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Original Article

Comparison of ROX Index and Surfactant Protein-D with HFNC Outcome in COVID-19 Patients

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Abstract

Background : In COVID-19, severe clinical deterioration can lead to respiratory distress. High Flow Nasal Cannula (HFNC) is an oxygenation treatment recommended in severe COVID-19 patients, with various studies showing decreased recovery time and intensive care needed. However, instruments to predict HNFC outcomes, specifically in COVID-19, are not yet widely studied. ROX index is a practical instrument proven effective in predicting HFNC outcome in pneumonia while showing high variabilities of optimum time of assessments and cut-off values in COVID-19. Surfactant Protein-D (SP-D) is an alveolar protein showing potential as a biomarker in acute lung injury and respiratory distress. In this study, we analyzed ROX index and SP-D potential as HFNC outcome predictors in COVID-19 patients.

Methods : This prospective study recruited severe and critical COVID-19 patients treated with HFNC. Patient characteristics, laboratory values including initial serum SP-D values, and ROX index were recorded. Significant differences were analyzed using Chi-Square and Mann-Whitney tests. Receiver operating characteristic (ROC) analysis was used to determine HFNC outcome predictive abilities of ROX index and serum SP-D.

Results : 31 subjects with successful HFNC outcomes in 19 subjects and failed HFNC outcomes in 12 subjects were included in this study. ROX index and SP-D value were significantly higher in subjects with successful HFNC compared to failed HFNC ($p < 0.05$). ROX index at 6, 12, and 24 hours showed good HFNC outcome predictive ability (AUC > 0.7, $p < 0.05$).

Conclusion : Successful HFNC outcome in COVID-19 was significantly related to higher ROX index and serum SP-D values. ROX index also showed good potential as an HFNC outcome predictor in COVID-19 patients.

Keywords : Surfactant Protein-D, COVID-19, High Flow Nasal Cannula, ROX index

INTRODUCTION

COVID-19 infection can cause various degrees of clinical manifestation, ranging from mild to critical clinical conditions. Fever, cough, and shortness of breath are the main symptoms of COVID-19, with other accompanying symptoms such as myalgia, lethargy, and gastrointestinal manifestation, including diarrhea and vomiting. In severe cases, progressive clinical deterioration happens, leading to acute respiratory distress, septic shock, metabolic acidosis, and coagulation dysfunction in a few days.[1]

High Flow Nasal Cannula (HFNC) is an oxygenation treatment recommended in severe and critical COVID-19 patients. HFNC is also recommended in COVID-19 patients without clinical improvement after the first hour of treatment. Previous studies showed HFNC's feasibility as a treatment strategy, with 60.3% of subjects weaned from HFNC and 67.7% of weaned subjects did not require intensive care treatment.[2] Another study showed that HFNC treatment decreased recovery time and the need for mechanical ventilation.[3]

ROX index is a practical instrument previously proven effective in predicting HFNC outcomes in pneumonia patients.[4] In COVID-19, a meta-analysis study showed good predictive ability of ROX index in HFNC outcome. However, high variabilities were found in the ROX index time of assessment and cut-off value to best predict HFNC outcome in COVID-19 patients.[5]

Surfactant Protein-D (SP-D) is a protein secreted by type 2 alveolar cells. SP-D is important in various immunological functions such as agglutination and opsonization. In COVID-19, an SP-D level increase was found to be correlated with COVID-19 severity.[6] A previous study showed SP-D potential as a biomarker in acute lung injury and respiratory distress because of its protective role in various etiologies of acute lung injury.[7] Although recommended as an oxygenation treatment in severe and critical COVID-19 patients, instruments to predict HNFC outcome, specifically in COVID-19 are not yet widely studied. In this study, we analyzed ROX index and SP-D potential as HFNC outcome predictors in COVID-19 patients.

METHODS

This prospective study was conducted in Saiful Anwar General Hospital, Malang, Indonesia, between May 2021 to August 2021. This study's research protocol was accepted by the Ethics Commission of Saiful Anwar General Hospital (Approval No: 400/244/K.3/102.7/2022). Patients confirmed with COVID-19 were classified based on clinical severity. Severe and critical patients who were ≥18 years old, fully alert, able to communicate, were not on a ventilator, with a respiratory rate of 20–30 times/min and oxygen saturation of ≥90% were included in this study. Subjects using ventilator from the start of the treatment were excluded from this study. Subjects were gathered using consecutive sampling method.

Data such as patient characteristics (age, gender, and comorbidity) and laboratory values (initial SP-D, LDH, CRP, procalcitonin, D-dimer) were recorded. ROX index at 1, 2, 6, 12, and 24 hours after HFNC were calculated and recorded. ROX index is defined by the ratio of oxygen saturation per inhaled oxygen fraction divided by respiratory rate ((SpO2/FiO2)/RR). SP-D is analyzed using enzyme-linked immunosorbent assay (ELISA) (Human SP-D ELISA Kit, Elabscience).

Categorical variables are shown by number and percentage and analyzed with Chi-Square test. Numerical variables are shown in Mean ± Standard Deviation and Median (Minimum – Maximum values), analyzed with Mann-Whitney test. HFNC outcome predictive model of ROX index and SP-D levels were analyzed using receiver operating characteristic (ROC) analysis to determine predictive abilities and optimum cut-off values.

RESULTS

Thirty-one subjects were included in this study, with successful HFNC outcomes in 19 subjects and failed HFNC outcomes in 12 subjects. Subjects with failed HFNC outcomes are all male and older compared to successful HFNC subjects, but these findings were insignificant. No subject had coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) as comorbidity. Subject characteristics can be seen in Table 1.

Respiratory findings showed varying results. There was no significant difference in P/F ratio between each HFNC outcome group, while significant differences were found in ROX index at all times of analysis. Laboratory values show insignificant findings between successful and failed HFNC outcomes in C-Reactive Protein (CRP), Procalcitonin, D-Dimer, and lactate dehydrogenase (LDH). A significant difference was found between each HFNC outcome group in surfactant protein D (SP-D).

Figure 1 showed a significantly higher SP-D value in successful HFNC patients. Aside from significantly higher ROX index values found in successful HFNC patients compared to failed HFNC patients at all times of assessments, an upward pattern of ROX index was found at each time of assessment in successful HFNC patients. In contrast, a downward pattern of ROX index was found at each time of assessment in failed HFNC patients.

ROC analysis showed that although ROX index at all times of assessments and SP-D showed good potential as a predictor of HFNC outcome (AUC > 0.7), Significant ROC findings were found in ROX index evaluated at 6, 12,

TABLE 1
Subject Characteristics between Each HFNC Outcome

Variables	Successful (N=19)	Failed (N=12)	p
Age (mean+SD)	50.9 + 12.4	56.8 + 16.0	0.239
Gender, n (%)			
Male	13 (41.9)	12 (38.7)	0.030*
Female	6 (19.4)	0	
Comorbidity, n (%)			
Diabetes	2 (10.5)	4 (33.3)	0.117
Hypertension	7 (36.8)	5 (41.7)	0.788
Heart Failure	0	1 (8.3)	0.201
P/F Ratio, Median (Min – Max)	169.30 (95.30–270.00)	148.50 ± 40.32	0.166
ROX Index, Median (Min – Max)			
1 hour	4.40 (3.16–5.02)	3.70 (2.32–4.94)	0.024*
2 hours	4.35 (3.31–5.24)	3.60 (2.21–5.44)	0.030*
6 hours	4.50 (3.33–5.80)	3.52 (2.21–5.44)	0.011*
12 hours	4.45 (3.33–6.10)	3.30 (2.02–6.87)	0.025*
24 hours	4.60 (3.39–6.30)	2.95 (2.32–4.20)	0.000*
Laboratory Values, Median (Min-Max)			
C-Reactive Protein	9.47 (1.2–30.49)	9.68 (0.34–35.04)	0.675
Procalcitonin	0.2 (0.03–1.36)	0.46 (0.07–2.95)	0.110
D-Dimer	0.7 (0.29–23.8)	1.24 (0.32–6.25)	0.367
Surfactant Protein D	4.05 (0.69–26.24)	0.79 (0.54–1.37)	0.000*
Lactate Dehydrogenase	416 (0–870)	490 (0–687)	0.454

*$p < 0.05$

and 24 hours ($p < 0.05$). The cut-off value with the highest sensitivity and specificity was found in 24 hours ROX Index, with a cut-off value of 3.63 ng/ml (Sensitivity: 84.21%; Specificity: 83.33%).

DISCUSSION

In this study, subjects with successful HFNC outcomes had significantly higher ROX Index and SP-D. A significant gender difference was found between different HFNC outcomes, with significantly higher male subjects with failed HFNC outcomes. Although previous studies showed a worse prognosis for males compared to females in COVID-19 outcomes, a significant gender difference in this study can also be attributed to the lack of subject gender variance (25 males vs. 6 females).[8] Subjects with failed outcomes were also found to be older, although not significant. This finding is similar to a previous meta-analysis study that showed an insignificant association between age and COVID-19 outcome after factoring in confounding factors such as age-related comorbidity (diabetes, hypertension, renal disease). This meta-analysis found that independently, age only increased the outcome risk of COVID-19 by 2.7% in two studies and found no increase in the other five studies.[9]

This study found a significantly higher ROX index at all times of assessments in subjects with successful HFNC outcomes. ROX index formula is adjusted to the fraction of oxygen received, and the respiratory rate of the patient. This can result in a more accurate assessment of the patient's clinical outcome, hence reflected in this study's findings. This finding is similar to a previous study by Prakash *et al.*, showing ROX index's ability to help predict subjects with worse outcomes. Predicting a patient with a worse outcome helps clinicians better

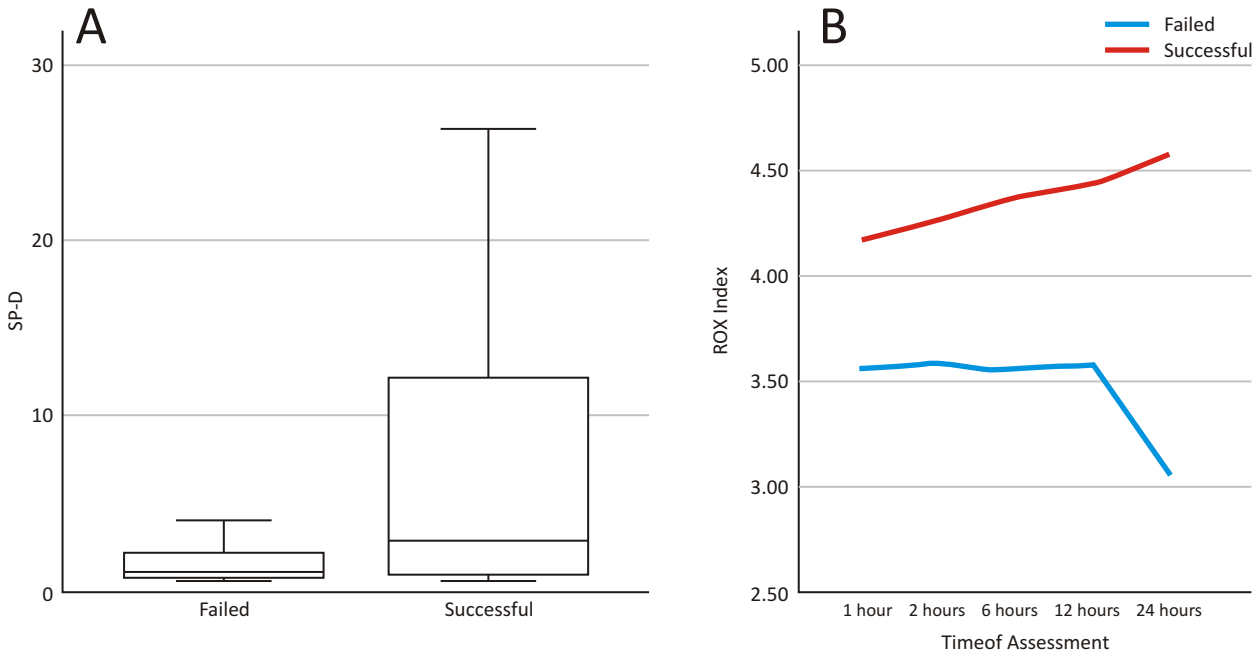

Figure 1. Graphical Representation of (A) SP-D and (B) ROX Index Pattern between HFNC Outcomes

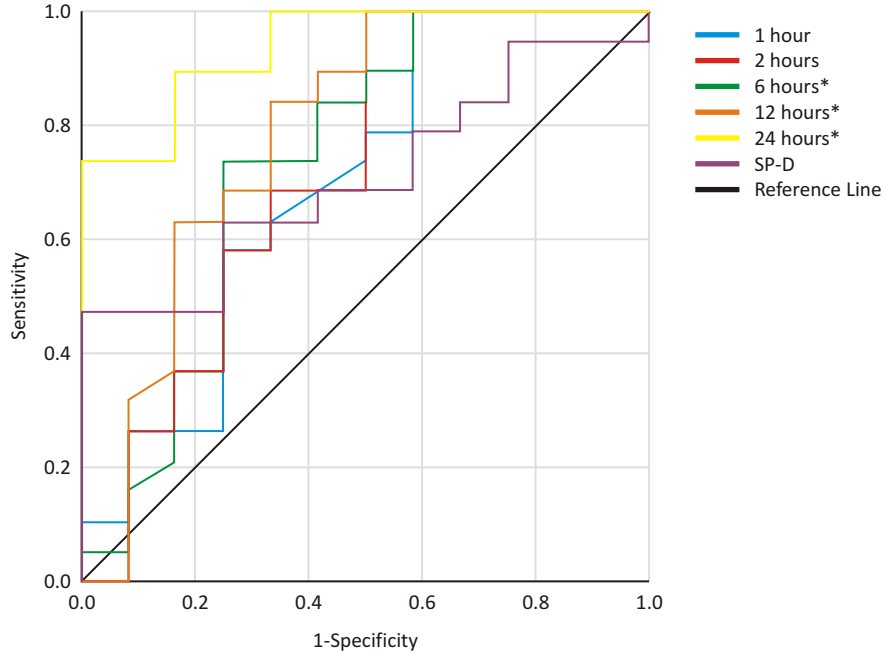

Figure 2. ROC Analysis of ROX Index and SP-D to Predict HFNC Outcome. *p < 0.05

prepare for various treatments, such as early invasive mechanical ventilation.[5] ROX index was also an excellent HFNC outcome predictor in other respiratory diseases. In a previous study, ROX index was proven to be an excellent HFNC outcome predictor in intensive-care pneumonia patients.[4]

A meta-analysis study showed that HFNC has a good predictive outcome ability, with high variance in time of assessment and cut off points. Although cumulatively proven to have a good predictive ability (sAUC: 0.81, sensitivity: 70%, specificity: 79%), there were wide variance of optimal cut-offs (3.63–3.99 ng/ml) and

TABLE 2
Cut-off Values, Sensitivity, and Specificity of ROX Indexes and SP-D to Predict HFNC Outcome

Variables	Cut-off	Sensitivity (%)	Specificity (%)
ROX Index			
1 hour	3.85	63.16	66.67
2 hours	3.90	68.42	66.67
6 hours	3.82	73.68	75.00
12 hours	3.99	68.42	66.67
24 hours	3.63	84.21	83.33
SP-D	1.14	84.20	83.30

time of assessments (1 to 24 hours) found in previous studies. Various potential confounding factors such as publication bias, comorbidity (diabetes, hypertension, heart disease), and subject characteristics (age, gender) were not found to cause these variabilities.[5] However, population difference is a potential confounding factor that can be further studied with an increasing number of studies in various populations. Future studies with a larger and more diverse population can contribute to a better understanding of ROX index predictive ability of HFNC outcome.

This study found higher serum SP-D values in patients with successful HFNC outcomes. This study is the first to analyze serum SP-D values and HFNC outcomes in COVID-19. A previous study showed higher SP-D values in COVID-19 patients with a worse clinical outcome, such as ARDS.[6] This finding is suggested to be related to the protective effect of SP-D. SP-D is known to be released by type II alveolar cells. Increased alveolar vascular permeability allows alveolar SP-D to be released to systemic circulation. SP-D contributes to various immune functions involving alveolar macrophage and dendritic cells, such as agglutination and opsonization of various microbes. In COVID-19, SP-D production increases in response to the pulmonary SARS-CoV-2 virus. This increase in production, accompanied by increased alveolar vascular permeability caused by the inflammatory condition, increased serum SP-D values in COVID-19.[7]

COVID-19 patients treated with HFNC are already in severe or critical clinical conditions. In these patients, serum SP-D values were similarly high in relation to high pulmonary viral load. High viral load and perialveolar inflammation resulted in high serum SP-D values.[10] In this study, patients with successful HFNC outcomes have higher SP-D values. This finding can be attributed to the more severe destruction of type II alveolar cells in patients with failed HFNC outcomes, which resulted in lower overall SP-D production. Higher SP-D production also helps with pulmonary immune function, which leads to a better clinical course in patients with successful HFNC outcomes.

The limitation of this study is the exclusion of smoking status and smoking history, both of which can influence the outcome and SP-D levels of the subjects. Further study with serial SP-D measurements must be conducted to know the correlation between SP-D values and the clinical course of COVID-19 patients with HFNC. Further multicenter study with a more significant number of samples is also necessary to conclude the most optimal time of assessment and cut-off value of ROX index to predict HFNC outcome.

CONCLUSION

This study showed a significant association between ROX index, SP-D values, and HFNC outcome in COVID-19 patients. This study also showed significant HFNC outcome predictive ability of ROX index in COVID-19 patients.

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