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STUDY OF OZONE THERAPY AS A COMPLEMENTARY TREATMENT IN SARS-COV-2 INFECTION

321.19 –Anesthesiology and Intensive Care

Summary of the Ph.D. Thesis in Medical Sciences

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The present Ph.D. thesis was developed at the Department of Anesthesiology and Resuscitation No. 1 "Valeriu Ghereg" of the Nicolae Testemițanu State University of Medicine and Pharmacy.

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INTRODUCTION

Relevance and importance of the research. Ozone therapy is a complementary treatment with a wide range of therapeutic applications. It can be used as a standalone therapy or as an adjunct to existing treatment protocols for patients with novel coronavirus disease 2019 (COVID-19). Evidence suggests that this therapy has led to improvements in the clinical picture, biochemical markers, and radiological signs of inflammation, with no reported side effects [1].

Ozone therapy, known for its antioxidant, anti-inflammatory, and antithrombotic properties, may be crucial in addressing hyperinflammation, immunodeficiency, hypercoagulability, and poor response to conventional therapies associated with COVID-19. Early studies suggest that ozone therapy could serve as a promising adjunctive treatment for mild to severe cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Therefore, ozone therapy could be an effective option, either as an alternative (standalone) treatment or, more realistically, as a valuable adjunct to standard therapies for COVID-19 patients, including those experiencing severe respiratory failure [2, 3, 4].

Evidence from the specialized literature suggests that introducing the ozone therapy into treatment protocols may help reduce morbidity and accelerate recovery in patients with COVID-19. However, randomized, controlled clinical trials are required to validate ozone therapy as a viable adjunctive treatment for COVID-19, to guide its clinical application, and evaluate its impact on the progression of SARS-CoV-2 infection [5].

Based on the forementioned information, this study aims to evaluate the clinical efficacy of ozone therapy (major autohemotherapy with ozone) in patients with SARS-CoV-2.

To achieve this **goal**, the following **research objectives** have been defined:

1. To assess the mortality rate in COVID-19 patients treated with intravenous ozone therapy versus those receiving standard care.
2. To estimate the impact of intravenous ozone therapy on the oxygenation index in patients with SARS-CoV-2 infection.
3. To determine the impact of intravenous ozone therapy on the profile of inflammatory markers in COVID-19 patients.
4. To conduct a comparative analysis of the incidence and duration of non-invasive and invasive mechanical ventilation in the study cohorts.
5. To evaluate the influence of intravenous ozone therapy on the length of stay in the Intensive Care Unit and the overall length of hospital stay.

Scientific novelty and originality. The scientific relevance of this study lies in the assessment of all the effects of ozone therapy on the intensity of the inflammatory process and respiratory parameters in COVID-19 patients, which play a decisive role in clinical progression and survival rates. In this way, the study provides opportunities for improving the condition of these patients.

Scientific problem solved. The scientific problem addressed consists in evaluating the efficacy of major ozonated autohemotherapy in the clinical progression of patients with SARS-CoV-2.

The theoretical significance and practical value of this research lies in how the results complement and substantiate treatment methods for patients with COVID-19. A comparative analysis was conducted on the clinical and evolutionary aspects of SARS-CoV-2 infected patients

with and without the adjunctive use of intravenous ozone therapy.

Thesis results approval. The study results were presented and discussed at the following national and international scientific forums:

1. The 5th International Conference on Nanotechnologies and Biomedical Engineering, ICNBME-2021. November 3-5, 2021, Chișinău, Republic of Moldova.
2. The 48th Congress of the Romanian Society of Anesthesia and Intensive Care (SRATI), May 11-15, 2022, Sinaia, Romania.
3. The 7th International Conference on Covid-19 Studies, September 5-6, 2022, Ankara, Turkey.

Keywords: ozone therapy, major ozonated autohemotherapy, COVID-19, SARS-CoV-2, Brixia score, oxygenation index, D-dimer.

Ethical approval for the study was obtained from the Research Ethics Committee on July 20, 2020, minute no. 1.

The work is presented on 125 pages of text and includes an introduction, 3 chapters, a synthesis of the obtained results, general conclusions, practical recommendations, and a bibliography with 264 references. The illustrative material includes 22 figures, 8 tables, 6 statistical formulas, and 3 annexes. As regarding the subject of the Ph.D. thesis, 15 scientific papers have been published, including 2 in impact factor journals, 3 single-author articles, and 10 articles in peer-reviewed journals.

1. OZONE THERAPY IN THE TREATMENT OF COVID-19 PATIENTS

The results of numerous studies have shown that the complementary use of ozone therapy, compared to conventional monotherapy treatment, has proved a more rapid improvement in the clinical picture (reduced fever, decreased need for oxygen support, and restoration of oxygen saturation), pro-inflammatory, coagulation, and imaging markers. It also significantly reduces the length of hospital stay and improves blood oxygenation parameters. Although minor side effects have been reported, ozone therapy does not cause adverse or toxic reactions in COVID-19 patients, making it an effective and beneficial treatment for this patient group. Ozone therapy in COVID-19 patients provides synergistic anticoagulant, immunosuppressive, and antiviral effects [2, 6].

Beyond the well-documented therapeutic capacity of medical ozone to counteract oxidative stress through the upregulation of key antioxidant enzymes, oxygen-ozone therapy has also proven effective in reducing chronic inflammation and immune thrombosis, two key elements involved in the exacerbation and severity of COVID-19. Chronic inflammation and oxidative stress are also among the main drivers of post-acute sequelae of SARS-CoV-2 infection. A growing body of research is investigating the potential of ozone therapy to reduce and/or prevent the wide range of post-COVID disorders [4, 7].

Despite preliminary data from clinical studies and expert opinions, there is still insufficient evidence to confirm ozone therapy as a viable treatment option for COVID-19. To date, very few observational cohort clinical trials have been conducted regarding this novel therapeutic strategy. Further elucidation of ozone's mechanisms of action is also necessary to fully understand its impact on COVID-19. Therefore, multicenter, randomized, double-blind clinical trials are required to evaluate the potential of ozone to restore pulmonary function and improve oxygenation in patients with COVID-19 [4, 6, 7].

2. MATERIALS AND METHODS

2.1. General study design.

The research was conducted at the Department of Anesthesiology and Resuscitation No. 1 "Valeriu Ghereg" of the Public Institution Nicolae Testemițanu State University of Medicine and Pharmacy (PI SUMPh). Biochemical parameter assessment in blood serum was performed at the Biochemistry Laboratory of the Emergency Medicine Institute of (EMI).

The study is a prospective, randomized clinical trial evaluating the clinical and paraclinical efficacy of conventional treatment combined with ozone therapy (major ozonated autohemotherapy) in patients infected with SARS-CoV-2. The research sample included two comparable groups of COVID-19 patients (one receiving conventional treatment and the other receiving conventional treatment combined with ozone therapy), randomly selected and assessed using a specially developed structured clinical questionnaire. All patients were monitored by their consulting physicians and underwent similar treatment. The evaluation criteria remained unchanged throughout the study.

The study population comprised adult patients (≥18 years) with COVID-19 admitted to the Intensive Care Unit (ICU) at EMI between July 2020 and February 2021. Patient identification for inclusion in the study was performed by the author upon admission to EMI.

The *Chi-squared power calculation statistical analysis program* indicated a minimum sample size of 87 patients to achieve 95% confidence interval. To ensure a representative sample with an accepted margin of error of 5%, 100 patients were enrolled within the study, exceeding the minimum representative threshold of 88 patients. Patients were then randomly grouped in a 1:1 ratio into: 50 COVID-19 patients treated according to the National Clinical Protocol and with ozone therapy (major autohemotherapy with ozone) (the study group – SG) and 50 COVID-19 patients treated according to the National Clinical Protocol (the control group – CG).

All patients were enrolled in the study following the provision of written informed consent for investigations, treatment administration, relevant clinical data collection, and outcome assessment.

The research was carried out in a series of phases, based on the inclusion and exclusion criteria (Figure 1):

Inclusion criteria for the study were as following:

1. Patients diagnosed with COVID-19 based on World Health Organization criteria and confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 viral RNA using nasopharyngeal swabs (a molecular biology technique).
2. COVID-19 patients aged 18 years or older.
3. COVID-19 patients with pneumonia confirmed by radiological imaging and a Brixia score ranging between 6 and 10 points.
4. COVID-19 patients with a mild oxygenation impairment (PaO2/FiO2 ratio >200-≤300 mmHg) and peripheral oxygen saturation of 88-96%.
5. Patients with no contraindications for systemic ozone therapy.
6. Patients who have read and signed the study's informed consent.

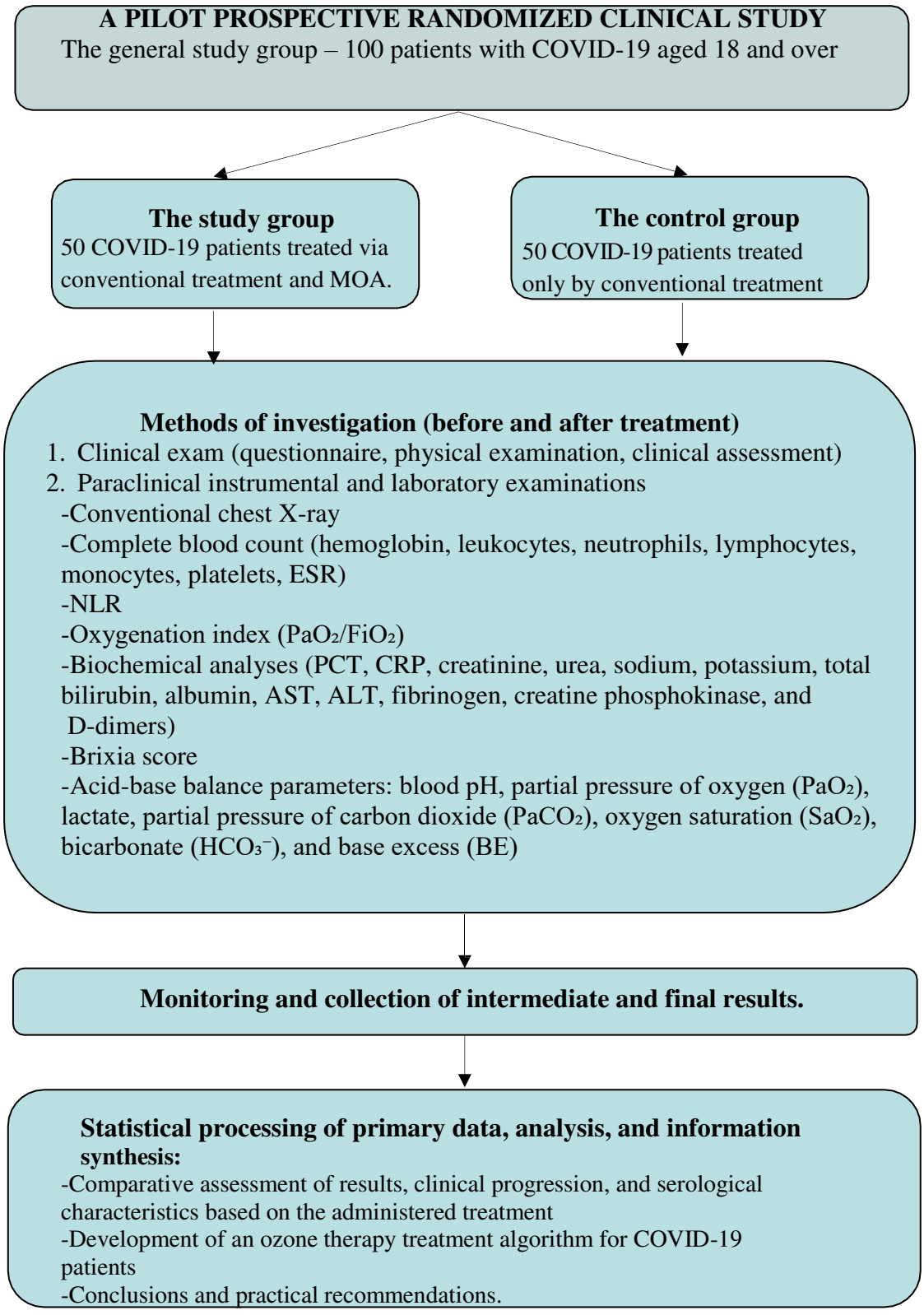

Figure 1. **The study design**

The exclusion criteria for the study were as follows:

1. Patients aged under 18.
2. Patients with multiple organ failure syndrome.
3. Pregnant women, postpartum women, and breastfeeding mothers.
4. Patients with acute surgical pathologies.
5. Patients receiving immunosuppressive therapy.
6. Patients with a history of organ transplantation.
7. Patients on mechanical ventilation at the time of study enrollment.
8. Patients with contraindications for systemic ozone therapy.
9. Patient refusal to participate in the study.

Once eligibility was confirmed, patients with COVID-19 received comprehensive information regarding the study's purpose and objectives, the potential benefits and risks of the investigations and treatment administered, the anticipated outcomes, and their practical implications.
All COVID-19 patients received standard medical care and monitoring, in accordance with national and institutional protocols for both inpatient and outpatient management of this patient population.

2.2. Investigation methods and diagnostic criteria.

All patients included in the study underwent examination using clinical assessment, medical history (anamnestic) collection, and paraclinical (laboratory and imaging) investigations.

Clinical Methods. To assess the characteristics and effectiveness of ozone therapy in patients with COVID-19, general clinical research methods were employed. All study participants were assessed through an interview-based approach using a structured clinical questionnaire specifically developed for this thesis. The questionnaire comprised 58 questions covering socio-demographic data, anthropometric parameters, risk factors, respiratory support and assisted ventilation methods, as well as the results of paraclinical laboratory and instrumental investigations conducted at admission and post-treatment.

Primary data were collected by extracting information from medical records, documenting findings from the initial and follow-up visits, and recording the results of clinical, instrumental, and laboratory investigations before and after treatment. The obtained data were then analyzed comparatively, both to track changes over time (longitudinally) and to compare the two study groups.

Treatment methods. The standard treatment for ICU patients infected with the SARS-CoV-2 virus was administered according to the guidelines outlined in the National Provisional Clinical Protocol (editions III and IV) [8, 9] and the Practical Guide for Managing Severe Complications of Coronavirus Infection (COVID-19) [10]. This approach included the following supportive strategies:

1. Conventional or standard treatment.
2. Major ozonated autohemotherapy – intravenous infusion of autologous whole blood ozonated under strict aseptic and antiseptic conditions. This involved drawing 80–120 mL of venous blood and mixing it with 10 mL of 3.13% sodium citrate solution as an anticoagulant. The blood was then enriched with an oxygen-ozone gas mixture in a 1:1 ratio, with an ozone concentration of 40 µgN/mL, and thoroughly mixed for 5 minutes. After ozonation, the blood was immediately reinfused into the same vein over approximately 10–15 minutes. The treatment consisted of 7 consecutive sessions, administered once every 24 hours for 7 days. Ozone was generated using the Medozon Herrmann medical device.

According to multiple clinical studies, the most effective approach for COVID-19 patients has been the administration of 200 mL of autologous blood enriched with 200 mL of an oxygen-ozone gas mixture containing ozone at a concentration of 40 µgN/mL. This method is widely used. The maximum recommended biologically relevant ozone concentration is 40 µg/mL of blood, and a seven-day course of daily major ozonated autohemotherapy is considered an appropriate duration for assessing its effects [11].

All ozone therapy methods used for COVID-19 patients comply with the recommendations of the World Federation of Oxygen-Ozone Therapy (*WFOT's Review on Evidence-Based Ozone Therapy*) and the international guideline (*The International Scientific Committee of Ozone Therapy – Madrid Declaration on Ozone Therapy*). These methods are also integrated into the ozone generator software [3].

Clinical assessment.

Fever was defined as an axillary temperature of ≥37.5°C.

Clinical improvement was determined by a two-point reduction on a six-point ordinal severity scale, assessed at the time of transfer from the ICU to the COVID-19 ward, at discharge, or upon death, compared to the patient's condition on the first day of ICU admission:

- **6 points** = Death
- **5 points** = Hospitalization requiring mechanical ventilation with intubation
- **4 points** = Hospitalization requiring non-invasive ventilation or high-flow oxygen therapy
- **3 points** = Hospitalization requiring oxygen therapy (without the need for high-flow oxygen therapy or non-invasive ventilation)
- **2 points** = Hospitalization without the need for oxygen therapy
- **1 point** = Transfer to the COVID-19 ward, meeting discharge criteria, or discharge from the hospital alive.

Discharge criteria included clear evidence of clinical recovery, specifically: a normal temperature, respiratory rate below 24 breaths per minute, oxygen saturation above 94% at an FiO_2 of 0.21%, and the absence of cough for at least 72 hours.

The decision to initiate mechanical ventilation, whether invasive (with intubation) or non-invasive, was made based on clinical guidelines and the attending physician's judgment.

Biochemical methods.

Blood samples were drawn from the cubital vein within the first 6–8 hours of admission and again on the seventh day of hospitalization for hematological (complete blood count, lymphocyte count, neutrophil count, NLR, platelet count) and biochemical analyses (PCT, CRP, creatinine,

urea, sodium, potassium, total bilirubin, aspartate aminotransferase, creatine phosphokinase, fibrinogen, and D-dimers).

General clinical and biochemical analyses were performed using the HumaStar 300SR and Mindray BS-240Pro automated biochemical analyzers in the Biochemistry Laboratory of IEM. D-dimer levels were determined by immunofluorescence assays and expressed in fibrinogen equivalent units (μg/mL).

The following reference ranges were used for biochemical tests: D-dimer <0.5 mg/mL, PCR – 0,8-3,0 mg/L, PCT – <0,5 ng/mL, and WBC– 4-109/L. Lymphocytopenia was defined as a lymphocyte count <1500 cells/mm³, and thrombocytopenia as a platelet count <150,000 cells/mm³.

Acid-base balance parameters were obtained with a Siemens RAPIDPOINT 500 analyzer. The reference ranges considered normal were as following: pH 7.35-7.45, partial pressure of oxygen (PaO_2) 90-110 mm Hg, partial pressure of carbon dioxide ($PaCO_2$) 35-45 mm Hg, oxygen saturation (SaO_2) 96-100%, bicarbonate (HCO_3^-) 22-26 mmol/L, base excess (BE) -2 to +2 mmol/L, and lactate 0.5-1.0 mmol/L. Acidosis was defined as a pH below 7.35, and alkalosis as a pH above 7.45.

Radiological examination.

A chest X-ray was performed to diagnose, determine the severity, and monitor the progression of lung abnormalities in patients with COVID-19. The examination was conducted according to standard radiographic protocol using a posteroanterior view, with a lateral view added as needed. A SHIMADZU Mobile Art Evolution portable X-ray unit was used.

The Brixia score was used to quantify the severity of COVID-19 pneumonia and to guide patient management in selecting the optimal ventilation support. The Brixia score is a semi-quantitative, effective, and reliable assessment of COVID-19 severity, based on an 18-point severity scale that ranks lung involvement according to the types and extent of lung abnormalities (Figure 2) [12].

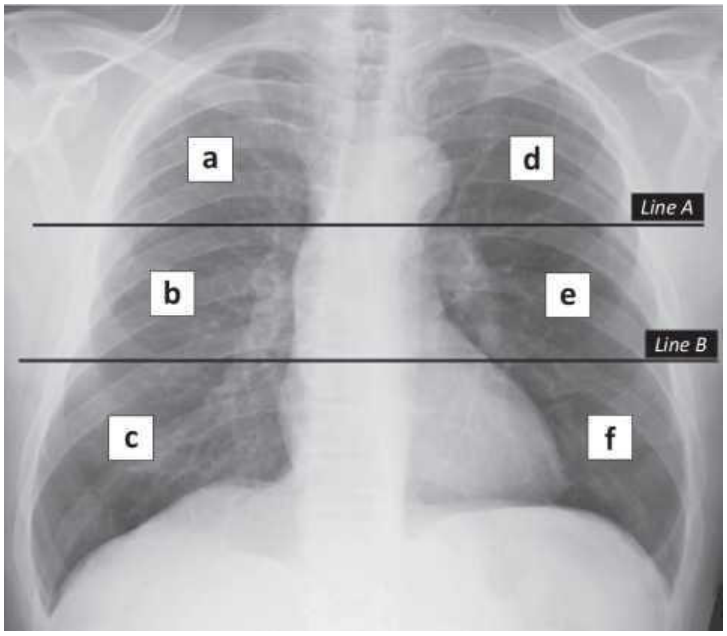

Figure 2. **Lung field division into six zones for Brixia score assessment.**

On a frontal chest radiograph, the lung fields are divided into 6 zones:

- Zones A and D: regions located above the lower border of the aortic arch.
- Zones B and E: regions located between the lower border of the aortic arch and the lower border of the right pulmonary vein.
- Zones C and F: regions located below the lower border of the right pulmonary vein.

Subsequently In the next step, each of these six zones is assessed using a score ranging from 0 to 3 points:

- Score 0 – No visible lesions.
- Score 1 – Interstitial infiltrates.
- Score 2 – Interstitial and alveolar infiltrates (with interstitial predominance).
- Score 3 – Interstitial and alveolar infiltrates (with alveolar predominance).

Therefore, the overall score for all 6 zones ranges from 0 to 18 points.

The following parameters were included for evaluating the **effectiveness of intravenous ozone therapy:**

1. Primary outcomes**:** a) mortality rate, b) clinical outcomes (rate of improvement in oxygenation index), c) hematological outcomes (reduction in leukocyte count, neutrophil count, and NLR; decrease in CRP, PCT, D-dimer, and urea concentrations; increase in hemoglobin, lymphocyte count, and platelet count), and d) radiological improvement (rate of improvement in Brixia score).
2. Secondary outcomes**:** a) length of hospital stay, b) need for non-invasive ventilation, c) need for invasive mechanical ventilation, d) duration of non-invasive ventilation, e) duration of invasive mechanical ventilation, f) length of ICU stay, g) time from completion of ozone therapy to hospital discharge, h) time from completion of ozone therapy to death.

2.3. Methods of statistical data processing.

The primary study data were introduced into an electronic database and processed using the functions and modules of SPSS version 16.0 for Windows (SPSS Inc., Belmont, CA, USA, 2008) and *Microsoft Office Excel 2019* on a personal computer through descriptive and inferential statistical procedures. Statistical processing involved a set of operations performed using specific procedures and techniques.

- Organizing the material through centralization and statistical grouping methods, based on parameters and levels, to obtain primary indicator values and statistical data series.
- Calculating derived indicators based on the distribution type, including relative indicators, measures of central tendency and dispersion, distribution shape, variation over time and space, and the Student's t-coefficient.
- Determining absolute (counts) and/or relative (points, percentages) frequencies for nominal or categorical variables, as well as the mean value and standard error of the mean for quantitative or continuous variables (interval or ratio scale).
- Comparing discrete variables using Pearson's χ^2 test for contingency tables with large samples; Pearson's χ^2 test with Yates' correction for 2x2 contingency tables when the sample size is small (40-50 observations) or when there are 20-50 observations and all

expected frequencies exceed 5; Fisher's exact test for 2x2 contingency tables that do not meet these criteria.

- Analyzing descriptive statistical parameters, including frequency tables, graphs, and numerical indicators (minimum and maximum values, mean, standard error of the mean, etc.), as well as inferential statistics for population estimation and hypothesis testing.
- Testing the normality of interval-scale variables using the Kolmogorov-Smirnov test.
- Comparing results and assessing the strength of statistical relationships and the influence of various factors on observed variations through correlation analysis: Pearson's correlation coefficient r for normally distributed variables and nonparametric rank correlation tests, such as Spearman's ρ or Kendall's τ, for non-normally distributed variables.
- Presenting statistical data using tables and graphical methods.
- Calculating effect size indicators for therapy, including relative risk, relative risk reduction, absolute risk reduction, and the number needed to treat, based on 2x2 contingency tables.

3. THE EFFICIENCY OF OZONE THERAPY IN THE TREATMENT OF PATIENTS WITH COVID-19

3.1. Clinical and paraclinical characteristics of deceased vs. surviving COVID-19 patients.

The mean age of deceased COVID-19 patients was higher (63.03±9.3 years) than that of survivors (59.07±11.4 years), though the difference was not statistically significant. The average time from symptom onset to ICU admission was similar in both groups. However, survivors had a significantly longer total hospital stay, while deceased patients had a significantly longer ICU stay. Oxygen therapy, non-invasive ventilation, and invasive mechanical ventilation were used significantly more often in patients who did not survive.

On the first day of hospitalization, deceased COVID-19 patients had significantly higher mean values for the clinical assessment score and urea levels compared to survivors, while the mean PaO2/FiO2 ratio was significantly lower. Over time (from day 1 to day 7 of hospitalization), deceased patients showed a statistically significant increase in the clinical assessment score, leukocyte count, NLR, D-dimer levels, and Brixia score, along with a significant decrease in the PaO2/FiO2 ratio, hemoglobin levels, and lymphocyte count. In contrast, survivors exhibited a significant increase in the PaO2/FiO2 ratio, platelet count, and D-dimer levels, while the clinical assessment score, hemoglobin levels, CRP, and PCT showed a statistically significant decrease.

On the 7th day of hospitalization, COVID-19 patients who did not survive had significantly higher mean values for the clinical assessment score, leukocyte count, NLR, CRP, urea, D-dimers, and Brixia score compared to those who survived. In contrast, their mean PaO_2/FiO_2 ratio and lymphocyte count were significantly lower. An analysis of oxygenation index severity on the 7th day of treatment showed that the moderate form was significantly more common among those who did not survive, while the mild form and normal values were significantly more frequent among survivors.

3.2. Efficacy of combined ozone therapy as an adjunct to conventional treatment in COVID-19 patients.

Patients in both study groups were similar in terms of sex distribution (44.0% men and 56.0% women in the study group; 46.0% men and 54.0% women in the control group; p>0.05), age (58.08±9.9 years in the SG vs. 62.36±11.6 years in the CG; p>0.05), comorbidities, and the average time from symptom onset to ICU admission (6.86±4.3 days in the SG vs. 7.94±3.8 days in the CG group; p>0.05). Additionally, both groups had comparable mean values for clinical assessment, PaO_2/FiO_2 ratio, hematological parameters, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), procalcitonin (PCT), urea levels, and Brixia score.

3.2.1. The Impact of ozone therapy on mortality, hospital stay, and oxygen therapy duration in COVID-19 patients.

The mean total hospital stay was similar in both study groups, with patients in the SG hospitalized for an average of 17.80±8.9 days and those in the CG for 17.06±10.6 days (p>0.05). The average ICU stay showed a slight reduction in the SG (8.56±5.3 days) compared to the CG (10.22±9.0 days), though the difference was not statistically significant (p>0.05). Although the mortality rate was notably lower in the SB (12–24.0%) than in the SG (17–34.0%), the difference did not show any statistical significance (p>0.05).

The frequency of oxygen therapy administration (35–70.0% in COVID-19 patients treated with ozone vs. 39–78.0% in those treated conventionally, p>0.05), non-invasive ventilation (35–70.0% vs. 38–76.0%, p>0.05), and invasive mechanical ventilation (11–22.0% vs. 19–38.0%, p>0.05) tended to be lower in the SG. However, this reduction did not reach statistical significance (Figure 3).

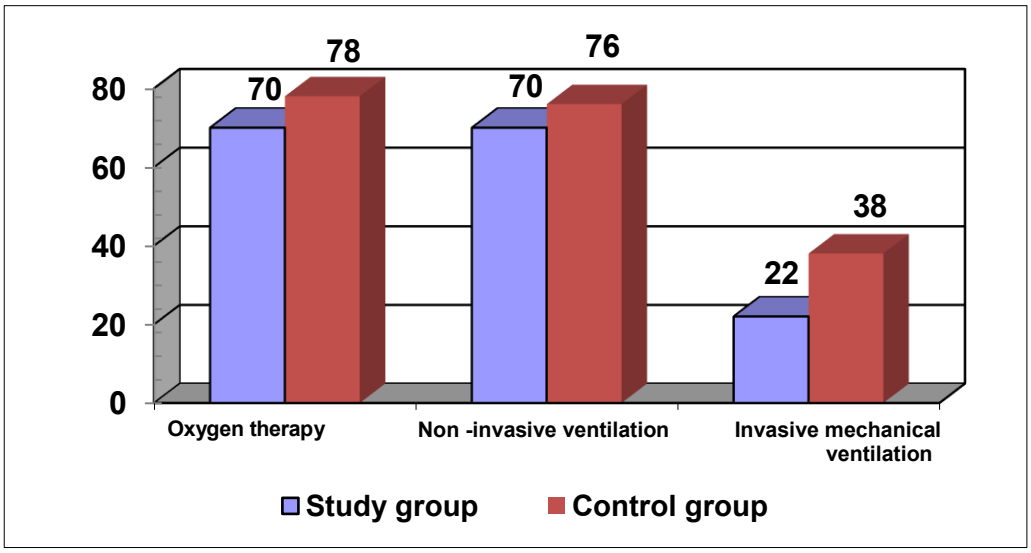

Figure 3. **Percentage of COVID-19 patients who received respiratory support in both the study group**

The mean duration of oxygen therapy (8.20±5.4 days in COVID-19 patients treated with ozone vs. 9.77±8.7 days in those receiving conventional treatment, p>0.05), non-invasive ventilation (6.06±3.9 days vs. 6.29±6.8 days, p>0.05), and invasive mechanical ventilation (6.82±5.5 days vs. 7.47±6.8 days, p>0.05) showed a non-significant tendency toward reduction in

the SG.

3.2.2. The impact of ozone therapy on clinical and paraclinical parameters in COVID-19 patients.

Ozone therapy significantly improved clinical outcomes in patients with COVID-19. A two-point reduction in clinical score, indicating clinical improvement, was observed in 27 (54.0%) patients treated with ozone and 25 (50.0%) patients who received conventional treatment ($p > 0.05$) (Table 1).

The mean oxygenation index (PaO_2/FiO_2) increased significantly in the SG but remained unchanged in the CG. By the 7th day of treatment, patients in the SG showed a trend toward normalization of PaO_2/FiO_2 values and a milder form of acute respiratory distress syndrome (ARDS). In contrast, ARDS worsened significantly more often in patients from the CG, although moderate and severe oxygenation index values in this group showed only a tendency to increase.

Although the initial oxygenation index values at ICU admission were similar in both study groups, the analysis of dynamic changes clearly demonstrated the effectiveness of ozone therapy. By the end of the 1st treatment week, the mean oxygenation index in the study group was significantly higher than in the control group receiving standard treatment.

Furthermore, the median absolute difference between the oxygenation index on the 7th day of ozone therapy and the initial value was positive at 53.5 mmHg (IQR -19.7 to 106), whereas in the control group, this parameter was negative at -19 mmHg (IQR -85.2 to 56.5) ($p<0.05$). These findings indicate a more favorable improvement in oxygenation dynamics with combined ozone therapy compared to standard treatment.

Similarly, the mean Brixia score was comparable between the two groups on the 1st day. However, by the 7th day, it showed a decreasing trend in the study group, while it increased in the control group.

The Brixia score decreased in 50% of cases in the SG compared to 42% in the CG ($p>0.05$). Notably, by day 7, patients treated with ozone showed a statistically significant improvement in pulmonary radiological findings compared to the control group. On the 7th day of treatment, the mean Brixia score was significantly higher in CG patients ($p<0.05$). The median absolute difference in the Brixia score was 0.5 (IQR: 2.0–3.0) points in the SG, compared to 0 (IQR: 4.0–2.0) points in the CG ($p<0.05$).

In both groups, the mean levels of hemoglobin and CRP decreased significantly, while ALT, platelets, and D-dimers increased significantly.

Albumin, leukocyte, and urea levels showed a decreasing trend in SG patients but a statistically significant increase in CG patients.

Table 1. **Table 1. Clinical, laboratory, and imaging parameters (X±SD) in COVID-19 patients from both study groups on the 1st and 7th day of treatment.**

Parameters	Study group		p	Control group		p	p (1-st day)	p (7-th day)
	1-st day	7-th day		1-st day	7-th day			
PaO2/FiO2 (mm Hg)	246,86±30,3	296,75±105,1	<0,01	235,86±33,4	232,82±110,6	NS	NS	<0,01
PCR (mg/L)	75,17±53,9	44,88±53,2	<0,01	82,52±59,9	44,85±57,9	<0,001	NS	NS
PCT (ng/mL)	0,18±0,3	0,17±0,3	NS	0,13±0,1	0,14±0,2	NS	NS	NS
Brixia Score (points)	8,30±1,6	7,48±4,0	NS	8,38±1,3	9,44±4,1	NS	NS	<0,05
D-Dimerii (µg/mL)	0,98±0,8	2,58±2,9	<0,01	1,98±2,5	2,97±2,9	<0,05	<0,01	NS
Fibrinogen (g/L)	4,36±0,8	3,60±1,2	<0,01	4,36±1,1	4,57±2,9	NS	NS	<0,05
Leucocytes ($x10^9$/L)	10,09±5,2	9,80±4,1	NS	9,25±4,5	11,79±7,9	<0,01	NS	NS
Neutrophiles (%)	71,68±13,3	72,08±12,8	NS	71,84±10,6	74,04±11,5	NS	NS	NS
Lymphocytes (%)	10,42±6,5	11,77±7,3	NS	11,88±7,1	11,30±6,9	NS	NS	NS
NLR	11,78±13,2	9,85±7,4	NS	9,02±5,9	10,74±9,0	NS	NS	NS
Monocytes ($x10^9$/L)	5,48±3,3	6,6±3,9	NS	5,66±3,0	5,58±3,7	NS	NS	NS
ESR (mm/h)	26,22±15,9	28,65±16,6	NS	26,14±15,4	32,58±16,2	<0,05	NS	NS
Thrombocytes ($x10^9$/L)	241,58±91,1	284,21±101,0	<0,01	219,84±80,0	276,48±112,3	<0,001	NS	NS
Haemoglobin (g/L)	128,78±14,6	119,85±17,1	<0,001	127,24±16,5	119,94±18,2	<0,01	NS	NS
Albumin (g/L)	36,52±4,1	31,77±4,1	<0,001	34,80±5,7	30,68±4,3	<0,001	NS	NS
Ureea (mmol/L)	7,41±3,4	7,32±2,9	NS	8,06±5,6	9,34±7,7	<0,05	NS	NS
Creatinine (mmol/l)	100,92±53,9	92,42±28,3	NS	107,66±63,1	99,88±75,5	NS	NS	NS
ALAT (U/l)	52,34±61,8	68,58±53,2	<0,05	48,04±33,2	67,64±58,8	<0,01	NS	NS
ASAT (U/l)	46,52±35,3	42,50±40,3	NS	51,82±39,6	42,84±33,1	NS	NS	NS
Clinical assessment (points)	3,66±0,5	2,52±1,6	<0,001	3,70±0,5	2,84±1,8	<0,001	NS	NS

Note: NS – not significant.

Fibrinogen, beyond its crucial role in blood coagulation, is also considered a marker of inflammation severity. Data analysis showed a significant reduction in fibrinogen levels by day 7 in SG of patients treated with ozone: 3.6 (IQR 2.7–4.2) g/L compared to 4.3 (IQR 3.9–4.8) g/L upon enrollment ($p<0.001$). In contrast, the CG showed no significant changes in plasma fibrinogen levels over time—4.6 (IQR 3.6–4.7) g/L on day 7 compared to 4.4 (IQR 3.9–4.6) g/L on day 1 ($p>0.05$). On the 7th day of treatment, the median fibrinogen level was significantly lower in the study group: 3.8 (IQR 2.7–4.2) g/L versus 4.0 (IQR 3.6–4.7) g/L in the control group ($p<0.05$). Additionally, the median absolute difference between the initial and final fibrinogen levels was significantly greater in the ozone-treated group: 0.55 (IQR 0.07–1.52) g/L compared to 0.25 (IQR -0.7–0.7) g/L in the CG

($p<0.05$).

3.2.3. Changes in acid-base balance in COVID-19 patients based on treatment administered.

At the beginning of the study, the mean values of acid-base balance parameters were similar in both groups. By day 7, compared to day 1, the SG showed a statistically significant decrease in mean pH levels (from 7.43±0.08 on day 1 to 7.41±0.06 on day 7; $p<0.05$) and lactate levels (from 1.87±0.61 mmol/L on day 1 to 1.49±0.59 mmol/L on day 7; $p<0.01$). In contrast, the mean values of PaO_2 (from 67.14±9.12 mm Hg on day 1 to 94.03±13.63 mm Hg on day 7; $p<0.001$), $PaCO_2$ (from 30.52±4.43 mm Hg on day 1 to 34.28±3.01 mm Hg on day 7; $p<0.001$), and SaO_2 (from 87.88±2.65% on day 1 to 95.46±2.36% on day 7; $p<0.001$) increased significantly.

In the CG, only the mean values of $PaCO_2$ (from 30.95±4.47 mm Hg on day 1 to 33.73±5.38 mm Hg on day 7; $p<0.01$) and SaO_2 (from 87.76±3.38% on day 1 to 90.84±2.79% on day 7; $p<0.001$) increased significantly. Moreover, on day 7, the mean values of PaO_2 (94.03±13.63 mm Hg and 72.77±12.53 mm Hg, respectively; $p<0.001$) and SaO_2 (95.46±2.36% and 90.84±2.79%, respectively; $p<0.001$) were significantly higher in the SG, whereas lactate levels (1.49±0.59 mmol/L and 1.82±0.77 mmol/L, respectively; $p<0.01$) were significantly lower in the SG.

3.2.4. Clinical and paraclinical characteristics of deceased patients vs. survivors in both groups

Clinical and paraclinical characteristics of deceased patients. In SG, compared to the CG, there was a lower mortality rate trend (24.0% vs. 34.0%, respectively; $p>0.05$) and a higher survival rate (76.0% vs. 66.0%, respectively; $p>0.05$). However, these differences were not statistically significant. No significant differences were observed based on sex (Figure 4).

Among patients undergoing combined treatment with ozone therapy and conventional care, the mortality risk was 0.24, whereas for those receiving only conventional treatment, it was 0.34. Ozone therapy proved to be effective—among patients treated with the combined approach, the relative risk of death was 0.706 (95% CI: 0.377–1.321). The relative risk reduction was clinically significant, amounting to 0.294 or 29.4%, while the absolute risk reduction was 0.10. The number of patients who needed to be treated to save one life was 10.

The mean age of deceased patients (60.83±6.6 years in the study group and 64.59±10.7 years in the control group) and the mean age of surviving patients (57.21±10.7 years in the study group and 61.21±12.0 years in the control group) were slightly lower in the COVID-19 patients treated with ozone compared to those who received conventional treatment, though the difference was not statistically significant.

Both groups (deceased patients treated conventionally and those treated with ozone) were comparable in terms of medical history, overall obesity prevalence, the average time from symptom onset to ICU admission, ICU length of stay, total hospitalization duration, as well as the frequency and duration of oxygen therapy, non-invasive ventilation, and invasive mechanical ventilation.

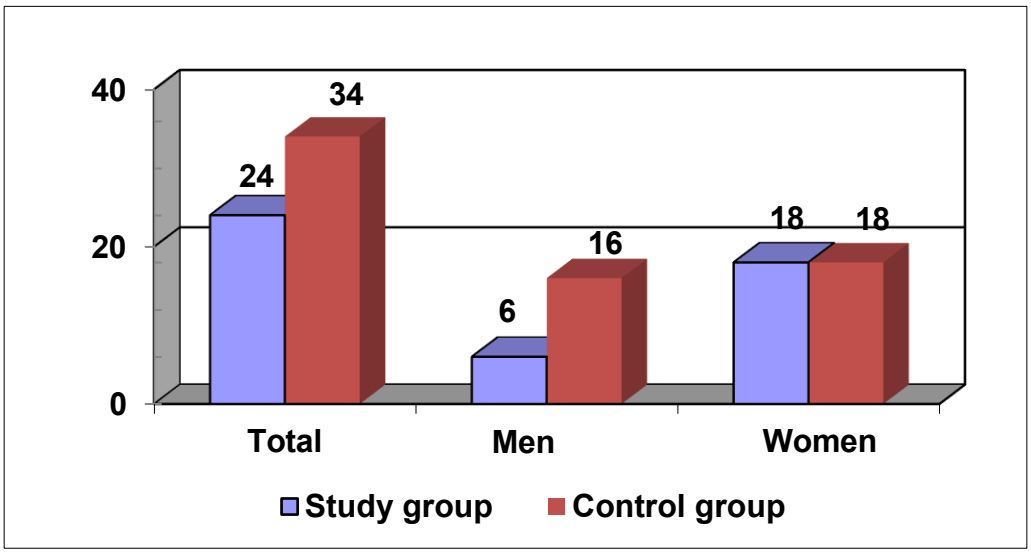

Figure 4. **Mortality rates among COVID-19 patients in the study groups by sex (%).**

Grade III obesity was significantly more common among deceased COVID-19 patients who underwent conventional treatment (55.6% vs. none, respectively; $p<0.01$). In contrast, Grade II and Grade I obesity, when combined, were more frequently observed in deceased COVID-19 patients treated with ozone therapy.

On the first day of hospitalization, deceased COVID-19 patients who underwent ozone therapy had a significantly higher mean PaO2/FiO2 ratio compared to those treated conventionally (247.33±27.3 mm Hg vs. 216.18±21.5 mm Hg, respectively; $p<0.05$) (Table 2).

At the initial stage (day 1 of hospitalization), patients with COVID-19 treated with ozone who later died had a significantly higher mean PaO2/FiO2 ratio compared to those treated conventionally who also died (247.33±27.3 mm Hg vs. 216.18±21.5 mm Hg, respectively; $p<0.05$).

Over time (days 1 and 7 of hospitalization), a statistically significant increase in the mean clinical assessment score (3.83±0.4 points vs. 4.67±0.8 points, respectively; $p<0.05$) and a statistically significant decrease in mean hemoglobin levels (121.75±17.0 g/L vs. 107.50±13.9 g/L, respectively; $p<0.05$) were observed in patients with COVID-19 treated with ozone who later died.

Similarly, over time (days 1 and 7 of hospitalization), patients with COVID-19 treated conventionally who later died showed a statistically significant increase in the mean clinical assessment score (3.94±0.2 points vs. 4.71±0.8 points, respectively; $p<0.01$), leukocyte count (8.95±4.9×10⁹/L vs. 14.92±12.1×10⁹/L, respectively; $p<0.01$), D-dimer levels (2.60±3.4 µg/mL vs. 4.32±3.1 µg/mL, respectively; $p<0.05$), and Brixia score (8.24±1.3 points vs. 11.76±3.61 points, respectively; $p<0.01$), along with a statistically significant decrease in mean hemoglobin levels (130.53±21.7 g/L vs. 121.12±19.1 g/L, respectively; $p<0.01$).

On the 7th day of hospitalization, patients with COVID-19 who were treated with ozone and subsequently died had a significantly lower mean Brixia score (8.60±3.7 points) compared to those who received conventional treatment and died (11.76±3.61 points; $p<0.05$).

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Table 2. **Clinical, laboratory, and imaging parameters (X±SD) in deceased COVID-19 patients from the study groups on the 1st and 7th day of treatment**

Parameters	Study group		Control group		P
	1st day (1)	7th day (2)	1st day (3)	7th day (4)	
PaO2/FiO2 (mm Hg)	247,33±27,3	186,30±134,8	216,18±21,5	186,76±110,6	1-3*
PCR (mg/L)	81,74±47,4	100,38±73,6	68,12±62,8	57,23±59,3	NS
PCT (ng/mL)	0,21±0,2	0,34±0,6	0,11±0,04	0,17±0,2	NS
Brixia Score (points)	8,58±1,8	8,60±3,7	8,24±1,3	11,76±3,6	2-4*, 3-4**
D-Dimers (µg/mL)	1,50±1,1	3,84±3,5	2,60±3,4	4,32±3,1	3-4*
Leucocytes ($x10^9$/L)	11,36±6,7	13,17±2,7	8,95±4,9	14,92±12,1	3-4**
Neutrophils (%)	75,25±11,4	78,00±7,2	72,53±7,4	75,82±13,1	NS
Lymphocytes (%)	8,67±4,3	6,80±1,9	13,18±6,9	9,47±6,6	NS
NLR	12,58±11,2	13,70±8,7	8,06±6,3	14,77±12,1	NS
Thrombocytes ($x10^9$/L)	236,25±95,7	255,20±99,2	217,41±93,0	256,24±117,4	NS
Haemoglobin (g/L)	121,75±17,0	107,50±13,9	130,53±21,7	121,12±19,1	1-2*, 3-4*
Urea (mmol/L)	8,13±3,1	9,24±4,4	10,86±7,8	14,24±11,6	NS
Clinical assessment (points)	3,83±0,4	4,67±0,8	3,94±0,2	4,71±0,8	1-2*, 3-4**

Note: * - p<0,05, ** - p<0,01, *** - p<0,001, NS – non-significant

Clinical and paraclinical characteristics of surviving patients. The mean age of surviving patients (57.21±10.7 years and 61.21±12.0 years) showed only a nonsignificant decreasing tendency in the group of COVID-19 patients treated with ozone compared to the group treated conventionally.

Both study groups (surviving COVID-19 patients treated conventionally and those treated with ozone) were similar in terms of medical history, obesity prevalence, mean duration from symptom onset to ICU admission, mean length of ICU stay, and mean total hospitalization duration.

The use of oxygen therapy, non-invasive ventilation, and invasive mechanical ventilation, as well as the average duration of oxygen therapy and non-invasive ventilation, showed a decreasing trend among COVID-19 patients treated with ozone who survived. However, this trend did not reach statistical significance. The only statistically significant difference was in the duration of invasive mechanical ventilation, which was significantly shorter in the ozone-treated group (0 days vs. 25.00±5.7 days, respectively; p<0.001) compared to those who underwent conventional treatment and survived.

At the initial stage (day 1 of hospitalization), during follow-up (days 1 and 7 of hospitalization), and on day 7 of hospitalization, the clinical, laboratory, and imaging parameters were similar in both groups of COVID-19 patients. However, on day 7, patients in the ozone-treated group who survived had a significantly higher mean PaO2/FiO2 ratio (325.82±73.9 mm Hg vs. 256.55±104.4 mm Hg, respectively; p<0.01) compared to those in the conventional treatment group who survived (Table 3).

Table 3. **Clinical, laboratory, and imaging parameters (X±SD) in COVID-19 patients from the study groups who survived on day 1 and day 7 of treatment**

Parametres	Study group (n=38)		Control group (n=33)		P
	1st day (1)	7th day (2)	1st day (3)	7th day (4)	
PaO2/FiO2 (mm Hg)	246,71±31,5	325,82±73,9	246,00±34,1	256,55±104,4	2-4**
PCR (mg/L)	73,10±56,2	30,27±35,1	90,00±57,9	38,86±57,1	NS
PCT (ng/mL)	0,17±0,4	0,12±0,1	0,15±0,1	0,13±0,2	NS
Scor Brixia (points)	8,21±1,6	7,18±4,1	8,45±1,3	8,24±3,9	NS
D-Dimers (µg/mL)	0,82±0,6	2,25±2,7	1,67±1,9	2,27±2,6	NS
Leucocytes ($x10^9$/L)	9,68±4,7	8,92±4,0	9,40±4,4	10,17±3,7	NS
Neutrophils (%)	70,53±13,8	70,53±13,5	71,49±12,0	73,12±10,6	NS
Lymphocytes (%)	10,97±7,0	13,08±7,6	11,21±7,2	12,24±6,9	NS
NLR	11,53±13,9	8,84±6,7	9,52±5,8	8,67±6,2	NS
Thrombocytes ($x10^9$/L)	243,26±90,8	291,84±101,4	221,10±73,9	286,91±109,9	NS
Hemoglobin (g/L)	131,00±13,3	123,11±16,5	125,55±13,1	119,33±18,1	NS
Urea (mmol/L)	7,18±3,5	6,82±2,1	6,62±3,4	6,82±2,2	NS
Clinical assessment (points)	3,61±0,5	1,84±1,2	3,58±0,5	1,88±1,4	NS

Note: * - p<0,05, ** - p<0,01, *** - p<0,001, NS – nesemnificativ.

The analysis of oxygenation index severity on the 7th day of treatment revealed a statistically significant increase in the frequency of the moderate form (18.2% vs. 2.6% of cases, p<0.05) and a tendency toward a higher frequency of the severe form (9.1% vs. none, p>0.05) among COVID-19 survivors who underwent conventional treatment. In contrast, among patients treated with ozone therapy, there was a higher frequency tendency of the mild form (44.7% vs. 39.4% of cases, p>0.05) and a higer incidence of patients with normal PaO2/FiO2 ratios (52.6% vs. 33.3% of cases, p>0.05).

SYNTHESIS OF OBTAINED RESULTS

An analysis of the existing studies found that the findings of the present research study align with those reported in other research. For instance, a single-center, continuous, interventional, randomized, and prospective study examined 14 COVID-19 patients who received ozone autohemotherapy (twice daily for 7 consecutive days), with a mean age of 63.3±12.1 years, and 14 COVID-19 patients in the control group, who received the best available treatment, with a mean age of 60.1±14.4 years. Ozone therapy did not significantly impact inflammatory markers, hematological profiles, or lymphocyte subpopulations. While it moderately reduced the need for ventilatory support, this effect did not reach statistical significance. The 30-day mortality rate was 8.3% in the ozone therapy group and 10% in the control group, though this difference was not statistically significant [13].

Other prospective, controlled studies have suggested that administering ozone therapy

alongside conventional medical treatment in hospitalized COVID-19 patients may help reduce mortality [14]. However, another study found that in cases of mild to moderate pneumonia caused by SARS-CoV-2 infection, adjunctive oxygen-ozone therapy had no effect on mortality or the need for mechanical intubation but did lead to clinical improvement by day 7 of treatment [15]. A systematic review and meta-analysis of the literature concluded that while adjunctive ozone therapy did not show significant benefits in most cases—such as improvements in clinical variables and certain laboratory biomarkers—the estimated effects were still noteworthy. Given its safety profile, ozone therapy may offer positive outcomes for COVID-19 patients [16].

Thus, both existing literature and our study's findings support the clinical benefits of ozone therapy in treating COVID-19 patients. As a promising treatment for SARS-CoV-2 infection, ozone therapy's mechanisms of action justify its use as an adjuvant therapy. Moreover, several clinical studies have reported positive outcomes. One main advantage of ozone therapy is its ability to enhance treatment outcomes when applied early in the disease, as well as in critically ill patients [5, 16]. The absence of statistically significant differences in our study's parameters may be attributed to the small sample size. Given the study's limited goal and its single-center design, larger randomized controlled trials are needed to provide more definitive conclusions [13, 14].

GENERAL CONCLUSIONS

1. Although the mortality rate of COVID-19 patients in the Intensive Care Unit treated with ozone was lower (24.0%) than that of patients undergoing conventional treatment (34.0%), the difference was not statistically significant.
2. The mean oxygenation index (PaO_2/FiO_2) increased significantly in the study group, rising from 246.86±30.3 mmHg on day 1 to 296.75±105.1 mmHg on day 7 ($p<0.01$), while no significant change was observed in the control group (235.86±33.4 mmHg on day 1 vs. 232.82±110.6 mmHg on day 7; $p>0.05$). Furthermore, the study group showed a statistically significant increase in $PaCO_2$ and SaO_2 levels, along with a significant lower lactate levels.
3. The mean fibrinogen level significantly decreased in patients treated with ozone, while it remained largely unchanged in the control group. By day 7, this parameter was significantly lower in the study group. In both groups, the mean C-reactive protein level decreased significantly, whereas platelet and D-dimer levels showed a statistically significant increase.
4. The use of oxygen therapy (70.0% in the study group vs. 78.0% in the control group, $p>0.05$), non-invasive ventilation (70.0% vs. 76.0%, $p>0.05$), and invasive mechanical ventilation (22.0% vs. 38.0%, $p>0.05$) showed a downward trend in the study group. However, these differences were not statistically significant.
5. The mean duration of oxygen therapy (8.20±5.4 days in COVID-19 patients treated with ozone and 9.77±8.7 days in those undergoing conventional treatment, $p>0.05$), non-invasive ventilation (6.06±3.9 days in COVID-19 patients treated with ozone and 6.29±6.8 days in those undergoing conventional treatment, $p>0.05$), and invasive mechanical ventilation (6.82±5.5 days in COVID-19 patients treated with ozone and 7.47±6.8 days in those receiving conventional treatment, $p>0.05$) were slightly lower in the ozone-treated group, these differences being not statistically significant.
6. The mean hospital stay length was 17.80±8.9 days for patients treated with ozone and

17.06±10.6 days for those undergoing conventional treatment (p>0.05). Similarly, the mean stay in the Intensive Care Unit was 8.56±5.3 days in the ozone group and 10.22±9.0 days in the conventional treatment group (p>0.05). These results indicate that ozone therapy did not significantly impact these parameters.

PRACTICAL RECOMMENDATIONS

1. Ozone has biological properties—including antioxidant, antihypoxic, anti-inflammatory, and immunomodulatory effects—that suggest a potential role in the treatment of COVID-19 patients.
2. Major ozonated autohemotherapy—intravenous infusion of 80–120 mL of venous blood enriched with an oxygen-ozone gas mixture in a 1:1 ratio, with an ozone concentration of 40 µgN/mL—may be administered to COVID-19 patients as an adjunct to standard treatment protocols.
3. To further explore the clinical use of ozone therapy and assess its impact on SARS-CoV-2 infection, large-scale, prospective, randomized, and controlled clinical trials are required.

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LIST OF PUBLICATIONS AND SCIENTIFIC EVENTS

featuring research findings from the PH.D. thesis in Medical Sciences:
"Study of Ozone Therapy as a Complementary Treatment for Patients with SARS-CoV-2", conducted within the Department of Anesthesiology and Resuscitation No. 1 "Valeriu Ghereg" by **Dr. Natalia Cernei**, at Nicolae Testemițanu State University of Medicine and Pharmacy.

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15. **Cernei Natalia** , Baltaga Ruslan, Șandru Serghei, Chesov Ion, Arnaut Oleg, Cobîlețchi Serghei. Metoda de perfecționare a terapiei combinate de tratament a pacienților cu covid-19 în departamentul Reanimare și terapie intensivă a IMU. În: Cataloque of Proceedings of The 16-th Edition of the EUROINVENT – European Exhibition of Creativity and Innovation, Iași, România,, Ed.: A.V. Sandu, 06-08 iunie 2024, Iași, România // Iași, ed. Ministerul Cercetării, Inovării și Digitalizării, ISSN Print: 2601-4564; Online: 2601-4572: 152.

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1. **Cernei Natalia**, Baltaga Ruslan, Șandru Serghei, Chesov Ion, Arnaut Oleg, Cobîlețchi Serghei. Particularităţile clinice și paraclinice la pacienții cu COVID-19 cu tratament convențional combinat cu ozonoterapie în departamentul reanimare și terapie intensivă. **Adeverința AGEPI MD seria OȘ , Nr. 7711 din 27.11.2023.**

2. **Cernei Natalia**, Baltaga Ruslan, Șandru Serghei, Chesov Ion, Arnaut Oleg, Cobîlețchi Serghei. Eficiența terapiei combinate cu ozon ca adjuvant la schema tradițională de tratament a pacienților cu COVID-19 în departamentul reanimare și terapie intensivă. **Adeverința AGEPI MD seria OȘ , Nr. 7712 din 27.11.2023.**

3. **CERNEI Natalia,** BALTAGA Ruslan, ȘANDRU Serghei, CHESOV Ion, ARNAUT Oleg, COBÎLEȚCHI Serghei. Metoda optimizată a terapiei combinate cu ozon ca adjuvant la schema convențională de tratament a pacienților cu COVID-19. **27 septembrie 2023, Nr. 6138/168.**

• Presentations at scientific forums:

✓ **International conferences held abroad**

1. **CERNEI N.** Grabovschi I., Arnaut O., Sandru S., Chesov I., Mogildea V., Baltaga R**.** „Is Ozonetherapy an efficient complementary treatment for COVID-19 intensive care unit patients?" Al 48-lea Congres al Societății Române de Anestezie și Terapie Intensivă **(SRATI),** 11-15 mai 2022, cu comunicarea orală, secțiunea medici, în calitate de autor.

2. **CERNEI N.** Grabovschi I., Arnaut O., Sandru S., Chesov I., Rusu V., Baltaga R. „Controlled unicenter clinical study of ozonotherapy efficiency as complementary therapy for COVID-19 patients"**.** A VII-a Conferință Internațională dedicată studiilor Covid-19, 5-6 septembrie, Ankara Turcia (VIIth International conference on COVID-19 studies), cu comunicare orală, ca și autor.

✓ **International events held in the Republic of Moldova**

3. **CERNEI N.,** Grabovschi I., Arnaut O., Sandru S., Chesov I., Mogildea V., Baltaga R**.** Ozone

Therapy efficiency as complementary treatment for COVID-19 Intensive Care Unit Patients. Controlled Unicenter Clinical Study. The 5th International Conference on Nanotechnologies and Biomedical Engineering, ICNBME-2021, comunicare orală în calitate de autor.

LIST OF ABBREVIATIONS

ALAT	-	alanine aminotransferase
ASAT	-	Aspartate aminotransferase
BE	-	Base excess
COVID-19	-	Coronavirus disease 2019
FiO_2	-	Fraction of inspired oxygen
HCO_3^-	-	Bicarbonate
EMI	-	Public Medical-Sanitary Institution Emergency Medicine Institute
PI SUMPh	-	Public Institution State University of Medicine and Pharmacy
PaO2	-	Partial pressure of oxygen
$PaCO_2$	-	Partial pressure of carbon dioxide
PCR	-	C-reactive protein
PCT	-	Procalcitonin
pH	-	Hydrogen ion concentration
NLR	-	Neutrophil-to-lymphocyte ratio
SaO_2	-	Arterial oxygen saturation
SARS-CoV-2	-	Severe acute respiratory syndrome coronavirus 2
ICU	-	Intensive care unit

CERNEI Natalia

A STUDY OF OZONE THERAPY AS A COMPLEMENTARY TREATMENT IN SARS-COV-2 INFECTION

321.19 –Anesthesiology and Intensive Care

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