CLINICAL OBSERVATION OF HFNC USE ALONG WITH NON-REBREATHER MASK ON CRITICAL COVID-19 DIABETIC PATIENTS

Bioresearch Communications
Volume 9, Issue 2, July 2023

DOI:
doi.org/10.3329/brc.v9i2.67080

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ABSTRACT

Purpose: This study aimed to observe and compare the efficacy of High-flow Nasal Cannula (HFNC) with/without a non-rebreather mask (NRM) on ICU-admitted COVID-19 diabetic patients. **Methodology:** We collected epidemiological, biochemical, and clinical information from patients (diabetic = 136; non-diabetic = 104) admitted into four hospitals in Chattogram, Bangladesh. SPSS v25 was used to analyze the data with the Chi-Square, Fisher's Exact, and Independent Samples T-test. We also built regression models to find out the impact of the variables. **Results:** Most of the patients with fever (59.1%) and hypertension (68.3%) had diabetes. We also noticed diabetic patients stayed in ICU longer (9.06±5.70) than non-diabetic patients (7.41±5.11). Moreover, elevated creatinine level was found in most diabetic cases (70.4%). After only HFNC administration, the partial pressure of oxygen significantly improved in non-diabetic patients. However, both diabetic and non-diabetic patients were observed to have an almost equal partial pressure of oxygen after HFNC with NRM management. Patients with elevated blood sugar additionally needed NRM more than fivefold compared to those with normal blood sugar levels. Besides, age and hypertension were significantly associated with HFNC+NRM-treated diabetic patients. **Future Implications:** The results of this study imply that oxygen supply with HFNC and NRM may be beneficial for elderly/hypertensive diabetic patients with COVID-19-associated AHRF; and that increased blood glucose level could be a determinant for the need for HFNC + NRM treatment.

KEYWORDS: HFNC; NRM; ICU; Diabetes; COVID-19.

RECEIVED: 12 February 2023, ACCEPTED: 16 May 2023

TYPE: Original Research

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Introduction

COVID-19 is induced by a newer variant of the SARS-CoV-2 virus which majorly affects the respiratory tract (Jin *et al.*, 2020). The breakout of the then novel virus was detected in Wuhan, China by the end of December 2019 and in a very short span of time, the SARS-CoV-2 being highly contagious was able to rapidly spread between populations. Fast global spread of this disease and its severe clinical outcomes prompted the World Health Organization to proclaim it a pandemic on March 11, 2020 (Alkundi *et al.*, 2020; Hussain, Bhowmik and do Vale Moreira, 2020).

During the outbreak, case-control studies on COVID-19 found that comorbid conditions like diabetes mellitus might predict COVID-19 advancement in patient (Alkundi *et al.*, 2020). Although the evidence is limited, recent research has suggested that diabetes and high blood sugar levels can operate as predictor variables in COVID-19-related disease burden; firstly, as because diabetic patients have a weakened immune system, they take longer to recover from viral infections, and secondly, since the virus may survive in a high-glucose condition. These denominators put people with diabetes in a susceptible position in terms of COVID-19 fatalities (Fadini *et al.*, 2020; Guo *et al.*, 2020; Muniyappa and Gubbi, 2020). Furthermore, several COVID-19 related long-term sequelae have been reported in current research, necessitating comprehensive inquiry and evaluation to confirm the evidence in depth (Carfì, Bernabei and Landi, 2020; Jiang and McCoy, 2020).

Bangladesh ranks eighth among the world's most populous countries, with almost 161 million people (UNDP, 2019). Diabetes, among other chronic disease states, seems to be on the upswing in Bangladesh at a rapid pace, with 8.4 million instances in adults, according to data from the International

Diabetes Federation (IDF) (Saeedi *et al.*, 2019). A number of studies reported strong correlation between diabetes and COVID-19 (Akter *et al.*, 2020; Saha *et al.*, 2021).
The high number of severe and critical COVID-19 cases has imposed an unprecedented strain on the healthcare system, emphasizing the need for rapid and effective COVID-19 treatment with complication management. Several investigations have found that a severe or critical progression of COVID-19 causes acute hypoxemic respiratory failure (AHRF), which necessitates a high fractional concentration of inspired oxygen (FiO_2) and noninvasive ventilation (NIV) techniques such as a face mask, a non-rebreather mask (NRM) etc (Antonelli *et al.*, 1998; Delclaux *et al.*, 2000; Hilbert *et al.*, 2000; Carrillo *et al.*, 2012). On the other hand, HFNC tends to be more successful as it can reach upto 100% humidification at 37°C and has a positive end-expiratory pressure (PEEP) effect while patients breathe with the mouth closed (Sztrymf *et al.*, 2011; Masclans and Roca, 2012).
The relation between COVID-19 and diabetes, as well as the condition's long-term effects on people, is still being researched and investigated. This study focuses on seeing how HFNC with NRM compares to mechanical ventilation (MV) in diabetic COVID-19 patients hospitalized in different ICUs in Bangladesh. Our goal was to shed light on this technique's usefulness in severe or critical instances where MV facilities are limited. The findings of this study can assist specialist doctors and the whole healthcare system of our country in expanding the range of treatment options available to individuals suffering from life-threatening COVID-19 consequences.

Materials and Methods

Study design and sites

This cross-sectional observational research was carried out in four hospitals: the 250 bedded Chattogram General Hospital, Chittagong Medical College Hospital, Chattagram Maa-Shishu O General Hospital, and Parkview Hospital. These hospitals have dedicated general as well as intensive care units for the treatment and management of COVID-19 patients. The study took place between April 15, 2021, and June 14, 2021.

rRT-PCR test

Throat swabs, nasopharyngeal swabs, and bronchial aspirates were obtained from patients and placed in a collection tube with a viral transport medium before being sent to the research laboratories. The SARS-CoV-2 RNA extraction for COVID-19 was carried out in the Molecular Biology laboratory of the Microbiology department of Chittagong Medical College in accordance with WHO guidelines (Rudra *et al.*, 2021).

Sample size calculation

We used Cochran's formula to determine our sample size (Cochran, 1963). The formula is as below:

$$n_0 = \frac{Z^2 p(1-p)}{e^2}$$
= 384.16

$$n = \frac{n_0}{1 + \frac{n_0 - 1}{N}}$$
= 383.95

Where, N = Number of COVID-19 cases (711,779) (Worldometer, 2021), p = estimated proportion of population (0.5), e = margin of error (5%= 0.05), z = z-score (95%- 1.96), n_0 = estimated sample size, n = corrected sample size
The calculated sample size is 384 for all COVID-19 patients. But our target population was the cirtical and severe cases. So, within the short period and with limited logistic resources, we collected 240 data for this study.

Inclusion and exclusion criteria

COVID-19 subjects with 6.5% HbA1c content and recently demonstrated any validated biochemical examination of diabetes mellitus were included in the diabetes cohort. Uncontrolled hyperglycemia was classified into two or more blood glucose level examinations that yielded a result more than 11.1 mmol/l, regardless of blood sugar levels.
Patients having dyspnea (respiratory rate of ≥ 30 beats per minute in rest and sustained SpO2 less than 90% after receiving 15 liters per minute of oxygen) were deemed candidates for HFNC. Besides, those who failed to maintain desired oxygen saturation (SpO2 >90%) after high flow were also given a face mask containing NRM and HFNC and were enlisted in the 'severe' category. So patients (diabetic or non-diabetic) with a requirement of HFNC with or without NRM were deemed candidates. Those with respiratory failure, sepsis, or shock, which necessitated MV, and those with multiple organ failures requiring ICU support, were placed in the 'critical' category. The exclusion criteria included the patients who required MV or NIV from the start of their ICU stay and refused to participate. The Berlin definition was used to specify acute respiratory distress syndrome (ARDS), and the Sepsis-3 criteria were utilized to define shock (Ranieri *et al.*, 2012; Singer *et al.*, 2016).

Data collection

As the primary sources of data, a pertinent questionnaire and medical history were used. The cases' epidemiological and demographic data were obtained by assigned investigators from the patients' treatment records and interviews with the accompanying personnel. All retrospective data gathered via telephone interviews were manually entered into an online format. All data entered on the questionnaire that matched the participants' responses were double-checked before being posted and the recordings were stored. 250 Bedded Chattogram General Hospital's Institutional Review Board approved this research and its protocol (Approval No.: 1724).

Statistical analysis

To check possible correlations between categorical variables, Pearson's Chi-Square ($\chi 2$) (where <20% of cells had expected count less than 5) and Fisher's Exact (where ≥20% of cells had expected count less than 5) evaluation methods were used. Categorical and continuous variables were tested for associations by applying Independent-Samples T-Test (95% confidence interval) and 'means' with 'standard deviations' were compared. *P* values less than 0.05 were considered statistically significant. *P* value of "Equal variance not assumed" was considered in case of categorical and continuous variable correlation. Factors that had significant differences when correlating with diabetic/non-diabetic group were further analyzed by dividing into two groups HFNC only and HFNC + NRM treated patients. Then the statistically significant factors were analyzed against HFNC only and HFNC + NRM by Simple bivariate logistic regression and multiple bivariate logistic regression to find the significant factors, crude odds ratio (COR), adjusted odds ratio (AOR), and their ranges at 95% confidence interval. Omnibus tests of model coefficients' *P values* less than 0.05 and Hosmer and Lemeshow Goodness of Fit test's *P values* greater than 0.05 were considered significant to test if the regression model had been fit for the data. Specificity and sensitivity of the data were also tested during regression analysis. All data analysis tests were performed in IBM SPSS version-25.

Results

Basic socio-demographic characteristics and Investigation result of the patients

Table 1 illustrates the basic demographic characteristics of HFNC treated patients. We found that the prevalence of diabetes among female patients (64.6%), those ≥ 50 years of age (64.1%), urban residents (57.9%), previously smokers (56.0%), and those who never smoked (57.6%) within the study sample (***Table 1***). Age was significantly related to diabetes mellitus (p< 0.001). In this data, 20.8% (50/240) patients did not have any comorbidities (p< 0.001). Among the hypertensive and IHD patients, 31.7% and 29.8% were non diabetic, respectively (p< 0.001 & p= 0.037) (***Table 1***). Persistence of fever had a significant association with diabetes mellitus (p= 0.012), and 59.1% of the feverish patients had diabetes. Other than fever, cough (72.5%; 174/240) and breathlessness (67.5%; 162/240) were common symptoms. Among 240 patients who comprised the study sample, 47.1% (113) patients were given HFNC and NRM oxygenation simultaneously, and 52.9% (127) patients were treated with HFNC only (***Table 1***). Among the 126 patients who died during the study period, 56.3% were diabetic. For diabetic cases, the duration (in days) between the first onset of COVID-19 associated symptoms and death was higher (17.48 ± 7.15) (p= 0.006). Additionally, for diabetic patients the stay in the ICU was longer (9.06 ± 5.70) as compared to the non-diabetic patients (7.41 ± 5.11) (p= 0.020) (***Table 1***). Data obtained from each patient's investigation report has been included in ***Table 1***. Random blood sugar (RBS) and serum creatinine levels were significantly related to diabetes mellitus (p= 0.039 & p= 0.005). Amongst those with high creatinine level, 70.4% were diabetic, and 29.6% were non-diabetic (***Table 1***).

Table 1. Basic Demographic Characteristics and Investigations of patients treated with HFNC.

Categories (Total N = 240)	Non-diabetic		Diabetic		χ2	p-value
	Count	Percentage (%)	Count	Percentage (%)	value	
Sex					3.22	0.073
Female (82/240)	29	35.40%	53	64.60%		
Male (158/240)	75	47.50%	83	52.50%		
Age (years)					17.89	<0.001*
Less than 50 (56/240)	38	67.90%	18	32.10%		
50 and above (184/240)	66	35.90%	118	64.10%		
Residence					0.18	0.669
Rural (107/240)	48	44.90%	59	55.10%		
Urban (133/240)	56	42.10%	77	57.90%		
Smoking history					0.32	0.851
Current smoker (14/240)	7	50.00%	7	50.00%		
Ex-smoker (75/240)	33	44.00%	42	56.00%		
Never (151/240)	64	42.40%	87	57.60%		
Comorbidity history						
No comorbidities (50/240)	50	100.00%	0	0.00%	82.59	<0.001*
Hypertension (145/240)	46	31.70%	99	68.30%	20.11	<0.001*
Ischemic heart disease (47/240)	14	29.80%	33	70.20%	4.37	0.037*
Asthma (23/240)	8	34.80%	15	65.20%	0.76	0.384

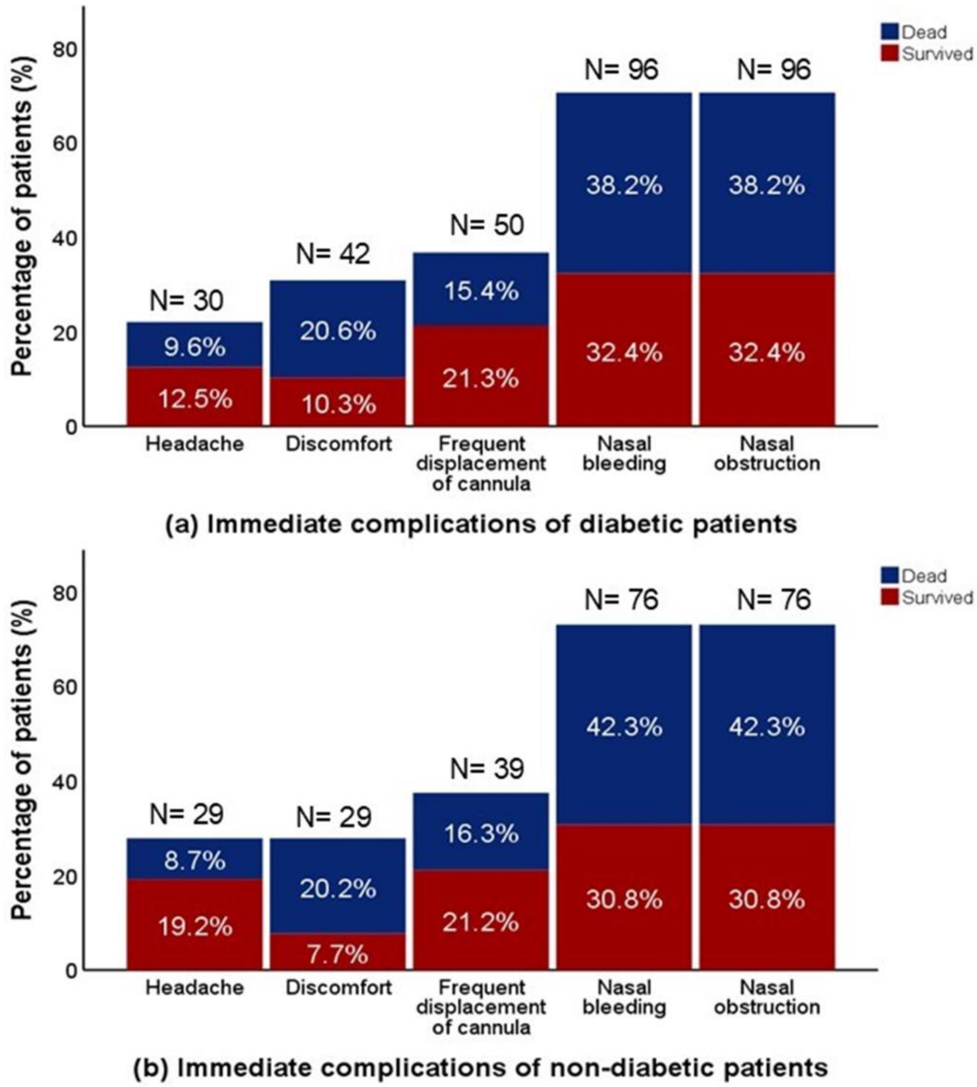
Chronic obstructive pulmonary disease (15/240)	5	33.30%	10	66.70%	0.65	0.42
Chronic kidney disease (19/240)	8	42.10%	11	57.90%	0.01	0.91
History of clinical symptoms						
No symptoms (8/240)	5	62.50%	3	37.50%	1.24	0.298
Fever (220/240)	90	40.90%	130	59.10%	6.32	0.012*
Cough (174/240)	75	43.10%	99	56.90%	0.01	0.907
Sore throat (22/240)	7	31.80%	15	68.20%	1.31	0.253
Anosmia (19/240)	8	42.10%	11	57.90%	0.01	0.91
Shortness of breath (162/240)	71	43.80%	91	56.20%	0.05	0.824
Diarrhea (17/240)	8	47.10%	9	52.90%	0.1	0.748
Weakness (85/240)	35	41.20%	50	58.80%	0.25	0.618
Confusion (15/240)	6	40.00%	9	60.00%	0.07	0.788
HFNC concomitant with/without NRM					0.26	0.608
Only HFNC (127/240)	57	44.90%	70	55.10%		
HFNC + NRM (113/240)	47	41.60%	66	58.40%		
Hospital outcome					0.011	0.917
Dead (126/240)	55	43.70%	71	56.30%		
Survived (114/240)	49	43.00%	65	57.00%		
Time from symptoms onset to hospitalization (days)	8.11 ± 4.93		7.40 ± 4.07		p= 0.241	
Time from symptoms onset to ICU admission (days)	8.37 ± 4.76		8.29 ± 4.36		p= 0.896	
Time from symptoms onset to start of HFNC (days)	8.17 ± 4.30		8.35 ± 4.24		p= 0.747	
Time from start of HFNC to weaning (days) (for survived patients)	7.82 ± 4.73		7.80 ± 4.58		p= 0.985	
Time from symptoms onset to death (days) (for dead patients)	13.40 ± 8.77		17.48 ± 7.15		p= 0.006*	
Hospital Stay (days)	10.50 ± 7.88		11.99 ± 7.25		p= 0.136	
ICU stay (days)	7.41 ± 5.11		9.06 ± 5.70		p= 0.020*	
Investigations						
Imaging & Radiology						
Chest X-ray					0.1	0.753
Unilateral consolidation	8	40.00%	12	60.00%		
Bilateral consolidation	96	43.60%	124	56.40%		
Biochemical Test						
WBC count					1.02	0.6
Decreased	2	50.00%	2	50.00%		
Normal	26	49.10%	27	50.90%		
Increased	76	41.50%	107	58.50%		

Neutrophils						
Normal	11	50.00%	11	50.00%	0.44	0.508
Increased	93	42.70%	125	57.30%		
Lymphocytes						
Decreased	94	43.30%	123	56.70%	0	0.988
Normal	10	43.50%	13	56.50%		
Random blood sugar (RBS)						
Normal	25	58.10%	18	41.90%	6.51	0.039*
Impaired glucose tolerance	25	48.10%	27	51.90%		
Increased	54	37.20%	91	62.80%		
Serum creatinine						
Normal	83	49.10%	86	50.90%	7.77	0.005*
Increased	21	29.60%	50	70.40%		
D-dimer						
Normal	17	45.90%	20	54.10%	0.12	0.727
Increased	87	42.90%	116	57.10%		
Serum Ferritin						
Normal	11	52.40%	10	47.60%	0.77	0.381
Increased	93	42.50%	126	57.50%		
Procalcitonin						
No systemic inflammatory response	80	44.20%	101	55.80%	2.32	0.509
Minor systemic inflammatory response	11	50.00%	11	50.00%		
Moderate systemic inflammatory response	6	28.60%	15	71.40%		
Severe systemic inflammatory response	7	43.80%	9	56.30%		

*Chi-Square Test, Fisher's Exact test, and Independent-Samples T-Test were used. N= total number of patients. Row percentages were used, and significant P-values are marked with *. (HFNC= High Flow Nasal Cannula, NRM= Face mask with Non-rebreather Reservoir Bag, ICU= Intensive Care Unit, IHD= Ischemic Heart Disease, WBC= White Blood Cells)*

Immediate complications of the patients

Supplementary Figure 1 (a) and (b) representing the complications of HFNC, show that non-visible nasal bleeding followed by nasal obstruction by clotted blood was the most observable complication. We found that in the study sample, non-diabetic patients (76/104; 73.1%) suffered from HFNC complications more than diabetic patients (96/136; 70.6%) (***Supplementary Figure 1***). In this study, 38.2% of the diabetic patients and 42.3% of the non-diabetic patients had the aforementioned complications before their death. Other complications of HFNC were headache (59/240; 24.6%), discomfort (71/240; 29.6%), and frequent displacement of the nasal cannula (89/240; 37.1%) (***Supplementary Figure 1***). In addition, complaints relating to the irritation in the nostrils were also reported by the patients, which is considered as an indication of discomfort in the current survey.



Supplementary Figure 1. Immediate complications of (a) diabetic and (b) non-diabetic patients, accordingly. X and Y axis indicate different complications and % of patients, respectively. Blue and red shades individually signify death and survival rates of the patients having faced the particular complication. N= total number of patients suffered from the specific complication.

Impact of HFNC and other treatments

The impact of HFNC and NRM on ICU admitted COVID-19 induced AHRF patients is illustrated in ***Table 2***. The partial pressure of oxygen (mmHg) after the administration of HFNC (only) was significantly ($p= 0.031$) higher for the non-diabetic patients (69.30 ± 23.56) than those with diabetes (61.50 ± 14.49) (***Table 2***).

Table 2. Impact of HFNC (with/without NRM) for ICU admitted COVID-19 patients.

Managements	**Non-diabetic (Mean ± SD)**	**Diabetic (Mean ± SD)**	**p-value**
Before starting HFNC- SpO_2%	82.47 ± 8.11	81.78 ± 6.78	0.484
On HFNC- average flow			
Only HFNC	57.98 ± 10.22	56.93 ± 12.32	0.599
HFNC + NRM	56.30 ± 11.02	53.18 ± 11.46	0.149
After HFNC- SpO_2 %			
Only HFNC	90.53 ± 6.03	91.07 ± 3.30	0.542
HFNC + NRM	89.98 ± 5.16	90.77 ± 4.21	0.387
On HFNC- FiO_2%			
Only HFNC	81.39 ± 15.66	80.93 ± 15.53	0.870
HFNC + NRM	80.13 ± 16.51	79.53 ± 14.85	0.844
On HFNC- PaO_2 (mmHg)			

Only HFNC	69.30 ± 23.56	61.50 ± 14.49	0.031*
HFNC + NRM	59.40 ± 13.22	62.64 ± 13.05	0.201
P/F ratio (mmHg)			
Only HFNC	90.73 ± 42.94	81.08 ± 32.95	0.166
HFNC + NRM	79.86 ± 32.30	82.76 ± 27.22	0.617

*Independent-Samples T-Test were used. Significant P-values are marked with *. (HFNC= High Flow Nasal Cannula, NRM= Face mask with Non-rebreather Reservoir Bag, ICU= Intensive Care Unit, AHRF= Acute Hypoxemic Respiratory Failure, SpO_2= Percent Saturation of Oxygen, FiO_2= Fraction of Inspired Oxygen, PaO_2= Partial Pressure of Oxygen, SD= Standard Deviation)*

Table 3 describes the impact of HFNC (with/without NRM) on diabetic and non-diabetic patients with COVID-19-induced AHRF. Among the patients who were treated with both HFNC and NRM, the prevalence of AHRF was higher for those aged ≥ 50 years with diabetes (67.4%) (p< 0.001). Elderly diabetic patients needed HFNC concomitant with NRM (***Table 3***). Most of the patients without any comorbidity (62.0%; 31/50) were managed with HFNC only (p< 0.001). Higher proportions of diabetic patients having hypertension had to be treated with HFNC combined with NRM (66.7%) than the non-diabetic hypertensive cases (***Table 3***). More than half (58.4%) of the patients treated with only HFNC had diabetes and elevated body temperature (p= 0.034). Besides, most of the patients who needed both HFNC and NRM had raised RBS (73.8%; p= 0.001) and creatinine levels (75.7%; p= 0.009) (***Table 3***).

Table 3. Impact of HFNC (with/without NRM) for ICU admitted COVID-19 (Diabetic/non-diabetic) patients.

Variables	Only HFNC				HFNC + NRM			
	Non-diabetic		Diabetic		Non-diabetic		Diabetic	
	Count	Percent (%)	Count	Percent (%)	Count	Percent (%)	Count	Percent (%)
Age (years)	p= 0.035*				p< 0.001*			
Less than 50	21	60.0%	14	40.0%	17	81.0%	4	19.0%
50 and above	36	39.1%	56	60.9%	30	32.6%	62	67.4%
	p< 0.001*				p< 0.001*			
No comorbidities	31	100.0%	0	0.0%	19	100.0%	0	0.0%
	p< 0.001*				p= 0.008*			
Hypertension	20	29.9%	47	70.1%	26	33.3%	52	66.7%
	p= 0.068				p= 0.270			
Ischemic heart disease	6	27.3%	16	72.7%	8	32.0%	17	68.0%
	p= 0.034*				p= 0.200			
Fever	47	41.6%	66	58.4%	43	40.2%	64	59.8%
Random blood sugar (RBS)	p= 0.206				p= 0.001*			
Normal	14	53.8%	12	46.2%	11	64.7%	6	35.3%
Impaired glucose tolerance	6	28.6%	15	71.4%	19	61.3%	12	38.7%
Increased	37	46.3%	43	53.8%	17	26.2%	48	73.8%
Serum creatinine	p= 0.189				p= 0.009*			
Normal	45	48.4%	48	51.6%	38	50.0%	38	50.0%
Increased	12	35.3%	22	64.7%	9	24.3%	28	75.7%
	p= 0.065				p= 0.035*			
Time from symptoms onset to death (days) (for dead patients)	13.45 ± 10.81		17.64 ± 7.06		13.33 ± 5.30		17.22 ± 7.42	
	p= 0.139				p= 0.070			
ICU stay (days)	7.63 ± 5.09		9.06 ± 5.57		7.15 ± 5.18		9.06 ± 5.87	

*Chi-Square Test, Fisher's Exact Test, and Independent-Samples T-Test were used. Row percentages were used, and significant P-values are marked with *. (HFNC= High Flow Nasal Cannula, NRM= Face mask with Non-rebreather Reservoir Bag, ICU= Intensive Care Unit, IHD= Ischemic Heart Disease, AHRF= Acute Hypoxemic Respiratory Failure, RBS= Random Blood Sugar)*

Figure 1 (a) and (b) show the treatment protocols alongside HFNC (with/without NRM) for the diabetic and non-diabetic patients, respectively. The protocol included antivirals, antibiotics, steroids, low molecular weight heparin, interleukin-6 inhibitor (Tocilizumab), and convalescent plasma therapy (***Figure 1***). Among patients with diabetes, the survival ratio after only HFNC was higher for those who were given oral (100.0%) antiviral drugs than those administered in intravenous (IV) (35.3%) form. But the response rate of IV antivirals (58.7%) increased when NRM was also used for treating them. On the contrary, the survival rate was high after using IV antivirals beside HFNC concomitant with (50.0%)/without (75.0%) NRM amongst the patients not having diabetes (***Figure 1***). The response rate of IV antibiotics to survival/death was not significantly different after HFNC administration with/without NRM for patients not/having diabetes. When plasma therapy was given with both HFNC and NRM, the survival rate was significantly high among non-diabetic patients with COVID-19 induced AHRF (100.0%). Another observation was a high survival rate among the diabetic patients after giving dexamethasone with HFNC + NRM (62.7%) (***Figure 1***). The majority of non-diabetic patients (62.5%) having administered both HFNC and NRM survived when they got tocilizumab treatment. Though the survival percentages among non-diabetic patients after HFNC (with/without NRM) and heparin were almost similar, a twice-daily dose of heparin with HFNC + NRM could save 63.6% of the diabetic patients (***Figure 1***).

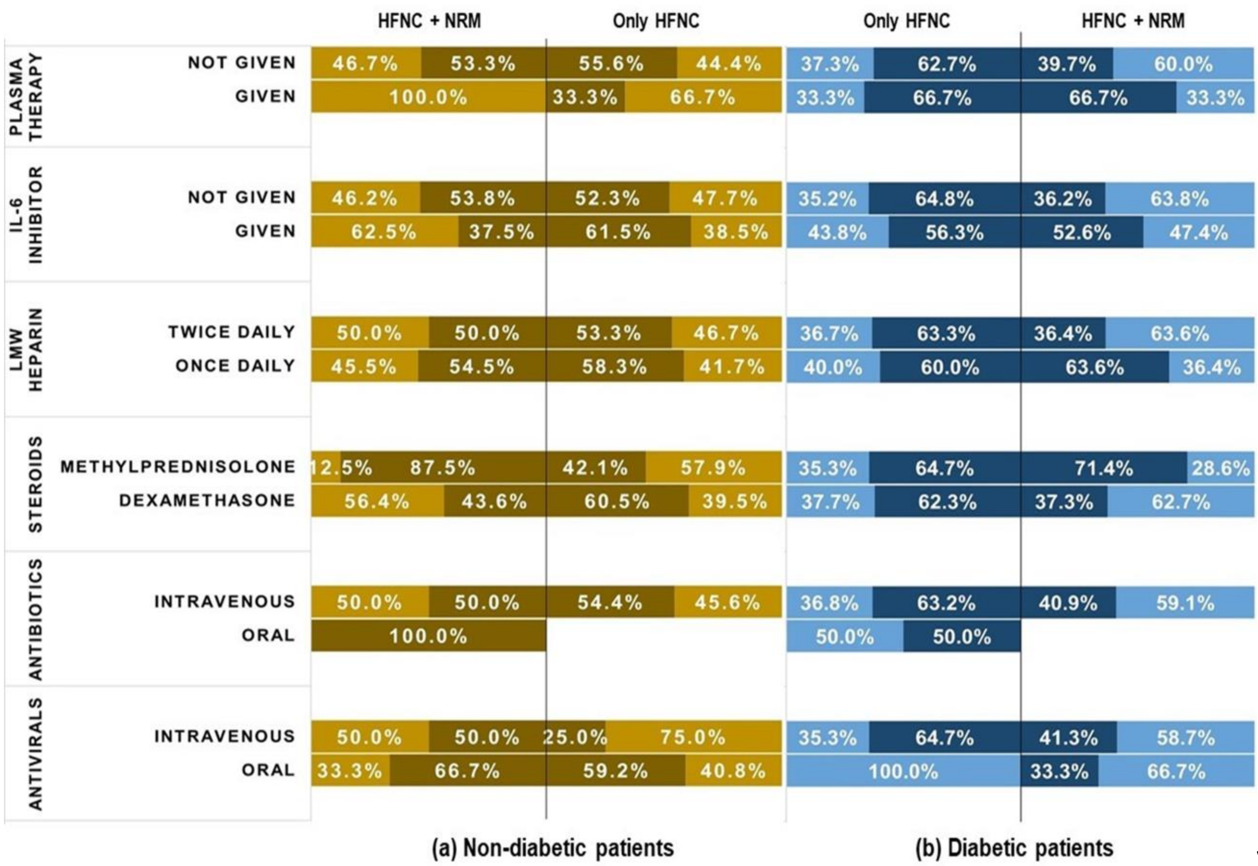


Figure 1. Brown (a) and blue (b) represent the treatments for non-diabetic and diabetic patients, respectively. Light and dark shades of (a) and (b) indicate survival and death rate after the treatments. One side of the black divider of each color denotes the percentage of patients treated with HFNC only, while another side signifies HFNC + NRM treated patients' percentage. HFNC= High Flow Nasal Cannula, NRM= Non-Rebreather Mask, IL-6 inhibitor= Interleukin-6 inhibitor, LMW Heparin= Low Molecular Weight Heparin

Factors associated with HFNC with/without NRM

Non-diabetic patients who were managed with only HFNC were 6.5 (1.3-33.1) times less feverish than diabetic patients. The chance of having IGT was about twelve times (AOR= 12, 1.1-129.8) high for the diabetic COVID-19 patients who were also given only HFNC to maintain their oxygenation (***Table 4***). The chance of being aged at least 50 years was almost six (AOR= 6.2, 1.1-31.2) times higher among diabetic HFNC + NRM treated patients. Non-diabetic patients (HFNC + NRM treated) were more likely to have hypertension than diabetic ones. Moreover, among HFNC + NRM treated patients, diabetic patients were five times (AOR=5.1, 1.2-20.8) more likely to have increased blood glucose levels (***Table 4***).

Table 4. Factors associated with HFNC only and HFNC+NRM management of ICU admitted diabetic COVID-19 patients.

Variables	Only HFNC		HFNC + NRM	
	COR with range (95% CI)	AOR with range (95% CI)	COR with range (95% CI)	AOR with range (95% CI)
Age (in years)				
Less than 50 (ref)	1.0	1.0	1.0	1.0
50 and above	**2.3 (1.1-5.2)***	2.5 (0.8-8.5)	**8.8 (2.7-28.4)***	**5.8 (1.1-31.2)***
Comorbidity history				
No comorbidities	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Hypertension	**3.8 (1.8-7.9)**	0.7 (0.2-2.2)	**3.0 (1.3-6.8)***	**0.1 (0.01-0.8)***
Clinical sign				
Fever	**3.5 (1.0-11.9)***	**6.5 (1.3-33.1)***	3.0 (0.5-17.0)	2.2 (0.3-18.7)
Random blood sugar				
Normal (ref)	1.0	1.0	1.0	1.0
Impaired glucose tolerance	2.9 (0.9-9.9)	**11.7 (1.1-129.8)***	1.2 (0.3-4.0)	1.2 (0.3-5.9)
Increased	1.4 (0.6-3.3)	1.5 (0.4-5.0)	**5.2 (1.7-16.2)***	**5.1 (1.2-20.8)***
Serum creatinine				
Normal (ref)	1.0	1.0	1.0	1.0
Increased	0.6 (0.3-1.3)	0.6 (0.2-1.8)	**3.1 (1.3-7.5)***	2.1 (0.7-6.3)

Simple and Multiple Bivariate logistic regression was used and p-values less 0.05 (marked with * and are bold) are considered significant. (COR= Crude Odds Ratio, AOR= Adjusted Odds Ratio.)
**Times from symptoms onset to death is removed from the analysis as it is strongly correlated with other factors.

Discussion

Because a previous study recommended the usage of HFNC for minimizing invasive/mechanical ventilation use (Matthay, Aldrich and Gotts, 2020), in this study, the clinical effect of HFNC as a mode of providing supplemental oxygenation to COVID-19 diabetic patients was observed to analyze whether the use of this mechanism is efficient enough to be reiterated on a large scale to reduce the burden of MV support in the context of Bangladesh's COVID-19 landscape. When HFNC failed to maintain the optimum oxygenation with at least 92% of SpO_2, NRM was also added to the ICU admitted patients. We also tried to find the success rate of using NRM concomitant with HFNC to the COVID-19 induced AHRF diabetic patients.

In this data, 136 among 240 HFNC treated AHRF patients had diabetes as comorbidity, which aligns with the statement by a study in China, which stated that diabetes mellitus is a commonly observed comorbidity in severe COVID-19 cases (F. Zhou *et al.*, 2020). Diabetes among elderly patients was considered a risk factor for the severe prognosis of COVID-19 (Akter *et al.*, 2020; P. Zhou *et al.*, 2020). Similar to a study in Bangladesh, the proportion of diabetic COVID-19 patients was significantly higher among those aged ≥ 50 years (Saha *et al.*, 2021). The findings of this survey showed that a great proportion (almost 6 times) of the elderly diabetic patients needed both HFNC and NRM to maintain their oxygenation because they could not maintain the optimum oxygen level with HFNC only.

Analogous to previous studies, we found a higher mortality rate among COVID-19 patients with type-2 diabetes compared with the non-diabetic patients, establishing diabetes as a risk factor for increased mortality (Acharya *et al.*, 2020; F. Zhou *et al.*, 2020; Shenoy, Ismaily and Bajaj, 2020). As per the current study's findings, face masks with non-rebreather reservoir bags were given together with HFNC to 113 patients, and among them, 58.4% were diabetic. After using nasal cannula only, non-diabetic patients showed more improvement of PaO_2 than the diabetic ones. So, to maintain oxygenation of the severely/critically ill COVID-19 diabetic patients, NRM was also needed along with HFNC.

Saha et al. asserted the high prevalence of hypertension among the diabetic COVID-19 patients, and it was an important factor in the progression of COVID-19 for severe/critical patients (Saha *et al.*, 2021). In this study, it was observed that hypertensive diabetic COVID-19 patients required NRM along with HFNC to maintain the oxygen saturation. Besides, a significant difference in the presence of heart disease among diabetic and non-diabetic patients was also found in this current study. High prevalence of fever was found among the AHRF patients with diabetes in this study and only HFNC treated diabetic patients being 6.5 times more feverish might prove that fever was common among diabetic patients. As all the patients in this study were admitted to the ICU due to hypoxemic respiratory failure following COVID-19, the duration of ICU stay of the diabetic and non-diabetic patients was also observed. This study found a noticeable difference between them. Diabetic patients had to stay in the ICU for a longer period than those who did not have diabetes.

Increased blood glucose level is established as a determinant in the pathogenesis of the infectious disease, like the SARS-CoV-2 virus, and can make the diabetic patients immunocompromised, leading to their critical conditions after

SARS-CoV-2 infection (Casqueiro, Casqueiro and Alves, 2012; Wu *et al.*, 2020). This data supporting these studies proved that most of the severely/critically ill patients faced a rise in blood sugar, and among them, more than 60% were previously diabetic. Moreover, among diabetic patients only HFNC treated ones showed a high odds ratio of having IGT and HFNC + NRM treated ones showed of having increased blood glucose level. This data might prove that those who had increased blood glucose level rather of having IGT needed both HFNC and NRM to maintain their oxygen level.

In a study in China, it was stated that COVID-19 patients gradually develop kidney dysfunctions/acute kidney injury (AKI) as SARS-CoV-2 uses ACE2 (angiotensin-converting enzyme II) as a cell entry receptor (Li *et al.*, 2020). A PubMed database indicates that ACE2 RNA expressions in gastrointestinal organs (small intestine, duodenum) and urinary organs (kidney) are much higher (nearly 100-fold) than that in lungs (Fagerberg *et al.*, 2014). Compliant with these data, this current study noticed that increased serum creatinine level was found significantly among critically ill COVID-19 patients, and most of them did not have a previous history of kidney disease. Moreover, creatinine rise was high for those who were diabetic, and this indicates that elevation of creatinine level might be a determining factor of severity during SARS-CoV-2 infection for diabetic patients. As the severity of the disease for ICU admitted COVID-19 patients might increase because of diabetes and lately developed kidney dysfunction, HFNC and NRM both were needed to support most of the patients with raised sugar and creatinine levels.

Non-visible nasal bleeding along with mucosal obstruction was common for both diabetic and non-diabetic patients. So, to prevent this, liquid paraffin and normal saline were used. As this was a locally practiced procedure, more research is needed to establish the process for averting these complications. In a study, it was established that glucocorticoids can induce varying degrees of diabetes and this was similar to our data when patients were given steroids (Yasuda, Hines and Kitabchi, 1982). So, insulin was administered to all who were previously diabetic/ had been taking oral hypoglycemic drugs or insulin (switched from oral to injectable form)/ developed diabetes as a side effect of steroids. Dexamethasone with HFNC and NRM showed a good survival ratio for the diabetic patients, but convalescent plasma therapy worked effectively (with HFNC and NRM) for the non-diabetic patients showing a survival rate of 100.0%.

Conclusion

This study was conducted for analyzing the clinical outcomes of HFNC with/without a NRM on severely ill COVID-19 diabetic patients. As per the findings, the majority of the elderly diabetic and hypertensive diabetic patients needed both HFNC and NRM to sustain their oxygenation. Furthermore, increased blood sugar might prove that it may be a determining factor for the need of HFN + NRM for COVID-19 induced AHRF diabetic patients. As it is a multicentric prospective study, the findings of this study are representative of the situation of most hospitals in Bangladesh. As HFNC with/without NRM as per this study, was found to have association with a significant clinical improvement in severe case of COVID-19 in both diabetic and non-diabetic cases, the burden on MV and clinical demand of MV in constrained clinical settings can be to some extent reduced by considering HFNC with/without NRM and other therapeutics as an efficient candidate for supplemental oxygenation.

Abbreviation

HFNC; High Flow Nasal Cannula, NRM; Face Mask with Non-Rebreathing Reservoir Bag/Non-Rebreather Mask, COVID-19; Coronavirus Disease 2019, ICU; Intensive Care Unit, RBS; Random Blood Sugar, SARS-CoV-2; Severe Acute Respiratory Syndrome related Coronavirus, AHRF; Acute Hypoxemic Respiratory Failure, FiO_2; Fractional Concentration of Inspired Oxygen, NIV; Non-Invasive Ventilation, MV; Mechanical ventilation, SpO_2; Percent Saturation of Oxygen, IHD; Ischemic Heart Disease, rRT-PCR; Real Time Reverse Transcriptase- Polymerase Chain Reaction, WHO; World Health Organization, WBC; White Blood Cell, PaO_2; Partial Pressure of Oxygen, SD; Standard Deviation

Funding

This study was self-funded by authors.

Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Authors' Contributions

AFMTB: Design, clinical studies, data acquisition; SDN: Data acquisition, data analysis, manuscript preparation; SD: Experimental studies, manuscript preparation; MD: Concepts, clinical studies; Moinul Ahsan: Statistical analysis; MIEAZ: Clinical studies; FKP: Clinical studies; RD: Clinical studies; AKMSA: Manuscript editing; FHZ: Clinical studies; AS: Design, Manuscript preparation.

Acknowledgements

Authors would like to thank the authorities of 250 bedded Chattogram General Hospital, Chittagong Medical College Hospital, Chattagram Maa-Shishu O General Hospital, and Parkview Hospital.

Preprint

Preprint of this study is available at:
https://doi.org/10.1101/2021.10.13.21264946

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