self-induced lung injury (P-SILI) has been cited as a theoretical contraindication to non-invasive methods of oxygenation. To date, however, P-SILI remains a conceptual model concept compared with Ventilator induced Lung injury (VILI).[38 39] Thus, use of HFNT should be a priority in patients with severe COVID-19 respiratory failure.

We elected to use SF ratio than traditional PF ratios in this study for several reasons. SF ratios have been well correlated to standard PF ratios in adult and paediatric populations.[40 41] SF ratios <235 predict moderate-to-severe respiratory failure with 85% specificity.[41] Our cohort overall showed moderate-to-severe hypoxaemic respiratory failure (mean SF ratio 123 overall), but nonetheless ~64.4% of our cohort could still be supported with high flow oxygen alone. In contrast, Wang *et al* showed only 37% of patients with COVID-19 did not progress on HFNT when the PF ratio was <200.[42] Additionally, lab draws, and arterial blood gases

were limited during a pandemic to minimise staff exposure when possible. Hence, ABGs were not routinely collected as part of standard clinical practice at our institution.

There has been debate worldwide about the use of HFNT or other methods of NIV out of concerns for increased disease transmission. During the 2003 SARS outbreak, hospital workers had development of SARS in only 8% of HFNT patients.[43] Studies have not shown that bacterial environmental contamination was increased in the setting of HFNT use.[13 14 44] An in vitro study mimicking clinical scenarios including HFNT with mannequins only revealed proximal dispersion of secretions to the face and nasal cannula itself.[45 46] A recent study with healthy volunteers wearing high flow nasal cannulas at both 30 and 60 L/min of gas flow did not report variable aerosolisation of particles between 10 and 10 000 nm, regardless of coughing, when compared with patients on room air or oxygen via regular nasal cannula.[47] In our department
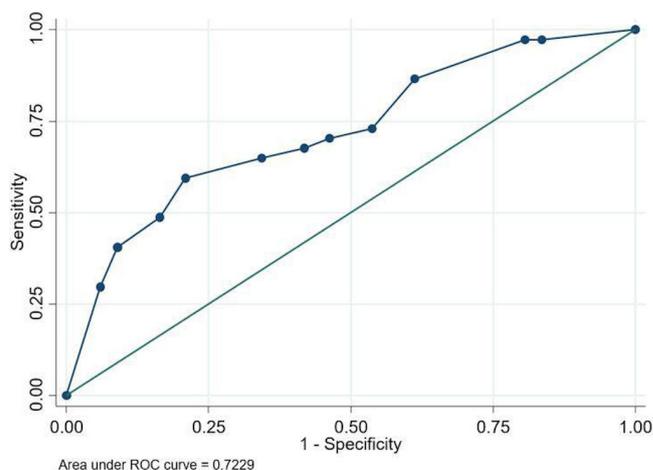

Figure 5 Receiver operating characteristic (ROC) curve of the predictive model for intubation.

Table 5 Demographic, clinical and laboratory predictors of intubation using multivariable logistic regression

	Univariate analysis (OR)	P value	Multivariate analysis (OR)	P value
Age (years)				
≤65	1	0.31		
>65	1.5			
BMI				
≤30		0.57		
>30	0.79			
Smoking				
No	1	0.32		
Yes	1.52			
Race				
Non-black	1	0.72		
Black	0.87			
Comorbidities				
Heart disease	1.48	0.41	2.59	0.047
Lung disease	1.79	0.19		
Diabetes	0.91	0.83		
HTN	2.1	0.07		
CKD	2.91	0.01		
Haemodialysis	1.49	0.57		
No comorbidity	1		2.7	0.11
Any comorbidity	3.51	0.03		
Laboratory markers				
Ferritin <400	1	0.79		
(ng/mL) ≥400	0.89			
D-dimer <1000	1	0.37		
(ng/mL) ≥1000	1.47			
AST <105	1	0.53		
(U/L) ≥105	1.6			
AST <180	1	0.26		
(U/L) ≥180	0.29			
Triglycerides <300	1	0.07		
(mg/dL) ≥300	4.81			
Fibrinogen >450	1	0.007	3.02	0.027
(mg/dL) ≤450	3.53			
Abs Lymph Ct ≥1	1	0.26		
(K/mm^3) <1	0.62			
LDH ≤350	1	0.18		
(U/L) >350	1.85			
CRP <6	1	0.22		
(mg/dL) ≥6	0.58			
Cumulative laboratory score (1 point per abnormality)				
<3	1	0.36		
≥3	1.5			

Continued

Table 5 Continued

	Univariate analysis (OR)	P value	Multivariate analysis (OR)	P value
SF ratio				
≥100	1	0.05	2.61	0.04
<100	2.3			

Abs Lymph Ct, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CKD, chronic kidney disease; CRP, C reactive protein; HTN, hypertension; LDH, lactate dehydrogenase; SF ratio, saturation to fraction ratio.

of 80 members which included advanced nurse practitioners, attending faculty and fellows, we had only two members who developed COVID-19 infection during the pandemic.

This study has several limitations. First, it was retrospective in nature as developing a prospective trial on the initial management of acute hypoxaemic respiratory failure in the face of an evolving public health crisis is difficult. Second, we could not reasonably analyse a control arm as our end point was prevention of mechanical ventilation. Developing a prospective study during a pandemic situation is impractical without first determining clinical equipoise. Third, we do not report on arterial pH or partial pressure of carbon dioxide ($PaCO_2$) as many patients did not have baseline or follow-up arterial blood gas measurements prior to initiation of HFNT. We recognise that in many clinical trials an elevated $PaCO_2$ was an exclusion criterion for enrolment.[7 10] Fourth, our data on hospital LOS was limited since several patients were still hospitalised at the time data were collected.

Institutions around the world have been sceptical about the use of HFNT in patients with COVID-19. However, based on our findings, we conclude that there is a role for HFNT in patients with COVID-19-related severe respiratory failure especially the L-phenotype. Use of HFNT can reduce intubation rates and has the potential to reduce mortality and morbidity associated with it.

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