# Novel Treatment Approach to the Novel Coronavirus (COVID-19) With a New Inhaler Theurapetic

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## ABSTRACT

**Background**

Current COVID-19 treatment methods are in the form of oral tablets or intravenous therapy. However, even if the efficacy of these agents is shown in in-vitro studies, the same effect cannot be seen in in-vivo. This is because these treatments are intended to reach the lungs through the blood. However, severe interstitial edema and blood alveolar barrier does not allow medications to reach the lungs effectively.

**Objective**

In the new inhaler treatment (NIT) given in this clinical study, the molecules that have antiviral, antioxidant and anti-inflammatory effects without any toxicity were brought together. This study aims to prevent rapid and effective clinical improvement in COVID-19 patients and prevent any complications related to COVID-19 infection.

**Methods**

This study approved by The Ministry of Health of Turkey. This clinical study was designed as a multi-center study and performed in Istanbul and Mersin, Turkey. The patients were divided into two groups. Patients were randomly assigned following simple randomization procedures. Eight patients received the normal treatment protocol, while eight patients received the new inhalation treatment protocol in addition to the normal treatment protocol. It was applied by connecting the T nebulizer device in intubated patients and with a nebulizer mask in non-intubated patients. Pulse oxygen saturation, respiratory rate, percentage of lung involvement, arterial blood gas, and duration of hospitalization were compared after the treatment.

**Results**

One of the most important points of this study is the duration of hospital stay between the two groups. The mean duration of hospitalization in group 1 was $6.5 \pm 1.8$; in group 2 it was $17.1 \pm 2.4$. The duration of stay in Group 1 was significantly lower than group 2. ($P < 0.05$) FOS (Finger oxygen saturation) values were $89.2 \pm 4.8$ and $96.1 \pm 4.7$ in group 1 at the end of the 3rd and 7th days, respectively. In group 2, it was $80.3 \pm 5.9$ and $84.6 \pm 4.4$. After treatment FOS levels were significantly higher in group 1 for days 3 and 7. ($P < 0.05$)

**Conclusion**

Methods of treatment with multiple molecules should be developed for complex diseases, not single molecule therapy. In this sense, this study is very important as it will bring a new perspective to the scientific world. With the treatment mentioned in the current study; It is important in terms of making a new prophylaxis and therapeutic plan for Covid-19. It is thought that it will be unique in terms of creating a treatment plan with low potential for natural and non-synthetic side effects instead of using toxic and side effects products.

**Keywords**
*coronavirus, covid-19, treatment, medication*

## BACKGROUND

Coronavirus infection (COVID-19, SARS-CoV-2) appeared in China in December 2019 and spread to the whole world very quickly. (Lai Chih-Cheng et al., 2020) The lung involvement of COVID-19 disease, which progressed very rapidly, caused interstitial lung infection, acute lung injury and respiratory failure. (Guan et al., 2020)

SARS-CoV-2 is an enveloped beta-coronavirus with single-stranded RNA (Chen et al., 2020). Genome sequences of COVID-19 have been described to resemble coronaviruses (SARS-CoV) associated with the severe acute respiratory distress syndrome (ARDS). (Zhou et al., 2020; Wu et al., 2020) On the other side, the spike protein of COVID-19 and SARS-CoV lead them to enter the alveolar epithelial cells through the angiotensin-converting enzyme-2 receptor (Zhou et al., 2020).

The treatments for COVID-19 were insufficient for such a rapidly progressing and transmitted disease. (Li et al., 2020) The incubation period of the spread of the disease can be extended up to 24 days. (Guan et al., 2020) In many patients, respiratory failure has emerged in the hospital, and thousands of patients have required advanced respiratory supports. (mechanical ventilation). [Vincent and Taccone, 2020] This situation has put all the countries in an unprecedented difficult situation.

Globally, approved drugs have not been sufficiently effective against COVID-19. This situation has led the scientific world to search for new treatments. Therefore, the treatment guidelines against COVID-19 are constantly changing. Inadequacies in treatments have caused more importance to disease prevention methods. However, current patients cannot be treated effectively all over the world. (Molina et al., 2020) Even if the disease is cured, it may cause serious lung fibrosis. For this reason, a patient with COVID-19 should be treated very quickly and effectively. [Wang et al., 2020]

Current treatment methods are in the form of oral tablets or intravenous therapy. However, even if the efficacy of these agents is shown in in-vitro studies, the same effect cannot be seen in in-vivo. (Yazdany, 2020) This is because these treatments are intended to reach the lungs through the blood. However, severe interstitial edema and blood alveolar barrier does not allow medications to reach the lungs effectively. (Cascella et al., 2020) Further studies are also needed to prove this situation. Therefore, our hypothesis is that if agents are given with inhalation, prevention of serious lung damage can be achieved. This effect can also be achieved in a short time.

Respiratory infections are an important global health problem. These diseases are often treated with parenteral administration of antibiotics. (Schuetz et al., 2018) Unhappily, systemic treatments for high-dose antibiotics or antivirals can have serious negative effects. It requires the development of inhaled therapies that create targeted drug distribution directly to the airways with minimum systemic drug exposure. (Velkov et al., 2014) Recent biotechnological advances have facilitated the development of inhaled anti-microbial treatments. Smaller porous nebulizers provided minimal drug residue, higher aerosolization efficiency and rapid application compared to conventional nebulizers. The new particle engineering and smart device design make it attractive for inhaler medication. (Zhou et al., 2015)

In the new inhaler treatment (NIT) given in this clinical study, the molecules that have antiviral, antioxidant and anti-inflammatory effects without any toxicity were brought together. This new treatment is based on the ancient traditional treatment methods of Anatolia. It is a treatment that has been applied in Anatolia for centuries. (Guvenmez and Keskin, 2019; Altintas, 2014) This treatment, which has been traditionally used for many years, is used for acute and chronic sinusitis, turbinate hypertrophy, nasal polyp, allergic rhinitis, acute and chronic pharyngitis, acute laryngitis, pneumonia, acute and chronic bronchitis, and chronic adenomas. We started to use in chronic facial pain, chronic headaches, shortness of breath and chronic cough diseases. We have seen in our clinical observations that The NIT has no toxic effects for 3 years.

The current supportive research aimed to prevent rapid and effective clinical improvement in patients by new inhaler treatment consisting of flavonoid essential oils patented in 2018, that have antiviral, antioxidant and anti-inflammatory effects and preventive effect on lung complications related to SARS-CoV-2 infection.

## METHODS

This study was carried out under the Ministry of Health and Istinye University Medical Park Hospital and Bagcilar Training and Research Hospital, with the necessary legal permissions. This study approved by The Ministry of Health of Turkey. Approved number is 2020-04-29T23. Also, Istanbul Bagcilar Training and Research Hospital ethics committee received approval for this study. (Apply number:2020.07.2.14.115) The new treatment protocol was explained to all patients and relatives to be treated, and consent forms were taken. The study was conducted between May 1, 2020 and July 1, 2020.

This clinical study was designed as a multi-center study and performed in Istanbul and Mersin, Turkey. A total of 16 COVID-19 positive patients was included in the study. The patients were divided into two groups. Patients were randomly assigned following simple randomization procedures (computerized random numbers) to 1 of 2 treatment groups. Eight patients received the normal treatment protocol, while eight patients received the new inhalation treatment protocol in addition to the normal treatment protocol.

### Inclusion criteria

According to the latest diagnostic criteria of the COVID-19 associated pneumonia published by the Ministry of Health; mild, moderate and severe COVID + patients. [15].

### Exclusion criteria

(1) Patients with diffuse drug allergies (2) infants and children (< 18 years) (3) patients with advanced multiorgan failure (4) pregnant patients (5) Patients with severe heart failure (6) Patients willing not to participate in the study.

Before the treatment; pulse oxygen saturation, respiratory rate, percentage of lung infiltration, arterial blood gas, and duration of hospitalization were noted. From the beginning of the treatment, the 1st day, 3rd day and 7th day, the above parameters were measured and noted. Each parameter was averaged in its own group. Pre-treatment and post-treatment findings of the two groups were compared. The duration of hospitalization was compared by taking the average for both groups.

### Group 1

8 patients, 2 females, 6 males (two patients as intubated)

### Group 2

8 patients, 2 females 6 males (two patients as intubated)

**Treatment Protocol**

**Group 1**

3 × 1 NIT with nebulization (5 days) + hydroxychloroquine 200 mg p.o. 2 × 1 + azithromycin 250 mg p.o. 2 × 1 + oseltamivir 75 mg p.o. 2 × 1 + lopinavir 200 mg/ ritanavir 50 mg p.o. 2 × 2, oxygen therapy with nasal cannula or mask (for non-intubated patients)

**Group 2**

Hydroxychloroquine 200 mg p.o. 2 × 1 + azithromycin 250 mg p.o. 2 × 1 + oseltamivir 75 mg p.o. 2 × 1 + lopinavir 200 mg/ ritanavir 50 mg p.o. 2 × 2, oxygen therapy with nasal cannula or mask (for non-intubated patients)

**NIT Application**

The NIT is a solution created by using plant extracts in therapeutic doses. The content is not disclosed because it is patent protected. The transition of all useful extracts of these plants into oil is provided by an ultrasonic bath with nanotechnological production and water distillation. NIT prepared in sterile 2 cc flacons.

The medical materials used in the application were sterile and disposable. It was applied by connecting the T nebulizer device in intubated patients and with a nebulizer mask in non-intubated patients.

Solution preparation; 2 cc flacons are drawn into the syringe. Then, it was 1/2 diluted with saline. The emulsion solution formed is poured into the nebulizer chamber. After the system is turned off, the nebulizer opens at a medium intensity. In this way, the entire solution is provided as an inhaler.

The new inhalation treatment applied to the patient was performed at least under the supervision of thoracic medicine, one otorhinolaryngology, one infection specialist and intensive care unit Specialist. The application time is 10 minutes for all patients.

**Statistical analysis**

Standard deviation, mean, median, lowest, highest, frequency, and ratio values were utilized in the descriptive statistics of the data. Categorical variables were compared with the Chi-square test. The distribution of the variables was assessed with the Kolmogorov Smirnov Test. Independent Sample t-test and Paired Sample t-test were used for the analysis. The analysis of data is made use of SPSS 21.0 program.

## RESULTS

When the demographic information of the cases included in this study were compared, there was no statistically significant difference. The mean age of the patients was 57.8 ± 16.3 in group 1; In group 2, it was 58.4 ± 15.8. 25% of each group was intensive care patients.

No significant difference was observed between the values of finger oxygen saturation (FOS), respiratory rates (RR), CRP, T used in the study on the 1st day after treatment when both groups were compared. ($P > 0.05$).

FOS values were $89.2 \pm 4.8$ and $96.1 \pm 4.7$ in group 1 at the end of the 3rd and 7th days, respectively. In group 2, it was $80.3 \pm 5.9$ and $84.6 \pm 4.4$. After treatment FOS levels were significantly higher in group 1 for days 3 and 7. ($P < 0.05$).

Table 1

DEMOGRAPHIC VARIABLES AND CLINICAL CHARACTERISTICS OF THE SAMPLE

| | | **Group I** | **Group II** | **p** |
|---|---|---|---|---|
| | | **Mean ± SD / N%** | **Mean ± SD / N%** | |
| **Age** | | 57.8 ± 16.3 | 58.4 ± 15.8 | 0.425 |
| **Gender** | Male | 6 / 75.0% | 6 / 75.0% | |
| | Female | 2 / 25.0% | 2 / 25.0% | |
| **ICU** | | 2 / 25.0% | 2 / 25.0% | |

ICU: Intensive Care Unit, Independent Sample *t*-test was used.

The averages of RR were $21.6 \pm 5.8$ and $16.1 \pm 5.7$ in group 1 at 3 and 7 days after treatment, respectively. The mean of RR was $26.2 \pm 5.3$ and $24.3 \pm 4.8$ in group 2 patients, respectively. When the respiratory rate was compared in both groups, the inhaler treatment group was significantly lower in terms of RR. ($P < 0.05$).

Statistically significant changes were observed in blood gas pressures, oxygen and carbon dioxide values in group 1 patients. Arterial oxygen pressure (APO2) averages were $78.7 \pm 9.2$ before treatment in group 1, and $84.7 \pm 8.4$, $90.8 \pm 8.9$ and $97.1 \pm 9.4$ on the 1st, 3rd and 7th days after treatment, respectively. APO2 averages were monitored in group 2, both before and after treatment at the 79 level. APCO2 averages were $45.8 \pm 5.3$ before treatment in group 1, and $37.1 \pm 6.4$, $34.1 \pm 5.8$ and $32.3 \pm 6.1$ on the 1st, 3rd and 7th days after treatment, respectively. APCO2 averages were monitored in group 2 at the level of 43–45 both before and after treatment.

When we evaluate blood gas, APO2 was found to be significantly high and arterial carbon dioxide pressure (ACO2) was significantly lower in group 1. Here, the effectiveness of the treatment we use as inhaler has been shown to be statistically significant ($P < 0.05$).

In group 1, CRP averages were $116.7 \pm 20.1$ before treatment and $71.5 \pm 12.5$, $42.7 \pm 8.2$ and $14.8 \pm 5.7$ on the 1st, 3rd, and 7th days after treatment, respectively.

In group 2, it was $114.1 \pm 22.3$ before the treatment and $112.1 \pm 21.2$, $134.4 \pm 24.1$ and $112.8 \pm 20.9$ on the 1st, 3rd and 7th days after treatment. On the other hand, it was observed that blood CRP results significantly decreased in the inhaler-treated group compared to the group not given. ($P < 0.05$).

No significant difference was observed in body temperature in both groups when compared before and after treatment. ($P > 0.05$)

One of the most important points of this study is the duration of hospital stay between the two groups. The mean duration of hospitalization in group 1 was $6.5 \pm 1.8$; in group 2 it was $17.1 \pm 2.4$. The duration of stay in Group 1 was significantly lower than group 2. ($P < 0.05$)

Table 2
THE COMPARISON OF GROUP I AND GROUP II

| | | **Group I** | **Group II** | **p** |
|---|---|---|---|---|
| | | **Mean ± SD** | **Mean ± SD** | |
| **FOS** | Before treatment | 80.7 ± 4.3 | 81.3 ± 4.5 | 0.623 |
| | AT (1. day) | 83.1 ± 5.1 | 83.8 ± 5.2 | 0.738 |
| | AT (3. day) | 89.2 ± 4.8 | 80.3 ± 5.9 | **0.031** |
| | AT (7. day) | 96.1 ± 4.7 | 84.6 ± 4.4 | **0.014** |
| **RR** | Before treatment | 26.1 ± 5.6 | 25.7 ± 4.8 | 0.621 |
| | AT (1. day) | 25.8 ± 6.1 | 26.1 ± 5.7 | 0.648 |
| | AT (3. day) | 21.6 ± 5.8 | 26.2 ± 5.3 | **0.039** |
| | AT (7. day) | 16.1 ± 5.7 | 24.3 ± 4.8 | **0.008** |
| **APO2** | Before treatment | 78.7 ± 9.2 | 79.1 ± 9.7 | 0.519 |
| | AT (1. day) | 84.7 ± 8.4 | 79.3 ± 8.2 | **0.048** |
| | AT (3. day) | 90.8 ± 8.9 | 77.3 ± 8.3 | **0.021** |
| | AT (7. day) | 97.1 ± 9.4 | 79.5 ± 8.5 | **0.012** |
| **ACO2** | Before treatment | 45.8 ± 5.3 | 45.1 ± 4.5 | 0.525 |
| | AT (1. day) | 37.1 ± 6.4 | 43.8 ± 5.2 | **0.046** |
| | AT (3. day) | 34.1 ± 5.8 | 44.7 ± 5.3 | **0.031** |
| | AT (7. day) | 32.3 ± 6.1 | 45.0 ± 5.8 | **0.014** |
| **CRP** | Before treatment | 116.7 ± 20.1 | 114.1 ± 22.3 | 0.316 |
| | AT (1. day) | 71.5 ± 12.5 | 112.5 ± 21.2 | **0.012** |
| | AT (3. day) | 42.7 ± 8.2 | 134.4 ± 24.1 | **0.005** |
| | AT (7. day) | 14.8 ± 5.7 | 112.8 ± 20.9 | **0.000** |
| **T** | Before treatment | 38.7 ± 1.4 | 38.6 ± 1.5 | 0.822 |
| | AT (1. day) | 38.1 ± 1.3 | 38.4 ± 1.4 | 0.738 |
| | AT (3. day) | 37.2 ± 1.6 | 38.0 ± 1.6 | 0.521 |
| | AT (7. day) | 36.7 ± 1.4 | 37.7 ± 1.2 | 0.132 |
| **HD** | | 6.5 ± 1.8 | 17.1 ± 2.4 | **0.014** |

FOS: Finger Oxygen Saturation, RR: Respiratory Rate, APO2: Arterial sPO2, ACO2: Arterial sPCO2 (ACO2), CRP: C-Reactive Protein, HD: Hospitalization Duration, T: Temperature AT: After Treatment

Independent Sample *t*-test was used. Paired Sample *t*-test was used

## DISCUSSION

Covid-19 is a viral infection that primarily involves the lungs. Therefore, it keeps the upper respiratory tract in the first stage. Then, it keeps the lower respiratory tract and creates interstitial pneumonia. This situation occurs clinically in the form of respiratory distress in the patient. Finger oxygen saturation tends to drop rapidly. In addition, patients experience fever and muscle pain and other signs of inflammation. (Ozdemir, 2020)

The common form of treatment all over the world is on mono molecules. Therefore, a molecule used in treatment can prevent pathology by affecting a mechanism.

However, COVID-19 constitutes many pathologies in the infection process. Despite all the researches, this mechanism of pathology has not been fully explained. The COVID-19 infection continues to progress rapidly throughout the world with high mortality. Therefore, it is imperative that we develop quick and effective treatment strategies.

If this Virus (COVID-19) causes complex pathology, treatment strategies should also be complex. (Yuki et al., 2020) The inflammation of Interstitium, diffuse alveolar damage, and necrotizing bronchitis-bronchiolitis are general histopathological findings of lung in this respiratory viral infections. (Burke and Aubry, 2016) Diffuse alveolar damage is the most commonly observed finding with respiratory virus infections both in acute and late (organizing) stages. The characteristic features of acute diffuse alveolar damage are intra-alveolar edema. This is followed by the formation and accumulation of fibrin and the formation of hyaline membranes covering the alveolar walls. Late diffuse alveolar damage stages are Type-II-pneumocyte proliferation, granulation tissue formation, followed by collagen deposition. (Jain, 2020)

For this reason, the NIT we use in the treatment is not just an effect, it is composed of complex molecules with complex effect anti-viral, anti-inflammatory, anti-oxidant, anti-allergic, anti-bacterial properties. This is why we use many molecules in the treatment. With the treatment we apply, we can say that the involvement in the lung decreases significantly. (Fig. 4.)

Current treatments against COVID-19 are given orally and parenterally. It can be said that the treatments do not reach the lung tissue through the blood because the disease causes serious edema and inflammation in the interstitium of the lung.

In previous studies, the effectiveness of the medications recommended in the treatment of COVID-19 has not been proven. (Cascella, 2020) This may be due to the reason we mentioned above.

Molina et al. reported any evidence of a strong anti-viral activity or clinical benefit of the combination of hydroxychloroquine and azithromycin for the treatment of hospitalized patients with severe SARS-CoV-2. (Molina et al., 2020)

Currently, used azithromycin, hydroxychloroquine and anti-viral agents are ineffective in stopping the progression of the disease. Therefore, new treatment approaches are required.

The most important clinical indicator of the disease is severe lung failure. Therefore, we think that an inhaler agent will be more effective than the agents given intravenously.

In our study, blood gases in all patients undergoing NIT;

While PO2 increased progressively significantly ($p < 0.05$); PCO2 decreased significantly ($p < 0.05$), finger oxygen saturation values increased significantly ($p < 0.05$), blood CRP levels decreased significantly ($p < 0.05$), in addition, hypoxia due to observationally intubated patients severe agitation and depression symptoms were observed to regress.

In addition to the treatment of most of the cases, traditional medicine methods have been widely used in the SARS-CoV infection that occurred in 2002–2003. (Patel and Verma, 2020) Clinical evidence of the efficacy and safety of traditional medicine has been shown in the treatment of patients infected with coronavirus that appeared in December 2019 and laboratory studies and analyzes providing an idea of the molecular basis of therapeutic and therapeutic effects. (Leung, 2007)

For example, in a study published in an A class scientific medical journal, researchers reported that glycyrrhizin, major active ingredient of licorice, strongly inhibits the proliferation of clinical isolates of the SARS virus [Yang et al., 2020]. According to another important study, it was determined by plaque reduction analyzes that glycyrrhizin and another herbal compound, baicalin, had anti-SARS activity. (Cinatl et al., 2003)

Some studies have shown that herbal extracts strongly inhibit cytokines (IL-1-, IL-6, TNF-α, IFN-y) and chemokines (MIP-1a) that can be seen in staphylococcal toxic shock syndrome (TSST-1 toxin). In accordance with studies, the herbal product has been shown to significantly reduce the levels of TNF a, IL-1 and IL-6 in murine alveolar macrophages. Thanks to NIT's herbal mixtures, it provides upper respiratory tract infection and improve upper respiratory mucosal immune system with anti-inflammatory and antioxidant effects. At the same time, the incidence of side effects is minimized. It has antiviral, anti-inflammatory and immunoregulatory effects. (Chen et al., 2004)

Experts of diseases caused by viruses should know that the research results related to viruses have shown that H1N1 - MERS - SARS cannot block the way of transmission even when changing the sheath from person to person and cannot be diagnosed early. (Gao et al., 2014; Shereen et al., 2020)

It should be admitted that even though there are many antiviral drugs and glucocorticoids in the clinic, they cannot be treated alone. The emergence of negative drug reactions in the bacterial infection treatment process caused by viruses becomes inevitable. Therefore, it is especially important to summarize the experience and potential advantages of Traditional Ancient Anatolian medicine treatment and to find effective prevention and treatment methods. (Jassim et al., 2003)

With traditional medicine practices, we can reduce clinical symptoms such as fatigue and shortness of breath, absorption of pulmonary inflammation and reduce hypoxemia. It can also reduce the dosage and side effects of glucocorticoids and antiviral drugs, and reduce the abnormal incidence of glutamic transferamine, lactate dehydrogenation, and so on, with traditional medical practices. Also, the treatment cost can be reduced.

It may not be discharged without antiviral drugs, antibiotics, glucocorticoids and immunomodulators. With the same age and basic diseases, the number of deaths in the combined Traditional Anatolian medicine and western medicine treatment group may have been reduced compared to the simple western medicine treatment group. Research and treatments on the use of known herbal remedies based on traditional evidence by the medical staff of patients with viral, bacterial infection can improve the quality of life with bacterial and viral infection cases and cold symptoms. In addition, it can be provided to increase the physical strength of patients, improve symptoms and have certain effects on pulmonary inflammation. (Reichling et al., 2009)

Therefore, experts should use the integrated Ancient medicine and Western medicine treatment methods in the future as early as possible and comprehensively, and to monitor relevant cases, to observe and compare the long-term effects of various treatments; To further improve the design of clinical research protocols and clinical features and the individualized diagnosis and

treatment model of Traditional Anatolian medicine can strengthen the quality control of clinical trials and reduce bias.

At the same time, we can strengthen the research on the incidence of viruses, optimize the treatment plan and see the combined effect of integrated Anatolian traditional medicine and Western medicine therapy. Include medicine in the clinical emergency treatment system for public health emergencies, establish a research network, and emergency plans and research plans can be prepared.

## CONCLUSION

Methods of treatment with multiple molecules should be developed for complex diseases, not single molecule therapy. In this sense, this study is very important as it will bring a new perspective to the scientific world.

With the treatment mentioned in the current study;

It is important in terms of making a new prophylaxis and therapeutic plan for Covid-19. It is thought that it will be unique in terms of creating a treatment plan with low potential for natural and non-synthetic side effects instead of using toxic and side effects products.

Rapid cytokine storm caused by Covid-19 and rapid decline of inflammatory response,

The rapid reduction and disappearance of symptomatic complaints related to Covid-19,

Proving and using it prophylactically against Covid-19,

We think that the pandemic table, which progresses rapidly and aggressively, will be under control quickly.

## ABBREVIATIONS

Covid-19, SARS-CoV-2

Coronavirus-19, ARDS:acute respiratory distress syndrome, NIT:new inhaler treatment, FOS:Finger oxygen saturation, RR:respiratory rates, APO2:Arterial oxygen pressure, ACO2:arterial carbon dioxide pressure, CRP:C-Reactive Protein, HD:Hospitalization Duration, T:Temperature

## DECLARATIONS

### Authors' Contributions

OG, SB, SS, BA, RD, and ND designed the study. HK, MSS, KT, AKU, MC, MK, and AYM participated in data collection. OG, HK, AK, MC, MFK analyzed the data and interpreted the results. OG and HK wrote the initial manuscript. All authors read and approved the final manuscript.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

The protocol of this study was approved by the ethical committee of Bağcılar Research and Training Hospital. The nature and purpose of the study were explained to all participants and informed consent was obtained.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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**Figures**

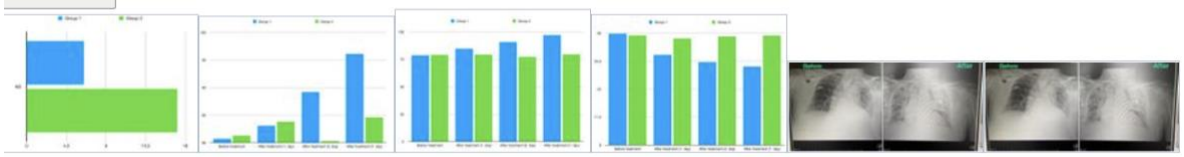

Figure 1 Figure 2 Figure 3 Figure 4 Figure 5 Figure 6