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Article

Prediction of High Flow Nasal Cannula Failure in Patients With COVID-19 Pneumonia Suffering from Acute Hypoxemic Respiratory Failure

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Abstract. Background: High flow nasal cannula (HFNC) is one of the most often employed methods of oxygen therapy for COVID-19 pneumonia and respiratory failure patients. Since the causes of HFNC failure and success are still undetermined, the goal of this study was to identify potential predictors of HFNC failure in COVID-19 pneumonia given that early detection of HFNC failure during episodes of acute hypoxemic respiratory failure (AHRF) can improve clinical treatment and accurately categorize patients for the best ventilation maneuver. **Patients and Methods:** This observational trial was conducted on 100 COVID-19 pneumonia cases with acute hypoxemic respiratory failure who were referred to our COVID-19 intensive care units from 1 August 2020 to 31 December 2022 and required HFNC therapy as rescue therapy. In patients who were finally weaned from this modality and have not been intubated, HFNC was considered successful; while patients who were intubated or put on continuous positive airway pressure (CPAP) were considered as failures. **Results*:*** there was a significant association between HFNC failure and obesity, high levels of inflammatory markers, and/or Sequential Organ Failure Assessment (SOFA) score. ROX score of less than 3.91 after 24 h of HFNC application and Procalcitonin were significant predictors of HFNC failure. **Conclusions*:*** In COVID-19 pneumonia, HFNC therapy can be a convenient tool to avoid invasive mechanical ventilation, however, patient selection is very crucial.

Keywords: Acute hypoxemic respiratory failure; COVID-19; High flow nasal cannula

Introduction

In December of 2019, the SARS-Cov-2 coronavirus was discovered for the first time in Wuhan, China. (1) By March 2020, the world health organization (WHO) declared

COVID-19 a worldwide pandemic. (2) The primary and most critical target for SARS-CoV-2 is the respiratory system, that can result in mild to severe pneumonia and in some cases acute respiratory distress syndrome (ARDS) and acute severe hypoxemia. (3, 4)

Patients with persistent hypoxia despite using lower flow devices for oxygen supply (such as a nasal cannula, oxygen mask, or venturi mask) may benefit from using a high flow nasal cannula (HFNC), especially if they are exhibiting increased labor of breathing. (5, 6) HFNC is the nasal administration of humidified and heated air to the patient with a high flow rate (20–70 Lt / min) and more stable oxygen support (FiO2: 21–100%). HFNC can boost airway pressure, improve end-expiratory lung capacity, oxygenation, and the rate of carbon dioxide (CO2) clearance of gas content in the dead space, so physiologically it improves acute respiratory failure, such as mild and moderate ARDS. (7) Moreover, HFNC is better tolerated as well as more comfortable than other noninvasive respiratory support devices. (8) In comparison to invasive mechanical ventilation, it needs less staff resources and sedation. (9, 10)

Many clinical and academic societies, including the Society of Critical Care Medicine, (6) the National Institutes of Health, (11) the Australian and New Zealand Intensive Care Society, (12) have provided their relatively positive opinions on the effectiveness of the HFNC treatment for respiratory failure brought on by COVID-19.

Although, HFNC therapy is one of the most frequently employed methods of oxygen therapy in COVID-19 pneumonia and respiratory failure, (13, 14), delaying the timing of intubation may be hazardous and impair the prognosis of patients, most likely as a result of self-inflicted lung damage brought on by persistent spontaneous breathing attempt and lung atelectasis. (15) Kang, in his retrospective cohort, discovered that late intubation (more than 48 hours after HFNC) was associated with higher patient mortality, a poorer rate of ventilator weaning success, and fewer ventilator-free days than early intubation (within 48 hours after HFNC). (16)

Since the causes of HFNC failure and success are still undetermined, the goal of this study was to identify potential predictors of HFNC failure in COVID-19 pneumonia given that early detection of HFNC failure during episodes of acute hypoxemic respiratory failure (AHRF) can improve clinical treatment and accurately categorize patients for the best ventilation maneuver. (15, 17)

Patients and Methods

Study design: This is an observational combined prospective and retrospective cohort study.

Participants: Our study involved 100 cases diagnosed with COVID-19 pneumonia with acute hypoxemic respiratory failure who were admitted to the new teaching hospital (COVID-19 intensive care units) from 1 August 2020 to 31 December 2022 and required HFNC therapy as rescue therapy. Corresponding to WHO interim guidelines, (18) COVID-19 pneumonia was diagnosed with real-time PCR on nasopharyngeal, clinical presentation, and the findings of consolidation or multifocal ground-glass opacities on computed tomography.

The exclusion criteria were patients <18 years old, pregnant or required immediate invasive mechanical ventilation because of hypercapnic respiratory failure ($PaCO_2$ > 50 mmHg), disability to protect the upper airway or hemodynamic instability.

HFNC was administered to patients who met inclusion criteria and possessed at least one of the following characteristics: [PaO_2 (mmHg)/FiO_2 (%)] < 200 despite FiO_2 > 40 %, respiratory rate ≥ 30 breaths/min and symptoms of respiratory distress with severe dyspnea and utilization of accessory respiratory muscles. (19)

Data collection: The research was approved by the Medical Ethical Committee of Alexandria Faculty of Medicine in February 2022 (IRP NO: 00012098). A written informed consent was taken before conducting the study from patient or the next of kin. Hospitalization information was collected from the hospital records for the retrospective portion of the investigation.

All COVID-19 pneumonia cases involved in the research and receiving conventional oxygen therapy and were indicated to start HFNC as rescue therapy, (19) underwent the following:

- Full history data collection (age, gender & body mass index), Immunosuppressive condition history (chronic steroid user, organ transplantation, malignancy, and/or HIV/AIDS), comorbidities (cardiac or pulmonary disease, diabetes mellitus & hypertension,).
- Clinical examination (heart rate, blood pressure & vital signs) & systemic examination including respiratory rate, pattern of breathing, and chest inspection, palpation and percussion. Sequential organ failure (SOFA) score on admission to ICU. (20)
- Laboratory results on admission were collected including complete blood count, interleukin 6, D- dimer, procalcitonin, serum ferritin, C- reactive protein, serum creatinine, lactate dehydrogenase, alanine aminotransferase & aspartate aminotransferase.
- Arterial blood gases and hypoxic index before starting HFNC therapy.

- The respiratory rate-oxygenation (ROX) index was measured 1, 6, 12, and 24 hrs. after the commencement of HFNC treatment. (21)
- Time from symptom onset to HFNC administration and duration of HFNC therapy were recorded.

The efficacy of the HFNC treatment was confirmed when FiO2 could be adjusted to ≤ 40% and HFNC was discontinued in favor of conventional oxygen therapy (COT), either a simple face mask or nasal cannula, indicating HFNC treatment success.

Patients who developed any of the following conditions were given ventilator support in the form of invasive or non-invasive mechanical ventilation: (1) no respiratory improvement despite HFNC setting of 40 L/min and FiO2 of 100%; (2) respiratory distress, increased work of breathing, or disturbed level of consciousness as determined by the evaluation for the presence of chest movement; (3) hemodynamic instability or multiple organ failure; or (4) Rapid oxygenation decline after a few hours, even when 100% FiO2 is administered by HFNC, indicating HFNC failure.

In patients who were finally weaned from this modality and were not intubated, were considered successful; while patients who were intubated or put on CPAP were considered failures. (22)

Statistical analysis

Data was analyzed using SPSS, v. 20. Qualitative aspects were described using frequency and percentage, whereas quantitative aspects were described using means and standard deviation (SD). Cases were classified into 2 primary groups according to the HFNC result. When comparing qualitative research variables between groups, the Chi-square test was performed. Student t-test was utilized for comparing the parametric quantitative data whereas Mann Whitney U test was for nonparametric data. The multivariate logistic regression analysis was used to assess the predictors of HFNC success. In the model used, the dependent variable was HFNC outcome and the independent variables were body mass index, immunosuppressive condition history, history of comorbidities, SOFA score on admission to ICU, Laboratory results on admission including complete blood count, interleukin 6, D- dimer, procalcitonin, serum ferritin, C- reactive protein, serum creatinine, lactate dehydrogenase, alanine aminotransferase & aspartate aminotransferase, arterial blood gases and hypoxic index before starting HFNC therapy, and ROX index measured at 1, 6, 12, and 24 hrs. Chi-square test was used to assess the significance of the regression model. The odds ratio was used as a measure of association. The validity and diagnostic capacity of ROX 24 as a screening tool for HFNC outcome was evaluated using ROC curve analysis, which yielded substantial findings. All results were interpreted using a significant P-values <0.05.

Results

During the research period, 111 cases who met the inclusion criteria had acute hypoxemic respiratory failure and were treated with HFNC. Following exclusion of 11 cases, 100 cases remained who had intermittent HFNC with Continuous Positive Airway Pressure (CPAP), were intubated within 24 hours of HFNC application, or discharged against medical advice. 36 were successful and 64 patients either received CPAP or were intubated and mechanically ventilated (Figure 1).

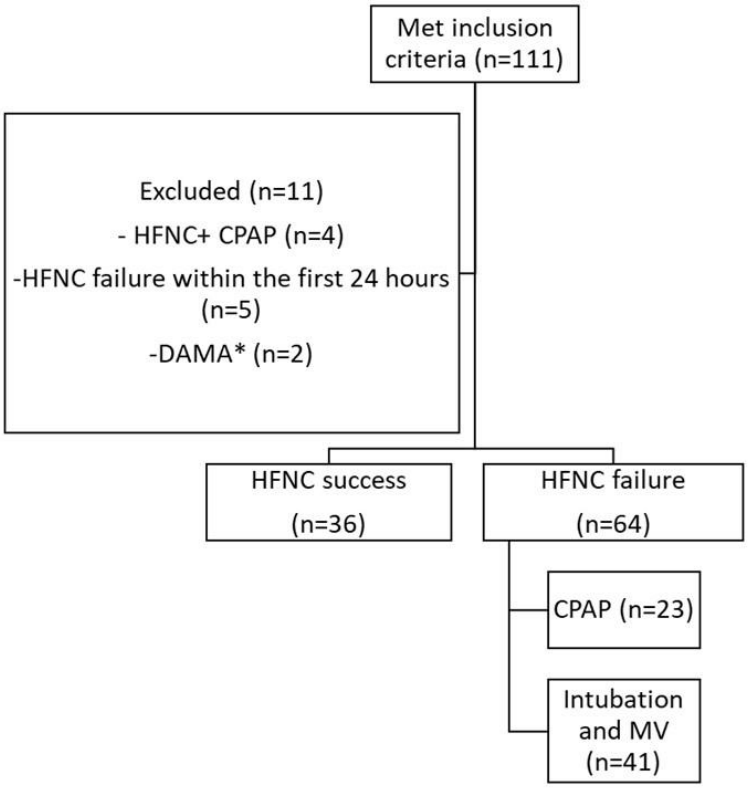

Figure 1: Flow chart of COVID 19 pneumonia cases who received HFNC management

As regard the demographic characteristics, about half (52%) of studied patients were males. The age of studied patients ranged from 23 to 96 years with a mean age of 65.6±16.3 years. Moreover, all of the studied patients were either overweight (BMI, 25.0 to 29.9 kg/M2) (54%), or obese (BMI, 30.0 to 39.9 kg/M2). Slightly more than half of the studied patients (53%) were diabetic, and about three quarters of the studied patients (72%) suffered from hypertension. About one third of patients (32%) had cardiovascular disease. The majority of patients had no pulmonary disease, malignancy, or immunosuppressive conditions (86%, 94%, and 94% respectively). History of organ transplantation or HIV infection were not encountered in any of the studied patients.

On studying the relation between patients' demographic data and the outcome of HFNC, it was found that HFNC was successful in slightly more than half (53.8%, n=24) of male patients compared to only a quarter (25%, n=12) of female patients and this difference was statistically significant (Chi square test X2=4.848, p=0.03). Moreover, the mean age of patients with whom HFNC showed success was 60.89 ± 15.13 years compared to 68.28 ± 16.47 years mean age among patients with HFNC failure and this was statistically significant (p=0.029). All patients on immunosuppressive therapy (100%) and most obese patients (87%) showed failure of HFNC. (Table 1)

Table (1): Distribution of studied cases according to presence of comorbidities and immunosuppressive conditions and HNFC outcome

Characteristics	**HFNC Failure (n=64) n (%)**	**HFNC success (n=36) n (%)**	**Test of significance Chi-square test**
Co-morbid condition			
DM	30 (63.8)	17 (36.2)	X^2= 0.001
- **No**	34 (64.2)	19 (35.8)	P=0.97
- **Yes**			
Hypertension			
- **No**	14 (50)	14 (50)	X^2= 3.308
- **Yes**	50 (69.4)	22 (30.6)	P=0.07
Cardiac disease			
- **No**	42 (61.8)	26 (38.2)	X^2= 0.461
- **Yes**	22 (68.8)	10 (31.3)	P=0.50
Chest disease			
- **No**	52 (60.5)	34 (39.5)	X^2= 3.331
- **Yes**	12 (85.7)	2 (14.3)	P=0.07
Malignancy			
- **No**	60 (63.8)	34 (36.2)	X^2= 0.2
- **Yes**	4 (66.7)	2 (33.3)	P=0.89
Immunosuppression	58 (61.7)	36 (38.3)	X^2= 3.59
- **No**	6 (100)	0	P=0.05*
- **Yes**			
Obesity			
- **Overweight**	24 (44.4)	30 (55.6)	X^2= 19.485
- **Obese**	40 (87)	6 (13)	P=0.001*

DM: diabetes mellitus, X2: chi square, *: statistically significant as P value<0.05

There was a significant difference between patients who showed HFNC success and those who failed regarding LDH, serum ferritin, IL-6, CRP, Procalcitonin & D-dimer (p= 0.001, 0.001, 0.04, 0.01,0.001, & 0.001). Assessment of clinical scores revealed that the mean SOFA score among patients who showed HFNC success was significantly decreased than those who showed HFNC failure (p=0.05). Moreover, the patients who showed success of HFNC had a significantly higher ROX index at 6, 12, and 24 hours than those who showed failure (p= 0.02, 0.001, 0.001). Time from ICU admission to HFNC application among patients with HFNC success (1.83 ± 1.59 days) and patients with HFNC failure (1.75± 2.29 days), and this observed difference was statistically insignificant (p=0.22). As regard total duration of HFNC use, there was no statistically significant difference between the mean duration (4.17 ±1.91 days) among patients with HFNC success, and (3.84± 2.07 days) in patients with whom HFNC showed failure. (Table 2)

Table 2: Association between studied patient's laboratory findings and arterial blood gases and the HFNC outcome, association between the estimated clinical scores and HFNC outcome and association between Time from admission to HFNC application and duration of use and its outcome among studied patients

	HFNC Failure (n=64) Mean ± SD	**HFNC success (n=36) Mean ± SD**	**Test of significance**
Laboratory findings			
LDH (U/L)	429.25±135.05	314.28 ±91.68	Student t test t= 4.548 p= 0.001*
Ferritin (ng/ml)	1797.34±896.38	1131.56±652.26	Mann-Whitney U Z= -3.636 P= 0.001*
IL6 (pg/ml)	71.78±47.03	62.92±55.14	Mann-Whitney U Z= -1.968 P= 0.04*
CRP (mg/dl)	77.06±64.96	52.21±41.21	Mann-Whitney U Z= -2.443 P=0.01*
Procalcitonin (ng/ml)	3.07±5.39	0.27±0.49	Mann-Whitney U Z= -5.062 P= 0.001*
Lymphocytes (10^3 cells/µl)	0.87±0.41	0.97±0.23	Student t test t= -1.526 p=0.13
Creatinine (mg/dl)	1.45±1.03	1.18±0.99	Mann-Whitney U Z=-0.981 P=0.32
ALT (U/L)	51.91±50.94	61.17±45.49	Mann-Whitney U

			Z= -1.423 P=0.15
AST (U/L)	60.47±51.2	46.67±27.28	Mann-Whitney U Z= -1.293 P=0.19
D dimer (ng/ml)	2169.66±2410.97	678.22±260.39	Mann-Whitney U Z=-5.604 P=0.001*
PH	7.46 ± 0.07	7.43 ± 0.05	t= 2.199 p=0.03*
PCO_2 (mm Hg)	34.24 ± 6.2	34.56 ± 5.13	t= -0.259 p=0.79
PaO_2/FiO_2 ratio	145.03 ± 25.67	166.67 ± 21.18	Student t test t= -4.298 p=0.001*
HCO_3 (mEq/L)	24.83 ± 5.01	23.76 ± 4.32	t=1.076 p=0.29
SO_2 (%)	89 ± 1.09	89.72 ±0.74	t=-3.517 p=0.001*
Score			
SOFA	3.31 ± 1.44	2.72 ± 1.003	Mann- Whitney U Z= -1.954 p=0.05*
ROX1 **(1 hr. post HFNC application)**	3.49 ± 0.57	3.55± 0.49	Student t test t=-0.526 p=0.6
ROX6 **(6 hr. post HFNC application)**	3.59 ± 0.52	3.84 ±0.62	Mann- Whitney U Z=-2.213 p=0.02*
ROX12 **(12 hr. post HFNC application)**	3.45±0.44	4.15±0.89	Mann- Whitney U Z= -4.974 p=0.001*
ROX24 **(24 hr. post HFNC application)**	3.4 ±0.48	4.9±1.35	Mann- Whitney U Z= -7.113 p=0.001*
Duration			
Time from admission to HNFC (days)	1.75± 2.29	1.83 ± 1.59	Mann- Whitney U Z= -1.214; p=0.22
Total duration of HNFC (days)	3.84± 2.07	4.17±1.91	Mann- Whitney U Z= -1.52; p=0.12

LDH: Lactate dehydrogenase, IL-6: Interleukin 6, CRP: C-reactive protein, ALT: alanine transaminase, AST: aspartate transaminase, SOFA: Sequential Organ Failure Assessment, *: statistically significant as P value <0.05

The AUC of ROX index at 24 h for HFNC success was 0.930 (P<0.001). The optimal cut-off value of the ROX index at 24 h was 3.91, with 83.33 % sensitivity, 90.62 % specificity, 83.3 %PPV & 90.6 % NPV (Figure 2).

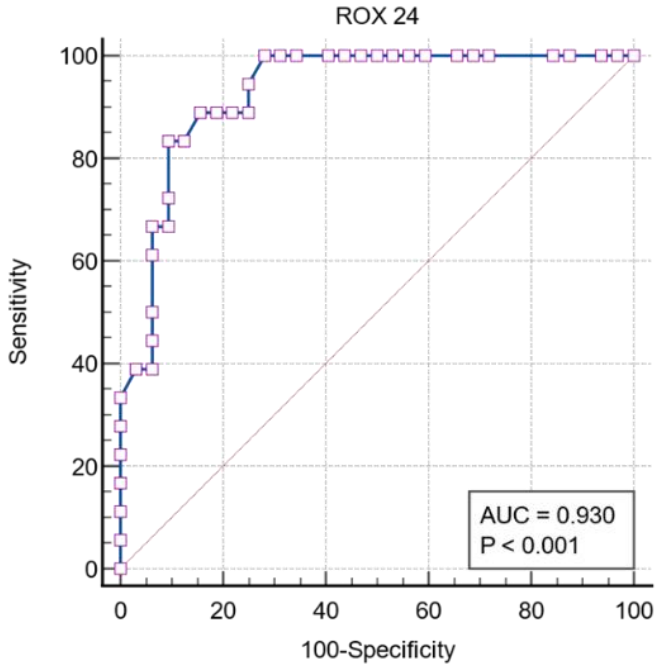

Figure 2: ROC curve analysis of ROX24 as a predictor of HFNC success

On multiple logistic regression analysis, Procalcitonin and ROX24 were significant predictors of HFNC success. Table (3) shows that, every 1unit increase in procalcitonin, the odds of success of HFNC will decrease by 0.89 times and every 1unit increase in ROX24, the odds of success of HFNC will increase by 42.5 times.

Table (3): Multiple logistic regression analysis of independent predictors of HFNC success

Independent predictors	B	Significance	Odds ratio (95% Confidence interval)
Procalcitonin	-2.170	0.001	0.11 (0.03 - 0.41)
ROX24	3.750	0.000	42.5 (8.12 – 222.73)

Model Chi-Square: 79.215, P=0.000; Constant: -14.037, P=0.000

Discussion

In agreement with our results, an insignificant difference between the studied patients regarding the presence of comorbidities was observed by Takeshita Y et al. (23) However, most obese patients (87%) showed failure of HFNC compared to (44.4% of) overweight patients and these differences are statistically significant. In

agreement with this result, Malik et al. (24, 25) demonstrated that HFNC success group had lower BMIs. According to the Centers for Disease Control and Prevention (CDC), extreme obesity is a common risk factor for bad prognosis & higher death in COVID-19 cases. (25) Even among COVID-19 individuals, any level of obesity is associated with a bad prognosis. (26, 27)

Regarding the laboratory test findings, we reported a significant difference between patients who showed HFNC success and patients failed in LDH, serum ferritin, IL-6, CRP, Procalcitonin, and D-dimer levels. However, the observed differences in mean levels of absolute lymphocytes, serum creatinine, and liver enzymes between both groups were statistically insignificant. A previously mentioned cohort study also suggested that COVID-19 patients with higher inflammatory markers did not get benefit from HFNC therapy. (22) Additionally, a significant difference in IL-6 levels between those who showed HFNC success and those who failed was reported by Ferrer et al. (28)

The WBC, lymphocyte count, CRP, and procalcitonin were compared before and at 72 hours after HFNC treatment in a previous retrospective study examining the effect of HFNC in treating COVID 19 pneumonia. However, the differences in WBC and procalcitonin were not statistically significant. They discovered that after 72 hours, Lymphocyte count and CRP had improved in the HFNC oxygen therapy group compared to the conventional oxygen therapy group. (29)

Additionally, Procalcitonin levels above 0.2 ng/mL were linked to an increased risk of all-cause mortality, the requirement for NIV, and a longer duration of mechanical ventilation, according to a retrospective study that looked at the role of procalcitonin in predicting invasive mechanical ventilation and mortality in COVID 19 patients. (30)

This might be explained by the secondary bacterial co-infection, which made the initial COVID-19 illness worse. Procalcitonin levels are positively correlated with disease severity and clinical worsening, which may be triggered by an increase in IL-6 and other cytokines, particularly in the context of a hyperinflammatory state. (31, 32)

Our study revealed that PaO2/FiO2 ratio & oxygen saturation were significantly lower before HFNC application in patients who failed HFNC. This was supported by Patel et Al.'s, (33) study on 104 consecutive cases diagnosed with severe or moderate Covid-19 pneumonia-related hypoxemia. In multivariate analysis they found that SpO2 / FiO2 ratio < 100 was independently linked to HFNC failure.

It was interesting to use scoring tools to predict the success or failure of this respiratory support method. As the pathology of COVID-19 affects multiple organ systems and mainly the respiratory system, resulting in acute respiratory failure and pneumonia, we used the SOFA score as a trustworthy predictor of HFNC failure or success. Our study found that the mean SOFA score among patients who showed HFNC success is significantly lower than those who showed HFNC failure.

In accordance with this result, Mellado-Artigas et al. (34) investigated 259 cases admitted with severe pneumonia caused by SARS-CoV-2 who received HFNC therapy. They revealed that a failure of HFNC therapy was associated with high SOFA score at admission.

The ROX index is the most effective non-invasive monitoring approach for measuring the success of HFNC therapy, according to a prior study. (35) Higher ROX index levels were linked to a decreased incidence of intubation in AHRF patients received HFNC, according to a previous study. This study found an elevated risk of eventual intubation or death for any ROX index less than 4.67 at 12 hours or 4.04 at 24 hours. (36)

Additionally, Duan J et al., (37) in another multicenter trial, found that the ROX index can be used as a predictor of HFNC failure among patients with COVID-19. When used to predict HFNC failure within 24 hours of use (at 1, 2, 4, 8, 12, and 24 hours after HFNC usage), the ROX index demonstrated significant discriminative values.

Moreover, the ROX index was shown to have a significant link with HFNC failure in a retrospective cohort research on critically ill patients with acute respiratory failure who received HFNC. After calculating the ROX index 1& 2 h after HFNC application, it was revealed that the HFNC failure group had lower values at both time intervals than the HFNC success group. (38) A meta-analysis of 8 retrospective or prospective cohorts with 1,301 individuals confirmed the results. This meta-analysis shown that the ROX index was a strong predictor of HFNC failure in patients with hypoxemia and COVID-19. (39)

One of our aims was to identify the rate of failure and success of HFNC in COVID 19 patients. According to our study, among the 100 studied patients, 64% failed HFNC which is higher than the range of 38 to 45% reported in several studies. (40-42) However, in agreement with our results, Ferrer et al. (28) and Calligaro GL et al. (43) also reported a rate of failure of 55% and 53% respectively.

Moreover, we found that time from ICU admission to HFNC application was insignificantly different between patients with HFNC success and patients with

HFNC failure. As regard total duration of HFNC use was insignificantly different between patients with HFNC success & whom HFNC showed failure. This variation may be explained by the variety of HFNC initiation criteria utilized in the various research, as well as the fact that the severity of sickness among patients enrolled in these trials may vary. Additionally, the burden of COVID 19 patients on our healthcare system and intensive care resources is also a concern.

Multiple logistic regression analysis demonstrated that Procalcitonin and ROX at 24 h (ROX24) were significant predictors of HFNC failure among the independent factors. In agreement with this result, Ferrer et al. (28) observed that among the variables associated with the severity of COVID-19, ROX24h was the sole variable that predicted HFNC success.

A 5-year retrospective cohort study was carried out in Hong Kong to determine the predictors of failure of HFNC because it is becoming more popular as a relatively new therapy utilized in critically sick patients suffering from hypoxemic respiratory failure due to various reasons. Regarding the primary causes of respiratory failure among the patients in the study, pneumonia was the most common (77.4%), followed by fluid overload or congestive heart failure (9.7%), and interstitial lung disease (4.8%). They claimed that between one and twelve hours following HFNC, the ROX index was considerably lower in the failure group. Failure of HFNC was connected by multivariate binary logistic regression to a lower ROX index at 12 hours after HFNC. (44)

Another retrospective analysis was conducted on AHRF patients who received HFNC treatment between January 2016 and January 2018. They discovered that the greatest indicators of HFNC effectiveness were RR after 2 hours of treatment, FiO2, and the ROX index measured after 8 hours of treatment. (45)

Study limitations

This investigation has numerous limitations. First, our research is single site based as opposed to multi-site and is prone to selection bias for the retrospective portion of the investigation. Therefore, we strongly suggest additional large-scale, multicenter prospective investigations to confirm the outcomes of our study. Additionally, due of the intense demand on our hospital and the significant shortage of HFNC devices, mechanical ventilators, and conventional oxygen therapy equipment during the pandemic, patient care in terms of the available intensive care resources may have been impaired.

Conclusion

In patients with COVID-19 pneumonia, HFNC therapy can be a useful technique to avoid invasive mechanical ventilation, but patient selection is extremely important. Our results show that those with obesity, high levels of LDH, serum ferritin, IL-6, CRP, Procalcitonin, and D-dimer and/or higher SOFA score were more likely to fail HFNC. Additionally, lower PaO2/FiO2 ratio and oxygen saturation before HFNC use were associated with HFNC failure. The ROX index at 6, 12, and 24 hours was significantly higher among patients who showed success of HFNC compared to those who showed failure. Among all patients, Procalcitonin and ROX score < 3.91 after 24 h of HFNC application were significant predictors of HFNC failure.

Ethics

The research was approved by the Medical Ethical Committee of Alexandria Faculty of Medicine. A written informed consent was taken before conducting the study from patient or the next of skin.

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Availability of Data and Materials

Please contact author for any data requests.

Competing Interests

None.

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