Original Article

Analysis of C-Reactive Protein, Neutrophil-to-Lymphocyte Ratio, PaO_2/FiO_2 Ratio on the Success of High Flow Nasal Cannula Usage in Hospitalized COVID-19 Patients

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Abstract

Background: Several studies had shown High Flow Nasal Cannula (HFNC) is effective in treating hypoxemic COVID-19 patients. The C-Reactive Protein and Neutrophil-to-Lymphocyte Ratio is an inflammatory marker that could predict the severity of COVID-19, where the P/F ratio infers oxygenation status. Since COVID-19-related ARDS is closely related to a hyper-inflammatory state and HFNC becomes widely utilized for hypoxemic patients, it has become important to discover reliable inflammatory biomarkers related to therapeutic HFNC success. This study aims to assess the factors that influence the success of HNFC therapy, in terms of demographic and laboratory profiles of CRP, NLR, and P/F ratio.

Method: A retrospective, single-center cohort study was conducted in a tertiary care hospital in Malang, East Java from January to March 2022. Subjects of 31 PCR-confirmed, hospitalized COVID-19 patients who were treated with HFNC were included.

Results: This study involved 2 groups comprised of 19 subjects with successful HFNC and 12 patients who failed. Significant demographic factors affecting successful HFNC were female gender (OR=1.46 95% CI=1.08-1.99; P=0.037) and occupation type (P=0.023). Whereas, biomarkers of CRP (8.90±6.8 mg/L vs 12.39±11.7 mg/L; P=0.656), NLR (7.24±4.66 vs 12.85±12.9; P=0.243) and P/F ratio (171.40±54 vs 148.00±40; P=0.219) were found to be non-significant between successful and failed HFNC cohorts, respectively.

Conclusion: HFNC could provide a specific positive end-expiratory pressure in COVID-19 patients with contributing factors of successful HFNC being female and occupational type. However, CRP, NLR, and P/F did not contribute significantly to HFNC's success.

Keywords: COVID-19, CRP, HFNC, P/F ratio

INTRODUCTION

The coronavirus disease 2019 (COVID–19) pandemic is a major global health problem. The disease was first reported in Wuhan City, Hubei Province, China, on December 31st, 2019, and was later identified as a new type of coronavirus, i.e. SARS-CoV-2.[1] Until June 2022, there were more than 500 million cumulative cases with a total of more than 6 million deaths due to COVID-19.[2]

Although the incidence of COVID-19 in Indonesia experienced a significant decrease, the coverage of vaccination in Indonesia is still low, where only 17% of the population had received a booster, i.e. the third dose of the COVID-19 vaccine.[3] Therefore, the possibility of an increase in COVID-19 cases would still likely happen.

Approximately, 14% of patients with COVID-19 would be at risk of developing hypoxemic respiratory failure, and 5% would require advanced oxygen therapy, including mechanical ventilation, and therefore respiratory support therapy is very crucial for these patients. Although the mechanism is still unclear and yet to be elucidated, patients with COVID-19 might develop pneumonia characterized by bilateral interstitial infiltrates, which could lead to acute respiratory distress syndrome (ARDS) and respiratory failure due to ventilation-perfusion mismatch and shunt effects.[4]

Several studies had mentioned the advantages of using HFNC over non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP) in acute hypoxemic respiratory failure due to COVID-19.[5] However, based on our recent study, there were currently no clear evidence-based guidelines in this regard.

High Flow Nasal Cannula for oxygen therapy is a new technology for respiratory support that is gaining attention. In recent years, it had attracted lots of attention for medical applications due to its advantages of stable oxygen performance and constant oxygen output.[6]

The utilization of HFNC in the management of COVID-19 was still controversial, mainly due to concerns regarding aerosol-generating effects, thus predisposing medical personnel to the risk of transmission. However, the evidence from recent studies further confirmed minimal effect of aerosolization and the risk of transmission to medical personnel with the use of HFNC.[7]

A report from two hospitals in Chongqing, China stated 63% of patients with acute respiratory failure due to COVID-19 were treated with HFNC as the first line; among these patients, 59% had a successful recovery, whereas 41% had a failure. However, the failure rate in patients with a PaO_2/FiO_2 (P/F) ratio >200, i.e., mild ARDS, was 0%. Several studies from China also found that early use of HFNC and NIV resulted in a lower mortality rate from COVID-19 with <1% requiring intubation, as compared to their national average mortality rate of 2.3%.[8]

The previous study noted that the severity of inflammation had been well correlated with the success rate of HFNC. Adult patients with acute hypoxemic respiratory failure from sepsis showed a higher P/F ratio and lower lactate contributed to successful HFNC. Another finding from this study also noted that lower SOFA scores were significantly correlated with successful HFNC.[9]

Several inflammatory biomarkers had been investigated for their correlation to predict the severity of pulmonary disease. C-reactive protein (CRP) is an acute-phase protein synthesized primarily by the liver in response to interleukin 6 (IL-6), a pro-inflammatory cytokine.[10] These properties made CRP an inflammatory marker and could assist in predicting the severity of community-acquired pneumonia (CAP).

As previously stated, COVID-19 pathophysiology is based on a cytokine-mediated hyper-inflammatory process that evolved into a cytokine storm. Hyper-inflammation biomarkers include CRP, IL-6, ferritin, D-dimers, lactate dehydrogenase (LDH), procalcitonin, lymphopenia, and thrombocytopenia.[11] Since COVID-19-related ARDS is closely related to a hyper-inflammatory state and HFNC becomes widely utilized for hypoxemic patients, it has become important to discover reliable biomarkers related to inflammation as an indicator of therapeutic HFNC success.

This study investigated factors related to a successful HFNC therapy in adult hypoxemic COVID-19 subjects in regards to mortality rate and the need for intubation, as well as linked it to inflammatory markers of CRP and NLR, s as well as oxygenation status of P/F ratio.

METHOD

This study was designed as a retrospective cohort, single-centered at Saiful Anwar General Hospital's integrated airborne-isolation ward, consecutively from January to March 2022. Subjects included in this study were hospitalized COVID-19 patients confirmed by reverse-transcriptase polymerase chain reaction (rt-PCR) or GeneXpert® SARS-CoV-2 rapid molecular testing method and treated with HFNC.

Demographic data were obtained. Further laboratory testing results were collected when the patient was first admitted. Nominal variables were expressed in frequency and percentage (%) and numeric parameters were noted at means±standard deviation (SD). Further bivariate analysis with T-test, Mann-Whitney, and Chi-square was conducted. All statistical analyses were performed with SPSS 25.0 to determine significant factors contributing to the success of HFNC. Consequently, the use of HFNC may improve the prognosis for COVID-19 patients. This study aims to assess the factors that influence the success of HNFC therapy in the management of severe COVID-19 patients.

RESULTS

Thirty-one subjects, consisted of 25 males and 6 females rt-PCR confirmed hospitalized COVID-19 patients requiring HFNC, were included in this present study. Most of the patients were between the ages of 50 and 64 years old. Chi-square test were conducted between categorical variables to yield odds ratio (OR). From demographic profiles, Fischer exact test showed that gender was statistically significant with P=0.037 and OR=1.46 (1.08-1.98), indicating that there was a correlation between gender and the success of HFNC, where males were more vulnerable to HFNC failure. Chi-square analysis showed a significant difference between occupation type and the success of HFNC with value of P=0.023, where laborers and unemployed people had a high risk of failing HFNC therapy.

Table 1. Distribution data according to age, between subjects

Age (years)	Frequency	P
15-49	11 (35.5%)	
50-64	17 (54.8%)	0.578%
>64	3 (9.7%)	

Note: *Statistical analysis with Chi-square test

Table 2. Distribution data according to gender and occupation between subjects

Parameter	HFNC Outcome (frequency, %)		P
	Success (n=19)	Failure (n=12)	
Gender			
Male	13 (41.9)	12 (38.7)	0.037*[b]
Female	6 (19.4)	0	1.46 (1.08-1.99)[c]
Occupation type			
Shopkeeper	5 (16.1)	1 (3.2)	
Civil servant	7 (22.6)	0 (0)	
Housewife	1 (3.2)	0 (0)	0.023*[a]
Nurse	1 (3.2)	0 (0)	
Laborers	2 (6.5)	5 (16.1)	
Unemployed	3 (9.7)	6 (19.4)	

Note: [a]Statistical analysis with Chi-square test; [b]Analysis with Fischer exact test; [c]Odds ratio (OR) with 95% confidence interval; *P<0.05 is considered statistically significant

Table 2. Laboratory differences between cohorts of COVID-19 inpatients who received successful and unsuccessful HFNC therapy

Parameter	HFNC Outcome (mean±SD)		P
	Success (n=19)	Failure (n=12)	
Leukocyte count (cell/mm^3)	7932.10 ± 2771.33	10270.83 ± 7740.25	0.715[a]
Lymphocyte (cell/mm^3)	1070 ± 380.37	988.88 ± 945.62	0.553[b]
Monocyte (cell/mm^3)	502.85 ± 177.40	610.07 ± 298.3	0.215[b]
Neutrophil (cell/mm^3)	6324.68 ± 2675.89	8524.64 ± 7797.31	0.746[a]
Platelets count (cell/mm^3)	253284.21 ± 106009	248916.66 ± 104936.74	0.911[a]
Haemoglobin (g/dL)	14.50 ± 1.39	13.65 ± 2.20	0.133[a]
C-reactive protein (mg/L)	8.9 ± 6.8	12.39 ± 11.7	0.656[a]
Procalcitonin (ng/mL)	0.298 ± 0.345	0.79 ± 0.87	0.109[a]
Serum ferritin (µg/L)	1223.93 ± 1415.71	1867.8 ± 1995.06	0.522[a]
Fibrinogen	497.85 ± 83.56	550.47 ± 103.79	0.460[b]
LDH	435.0 ± 77.06	502.0 ± 261.62	1.000[a]
AST	76.94 ± 47	51.83 ± 29.1	0.118[a]
ALT	69.68 ± 56.5	48.08 ± 34.65	0.133[a]
Random blood glucose (mg/dl)	147.05 ± 58.7	156.83 ± 45.21	0.453[a]
Ureum	37.82 ± 57.57	59.45 ± 57.57	0.465[a]
Serum Creatinine	10.90 ± 0.39	1.37 ± 1.12	0.951[a]
PaO_2/FiO_2 Ratio	171.40 ± 54	148 ± 40	0.219[b]
D-dimer	3.25 ± 6.3	1.75 ± 1.7	0.500[a]
NLR	7.24 ± 4.66	12.85 ± 12.9	0.243[b]
Lactate	2.78 ± 0.88	3.30 ± 1.4	0.242[b]
SP-D	6.94 ± 7.8	1.54 ± 1.19	0.052[a]

Note: [a]Statistical analysis with Mann-Whitney test; [b]Analysis with independent t-test; LDH=lactate dehydrogenase; AST=aspartate transaminase; ALT=alanine transaminase; NLR=neutrophil-to-lymphocyte ratio; SP-D=surfactant protein-D.

The average CRP value in our cohorts who failed HFNC therapy was 12.39±11.7 mg/L. This finding was higher than patients who were successfully treated with an average of 8.9±6.8 mg/L. Through the Mann-Whitney test, the value of P=0.656, a non-significant difference between the two groups. The average NLR value in patients who failed therapy was 12.85±12.9, while in patients who were successfully treated was 7.24±4.66, through the Mann-Whitney test, with P=0.243, so it can be concluded that there is no significant difference between the two groups. The P/F Ratio in patients who failed therapy was 148.40, while it was 171.40 in patients who were successful in HFNC therapy.

DISCUSSION

Currently, non-invasive mechanical ventilation has become the first-line choice in the ventilation procedure for critically ill patients. One of the non-invasive mechanical ventilations widely utilized is HFNC. HFNC is considered an alternative to CPAP for respiratory support in critically ill patients.[12] HFNC is a sophisticated and high-cost mechanical ventilation system that uses oxygen. Therefore, the use of HFNC should be considered clinically by attending physician jurisdiction.[13]

High flow nasal cannula system consisted of an oxygen or air mixer, an active hot humidifier, a single heated circuit, and a nasal cannula. In the air/oxygen mixer, the value of the inspired oxygen fraction (FiO_2) is adjusted from 0.21 to 1.0 in flows up to 60 L/min.[12] From clinical aspects, HFNC is also beneficial for patients' comfort and ease of use, as well as physiological aspects, including higher oxygenation, alveolar recruitment, humidification and heating, increased clearance of secretions, and reduction of dead space, as well as preventing damage to lung function and endotracheal intubation.[14]

The average NLR value in patients with failed HNFC therapy showed a higher value, but this was statistically non-significant. The average CRP value in our cohorts who failed HFNC therapy was higher than patients who were successfully treated, value of P=0.656, a non-significant difference between the two groups. Although non-significant, the trend of these findings were in concordance with previous studies. Based on Zablockis et al study, the NLR and CRP value showed that there was a progressively higher level of NLR and CRP among subjects who failed non-invasive oxygen therapy.[15]

However, there was a non-significant difference in NLR and CRP levels between NIV failure groups and HFNC failure groups.[15] In this regard, NLR and CRP might be reliable biomarkers for inflammatory states,[16] but could not predict the event of failed or successful HFNC treatment.

From previous studies, the uses of HFNC could improve patient’s oxygenation, reduce the work of respiratory muscle and energy consumption, also accelerate the recovery of patient’s physical condition. However, due to small number of cases and poor representativeness in this study, data from a large sample is needed to verify this study. Furthermore, HFNC reduces the rate of intubation and improve clinical prognosis of patients with acute respiratory failure as stated in previous study.[17]

In this study, the P/F ratio in subjects with failed HFNC treatment was lower, but statistically non-significant. A higher P/F ratio meant a milder degree of respiratory failure, thus inferring better oxygenation, and vice versa.[18] This finding exhibited a similar trend to the previous study, i.e. higher P/F ratio in successful HFNC treatment. Eryuksel et al that stated higher PaO_2 and higher P/F ratio could predict significantly the odds of successful HFNC treatment.[9]

In this study, Eryuksel et al emphasized that HFNC was associated with a considerable risk of mortality in cases where it was not successful; therefore, identifying the factors that contribute to the prediction of unsuccessful outcomes could be valuable in reducing mortality rates of hypoxemic respiratory failure.[9]

Geng et al showed that after providing HFNC for 2 hours, the rate of oxygenation was improved. During treatment, 8 patients with COVID-19 found that HFNC could meet their oxygen requirements, characterized by increased P/F ratio and higher ROX (rate of oxygenation).[19]

In 2020, Teng et al compared HFNC oxygen therapy with conventional oxygen therapy, including nasal cannula and simple mask within severe COVID-19 cohorts. In Teng et al study, it was found that after 6 hours of use, PaO_2/FiO_2 was better in HFNC group with value of P=0.045.[6]

High-flow nasal cannula oxygen therapy is more effective in improving the P/F Ratio compared with conventional oxygen therapy. In this regard, HFNC is superior because of its ability to produce a specific positive end-expiratory pressure (PEEP), therefore it is beneficial for mild and moderate type I respiratory failure. HFNC also reduces the metabolic work associated with atmospheric gas conditioning because HFNC provides warm, humidified gas through the nasal pharynx, conducive to the recovery of airway ciliary function, promoting the discharge of secretion, and reduces the loss of heat and water in the respiratory tract.[17] After treatment HNFC, P/F Ratio had improved significantly with the prolongation of treatment time.

However, there are several factors affecting the failure of HFNC. Abboud et al, which examined HFNC in patients with bronchiolitis, stated HFNC failure was associated with low respiratory rates and high pCO_2 values.[20] Guillot et al study also stated that pCO_2 affects HFNC failure.[17] Kim et al found that HFNC failure was significantly related to the attending physician's decision to use HFNC, respiratory rate, SaO_2, SpO_2 <6 hours before HFNC insertion, and ROX index <6 hours preceding HFNC insertion.[13]

This present study showed several biomarkers that could potentially predict HFNC outcomes in COVID-19 patients admitted to the hospital. However, there are some limitations of this study, i.e. single-centered and retrospective manner of the study. The other limitation would be the limited sample size and this study was not considering an early usage of HNFC as demonstrated by Duan et al, where sooner HFNC commencement to the patient, the more optimal the effect would be.[8] Further investigation is required to analyze potential inflammatory biomarkers in a prospective, longitudinal manner with a larger population.

CONCLUSION

HFNC could provide a specific positive end-expiratory pressure for mild and moderate type I respiratory failure in COVID-19 patients with significant contributing factors to a successful HFNC being female and occupational type, in this study. From laboratory profiles, subjects with successful HFNC treatment exhibited lower CRP, lower NLR, and higher P/F ratio. Despite being considered potential factors, CRP, NLR, and P/F were found to have no significant contribution toward the efficacy of HFNC treatment in our study. Further investigations were required to analyze biomarkers that could predict the success of HFNC usage.

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