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Factors affecting the failure of High Flow Nasal Cannula Oxygen therapy in Intensive Care follow-up of COVID-19 Severe Respiratory Failure

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Abstract

Aim

Acute respiratory distress syndrome is the primary clinical problem that requires follow-up at the intensive care units. High Flow Nasal Cannula Oxygen Therapy has become an increasingly popular method by reducing the need for intubation but determining which patient will benefit from High Flow Nasal Cannula Oxygen Therapy is an important issue.

Methods

Seventy patients who followed up with acute respiratory distress syndrome related COVID-19 treated with High Flow Nasal Cannula Oxygen Systems as initial treatment at the intensive care units were retrospectively review. The primary endpoint of this study is to identify factors correlating with failure (mortality and invasive mechanical ventilator requirement) of High Flow Nasal Cannula Oxygen Therapy in the treatment of COVID-19-related severe ARDS. The secondary aim of this study is to determine the ROX index measured at the 12th hour, which will indicate the need for intubation in critically ill patients followed up with HFNC.

Results

Advanced age, male gender, and low ROX index were independent variables affecting High Flow Nasal Cannula Oxygen Therapy failure. While mortality was lowest in patients who completed the process with High Flow Nasal Cannula Oxygen Therapy treatment, patients who were intubated early (12-24h) had lower mortality than those who were intubated later (>24h) (Mortality rates were %4,3 ,%65,6 ,%93,3 respectively). The cut-off value for ROX index, which will indicate the need for intubation, was found to be 2.84.

Conclusion

High Flow Nasal Cannula Oxygen Therapy can be an effective treatment method in the follow-up of patients with COVID-19-related severe respiratory failure. Despite this, the requirement for intubation develops in two third of the patients. Early intubation reduces mortality in patients who fail High Flow Nasal Cannula Oxygen Therapy, and the easily calculated ROX index is a useful parameter to determine the need for intubation.

Keywords: COVID-19, high-flow nasal cannula oxygen therapy, intensive care units, predictive factor, ROX index, severe ARDS

Introduction

Coronavirus Disease 2019 (COVID-19), began in Wuhan, China in December 2019 and caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has spread rapidly throughout the world in 3 months and was declared a pandemic by the World Health Organization[1]. Acute respiratory distress syndrome (ARDS) is the main clinical problem that requires follow-up in the intensive care unit (ICU) due to destructive lung damage and is responsible for approximately 20% of the patients with high mortality rates up to %80[2].

COVID 19-related ARDS and the need for intensive care prolong hospital stays and have a high cost on healthcare systems worldwide, especially in those receiving invasive mechanical ventilator (IMV) therapy[3,4]. In addition, in many different studies in the literature, it has been emphasized that the follow-up of COVID-19 patients with IMV causes secondary infections, difficulties in prone positioning, difficulties in weaning, unnecessary sedation practices, and is associated with higher mortality[5,6]. It is mentioned that high-flow nasal cannula oxygen systems (HFNC) can be an effective method of respiratory support reducing complications associated with IMV, as suggested by the Surviving Sepsis Campaign, and has become an increasingly popular method among clinicians[7-9].

Determining which patients will benefit from HFNC or need IMV support in ICU follow-up of COVID-19 patients is a complex and important issue[10]. Various predictors such as ROX index have been developed by Roca et al. to support clinicians in making this critical decision in patients with respiratory failure in 2016[11].

However, it is known that severe respiratory failure caused by COVID-19 has a feature and phenotype different from the clinical features of known ARDS[12]. A re-evaluation of the effectiveness of the ROX index was needed in this special patient group, and different cut-off values have been reported, albeit limited, in the literature[13-15].

The main aim of this study is to identify factors correlating with failure of HFNC in the treatment of COVID-19-related severe ARDS. Our secondary aim is to determine the ROX index, which will indicate the need for intubation in critically ill patients followed up with HFNC.

Patients/ Material and Methods

Following the approval of the Institutional Ethics Committee [Protocol no: 2020/514/179/13, date: 11/06/2020] and take informed consent from all patients or their first degree relatives in the beginning of HFNC treatment at admission to ICU, between the 23rd of June and 30th of October in the ICU who treated COVID-19 patients in XXX Hospital, data of patients who are followed up with severe ARDS related COVID-19 and who treated with HFNC as initial treatment were reviewed. This retrospective cohort study was conducted by following the ethical principles stated in the Declaration of Helsinki, "Good Medical Practice Guidelines" and "Good Laboratory Practice Guidelines"

Study population

In all patients, COVID-19 was diagnosed with a positive result measured by Real-Time Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR). Among the positive patients, those who were evaluated as severe ARDS according to the Berlin criteria[16] and who received HFNC treatment as the initial treatment indicated for follow-up in the intensive care unit were included in the study. Since the management of Covid-19-related ARDS in intensive care differs from known ARDS, according to our institutional guideline, HFNC was applied to patients with the following parameters as initial therapy: Respiratory rate (RR)<45/min, blood oxygen saturation (SpO2) <85%, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) < 100 mmHg, use of auxiliary respiratory muscle and being conscious.

Including antiviral drugs (favipiravir 2x1600 mg loading, 2x600mg/day maintenance, 5 days to complete), anticoagulant treatment (low molecular weight heparin 2x0.4-0.6ml/day), hydroxychloroquine 2x200 mg/day and dexamethasone 6 mg/day. Treatment was applied with a protocol under the treatment algorithm of the Ministry of Health[17].

The application method of HFNC

Treatment was started using a heated humidifier and a heated inspiratory circuit to deliver high flow oxygen therapy through the nasal cannula, with a programmed temperature between 32°C and 37°C according to tolerance, high flows of 30-60 L / min, and FiO2 adjusted to provide SpO2> 88-92% levels. The patients were placed in a prone awake position with a minimum of 6 hours and a maximum of 12 hours of intervals daily. Throughout therapy, patients were monitored by non-invasive measurement of heart rate, SpO2, and RR. Surgical masks were worn in all patients during high-flow therapy to reduce the risk of virus transmission via droplets or aerosols[18].

ROX index was calculated with the formula " [SpO 2 / FiO 2] / RR "[11].

Intubation decision;

Intubation decision is made if there is a change in consciousness, presence of aspiration risk, severe metabolic and respiratory acidosis, development of cardiopulmonary arrest, SO2 below 85 despite maximum oxygen support, RR> 35 and its continuation according to our institution guidelines.

Inclusion criteria

1. All conscious patients older than 18 years of age, diagnosed with Covid-19 according to the results of RT-PCR and treated with HFNC as the initial treatment when taken to the ICU were included in the study.

Exclusion criteria

1. Patients under the age of 18,

2. Patients who received conventional oxygen therapy with reservoir mask or noninvasive positive pressure ventilation (NIPPV) as initial therapy at ICU admission

3. Patients intubated before or at the time of ICU admission

Patients were withdrawn during the study

1. Patients whose treatment needs to be discontinued due to HFNC side effects (abdominal distention, nasal irritation)

2. Patients who were intubated within 12 hours after admission to intensive care and started IMV support,

3. Patients who cannot tolerate simultaneous prone position application with HFNC application (obesity, agitation, abdominal distension, etc.)

4. Patients who have received any treatment other than the standard treatment protocol like anti-cytokine therapy (cytokine filter, Interleukin-6 antagonist therapy) and convalescent plasma,

5. Patients whose data are not available.

Data collection

Demographic data such as age, gender, accompanying comorbid disease APACHE-II score and PaO2 / FiO2 ratio evaluated during admission to ICU, the number of treatment days before admission to ICU, respiratory parameters such as SpO2, FiO2, RR at 12th hour, intubation necessity and time, ICU mortality, were obtained from prospectively recorded data.

Endpoints of the study

The primary endpoint of this study is to identify factors correlating with failure of HFNC in the treatment of COVID-19-related severe ARDS. HFNC treatment failure was defined as the development of mortality in the ICU and the requirement for an IMV. According to the development of mortality in the ICU, the patients were divided into group 1 who survived and group 2 who developed mortality. When the patients were evaluated in terms of IMV requirement, those that were not required were named group A, and those that were required were named group B.

The secondary aim of this study is to determine whether the ROX index is a usable parameter in deciding the need and timing of intubation. For this purpose, all patients were divided into three subgroups according to the presence and timing of intubation as HFNC group (whose treatment was completed with HFNC), Early intubation group (who were intubated between 12-24 hours after admission to ICU) and Late intubation group (who were intubated after 24 hours from admission to ICU).

Statistics

Statistical analyzes were made with the SPSS 21 program. Since the design of the study was a retrospective cohort, only patients between the dates we specified were included in the study. Sample size was not calculated. Quantitative variables, expressed as mean ± Standard deviation, were compared using the Oneway Anova test. The qualitative variables were expressed in percentages and compared using either the chi-square test or Fisher's exact test. Oneway anova test was used in the evaluation of three independent groups, and post-Hoc Bonferroni or Tamhane's tests were applied to values with $p < 0.05$. Nonparametric variables among 3 independent

Table 1: Analysis of factors affecting mortality

	Group 1 Mortality (-) N:34	Group 2 Mortality (+) N:36	Overall N:70	Univariate Analysis	Multivariate Analysis
Age	57.15±15.4	70.1±15.1	63.8±16.5	0.001[a]	0.005[c]
GenderFemale	15 (44.1%)	7 (19.4%)	22 (31.4%)	0.024[b]	0.015[c]
Male	19 (55.9%)	29 (80.6%)	48 (68.6%)		
Comorbidities	25 (73.5%)	30 (83.3%)	55 (78.6%)	0.240[b]	-
Hypertension	16 (47.1%)	21 (58.3%)	37 (52.9%)	0.241[b]	-
DM	11 (32.4%)	12 (33.3%)	23 (32.9%)	0.567[b]	-
CAD	7 (20.6%)	11 (30.6%)	18 (25.7%)	0.249[b]	-
Cancer	2 (5.9%)	6 (16.7%)	8 (11.4%)	0.149[b]	-
Asthma	5 (14.7%)	10 (27.8%)	15 (21.4%)	0.149[b]	-
CRF	3 (8.8%)	2 (5.6%)	5 (7.1%)	0.472[b]	-
Treatmentday before ICU	5.18±5.60	4.47±4.61	4.81±5.09	0.567[a]	-
APACHE II	19.74±9.06	21.19±7.4	20.49±8.23	0.462[a]	-
Admission P/F	90.61±4.96	91.63±4.29	91.13±4.62	0.36[a]	
ROX Index	3.01±0.62	2.72±0.41	2.86±0.54	0.027[a]	0.121[c]
IMV treatment	12 (%35.3)	35 (%97.2)	47 (%67.1)	0.000[b]	0.001[c]

DM: Diabetes Mellitus, CAD: Coronary Artery Disease, CRF: Chronic Renal Failure , ICU: Intensive Care Unit, P / F: PaO_2/ FO_2, IMV: Invasive Mechanical Ventilator, P / F:PaO2 / FiO2
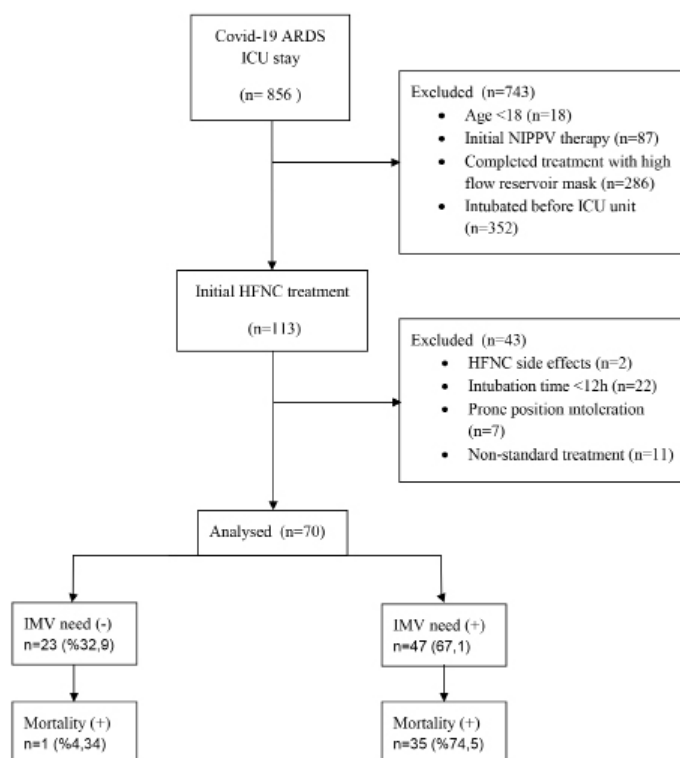
[a]Oneway Anova, [b]Pearson Chi-Square, [c]Binary Logistic regression

Figure 1: Flow diagram of patients treated with high- flow nasal cannula oxygen therapy.

groups were evaluated with the K independent test, and the Mann-Whitney test was used to identify the relationship between the groups that were found to be significant. A multivariate analysis was performed to evaluate the significant variables associated with intubation and mortality. We explored the optimal cut-off point for the ROX index at the 12'th hour to predict failure of high flow oxygen therapy by analyzing diagnostic performance with ROC curves. The area under the curve was analyzed for overall accuracy. A p < 0.05 was considered significant.

Results

A total of 856 COVID-19 patients were followed up at the ICU between March and November 2020. HFNC treatment was initiated in 113 of them while they were admitted to ICU. 43 patients were excluded from the study because 22 patients with %68,1 mortality were intubated within the first 12 hours, 7 patients did not tolerate prone positioning, 11 patients received non-standard treatments, 2 patients developed HFNC complications (nasal irritation in 1 patient and abdominal distention in 1 patient) and 1 patient due to missing data. 70 COVID-19-related severe ARDS patients were included in the study and statistical analysis was performed (Figure 1).

Thirty-four (48.6%) of 70 patients were discharged from ICU and while these patients were Group 1, mortality occurred in 36 (51.4%) of them in ICU and these patients constituted Group 2. Factors affecting mortality in predicting HFNC failure are given in Table 1. Accordingly,

Table 2: Factors affecting intubation

	Group A IMV(-) N:23	Group B IMV(+) N:47	Overall N:70	Univariate Analysis	Multivariate Analysis
Age	53,91±14,2	68,64±15,48	63,8±16,51	0,000[a]	0,002[c]
GenderFemale	9 (%39,1)	13 (%27,7)	22 (%31,4)	0,241[b]	-
Male	14 (%60,9)	34 (%72,3)	48 (%68,6)		
Comorbidities	16 (%69,6)	39 (%83,0)	55 (%78,6)	0,165[b]	-
Hypertension	10 (%43,5)	27 (%57,4)	37 (%52,9)	0,199[b]	-
DM	9 (%39,1)	14 (%29,8)	23 (%32,9)	0,302[b]	-
CAD	5 (%21,7)	13 (%27,7)	18 (%25,7)	0,411[b]	-
Cancer	2 (%8,7)	6 (%12,8)	8 (%11,4)	0,474[b]	-
Asthma	3 (%13,0)	12 (%25,5)	15 (%21,4)	0,190[b]	-
CRF	2 (%8,7)	3 (%6,4)	5 (%7,1)	0,534[b]	-
Treatmentday before ICU	4,78±4,48	4,83±5,41	4,81±5,09	0,971[a]	-
APACHE II	17,91±8,60	21,74±7,82	20,49±8,23	0,067[a]	-
ROX Index	3,13±0,70	2,73±0,38	2,86±0,54	0,002[a]	0,011[c]
Mortality	1 (%4,3)	35 (%74,5)	36 (%51,4)	0,000[b]	0,003[c]

DM:Diabetes Mellitus, CAD: Coronary Artery Disease, CRF: Chronic Renal Failure , ICU: Intensive Care Unit, P/F: PaO_2/FO_2, IMV: Invasive Mechanical Ventilator

[a]Oneway Anova, [b]Pearson Chi-Square, [c]Binary Logistic regression

Table 3: Comparison of subgroups with clinical data according to IMV need and timing

	IMV (-) N:23	IMV <24 h N:32	IMV >24 h N:15	P value
Age	53,91±14,21	66,91±15,57	72,33±15,14	0,007*[a]
ROX Index	3,13±0,70	2,75±0,41	2,68±0,31	0,032*[b]
Mortality (n,%)	1, %4,3	21, %65,6	14, %93,3	0,000[b]

*Oneway Anova, postHoc [a]Bonferroni test, [b]Tamhane's T2 test p<0,017 is statistically significant [a](Group 1 vs Group 2 and Group 3; p:0,007; Group 2 vs group 3; p:0.760), [c]Mann-Whitney test, p<0,05 statistically significant (Group 1 vsGroup 2 and Group 3, p:0,000;

Group 2 vs Group 3, p:0,045)

the mean age of the patients included in the study was 63.8, and there was a significant difference between the two groups (57.1 vs 70.1 p: 0.001, respectively). The groups were similar to each other in terms of the presence of additional diseases, but the number of male genders was higher in Group 2. APACHE II scores and PaO2 / FiO2 ratios at admission and the treatment days before admission to the ICU were similar between the two groups. The ROX index of the patients in Group 2 was found to be significantly lower than the other (2.72 vs 3.01 p: 0.027, respectively). There was a significant relationship between IMV requiring and ICU mortality. In multivariate analysis, we found that advanced age, male gender, and requirement of IMV are independent variables affecting ICU mortality.

In terms of IMV requirement as a predictor of HFNC failure, the patients were evaluated in Table 2. The median age of patients in Group A (53.9 vs 68.6, respectively; p: 0.000) and ROX index (3.13 vs 2.73, respectively; p: 0,002)

were lower than those in Group B. Age and ROX index were found as independent variables in multivariate analysis to determine the need for mechanical ventilation.

The cutoff value of the ROX index in determining the need for intubation was found to be < 2.84 (63.8% sensitivity, 69.6% specificity, AUC: 0.687) (Table 2). In subgroup analysis there was no statistically significant difference between the groups in terms of ROX index (Table 3). HFNC group were younger than the patients in the other two groups and mortality was lower in the early intubation group compared to the latter (65.6% vs 93.3%, respectively).

Discussion

In this study, in which we examined the parameters that may be effective in deciding to continue HFNC treatment in 70 patients who began ICU follow-up with HFNC due to COVID-19-related severe ARDS, IMV requirement developed in 67.1% of patients and ICU mortality was

51.4%.

Advanced age and male gender were found to be independent variables that negatively affect HFNC success and increase both IMV requirement and ICU mortality. Besides, it was found that patients with a ROX index of less than 2.84 at the 12th hour had a higher rate of intubation need and there was a significant relationship between delayed intubation time and mortality.

ICU mortality rates due to COVID-19 disease have been reported between 0-85% in a review of 24 studies[19]. In an other review where the data of 12,437 patients were analyzed, it was reported that the ICU hospitalization rate was 21%, the mortality rate was 28.3%, and the need for IMV was 43%. Similar to our results, male gender (OR: 1.37), advanced age (> 60 years, OR: 3.7), need for IMV (OR: 16.4) and presence of ARDS (OR: 6.5) were reported as independent prognostic variables in determining ICU mortality[20]. According to these data, the mortality rate was higher in our study and we attribute this to the fact that all patients included in the study had severe ARDS.

The method of respiratory support treatment to be applied to patients in the ICU follow-up of COVID-19-related ARDS is still a controversial issue[13]. In a study comparing 146 critically ill patients followed up with HFNC within the first 24 hours in the ICU and 233 who did not undergo HFNC, no significant difference was found in terms of mortality. However, less IMV requirement was seen in the HFNC-treated group.21 On the contrary, in another study with moderate-severe COVID-19 releated ARDS, mortality was 11.2% in patients whose treatment was completed with HFNC, while the mortality increased to 47.5% in patients requiring intubation[13]. However, in the details of this study, the rate of patients with severe ARDS has not been reported. In our study, which consisted entirely of severe ARDS patients, a direct relationship was found between IMV requirement and ICU mortality, which was valuable in recommending continuation of treatment with HFNC in patients who can tolerate it.

When NIPPV support such as HFNC is applied, the most feared point is the concern that patients who worsen under treatment and require a more invasive treatment method may be overlooked[10]. The recommendation of German investigators for COVID-19 critical patient follow-up is to perform early intubation and IMV in patients who fail with HFNC or NIPPV[22].

The study of Roca et al.[23] in 2019 may be a guide in deciding the success of HFNC treatment. In this study examining patients with ARDS due to pneumonia, they reported that HFNC treatment was unsuccessful in patients with a ROX index of less than 3.85.

Studies related to the ROX index have been conducted to evaluate the success of HFNC treatment during the COVID 19 pandemic. In a retrospective study conducted in Spain, they stated that HFNC is a useful treatment as a bridge therapy to avoid intubation in COVID-19-related ARDS, and that a ROX index below 4.94 is the cut-off to predict the need for intubation after HFNC is initiated[14].

Patel et al. reported that the requirement for intubation increased approximately 2-fold in patients with a ROX index < 5 at the beginning, however, any ROX index decrease in daily follow-ups under HFNC treatment increased the intubation requirement 14-fold[13].

In another study Chandel A et al found ROX index >3.0 at 2, 6, and 12 hours after initiation of HFNC was 85.3% sensitive for identifying subsequent HFNC success[24].

In our study, we found that a ROX index of < 2.84 , evaluated at the 12th hour, increased the requirement for IMV. The reason for this value is lower than the cut-off values given in other studies in the literature may be that the patient group in our study consisted of severe ARDS patients at the border of the intubation which is why our study is unique.

The limitation of this study is its retrospective design and the small number of patients. However, analyzing 70 patients, all of whom have severe ARDS, increases the strength of this study.

Conclusions

HFNC can be an effective treatment method in the follow-up of patients with COVID-19-related severe ARDS. Despite this, the requirement for intubation develops in two third of the patients. Preferring intubation instead of HFNC in advanced age male patients with a ROX index of <2.84 at 12 hours will reduce mortality.

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