INTRODUCTION

The COVID-19 outbreak that began at the end of 2019 continues to affect the whole world. Although there was a decrease in the severity of the pandemic in the summer of 2020, the increase in the number of cases with the arrival of autumn made the whole world uneasy again. SARS-CoV-2 is transmitted from person to person via droplets or direct contact, and the most common symptoms presented during the prodromal phase are fever, dry cough, myalgia and fatigue.\(^1\)\(^2\) Although the cases can be asymptomatic or
have mild symptoms, it has also been reported that approximately 20% of the hospitalised patients who have a more severe clinical presentation further develop acute respiratory distress syndrome (ARDS). The leading causes of death due to the virus are respiratory failure, hyperinflammation, cytokine storm or multiorgan failure. 

There is no specific antiviral drug approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) in the treatment of COVID-19 as of 5 February 2021. WHO also shares the opinion that a specific treatment still does not exist. Because an effective and specific treatment for SARS-CoV-2 has not been developed yet, interest in supportive treatments with proven safety, such as vitamin D supplementation, has increased to prevent mortality and morbidity in the management of the disease.

Ozone therapy has been known for more than 150 years. Its effectiveness, particularly in the treatment of infectious diseases, has been demonstrated in many studies conducted in Cuba, Italy, Germany, Russia and Spain. The beneficial effects of ozone have been demonstrated in various studies. These strong, low cost and non-pharmacological effects have also enabled ozone to be widely used for more than 50 pathological diseases, such as degenerative disorders, neurological, orthopaedic and genitourinary disorders.

Ozone has been reported to be helpful in the treatment of these pathological disorders by inducing oxidative-antioxidative mechanisms. Besides, ozone provides oxygen substantially to tissues with poor oxygenation.

In this study, we investigated the effectiveness of ozone therapy to reduce mortality rates in patients hospitalised due to COVID-19.

2 | MATERIALS AND METHODS

2.1 | Study population and data collection

This study was approved by the Ethical Committee of the University of Health Sciences Haydarpasa Numune Training and Research Hospital and conducted following the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients or their legal representatives. We performed a prospective quasi-experimental before-and-after pilot study. This study included mild and severe COVID-19 patients hospitalised in the Haydarpasa Numune Training and Research Hospital, with lung involvement and RT-PCR (reverse transcriptase-polymerase chain reaction) positivity for SARS-CoV-2.

The required sample size of this study was calculated using the Gpower 3.1. Drawing on the literature, a sample size of 51 patients was required to provide 80% power with 5% alpha and effect size $w = 0.394$. The participants were randomly assigned in a 2:1 allocation to the control (n:18) and treatment (n:37) groups using a computer-generated randomisation.

Thirty-seven patients who met the following criteria were included in the ozone group of our study. Inclusion criteria were as follows: application to the emergency department with fever and respiratory system complaints, being 18 years or older, lung tomography findings indicating COVID-19 in accordance with the literature, positivity for SARS-CoV-2 nucleic acid (RT-PCR) test, acceptance of ozone therapy (by the patient or his/her legal guardian) by written consent. Patients who were breastfeeding, pregnant or patients with a diagnosis of glucose 6-phosphate dehydrogenase (G-6PD) deficiency were excluded from this study.

For the control group, 18 patients were included who met the above-mentioned inclusion criteria but did not consent to the ozone treatment protocol and accepted to participate in this study in the control group by giving written consent. Leucocyte and lymphocyte count, ferritin, D-Dimer, procalcitonin, C-reactive protein and IL-6 measurement tests were performed at the time of admission among patients with findings consistent with COVID-19 in lung tomography, and then patients were hospitalised.

2.2 | Procedures

Patients in the ozone and control groups received the appropriate medical treatment according to the COVID-19 protocol determined by the infectious diseases committee of our hospital and according to their individual clinical status. The main drugs in this treatment protocol consisted of hydroxychloroquine (400 mg every 12 hours on the first day and 200 mg every 12 hours for the next 4 days), enoxaparin, favipiravir and antibiotics if a secondary bacterial infection is considered and antipyretics if required. Other symptomatic treatment measures were also taken according to the patient’s clinical picture. Ozone major autohemotherapy (MAH) was applied to the ozone patient group, along with the conventional medical treatment that was deemed appropriate. Ozone was produced by the Turkozone Blue S CE medical device. The ozone bottle and set were disposable, made of medical-grade materials, and fully ozone compatible.

MAH was administered to the patients once daily for seven consecutive days. Each time, 100 ml of venous blood was collected and mixed with O3 gas. In our study in accordance with the literature, the mixture composed of oxygen (95%-100%) and ozone (1%-5%) with a 0.8 lit/min flow rate, and the final pressure of the gas remained at the normal atmospheric pressure. In this study, whole blood samples
were exposed to ozone gas at 30 μg/mL of ozone with five minute effective mixing (that is the best time for the homogeneous balance of ozone gas and blood) at a 1:1 ratio of oxygen-ozone to blood volume. The sodium citrate ratio contained in the ozone bottles was 3.13%, in line with the recommendation of the world ozone federation. In our study, to provide standard treatment, 100 mL of blood was taken from each patient in special ozone bottles and ozonized, and reinfusion was performed in 10-15 minutes in accordance with the World Federation of Ozone recommendation.

Patients were followed up until they were discharged from the hospital or mortality occurred. In our study, the pre-treatment biochemical test results of the patients were compared, and the mortality rate observed in the groups was calculated. The discharge and mortality rates of the patients in the control group and the patients in the ozone group were compared.

2.3 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). The normality assessment was performed using the Shapiro–Wilks test. Descriptive analyses were presented using mean ± SD (range), median (range) or n (%), where appropriate. Categorical data were analysed using the Pearson chi-square test and Fisher’s exact test. Mann–Whitney U test and Student’s t test were utilised for analysis of non-normally distributed numerical data, respectively. Wilcoxon signed ranks test was used to compare the measured parameters of patients before and after the treatment. Univariate and multivariate logistic regression analysis was used to determine independent risk factors associated with mortality. The variables with P < .1 in the univariate analyses were further tested in the multivariate models. Odds ratio (OR) with corresponding 95% CIs was reported. A p value of less than 0.05 was considered statistically significant.

3 | RESULTS

In this study, 55 patients diagnosed with COVID-19 pneumonia and hospitalised were included. The mean age of the patients was 60.2 ± 14.8 (min: 25, max: 88) and 52.7% (n = 29) of the participants were male. The mean age of the patients in the group in which ozone therapy was not applied (n = 18) was 64.7 ± 10.4, while the mean age of the patients in the ozone group (n = 37) was 58.03 ± 16.3. While 44.4% of the patients in the group that did not receive ozone treatment were females, 48.6% of the patients in the ozone group were women. Mean age (P = .118) and gender distribution (P = .769) of the patients according to the patient groups were similar (Table 1).

When the distribution of patients in both groups for comorbidity was compared, there was no significant difference concerning diabetes mellitus (DM) (P = .713), hypertension (P = .925), congestive heart failure (CHF) (P = .999), coronary artery disease (CAD) (P = .346) and neoplasms (P = .590). However, chronic renal failure (CRF) (P = .043) was observed with a higher rate in patients receiving ozone therapy (Table 1). Although the rate of chronic obstructive pulmonary disease (COPD) was observed to be higher in patients who received ozone therapy, this difference was not statistically significant (P = .078). In this ongoing pandemic, especially patients over the age of 50 and infected with COVID-19 with comorbidities were hospitalised in our hospital in line with the recommendation of the science committee of the Turkish Ministry of Health. For this reason, the demographic characteristics of patients who received and did not receive ozone therapy were similar in our study. Interestingly, patients with CRF were more likely to accept ozone therapy, which might be because they thought that the course of COVID-19 would be worse in CRF disease and relied more on ozone therapy as an alternative therapy. Therefore, randomisation could not provide a homogeneous distribution of all variables examined between the two groups. When the vital signs of the patients during the admission to the hospital were evaluated, no significant difference was found between the groups concerning body temperature (P = .619), heart rate (P = .109), systolic blood pressure (P = .663) and saturation of O2 (P = .068). There was no difference in pre-treatment levels of IL-6 (P = .993), D-Dimer (P = .167), ferritin (P = .893) and procalcitonin (P = .352) according to the study groups. The rate of hospitalisation in the intensive care unit (ICU) was similar according to the study groups (P = .713) (Table 1).

All hospitalised patients received the best available therapy with the same standard care of the Turkish Ministry of Health protocol. All patients received hydroxychloroquine and enoxaparin treatment in both groups. In addition to hydroxychloroquine treatment, Favipiravir was added to the treatment of 7.3% of the patients, and Ritonavir was added to 3.6% of the patients. No significant difference was determined between patients who received favipiravir and ritonavir treatment regarding ozone and the control group (P = .590, P = .999, respectively). Intravenous antibiotic treatment was administered to 94.8% of the total patients. Non-invasive treatment was applied to 10.9% of the patients and there was no significant difference between the groups (P = .999). Mechanical ventilation was applied to 9.1% of the patients in total. No significant difference was determined between patients who received mechanical ventilation regarding ozone and the control group (P = .999).

In our study, the findings showed that the mortality rate in the ozone group (n = 37) was significantly lower than the control group (n = 18) (P = .032). When all participants were evaluated, the mortality rate was 50% (n = 5) in patients hospitalised in the ICU and 4.4% (n = 2) in patients hospitalised in the regular ward. The mortality rate was higher in patients hospitalised in the ICU (n = 10) (P = .001). In the group of patients who did not receive ozone treatment (n = 18), the mortality rate of the patients hospitalised in the ICU (75%, n = 3) was higher than the patients followed up in the regular ward (14.3%, n = 2) (P = .044). Similarly, in the group that received ozone therapy (n = 37), the mortality rate in patients requiring intensive care (33.3%, n = 2) was higher than in patients followed up in the ward (0%) (P = .023). When the mortality rates of patients who were
hospitalised in ICU (n = 10) were compared concerning the treatment groups, it was observed that the mortality rate of patients who received ozone therapy (33.3%) was lower than patients who did not (75%), while this difference was not statistically significant (P = .524). We think that this difference is not statistically significant due to the small number of patients in the study groups. All our patients had pneumonia. Complications we observed in intensive care patients; ARDS (n = 4), multiorgan failure (n = 4), gastrointestinal bleeding (n = 1) and acute cardiac injury (n = 1). Among the patients treated in the ward (n = 45), all the 31 patients who received ozone therapy were discharged after successful treatment, while mortality occurred in 6.1% (n = 2) of 14 patients who did not receive ozone therapy. Although there was no significant difference between the death rates of the patients hospitalised in the regular ward concerning the treatment groups (P = .092), there was no death in the ozone group.

Ozone therapy was found effective in the univariate regression analysis performed to determine the factors affecting mortality (OR: 0.149; %95 CI: 0.026-0.863; P = .034) (Table 2).

### DISCUSSION

In our study, we applied ozone therapy to patients infected with SARS-CoV-2 in addition to conventional treatment and investigated the clinical outcomes of the patients compared to the group that did not receive ozone therapy. When we compared the results in the two groups that were similar regarding age, gender and comorbid diseases, we found that the mortality rate was significantly lower in the ozone treatment group. In the univariate regression analysis of factors affecting mortality, the findings suggest the effectiveness of ozone therapy in COVID-19 treatment.

The specific treatment of COVID-19 has not been developed yet, but the fight against coronavirus with antiviral drugs and symptomatic treatments goes on worldwide. In vaccine studies, no one has yet achieved a definite success so far. The development of alternative treatments to reduce the mortality of COVID-19 continues. In addition, ozone therapy, known for its high oxidant properties, is a method of treatment that has been used safely in many countries in infectious, immunological and vascular diseases.

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**TABLE 1** Comparison of the control group and ozone group, regarding age, gender, comorbidities, temperature, pulse, systolic blood pressure, saturation O\textsubscript{2} and laboratory parameters based on the in-hospital mortality

|                  | Control group (n:18) | Ozone group (n:37) | P   |
|------------------|----------------------|--------------------|-----|
| **Age**          |                      |                    |     |
| min–max          | 42.0–83.0            | 25.0–88.0          | .118|
| mean ± sd        | 64.7 ± 10.4          | 58.03 ± 16.3       |     |
| **Gender**       |                      |                    |     |
| Male             | 10 (55.6)            | 19 (51.4)          | .769|
| Female           | 8 (44.4)             | 18 (48.6)          |     |
| **Co-morbidities**|                     |                    |     |
| Diabetes         | 4 (22.2)             | 6 (16.2)           | .713|
| Hypertension     | 9 (50)               | 19 (51.4)          | .925|
| Coronary artery disease | 3 (16.7) | 11 (29.7)         | .346|
| COPD             | 1 (5.6)              | 11 (29.7)          | .078|
| Congestive heart failure | 1 (5.6) | 4 (10.8)         | .999|
| Neoplastic disease | 2 (11.1)            | 2 (5.4)           | .590|
| Chronic renal failure | 0 (0)               | 8 (21.6)         | .043|
| **Temperature °C (med, min–max)** | 36.65 (36-38) | 36.5 (36-38.3) | .619|
| **Pulse bpm (med, min–max)** | 90.78 ± 9.97 (74-108) | 86.46 ± 8.86 (72-110) | .109|
| **SBP mmHg (med, min–max)** | 129.5 ± 22.54 (93-170) | 132.35 ± 22.65 (90-181) | .663|
| **Saturation O\textsubscript{2} (med, min–max)** | 95 (80-99) | 93 (82-99) | .068|
| **IL-6 pg/ml (med, min–max)** | 19.05 (3.5-69) | 17.5 (2.84-87.5) | .993|
| **D-Dimer ng/ml (med, min–max)** | 785 (240-10,190) | 1165 (417-7504) | .167|
| **Ferritin ng/ml (med, min–max)** | 234.5 (95-1165) | 334 (6-2907) | .893|
| **Procalcitonin ng/ml (med, min–max)** | 0.05 (0.05-16) | 0.05 (0.05-3.39) | .352|
| **Intensive care unit** | 4 (22.2) | 6 (16.2) | .713|
| **Mortality**    | 5 (27.8)             | 2 (5.4)            | .032|

*Note: Data are presented as mean ± SD (range), median (range) or n (%). Student’s t test, Mann–Whitney U test, Pearson chi-square test and Fisher’s exact test.*

*Abbreviations: COPD, chronic obstructive pulmonary disease; LC, laboratory characteristics; SBP, systolic blood pressure.*
for many years. SARS-CoV-2 is an enveloped virus and the high
density of double-bonded molecular bodies in the structure of it,
which facilitates such oxidant agents to damage the integrity of
the virus. Similar to the Ebola virus, the spike and envelope pro-
teins of SARS-CoV-2 are rich in cysteine and tryptophan amino
acids, which make them vulnerable to oxidation. Ozone ther-
apy thus causes oxidation in the cysteine and tryptophan residues
formation suggests that ozone therapy is quite valuable in pre-
vention of infection as effective as dexamethasone treatment in reducing tumor necrosis factor α levels. Information suggests that ozone therapy is quite valuable in pre-
venting a cytokine storm, one of the leading causes of death in
patients infected with COVID-19. In our study, patients with
RT-PCR positiveness for SARS-CoV-2 were categorised as mild
and severe COVID-19 infection according to the literature. Mild
type characterised with mild pneumonia cases. Patients with
dyspnea, respiratory rate ≥30 breaths per minute, blood oxygen
saturation ≤93% and partial pressure of oxygen (PaO2)/fraction
of inspired oxygen (FiO2) ratio <300 were included in the severe
type. Among 55 patients infected with COVID-19, 10 required ICU
admission with a diagnosis of severe type COVID-19. The propor-
tion of patients hospitalised in ICU between the ozone and control
groups was similar (Table 1). We found that the mortality rate in
ward and intensive care patients in the group receiving ozone
therapy was significantly lower than the control group who did
not receive ozone therapy (P = .032).

Many studies have reported that advanced age and comorbid
diseases may negatively affect the prognosis of COVID-19 and in-
crease mortality. Diabetes, hypertension, cardiovascular disease,
chronic respiratory disease, cancer and cerebrovascular disease are
mainly known risk factors in this respect. It has also been re-
ported that acute kidney injury (AKI) may develop during the course
of patients infected with COVID-19, and this situation may signifi-
cantly increase the risk of mortality. The development of AKI
also may lead to a poor prognosis in patients who are infected with
COVID-19 with chronic kidney failure (CRF) or with a history of renal
transplant. In a study conducted on 101 cases that died due to
COVID-19, it was reported that 11% of the patients had CRF and
23% developed AKI. In our study, we could not find any significant
difference between the groups concerning DM, hypertension, CAD,
COPD, CHF or neoplasm rates. At the same time, although 21.6% of
patients in the ozone group had a history of CRF (P = .043), a lower mortality rate was observed compared to the other group. We think
this finding supports the effectiveness of ozone therapy.

Another prognostic factor in patients with COVID-19 is the el-
evation of D dimer, ferritin and Interleukin-6 levels. These param-
eters were associated with poor prognosis in many studies. In our
study, when the laboratory tests performed before treatment
between the ozone group and the control group were compared,
IL-6, D-Dimer, Ferritin and procalcitonin levels and vital parame-
ters (fever, pulse, systolic blood pressure [SBP] and saturation) were
similar.

In COVID-19, for which a specific treatment is not yet available,
clinical management sometimes challenges both physicians and pa-
nents. Not every patient gives the same response to every drug. At
the same time, the toxic side effects of the drugs used may negatively
affect the course of the disease. Ozone therapy, on the other hand,
is an inexpensive, reliable and well-known method of treatment for
many years. In our study, no side effects that could be associated
with ozone treatment were observed in the group that received it.
We consider that mortality rates can be further decreased with
ozone therapy to be applied in addition to the existing conventional
treatment modalities.

The limitations of our study are that this study was conducted
in a single centre, and the number of patients was small. Another
limitation of our study is that the body mass index (BMI) of the pa-
nents could not be calculated. The reason for this is that there are
no special scales for every patient in our hospital and the use of
common scales is not possible under pandemic conditions. Because
each patient does not know his/her own weight and height values,
BMI data of the patients could not be included in our study. For this
reason, there was no homogeneity between the groups in terms of
BMI. Multi-centre studies on a larger patient population, including
patients’ BMI, will further provide valuable insights into the under-
standing of the effectiveness and significance of ozone therapy.

| Variables     | Univariate model | OR (95% CI) | P      |
|---------------|------------------|------------|-------|
| Age           |                   | 1.059 (0.999-1.133) | .098  |
| Male          |                   | 0.635 (0.128-3.146) | .578  |
| Diabetes      |                   | 4.393 (0.804-23.999) | .088  |
| Hypertension  |                   | 1.333 (0.269-6.606) | .725  |
| CAD           |                   | 1.2 (0.205-7.011) | .840  |
| COPD          |                   | 1.52 (0.256-9.028) | .645  |
| CHF           |                   | 1.833 (0.175-19.252) | .613  |
| CRF           |                   | 2.8 (0.440-17.799) | .275  |
| Temperature   |                   | 0.42 (0.070-2.532) | .344  |
| Pulse         |                   | 1.046 (0.963-1.136) | .286  |
| SBP           |                   | 0.985 (0.949-1.023) | .438  |
| Saturation O2 |                   | 1.017 (0.849-1.219) | .851  |
| Ozone therapy |                   | 0.149 (0.026-0.863) | .034  |

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; OR, odds ratio; SBP, systolic blood pressure.

TABLE 2 Univariate regression analysis of factors affecting mortality
CONCLUSION

In conclusion, in this study, we demonstrated that applying ozone therapy to patients hospitalised for COVID-19 could contribute to clinical outcomes. No side effects related to ozone therapy were observed in our study. At the same time, the positive effects of ozone on the control of oxidative stress and immunomodulation have been supported by decreasing mortality rates and univariate regression analysis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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