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Factors affecting the outcome of the usage of high-flow nasal cannula on severe or critically ill COVID-19 patients: a multicentric study from a developing nation

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Abstract: In resource-constrained settings, High-Flow Nasal Cannula (HFNC) can reduce the burden on mechanical ventilation in COVID-19 induced Acute Hypoxemic Respiratory Failure (AHRF). The aim was to observe the factors those might affect the outcome of the usage of HFNC on severe/critically ill COVID-19 patients. This is a multicentric prospective observational study. We observed rRT-PCR positive severe/critically ill ICU patients requiring HFNC for more than six hours. Statistical analysis was done to correlate between factors and outcome. Weaning from HFNC was successful in 47.5% of patients. The death rate was higher in ≥ 50 years older (56.50%), and patients with asthma (60.57%), COPD (60.00%), and CKD (68.42%). Fever (91.67%), cough (72.5%), and dyspnea (67.5%) were the most common symptoms. Mortality rates were higher for patients with raised blood sugar, creatinine levels. Severely systemic inflammatory response was seen very high for the expired patients. On HFNC, percent saturation of oxygen (SpO₂) and partial pressure of oxygen (PaO₂) progression was significantly high for the surviving patients requiring less inspired fraction of oxygen (FiO₂%). The survival rate was higher for the patients using both HFNC and non-rebreather mask (NRM) concomitantly. While after HFNC- SpO₂% and FiO₂% were significantly related with outcome of the HFNC only treated patients, duration of hospital stay and on HFNC- FiO₂% affected the HFNC + NRM treated patients' outcome. HFNC could save more lives of critically ill AHRF patients who otherwise might need invasive or noninvasive ventilation. Some biochemical tests were observed to have association with the prognosis of the disease though HFNC was given to all. Survival benefit of dual HFNC and NRM therapy needs future study.

Keywords: HFNC; COVID-19; ICU; NRM; SpO₂

1. Introduction

Since its outbreak in China in December 2019, COVID-19's rapid spread worldwide has forced the global population to live in a pandemic situation with dread for life (Zhu *et al.*, 2020). Among the previously identified six human CoVs (coronaviruses) (Tang *et al.*, 2015), severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) were considered to be highly infectious (Cui *et al.*, 2019). However, the COVID-19 contagion, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was in no way behind its beta coronavirus counterparts in terms of infection rates and manifesting severe health complications. As of now, SARS-CoV-2 has affected 220 countries and territories drastically (Worldometers, 2021a). As of September 1, 2021, SARS-CoV-2 has infected over 210 million

people and has caused 4,542,691 deaths, most of which have been identified in countries other than China (Worldometers, 2021a). COVID-19's first instance was detected in Bangladesh on March 8, 2020 (Islam *et al.*, 2020). To date, about 1.5 million COVID-19 positive cases have been identified and more than 25,000 deaths have been reported in Bangladesh (Worldometers, 2021b).

As SARS-CoV-2's entry route involves various organs of the respiratory tract and its localization is majorly in the lung cells, a range of symptoms mutual to other diseases of the respiratory tract is triggered. Clinical manifestations often range from fever and can take an even severe form, such as pneumonia. A significant number of cases become critical (EWGNER, 2020; Wu and McGoogan, 2020). The burden of severe cases has created an unusual freight on the health sector, presenting the urgency of worthwhile therapies for COVID-19. Several studies reported that severe COVID-19 leads to acute hypoxemic respiratory failure (AHRF), which requires a high fractional concentration of inspired oxygen (FiO₂) and noninvasive ventilation (NIV) procedures (Antonelli *et al.*, 1998; Carrillo *et al.*, 2012; Delclaux *et al.*, 2000).

Several devices are being used in intensive care units (ICUs) to deliver supplemental oxygen to COVID-19 patients who have developed hypoxemic respiratory failure including simple face mask, face mask with a non-rebreathing reservoir bag, venturi masks, etc. HFNC, on the other hand, tends to be more successful than others because it can reach 100% humidification at 37°C and has a positive end-expiratory pressure (PEEP) effect while patients breathe with the mouth closed (Roca *et al.*, 2010; Sztrymf *et al.*, 2011). It acts as a noninvasive setup to improve oxygen level and decrease dead space carbon dioxide level. Relative to other oxygen delivery devices, HFNC foremost balances the patients' inspiratory demands by delivering up to 60 L/min of air flow with a FiO₂ up to 1.0. In this way, it reduces the adverse effects more as there is no risk of tooth avulsion, intubation of the esophagus, Ventilator-Associated Pneumonia (VAP), Ventilator Induced Lung Injury (VILI), and use of neuromuscular blocker and sedatives are not required in HFNC in contrast to endotracheal intubation (Huang *et al.*, 2018; Lee *et al.*, 2016; Maitra *et al.*, 2016; Ni *et al.*, 2017). Wake-prone positioning is a striking benefit of HFNC, a patient could eat and drink himself as well and there is very little need for maintenance as this is a very simple device. HFNC also decreases the burden of mechanical ventilation during a phase where mechanical ventilation is demanding owing to the rise in critical cases every minute. In previous studies, it was found that HFNC to some extent reduces the need for intubation in patients requiring supplemental oxygen and was also found to have contributed to reducing mortality rates (Frat *et al.*, 2015; Rochweg *et al.*, 2019).

The goal of this study is to evaluate the associated factors affecting the outcome of HFNC usage on severe/critically ill ICU admitted COVID-19 induced AHRF patients.

2. Materials and Methods

2.1. Patients and data collection

This multicentric prospective observational study was conducted on 240 COVID-19 patients admitted to ICUs in 250 bedded Chattogram General Hospital, Chittagong Medical College Hospital, Chattogram Maa-O-Shishu General Hospital, Parkview Hospital, and Surgiscope Hospital Ltd. between February 15, 2021, and June 14, 2021. These are specialized hospitals authorized to manage the most critical COVID-19 patients with 50 ICU beds within the ICUs of the port city of Bangladesh, Chattogram. Epidemiological and demographic data for the cases were collected by designated researchers from the patients' treatment records and by interviewing the corresponding attendants.

2.2. Ethical clearance

The Institutional Review Board of the 250 bedded Chattogram General Hospital approved this study (Approval No.: 1724).

2.3. Inclusion and exclusion criteria

This survey included Real-time Reverse-Transcriptase Polymerase Chain Reaction (rRT-PCR) positive patients with AHRF admitted to COVID ICU and received HFNC oxygenation for more than six hours. Patients' having SpO₂ less than 90% persistently after providing 15 liters per minute oxygen was considered as an indication for HFNC. On the contrary, patients who needed MV or NIV from the beginning of ICU admission and those who did not want to participate in the study willingly were excluded. Additionally, a face mask with NRM along with HFNC was provided to the patients who failed to maintain target oxygen saturation (>90%) after high flow.

2.4. The criteria for ICU admission

Most of the severe and critically ill patients were admitted to the ICU. Patients having dyspnea, i.e., a respiratory rate of ≥ 30 beats per minute in rest and oxygen saturation (SpO₂) of $\leq 92\%$, were enlisted in the

'severe' category. The 'critical' group, on the other hand, included those who had respiratory failure, sepsis, or shock, necessitating mechanical ventilation, as well as those who had multiple organ failures requiring ICU support. Here, acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition (Ranieri *et al.*, 2012), and shock was defined according to the Sepsis-3 criteria (Singer *et al.*, 2016).

2.5. rRT-PCR Test

Respiratory tract samples were used to do rRT-PCR to confirm whether the sample cases were positive for COVID-19 (Mannan *et al.*, 2021). Throat swabs, nasopharyngeal swabs, and bronchial aspirates were collected from the patients in a tube containing a viral transport medium, and all of them were shifted to the laboratories later. According to the World Health Organization's (WHO) guideline, the SARS-CoV-2 RNA extraction for COVID-19 was conducted in the Molecular Biology laboratory of the Microbiology department of Chittagong Medical College (Rudra *et al.*, 2021) and Chattagram Maa-Shishu O General Hospital.

2.6. Statistical analysis

IBM SPSS version-25 was used for data analysis and figure preparation. To check significant differences between categorical variables, Pearson's Chi-Square (χ^2) evaluation method was used. Categorical and continuous variables were tested for difference by applying Independent-Sample T-Test (95% confidence interval) and compared 'means' with 'standard deviations'. *P* values less than 0.05 were considered statistically significant, and in the case of categorical and continuous variable correlation, a *P* value of "Equal variance not assumed" was considered. Factors having significant differences when comparing with the outcome of the patients were further analyzed by Simple bivariate logistic regression and multiple bivariate logistic regression to find the correlating factors. The variables strongly correlated (value > 0.7) with other variables (determined by Pearson's Correlation Coefficient analysis) were omitted from the regression analysis. Then the significant factors were further analyzed (Simple bivariate logistic regression and multiple bivariate logistic regression) by dividing into two groups HFNC only, and HFNC + NRM treated concerning the outcome of the patients. Results were shown in crude odds ratio (COR), adjusted odds ratio (AOR), and their ranges at 95% confidence interval. Omnibus tests of model coefficients' *P* value less than 0.05 and 'Hosmer and Lemeshow Goodness of Fit' test's *P* value greater than 0.05 were considered significant to assess, if the regression model had been fit for the data. The specificity and sensitivity of the data were also tested during regression analysis.

3. Results

3.1. Relationships of Outcomes with Patient Demographics and Clinical biomarkers

In our study, 240 critically ill COVID patients treated with HFNC were included, and 47.5% (126) of them survived. The mortality rate among patients with less than 50 years (39.30%) was significantly ($P = 0.024$) lower than with ≥ 50 years (56.50%). Death among rural residents (54.20%) was higher than urban residents (51.10%). But the total number of cases was high in urban residents (Table 1). The death rate was higher among patients having a history of smoking (61.30%) than those who never smoked (49.70%). According to our study, 50 patients did not have any comorbidities and the mortality rate was significantly higher (55.80%) among comorbid patients. With *P* values of <0.001, the mean \pm SD of hospital stay (14.07 ± 7.91), and ICU stay (9.65 ± 5.64) in days was significantly higher among surviving patients (Table 1). A total of 133 patients received HFNC with NRM and the survival rate (59.4%) was more than those who were only on HFNC (32.2%) (Table 1).

Correlations between investigations and patients' outcomes have been shown in Table 1. Random blood sugar level was significantly related to the outcome ($P = 0.038$). The mortality rate was 58.6% among patients with increased blood sugar levels, while the rates among normal and impaired glucose tolerance blood sugar levels were below 50%. We witnessed another significant correlation between serum Creatinine levels ($P = 0.013$) and the death rate. The death rate among patients with elevated Creatinine (64.8%) was higher than normal ones (47.3%) (Table 1). D-dimer level among deceased patients (2.39 ± 2.90) was higher than survived patients (1.173 ± 1.45), and this relation was significant ($P = <0.001$). The mortality rate increased proportionally with the level (from 'no' to 'severe') of the systemic inflammatory response ($P = 0.006$). 93.8% of the patients with severe systemic inflammatory responses died, while 48.1% with no inflammatory responses expired in the ICU (Table 1).

3.2. Impact of Comorbidities and Clinical Features on Outcomes

Death and survival rates of patients with comorbidities are illustrated in Figure 1-A. Common comorbidities for HFNC treated patients were Hypertension (HTN) (60.4%), Diabetes Mellitus (DM) (56.7%), Ischemic Heart

Disease (IHD) (19.6%), Asthma (9.6%), Chronic Kidney Disease (CKD) (7.9%), and Chronic Obstructive Pulmonary Disease (6.3%). DM and HTN constituted more than 50% of the patients, and among them, 52.21% and 55.17% of patients died in the hospital. The survival rate was less than 40% for the patients with CKD and Asthma (Figure 1-A).

Relations between clinical features of HFNC treated COVID-19 induced AHRF patients and hospital outcome were also observed (Table 2). Having a cough was significantly related to the outcome of the patients ($P = 0.003$). A total of 220 patients suffered from fever, and 51.4% of them died. Besides, 162 patients had difficulties breathing, and 54.9% of them expired. Other symptoms were sore throat (9.17%), loss of smell (7.92%), diarrhea (7.08%), weakness (35.42%), and confusion (6.25%) (Table 2).

3.3. Changes in Oxygenation Status Observed Before and After Commencing HFNC

'On HFNC-SpO₂%' (93.11 ± 2.53) was significantly higher than 'Before HFNC- SpO₂%' (83.71 ± 6.61) for the patients that survived (Table 3). Average flow through the course of HFNC therapy was associated with the outcome of the patients ($P = <0.001$). The level of FiO₂% required after high flow nasal cannula insertion was lower for the surviving patients (69.82 ± 14.09). Besides, 'On HFNC-PaO₂' (mmHg) was significantly lower for the patients who died later (56.99 ± 13.89) ($P = <0.001$). Additionally, the P/F ratio of death cases (64.07 ± 17.47) was lower than survived ones (105.18 ± 35.09) ($P = <0.001$). In another relation, the rates of death among patients with diminished SpO₂% and PaO₂ after HFNC were more than 50% (Table 3).

3.4. Immediate Complications Observed during HFNC Therapy

Immediate complications of HFNC have been shown in Figure 1-B. The percentages of non-visible nasal bleeding and nasal obstruction (evidenced by the removal of clotted blood) were 40% and 31.67% of the total cases for the death and survived ones, respectively (Figure 1-B). A total of 30% of the patients faced discomfort (irritation and burning sensation in the nose) because of HFNC.

As per our finding, non-visible nasal bleeding and obstruction by clot were much more common than other HFNC complications. These led to more breathing difficulty for the patients. To protect nasal passage from drying out from high flow and prevent non-visible nose bleeds from culminating in partial/complete obstruction of nostrils, 'Liquid paraffin' and 'Normal saline' were used.

3.5. Common Medications Used in HFNC Treated Patients

We illustrated the post-admission medications administered in Figure 2. The frequently used medications were antibiotics (intravenous/oral), antiviral drugs (intravenous/oral), low molecular weight heparin (twice/once daily), and steroid (dexamethasone/methylprednisolone). According to our data, plasma therapy and interleukin-6 inhibitors were not common like other treatments along with HFNC in ICU for COVID-19 patients (Figure 2). About 55% of patients treated with IL-6 inhibitor died.

3.6. Factors affecting outcome of the patients

Two variables like duration of ICU stay and P/F ratio was removed from the analysis, because they were strongly correlated with other variables. Almost three times (2.9, 1.1-7.4) more of the patients who survived later in hospital/ICU due to COVID-29 related AHRF were given NRM too. Duration of hospital stay was slightly lower (1.1, 1.0-1.4) for the deceased patients (Table 4). Those who survived suffered less (0.1, 0.01-0.9) from severe systemic inflammatory response syndrome. The improvement of SpO₂ % was 1.2 times (1.0-1.5) better for the survived patients, and they required less (0.9, 0.87-0.94) FiO₂%. Another factor that was found significant with the outcome was On HFNC- PaO₂ and this factor showed more progression (1.1, 1.0-1.1) for survived patients more than the dead ones (Table 4).

3.7. Factors affecting HFNC ± NRM concerning outcome of the patients

As HFNC ± NRM was observed as one of the significant factors relating to the outcome of the patients, the effects of other factors on patients treated with HFNC only and HFNC + NRM were also analyzed in this study. Those who were managed with only HFNC and also survived were seen to improve their SpO₂ % almost two times (1.8, 1.3-2.6) more than the dead ones, and they needed less (0.9, 0.8-0.9) fraction of inspired oxygen (FiO₂%) through HFNC (Table 5).

Duration of hospital stay was more (1.1, 1.0-1.3) for the HFNC + NRM treated survived patients, and the HFNC + NRM treated expired patients needed more (0.9, 0.8-0.9) fraction of inspired oxygen (FiO₂%) through a nasal cannula (Table 5). Further studies with larger sample regarding dual therapy are needed.

Table 1. Baseline information and Investigations of COVID-19 patients treated with HFNC.

Demographic Variables	Categories	Total (n = 240)				χ^2 value	P value
		Dead (n=127)		Survived (n=113)			
		Count	Percentage (%)	Count	Percentage (%)		
Sex	Female	35	42.7%	47	57.3%	4.81	0.280
	Male	91	57.6%	67	42.4%		
Age (years)	Less than 50	22	39.3%	34	60.7%	5.12	0.024*
	50 and above	104	56.5%	80	43.5%		
Dwelling place	Rural	58	54.2%	49	45.8%	0.23	0.635
	Urban	68	51.1%	65	48.9%		
Smoking history	Current smoker	5	35.7%	9	64.3%	4.41	0.110
	Ex-smoker	46	61.3%	29	38.7%		
	Never	75	49.7%	76	50.3%		
Previous comorbidities	Present	106	55.8%	84	44.2%	3.96	0.047*
	Absent	20	40.0%	30	60.0%		
HFNC with/without NRM	Only HFNC	72	67.3%	35	32.7%	16.94	<0.001*
	HFNC+NRM	54	40.6%	79	59.4%		
Duration of hospital stay (days)	Mean \pm SD	8.87 \pm 6.29		14.07 \pm 7.91		$P < 0.001^*$	
Duration of ICU stay (days)	Mean \pm SD	7.17 \pm 5.11		9.65 \pm 5.64		$P < 0.001^*$	
Investigations							
Imaging & Radiology							
Chest X-ray	Unilateral consolidation	8	40.0%	12	60.0%	1.37	0.242
	Bilateral consolidation	118	53.6%	102	46.4%		
Biochemical Test							
WBC count	Decreased	3	75.0%	1	25.0%	1.08	0.582
	Normal	26	49.1%	27	50.9%		
	Increased	97	53.0%	86	47.0%		
Neutrophils	Normal	15	68.2%	7	31.8%	2.39	0.122
	Increased	111	50.9%	107	49.1%		
Lymphocytes	Decreased	111	51.2%	106	48.8%	1.65	0.199
	Normal	15	65.2%	8	34.8%		
RBS	Normal	21	48.8%	22	51.2%	6.52	0.038*
	Impaired glucose tolerance	20	38.5%	32	61.5%		
	Increased	85	58.6%	60	41.4%		
Serum Creatinine	Normal	80	47.3%	89	52.7%	6.11	0.013*

	Increased	46	64.8%	25	35.2%		
D - dimer	Mean \pm SD	2.39 \pm 2.90		1.173 \pm 1.45		$P = 0.001^*$	
S. Ferritin	Normal	12	57.1%	9	42.9%	0.20	0.656
	Increased	114	52.1%	105	47.9%		
Procalcitonin	No systemic inflammatory response	87	48.1%	94	51.9%	12.56	0.006*
	Minor systemic inflammatory response	12	54.5%	10	45.5%		
	Moderate systemic inflammatory response	12	57.1%	9	42.9%		
	Severe systemic inflammatory response	15	93.8%	1	6.3%		

Pearson's Chi-Square and Independent-Samples T-test methods are used. Row (%) is given which means percentages of the outcomes dependent on the variables' categories. P values marked with * are significant. WBC: White Blood cell, RBS: Random Blood Sugar, SD: Standard Deviation, HFNC: High Flow Nasal Cannula, NRM: Non-rebreather Mask

Table 2. Clinical features of the HFNC treated COVID-19 patients.

Clinical features	Total number (%)	Dead		Survived		χ^2 value	P value
		Count	Percentage (%)	Count	Percentage (%)		
Fever	220/240 (91.67%)	113	51.4%	107	48.6%	1.37	0.242
Cough	174/240 (72.5%)	81	46.6%	93	53.4%	8.98	0.003*
Sore Throat	22/240 (9.17%)	12	54.5%	10	45.5%	0.04	0.84
Loss of smell	19/220 (7.92%)	11	57.9%	8	42.1%	0.24	0.624
Shortness of breath	162/240 (67.5%)	89	54.9%	73	45.1%	1.19	0.276
Diarrhea	17/240 (7.08%)	8	47.1%	9	52.9%	0.22	0.641
Weakness	85/240 (35.42%)	39	45.9%	46	54.1%	2.31	0.128
Confusion	15/240 (6.25%)	9	60.0%	6	40.0%	0.36	0.548

Pearson's Chi-Square method is used. Row (%) is given which means percentages of the outcomes dependent on the variables' categories. P values marked with * are significant. HFNC: High Flow Nasal Cannula.

Table 3. Outcomes of HFNC given to ICU admitted COVID-19 patients.

Managements effects	Tests/Conditions	Dead		Survived		P value
Before starting HFNC- SpO ₂ %	Mean ± SD	80.60 ± 7.77		83.71 ± 6.61		0.001*
On HFNC- Average flow	Mean ± SD	61 ± 10.32		50.53 ± 10.05		<0.001*
After HFNC- SpO ₂ %	Mean ± SD	88.41 ± 5.02		93.11 ± 2.53		<0.001*
After HFNC- SpO ₂ % (count & %)	Decreased	120	58.8%	84	41.2%	<0.001*
	Normal	6	16.7%	30	83.3%	
On HFNC- FiO ₂ %	Mean ± SD	90.16 ± 9.03		69.82 ± 14.09		<0.001*
On HFNC- PaO ₂ (mmHg)	Mean ± SD	56.99 ± 13.89		70.18 ± 17.13		<0.001*
On HFNC- PaO ₂ (mmHg) (count & %)	Decreased	120	56.1%	94	43.9%	0.001*
	Normal	6	23.1%	20	76.9%	
P/F ratio (mmHg)	Mean ± SD	64.07 ± 17.47		105.18 ± 35.09		<0.001*

Pearson's Chi-Square and Independent-Samples T-test methods are used. Row (%) is used which means percentages of outcomes dependent on the variables' categories. P values marked with * are significant. SD: Standard Deviation, HFNC: High Flow Nasal Cannula, SpO₂: Percent Saturation of Oxygen, FiO₂: Fraction of Inspired Oxygen, PaO₂: Partial Pressure of Oxygen, ICU: Intensive Care Unit.

Table 4. Factors related to the outcome of the HFNC treated ICU patients.

Variables	COR with range (95% CI)	AOR with range (95% CI)
Age (years)		
Less than 50 (ref)	1.0	1.0
50 and above	0.5 (0.3-0.9)*	0.7 (0.2-2.4)
Symptoms		
Cough	2.5 (1.4-4.5)*	2.7 (1.0-7.3)
Previous comorbidities		
Absent (ref)	1.000	1.0
Present	1.9 (1.0-3.6)*	1.3 (0.3-4.8)
HFNC with/without NRM		
Only HFNC (ref)	1.0	1.000
HFNC+NRM	1.8 (1.1-2.9)*	2.9 (1.1-7.4)*
Duration of hospital stay (days)		
	1.1 (1.1-1.2)*	1.1 (1.0-1.4)*
Random blood sugar		
Normal (ref)	1.000	1.0
Impaired glucose tolerance (IGT)	1.5 (0.7-3.5)	2.5 (0.6-10.8)
Increased	0.7 (0.3-1.3)	2.0 (0.6-6.8)
Serum Creatinine		
Normal (ref)	1.0	1.0

Increased	0.5 (0.3-0.9)*	0.6 (0.2-1.5)
D – dimer	0.8 (0.7-0.9)*	0.9 (0.7-1.2)
Procalcitonin		
No systemic inflammatory response (ref)	1.0	1.0
Minor systemic inflammatory response	0.7 (0.3-1.9)	0.5 (0.1-2.3)
Moderate systemic inflammatory response	0.7 (0.3-1.7)	1.1 (0.2-6.3)
Severe systemic inflammatory response	0.1 (0.01-0.5)*	0.1 (0.01-0.9)*
Management effects (before and after)		
Before starting HFNC- SpO ₂ %	1.1 (1.0-1.1)*	1.0 (0.9-1.1)
On HFNC- Average flow	0.9 (0.9-0.9)*	1.0 (0.9-1.0)
After HFNC- SpO ₂ %	1.5 (1.4-1.8)*	1.2 (1.0-1.5)*
On HFNC- FiO ₂ %	0.9 (0.85-0.90)*	0.9 (0.87-0.94)*
On HFNC- PaO ₂ (mmHg)	1.1 (1.0-1.1)*	1.1 (1.0-1.1)*

Simple and Multiple Bivariate logistic regression were used and p-values less 0.05 (marked with * and are bold) are considered significant. COR: Crude Odds Ratio, AOR: Adjusted Odds Ratio, CI: Confidence Interval, HFNC: High Flow Nasal Cannula, NRM: Non-rebreather Mask, SpO₂: Percent Saturation of Oxygen, FiO₂: Fraction of Inspired Oxygen, PaO₂: Partial Pressure of Oxygen.

Table 5. Factors related to the outcome of the HFNC with/without NRM for severely ill COVID-19 patients.

Variables	HFNC only		HFNC + NRM	
	COR with range (95% CI)	AOR with range (95% CI)	COR with range (95% CI)	AOR with range (95% CI)
Duration of hospital stay (days)	1.1 (1.1-1.2)*	1.1 (1.0-1.2)	1.1 (1.0-1.2)*	1.1 (1.0-1.3)*
Procalcitonin				
No systemic inflammatory response (ref)	1.0	1.0	1.0	1.0
Minor systemic inflammatory response	0.9 (0.3-2.4)	1.1 (0.2-6.7)	1.0 (0.2-6.6)	0.4 (0.03-4.5)
Moderate systemic inflammatory response	0.5 (0.1-1.8)	0.9 (0.1-9.2)	1.7 (0.3-9.5)	1.7 (0.1-29.9)
Severe systemic inflammatory response	0.0 (0.0)	0.0 (0.0)	0.1 (0.01-0.6)*	0.1 (0.01-1.8)
Management effects				
After HFNC- SpO ₂ %	1.8 (1.5-2.2)*	1.8 (1.3-2.6)*	1.4 (1.2-1.6)*	1.1 (0.9 -1.4)
On HFNC- FiO ₂ %	0.9 (0.8-0.9)*	0.9 (0.8-0.9)*	0.9 (0.8-0.9)*	0.9 (0.8-0.9)*
On HFNC- PaO ₂ (mmHg)	1.1 (1.0-1.1)*	1.0 (1.0-1.1)	1.1 (1.1-1.2)*	1.0 (1.0-1.1)

Simple and Multiple Bivariate logistic regression were used and p-values less 0.05 (marked with * and are bold) are considered significant. COR: Crude Odds Ratio, AOR: Adjusted Odds Ratio, CI: Confidence Interval, HFNC: High Flow Nasal Cannula, NRM: Non-rebreather Mask, SpO₂: Percent Saturation of Oxygen, FiO₂: Fraction of Inspired Oxygen, PaO₂: Partial Pressure of Oxygen.

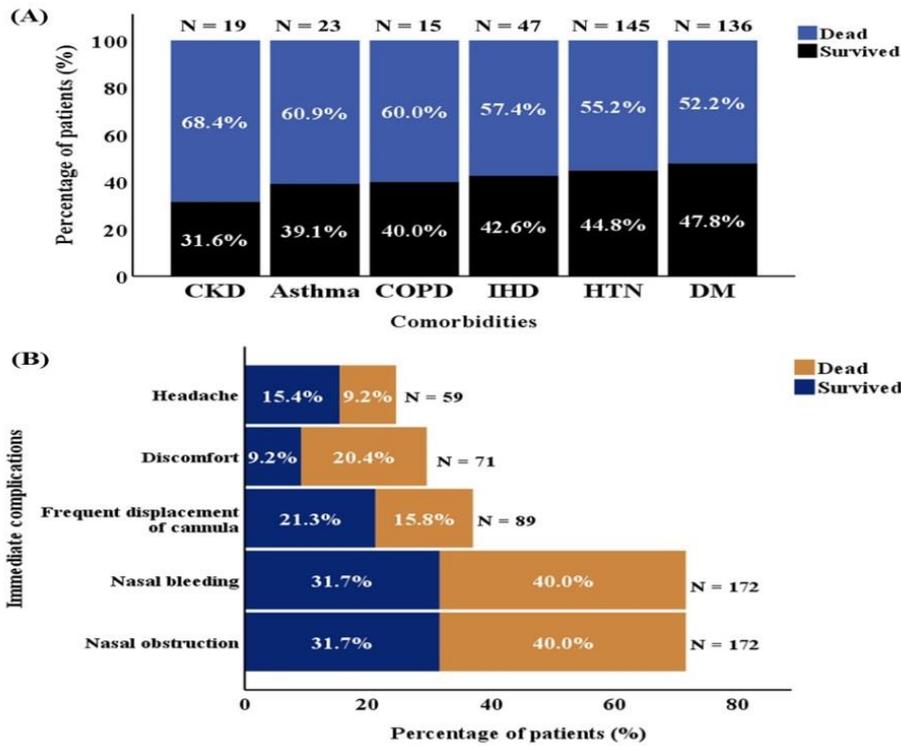


Figure 1. Comorbidities and immediate complications of HFNC treated patients. (A) Comorbidities of HFNC treated patients. X-axis and Y-axis imply comorbidities and percentage of patients, respectively. Blue and Black areas signify the rates of having the individual comorbidity for the death (before death) and survived cases, correspondingly. (B) Immediate complications of HFNC treated patients. . X-axis and Y-axis imply patients' percentages and immediate complications, respectively. Brown and Blue areas signify individual complication's rates for death (before death) and survived cases, correspondingly. N = Total cases having the particular comorbidity. CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, IHD: Ischemic Heart Disease, HTN: Hypertension, DM: Diabetes Mellitus, HFNC: High Flow Nasal Cannula.

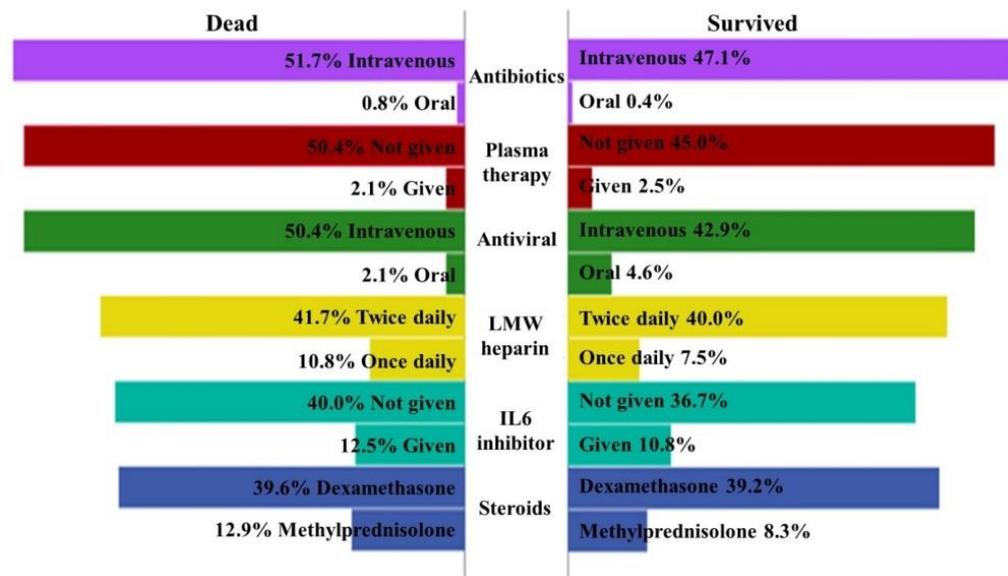


Figure 2. Medications for COVID-19 induced AHRF patients. Right and left side indicate medications of dead (before death) and survived cases, correspondingly. Different colors with two bars signify different medications and their sub-types. AHRF: Acute Hypoxemic Respiratory Failure, LMW heparin: Low Molecular Weight Heparin, IL6 inhibitor: Interleukin 6 inhibitor.

4. Discussion

Symptomatic treatment protocols not being sufficient for ICU admitted COVID-19 patients had become a worldwide phenomenon for restoring their health (Demoule *et al.*, 2020). Aligning to a previous study that recommends the use of HFNC for lessening invasive/mechanical ventilation use, our study found that HFNC substantially helped reduce mortality rates in cases having COVID-19 induced AHRF; by maintaining optimal oxygen saturation (Matthay *et al.*, 2020). Heated and humidified oxygen (at high flow) was administered through high flow nasal cannula to 240 ICU admitted COVID-19 patients, and 47.5% of severely/critically ill AHRF patients' lives were saved by using HFNC who failed to maintain oxygenation by 15 L/min oxygen.

We also found that in this study population of critically ill COVID-19 cases, the instance of fever and cough was higher as compared to similar populations of COVID-19 induced AHRF patients reported in a previous study (Saha *et al.*, 2021). However, in that study, a higher instance of breathing difficulty was found in patients. Mortality was very high in patients with elevated body temperature in this study, which corresponds to the observations by Saha *et al.* (Saha *et al.*, 2021) Patients feeling severe weakness were also typical in our study. But sore throat, diarrhea, and anosmia were rarely experienced by patients.

Previous studies have stated that comorbidities like HTN and DM can make the patients more vulnerable to COVID-19 (Akter *et al.*, 2020; Rudra *et al.*, 2021). In a study in the southern region of Bangladesh, the death rate of diabetic patients was 60.2%, which was 1.2 times higher than our study (Saha *et al.*, 2021). Though the mortality percentage of hypertensive COVID-19 patients was almost equal to another study of Bangladesh, IHD patients died at about 1.5 times the higher frequency in their study (Saha *et al.*, 2021). Leonardo Antonicelli *et al.* found out that Asthma seems to play a minimal role in clinical severity for COVID-19 patients, which contradicts our finding (Antonicelli *et al.*, 2021). The mortality percentages for patients with CKD, Asthma, and COPD were very high in our study. Further studies are obligatory for the proper management of COVID-19 patients with these diseases.

Additionally, the death rate of the COVID-19 affected was very high among patients with high RBS, serum Creatinine, and Procalcitonin levels. Another significant finding of this study was a number of patients with high RBS being more likely to die than those with standard RBS. The mortality rate substantially increased with the rise of the Procalcitonin levels, and almost 94% of patients with severe systemic inflammatory responses died which is significantly affected the death rate of the patients. The death rate of patients with elevated D-dimer was high in a study in Bangladesh, and our finding was D-dimer of the in-hospital death cases being double from those of survived patients (Saha *et al.*, 2021). High levels of RBS, Creatinine, Procalcitonin and D-dimer could be denominators to HFNC treated COVID-19 patients' mortality.

After HFNC only, the SpO₂% for survived patients increased about two times more than those who died later in our study. Patients' death with decreased SpO₂% in a study was higher than ours, which indicates the benefit of using HFNC (Saha *et al.*, 2021). On HFNC, oxygen saturation among both dead (died later) and surviving patients increased compared to before starting-HFNC. But the SpO₂% progression was comparatively better among patients who survived post COVID-19 treatment. Though the P/F ratio was more than 1.5 times higher for the surviving patients, the level of P/F ratio was below the standard level for both deaths and survived cases. Moreover, NRM was tested when only HFNC failed to meet the oxygen saturation to the target level. We found that the survival rate increased after providing both HFNC and NRM. HFNC with NRM also increased the SpO₂% and PaO₂ of the patients more than those with only HFNC administration. Survived patients needed less fraction of inspired oxygen for both HFNC only and HFNC + NRM treatment which proved their better condition than the others.

Convalescent plasma therapy is an effective treatment for COVID patients within the first week of the onset of the symptoms (Kesici *et al.*, 2020). But in this study, the plasma exchange was a rare treatment protocol, and it did not affect the mortality of the patient it was administered upon. The survival rate after using dexamethasone was greater than methylprednisolone usage. A similar result on the administration of these drugs was found by Heidi Ledford (Ledford, 2020). A total of 55.4% of the patients who got IL-6 inhibitors (Tocilizumab) (N = 56) died. But it has become a very commonly used medication in our country. A recent RCT (recovery trial) found that tocilizumab improved survival and other clinical outcomes in hospitalized Covid-19 patients with hypoxia and systemic inflammation (RECOVERY Collaborative Group, 2021). It was done in a high resource setup, but further research is needed in the context of lower income countries. Additional study is also required to prevent complications like partial or complete obstruction of the nasal passage due to mucosal injury caused by high flow jet of air.

Further insights and comparison could be made on the contribution of HFNC in surviving a patient if the effects of other modes of ventilation (e.g. CPAP or MV) could have been observed. We observed that locally practiced preventive measures to protect against high flow induced nasal mucosal injury were not sufficient in some

cases. Though concomitant use of NRM seems to work, it is not an established practice. The duration of the study was short. Lastly, although our results were significant, larger sample size is needed for more accurate correlations.

5. Conclusions

According to the findings of our study, HFNC is indeed an effective mode of delivering supplemental oxygen and improving SpO₂% to critically affected COVID-19 AHRF patients. About half of the patients' lives could have been saved as observed in this study. However, comorbidity and the levels of some specific biomarkers were found to be major caveats in controlling the progression of the disease, even after HFNC administration. It was also observed that NRM concomitant with HFNC improves survival rate in patients. To corroborate the usage of HFNC + NRM and reduce the complications of HFNC for COVID-19 affected AHRF patients, studies with larger samples are needed.

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Conflict of interest

None to declare.

Authors' contribution

Moumita Das: Conceptualization, Supervision; Shuva Das: Formal analysis, Methodology, Writing - original draft; AFM T. Bhuiyan: Conceptualization, Funding acquisition; Sudipta Deb Nath: Formal analysis, Software, Writing - original draft; Rajdeep Biswas: Conceptualization, Project administration; Jitu D. Gupta: Data curation, Software; Anjan Ball: Data curation, Investigation; Mohammad J. Alam: Data curation, Validation, Visualization; Md. H. Karim: Data curation, Funding acquisition; Ranjan K. Nath: Validation, Visualization, Writing - review & editing; Ayan Saha: Software, Writing - original draft, Writing - review & editing.

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