

Promising Treatments for Acute Respiratory Distress Syndrome Associated with Covid-19

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Abstract: Acute Respiratory Distress Syndrome (ARDS) can occur in critically ill people due to COVID-19. These combinations of ARDS and COVID-19 are usually fatal, and the risk increases with age and severity of the disease. The main clinical aspect is the intense shortness of breath and often cannot breathe on their own, requiring mechanical ventilatory support. Treatment includes the administration of oxygen and medications. As a result, the aim of the study was to address the promising treatments for COVID-19-associated ARDS, reporting the main forms of recommendation of therapies such as corticosteroid use, ozone therapy and hyperbaric oxygenation (HBO). This study is a systematic review conducted through international articles with English language located in PubMed and VHL in addition to Clinicaltrials.gov. In the study, we found 117 studies that were submitted to eligibility analysis and, subsequently, 59 studies were included and discussed in this study. Recent studies show that corticosteroids used in ARDS with COVID-19 have achieved clinical improvement, especially during mechanical ventilation. In ozone therapy, improvement was found in the pulmonary parenchyma and in the release of plasma cytokines such as interleukin-6 (IL-6), lymphocyte typing for CD3, CD4, CD8, HLA-DR, CD45. In HBO, it is a useful alternative in the treatment of the disease since it provided inflammatory relief and facilitated the reversal of hypoxemia. As there is little evidence of damage, the data suggest the use of these promising treatments; however, more studies are needed to prove the efficacy of these therapies.

Keywords: Respiratory Distress Syndrome, COVID-19, SARS-CoV-2, Therapeutic Measures, Corticosteroids, Drugs, Drug Induced Liver Injury, Rousset Uclaf Causality Assessment Method.

1. INTRODUCTION

Acute respiratory distress syndrome (ARDS) is pathologically characterized by diffuse alveolar damage and, physiologically, by the development of noncardiogenic pulmonary edema due to increased permeability of the pulmonary alveolo-capillary membrane. Its clinical expression is hypoxemic respiratory failure and bilateral pulmonary infiltrate on chest X-ray in patients with pulmonary and/or extrapulmonary risk factors [1,2]. It should be noted that aggression of the alveolo-capillary barrier may occur due to one or more etiological or causal factors, usually severe and with inflammatory characteristics,

constituting the so-called risk factors for ARDS such as pneumonia, sepsis, polytrauma and high-risk surgeries [3-5].

The clinical picture is recognized by the rapid onset of severe dyspnea, shallow and rapid breathing. The patient has crepitant or wheezing sounds that can be auscultated in the lungs and, due to low oxygen (O₂) levels in the blood, central cyanosis and/or extremities may occur. Due to the lack of O₂, it may produce complications in other organs soon after the onset of clinical symptoms or, when there is no improvement in days or weeks. This prolonged lack can cause serious problems such as acute renal failure or in advanced stages until the death of the patient [6-8].

Due to these situations, it is essential to relate ARDS to the emergence of the new coronavirus, which

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is a milestone in the 21st century, as it represents an imminent threat to the health of the population, as declared in December 2019 by the World Health Organization [9].

The course of the disease "COVID-19" is different in each patient, some asymptomatic, others with mild symptoms and others with serious problems, such as severe respiratory manifestations, requiring hospitalization [10]. SARS-CoV-2 spread rapidly around the world in a brief period, which surprised most epidemiologists, due to the several types of transmission routes (Figure 1) [11,12].

When a person is infected with SARS-CoV-2, the virus binds to epithelial cells of the nasal cavity, replicates through the conductive airways and has a limited innate immune response. At this stage, the individual is low viral load. The virus proliferates in the upper airways, leading to a greater innate immune response. The virus then preferentially infects type II cells, causing cellular apoptosis, which results in the release of self-replicating lung toxins, infecting adjacent cells. The pathological result is diffuse alveolar damage with hyaline membranes rich in fibrin and some multinucleated giant cells, in addition to the occurrence of scars and pulmonary fibrosis [13-14]. After this process, the virus can lodge in various organs of the human body, in the lungs, which is the central organ of the coronavirus. It is understood that the main morbidity and mortality of patients hospitalized with the

new virus is attributed to acute viral pneumonitis, leading to ARDS [10,15].

It is emphasized that ARDS associated with COVID-19 usually develops from the second week on. This is not only because of uncontrolled viral replication, but also because of an explosive immune response from the host. In the presence of uncontrolled viral replication, the presence of an increased number of infected epithelial cells and cell fragments triggers a cytokine storm with hyperinflammation and immunological suppression, characterized by CD4+ auxiliary T cells of decreased memory and increased cytotoxic activity of CD8 [16-18].

In the current context, there are still no proven specific therapies available for COVID-19, but it is essential to identify the potential risk factor that affects severity and prognosis, performing an individualized treatment, focusing on the prevention and recovery of the patient [19].

As a form of therapy, oxygen therapy should be directed to all patients admitted to the intensive care unit (ICU), regarding medications, corticosteroids [20] and severe patients with O₂ saturation (SpO₂) below 93% indicated mechanical ventilation support are observed.

Thus, SARS-CoV-2 induced lung disease is a novelty and unusual cause of respiratory failure and

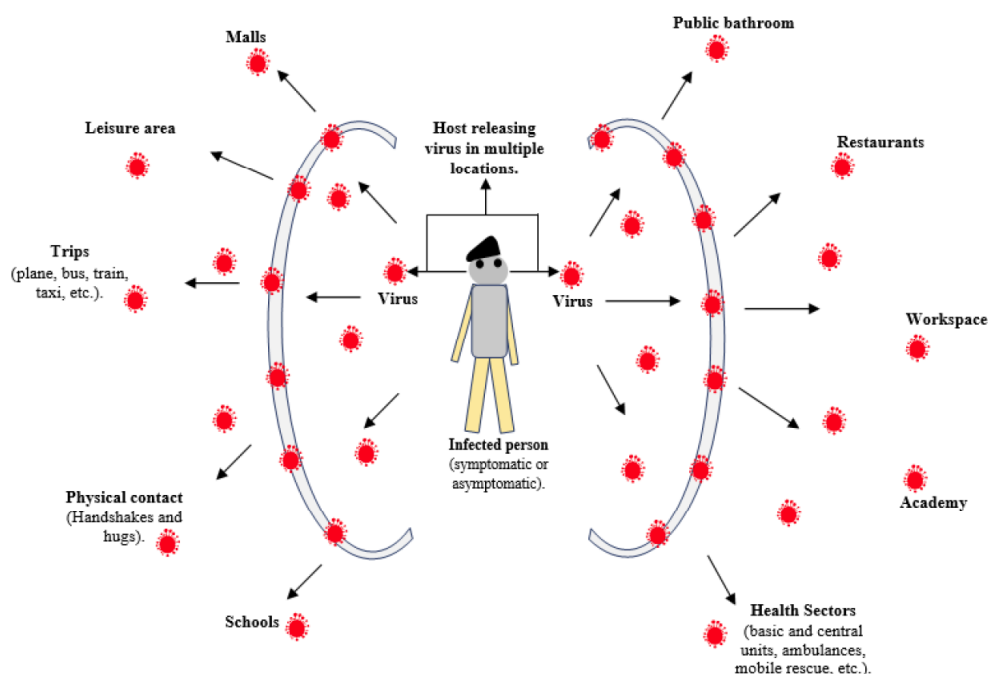


Figure 1: Transmission route of the SARS-CoV-2, but also applicable to other cold infections. Source: Own authors.

behaves differently from what was once considered clinical disease syndromes, requiring adequate and safe treatment for the patient. In view of these facts, the aim of this study was to address the promising treatments for acute respiratory distress syndrome associated with COVID-19, addressing the main forms of recommendation of therapies such as the use of corticosteroids, ozone therapy and oxygen therapy.

2. METHODOLOGY

Two databases (PubMed and Virtual Health Library - VHL) were chosen for systematic research. As a search strategy, the descriptors of The MeSH were adopted: Respiratory Distress Syndrome, COVID-19, SARS-CoV-2, Corticosteroids, Therapeutic Measures, Drugs, Drug Induced Liver Injury and an alternative term Rousset Uclaf Causality Assessment Method and used "AND" and "OR" as Boolean operator.

Inclusion criteria were articles published in international scientific journals from 2015 to 2022, only in English, with description of ARDS and COVID-19 with therapeutic measures with corticosteroids, ozone therapy and hyperbaric oxygenation in the titles and abstracts. Theses, dissertations and book chapters and other media that did not participate in this study were excluded. The Clinicaltrials.gov was used to investigate clinical trials (<https://clinicaltrials.gov/>).

For the selection of articles, the thematic contents were analyzed through the qualitative approach found in the titles and abstracts [14]. After selecting the articles, the bibliographic references were analyzed according to the research theme.

The risk of bias of the selected articles were evaluated for systematic errors or limitations in the design of the randomized and/or non-randomized research, in clinical trials, conducting or analyzing the review influencing the results, therefore, articles with discrepancies found in the abstract, in the body of the text and articles that did not present a conflict of interest were excluded.

3. STUDY CHARACTERISTICS

3.1. Context Article Series

A total of 117 articles were found in the databases. Analyzing the duplication among the bases, 15 articles were removed because they were repeated. Articles were submitted to eligibility analysis and 43 articles were excluded because they were not in accordance

with the study proposal and only 59 articles were selected for qualitative data analysis, meeting the inclusion criteria (Figure 2).

Thus, the quality of the data was observed and evaluated, and pertinent information was collected, in addition to the year of publication, study design, clinical outcomes and clinical interventions.

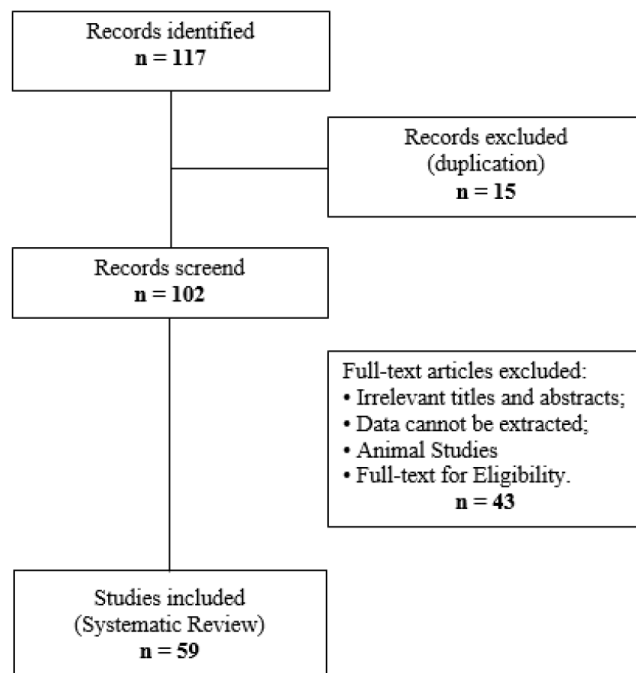


Figure 2: Flowchart.

3.2. Main Clinical Features and Outcomes in Patients with COVID-19 Associated with the Development of ARDS

Patients with fever, tiredness, cough, loss of taste and/or smell, dyspnea, $SpO_2 < 93\%$, myalgia, in addition to matte glass opacity in hemithorax and/or bilateral, and often attributed to comorbidities such as obesity, smoking, diabetes mellitus, alcohol consumption and advanced age are potentially significant aspects that can affect the severity and prognosis of the disease.

4. CORTICOSTEROIDS

4.1. Effects of Corticosteroids in Patients with ARDS Secondary to COVID-19

Clinical trials are underway in several countries to assess the good efficacy of corticosteroids, hyperbaric oxygenation (HBO) and ozone therapy for the treatment of COVID-19. In addition, data are limited and should be interpreted with caution, as primary and

secondary outcomes are essential for researchers seeking adequate responses and treatment for patients. Due to the purpose of the research, the study brings up-to-date references and data, with the possibility of showing the effects of therapy in patients with ARDS associated with COVID-19 and the appropriate and indicated treatments.

4.2. Methylprednisolone

The methylprednisolone study (Clinicaltrials.gov NCT04438980) is a randomized clinical trial with 72 participants with SARS-CoV-2 pneumonia (Table 1). This study found that about 30% of patients hospitalized with SARS-CoV-2 pneumonia developed a hyperinflammatory state whose progression to ARDS could be prevented with the early onset of immunomodulatory agents. To verify the possibility of prevention, the study aimed to evaluate the safety and efficacy of glucocorticoid effects to improve clinical outcomes in patients with SARS-CoV-2 pneumonia and increased inflammatory biomarkers. The primary result reveals that after 14 days of randomized study there was failure in treatment and through this there were deaths of patients, demand of patients admitted to the ICU, reduction of SpO₂ <90% requiring mechanical ventilation. Regarding the secondary result, the study describes that after 14 days of randomization, patients presented evolution of inflammatory biomarkers related to COVID-19, which is: changes in plasma levels of lactic dehydrogenase, changes in plasma levels of C-reactive protein, ferritin, D-dimer and interleukin-6 (IL-6), and a rescue therapy with tocilizumab (TCZ). However, on the twenty-eighth day, the study addresses that there was death of patients, not counting the proportion of bacterial, fungal or opportunistic infections after this study period [21]. TCZ is an IL-6 receptor antagonist, the justification for this therapy is based on the understanding that IL-6 is a predictor of disease severity, thus playing a key role in the COVID-19-induced cytokine storm [22], cytokine release syndrome followed by infiltration of inflammatory monocytes/macrophages and lymphocytes in the lung [23].

The study reveals that methylprednisolone had significant results in inflammatory biomarkers related to COVID-19. However, in the general clinical picture of the patients, it is observed that the study showed no benefit in the progression of respiratory impairment, requiring ICU admission and intubation, later death of the patient. A critical factor that should be evidenced is that if the study had started the use of

methylprednisolone early, it is thought that there would have been a reduction in the number of deaths among patients.

4.2.1. Effect on Immune Cell Profile

It is important to highlight the effect of methylprednisolone on the profile of immune cells in studies by Tang *et al.* [24]. The authors provide evidence that methylprednisolone can slow the spread of the virus by suppressing immune cells in patients with COVID-19 pneumonia, such as T cells and Natural Killer (NK) cells. Cd45 immune cell mass cytometry analysis in the blood showed that the profile of the main subgroups of total CD45 cells changed after treatment with methylprednisolone. Additional analyses found that 7 days after treatment with methylprednisolone, T cells (CD3 and CD8) were significantly smaller than those in the control group (both $p < 0.05$). 14 days after randomization, NK cells in the methylprednisolone group were significantly smaller than those in the control group ($p < 0.05$). It was also found that treatment with methylprednisolone led to an increase in CD11b myeloid cells. In addition, T cells (CD4 and CD8) were reduced on day 7 after treatment with methylprednisolone compared to day 0 (zero) [24]. The data revealed are significant, but for prophylactic medication with methylprednisolone in a high-risk population, more research is needed *in vivo* evidencing the pharmacodynamic (mechanism of action) and pharmacokinetic (effects that the body makes with the drug) of the drug against COVID-19.

4.3. Prednisone

Study in Clinicaltrials.gov (NCT04451174), the corticosteroid assay with a chance to decrease the progression of respiratory failure and death. The aim of the study is to evaluate the effect of initial treatment with prednisone to slow disease progression. This is a pragmatic, non-blind randomized trial with 60 participants (Table 1). The experiment was treated with prednisone 40 mg/day from the 1st to the 4th day, reduced to 20 mg/day from the 5th to the 8th day. The study brings measures of primary outcome, referring to the admission of patients to the ICU, in addition to the need for mechanical ventilation, as well as death from all causes. In the secondary outcome, there is respiratory deterioration; incidence of patients requiring mechanical ventilation; deterioration of the glycemic profile that requires the use of insulin; delirium; incidence of nosocomial infections such as pneumonia, urinary tract infection, device-associated infections;

Table 1: Clinical Trials with Corticosteroids, Ozone Therapy, and Oxygen Therapy under COVID-19/ARDS Conditions, at Clinicaltrials.gov

Name and start (date) of the study	Country	Title	n ¹	Age	Intervention/ treatment	Placebo	Measurement Results		References
							Primary	Secondary	
NCT04438980 May 2020	Spain	Glucocorticoids in COVID-19	72	18-75 years old	Methylprednisolone 120 mg/day (3x)	Yes	Death; Need for admission in an ICU; need for MV; < SpO ₂ ;	Change in plasma levels of ferritin, IL-6, LDH and DD, CRP; Death;	Les Bujanda <i>et al.</i> [21]
NCT04451174 June 2020	Chile	Early use of corticosteroids in non-critical patients with COVID-19 pneumonia (PREDCOVID)	60	18 years to 90 years	Prednisone 40 mg/day 1 to 4. 20 mg/day 5 to 8.	No	Admission to ICU; need for invasive MV; Death;	ICU; MV; Death;	Salinas <i>et al.</i> [24]
NCT04388514 April 2020	Italy	Blood ozonization in patients with SARS-CoV-2 respiratory failure (CORMOR)	90	18 years to 99 years	Medical ozone procedure	No	ABG;	ICU; Stability of the chest imaging; Evaluation of plasmatic cytokine;	Tascini <i>et al.</i> [34]
NCT04251871 January 2020	China, Beijing	Treatment and prevention of traditional Chinese medicines (TCMs) on COVID-19 infection	150	14 years to 80 years	Oxygen therapy	No	ARDS development;	Improvement of chest radiographic evidence; Fever;	Xiao [45]

¹Number of total participants. (ICU) intensive care unit; (MV) mechanical ventilation; (< SpO₂) decrease in SpO₂ < 90%; (IL-6) interleukin-6; (LDH) lactate dehydrogenase; (DD) D-dimer; (CRP) C-reactive protein; (ABG) arterial blood gas; (ARDS) acute respiratory distress syndrome.

cumulative incidence of grade 3 (severe) and 4 (life-threatening) adverse events; and temporary discontinuation or suspension of treatment for any reason [25].

However, in another study with patients with ARDS secondary to COVID-19 infection with mechanical ventilatory support, clinical improvement was achieved with the administration of methylprednisolone in high doses (0.5g to 1g/day for 3 days). Drug therapy began at the time of intubation, then slowly decreased for an average of 13 days [26]. One point to be highlighted is that, prior to the pandemic, corticosteroids had no function for use in respiratory failure due to viral etiologies, only steroids were recommended for patients with moderate to severe ARDS due to their association with faster resolution of the disease in patients with sepsis or acquired pneumonia. Currently and with limited data available, the Society of Critical Care Medicine (SCCM) suggests for COVID-19 and ARDS therapy the use of mechanically ventilated adult systemic corticosteroids [27-29]. It is believed that the suggestion of MCSS is due to research that confirms the beneficial effect of corticosteroids on short-term mortality and reduction of mechanical ventilation [30] and by researchers who present data that recommend its use in association with COVID-19 and ARDS with little evidence of damage [29]. However, there is a need to investigate and learn more about the nature of corticosteroids alone in the intervention in COVID-19-associated lung injury, identifying other subgroups of ARDS patients who will benefit from corticosteroid therapy.

To Mongardon *et al.* [31], high-dose corticosteroids do not seem to be beneficial in ARDS, as a lower dose was found in their study, an average dose of 1 (1.2) mg/kg of methylprednisolone for 21 (18-26) days. Corticosteroids were applied before (early) and after (late) of the signs and symptoms of the disease. The result shows that initial treatment with methylprednisolone demonstrates survival benefits in severe pneumonia caused by SARS-CoV-2. Another relevant point that deserves to be highlighted are the Surviving Sepsis Campaign Guidelines for COVID-19 published in March 2020, which guide the weak recommendation for the use of corticosteroids in patients with COVID-19 and ARDS who require mechanical ventilation [32,33]. On the other hand, the Infectious Diseases Society of America Guidelines published in April 2020 issued a recommendation against corticosteroids, except for patients with COVID-

19 and ARDS treated in the context of a clinical trial [34].

It is observed that corticosteroids in ARDS secondary to COVID-19 infection have been gaining ground in scientific research due to reliable results in the clinical management of patients using corticosteroid therapy, remembering that it requires strict control due to the magnitude of consequences in the human body.

5. OXYGEN/OZONE THERAPY AS INTERVENTION FOR COVID-19

5.1. Ozone Therapy

The clinical trial (Clinicaltrials.gov NCT04388514) addresses ozone therapy and coronavirus disease with modest to moderate respiratory failure (Table 1). The clinical presentations of the participants are based on clinical phenotypes identified by the Italian Society of Emergency Medicine Urgency (SIMEU) and patients who meet the criteria for phenotypes 2 to 4 (Table 2) participated in the study. Thus, the study aims to evaluate the use of the treatment of autohemotherapy with ozone as adjuvant therapy and to verify whether it is associated with decreased time of clinical improvement. This trial is a randomized multicenter study involving 90 people. It is noteworthy that the patient's blood was then homogenized to a gas mixture of 200 cc composed of 96% oxygen and 4% ozone with an O₃ therapeutic solution of 40 µg/mL of gas per mL of blood. To ensure the homogeneous diffusion of O₂/O₃ in the blood, the pouch was gently mixed for about 10 minutes, reinfused blood in patients. The duration of ozone treatment lasted 3 consecutive days. The primary results show improvement in respiratory pattern and early weaning of oxygen support in the period of 3 and 10 days of randomized study, and normal arterial blood gas parameters. The secondary outcome measurements show improvement in chest imaging findings at 10 days and in the release of plasma cytokines such as IL-6, lymphocyte typing for CD3, CD4, CD8, HLA-DR, CD45 [35]. The results are considered significant, due to the improvement of the cytokine storm, in addition to the lymphopenia [14].

5.1.1. Effects of Ozone Therapy

To Cattel *et al.* [36] ozone therapy has several positive effects, such as inflammation control, immunity stimulation, low antiviral activity. This therapy may be a new method of immunological therapy, therefore its use in combination with other antiviral drugs in COVID-19-positive patients may be justified, useful and

synergistic. The same authors report that the therapy does not bring adverse or toxic effects, when performed, so it is essential to train the professional to apply ozone therapy.

These satisfactory effects can be justified by their mechanism of action. Ozone reacts with organic compounds containing double bonds (polyunsaturated fatty acids) and adds the three O₂ atoms to the unsaturated bond, forming ozone. In the blood, ozone is immediately transformed into stable hydroperoxides, which can release O₂ when pH increases as it occurs in degenerative processes and/or ischemic conditions [37,38]. Ozone is a molecule that can exert antiviral action interfering in the replication phase of the virus; this characteristic is linked to the ozone's ability to oxidize cysteine residues by forming disulfide bridges present in the structures of the virus itself in copious quantities. Coronavirus, including SARS-CoV-2, is rich in cysteine and these residues must be intact for viral activity [39,40]. The action of ozone consists of oxidation and inactivation of the specific viral receptors used for the creation of the cell membrane binding structure, thus inhibiting the level of its first phase: cell penetration. The activity of ACE2 receptors (angiotensin-s-nare-2-converter enzyme) can be regulated and blocked by controlling the nuclear message transducer "Nrf2" (nuclear factor erythroid 2-related factor 2). Ozone acts directly on Nrf2 and can be an important physiological mechanism to block endogenous replication of COVID-19, avoiding contact with SARS-CoV-2 receptors. In addition, Nrf2 activation leads to a reduction in iron overload and subsequent oxidative stress induced by elevated ferritin; thus, this ozone activity protects from oxidative stress-induced apoptosis [36,37,41]. The inflammasome of NLRP3 (NLR family pyrin domain containing 3), a cytosolic complex responsible to produce IL-1 β and IL-18, plays a crucial role in the onset and during inflammation in various diseases, including viral infections such as COVID-19. Ozone shows its anti-inflammatory activity by modulating the NLRP3 inflammasome. Therefore, it can protect against ischemia reperfusion damage that occurs in the lungs of patients affected by COVID-19, attenuating NLRP3-mediated inflammation, increasing the antioxidant activity of Nrf2 and inhibiting apoptosis [36,42].

This context shows that ozone therapy is a possible and particularly useful option because its mechanism of action has been shown to be remarkably effective as a complementary therapy to COVID-19. As a result of this reality, ozone therapy can be suggested as a

treatment to avoid or reduce the time of hospitalization, or even decrease the severity of the patient's clinical picture.

5.2. Hyperbaric Oxygenation

HBO is a therapeutic method by which the patient breathes O₂ at 100%, inside a hyperbaric chamber, at a pressure greater than atmospheric pressure. After the establishment of safety standards related to the procedure, HBO began to be used in the treatment of several diseases, since it fights severe infections and the extent of its indications indicates its importance for health, which, consequently, can help in the treatment of COVID-19 [43-45].

The research (NCT04251871) addresses traditional Chinese medicines, especially HBO as a treatment for COVID-19 infection (Table 1). The study is a randomized controlled trial with 150 people. The aim of the study is to evaluate whether traditional Chinese drugs are effective and safe for the treatment of COVID-19 infection. The intervention is adopted with oxygen therapy, in addition to interferon alpha by inhalation of aerosol and lopinavir/ritonavir. The study brings measures of primary and secondary outcomes. The primary outcome reports the development of ARDS. It also highlights the time for the fever resolution rate and the time for recovery of lung injury with chest x-ray evidence indirectly reflects recovery in patients infected with COVID-19 in secondary outcome. It is important to highlight that the study describes other measures of results, such as the rate of individuals who die in a period of 28 days and the duration of respiratory support, including invasive and noninvasive mechanical ventilation [46].

In the study by Gonzalez-Ramirez *et al.* [47] investigated whether HBO can benefit a sample of 36 patients with COVID-19. As a result of the first HBO session, 7 patients were immediately relieved of dyspnea, while in 22 patients, this shortness of breath was markedly relieved after 7.57 ± 0.63 days of HBO. In addition, the other 7 patients had a slow recovery of breathing after performing the activity, suggesting that they should continue HBO. In general, the study demonstrates that HBO for 7.57 ± 0.63 days improves the symptoms of COVID-19, indicating that it may be \pm useful alternative in the treatment of this disease. The authors reported that HBO represents an attractive alternative to the current oxygen supply systems available to patients with COVID-19, providing inflammatory relief and facilitating the reversal of hypoxemia [47].

Treatment with HBO is of extreme relevance, especially in patients with ARDS secondary to COVID-19. Although it is not a specific treatment for COVID-19 and with few articles on its efficacy on SARS-CoV-2, it was observed in publications and Clinicaltrials.gov clinical outcomes and empirical initiatives to support oxygenation for the treatment of the disease.

6. SOME CONSEQUENCES OF DRUG HEPATOTOXICITY

Given the situation of COVID-19, with broad clinical manifestations, including patients considered at risk with hospitalizations and among the search for several drugs for the effective treatment of SARS-COV-2, discrepant effects on drug metabolism have been observed, especially in liver enzymes "aspartate aminotransferase" (AST) and "alanine aminotransferase" (ALT) by modifying therapeutic action or exacerbating hepatotoxic effects, causing drug-induced liver injury (DILI) [48,49]. This is usually due to the interaction between the drug used at the recommended and/or combined daily doses and a susceptible individual. Each year, DILI gains attention from physicians and researchers because it represents a significant risk to the patient's health [50,51].

For the evaluation and exploration of DILI, the Roussel Uclaf Causality Assessment Method (RUCAM) is pointed out as a valuable diagnostic tool, based on artificial intelligence (AI) principles, besides being a diagnostic algorithm widely used worldwide and applied in many other complex diseases for diagnostic and therapeutic reasons [50-53]. RUCAM was the first method of causality assessment (CAM) to consider threshold criteria, through ALT and/or alkaline phosphatase (ALP), so patients with suspected DILI who have lower than expected liver test (LT) threshold values are considered without clinically significant liver injury, but with hepatic adaptation or tolerance [54]. Moreover, RUCAM was also the first CAM to differentiate patterns of liver injury, based on LT without the need for liver histology, thus presenting two available scales, one for hepatocellular injury and the other for cholestatic/mixed liver injury [55].

Thus, RUCAM includes the fundamentals of AI and is based on different domains, comprising well-defined key elements, such as hepatocellular injury, which is the time of initiation or cessation of drug use; course of ALT after cessation of the drug; risk factors; concomitant drug(s); search for alternative causes; knowledge of the hepatotoxicity of the product and the response to unintentional re-exposure, the score range

reflects the variability of some criteria and allows the selection of a precise attribution [55].

Several drugs used to treat COVID-19 have been theorized as probable causes of DILI, although evidence of a causal relationship is limited. A study conducted in China with 417 patients with COVID-19 showed that the use of Lopinavir/Ritonavir increased the chances of liver injury by four times compared to one patient who did not receive the drug. As there is not yet a single definitive biochemical test, DILI remains a diagnosis of exclusion [56].

Other medicines are potentially hepatotoxic, such as remdesivir, hydroxychloroquine, azithromycin, acetaminophen and tocilizumab, which can also cause DILI. Another worrisome factor is obese patients with COVID-19, with medications that can cause more severe DILI, while others can trigger the transition to fatty liver; non-alcoholic steatohepatitis or worsening of pre-existing steatosis; necroinflammation and fibrosis [51,57]. Comorbidities such as obesity, fatty liver disease associated with metabolic dysfunction, and diabetes may additionally increase the risk of hepatotoxicity. Although liver injury is not the leading cause of death in patients with COVID 19, liver dysfunction can undoubtedly worsen the patient's condition [57].

In addition, mild liver biochemical abnormalities in patients with COVID-19 are usually transient and may recover without special treatment. However, for patients with severe acute liver injury, the probable causes of the injury should be fully considered, including a history of preexisting liver disease, exposure to hepatotoxins, hypoxia, and circulatory status. Meanwhile, biochemical indicators of the liver should also be monitored to prevent the occurrence of acute liver failure. For patients with suspected DILI, discontinuation or drug reduction should be considered [58].

Despite the challenges of a worldwide pandemic, patients with COVID-19, especially the most critical, need to take several combined medications in therapy, which is more likely to increase the risk of DILI under the condition of systemic immune disorder, in addition to multiple adverse effects. Therefore, the use of medications should be rational to reduce the chance of DILI in clinical practice [51,56].

Therefore, the incidence of abnormal liver enzymes is high in patients with COVID-19, especially in severe

Table 2: Classification of COVID-19 Patients in 5 Clinical Phenotypes, according to SIMEU

Classification	Clinical description of phenotypes
Phenotype 1	subjects with fever and without respiratory failure (normal ABG analysis - six-minute walking test - 6mWT - and Chest XR). These patients usually can manage at home maintaining quarantine period.
Phenotype 2	subjects with fever but with ABG and/or Chest XR indicative of modest respiratory insufficiency ($PO_2 > 60$ mmHg in ambient air) and / or pulmonary consolidation area. These patients need to be hospitalized because they can get quickly worse.
Phenotype 3	subjects with fever associate to moderate-severe respiratory insufficiency (at triage $PO_2 < 60$ mmHg in ambient air) and /or bilateral pulmonary consolidation area at Chest XR. These patients need to be treated with high flow oxygen therapy.
Phenotype 4	subjects with respiratory failure with suspected ARDS or complicated pneumonia. These patients require hospitalization in sub-intensive care unit.
Phenotype 5	subject with ARDS at the beginning. These patients will require ICU admission and NIPPV or mechanical ventilation.

(PO_2) oxygen partial pressure; (mmHg) millimeters the mercury; (ABG) arterial blood gas; (ARDS) acute respiratory distress syndrome; (ICU) intensive care unit; (NIPPV) non-invasive positive pressure ventilation. Adapted font: Tascini *et al.* [34].

cases, and is associated with a poor prognosis, not to mention that SARS-COV-2 can worsen their primary liver diseases [58]. To verify causality in dubious cases of liver injury, RUCAM is suggested for the diagnosis of DILI, besides contributing to the good prognosis of the disease [57,59], especially because it increases the patient's chances of obtaining more effective treatment.

6. CONCLUSION

The severity of the disease, transmission and symptoms of ARDS associated with COVID-19 are a cause for concern in the current society and therefore clinical-therapeutic knowledge, appropriate and promising interventions for the treatment of the disease, in addition to the results of clinical trials are of paramount importance in this pandemic. Therefore, this study found current evidence and varieties of drug options, with significant results, but it is emphasized that the scientific evidence is still preliminary, there is still no proven efficacy and safety of a specific drug for the treatment of COVID-19, especially associated with ARDS.

However, it is essential to emphasize that corticosteroids have shown improvement in inflammatory biomarkers and mechanical ventilatory support, as well as a survival benefit in severe pneumonia caused by SARS-CoV-2, which can be appreciated as a favorable factor for the good prognosis of the disease. It is good to remember that any drug can cause complications, but it is remarkable that patients overcome the risks found and show clinical improvements. HBO is an option for the intervention because it is a safe modality, with few contraindications and still able to provide relief,

assisting in the recovery of the patient. Ozone therapy, on the other hand, helps modulate the inflammatory process and optimizes the release of O_2 by tissues, a low-risk and high potential auxiliary treatment for patients with COVID-19, preventing the worsening of the disease and helping to rapidly reverse respiratory failure and orotracheal intubation.

Therefore, COVID-19 is an emerging and rapidly evolving situation that has impacted the world and cost many lives throughout the country, due to the severe course of the disease by the new coronavirus, more randomized clinical trials revealing the stages of clinical research, demonstrating the safety of short- and long-term therapy and the efficacy of human interventions and for the early diagnosis of liver lesions caused during drug treatment or after therapy, RUCAM is recommended as a standard tool for the diagnosis of liver enzyme changes due to its high sensitivity and specificity in DILI.

AUTHOR CONTRIBUTIONS

All the authors responsible for the research participated in the systematic review study. Five independent reviewers (MBM, MMS, TFQS, AWL and LES) conducted the research and selection of the study. Reviewers (JMPN, WRS, NCPB, FZP and FJSA) performed data extraction and fully reviewed by reviewers RRR and JMPG. The third investigator decided on some conflicting points and made the final decision to choose the articles.

FUNDING

There was no funding for this study.

ACKNOWLEDGEMENT

I would like to thank my colleagues at Brazil University who contributed to the development of the research.

POTENTIAL CONFLICT OF INTEREST STATEMENT

The authors declare to have no conflict of interest.

ABBREVIATIONS

ABG	=	Arterial blood gas
ACE2	=	Angiotensin-converting enzyme 2
ALP	=	Alkaline phosphatase
ALT	=	Alanine aminotransferase
ARDS	=	Acute respiratory distress syndrome
AST	=	Aspartate aminotransferase
CAM	=	Causality assessment
CRP	=	C-reactive protein
DD	=	D-dimer
DILI	=	Drug-induced liver injury
HBO	=	Hyperbaric oxygenation
IA	=	Artificial Intelligenci
ICU	=	Intensive care unit
IL-6	=	Interleukin-6
LDH	=	Lactate dehydrogenase
LT	=	Liver test
mmHg	=	Millimeters the mercury
MV	=	Mechanical ventilation
NIPPV	=	Non-invasive positive pressure ventilation
NLRP3	=	NLR family pyrin domain containing 3
NK	=	Natural killer
Nrf2	=	Nuclear factor erythroid 2-related factor 2
O ₂	=	Oxygen
PO ₂	=	Oxygen partial pressure

RUCAM = Rousel Uclaf Causality Assessment Method

SCCM = Society of Critical Care Medicine

SIMEU = Italian Society of Emergency Medicine Urgency

SpO₂ = O₂ saturation

TCZ = Tocilizumab

VHL = Virtual Health Library

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Received on 20-01-2022

Accepted on 10-02-2022

Published on 10-03-2022

<https://doi.org/10.12970/2308-8044.2022.10.01>© 2022 Mezanini *et al.*; Licensee Synergy Publishers.

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