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RESEARCH ARTICLE

# Comparison of Invasive and Non-Invasive Mechanical Ventilation in COVID-19 Patients Followed with Respiratory Failure

**Döndü Genç Moralar, Ülkü Aygen Türkmen, Osman Çelik, Aleaddin Uluç, Serpil Şehirlioğlu Şahin**

Department of Anesthesia and Reanimation, University of Health Sciences, Gaziosmanpaşa Training and Research Hospital, İstanbul, Türkiye

## ABSTRACT

**Objective:** The most important complication associated with coronavirus disease-19 (COVID-19) is respiratory failure, which requires mechanical ventilation. The aim of our study is to evaluate the effectiveness of the use of invasive and non-invasive mechanical ventilation (NIV) on oxygenation in patients with COVID-19 who had respiratory failure and needed ventilation support.

**Materials and Methods:** According to the ventilation support used, the patients were divided into two groups: Those for whom NIV was initially preferred (n=48) and those who were initially intubated and received invasive mechanical ventilation (n=50). Arterial blood gas analyzes of the patients were evaluated. The changes in oxygenation and ventilation, the incidence of complications such as hypotension and hypertension, and mortality rates were compared.

**Results:** The partial arterial oxygen pressure ($PaO_2$) values were similar during the follow-up of the patients who were initiated on treatment with NIV and those who were initiated on treatment with invasive mechanical ventilation. However, the survival rate was higher in the patients who were initiated on treatment with non-invasive mechanical ventilation. It was remarkable that the partial arterial carbon dioxide pressure value was higher in the invasive mechanical ventilation group than in the NIV group. The incidence of complications such as hypotension or hypertension was less in the non-invasive mechanical ventilation group.

**Conclusion:** Although $PaO_2$ values are similar, it was found that the survival rate was higher and the complication rate was lower in the patients for whom NIV was preferred. Therefore, we think that NIV should be preferred as much as possible.

**Keywords:** Acute respiratory distress syndrome, coronavirus disease-19, intensive care unit, non-invasive mechanical ventilation

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## INTRODUCTION

The most important complication associated with coronavirus disease-19 (COVID-19) is acute hypoxemic respiratory failure, which requires mechanical ventilation. Numerous mechanisms that cause hypoxemia have been proposed. These include hemoglobinopathies, microthrombus, vascular occlusion, ventilation-perfusion mismatch, pulmonary edema, and acute respiratory distress syndrome (ARDS) due to diffuse massive alveolar damage.[1–4]

In the first data from China, it was stated that 19% of COVID-19 patients had severe hypoxic respiratory failure, and 5% needed mechanical ventilation and intensive care unit (ICU).[5]

Gattinoni et al.[6] emphasized that more than 50% of COVID-19 pneumonia with Berlin ARDS criteria developed silent hypoxemia, these patients had normal lung compliance, and these non-dyspneic patients should only receive complementary oxygen. They suggested using high-flow nasal oxygen (HFNO) therapy, continuous positive airway pressure (CPAP), or non-invasive mechanical ventilation (NIV) in the development of dyspnea. They stated that if the patient had an increase in work of breathing, intubation, and invasive mechanical ventilation (IMV) which should be started. Analysis of the NIV/HFNO process before IMV is very important.[6] It is recommended to target 92–96% oxygen saturation ($SaO_2$) using complementary oxygen when required.[7]

**Address for Correspondence:** Döndü Genç Moralar, Department of Anesthesia and Reanimation, University of Health Sciences, Gaziosmanpaşa Training and Research Hospital, İstanbul, Türkiye
**E-mail:** dondugencm@gmail.com **ORCID ID:** 0000-0002-4229-4903

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In addition, there are authors who argue that ARDS caused by COVID-19 should be treated according to ARDS treatment principles, and strategies supporting ventilation should be similar. It is also recommended that the patient should be intubated and low tidal volume, low drive pressure, and positive end-expiratory pressure titration should be applied.[1]

The primary aim of our study is to evaluate the effectiveness of the use of NIV and IMV on oxygenation in patients with COVID-19 who had respiratory failure and needed ventilation support by arterial blood gas (ABG) analysis. Our secondary aims are to investigate the effect of NIV and IMV use on developing complications and mortality.

## MATERIALS and METHODS

This study was approved by the Ministry of Health (dated February 05, 2020, numbered 2020-05-02T01-47-24) and our Training and Research Hospital Clinical Research Ethics Committee (dated May 28, 2020, numbered 78). The principles of the Declaration of Helsinki conducted the study. The study was performed on patients hospitalized in our hospital Anesthesia and Reanimation Clinic ICUs between March 23, 2020, and May 19, 2020, with the diagnosis of COVID-19.

The study was performed by retrospectively scanning patient files of patients who were in the ICU due to acute respiratory failure with COVID-19 diagnosis and were over 18 years of age, whose the partial arterial oxygen pressure ($PaO_2$) values were below 60 mmHg despite mask oxygen (5 L/min) support. The 2019-nCoV was confirmed by real-time reverse transcription-polymerase chain reaction assay.[2]

Four patients with chronic kidney failure and six patient with metabolic acidosis (BE value accepted as ≤3) in intensive care admission were excluded from the study. One patient who underwent a pneumonectomy operation, two patients who had lung cancer with space-occupying mass, one patient with sarcoidosis, and one with scoliosis were excluded from the study. Ninety-eight patients were included in the study. The patients were divided into two groups according to the preferred initial ventilation strategy (Fig. 1).

Group IMV: Patients intubated on intensive care admission, whose treatment started with IMV (n=50)

Group NIV: Patients whose treatment started with NIV on intensive care admission (patients who underwent NIV in pressure support ventilation (PSV)-CPAP mode and/or HFNO (n=48).

Demographic data such as age, gender, and concomitant diseases of the patients were recorded.

Hospitalization time, intensive care hospitalization time, invasive and NIV times, whether the prone position was applied, and whether an intubation was required for NIV patients were considered for both groups.

The two groups were compared in terms of ABG analysis using the values at the time of admission to the ICU (initial), lowest values (minimum), and highest values (maximum) during the intensive care follow-ups. In ABG analysis of the patients, $PaO_2$, partial arterial carbon dioxide pressure ($PaCO_2$), ($SaO_2$), pH, base excess (BE), lactate values, and $PaO_2/FiO_2$ ($FiO_2$=-Fraction of inspired oxygen) ratio were evaluated. When calculating the initial value of $PaO_2/FiO_2$, the value of $FiO_2$ is considered as 40–60% for 5–8 L/min simple oxygen face mask, as 60–80% for 8–10 L/min partial rebreather mask, and as 80–100% for 10–15 L/min non-rebreather mask, $FiO_2$ values written in the patient files are accepted.

The patients were evaluated in terms of complications such as hypertension and hypotension developed during intensive care follow-ups. The application of antihypertensive therapy was considered as the development of hypertension, and the administration of drugs to increase arterial blood pressure was considered as the development of hypotension. 28-day mortality rates were compared.

### Statistical Analysis

Numerical data were summarized as mean ± standard deviation along with median interquartile range (IQR), whereas frequency and percentage were used for categorical data. Shapiro Wilk's test was used to test the normality of numerical data. Groups were compared regarding demographical and clinical characteristics by Student's t-test, Mann–Whitney U-test, or Pearson's Chi-square test, where appropriate. All analyses were performed using R (version 3.6.3 R Foundation for Statistical Computing, Vienna, Austria), a statistical computing language. "coin" was used for non-parametric analyses. $P<0.05$ was considered statistically significant.

## RESULTS

The general characteristics of the study sample are expressed in mean and standard deviations. According to this, the mean age of the patients was calculated as 64±14. Mean age and gender distribution were similar in both groups (Table 1). Intensive care hospitalization times were similar in both groups (Table 2).

Invasive and NIV durations were 9.47±8.37 and 5.49±4.75 day, respectively. The number of days with invasive and NIV is given in Table 2.

The two groups were compared in terms of ABG analysis using the values at the time of admission to the ICU (initial), lowest values (minimum), and highest values (maximum)

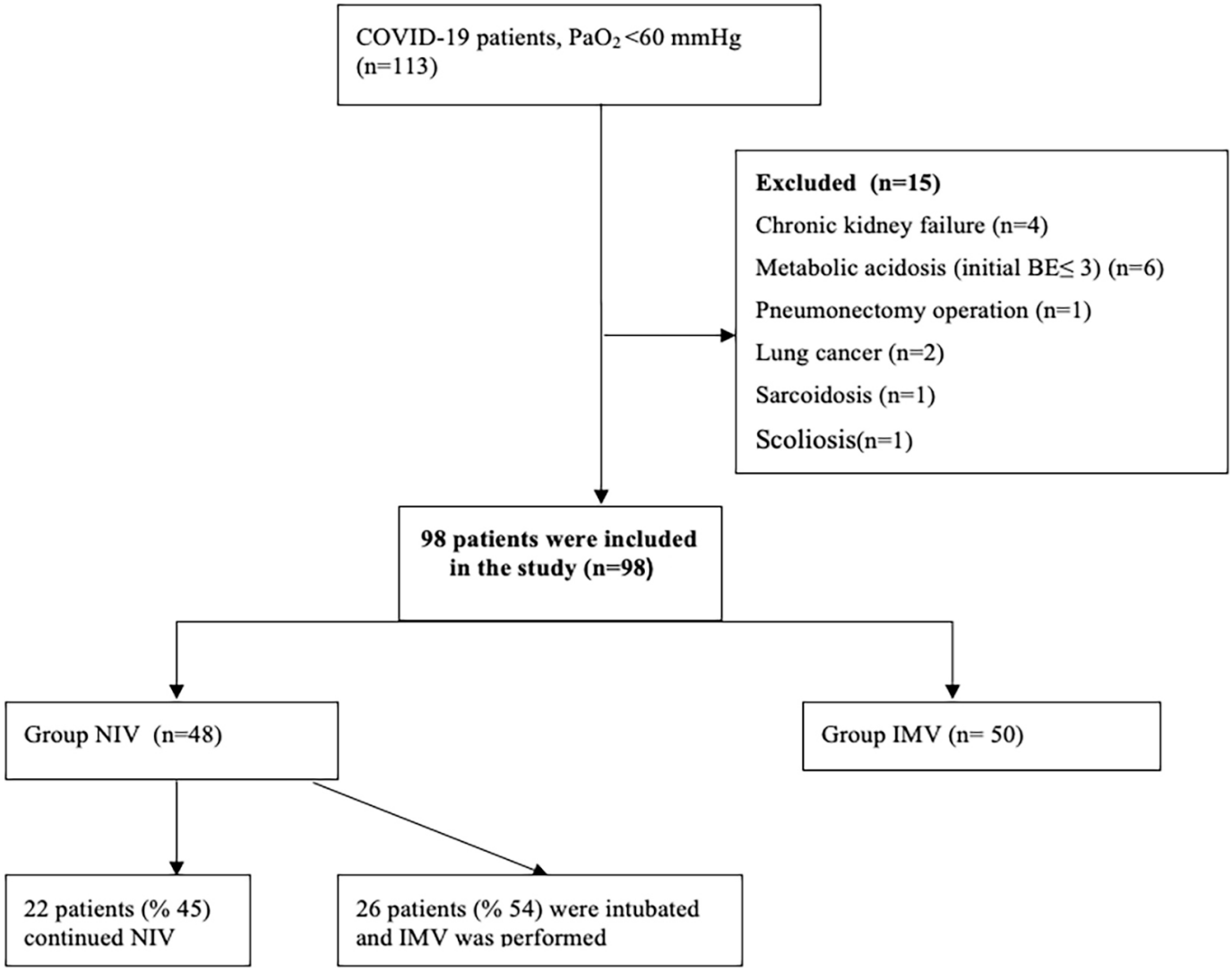


**Figure 1.** Consort flow diagram

*$PaO_2$: Partial arterial oxygen pressure; NIV: Non-invasive mechanical ventilation; IMV: Invasive mechanical ventilation*

during the intensive care follow-ups. The data obtained are shown in Table 2. For group comparisons for the initial, minimum, and maximum values of parameters such as pH, $PaO_2$, $PaCO_2$, BE, $SaO_2$, and $PaO_2/FiO_2$, we used Student's t-test or Mann–Whitney U-test according to whether or not they meet the normal distribution assumption (Table 3).

Initial $PaO_2$, $PaCO_2$, and $SaO_2$ values, which were measured at the time of admission to the ICU, were similar in both groups of patients. Initial $PaO_2/FiO_2$ ratios, measured at intensive care admission, were observed to be lower in Group IMV compared to the Group NIV (p=0.036). When the $PaO_2/FiO_2$ ratios measured during intensive care follow-ups were compared, minimum and maximum values were similar in both groups. The two groups were similar in terms of minimum $PaO_2$ values measured during intensive care follow-ups. However, minimum $SaO_2$ values measured during follow-ups were lower in Group IMV compared to Group NIV (p=0.046). Means of the variable $SaO_2$ minimum were calculated as 66.73±18.82 and 59.18±18.03 for Group NIV and Group IMV, respectively (Table 3). For the variable $SaO_2$ maximum, the results were presented as median and IQR, and the median of Group IMV, which was 99.2 (98.57; 99.4), was found to be significantly higher than the Group NIV, which was 98.85 (96.84; 99.2) (p=0.033) (Table 3).

According to the results obtained, the median values for $PaCO_2$ maximum was found to be significantly higher in Group IMV compared to Group NIV (p<0.001) (Table 3).

**Table 1. Comparison of demographic data and concomitant diseases**

| | Group NIV Mean±SD Med (IQR) | | Group IMV Mean±SD Med (IQR) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Age | 61.81±15.3<br>63 (52.75;70.25) | | 65.76±12.04<br>69.5 (56.25;72) | | 0.160[a] |
| Gender | | | | | |
| Male | 18 | 37.5 | 28 | 56 | 0.338 |
| Female | 6 | 12.5 | 16 | 32 | |
| Concomitant disease | | | | | |
| 1 | 25 | 52.1 | 17 | 34 | |
| 2 | 12 | 25 | 15 | 30 | |
| 3 | 5 | 10.4 | 6 | 12 | |
| 4 | 7 | 14.6 | 5 | 10 | |
| 5 | 18 | 37.5 | 13 | 26 | |
| Absent | 19 | 39.6 | 14 | 28 | |

P values are based on [a]: Student's t-test. NIV: Non-invasive mechanical ventilation; IMV: Invasive mechanical ventilation; SD: Standard deviation; Med: Median; IQR: Inter quartile range; 1: Hypertension; 2: Diabetes mellitus; 3: Cardiovascular diseases; 4: Chronic obstructive pulmonary disease; 5: Other diseases

**Table 2. Evaluation of duration of mechanical ventilation, length of stay in ICU and hospital**

| | Group NIV | | Group IMV | | p |
|---|---|---|---|---|---|
| | Mean±SD | Med (IQR) | Mean±SD | Med (IQR) | |
| Length of stay in ICU (days) | 10.75±8 | 8 (6;11) | 12.48±9.6 | 9.5(4;18) | 0.806[b] |
| Duration of invasive mechanical ventilation (days) | 7.92±7.96 | 5 (2.25;8.75) | 11.02±8.78 | 6.5(4;17.75) | 0.103[b] |
| Duration of noninvasive ventilation (days) | 6.77±5.31 | 7 (3;8) | 4.21±4.24 | 2(1.5;4.5) | 0.019[b] |

P values are based on [b]: Mann–Whitney U-test. ICU: Intensive care unit

In the group comprising 48 patients whose treatment started with NIV, 26 patients (54%) were subsequently intubated, and IMV was applied, the remaining 22 patients (45%) were observed to undergo only non-invasive ventilation during ICU follow-ups. When all patients included in the study were evaluated, it was seen that only 21.5% of patients were treated only with NIV.

While 68.36% of the patients were not prone positioned (67 individuals), 31.63% (31 individuals) were prone positioned. It was determined that 34% of patients in Group IMV and 29.2% of patients in Group NIV were prone positioned, both groups were similar (Table 4).

The number of hypertensives in need of antihypertension medication was higher in the Group IMV than in the Group NIV (p=0.008). The number of patients with hypotension requiring drug treatment was significantly higher in Group IMV than Group NIV (p=0.001). Among 48 patients in Group NIV, 21 (43.8%) developed hypotension and 3 (6.3%) developed hypertension. Among 50 patients in group IMV, 38 (76%) developed hypotension, and 13 patients (26%) developed hypertension (Table 5).

Fifty (51%) patients, of the 98 patients included in the study, died. The difference was significant considering that 72% of those who died were in the group whose treatment initially started with intubation (Group IMV), and the remaining 28% were in the group whose treatment initially started with non-invasive ventilation (Group NIV) (p<0.001).

## DISCUSSION

Patients' initial $PaO_2$, $PaCO_2$, and $SaO_2$ values at the time of ICU admission were similar. According to the medical eval-

**Table 3. Comparison of arterial blood gas analysis values of patients by groups**

| | Group NIV | | Group IMV | | p |
|---|---|---|---|---|---|
| | Mean±SD | Med (IQR) | Mean±SD | Med (IQR) | |
| PH initial | 7.42±0.07 | 7.42 (7.38;7.47) | 7.38±0.11 | 7.41 (7.32;7.46) | 0.121[b] |
| Ph min | 7.26±0.15 | 7.3 (7.2;7.36) | 7.14±0.15 | 7.15 (7.04;7.25) | **<0.001[b]** |
| Ph max | 7.49±0.05 | 7.5 (7.47;7.52) | 7.49±0.07 | 7.5 (7.46;7.52) | 0.679[b] |
| $PaO_2$ initial | 51.59±10.7 | 55.55 (46.78;59.25) | 51.4±11.37 | 56.25 (43.5;60) | 0.641[b] |
| $PaO_2$ min | 45.22±11.17 | 44 (38.53;56.1) | 42.54±11.25 | 42.2 (34.1;49.75) | 0.239[a] |
| $PaO_2$ max | 168.49±51 | 174 (139.75;202.5) | 173.32±58.82 | 171.7 (139.63;206.83) | 0.665[a] |
| $PaCO_2$ initial | 37.78±9.3 | 37 (33.15;40) | 39.4±11.78 | 37.65 (32.3;43.08) | 0.546[b] |
| $PaCO_2$ min | 32.59±6.09 | 32.95 (28.45;35.08) | 32.34±6.74 | 32.95 (29;36.5) | 0.79[b] |
| $PaCO_2$ max | 61.4±19.76 | 56.8 (47;71.08) | 92.7±38.38 | 83.6 (60.18;115.5) | **<0.001[b]** |
| BE initial | −0.12±4.64 | −0.23 (−2.53;2.4) | −0.34±4.8 | −0.3 (−2.95;2.53) | 0.822[a] |
| BE min | −4.51±5.46 | −3.6 (−7.1; −0.85) | −7.28±6.84 | −6.7 (−11.83; −1.83) | **0.044[b]** |
| BE max | 7.48±8.03 | 8.4 (3.4;11.63) | 11.54±8.68 | 11.37 (5.88;17.78) | **0.022[b]** |
| $SaO_2$ initial | 78.03±14.4 | 83.2 (73.83;88.55) | 72.91±21.81 | 82.95 (54.1;90) | 0.87[b] |
| $SaO_2$ min | 66.73±18.82 | 68 (54.78;83) | 59.18±18.03 | 59.18 (49.33;71.18) | **0.046[a]** |
| $SaO_2$ max | 96.89±5.8 | 98.85 (96.84;99.2) | 98.55±1.5 | 99.2 (98.57;99.4) | **0.033[b]** |
| P/f initial | 111.69±75.34 | 99 (59.28;150) | 80.77±36.56 | 74.7 (58.13;99.5) | **0.036[b]** |
| P/f min | 85.83±58.94 | 80 (41.88;103.5) | 66.22±27.64 | 59.6 (46.38;85.68) | 0.191[b] |
| P/f max | 286.27±134.95 | 298.5 (187.5;360) | 298.77±152.59 | 292.39 (153;420) | 0.668[a] |

İnitial: The values at the time of admission to the ICU; min: Lowest values; max: Highest values during the intensive care follow-ups. P values are based on [a]: Student's t-test; [b]: Mann–Whitney U-test. $PaO_2$: Partial arterial oxygen pressure; $PaCO_2$: Partial arterial carbon dioxide pressure; BE: Base excess; $SaO_2$: Oxygen saturation

uation of the evaluating physician, the patients were intubated and IMV was applied, or NIV in CPAP-PSV mode and/or HFNO was performed without intubation. Although initial $PaO_2/FiO_2$ values, measured at the admission to ICU, of the group whose treatment was started with NIV were higher compared to the other group, they were low enough to require intubation conditions. However, it was observed that NIV was preferred presumably because the general condition of the patients was good.

In the previous studies, for COVID-19 patients with acute hypoxemic respiratory failure, HFNO, NIV, and close follow-up were recommended if there is no urgent need for intubation. [7] Past studies reported that HFNO application reduces tracheal intubation and mortality rate.[8]

Rahmanzade et al.[9] reported that the application of intubation and mechanical ventilation is logical when NIV is insufficient for the patient.

It is recommended to use HFNO and CPAP application in treatment for patients who are considered not suitable for tracheal intubation but worsen despite standard mask oxygen administration.[10]

**Table 4. Comparing the prone position application by groups**

| | Group NIV | | Group IMV | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Prone position | | | | | |
| No | 34 | 70.8 | 33 | 66 | 0.607 |
| Yes | 14 | 29.2 | 17 | 34 | |

P values are based on Pearson's Chi-square test.

It was stated that all acute respiratory failure caused by COVID-19 was not ARDS, although there are consolidation and exudation in computed tomography images, this is not accepted as a "typical" ARDS image. In addition, it has been emphasized that, in some COVID-19-associated ARDS patients, lung compliance is high, inconsistent with the severity of hypoxemia.[11]

The hypothesis that COVID-19 cannot cause classical ARDS has raised concerns about the use of mechanical ventilation.[6,11,12]

In our study, when the effectiveness of ventilation is compared using $PaO_2$ values, oxygenation was similar in both groups during intensive care follow-ups. However, it was

**Table 5. Comparison of complication and mortality rates by groups**

| | Group NIV | | Group IMV | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Hypotension | | | | | |
| No | 27 | 56.3 | 12 | 24 | **0.001** |
| Yes | 21 | 43.8 | 38 | 76 | |
| Hypertension | | | | | |
| No | 45 | 93.8 | 37 | 74 | **0.008** |
| Yes | 3 | 6.3 | 13 | 26 | |
| Survival | | | | | |
| Non survivor | 14 | 29.2 | 36 | 72 | **<0.001** |
| Survivor | 34 | 70.8 | 14 | 28 | |
| Total | 48 | 100 | 50 | 100 | |

P values are based on Pearson's Chi-square test.

shown that survival was higher in the group whose treatment started with non-invasive ventilation.

Another remarkable feature of the group whose treatment started with intubation was that $PaCO_2$ values were higher in these patients. The reason for the $PaCO_2$ values, which were initially within normal limits in both groups, to be higher in Group IMV during ICU follow-ups should be investigated and randomized controlled studies should be conducted in this regard.

In some studies, the prone position has been reported to have positive effects on ventilation.

Sartini et al.[13] in their study on prone positioned patients undergoing NIV, reported that during pronation respiratory rate decreased and improvements are observed in $SpO_2$ and $PaO_2/FiO_2$ values in all patients, and there were improvements in $SpO_2$ and $PaO_2/FiO_2$ after pronation in 80% of the patients.

In a previous study, it was stated that the prone position added to HFNO or NIV eliminates the need for intubation in approximately half of the patients with moderate to severe ARDS, including those with viral pneumonia.[14]

Similarly, some studies from China suggest that early intervention with prone position and/or HFNO and NIV can lead to mortality less than 1% of the cases requiring intubation (compared to 2.3% of the national average).[6]

In this study, prone position preferred in 29.2% of the patients in the group whose treatment was started with NIV and it was preferred in 34% of the patients in the group whose treatment was started with IMV, the prone position preference rates were similar in both groups.

In a study conducted in China, 63% of patients with severe acute respiratory failure were treated with HFNO as primary treatment, 33% were treated with NIV, and 4% were treated with invasive mechanical ventilation. It has been reported that 41% of patients who were treated with HFNO subsequently required NIV or intubation, this rate was 63% in patients with $PaO_2/FiO_2 \leq 200$, and 29% of the patients for whom HFNO was insufficient were intubated after being switched to NIV.[15]

We did not evaluate our patients who underwent HFNO and PSV-CPAP in separate groups because these two treatments were applied intermittently to our patients.

In our study, although 54% of patients in the group whose treatment was started with NIV were intubated later, the mortality rates were lower in this group. We can attribute this to keeping the respiratory and cardiac complications associated with intubation to a lesser extent by reducing the duration of the intubation and IMV.

In our study, it was observed that the development of cardiac complications such as hypotension and hypertension was more common in the group whose treatment was started with IMV. These complications may be due to previous diseases, course of the disease, and medications used in treatment, but may be due to IMV incompatibility or sedative drugs used to achieve IMV compliance.

Rahmanzade et al.[9] emphasized that in the risk-benefit assessment of IMV and NIV, complications related to mechanical ventilation such as ventilation-induced lung injury, ventilation-induced pneumonia, and finally difficulty weaning from mechanical ventilation should be taken into account.

The method of increasing oxygen therapy as controlled and gradually as possible should be applied. It is emphasized that such an approach should be standardized.[16]

A small retrospective case series from Wuhan reported that 72% of COVID-19 patients who received NIV died, but the mortality rates were higher for patients intubated from the start.

A previous study reported that, of 52 critical patients who developed severe hypoxemia, 71% received mechanical ventilation (42% invasive, 56% non-invasive), 63% received HFNO, 11% were prone positioned, and 32 of 52 patients died.[17]

Yang et al.[17] reported an alarmingly high mortality rate in patients with acute respiratory failure associated with COVID-19 requiring mechanical ventilator support.

In some studies, high mortality rates such as 79% and 97% have been reported among patients requiring mechanical ventilation.[12–18]

### Limitations

The present study is a retrospective observational study. The decision for NIV or intubation has been made by the treating physicians and there was no standardization. Different physicians have different opinions about switching to NIV or intubation.

The oxygen flow applied in oxygen therapy with the mask (Simple face mask, with or without reservoir) is determined by the attending physician and the $FiO_2$ values accepted as the initial $FiO_2$ at the time of admission to ICU were determined by scanning the intensive care follow-up forms recorded by the physician providing the treatment. $FiO_2$ values for mask $O_2$ were not standard but varied.

In this ICUs, mechanical ventilation changes are considered by performing blood gas analysis at least twice a day. All blood gases of all patients participating in the study were scanned, and the maximum and minimum values were obtained, accordingly, the ranges of the values were tried to be predicted. There was no similar study evaluating ventilation by ABG analysis. In this respect, this is the power of our study. However, there was no previous study to compare to in the literature.

## CONCLUSION

It was observed in our study that patients whose treatment started with NIV had similar oxygenation compared to Group IMV, but fewer complications and less mortality were present. We think that in the acute respiratory failure developing in patients with COVID-19, oxygenation should be provided with NIV as much as possible, and HFNO, NIV, and IMV treatments should be administered in this order.

### Disclosures

**Ethics Committee Approval:** The study was approved by the Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (No: 78, Date: 28/05/2020).

**Informed Consent:** Written informed consent was obtained from all patients.

**Peer-review:** Externally peer reviewed.

**Authorship Contributions:** Concept: D.G.M., A.U.; Design: D.G.M., Ü.A.T.; Supervision: D.G.M., Ü.A.T.; Funding: O.Ç., A.U., S.Ş.Ş.; Materials: O.Ç., A.U., S.Ş.Ş.; Data Collection or Processing: D.G.M., O.Ç., A.U., S.Ş.Ş.; Analysis or Interpretation: D.G.M., Ü.A.T., A.U., O.Ç., S.Ş.Ş.; Literature Search: D.G.M., O.Ç., A.U.; Writing: D.G.M., Ü.A.T., S.Ş.Ş.; Critical review: D.G.M., Ü.A.T., S.Ş.Ş.

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