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Original Article



# Evaluating the Effectiveness of Intravenous Ozonated Normal Saline in the Treatment of Severe COVID-19 Disease: A randomized control trial

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**Abstract**

**Background:** There is still no specific treatment strategy for COVID-19 other than supportive management. The potential biological benefits of ozone therapy include reduced tissue hypoxia, decreased hypercoagulability, modulated immune function by inhibiting inflammatory mediators, improved phagocytic function, and impaired viral replication. This study aimed to evaluate the effect of intravenous ozonated normal saline on patients with severe COVID-19 disease.

**Methods**: In this study, a single centralized randomized clinical trial was conducted on 80 hospitalized patients with severe COVID-19. The patients were selected by random allocation method and divided into two groups A and B. In group A (control group), patients were given standard drug treatment, and in group B (intervention group), patients received ozonated normal saline in addition to the standard drug treatment. In the intervention group, 400 mL of normal saline was weighed by 40 µg/kg of body weight and was injected into patients within 15 to 30 minutes (80 to 120 drops per minute). This process was done daily every morning for a week. Primary and secondary outcomes of the disease included changes in the following items: length of hospital stay, inflammatory markers including C-reactive protein (CRP), clinical recovery, arterial blood oxygen status, improvement of blood disorders such as leukopenia and leukocytosis, duration of ventilator attachment, and rapid clearance of lung lesions on CT scans. The need for intensive care unit (ICU) hospitalization, the length of ICU stay, and the mortality rate in patients of the two groups was compared.

**Results**: According to the results of the initial outcome variable analysis, the probability of discharge of patients who received the normal ozonated saline intervention was 33% higher than patients who did not receive this intervention; however, this relationship was not statistically significant (HR = 0.67, 95%, CI = 0.42-1.06, *P* value = 0.089). The chance of ICU hospitalization in patients of the intervention group was three times more than that of the comparison group, but this relationship was not significant (odds ratio = 4.4 95% CI = 1.32-14.50, *P* value = 0.016). The use of ozonated normal saline was found to increase the risk of death by 1.5 times but this relationship was not statistically significant (odds ratio = 1.5, 95% CI = .24-9.75, *P* value = 0.646). Ozonated normal saline had a significant effect on changes in respiration rate (in the intervention group the number of breaths was decreased) and the erythrocyte sedimentation rate (in the intervention group the erythrocyte sedimentation rate was increased); however, it had no significant effect on other indicators.

**Conclusion**: The present study showed that ozone therapy in hospitalized patients with severe COVID-19 could help improve some primary and secondary outcomes of the disease. Governments and health policymakers should make ozone therapy an available care service so that the need for advanced treatment facilities decreases; consequently, this measure may improve patient safety, prevent lung tissue destruction, and control cytokine storms in patients. Additionally, health decision-makers need to aim for the effective clinical improvement of patients, especially severe ones, and the reduction of their mortality. However, further large-scale multicenter studies with larger sample sizes considering drug side effects and other variables influencing the clinical course of COVID-19 can provide more information on the effectiveness and importance of ozone therapy.

**Keywords:** COVID-19, Integrative medicine, Oxygen therapy, Ozone therapy, SARS-CoV-2

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## Introduction

Coronaviruses (CoVs) are enveloped, non-segmented, positive-sense RNA viruses which belong to the family of Coronaviridae, the order Nidovirales, and the genus Coronavirus (1,2). The coronavirus subfamily is further divided into four genera: alpha, beta, gamma, and delta coronaviruses (3,4). Coronaviruses are a large family of viruses causing illnesses ranging from the common cold in adults to gastrointestinal illness in children (5). Since December 2019, an acute respiratory infection caused by a new type of coronavirus in Wuhan, China (later called COVID-19), which rapidly spread all over China and the world, has become a new global public health crisis (6,7). COVID-19 can cause symptoms including cough,

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breathlessness, fever, fatigue, gastrointestinal symptoms, muscle aches, pneumonia, and even death (6). The manifestation of these symptoms primarily is related to cytokine storm induced by COVID-19 (7). In severe cases, cytokine storms trigger systemic inflammation with multi-organ failure and high mortality rates (8). Although some COVID-19 vaccines have been approved by the World Health Organization, due to the lack of vaccination of all population groups worldwide and the potential mutation in the virus causing new strains with higher transmission power and greater pathogenicity, there still exist challenges in treating COVID-19 (9,10). Since there are no approved definitive therapies for COVID-19, currently symptomatic treatment with general supportive and critical care is the available cure. Some of the introduced drugs such as chloroquine, lopinavir/ritonavir combination, and sofosbuvir have been used globally across many countries; however, they have shown little to no effectivity (11). In the meantime, some complementary therapies may be effective along with other supportive therapies. Despite all these measures, the world is struggling with the high mortality of COVID-19. Scientists are exploring new multidisciplinary therapies to combat this disease (12).

Ozone therapy is a complementary medicine in which ozone enters the body through oral, injectable, or dermal administration and helps cure various diseases. This gas has bactericidal, fungicidal, and growth-inhibitory properties (13). The therapeutic effect of ozone gas has been considered for many years and this method has been used in various ways to treat several diseases in many countries (14). One of the important effects of ozone is its antiseptic feature. Most bacteria, viruses, and fungi cannot replicate in the presence of ozone. Therefore, this gas has been considered for treating skin and intestinal infections with different methods (15).

Ozone therapy with antioxidant, antiviral, anti-inflammatory, and oxygenation-improving properties is a potential treatment candidate for COVID-19 (16). The effective antimicrobial activity of ozone in reducing the virulence activity of viruses such as HPV, HIV, HBV, HCV, and VZV has been demonstrated in preclinical and clinical studies (17). Ozone therapy is also used to modulate biological responses and increase antioxidant capacity in patients with inflammatory and age-related diseases such as vascular diseases (stroke and heart and peripheral arteries disease), the treatment of type 1 and type 2 diabetes, and respiratory disorders such as asthma and chronic obstructive pulmonary disorder (COPD) (18). The current clinical trial has shown significant positive outcomes in COVID-19 patients.

## Materials and Methods

### *Study design*

This randomized, single-center, pilot study was conducted on 80 participants with COVID-19 confirmed by quantitative reverse transcription polymerase chain reaction (qRT-PCR). It was done without blinding and included placebo-controlled and parallel groups as well. The primary aim of this study was to evaluate the safety and efficacy of intravenous ozonized saline infusion in treating severe COVID-19 disease.

### *Study population, grouping, and randomization*

Patient selection was based on principles of the World Medical Association Declaration of Helsinki for Ethical Principles for medical research involving human subjects. The present study was carried out in the infectious diseases ward of Razi hospital in Ahvaz, which is the infectious diseases referral center in Khuzestan province and Ahvaz city in southwestern Iran. At the time of hospital admission, patients with symptoms such as sore throat, cough, fever, or chills were isolated in the emergency department. Chest CT was performed on patients and then a blood sample was taken from the patients for routine laboratory evaluation including a complete blood count and C-reactive protein (CRP). Patient inclusion criteria, also served as admission criteria, were as follows: severe cases of COVID-19 with chest CT changes in the form of peripheral, unilateral, or bilateral ground-glass opacity(s) in combination with any of the below: RR greater than 24, O2 saturation less than 93%, BP less than 90/60, and decreased level of consciousness. The patients were admitted to the infectious diseases ward or intensive care unit (ICU) if ventilation and/or intubation were required. Then, samples for real-time PCR tests were obtained from the throat and nasopharynx in patients suspected of COVID-19 infection, and if positive, COVID-19 was confirmed and they were included in the study. Sample size calculations are not provided in this study due to its pilot nature. Eighty patients were included in the study according to the study criteria and were divided into the intervention and control groups by block randomization, the number of samples in each group was 40 patients. Patients participating in the study were randomly divided into groups A and B. The block randomization method was used for randomization, and the individuals were randomly divided into two groups based on the first four randomized trials (by a person who was not involved in the study process). For this purpose, six blocks of AABB, ABAB, ABBA, BAAB, BBAA, and BABA were considered. The blocks were arranged in a random order, and the patients were added to the chain in the same random order they had entered the trial. Due to the nature of the intervention, blinding was not possible.

### *Intervention procedure*

A total of 80 patients with severe COVID-19 who participated in the study were randomly divided into two groups. The control group received standard of

care (SOC) according to national COVID-19 guidelines including any of the following based on indication: Remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 5 additional days), favipiravir (1600 mg every 12 hours on the first day and then 600 mg every 12 hours for 5 days), recombinant human interferon beta-1a subcutaneous injection for two weeks, intravenous bolus injection of dexamethasone 8 mg once daily or methylprednisolone 100 mg daily, co-amoxiclav 1 g every 12 hours, and levofloxacin 750 mg/daily. In the intervention group, patients received SOC plus ozone therapy. The ozone therapy included 400 mL of normal saline by 40 μg/kg of patients' body weight every morning for a week and 2–3 mL venous blood along with 5 mL ozone at 25 μg/mL along with SOC. The ozone/oxygen mixture was generated based on the Russian protocol using the Medozon ozone generator (Herrmann, Elsenfeld, Germany), which is automated and standardized for time, volume, and concentration.

***Evaluation of primary and secondary outcome variables***

The present study looked at a variety of outcome variables correlated to the prognosis of COVID-19. The primary outcome measures were:

1. Duration of hospitalization
2. Changes in oxygenation index (SpO2)
3. Changes in inflammatory markers including CRP

Additionally, secondary outcome variables were included:

1. Requirement of admission to ICU
2. Duration of hospital admission
3. Rapid clearance of lung lesions on CT scan
4. Clinical status (expressed in percentage) of subjects reporting each severity, rating on a 6-point ordinal scale:

- Death (1)
- Hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (2)
- Hospitalized, requiring non-invasive ventilation or high-flow oxygen devices (3)
- Hospitalized, requiring supplemental oxygen (4)
- Hospitalized, not requiring supplemental oxygen (5)
- Not hospitalized (6)

5. Case fatality rate: The primary and secondary outcomes of the disease were checked twice a week and all patients were followed up for two weeks after the end of the procedure, in terms of general health, by referring to the clinic or by phone.

***Data analysis***

Demographic and basic information including age and other characteristics were analyzed using descriptive statistics including frequency and percentage, and mean and standard deviation. Survival analysis, Cox regression, and Kaplan-Meier diagram were used to evaluate the initial outcome of the length of hospital stay. Logistic regression was used to compare the two groups in terms of the need for ICU hospitalization. To report the case fatality rate, the number of deaths was divided by the number of patients, and logistic regression was used to compare the death rate in the two groups. The generalized estimating equation was used to compare white blood cell (WBC) and erythrocyte sedimentation rate (ESR) in the two groups due to repetition in measurements. All analyses were conducted using Stata version 13.1 (StataCorp., College Station, Texas 77845 USA).

## Results

Eighty patients were included in the study divided into two groups (40 patients in each) by random allocation. No patient was excluded from the study according to the inclusion and exclusion criteria. The mean age of the men and women in the standard therapy group was 56.31 (±14.01) and 54.85 (±12.54), respectively, while in the intervention group, it was 53.31 (±14.33) and 53.39 (±16.41). In terms of background disease, 16 patients in the intervention group (ozone therapy + standard drug treatment) and 10 patients in the control group (standard drug treatment) had a history of diabetes. Figure 1 shows the flow of patients in the study and Table 1 shows the characteristics of patients including age, sex, background disease, and chest CT score.

According to Table 1, the variables of diabetes and blood pressure have an imbalance between the two groups, and these variables can be controlled as possible distorted variables.

According to the results of the initial outcome variable analysis, the probability of discharge of patients who received normal ozonated saline intervention is 33% higher than patients who did not receive this intervention, but this relationship was not statistically significant (HR = 0.67, 95% CI = 0.42-1.06, *P* value = 0.089). The relationship is partially non-significant and is likely to increase as the sample size increases. Reanalysis using the bootstrap method made the relationship significant (HR = 0.67, 95% CI = 0.49-0.92, *P* value = 0.014).

**Table 1.** Demographic and clinical data of patients in the two groups at the beginning of the study

| | | Control (n = 40) | Intervention (n = 40) |
|---|---|---|---|
| Age | | 55.325 (12.87292428) | 53.4 (15.36529556) |
| Gender | | 27 (68%) | 23 (57%) |
| Background disease | No | 16 (40%) | 17 (43%) |
| | Diabetes | 10 (25%) | 16 (40%) |
| | BP | 10 (25%) | 4 (10%) |
| | Other | 1 (3%) | 0 (0%) |
| | Diabetes + BP | 3 (8%) | 3 (8%) |
| Chest CT score | | 10.25 (3.102934922) | 9.35 (2.337541992) |

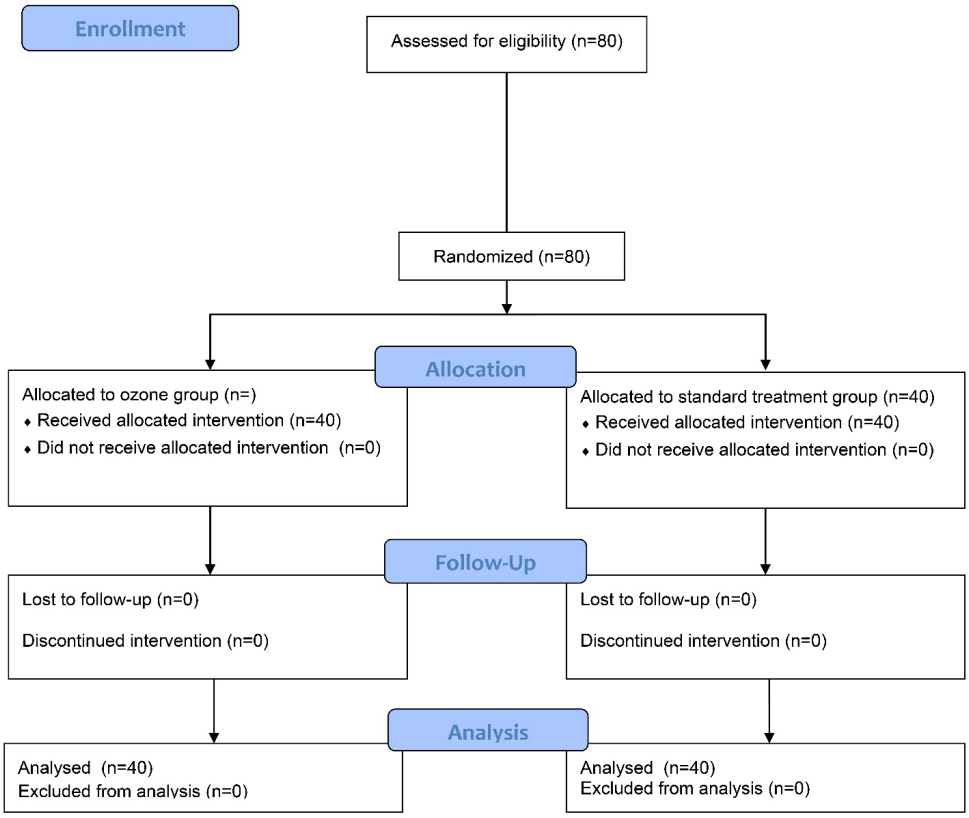


**Figure 1.** CONSORT flow chart of the trial events.

Kaplan-Meier diagram in Figure 2 showed that with control over variables of diabetes and blood pressure, the duration of treatment in the intervention group remained non-significant (blood pressure: HR = 0.67, 95% CI = 0.42-1.06, *P* value = 0.08, diabetes: HR = 0.66, 95% CI = 0.41-1.05, *P* value = 0.093). The chance of hospitalization in the ICU for patients in the intervention group was three times more than that of the control group, which was not statistically significant (odds ratio = 4.4, 95% CI = 1.32-14.50, *P* value = 0.016). Analysis of the relationship between death and ozone therapy by logistic regression method showed that using ozonated normal saline increases the risk of death by 1.5 times, but this relationship is not statistically significant (odds ratio = 1.5, 95% CI = .24-9.75, *P* value = 0.646). Repeated measure analysis by examining the effect of ozonated normal saline on changes in respiratory rate (RR), lymphocyte, hemoglobin, and platelets count, ESR, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) showed that treatment in intervention group had a significant effect on changes in RR. Ozone-containing normal saline treatment reduced the number of breaths, and had a significant effect on the ESR (in the intervention group the ESR was increased) and had no significant effect on other variables (Table 2).

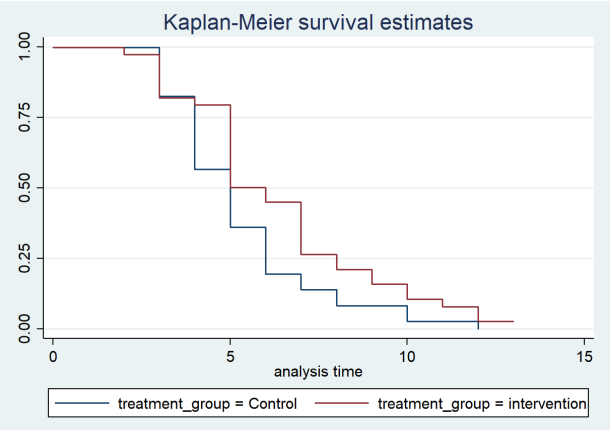


**Figure 2.** Kaplan-Meier diagram comparing the length of treatment in the two groups.

**Table 2.** Evaluation of the effect of ozone therapy on laboratory parameters

| Variable | Regression coefficient | Lower | Upper | *P* value |
|---|---|---|---|---|
| RR | -2.27 | -1.01 | -3.54 | 0.000 |
| Lymphocyte count | 271.83 | 834.38 | -290.72 | 0.344 |
| Hemoglobin | -.72 | .15 | -1.60 | 0.106 |
| Platelets | 18.66 | 57.12 | -19.80 | 0.342 |
| AST | .27 | 13.26 | -12.71 | 0.967 |
| ALT | -1.26 | 80.17 | -17.37 | 0.878 |
| ESR | 43.21 | 85.15 | 1.26 | 0.043 |

RR, respiratory rate, ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate.

## Discussion

The results of the present study showed that the

combination of ozone therapy + standard drug treatment increases the likelihood of patient discharge and reduces the duration of treatment, the number of breaths/minute, hemoglobin, and ALT compared to standard drug therapy alone in patients with the severe COVID-19. While the chance of ICU hospitalization, risk of death, lymphocyte count, platelets, ESR, and AST in the combination therapy group increases compared to the group with standard drug treatment, the difference is not statistically significant.

There are few reports declaring that ozone therapy is used to treat COVID-19. These reports/studies suggest the potential role of ozone in COVID-19. Also, good clinical trials are designed to assess the possible concentration of ozone, possible ways of administration, safety, disease stage in which ozone should be prescribed, contraindications, concomitant administration of antioxidants, etc (19).

In the present study, ozone therapy was compared with standard treatment in patients with severe COVID-19 in terms of clinical efficacy. Since various variables such as patient discharge, duration of treatment, number of breaths, hemoglobin, and ALT in the combination treatment group have been improved compared to the standard drug treatment group, the results are promising.

There is no specific treatment for COVID-19, but the fight against coronavirus using antiviral drugs and symptomatic therapies continues around the world. The development of alternative therapies to reduce COVID-19 mortality continues (20). In addition, ozone therapy, known for its high oxidizing properties, is a method that has been used safely in many countries against infectious, immunological, and vascular diseases for many years. Some of the findings of the present study are consistent with recent clinical trial studies that describe the potential biological benefits of ozone therapy for COVID-19 (21).

Shah et al conducted a case study to evaluate the safety and effectiveness of ozone therapy as an adjuvant with standard treatment on 60 patients with mild or moderate COVID-19 in two groups of control (30 patients) and treatment (30 patients). Patients in the control group received standard drug therapy, while patients in the other group, in addition to standard drug therapy, received ozone therapy consisting of 40 µg/mL ozone at a dose of about 150 mL twice a day with a rectal injection and 2-3 ml intravenous injection. They received 5 mL of ozone with 25 µg/mL of partial autoimmune therapy once daily. The results showed that ozone therapy combined with standard drug therapy reduced clinical recovery time, mortality, or virus clearance time in patients with mild to moderate COVID-19 compared to patients receiving standard drug treatment only. Also, in the study by Shah et al, they indicated that the SpO2 level in patients increased significantly following ozone therapy compared to baseline, which may be the cause of the improvement in shortness of breath. Only the ALT and respiration rate changed significantly in the current trial, as opposed to the Shah et al study where the majority of the inflammatory indices were significantly improved. Also, considering the above-said study, ozone therapy has reduced mortality, while in our study, ozone therapy has increased mortality. The difference in the status of the participants in terms of disease and the type of ozone therapy method are other reasons for the difference between some of the results of this study and our study (22).

Alberto Hernández et al conducted a study on 18 patients with severe COVID-19 pneumonia, in two groups of control and treatment (9 patients in each group), in Spain to determine the effect of using ozonated blood on their clinical improvement. Patients in the standard clinical treatment control group received oxygen support therapy, hydroxychloroquine, lopinavir/ritonavir, corticosteroids, and antibiotics (including azithromycin). Patients in the ozone therapy group received blood with ozone twice daily for four days, including the day of admission. Each treatment session consisted of administering 200 mL of whole autologous blood enriched with 200 mL of the oxygen-ozone mixture at a concentration of 40 µg/mL ozone. The results revealed that ozone therapy caused a shorter recovery time of clinical improvement and clinical outcomes compared with standard drug therapy (days [6–10] vs 28 days [8–31], $P = 0.04$). Comparing ozone therapy with standard drug therapy, the following variables' levels were reduced by twice as much in half the time: CRP (3.5 days vs. 13 days, $p = 0.008$), ferritin (8 days vs. 15 days, $P = 0.016$), D-dimer (4 days vs. 19.5 days, $p = 0.009$), and lactate dehydrogenase (9 days vs. 25 days, $P = 0.01$). Therefore, the results of this study are consistent with our study (23).

A study by Araimo et al evaluated the use of ozone therapy as an adjuvant in the initial control of disease progression in patients with COVID-19 pneumonia, in which 152 patients were randomly assigned to two groups of control and treatment (76 patients in each group). Patients in the control group received standard drug therapy including antiviral drugs with lopinavir/ritonavir 50/200 mg (2 tablets recommended) or azithromycin 500 mg/d plus hydroxychloroquine 200 mg/day. If serum interleukin-6 (IL-6) levels increased or respiratory function deteriorated, tocilizumab 8 mg/kg IV (maximum 800 mg dose) was administered twice 12 hours apart. Patients in the treatment group received ozonated blood at a concentration of 30 µg/mL). In this study, in terms of the effect of ozone therapy on inflammatory markers and hematology, the results showed that according to analysis before and after the intervention, the blood lymphocyte count on the seventh day after the intervention compared with baseline in the group receiving ozone therapy + standard drug has been significantly improved. The level of CRP decreased in both groups but this decrease was significant only in the ozone therapy + standard drug

treatment group. Ozone therapy also slightly reduced the need for a ventilator but the alteration was not statistically significant. In our study, similar to this study, ozone therapy reduced the need for ventilators and improved lymphocytes, while in terms of mortality, our study showed that ozone increases mortality (19).

A study by Çolak et al in 2021 was conducted on 55 patients admitted to a training hospital in Turkey with mild and severe COVID-19 infection to indicate the effectiveness of ozone therapy on the mortality rate of COVID-19 patients. Patients were randomly divided into two groups: control (18 patients) and treatment (37 patients). Patients in the standard treatment group were given hydroxychloroquine (400 mg on day one and 200 mg on days two through four), enoxaparin, favipiravir, and antibiotics if a secondary bacterial infection was noticed. Patients in the experimental group, however, also received ozone therapy (in the form of major autohemotherapy) throughout seven sessions (one session per day), which included preparing a patient blood sample. The results reported the need for ICU hospitalization in 6 of 37 patients (16.2%) in the group treated with ozone therapy + standard drug treatment, while 4 out of 18 patients (22.2%) in the standard drug treatment group required ICU hospitalization, exhibiting a statistically non-significant difference ($P = 0.7$). Also, the mortality rate was lower in the ozone-treated group ($P = 0.03$). In general, their results showed that the ozone therapy group had a lower risk of mortality ($P = 0.034$) while concerning our study, ozone therapy increased mortality. One of the reasons for the discrepancy between the results of these studies may be the difference in the type of ozone therapy. In our study, ozonated normal saline was used, but in the mentioned study ozonated blood was used.

Ozone therapy plays an important role in the treatment of severe COVID-19 pneumonia through several biological mechanisms. When human blood is exposed to a mixture of oxygen and ozone, oxygen binds to extracellular water before binding to hemoglobin until it is fully oxygenated; in contrast, ozone, which is more soluble than oxygen, dissolves easily in water and reacts with biomolecules such as amino acids (especially cysteine, tryptophan, methionine, phenylalanine, and tyrosine) and lipids (especially unsaturated fatty acids in membranes) (24,25). Compounds formed during reactions, including reactive oxygen species and fat products (LOPs), represent "ozone messengers" and are responsible for their biological and therapeutic effects; therefore, ozone can be considered a supportive drug that produces biochemical messengers (17). The specific potential use of ozone against coronavirus and the efficacy of ozone against pathogens are well known. Ozone appears to be the best available agent for water disinfection, although the virus activity in the presence of ozone in the body at the dose used in this study is unknown (26). It has been declared that ozone can act as a signal molecule in the body; it is produced by human neutrophils and is essential for the formation of antibodies that are involved in the natural humoral response to infection (27). Ozone can also release and modulate the stimulatory factors IFN-γ and TNF-α and clonal stimulating factors; it can also modulate and stimulate phagocytic function, which may have a very positive effect on COVID-19 infection (28). On the other hand, previous studies have shown that ozone can inhibit the proliferation of SARS and MERS coronaviruses. The SARS-CoV-2 receptors, also known as ACE2 cellular receptors, are known as SARS-CoV-2 receptors, can be regulated and blocked by managing Nrf2, in addition to being blocked by particular monoclonal antibodies (29). Ozone is capable of rapidly activating Nrf2 and this appears to be an important physiological mechanism to prevent COVID-19 from binding to this receptor. In addition, S proteins are responsible for receptor binding and membrane fusion. These proteins consist of a highly protected membrane domain including three parts: a tryptophan N-rich domain, a central domain, and a cysteine-rich C-terminal domain. Both the cysteine-rich domain and the tryptophan-rich domain are essential for fusion. Cysteine and tryptophan are both sensitive to oxidation (30). Ozone metabolites have been hypothesized to oxidize cysteine residues, making it difficult for the virus to enter the host cell and prevent the virus from replicating. Ozone is an antiviral drug that appears to have a low antiviral activity by inhibiting virus replication and activity. Ozone is not a substitute for antiviral drugs, but viral activity is reduced by combining ozone therapy and antiviral drugs (31). The combination of ozone therapy and antiviral drugs reduces inflammation and lung damage and helps increase the host's immunity to infection. It can also activate the cellular and humoral immune systems and reduce inflammatory processes/apoptosis. Recent studies have shown the effectiveness of ozone therapy in the early stages of viral diseases before the need for invasive ventilation. However, in serious or critical situations, the effectiveness of ozone therapy is not very successful (13). Ozone therapy is very cheap, reliable, safe, and known for many years and does not cause resistance; therefore, it may be used for vulnerabilities of many viruses including SARS-CoV-2 (32).

The results of the present study showed that ozone as an adjuvant can be effective in increasing the likelihood of discharge, reducing the duration of treatment, the number of breaths, hemoglobin, and ALT, and increasing the number of lymphocytes in patients with severe COVID-19. One of the limitations of the present study is that it was performed in a single center and the number of patients was small. Other limitations of the present study are that the side effects of the drug and other important

factors in COVID-19 disease were not looked at.

## Conclusion

The present study showed that the use of ozone therapy for hospitalized patients with severe COVID-19 can help improve a number of primary and secondary outcomes of the disease. Ozone therapy may be effective in improving the patient's clinical condition, preventing lung tissue damage, controlling cytokine storms in patients (especially severe COVID-19 patients), and reducing their mortality. However, further large-scale multicenter studies with larger sample sizes evaluating drug side effects and other variables influencing the clinical course of COVID-19 can provide more information on the effectiveness and importance of ozone therapy.

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**Authors' Contribution**

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**Investigation:** Amir Janadliean, Shokrollah Salmanzadeh, Roohangiz Nashibi, Seyed Mohammad Alavi, Sasan Moogahi, Saeid Bitaraf.
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**Competing Interests**

The authors declare that there is no conflict of interest.

**Ethical Approval**

The study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1399.363). Written informed consent was received from patients. The study was listed in the Iranian Registry of Clinical Trials (identifier: IRCT20200730048253N1; https://www.irct.ir/).

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