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COROnavirus-19 mild to moderate pneumonia Management with blood Ozonization in patients with Respiratory failure (CORMOR) multicentric prospective randomized clinical trial

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ABSTRACT

Background: Following positive experience on the use of blood ozonation in SARS-CoV-2, the CORMOR randomized trial was designed to evaluate the adjuvant role of oxygen/ozone therapy in mild to moderate SARS-CoV-2 pneumonia.

Methods: The trial (ClinicalTrial.gov NCT04388514) was conducted in four different Italian centers (April-October 2020). Patients were treated according to best available standard of care (SoC) therapy, with or without O3-autohemotherapy (O3-AHT).

Results: A total of 92 patients were enrolled: SoC + O3-AHT (48 patients) were compared to the SoC treatment (44 patients).

The two groups differed in steroids therapy administration (72.7% in SoC arm vs. 50.0% in O3-AHT arm; $p = 0.044$). Steroid therapy was routinely started when it was subsequently deemed as effective for the treatment of COVID-19 disease.

No significant differences in mortality rates, length of hospital stay, mechanical ventilation requirement and ICU admission were observed. Clinical improvement in patients with pneumonia was assessed according to a specifically designed score (decrease in SIMEU class, improvement in radiology imaging, improvement in PaO2/FiO2, reduction in LDH and requirement of oxygen therapy ≤ 5 days). Score assessment was performed on day-3 (T3) and day-7 (TEnd) of O3-AHT treatment. A significant increase in the score was reported at TEnd, in the O3-AHT treatment arm (0 [0–1] in the SoC arm vs. 2 [1–3] the O3-AHT arm; $p = 0.018$). No adverse events related O3-AHT treatment was observed.

Conclusion: In mild-to-moderate pneumonia due to SARS-CoV-2, adjuvant oxygen/ozone therapy did not show any effect on mortality, or mechanical intubation but show a clinical improvement a day 7 from randomization in

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a composite clinical endpoint. Larger Randomized prospective studies alone or in combination with steroids are needed to confirm our results.

1. Introduction

Since December 2019, the coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2) has seriously threatened public health at global level, causing potentially fatal outcomes in a relevant part of affected cases.

Nowadays, in vitro studies have demonstrated a beneficial impact of early therapy administration whereby serious complications of the disease such as acute respiratory failure are reduced [1]. Concerning the best therapeutic approach, we refer to lessons learned from the use of viral agents on viruses belonging to the same Betacoronavirus family such as viruses belonging to the SARS, MERS (Middle East respiratory syndrome) and Ebola virus outbreaks [2,3].

Currently, there are no specific therapeutic agents available for the treatment of SARS COV 2 disease, although treatment with lopinavir/ritonavir did show decreased risk of adverse clinical outcomes as well as reduction of viral loads for the treatment of SARS infection during the 2003 outbreak [4]. Moreover, preclinical data suggests in vitro antiviral activity against SARS–CoV-2 by hydroxychloroquine (HCQ) [5–7].

In the present study, designed in the initial phase of the pandemic in 2020, we considered these drugs as backbone therapy and thus evaluated their efficacy and safety as well as assessing the effects of additional blood ozonization.

The Italian Medical Agency (AIFA) approved the “off label” use of Lopinavir / Ritonavir (or Darunavir in combination with Cobicistat or Ritonavir) along with antimalarial HCQ for the treatment of SARS-CoV-2, only in prospective randomized trials [8].

Following a positive case-control experience employing blood ozonation [9], and the confirmed lack of toxicity [10], this study aimed to assess the adjuvant effects of blood ozonization in patients with SARS-CoV-2 respiratory failure by means of a multicentric randomized trial.

Since the First World War, blood ozonization provided effective bactericidal activity for the treatment of infections, wounds and multiple disease. Furthermore, cases of Ebola treatment with ozone therapy are reported in the literature, showing stimulation of oxygen metabolism and activation of the immune system along with a direct-action on human lung [11–22].

The rationale of the CORMOR (CORonavirus-19 mild to moderate pneumonia Management with blood Ozonization in patients with Respiratory failure) study is to evaluate the additive anti-inflammatory and immunomodulatory ozone-mediated action on hospitalized patients affected by SARS-CoV-2 [23,24].

2. Materials and methods

Trial design and oversight: the CORMOR study was a randomized trial conducted in four different Italian centers. Hospitalized adult patients with confirmed COVID-19 related mild to moderate pneumonia were eligible for enrolment.

The enrolling sites were: Università di Udine e Azienda Sanitaria Universitaria Integrata di Udine, A.O. Ordine Mauriziano di Torino, Ospedale “Campo di Marte” in Lucca and Ospedale “Giuseppe Mazzini” in Teramo.

This study was approved by the Friuli Venezia Giulia ethics committee (Unique Protocol ID: Z7C2CA5837).

Trial population: eligible patients included subjects >18 years of age with positive SARS COV 2 RT-PCR results along with signs and symptoms of pneumonia confirmed by chest imaging and requiring hospitalization. Patients were requested to give their informed consent in order to take part in the study. Exclusion criteria included pregnancy, G6PHD (glucose 6 phosphate dehydrogenase) deficiency, concomitant life-threatening disease.

The full spectrum of COVID-19 disease ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure leading to death. The Italian Society of Emergency and Urgency Medicine (SIMEU) suggested classification of COVID-19 patients in five clinical phenotypes described as follows [25]:

- Phenotype 1: subjects presenting with fever in the absence of respiratory failure (normal Arterial Blood Gas analysis – ABG –, six-minute walking test – 6mWT – and Chest XR). These patients may be managed through home care while home-quarantined.
- Phenotype 2: subjects presenting with fever along with ABG and/or Chest XR indicative of modest respiratory failure ($PaO_2 > 60$ mmHg in ambient air) and / or pulmonary consolidation area. These patients require hospitalization as they may rapidly deteriorate.
- Phenotype 3: subjects with fever associated to moderate-to-severe respiratory failure ($PaO_2 < 60$ mmHg in ambient air as assessed at presentation) and /or with a bilateral pulmonary consolidation area at Chest XR. These patients require treatment with high flow oxygen therapy.
- Phenotype 4: subjects presenting with respiratory failure and suspected ARDS (Acute Respiratory Distress Syndrome) or complicated pneumonia. These patients require hospitalization in sub-intensive care units.
- Phenotype 5: subject presenting with ARDS. These patients will require Intensive Care Unit (ICU) upon admission and non-invasive positive pressure ventilation (NIPPV) or mechanical ventilation.

Enrolled study participants included patients presenting with modest to severe respiratory failure requiring management in either infectious disease or internal medicine wards (SIMEU clinical phenotype 2 or 3).

CORMOR study protocol: eligible patients were randomly assigned to either the Standard of Care (SoC) or to the SoC + O_3-autohemotherapy (O_3-AHT) groups according to a 1:1 randomization.

Randomization was performed by a central computer system whereby stratification occurred according to the number of patients to be assigned to the two study arms. The flow chart is depicted in Fig. 1 while Table 1 reports the CORMOR study schedule of assessments. Clinical biochemistry and total blood count assessments were determined at baseline upon admission, including ABG, White Blood Cells (WBC), lymphocytes and platelet count, creatine phosphokinase

(CPK), lactate dehydrogenase (LDH), Mid Regional pro-ADM (MR-proADM) and interleukin-6 (IL-6) blood level.

- Standard of Care (SoC) therapy. Best available therapy included the following treatment options: antiretroviral therapy (Lopinavir/Ritonavir 200/50 mg 2 tablets every 12 h or Darunavir/Cobicistat 800/150 mg 1 tablet per day) and HCQ 400 mg every 12 h on the first day, followed by 200 mg every 12 h for the following 4 days. Other therapy used for the treatment of COVID-19 pneumonia were administered by caring physicians accordingly. Of notice, steroid therapy was only supported by WHO and endorsed by AIFA in June 2020 [26,27] hence, many patients were subsequently also treated with steroids (Dexamethasone 6 mg once daily for up to 10 days) even if this therapy was not initially included in the planned protocol drafting.
- Medical Ozone (O_3) procedure: upon randomization, systemic ozone treatment procedure was started preliminarily at the patient’s bed. Autologous blood withdrawal and O_2/O_3 mixing were performed as appropriate, followed by reinfusion. After junction of an adequate

venous access with a dedicated latex free plastic bag containing 35 mL of sodium citrate, 200 mL of blood were drawn. The line was washed at one end and the reinfusion end was filled with saline solution. In the absence of any patient disconnection, the drawn blood was then mixed with 200 mL of gas mixture composed by 96% of Oxygen and 4% of Ozone with a therapeutic O_3 range of 40 μg/mL of gas per mL of blood. In order to guarantee the O_2/O_3 homogeneous diffusion into the blood, the bag was gently mixed for about 10 min whereby the blood was then reinfused into the patients. The ozone treatment was performed for 3 consecutive days [9].

End points and outcomes: The *primary outcomes* end points are enlisted as follows: i) negative SIMEU delta classes (negative values implying clinical improvement) assessed on the day following day 3 of blood ozonization treatment (T_3) as well as at follow-up visit one week from end of blood ozonisation (T_{End}) treatment; ii) admission to Intensive Care Unit (ICU) and iii) death.

Secondary outcome end points were: i) length of hospitalization; ii) improved chest imaging assessments (chest CT, Chest XR and/or Point-of-Care Ultrasound); iii) oxygen therapy, CPAP non-invasive ventilation or orotracheal intubation (IOT) requirements; and iv) improved cytokine release syndrome determined by means of plasmatic cytokine response in both arms.

Furthermore, a score for the assessment of patient improvement was elaborated during their in-hospital stay. The score was evaluated at T_3 as: improvement of SIMEU class, presence of radiological improvement, 10% improvement in the PaO_2/FiO_2 ratio, 10% reduction in LDH concentration (score from 0 to 4); while at T_{End} the Pulmonary improvement score was evaluated as: improvement of SIMEU class, presence of radiological improvement, 10% improvement in the PaO_2/FiO_2 ratio, 10% reduction in LDH concentration and length of oxygen therapy < 5 days (score from 0 to 5). This score denotes patient improvement based on Clinical, Biochemical and Radiological variables. Because it considered: i) clinical aspects (SIMEU phenotype, length of O_2 therapy and PaO_2/FiO_2 ratio); ii) biochemical parameters (LDH improvement); and iii) radiologic improvement.

Statistical analyses: All variables were expressed as mean ± standard deviation, median and interquartile interval or proportion, depending on their distributions. Consequently, comparisons between groups were performed with unpaired sample *t*-test, Mann-Whitney test or chi-squared test with continuity correction. In order to quantify the improvement of patients during their in-hospital stay, we computed a score given by the sum of five binary variables, each indicating a specific condition: a percentual decrease of a least 10% in LDH, a percentual increase of at least 10% in PaO_2/FiO_2 ratio, a decrease of at least 1 point in SIMEU class, the presence of radiological improvement, a <5 days duration of oxygen therapy. All the analyses were performed in the R software environment [28], a p value <0.05 was considered statistically significant.

Table 1
Schedule of assessments of CORMOR study.

	T_0	T_3	T_{End}
Informed consent	X		
Inclusionand exclusion criteria	X		
Demography and physical examination (including height and weight)	X	X	X
SOFA score	X		
Charlson Comorbidity Index	X		
Medical history	X		
Concomitant systemic therapy	X		
Arterial Blood Gas analysis	X	X	X
P/F ratio and respiratory assistance assessment	X	X	X
Thoracic CT scan or Chest XR or Chest echo*	X	X	X
12-lead ECG	X		
Laboratory assessment §	X	X	X
IL-6, HLA-DR, lymphocyte typing °	X	X	X
2019-nCoV testing by RT-PCR by upper respiratory tract and expectorated sputum	X	X	X
AE review	X	X	X
Concomitant medical review	X	X	X
Survival follow-up			X

Legend: AE – Adverse event; SOFA – Sequential Organ Failure Assessment score; T_0 – study inclusion; T_3 – after the 3rd blood ozonization treatment; T_{End} – follow-up visit at one week after the end of blood ozonization; * - if it is not possible to perform a thoracic CT scan is recommended to perform a chest x-ray and/or chest ultrasound (POCUS - Point-of-Care Ultrasound); § - blood count, bilirubin, AST, ALT, LDH, creatinine, PCR, PCT, CPK, PT, aPTT, D-dimer, fibrinogen, serum electrolytes; ° - lymphocyte typing for CD4, CD3, CD8, HLA-DR, CD45.

3. Results

Patients: From April 1st through to October 21st 2020, a total of 96 patients underwent randomization in the CORMOR study. Four patients were excluded as they did not meet study inclusion criteria. A total of 92 patients were therefore available for the analysis. Of these, 48/92 (52%) were included in the SoC + oxygen/ozone mixture therapy (O_3-AHT) arm whereas 44/92 (48%) were available as controls undergoing SoC only (SoC arm).

The baseline characteristics of the patients in the two groups were well matched and balanced and are reported in Table 2. A significant difference in symptoms was seen in patients reporting dyspnea.

Drug therapy and safety: The SoC therapies were comparable, with the exception of steroids, among both groups as shown in Table 3). Steroid therapy was started after seven days from onset of COVID-19 symptoms. Within the SoC cohort, 72,7% of patients received concomitant steroid therapy whereas 50% of patients in the O_3-AHT arm ($p = 0.043$) were administered steroids.

No adverse event related to O_3-AHT was reported. Diarrhoea and QT interval prolongation were the main adverse event reported (see Table 3) in association with subsequent antiretroviral and/or HCQ

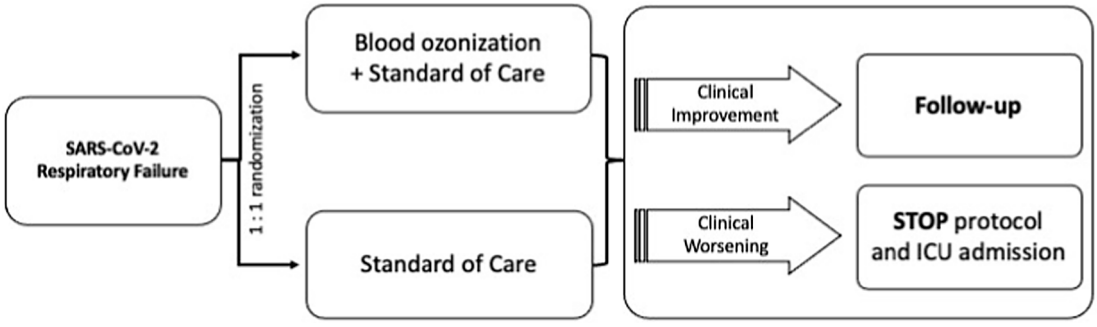

Fig. 1. Flow chart of CORMOR study. Legend: ICU: intensive care unit. Standard of Care – Lopinavir/Ritonavir 200/50 mg 2 tablets every 12 h or Darunavir/Cobicistat 800/150 mg 1 tablet per day; Hydroxychloroquine 400 mg every 12 h on the first day, followed by 200 mg every 12 h for the following 4 days; Dexamethasone 6 mg once daily for up to 10 days (see Table 3 for detail).

Table 2
Clinical characteristics of patients.

	Overall patients (n = 92)	Control Group (n = 44)	Blood Ozonization Group (n = 48)	P
Age (years)	63.8 ± 13.2	64.2 ± 14.1	63.5 ± 12.5	0.784
Male	55 (59.8%)	24 (54.5%)	31 (64.6%)	0.443
BMI	27.0 ± 5.2	27.41 ± 6.02	26.6 ± 4.5	0.564
Charlson Comorbidity Index	2.0 [1.0–4.0]	3.0 [1.0–5.0]	2.0 [1.0–3.3]	0.444
Diabetes	15 (16.3%)	8 (18.2%)	7 (14.6%)	0.859
COPD	3 (3.3%)	3 (6.8%)	0 (0.0%)	0.218
Cronic heart disease	21 (22.8%)	9 (20.5%)	12 (26.1%)	0.702
Cronic renal failure	4 (4.4%)	3 (6.8%)	1 (2.1%)	0.563
Arterial hypertension	42 (45.7%)	19 (45.2%)	23 (47.9%)	0.966
Chronic home therapy				
• ACE inibitors	14 (15.2%)	9 (20.5%)	5 (10.4%)	0.294
• Sartanics	15 (16.3%)	4 (9.1%)	11 (22.9%)	0.131
• Diuretics	18 (19.6%)	11 (25.0%)	7 (14.6%)	0.320
• Statins	11 (12.0%)	6 (13.6%)	5 (10.4%)	0.878
• Acetil salicilic acid	11 (12.0%)	5 (11.4%)	6 (12.5%)	1.000
• Other antiplatelet agents	3 (3.3%)	2 (4.6%)	1 (2.1%)	0.939
• Steroids	7 (7.6%)	3 (6.8%)	4 (8.3%)	1.000
• Proton pump inhibitors	17 (18.5%)	10 (22.7%)	7 (14.6%)	0.461
• Ormonal replacement therapy	5 (5.4%)	3 (6.8%)	2 (4.2%)	0.920
• Hydroxychloroquine	1 (1.1%)	1 (2.3%)	0 (0.0%)	0.965
Symptoms at COVID-19 onset				
• Fever	80 (87.0%)	34 (77.3%)	46 (96.0%)	0.020
• Cough	46 (50.0%)	22 (50.0%)	24 (50.0%)	1.000
• Dyspnea	23 (25.0%)	16 (36.4%)	7 (14.6%)	0.030
• Myalgia	17 (18.5%)	9 (20.5%)	8 (16.7%)	0.843
• Sincope	3 (3.7%)	2 (4.6%)	1 (2.1%)	0.939
• Headache	8 (8.7%)	4 (9.1%)	4 (8.3%)	1.000
• Diarrhoea	25 (27.2%)	11 (25.0%)	14 (29.2%)	0.830
• Hypo/dysgeusia	8 (8.7%)	4 (9.1%)	4 (8.3%)	1.000
• Hypo/anosmia	8 (8.7%)	2 (4.6%)	6 (12.5%)	0.326
• Asthenia	9 (9.8%)	4 (9.1%)	5 (10.4%)	1.000

Legend: ACE - angiotensin-converting enzyme; BMI – body mass index; COPD - chronic obstructive pulmonary disease.

Table 3
Concomitant therapy administered and adverse events reported.

	Overall patients (n = 92)	Control Group (n = 44)	Blood Ozonization Group (n = 48)	P
Concomitant therapy				
• Antiretroviral therapy	87 (94.6%)	42 (95.5%)	45 (93.8%)	1.000
• Hydroxychloroquine	92 (100%)	44 (100%)	48 (100%)	1.000
• Systemic steroids	56 (60.9%)	32 (72.7%)	24 (50.0%)	0.044
• LMWE	68 (73.9%)	31 (70.5%)	37 (77.1%)	0.627
• Antibiotic therapy	43 (46.7%)	20 (45.5%)	23 (47.9%)	0.978
• Tocilizumab	5 (5.4%)	1 (2.3%)	4 (8.3%)	0.412
Adverse events				
• Overall Adverse events	15 (16.3%)	7 (16.3%)	8 (16.7%)	1.000
• Diarrhoea	4 (4.4%)	3 (6.8%)	1 (2.1%)	0.548
• QT interval prolongation	7 (7.6%)	3 (6.8%)	4 (8.3%)	1.000
• Increase liver enzyme	3 (3.3%)	0 (0.0%)	3 (6.3%)	0.272
• Antiretroviral discontinuation	10 (10.9%)	5 (11.4%)	5 (10.4%)	1.000
• Hydroxychloroquine discontinuation	6 (6.5%)	3 (6.8%)	3 (6.3%)	1.000

discontinuation.

Efficacy end points: No differences in SIMEU class improvement at T_3 and at T_{End} in terms of admission to ICU, mortality rate, length of hospital stays, improving of the chest imaging, invasive ventilation or IOT need and cytokine levels (Table 4) were observed between the two treatment groups. At the T_3 timepoint, the O_3-ATH group presented a significant difference in terms of low white blood cells count and elevated C reactive protein as opposed to the SoC arm. These differences were not observed at the T_{End} timepoint (Table 4). To note that no significant differences were note in IL-6 and MR-proADM levels. Moreover, the laboratory parameters time course is showed in Table 5).

Furthermore, a significant increase in the ad-hoc designed score values (for the assessment of patient improvement during their in-hospital stay), was reported at T_{End} (score 0 [0–1] in SoC group vs. score 2 [1–3] the O_3-AHT group; $p = 0.018$) timepoint demonstrating a clinical improvement of the patients with O_3-AHT (Fig. 2).

4. Discussion

The CORMOR study is the first randomized trial for the evaluation of blood ozonization as adjuvant therapy in the treatment of adult patients with confirmed COVID-19 mild to moderate pneumonia.

Ozone therapy application is known to reduce oxidative stress whereas COVID-19 activates renin-angiotensin-aldosterone system inducing oxidative stress leading eventually to cytokine storm. Ozone therapy is recommended to counter the disruptive effects of severe COVID-19 on lung tissues, especially if administered in early stages of the disease, thereby preventing the progression of COVID-19 lung disease [23], as well as the favourable rheological and tissue perfusion properties to limit ischemic lung damage [29–31].

The therapeutic effect of ozone is maximized in the early phases of disease development when blood oxygenation is hampered by interstitial edema and alveoli fluid exudates, but only with a limited extension of lung tissue consolidation [32,33]. Our approach with respect to enrolled patients stratified according to SIMEU clinical phenotype 2 or 3 was thus based on these pathophysiological arguments. Although the two groups had a baseline significant difference in dyspnea it has not a significant change in the baseline PaO_2/FiO_2 ratio (Table 4) and this parameter had better time-course in the O_3-AHT arm (Table 5).

In this randomized trial we observed a significant improvement in patient's lung function during their in-hospital stay (Fig. 2) albeit missing the primary efficacy end point.

Furthermore, compared to other case-control study, we did not detect a shorter time to clinical improvement [34] or preliminary evidence in inflammatory biomarkers response [31,35].

A possible explanation of this may reside in the fact that a good proportion of enrolled patients were administered concomitant steroid therapy, although this drug was not allowed in the baseline protocol. Moreover, the SoC arm had a significantly higher use of steroid therapy as opposed to the SoC + O_3-AHT one (see Table 3), demonstrating a possible positive effect of ozone in the treated arm with respect to the SOC therapy choose in this study.

Unfortunately, this study required approximately two months for ethics committee approval and was started in April 2020. During this time, thanks to lock-down measures, the contagion curve progressively decreased and enrolment was mainly carried out throughout the second Italian wave of COVID-19 pandemics (September and October 2020). This had major consequences on the best available therapy due to the controversies relatively to HCQ use [36] when steroid therapy was confirmed to be effective, according to this the attending physicians started steroids in case of clinical deterioration, more frequent in SOC arm [26,27]. These conditions had consequences on the full comparability of the two study arms and may have masked the positive effect of O_3-AHT yielding partially discordant results with the other case-control studies.

Hernández A et al., in a prospective case–control study, observed

Table 4
Patient's outcomes.

	Overall patients (n = 92)	Control Group (n = 44)	Blood Ozonization Group (n = 48)	P
Lenght of hospital stay (days)	10 [6.5–13.5]	9 [6.5–13]	10 [6.75–15]	0.182
Low flow oxygen therapy	36 (39.1%)	17 (39.5%)	19 (39.6%)	1.000
High flow oxygen therapy	42 (45.7%)	21 (48.8%)	21 (45.7%)	0.930
CPAP	28 (30.4%)	12 (27.9%)	16 (33.3%)	0.740
Length of oxygen therapy (days)	7.0 [4.0–10.0]	7.0 [3.3–9.0]	6.0 [4.0–11.3]	0.679
ICU admission	9 (9.8%)	3 (6.8%)	6 (12.5%)	0.572
IOT	8 (8.7%)	4 (9.3%)	4 (8.3%)	1.000
Death	4 (4.4%)	2 (4.7%)	2 (4.2%)	1.000
T0 – study inclusion				
COVID-19 pneumoniae	90 (97.8%)	43 (97.7%)	47 (97.9%)	1.000
SOFA score	2.0 [1.0–3.0]	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.564
SIMEU class	2.3 ± 0.5	2.3 ± 0.5	2.3 ± 0.4	0.475
PaO_2/FiO_2 ratio	326.6 ± 74.8	334.7 ± 84.2	319.3 ± 65.0	0.332
WBC (/mmc)	5.62 [4.24–7.63]	5.9 [4.16–8.45]	5.58 [4.29–6.89]	0.603
Lymphocytes (/mmc)	0.85 [0.68–1.25]	0.79 [0.65–1.29]	0.9 [0.72–1.18]	0.375
Platelets (/mmc)	204 ± 95	202 ± 97	207 ± 94	0.799
LDH (U/L)	528 ± 189	525 ± 216	531 ± 162	0.866
C reactive protein (mg/L)	46.6 [16.4–85.7]	42.0 [13.1–71.2]	48.0 [18.2–87.8]	0.472
Procalcitonine (ng/ml)	0.06 [0.03–0.10]	0.06 [0.03–0.10]	0.05 [0.03–0.11]	0.510
D-dimer (ng/ml)	522 [353–872]	558 [357–904]	451 [344–740]	0.429
IL6 (pg/ml)	30.0 [15.2–68.0]	30.5 [10.4–64.3]	30.0 [19.5–81.0]	0.220
MR-proADM (nMol/L)	0.81 [0.66–1.02]	0.84 [0.69–1.01]	0.79 [0.64–1.02]	0.497
T_3 – day after the 3rd blood ozonization treatment				
Chest radiological improvement	12 (13.0%)	2 (11.8%)	10 (38.5%)	0.119
Clinical variables				
• SIMEU class	2.5 ± 0.9	2.6 ± 0.9	2.5 ± 0.9	0.638
• PaO_2/FiO_2 ratio	249.7 ± 99.7	246.0 ± 86.5	252.6 ± 109.8	0.774
Biochemical variables				
• WBC (/mmc)	8.21 ± 3.64	9.21 ± 3.82	7.32 ± 3.25	0.016
• Lymphocytes (/mmc)	0.85 [0.58–1.19]	0.89 [0.65–1.23]	0.82 [0.53–1.13]	0.592
• Platelets (/mmc)	292 ± 123	298 ± 120	287 ± 127	0.687
• LDH (U/L)	494 ± 159	500 ± 147	488 ± 170	0.752
• C reactive protein (mg/L)	12.2 [5.0–35.0]	8.1 [4.7–22.8]	21.4 [7.9–41.7]	0.016
• Procalcitonine (ng/ml)	0.03 [0.01–0.08]	0.04 [0.02–0.07]	0.03 [0.01–0.1]	0.382
• D-dimer (ng/ml)	584 [365–981]	579 [354–903]	589 [386–1000]	0.967
• IL6 (pg/ml)	13.0 [4.0–35.5]	10.0 [2.0–33.5]	14.0 [5.9–35.5]	0.145
• MR-proADM (nMol/L)	0.76 [0.62–1.14]	0.76 [0.6–1.17]	0.78 [0.63–1.11]	0.813
T_{End} – follow-up visit at one week after the end of blood ozonization				
Chest radiological improvement	15 (16.3%)	3 (30.0%)	12 (57.1%)	0.303
Clinical variables				
• SIMEU class	2.0 [1.0–3.0]	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.689
• PaO_2/FiO_2 ratio	285.0 ± 120.9	261.7 ± 127.4	300.7 ± 115.9	0.293
Biochemical variables				
• WBC (/mmc)	8.56 ± 3.85	9.62 ± 3.62	7.79 ± 3.88	0.058
• Lymphocytes (/mmc)	0.98 [0.64–1.33]	1.02 [0.74–1.28]	0.96 [0.61–1.41]	0.785
• Platelets (/mmc)	315 ± 132	304 ± 147	323 ± 122	0.594
• LDH (U/L)	483 ± 173	489 ± 168	478 ± 180	0.823
			9.2 [1.9–24.9]	0.199
• C reactive protein (mg/L)	5.6 [1.7–19.6]	3.2 [1.6–11.5]		
• Procalcitonine (ng/ml)	0.03 [0.01–0.05]	0.03 [0.01–0.08]	0.04 [0.01–0.05]	0.861
• D-dimer (ng/ml)	586 [417–1068]	643 [418–994]	529 [397–1180]	0.897
• IL6 (pg/ml)	5.5 [2.5–17.1]	7.0 [3.0–16.3]	4.0 [2.0–19.0]	0.502
• MR-proADM (nMol/L)	0.76 [0.62–1.00]	0.72 [0.64–1.00]	0.80 [0.57–0.98]	0.909

Legend: CPAP – continues positive air pressure; ICU - intensive care unit; IL-6 - interleukin-6; IOT - orotracheal intubation; LDH - lactate dehydrogenase; MR-proADM - mid Regional pro-ADM; SIMEU - Italian Society of Emergency and Urgency Medicine; SOFA – Sequential Organ Failure Assessment score; WBC - white blood cells.

that ozonated autohemotherapy was associated with a significantly shorter time to clinical improvement, like in our previous experience. In this study the total dose of gas mixture oxygen-ozone administered was similar to the one used in this study even if spread over five consecutive days [34]. Probably this is the right length of treatment with O_3-AHT but the lower number of O3 -AHT sessions we performed, was due to the previous satisfactory clinical results and also to the enormous number of admitted patients to take care.

Furthermore, other single centre experiences reported clinical, radiological and biochemical improvement using of Ozone with different administration techniques as rectal ozone or ozonized saline solution [10,37–39].

However, in own experience, clinical and radiological differences were observed in Ozone group, based on improve in SIMEU class, radiological finding, LDH reduction, days of Oxygen use, as stated by Schwartz, Araimo, Franzini, Fernandez-Cuadros [10,35,37,38] and ozone is not inferior to SOC group based on anti-inflammatory variables (PCR, LDH, IL-6).

We believe that the therapeutic effect of ozone is maximized in the early development of the disease when blood oxygenation is hampered by interstitial edema and exudation of fluid into the alveoli leading to ventilation/perfusion mismatch. This is the clinical evolution described by CT scan features as ground glass opacities image and crazy paving appearance. Ozone treatment in this phase might prevent further evolution of lung damage, when the ARDS develop and treatment is more difficult.

For Ozone therapy it has been postulated an anti-inflammatory effect especially in reducing pro-inflammatory cytokines and other authors have also observed a decreased of IL-6 levels after ozone treatment [10,35,38]. In our prospective study, we did not observe this effect, respect to the control group, on the reduction of IL-6 level.

In own study, the mortality rate was the same in both groups of patients with mild to moderate COVID-19 pneumonia (4.7% in SOC and 4.2% in O3-ATH). This data agrees with Italian epidemiology [40].

O_3 therapy carries virtually no known adverse or toxic effects when performed properly (other than sporadic vein issues, as can other intravenous therapies), indeed we did not observe any adverse event related to O_3-AHT treatment, neither haemolysis nor anemia or other line related adverse events.

5. Conclusion

Oxygen/ozone therapy as adjuvant therapy did not show any effect on mortality, or mechanical intubation but show a clinical improvement a day 7 from randomization only using a composite clinical endpoint (ClinicalTrial.gov number, NCT04388514). Notably, in the SOC arm, more patients were treated with steroids thus reducing the clinical

Table 5
Laboratory parameters time course.

	Control Group(n = 44)				Blood Ozonization Group (n = 48)			
	T_0	T_3	T_{END}	P	T_0	T_3	T_{END}	P
PaO_2/FiO_2 ratio	334.7 ± 84.2 *	246.0 ± 86.5	261.7 ± 127.4	0.003	319.3 ± 65.0 *	252.6 ± 109.8 #	300.7 ± 115.9	<0.001
WBC (/mmc)	5.9 [4.16–8.45] §	9.21 ± 3.82	9.62 ± 3.62	0.005	5.58 [4.29–6.89] §	7.32 ± 3.25	7.79 ± 3.88	<0.001
Lymphocytes (/mmc)	0.79 [0.65–1.29]	0.89 [0.65–1.23]	1.02 [0.74–1.28]	0.704	0.9 [0.72–1.18]	0.82 [0.53–1.13]	0.96 [0.61–1.41]	0.322
Platelets (/mmc)	202 ± 97 *,§	298 ± 120	304 ± 147	<0.001	207 ± 94*,§	287 ± 127 #	323 ± 122	<0.001
LDH (U/L)	525 ± 216	500 ± 147	489 ± 168	0.891	531 ± 162 §	488 ± 170	478 ± 180	0.012
C reactive protein (mg/L)	42.0 [13.1–71.2] *,§	8.1 [4.7–22.8]	3.2 [1.6–11.5]	<0.001	48.0 [18.2–87.8] §	21.4 [7.9–41.7] #	9.2 [1.9–24.9]	<0.001
Procalcitonine (ng/ml)	0.06 [0.03–0.10]	0.04 [0.02–0.07]	0.03 [0.01–0.08]	0.412	0.05 [0.03–0.11]	0.03 [0.01–0.1]	0.04 [0.01–0.05]	0.271
D-dimer (ng/ml)	558 [357–904]	579 [354–903]	643 [418–994]	0.211	451 [344–740]	589 [386–1000]	529 [397–1180]	0.446
IL6 (pg/ml)	30.5 [10.4–64.3]	10.0 [2.0–33.5]	7.0 [3.0–16.3]	0.341	30.0 [19.5–81.0]	14.0 [5.9–35.5]	4.0 [2.0–19.0]	0.107
MR-proADM (nMol/L)	0.84 [0.69–1.01]	0.76 [0.6–1.17]	0.72 [0.64–1.00]	0.203	0.79 [0.64–1.02]	0.78 [0.63–1.11]	0.80 [0.57–0.98]	0.513

Legend: T_0 – study inclusion; T_3 – after the 3rd blood ozonization treatment; T_{End} – follow-up visit at one week after the end of blood ozonization. IL-6 - interleukin-6; LDH - lactate dehydrogenase; MR-proADM - mid Regional pro-ADM; WBC - white blood cells.
* T_0 vs. T_3 ($p < 0.05$).
§ T_0 vs. T_{END} ($p < 0.05$).
# T_3 vs. T_{END} ($p < 0.05$).

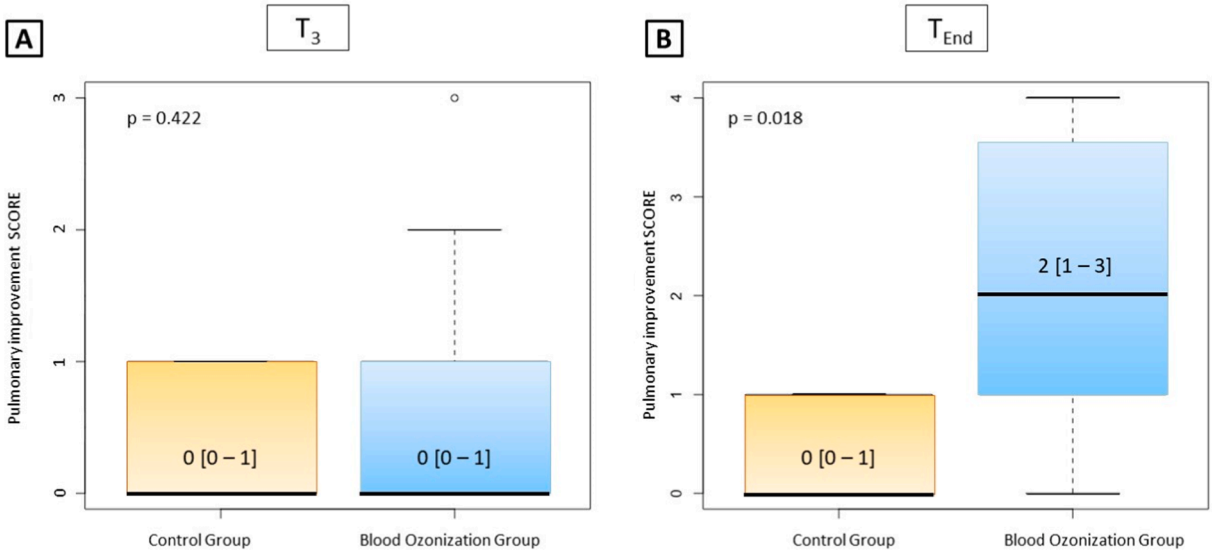

Fig. 2. Pulmonary improvement score evaluated at T_3 (Panel A) and at T_{End} (Panel B). Legend: At T_3 the Pulmonary improvement score was evaluated as improvement of SIMEU class, presence of radiological improvement, 10% improvement in the PaO_2/FiO_2 ratio, 10% reduction in LDH concentration (score from 0 to 4). At T_{End} the Pulmonary improvement score was evaluated as improvement of SIMEU class, presence of radiological improvement, 10% improvement in the PaO_2/FiO_2 ratio, 10% reduction in LDH concentration and length of oxygen therapy < 5 days (score from 0 to 5).

failure. No adverse event related to O_3-AHT was described in this study. Probably a longer treatment for five days could be more effective, therefore larger randomized prospective studies alone or in combination with steroids and or antivirals are needed in order to confirm our observations.

Ethics approval and consent to participate

All research was performed in accordance with the relevant guidelines and regulations and the study was evaluated by the Friuli Venezia Giulia ethics committee (Unique Protocol ID: Z7C2CA5837).

Data sharing statement

No additional data available.

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Contributors

ES, ADM, GS, CT: protocol design, patient care and manuscript preparation; FS, AR: protocol design, manuscript preparation; FB, DS, FC, MF, SM, DI, DLB: protocol design and patient care. All authors read and approved the final version of the manuscript.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication

Not required.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [C.T. has received funds for speaking at symposia organized on behalf of Pfizer, Novartis, Merck, Angelini, Zambon, Thermofischer, Biotest, Gilead, Hikma, Biomerieux and Astellas. All other authors: None.]

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