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TANAFFOS

Is Non-Invasive Ventilation a Good Choice in All Patients with Severe COVID-19? A Cohort Retrospective Study

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Background: The recent outbreak of Coronavirus 2019 (COVID-19) is a respiratory disorder caused by the Acute Respiratory Syndrome Coronavirus 2. At the start of the epidemic, early intubation was the optimal strategy for managing ARDS caused by COVID-19. Several non-invasive methods for respiratory support in patients with moderate to severe COVID-19 may reduce intubation, disease severity, ventilator use, and hospitalization in the intensive care unit (ICU). In this study, the characteristics of COVID-19 patients who failed NIV therapy were compared with those who had successful NIV.

Materials and Methods: The present descriptive-analytical study was conducted at the COVID-19 center of KHORSHID University Hospital. Patients were aged > 18 years with confirmed COVID-19 and hospitalized in the ICU from the beginning of January to the end of March 2021. They had an oxygen level of < 88% despite receiving 15 L of oxygen with reserve masks and were undergoing non-invasive ventilation (NIV) treatment. Data collection included patients' demographic information, vital signs, and test results upon hospital admission, and assessed disease severity using APACHE, SAPS, and SOFA scores. Patients were categorized into responders (R) and non-responders (NR) to determine predictors of non-invasive ventilation (NIV) success, with follow-up based on device tolerance and changes in vital signs.

Results: 71 Individuals were candidates for NIV. Twenty patients were excluded from the study, and 51 patients were included in the study. Of these, 35 patients underwent NIV treatment failure (NR). On the other hand, 16 (31.4%) patients completely recovered after receiving NIV (R) and they were discharged from the ICU.

Conclusion: Serum Albumin and BMI levels of COVID-19 patients undergoing NIV therapy seem to affect their responses to treatment. Hence, it is recommended to evaluate the nutritional status of patients before the start of NIV.

Keywords: Noninvasive ventilation; COVID-19; ARDS

INTRODUCTION

The recent outbreak of Coronavirus 2019 (COVID-19) is a respiratory disorder caused by the Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On January 30th, 2020, the World Health Organization (WHO) director-general declared the disease as a public and international health emergency, which is the highest level of alert in the WHO (1). The virus spread rapidly to other Chinese provinces and to more than 27 other countries such that the number of patients reached more than 70,000 known cases on February 17, 2020 (2). According to the latest figures from the WHO (when preparing this paper on May 21, 2021), approximately 165 million people have been infected

with the disease worldwide of which, 3.4 million have died after a year of the disease outbreak (3).

The clinical symptoms of COVID-19 vary from asymptomatic to acute respiratory failure requiring mechanical ventilation. Fever, dry cough, lethargy and fatigue, dyspnea, and gastrointestinal symptoms are the most common symptoms of the disease (4, 5). Most patients with COVID-19 present mild to moderate symptoms, but approximately 15% develop severe pneumonia, and about 5% eventually suffer from acute respiratory distress syndrome (ARDS), septic shock, or multiple organ dysfunction (5, 6). Up to 50% of deaths have been reported in patients with acute respiratory problems induced by COVID-19 (4).

At the start of the epidemic, early intubation was the optimal strategy for managing ARDS caused by COVID-19. The clinical picture of COVID-19-induced severe hypoxia differs from the mechanism of typical ARDS. Interestingly, in most cases of COVID-19-induced ARDS, the mechanical properties of the respiratory system are preserved such that good pulmonary compliance is observed (7). Meanwhile, the stretchability and pulmonary compliance decrease in typical ARDS, indicating the need for updating treatment protocols (7, 8). Several non-invasive methods for respiratory support in patients with mild to moderate COVID-19 may reduce intubation, disease severity, ventilator use, and hospitalization in the intensive care unit (ICU) (9). In addition, any oxygen therapy method and respiratory support can eliminate the pathogen (10-12).

Clinical experience has demonstrated that non-invasive ventilation (NIV) plays a vital role in managing COVID-19-induced ARDS. In general, this method can improve oxygen delivery, limit the work of respiratory muscles, and prevent damage to the patient's lungs (7). However, intubation after NIV has been reported with a probability of 26-26%, and some studies even indicate that the use of NIV can deteriorate a patient's survival by delayed intubation (13).

Accurate selection of patients for NIV treatment is a challenge posed to physicians because the conditions for NIV initiation in patients with COVID-19 are not the same. In this study, the characteristics of COVID-19 patients who failed NIV therapy were compared with those who had successful NIV.

MATERIALS AND METHODS

Study design

After ethical approval of the proposal by the Isfahan University of Medical Science committee with ID number: "IR.MUI.MED.REC.1399.760", the present descriptive-analytical study was carried out at the COVID-19 center of KHORSHID University Hospital. Patients were aged > 18 years with confirmed COVID-19 (positive PCR test for COVID- 9), hospitalized in the ICU from the beginning of January to the end of March 2021, had an oxygen level of < 88% despite receiving 15 L of oxygen with reserve masks, and were undergoing NIV treatment. Patients with intubation upon admission, hemodynamic instability, agitation and GCS < 15, NIV intolerance, facial anatomical abnormality, barotrauma, excessive sputum, recurrent vomiting, and dissatisfaction were excluded from the study.

Data collection

Patients' demographic information (i.e., age, sex, body mass index or BMI, and smoking history) was collected from their records. Also, their vital signs and test results were recorded from values measured at admission. On the first day of hospitalization, disease severity was also assessed based on APACHE, SAPS, and SOFA scores. Patients were followed up until the outcome (discharge from the ICU or intubation). Based on their response to treatment, we divided the patients into two groups: responders (R) and non-responders (NR). The clinical and paraclinical characteristics of these patients were compared to determine the predictors of NIV success.

NIV settings and follow-up of patients

BIPAP initially was started with PEEP settings: 5-10 and PS: 10 (based on CO_2 levels and hypoxia intensity) and an oxygen level of 15 L/min. Patients were monitored for

alertness, device tolerance, and vital signs for 1 h. The device settings were changed according to VBG taken 1 h after the start of treatment. If the device was not tolerated for 1 h, the patient was excluded from the study. The ICU patients were monitored continuously and evaluated to continue or discontinue treatment in the occurrence of new problems. In the event of NIV intolerance after 1 h or complications that led to discontinuation of treatment, the NIV was discontinued, and the patient was assigned to the NR group. The intubation criteria included respiratory fatigue and increased blood CO_2 levels (>60 mmHg), sat <90 despite receiving NIV with a tolerable setting, or hemodynamic instability.

Treatment of patients

In all patients, treatment was based on the national COVID-19 treatment protocol in the ICU. In addition to NIV treatment, patients with low CRP levels (CRP < 20) in the first week of illness received antiviral treatment with 200 mg of Remdesivir on the first day and 100 mg daily with no use of corticosteroids. Patients with CRP > 20 or in the second phase of the disease received systemic corticosteroids. Patients had relatively negative fluid balance and received DVT prophylaxis with enoxaparin 40 mg daily.

RESULTS

Among the patients with respiratory failure, 71 individuals were candidates for NIV. Twenty patients were excluded from the study (2, 7, 8, and 3 patients with hemodynamic instability, malaise, NIV intolerance in the first hour, and early intubation, respectively). Finally, 51 patients were included in the study. Of these, 35 (68.6%) patients underwent NIV treatment failure (NR). On the other hand, 16 (31.4%) patients completely recovered after receiving NIV (R) and they were discharged from the ICU (Figure 1).

The results of patients' demographic information, clinical findings, and vital signs (Table 1) indicate that only BMI is significantly different between the two groups (P-value<0.05). The clinical findings reveal a significant difference in the number of days of NIV administration between the two groups, i.e., the duration of NIV was significantly shorter in the NR group than in the R patients (P-value = 0.02). According to SOFA and SAPA criteria, the severity of the disease at the time of hospitalization did not differ between the two groups.

Among the laboratory findings of this research, only albumin (Alb) levels were significantly different in the two groups, and neither was different in the other experiments (Table 2).

In this study, six (11%) patients treated with interferon, 28 (54%) patients received Remdesivir treatment as an antiviral, and 17 (34%) patients did not receive any antiviral drugs according to the time of admission. In 96.1% of the patients, the total dose of corticosteroids was above 500 mg of methylprednisolone, which resulted in no significant difference in the prognosis of R and NR patients (Table 3).

Table 1. Demographics and clinical results

	Variables	Total N=51	Group NR N=35 (68.6%)	Group R N= 16 (31.4%)	p-Value
Demographics	Age, Mean (SD)	59.55 (11.49)	60.29 (11.85)	57.94 (10.84)	0.504
	Sex, (male) N (%)	41 (80.4%)	27 (77.1%)	14 (87.5%)	0.474
	BMI, Mean (SD)	25.39 (23.88- 27.34)	25 (23.67 - 27)	26.25 (25.20 - 31.15)	0.051
	Smoking status (Yes) N (%)	6 (13.0%)	4 (12.9%)	2 (13.3%)	0.99
	Days from symptoms onset to hospitalization (Symptom duration), Mean (SD)	9 (8 - 11)	9 (8- 11)	8.5 (8- 10.5)	0.621
	Days from hospitalization to NIV (NIV duration), Mean (SD)	4 (2-8)	4 (2- 7)	7.5 (3.5 -11)	0.025
Clinical	O_2 (Sat1), Mean (SD)	78 (70- 84)	77 (70- 83)	81 (75.50 – 85)	0.060
	Hospitalization duration, Mean (SD)	9 (5- 12)	8 (4- 11)	11 (6.5- 17)	0.080
	Sofa, Mean (SD)	4 (3- 5)	4 (3- 5)	3 (3 -4)	0.255
	Saps, Mean (SD)	38.29 (7)	39 (7.24)	36.75 (6.4)	0.291

Table 2. Laboratory findings

Variables	Total (Mean (SD))	Group NR (Mean (SD))	Group R (Mean (SD))	p-Value
White blood cell	6.8 (5.5- 11)	6.90 (5.50- 10.70)	5.75(4.70- 12.45)	0.563
Hemoglobin	13.6 (12.5- 14.4)	13.5 (12- 14.20)	14.30 (12.85- 15.05)	0.062
Albumin	3.5 (3.30- 3.90)	3.5 (3.30- 3.80)	3.75 (3.60- 3.95)	0.029*
CRP	102 (54.69)	97.57 (55.92)	112.33 (52.06)	0.341
ESR	52.42 (28.61)	53.03 (30.16)	51 (25.55)	0.941
Troponin	9.5 (1.90- 14.50)	10 (1.90- 18.90)	5 (0- 14.20)	0.302
ALT	44.76 (22.27)	46.43(25.38)	41.13(13.14)	0.436
AST	61.10(43)	66.46 (49.15)	65.31 (26.21)	0.931
PCO_2	40.99 (8.48)	40.46 (7.72)	42.16 (10.13)	0.512

* Significant, ALT: Alanine transaminase, AST: Aspartate transaminase, ALP: Alkaline phosphatase, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Table 3. Medications that are prescribed for the patients

Variables		Total	Group NR	Group R	p-Value
Antiviral, N (%)	Interferon	6 (11.8%)	5 (14.3%)	1 (6.3%)	0.379
	Remdesivir	28 (54.9%)	19 (54.3%)	9 (56.3%)	0.99
Corticosteroid, N (%)	Less than 250	0 (.0%)	-	-	
	250-500	2 (3.9%)	2 (5.7%)	-	0.467
	More than 500	49 (96.1%)	33 (94.3%)	16 (100%)	

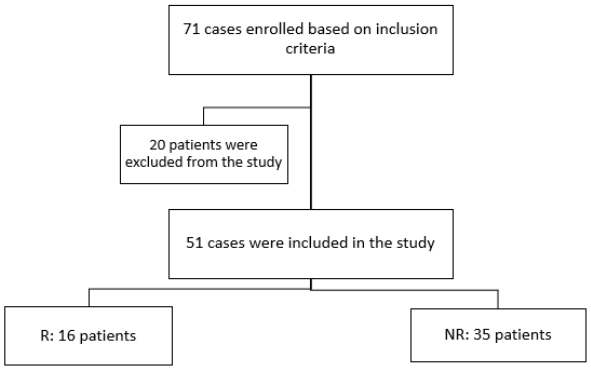

Figure 1. The study protocol

DISCUSSION

Unlike intubation, NIV is a non-invasive method that delivers oxygen to patients. Although intuition is a life-saving option in severe cases of COVID-19, mortality rates are still high in patients undergoing intubation (14, 15). NIV has been proposed to reduce the effects of invasive mechanical ventilation (2). At the beginning of the COVID-19 crisis, early intubation was assumed to reduce injuries from barotrauma effectively and increase tidal volume (16, 17). However, early intubation, profound sedation, and delayed separation from the ventilator are the leading causes of elevated mortality (17). Early intubation also increases the chance of ventilator-induced infections.

On the other hand, the use of NIV methods does not reduce the need for intubation. Failure in the NIV is equivalent to the death of a patient with or without COVID-19. Therefore, it is essential to identify patients who do not have a good prognosis regarding earlier intubation despite receiving NIV. Previous studies on the use of NIV in treating ICU-admitted patients with COVID-19 have not reported similar results.

This study compares the characteristics of patients with successful NIV with those with NIV failure. Overall, our results showed that out of 51 patients undergoing NIV, 35 individuals underwent NIV treatment failure and proceeded to intubation. According to a recently published study, the use of NIV as a primary intervention in COVID-19 patients who need ventilation is significantly associated with survival benefits. Additionally, the mortality rate for patients with NIV failure is lower than those undergoing intubation as their primary intervention (18). Avdeev et al. presented evidence that the use of NIV only improved oxygenation during hospitalization and was not significantly effective on mortality (19).

In the present study, NIV was more effective in patients with higher BMI. Previous studies have shown that high BMI in patients with COVID-19 is a risk factor for the disease progress. As reported by Kim et al., patients with high BMIs and obesity have a higher chance of death and intubation (20). De Vita et al. found that a BMI > 35 had adverse consequences for patients with COVID-19 (21). Although obesity and high BMI are a risk for patients with COVID-19, the mean BMI of our studied patients was less than 27. It can be argued that patients with higher BMI had better nutrition, which might have also increased Albumin. Therefore, it can be concluded that proper nutrition in group R patients may be among the causes of successful NIV. Pironi et al. observed that most patients with COVID-19 were prone to malnutrition, which could control the severity of their disease (22).

The laboratory findings of the present study showed that only the blood Albumin levels differed between the two groups. In other words, patients with higher Albumin showed a better response to NIV treatment. This result is consistent with the findings of Ramirez et al. (23). A previous study on H1N1 influenza revealed the role of serum Alb levels on admission in the severity of respiratory disease (24). Additionally, Alb is a negative phase reactant protein during inflammation that usually declines in acute inflammation and can exert an antioxidant effect (25). It is the main index of renal and liver function adequacy, and it can decrease in malnourished patients suffering from severe disease. This serious role extended to antiplatelet and anticoagulant properties through a mechanism possibly related to its antioxidant effect (26-28).

Moreover, it can reduce platelet aggregation by downregulation of the Nox2 (26). According to some studies, Alb prevents fibrin polymerization, increases the effect of antithrombin III, and modulates the hepatic synthesis of factor V, factor VIII, and fibrinogen (27). Salinas et al. suggest hypoalbuminemia as a factor in increasing blood coagulation, thrombosis, and death in patients with COVID-19 (28). Since coagulation disorders caused by COVID-19 increase the risk of intravascular thrombosis and mortality (29), it seems that low Alb levels exacerbate this problem and increase the risk of mortality by the abovementioned mechanisms. Therefore, Alb levels seem to be a predictor of NIV success. As noted above, Alb may also indicate the patient's nutritional level such that better therapeutic success may be obtained in well-nourished patients (22).

In the present study, a better response to treatment was observed in patients who tolerated NIV treatment. In other words, the longer duration of NIV administration will increase NIV's success rate. Menzella et al. reached similar results and found that NIV treatment was more successful in patients who tolerated NIV for a longer duration (30). In the current study, higher severity of the disease and lower levels of O2 saturation were recorded in the NR group than in the R patients, but this difference was not statistically significant. Overall, patients who tolerated NIV for a longer duration appeared to have better general conditions. Further studies are recommended in this field.

Very limited studies are available on the success of NIV in severe COVID-19 patients. Although some predictor variables of the NIV success were examined in the present study, the small sample size, and no examination of some important variables such as underlying diseases, clinical symptoms, and lung involvement were some limitations of this work. We tried to determine the relationship between patients' prognosis at admission and their responses to NIV treatment with laboratory conditions, emphasizing various demographic and inflammatory factors, which led to contradictory results. This study can be confirmed by examining a greater number of patients and preventing unnecessary intubation by focusing on predictors of patient mortality and further studies. Overall, serum Alb and BMI levels of COVID-19 patients undergoing NIV therapy seem to affect their responses to treatment. Hence, it is recommended to evaluate the nutritional status of patients before the start of NIV.

Declarations

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflicts of interest

The authors declare that they have no competing interests.

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