Chapter

COVID-19: From Pathophysiology to Treatment

Joise Wottrich, Eduardo Gonçalves, Carina Echer de Souza, Pauline Brendler Goettems Fiorin, Mirna Stela Ludwig, Thiago Gomes Heck and Matias Nunes Frizzo

Abstract

The new coronavirus first appeared in December 2019 in Wuhan, China, being officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV), as well as the name of the disease has been described as COVID-19 (coronavirus disease 2019). In March 2020, the disease was considered a global pandemic, with currently more than 514 million cases worldwide, with 6.4 million deaths. Severe cases of COVID-19 progress to acute respiratory distress syndrome (ARDS), on average about 8–9 days after the onset of symptoms. It is also worth mentioning that the severity of the disease in patients is not only due to the viral infection but also due to the host response. This phase, called a cytokine storm, reflects a state of systemic immune activation, with high levels of cytokines, such as IL-6, IL-1b, IL-2, IL-12, IL-18, TNF, and interferon gamma (IFN-γ). In this sense, the management of the disease largely depends on symptomatic and supportive treatments. For severely or critically ill patients with acute respiratory distress syndrome (ARDS) and sepsis, in addition to supplemental oxygen, mechanical ventilation, and ARDS-specific therapies, antiviral and antibiotic treatments should also be considered. Thus, the purpose of this chapter is to describe the pathophysiology and treatment of SARS-CoV-2 infection.

Keywords: SARS-CoV-2, COVID-19, pathophysiology, treatment

1. Introduction

Coronaviruses (CoVs) belong to the *order of Nidovirales*, *family of Coronaviridae*, *and* are divided into four genera: *alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus*. The term "Corona" is used because the virus has crown-like spikes on its external surface [1]. CoVs cause diseases in a wide variety of birds and mammals and have been found in humans since 1960. To date, seven human CoVs have been identified, including the alpha-CoVs HCoVs-NL63 and HCoVs-229E and the beta-CoVs HCoVs-OC43, HCoVs-HKU1, severe acute respiratory syndrome-CoV (SARS-CoV), and Middle East respiratory syndrome-CoV (MERS-CoV). The new coronavirus was first identified in December 2019 in Wuhan, China, being officially

named by the International Committee on Virus Taxonomy (ICTV), as well as the name of the disease has been designated COVID-19 [2, 3].

SARS-CoV-2 is very contagious since it is able to spread easily from human to human through different routes of infection, such as droplets, contact, and aerosol transmission. Coronaviruses (CoVs) are the largest known RNA viruses, their size ranges from 65 to 125 nm in diameter, and their nucleic acid genome is a single-tape RNA, with a size ranging from 26 to 32 Kb. The CoVs HKU1, NL63, OC43, and 229E are associated with mild symptoms in humans, while SARS-CoV, MERS-CoV, and SARS-CoV-2, which belong to the genus betacoronavirus, cause severe pneumonia in humans [3].

CoVs were believed to infect only animals until an outbreak of severe acute respiratory syndrome (SARS) caused by SARS-CoV occurred in 2002 in Guangdong, China. A decade later, another pathogenic coronavirus, known as middle eastern respiratory syndrome coronavirus (MERS-CoV), caused an endemic disease in Middle Eastern countries. In late 2019, Wuhan, an emerging business center in China, experienced an outbreak of a new coronavirus that killed more than 1,800 people and infected more than 70,000 in the first fifty days of the epidemic. From the sequence-based analysis of isolates from patients, the virus was identified as a new coronavirus. In a recent review, it was demonstrated that the epicenter of the COVID-19 pandemic was similar to that of SARS-CoV-1, that is, a zoonotic origin. The most robust evidence points out that the Huanan market was the epicenter of the pandemic, probably the wildlife trade [4].

Because it is an RNA virus, SARS-CoV-2 presents a high mutation rate as its characteristic. This aspect provides conditions for this viral zoonotic pathogen to become more efficiently transmitted from person to person and possibly becoming more virulent. These observations indicated the ability of this virus to contaminate from human to human, which was subsequently reported worldwide [5]. In this sense, in March 2020, the disease was considered a global pandemic. Since then, there have been more than 575 million cases and 6.4 million deaths worldwide, according to data of the World Health Organization (WHO) in July 2022. In the same period, in Brazil, there were 33 million cases, with 679,000 deaths. The mortality rate in this country, according to the Brazilian Ministry of Health, is 32 people per 100,000 habitants.

Considering the epidemiological aspects of the pandemic, with emphasis on the mortality of COVID-19, disease therapy is a decisive tool in the conduction of patients and is fundamental for clinical improvement. Without specific treatment established for COVID-19 up to now, therapeutic support, such as the use of corticosteroids and oxygen supplementation, delivered the best results in large *trials.* In addition, interleukin blockers presented a good response in patients with the potential to progress to cytokine storm and acute respiratory distress syndrome (ARDS). Thus, the objective of this chapter is to describe the pathophysiology and treatment of SARS-CoV-2 infection, highlighting the importance of inflammatory biomarkers and knowledge of pathophysiology, and their interaction for early recognition of therapeutic targets (corticosteroids, oxygen supplementation), the need for hospitalization in intensive care units, as well as predict the evolution of the disease.

2. COVID-19

COVID-19 is a disease with high contagious power and clinical manifestations ranging from mild to severe, with the majority of the cases being mild. In current

data, 81% of cases present mild symptoms and 1.2% are asymptomatic. The WHO estimates the reproductive number (R0) of SARS-CoV-2 between 2 and 2.5, which is higher than SARS (1.7–1.9) and MERS (<1), and demonstrates the highest pandemic potential of SARS-CoV-2. SARS-CoV-2 can spread rapidly in the community, unlike SARS-CoV and MERS-CoV, which have a higher mortality rate and a higher hospital admission rate [3]. Two main strains called "A" and "B" helped to track and know the viral genome of SARS-CoV-2, the difference between these two strains is only two nucleotides, and these characteristics are also found in coronavirus *of Rhinolophus*, the supposed host reservoir. Strain B has been the most common in the entire pandemic and includes all eleven sequenced human genomes directly associated with the Huanan market, The oldest human-line A genomes do not have a direct epidemiological connection with the Huanan market but have been identified in patients who have circulated in the vicinity of the market [6].

To enter host cells, SARS-CoV-2 shares the same human cell receptor with SARS-CoV, the angiotensin 2 converting enzyme (ACE-2), which is an ectoenzyme anchored in the plasma membrane of cells of various tissues, mainly in the lower respiratory tract, heart, kidneys, and gastrointestinal tract. The first critical step for the entry of the virus into sensitive host cells involves a specific receptor, usually, the CoVs enter the host cell using the transmembrane Spike glycoprotein (S). After the viral anchorage, transmembrane serine protease 2 (TMPRSS2) cleaves and activates the Spike protein: S1 binds to the receptor through its receptor-binding domain and S2 fuses the host membrane with the viral counterpart, an event that allows SARS-CoV-2 to enter the cells by endocytosis or direct fusion of the viral envelope with the host membrane [7].

Active replication and virus release cause the host cell to suffer pyroptosis and the discharge of pro-inflammatory chemical mediators, which are recognized by neighboring epithelial cells, endothelial cells, and alveolar macrophages, triggering the generation of pro-inflammatory and chemokine cytokines, including IL-6. Chemokines and pro-inflammatory cytokines attract monocytes, macrophages, and T cells to the site of infection, increasing the inflammatory picture (with the addition of IFNγ produced by T cells) and establishing a pro-inflammatory feedback cycle (**Figures 1** and **2**) [8].

In an impaired immune response, there may be a greater accumulation of immune cells in the lungs, causing overproduction of pro-inflammatory cytokines, which damages the lung infrastructure. The resulting cytokine storm circulates to other organs, promoting damage to various organs. In addition, non-neutralizing antibodies produced by B cells can increase SARS-CoV-2 infection through antibody-dependent enhancement, further exacerbating organ damage. Alternatively, in a healthy immune response, initial inflammation attracts virus-specific T cells to the site of infection, where they can eliminate infected cells before viral spread. Neutralizing antibodies in these individuals can block viral infection, and alveolar macrophages recognize neutralized viruses and apoptotic cells and eliminate them by phagocytosis, generating minimal inflammatory damage [8].

The mean incubation period of COVID-19 is 5 to 6 days, the mean age of COVID-19 cases ranges from 49 to 57 years, and the mean time from the first symptom to death is 14 days. Within 5 to 6 days of the onset of symptoms, the viral load of SARS-CoV-2 reaches its peak, being significantly earlier than that of SARS-CoV, in which the period of viral load peak is about 10 days after the onset of symptoms [9].

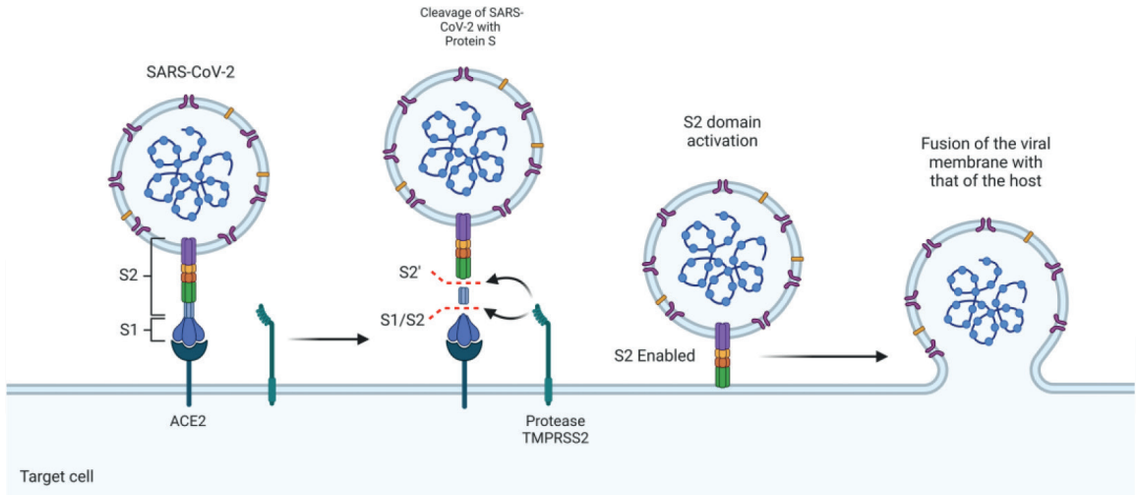

Figure 1.
Connection of SARS-CoV-2 to ACE-2 receptors. Figure describes: The connection of SARS-Cov-2 with the ACE2 receptor on the target cell, followed by cleavage of SARS-CoV-2 with the S protein, activation of the S2 domain, and fusion of the viral membrane with the host cell. Source: Figure of the authors.

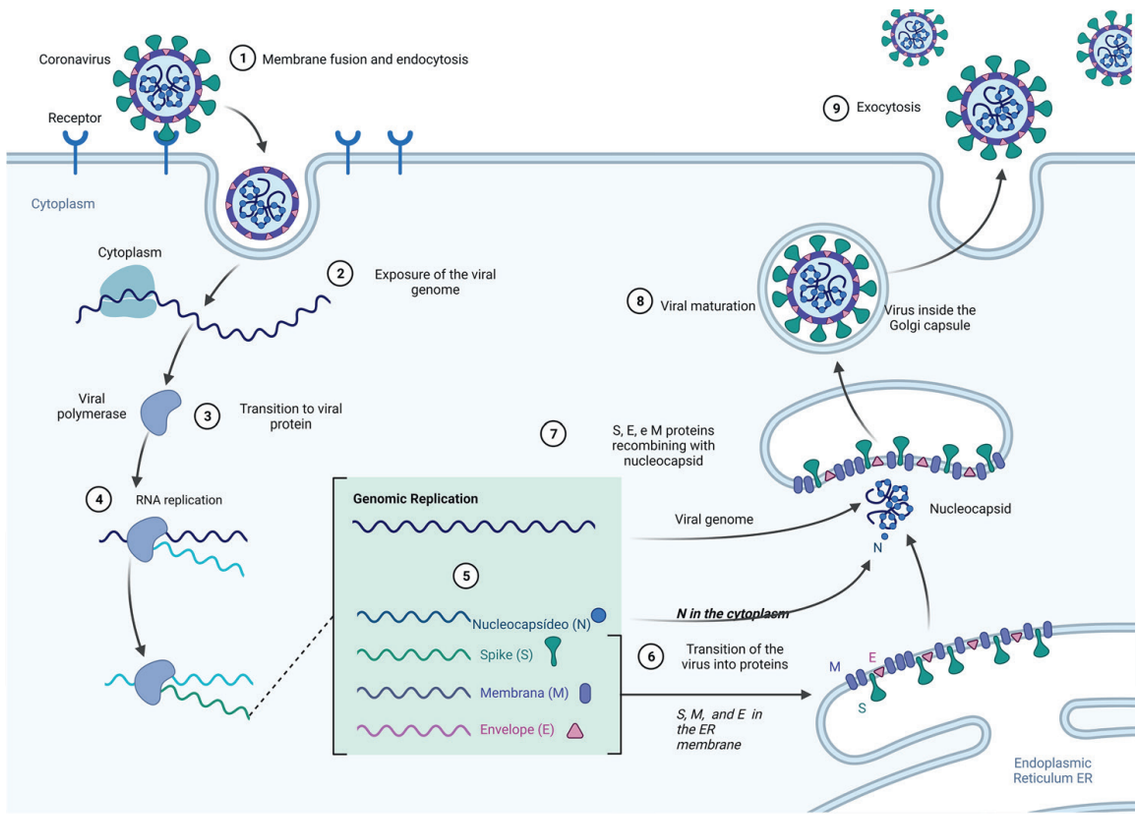

Figure 2.
Viral replication of SARS-CoV-2. Figure describes: 1) Fusion of the virus to the host membrane, occurring endocytosis; 2) Exposure of the viral genome; 3) viral polymerase performs transcription for viral protein; 4) viral replication occurs; 5) genomic replication; 6) transition of the virus into proteins in the membrane of the endoplasmic reticulum; 7) proteins S, E, and M recombining with nucleocapsid; 8) viruses within the Golgi capsule, performing viral maturation; and 9) viral exocytosis. Source: Figure of the authors.

Severe cases of COVID-19 progress to acute respiratory distress syndrome (ARDS), on average, about 8–9 days after the onset of symptoms. It is also worth mentioning that the severity of the disease in patients is not only due to viral infection but also due to the response of the host [8], as shown in **Figures 3** and **4**.

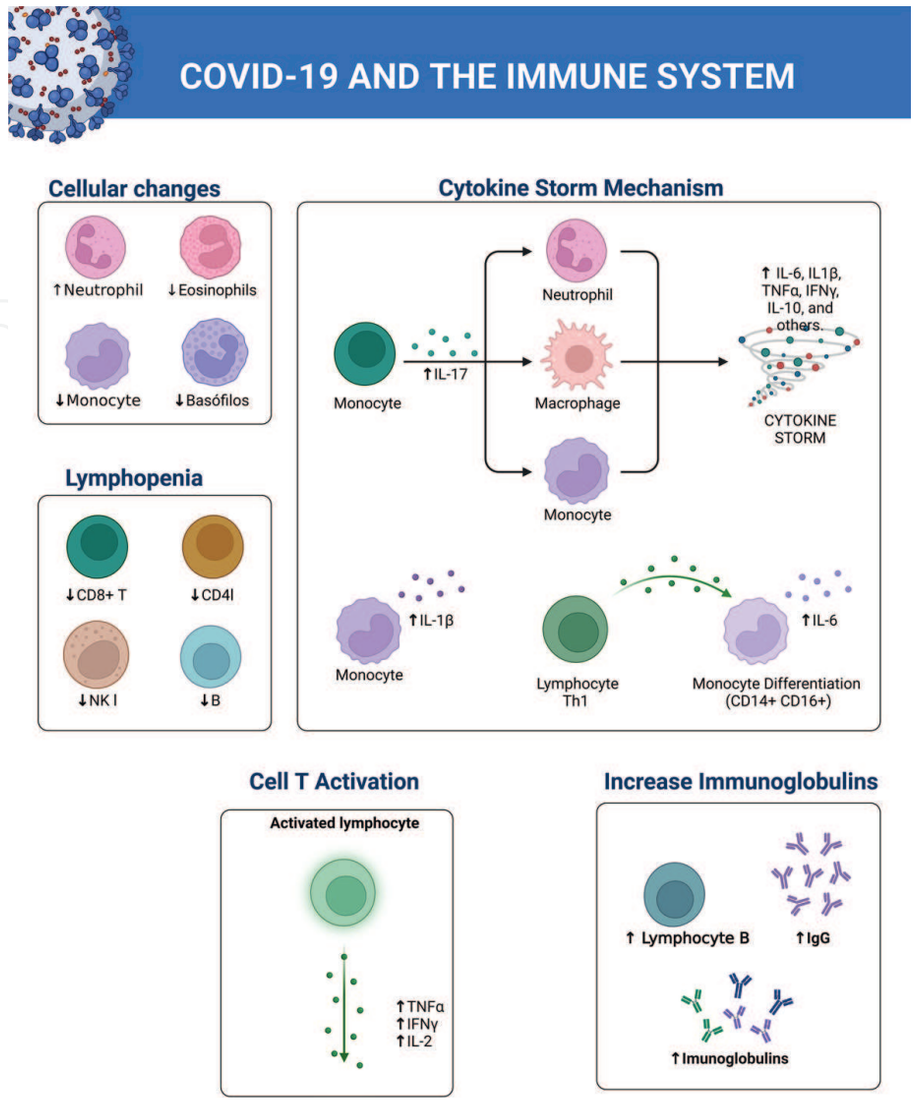

Figure 3.
Innate and adaptive immune response at COVID-19. Description of the most frequent cellular alterations in COVID-19: increase of neutrophils and decrease of eosinophils, monocytes, and basophils. Lymphopenia occurs due to a decrease in CD4, Cd8, B and natural killer lymphocytes. The activated T lymphocyte promotes the increase of TNF, Interferon, and IL-2. The activation of B lymphocytes promotes the increase of immunoglobulins G. In the storm of cytokines occurs an uncontrolled elevation of IL-6, IL-1, TNF, interferon gamma, and IL-10. Source: Figure of the authors.

SARS-CoV-2 infection in severe cases leads to activation of macrophages and dendritic cells and consequent exacerbated release of pro-inflammatory cytokines. In addition, the presentation of SARS-CoV-2 antigens through the main histocompatibility complexes I and II (MHC I and II) stimulates humoral and cellular immunity, also resulting in the high production of cytokines. When the virus reaches the lower respiratory tract and infects type II pneumocytes, it promotes apoptosis and loss of surfactant, capillary extravasation, and alveolar edema, resulting in lung damage and collapse, impairing gas exchange [10].

The onset and duration of the cytokine storm vary, depending on the cause and treatments administered. Most patients with cytokine storm present fever, fatigue, anorexia, headache, rash, diarrhea, arthralgia, myalgia, and neuropsychiatric findings. These symptoms may be directly due to cytokine-induced tissue damage or acute phase physiological changes or may result from immune cell-mediated responses. Cases may progress rapidly to disseminated intravascular coagulation with vascular

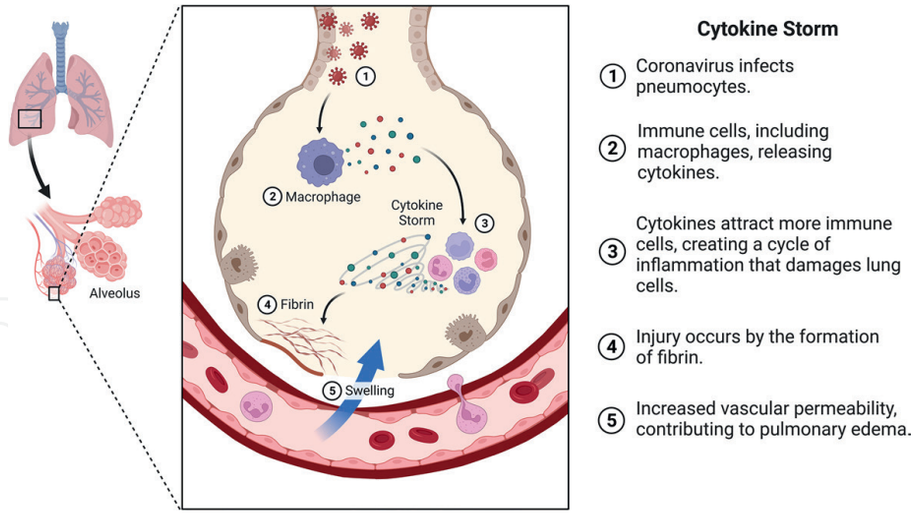

Figure 4.
Cytokine storm at COVID-19. Description of the pathophysiology of cytokine storm, after the entry of the virus into the pneumocyte, occurs activation of macrophages with the release of cytokines, generating damage to lung cells, with fibrin formation, increased vascular permeability, and pulmonary edema. Source: Figure of the authors.

occlusion or catastrophic hemorrhage, dyspnea, hypoxemia, hypotension, hemostatic imbalance, septic shock, and death [11].

Since the initial phase of the pandemic, the cytokine storm has become peculiar to SARS-COV-2 infection, at least in severe cases. It is responsible for damaging the respiratory tract and subsequent failure of multiple organs. It results from a complex network involving cytokines/chemokines/infiltrating immune cells that orchestrate the aberrant immune response in COVID-19. This term covers several disorders of immune dysregulation and is characterized by constitutional symptoms, systemic inflammation, and multiple organ dysfunction [12].

The combination of hyperinflammation, coagulopathy, and low platelet count puts patients with cytokine storm at high risk of spontaneous bleeding. Among the most commonly described biomarkers are interleukin I 1β, IL-6, tumor necrosis factor (TNF) α, interferon (IFN) γ, and IL-10. The cytokine storm sustains too much inflammatory response in the blood, causing the immune system to attack the body involving various organs, such as the lungs. This, in turn, causes injury to the alveolar-capillary membrane, increased pulmonary permeability, acute respiratory distress syndrome, and multiple organ failure [13].

In the pathophysiology of cytokine storm, we can highlight macrophage activation, a hyperinflammatory condition associated with different triggers, including infections, autoimmune diseases, and neoplasms, being characterized by fever, hepatosplenomegaly, cytopenias, elevated levels of ferritin, triglycerides, lactic dehydrogenase, D-dimer and aminotransferases, as well as hypofibrinogenemia. The acute phase of the syndrome reflects a state of systemic immune activation, with elevated cytokine levels such as IL-6, IL-1b, IL-2, IL-12, IL-18, TNF, and interferon gamma (IFN-γ). The term macrophage activation syndrome (AMS) refers to a subgroup of patients with secondary hemophagocytic lymphohistiocytosis, in a context of self-ignition or systemic autoimmunity, characterized by hyperinflammatory and hyperferritinemic immune responses, directed by different T lymphocyte subpopulations and associated with cytokine release syndrome [9], as illustrated in **Figure 4**.

3. Treatment of COVID-19

To date, no pharmacological intervention has been shown to be effective and safe to ensure its use in the routine treatment of patients with COVID-19; therefore, ideally, these patients have been treated in the context of clinical trials and guidelines for good clinical practice. In newly emerging diseases, such as COVID-19, especially in a pandemic situation, interventions are mainly performed *based on in vitro experiments, personal experiments,* and small limited observational studies. The management of the disease depends largely on symptomatic and supportive treatments [14].

Worldwide, several pharmacological interventions have been proposed for COVID-19, such as anticoagulants, antimicrobials, chloroquine, hydroxychloroquine, convalescent plasma, remdesivir, and tocilizumab [14]. For severely or critically ill patients with acute respiratory distress syndrome (ARDS) and sepsis, in addition to supplemental oxygen, mechanical ventilation and specific therapies for ARDS, antiviral and antibiotic treatments should also be considered [15, 16].

3.1 Steroids

The use of systemic corticosteroid therapy in the treatment of infectious diseases is controversial, however, widely used. Corticosteroids have received worldwide attention as a potentially effective treatment for COVID-19 infection [15]. In the COVID-19 Randomized Trial of Therapy (RECOVERY), the use of dexamethasone resulted in lower mortality rates in individuals with COVID-19 who received mechanical ventilation or supplemental oxygen [17]. In the CoDEX study in patients with COVID-19 and moderate or severe ARDS, the use of dexamethasone resulted in a statistically significant increase in the number of days without mechanical ventilation, but without impact on mortality [18].

Pathologies that present an increase in endogenous levels of glucocorticoids (CG) are sepsis, cachexia, metabolic acidosis, and severe insulinopenia. GC-induced muscle atrophy is characterized by rapidly contracting glycolytic muscle atrophy, decreased fiber cross-sectional area, and reduced myofibrillar protein content [19, 20]. Glucocorticoids lead to an imbalance between the rate of synthesis and degradation of proteins. Dexamethasone, a synthetic glucocorticoid, stimulates skeletal muscle atrophy by promoting protein degradation [19] through the ubiquitin-proteasome pathways and by inhibiting protein synthesis via Akt/(mTOR) [21].

According to Shang et al. [22], patients with COVID-19 release elevated cytokine levels, showing that alveolar damage is steroid-responsive. The RECOVERY study established that dexamethasone can significantly decrease mortality in severe cases of COVID-19, especially in critical conditions when ventilatory support is necessary, presumably because the severity of lung injury reflects worsening of the hyperinflammation. The reason for dexamethasone to be chosen included its anti-inflammatory potency, lack of mineralocorticoid effect, and longer action profile [23]. Pharmacological responses require exposure to high doses of corticosteroids, *and in vitro studies have shown* a higher response with methylprednisolone than with dexamethasone [24], and this preference is sustained when the inflammatory pathway and characteristics of the different corticosteroids are considered. In addition, treatment with methylprednisolone for a shorter period may also minimize systemic side effects [25]. The trial of Ko et al. [26], provided evidence that the mortality benefit of dexamethasone in severe COVID-19 is not drug-specific but

rather the general anti-inflammatory effect of corticosteroids. In this study, the higher anti-inflammatory potency of methylprednisolone showed additional mortality benefits, especially in patients who required mechanical ventilation.

The Brazilian guideline for the pharmacological treatment of hospitalized patients reviewed several studies worldwide, bringing a strong recommendation for the use of dexamethasone (6 mg/day for 10 days) only in individuals who are under the use of supplemental oxygen therapy since at the Brazilian level, this drug has good tolerance on the part of the patient and low cost for health institutions. There is no evidence for the use of routine corticosteroids in patients with COVID-19, especially, this should still be avoided within the first 7 to 10 days of the onset of the symptoms, when the host response is fighting the viral infection. Some evidence suggests retardation in viral clearance when corticosteroids are used early. The potential benefit of its use would be in patients with moderate to severe ARDS, in selected cases and without suspicion of uncontrolled bacterial infection, 10–14 days after the onset of COVID-19 symptoms. The doses used in the studies ranged from 10 mg to 20 mg of dexamethasone and 40 mg to 120 mg of methylprednisolone per day for 5–10 days [14].

The Brazilian recommendation is in accordance with the WHO guideline Corticosteroids for COVID-19 launched in September 2020, which reviewed meta-analyses and randomized trials with data from more than 7,000 patients. The WHO panel recommends the use of oral or intravenous glucocorticoids for 7 to 10 days in patients with severe and critical COVID-19, defined by the presence of signs of respiratory distress, increase in respiratory rate, hypoxemia, necessity of vasopressor therapy, and/or mechanical ventilation, regardless of their hospitalization status. The recommendation is supported by evidence of 6.7 to 8.7% reduction in 28-day mortality and reduction in the need for invasive mechanical ventilation. Different GC can be selected, according to availability and observing equivalent doses. The daily dose of 6 mg of dexamethasone is equivalent to 40 mg of prednisone, 160 mg of hydrocortisone (e.g., 50 mg every 8 hours or 100 mg every 12 hours), or 32 mg of methylprednisolone (e.g., 8 mg every 6 hours or 16 mg every 12 hours). The panel also recommends to monitor glucose levels and other potential GC adverse effects, and not to use GC in non-severe COVID-19, due to a potential risk of increasing death in this setting. One should also adjudicate the risk of secondary and endemic infections and act to minimize their risk.

An important aspect to consider is that the increase in cortisol and bed rest act synergistically on the decrease in muscle mass. It has been demonstrated that after 28 days, healthy young individuals lost more muscles when confined to bed and received hydrocortisone than only at rest [27]. The restriction of movements during hospitalization of COVID-19 in the ICU is different from other clinical conditions, because the patient with COVID-19 may present deep weakness, spend hours on high-flow oxygen therapy or in ventral decubitus. A median reduction of 18.5% of the rectus femoris muscle between the first and seventh day of ICU stay may occur [28]. In addition, the study by Kirwan et al. [29] demonstrated an unadjusted risk of sarcopenia of 38.4% associated with an average time of 11 days in hospital stay by COVID-19.

One of the main side effects of GC use is hyperglycemia, and this condition is also induced by the course of critical disease [30]. The diabetogenic effect of steroids in susceptible patients can aggravate the problem of anabolic resistance. The hyperglycemia of the critically ill patient is related to insulin resistance, that is, the impossibility of insulin to stimulate glucose uptake in skeletal muscle or to

inhibit gluconeogenesis in the liver. During critical disease, the abrupt development of hyperglycemia involves complex interactions between some counterregulatory hormones (glucagon, catecholamines, growth hormone, and cortisol), adipokines, and inflammatory cytokines that cause increased glucose production by the liver and insulin resistance in tissues. This hyperglycemia can affect the functions of respiratory muscles, leading to respiratory muscle weakness acquired in the ICU, as well as increase mortality in these patients [5]. Insulin resistance ultimately promotes a catabolic state that implies lipolysis and loss of muscle mass [31].

3.2 IL-6 antagonists

Tocilizumab is an interleukin 6 inhibitor approved for the treatment of rheumatoid arthritis, giant cell arteritis, and cytokine release syndrome during chimeric antigen receptor (CAR-T) T-cell therapy. Interleukin 6 is an inflammatory cytokine that exerts its effects on the liver and lymphocytes, inducing acute phase reagents such as C-reactive protein, fibrinogen, and hepatocytes hepcidin, and promotes the differentiation of cytotoxic T cells CD4 (T helper 17) and CD8 and antibody production. Interleukin 6 plays an important role in controlling viral infections such as influenza A, acute severe respiratory syndrome coronavirus 1, and herpes virus. In COVID-19, an increased level of interleukin 6 and C-reactive protein correlates with the severity and mortality of the disease. Thus, blocking the activity of interleukin 6 may play a role in mitigating the inflammatory response and improving clinical outcomes in patients with COVID-19 [32].

The World Health Organization's (WHO) Rapid Evidence Assessment Working Group (REACT) developed a protocol to perform a prospective meta-analysis of IL-6 antagonists in patients hospitalized by COVID-19. The IL-6 antagonists investigated were monoclonal antibodies that bind to soluble, membrane-bound IL-6 receptors (e.g., tocilizumab and sarilumab) or directly to IL-6 (e.g., siltuximab). Administration of IL-6 antagonists, compared to usual treatment or placebo, was associated with lower all-cause mortality in 28 days [33]. Tocilizumab is a humanized antibody against IL-6 and has been used in patients with pronounced cytokine storm. Patients with rheumatoid arthritis who regularly use this medication have demonstrated that long-term treatment with tocilizumab leads to increased muscle mass, as assessed with *dual X-ray absorptiometry* (DEXA) [34]. Tocilizumab reduces the risk of mechanical ventilation in hospitalized patients [35] and also reduces all-cause mortality on day 28 compared to standard treatment alone or with placebo [36] (**Figure 5**).

According to the available studies [17, 37], tocilizumab was recommended by Brazilian treatment guidelines for patients with COVID-19, who are using NIV (non-invasive mechanical ventilation) or CNAF (high flow nasal catheter) and not recommended in patients under mechanical ventilation. To date, the studies have not shown clear benefits in patients under mechanical ventilation; however, there is a tendency to prescribe it in the first 24 hours of IMV, at medical discretion. However, the authors indicate that the package leaflet of this medicine does not present this indication [28], that is, its use in MV *would be off-label,* and access to this drug may be limited by availability and also financial reasons.

The indicated dosage is 8 mg/kg, with a maximum administration of 800 mg, and a second application should only be performed after careful medical reassessment. Evidence also suggests that the benefits of tocilizumab are associated with corticosteroid co-administration [17] and may preferably be used in patients with increased inflammatory markers (C-reactive protein test, ferritin, and lactic dehydrogenase).

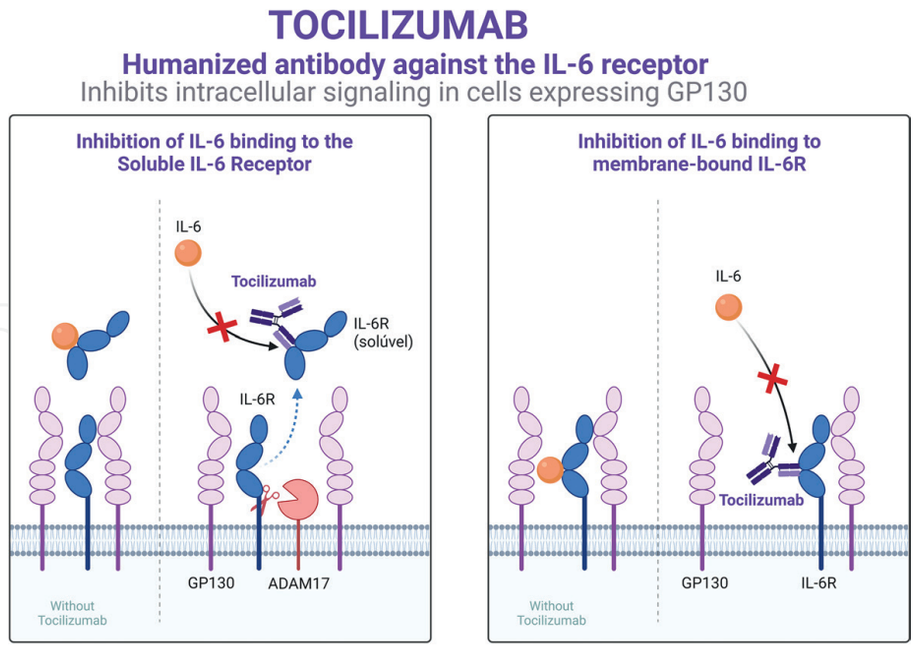

Figure 5.
Tocilizumab mechanism of action. Tocilizumab is a recombinant humanized monoclonal antibody, which acts as an interleukin 6 receptor antagonist (IL-6), blocking the transduction of the signal of this pro-inflammatory cytokine, preventing the dimerization of GP130 in the cell membrane and, consequently, blocks the proinflammatory effects of IL-6. In addition, it has the ability to dissociate IL-6/IL-6R complexes that have already formed. The IL-6 receptor has two presentations: membrane-bound IL-6 receptor and soluble IL-6 receptor. IL-6 is binding with IL-6R for the formation of a complex, which is coupled to the transmembrane protein gp130 so that signal transduction occurs and pro-inflammatory function is performed. Source: Figure of the authors.

For patients with signs of bacterial infection, with latent infections such as tuberculosis or parasitic, care should be given to the possibility of reactivation of these with the administration of tocilizumab. In immunosuppressed patients, its use should be with caution, and in neutropenic individuals (<500 cells/mm^3), thrombocytopenic (< 50,000 platelets/mm^3) or with transaminases at levels five times greater than physiological value, tocilizumab should not be used at all [14].

In addition to tocilizumab, other trials that use Casirivimab and Imdevimab are presenting significantly promising results, however, only in patients in the early stages of the disease [38, 39] and not in hospitalized patients. Recommendations of the treatment panel for COVID-19 for the treatment of outpatients, by order of preference, are nirmatrelvir enhanced with ritonavir (Paxlovid) (AIIa) and remdesivir (BIIa). Other alternative medicines, such as Bebtelovimab (CIII) and Molnupiravir (IIC), should be used only when none of the first-rate medicines are available.

It is also worth noting that the treatments with antiviral drugs that the WHO panel against indicates are interferons for outpatients (AIIa), interferon alpha or lambda for hospitalized patients (AIIa), Ivermectin (AIIa), Nitazoxanide (BIIa), Chloroquine or hydroxychloroquine and/or azithromycin for hospitalization (AI) and not hospitalization situation (AIIa), Lopinavir/ritonavir and other HIV protease inhibitors for hospitalized patients (AI) and outpatients (AIII) and systemic interferon beta for hospitalized patients (AI). Due to these concerns and data gaps, Molnupiravir should be provided only to non-severe patients with COVID-19 at higher risk of hospitalization. Typically, they are people who have not received COVID-19 vaccination, elderly people with immunodeficiencies or people living with chronic diseases.

Treatment with anti-SARS-CoV-2 mAbs should be considered for patients with mild-to-moderate COVID-19 who are hospitalized, considering that the risk of

progression to severe COVID-19 in high-risk patients is substantially higher for those who are not vaccinated. It is also interesting to note that severely immunocompromised patients may have prolonged replication of SARS-CoV-2, leading to faster viral evolution, with consequent worse clinical outcomes. Anti-SARS-CoV-2 monoclonal antibodies (mAbs) have their results variable, depending on the circulating strain. As a suggestion, the use of anti-SARS-CoV-2 mAbs is based on current knowledge of SARS-CoV-2 in vitro activities. At the moment, the recommendations of the panel's anti-SARS-CoV-2 mAb are for the treatment of patients with mild-to-moderate COVID-19 who are at high risk of progressing to severe disease.

Intravenous Bebtelovimab has its use only for patients aged ≥12 years as an alternative therapy when nirmatrelvir (Paxlovid) and remdesivir potentiated with ritonavir are not available, viable to use, or clinically appropriate (CIII). Treatment should be started as soon as possible and within 7 days after the onset of symptoms. Anti-SARS-CoV-2 mAbs should be administered in an environment where severe hypersensitivity reactions such as anaphylaxis can be controlled. Patients should be monitored during the infusion and observed for at least 1 hour after infusion.

3.3 Anticoagulants

The care team should pay attention to the development of signs and symptoms of thromboembolic events. Due to this risk, patients hospitalized due to COVID-19 should receive prophylaxis of thromboembolism according to their risk stratification, according to current hospital protocols, for presenting in a high state of hypercoagulability, with a high rate of thromboembolic events being observed in observational and postmortem clinical studies. The dose to be used may vary according to the chosen class, for example, enoxaparin 40 to 60 mg SC once a day or the unfractionated heparin 5,000IU SC two to three times a day. Although evidence for pharmacological prophylaxis in the context of COVID-19 is limited, the intervention is low cost and well-tolerated, with the potential to avoid events of high clinical importance. Heparin should not be used in the case of contraindications of high risk of bleeding, active bleeding, and severe thrombocytopenia [40].

Critically ill patients have a strong recommendation for prophylactic doses for venous thromboembolism with anticoagulant (mainly with the use of vasoactive drugs, on hemodialysis or using CNAF, NIV, or MV), according to the Brazilian guidelines for pharmacological treatment for COVID-19. But there is no recommendation for the use of intermediate doses in patients without signs of thromboembolism. Anticoagulants should be used, following a careful assessment of bleeding risk and presence of thrombocytopenias [14].

In a study evaluating 42 patients, all using immunosuppressant or glucocorticosteroids, with severe to moderate COVID-19, with 21 patients receiving low-molecular weight heparin and 21 controls, there was a significant reduction. In IL-6 dosage and increased lymphocytes. The results of this study contribute to the use of low-molecular weight heparin as a potential therapeutic drug for the treatment of COVID-19. Changes in D-dimer levels and fibrinogen degradation products in the group that received heparin before and after treatment were significantly different from those in the control group ($P = 0.035$). Together, IL-6 levels have also been reduced after heparin treatment ($P = 0.006$), indicating that, in addition to other beneficial properties, it can exert an anti-inflammatory effect and partly attenuate the virus-induced "cytokine storm" [41].

There is no indication of routine use of anticoagulants in post-discharge due to COVID-19. The indication of the use of anticoagulants in a post-discharge setting

should follow the same criteria as for patients without COVID-19, according to institutional protocols.

3.4 Antimicrobials (antibiotics)

Patients with COVID-19 without signs of sepsis or infection are not recommended for antibiotic therapy. However, individuals who present potential infectious foci on admission, with suspected sepsis, presenting or not being diagnosed for COVID-19, are indicated for the use of antibiotics (empirically). Also, patients with worsening due to COVID-19, who require care in intensive care units, are exposed to processes that potentiate the risk of infection, such as mechanical ventilation, bladder catheter, and arterial and venous accesses, which can lead to the need for the use of antibiotic therapy to this population [14].

To date, there is no randomized clinical trial evaluating the effectiveness of empirical antibacterials in patients with COVID-19 without evidence of bacterial infection, that is, clinical data are insufficient to demonstrate benefits or risks in the use of antibacterials in patients with COVID-19 without evidence of bacterial infection, so in the absence of evidence, there is no basis to indicate prophylactic antibacterials in patients with COVID-19. In addition to the absence of evidence of benefit, this practice may result in adverse events, increased antimicrobial resistance, and costs. There are no adequate data on bacterial co-infection in patients with COVID-19; however, it should be noted that the overlap of infections is possible to occur, mainly due to immunosuppression and exposure to the hospital environment, often colonized by multidrug-resistant germs. It is understood that these patients should receive antibacterials in a similar way to patients without COVID-19, following local protocols.

In the meta-analysis of Lanford [42] with 3,338 eligible patients, bacterial co-infection (estimated at presentation) was identified in 3.5% of patients (95% CI 0.4–6.7%) and secondary bacterial infection in 14.3% of patients (95% CI 9.6–18.9%). The overall proportion of patients with COVID-19 with bacterial infection was 6.9% (95% CI 4.3–9.5%). Bacterial infection was more common in critically ill patients (8.1%, 95% CI 2.3–13.8%). Since bacterial co-infection is relatively infrequent in patients hospitalized with COVID-19, therefore, most of these patients may not require empirical antibacterial treatment, reinforcing the guidelines of following institutional protocols for sepsis.

3.5 Oxygen therapy

Lung injury due to the new coronavirus resembles other causes of ARDS, but initial clinical features include more evident hypoxemia and loss of dyspnea perception. Due to the various forms of presentation of COVID-19, oxygen supplementation levels may vary according to clinical and laboratory signs. According to Guan [9], almost half (42%) of patients admitted to the hospital environment will require supplemental oxygen therapy. Nationwide, in the first five months of the pandemic, 49% of those infected required noninvasive respiratory support [43].

Oxygen therapy is defined as oxygen therapy, the administration of oxygen above the ambient air concentration (~21%), aiming to maintain adequate oxygenation of tissues. Its use has the potential to correct hypoxemia by reducing cardiorespiratory work overload [18]. Therefore, oxygen therapy is one of the treatments for the clinical condition in more severe cases of SARS-CoV-2 infection, since patients presenting hypoxemia or signs of respiratory effort may benefit from its use, either via the ocular

nasal catheter, mask with a non-rebreathing oxygen mask, noninvasive ventilation (NIV), or high-flow nasal catheter (HFNC) [44]. If there is a need for oxygen therapy, it is recommended to be given its administration according to peripheral oxygen saturation (SpO2), with a strong recommendation of its onset when SpO2 <90%, in order to keep it between 92% and 96% in previously healthy patients and between 88% and 92% for patients with chronic lung disease [45].

3.5.1 High flow nasal cannula – HFNC

Prior to the COVID-19 pandemic, HFNC was already recommended in patients with moderate respiratory failure [46] and demonstrated efficacy in the treatment of acute hypercapnic respiratory failure [47, 48]. In CNAF, the supplementary supply of oxygen allows the administration of high flows (up to 60 liters per minute) and precise oxygen concentrations (21% to 100%) [49]. Even if there is no routine recommendation, when HFNC is indicated, it can be used in selected patients with hypoxemic respiratory failure associated with COVID-19, who have clinical signs and symptoms such as SpO2 < 93%, PaO2/FiO2 <300 mmHg, and respiratory rate > 25 incursions per minute [50].

3.5.2 Noninvasive mechanical ventilation – NIV

NIV contributes to the improvement of oxygenation and reduction of respiratory work and may prevent orotracheal intubation [51]. In viral pandemic disease, NIV has no recommendations for the treatment of hypoxemic respiratory failure [52], and depending on the interface used, large aerosol dispersion (COVID-19 dissemination medium) [53] can occur, so its indication should be judicious, and its application should be closely monitored.

The success of NIV to avoid intubation seems to be associated with patients with PaO2/FiO2 ratio > 100 mmHg and without multiple organ failure (APACHE < 20 score). During the first 30 minutes, ventilometry monitoring is very important, because a minute volume > 10l/min, current volume > 9 ml/kg predicted, respiratory rate > 25 irpm, requiring final expiratory positive pressure > 10 cmH20 with FiO2 > 50%, indicate its failure [50, 54].

3.5.3 Invasive mechanical ventilation – IMV

Among individuals infected with SARS-CoV-2, approximately 80% of the cases are asymptomatic, 15% present a more severe form (requiring supplemental oxygen), and 5% evolve to the most critical form, requiring advanced life support [41, 44]. This can occur mainly in patients with chronic heart or lung diseases, diabetes, obesity (BMI > 40), and in the elderly [51]. A recent study with biopsy of the diaphragm muscle showed the expression of ECA 2 and viral infiltration SARS-CoV-2 in the diaphragm of a subset of patients and histological evidence for the development of fibrosis [41].

The findings in the severe form of COVID-19 meet the diagnostic criteria for ARDS [55], and when hypoxemia worsens, hypercapnia, acidemia, respiratory fatigue, hemodynamic instability, or even mental status alterations, intubation should be strongly considered [50, 56], consequently requiring invasive mechanical ventilation (IMV). For those who need IMV, the objectives of this therapy are based on: maintenance of gas exchange (by correction of hypoxemia and respiratory acidosis

associated with hypercapnia), reduction of respiratory work (with reversal or prevention of fatigue of respiratory muscles), and application of other specific and necessary treatment routes [57].

The long-term prognosis of patients who survive intensive care is affected by physical disabilities, cognitive impairments, and mental disorders that may occur after discharge from the ICU [58]. In relation to muscle mass loss, it may occur more frequently in older adults and patients with comorbidities who are more likely to have pre-existing catabolism. In addition, these groups of patients may be prone to develop more intense catabolic responses due to COVID-19 and prolonged ICU stay [59].

In addition to the systemic inflammatory process with cytokine release that contributes to the evolution of ARDS in critically ill patients with COVID-19, these patients also have an increased risk for weakness and sarcopenia due to the same inflammatory mechanism of loss of muscle mass. Associated with these factors, the length of stay on mechanical ventilation is high (mean of 11.7 days). About 75%–80% of patients hospitalized with COVID-19 have extended hospital stays, with about 21 days. When admitted to the ICU, they may have multiple organ failures, including ARDS, acute kidney injury, heart injury, and liver dysfunction [60]. Evidence has shown that organic dysfunction is highly associated with muscle dysfunction [61]. Additionally, some of these patients have associated comorbidities, such as advanced age, renal dysfunction, hypertension, diabetes, and heart disease, which may contribute to the incidence of weakness and sarcopenia. Thus, critical patients with COVID-19 may face a vicious cycle, in which the severity of the disease itself, the presence of comorbidities, prolonged invasive ventilatory support, and the use of sedatives and neuromuscular blockers may contribute to the development of weakness, sarcopenia, and functional dysfunctions in the short and long term [60].

4. Final considerations

Research and science are essential for the successful conduction of the COVID-19 pandemic. In this context, discovering the entry mechanism of the virus into a cell, the expected response of the host, and especially the exacerbated response in the form of the cytokine storm were fundamental for the initiation of clinical reasoning of diagnostic and therapeutic approaches. The unfavorable evolution of the clinical presentation of COVID-19 has led and still leads countless patients to need treatment in the intensive care unit (ICU), and sarcopenia and secondary infectious processes are a potential risk for the worsening of the clinical outcome [42, 62–87].

Thus, the intense scientific and technological advances in recent years of this pandemic favored the understanding and elucidation of the pathophysiology of the disease, and this knowledge is a crucial point for the use of existing drugs, such as tocilizumab, for the development of promising drugs and application of assistance protocols. The application of biomarkers, both clinical and laboratory, is differential when managing COVID-19, especially to stratify risk groups, monitor evolution, make therapeutic decisions, and in prognosis.

COVID-19: From Pathophysiology to Treatment
DOI: http://dx.doi.org/10.5772/intechopen.107146

Author details

Joise Wottrich[1*], Eduardo Gonçalves[2], Carina Echer de Souza[3],
Pauline Brendler Goettems Fiorin[1], Mirna Stela Ludwig[1], Thiago Gomes Heck[1]
and Matias Nunes Frizzo[1]

1 Regional University of the Northwest of the State of Rio Grande do Sul, Brazil

2 Brazilian Association of Cardiorespiratory Physiotherapy and Intensive Care Physiotherapy, Brazil

3 Oncology Institute of Ijui, Brazil

*Address all correspondence to: joise.wottrich@sou.unijui.edu.br

References

[1] Shereen MA, Khan S, Kazmi A, et al. COVID-19 infection: Emergence, transmission and characteristics of human coronavirus. Journal of Advanced Research. 2020;**24**:91

[2] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2019. National Institutes of Health. Available from: https://www. covid19treatmentguidelines.nih.gov/ [Accessed: August 2, 2022]

[3] Bchetnia M, Girard C, Duchaine C, et al. The outbreak of the new acute severe respiratory syndrome coronavirus 2 (SARS-CoV-2): A review of the current global status. Journal of Infection and Public Health. 2020;**13**(11):1601-1610

[4] Worobey M et al. The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic. Science. 2022;**87**:8715

[5] Wang C, Horby PW, Hayden FG, et al. A new outbreak of coronavirus of global health concern. The Lancet, [S.L.] (Elsevier BV). Feb 2020;**395**(10223):470-473. DOI: 10.1016/s0140-6736(20)30185-9. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30185-9/fulltext [Accessed: 10 May, 2021]

[6] Pekar JE et al. The molecular epidemiology of multiple zoonotic origins of SARS-CoV-2. Science. 2022;**83**:37

[7] Romano M, Ruggiero A, Squeglia F, et al. A structural view of the SARS-CoV-2 RNA replication machine: RNA synthesis, revision and final capping. Cells. 2020;**9**:1267

[8] Tay MZ, Poh CM, Rénia L, et al. The trinity of COVID-19: Immunity, inflammation and intervention. Nature Reviews Imunology. 2020;**20**:363

[9] Guan WJ, Ni ZY, Hu Y, et al. Clinical features of coronavirus disease 2019 in China. New England Journal of Medicine. 2021;**382**(18):1708

[10] Rabi FA, Zoubi MSA, Kasasbeh GA, et al. SARS-CoV-2 and Coronavirus Disease 2019: What we know so far. Pathogens. 2020;**9**:231

[11] Fajgenbaum DC, June CH. Cytokine storm. New England Journal of Medicine. 2021;**383**(23):2255-2273

[12] Coperchini F, Chiovato L, Rotondi M. Interleukin-6, CXCL10 and infiltrating macrophages in COVID-19-related cytokine storm: Not one for everyone, but for all for one! Borders in Immunology. 2021;**12**:1-8

[13] Xiong F, Tang H, Liu L, et al. Clinical features and medical interventions for COVID-19 in Hemodialysis Patients in Wuhan, China. JASN. 2020;**31**:1387

[14] Falavigna M, Stein C, Amaral JLG, et al. Brazilian guidelines for the pharmacological treatment of patients hospitalized with COVID-19. Rev Bras Have Intensive. 2022;**34**(1):1-12

[15] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review. JAMA. 2020;**323**(18):1824-1836. DOI: 10.1001/jama.2020.6019

[16] Hossen MS, Barek MA, Jahan N, Safiqul Islam M. A review on current repurposing drugs for the treatment of COVID-19: Reality and challenges. SN Comprehensive Clinical Medicine.

2020;**2**(10):1777-1789. DOI: 10.1007/s42399-020-00485-9

[17] Collaborative Recovery Group. Tocilizumab in patients admitted to the hospital with COVID-19 (RECOVERY): A randomized, controlled, open, platform trial. Lancet. 2021;**397**(10285):1637-1645

[18] Tomazini BM, Maia IS, Bueno FR, et al. COVID-19-associated ARDS treated with DEXamethasone (CoDEX): Study design and rationale for a randomized trial. Revista Brasileira de Terapia Intensiva, [S.L.] (GN1 Genesis Network). 2020;**32**(3):354-362. DOI: 10.5935/0103-507x.20200063. Disponível em: https://www.scielo.br/j/rbti/a/b7fXwJt3KTmc4zhM7p8vKhf/?lang=en. Acesso em: 21 abr. 2021

[19] Schakman O, Kalista S, Barbé C, et al. Glucocorticoid-induced skeletal muscle atrophy. The International Journal of Biochemistry & Cell Biology, [S.L.] (Elsevier BV). out. 2013;**45**(10):2163-2172. DOI: 10.1016/j.biocel.2013.05.036. Disponível em: https://www.sciencedirect.com/science/article/abs/pii/S1357272513001817?via%3Dihub. Acesso em: 07 fev. 2021

[20] Hermans G, Berghe GVD. Clinical review: Intensive care unit acquired weakness. Critical Care, [S.L.] (Springer Science and Business Media LLC). dez 2015;**19**(1):1-9. DOI: 10.1186/s13054-015-0993-7. Disponível em: https://ccforum.biomedcentral.com/articles/10.1186/s13054-015-0993-7. Acesso em: 06 abr. 2021

[21] Park HY, Jung J, Park HY, Lee SH, Kim ES, Kim HB, et al. Psychological consequences of survivors of COVID-19 pneumonia 1 month after discharge. Journal of Korean Medical Science. 2020;**35**(47):e409. DOI: 10.3346/jkms.2020.35.e409

[22] Shang L, Zhao J, Hu Y, et al. On the use of corticosteroids for 2019-nCoV pneumonia. The Lancet, [S.L.] (Elsevier BV). fev 2020;**395**(10225):683-684. DOI: 10.1016/s0140-6736(20)30361-5. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7159292/. Acesso em: 10 fev. 2021

[23] Horby P, Lim WS, Emberson JR. Dexamethasone in hospitalized patients with Covid-19: Preliminary report. New England Journal of Medicine, [S.L.] (Massachusetts Medical Society). 25 fev. 2021;**384**(8):693-704. DOI: 10.1056/nejmoa2021436. Disponível em: https://www.nejm.org/doi/suppl/10.1056/NEJMoa2021436/suppl_file/nejmoa2021436_preliminary.pdf. Acesso em: 05 abr. 2021

[24] Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids — New mechanisms for old drugs. New England Journal of Medicine, [S.L.] (Massachusetts Medical Society). 20 out. 2005;**353**(16):1711-1723. DOI: 10.1056/nejmra050541. Disponível em: https://www.nejm.org/doi/10.1056/NEJMra050541?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed. Acesso em: 09 fev. 2021

[25] Meduri GU, Siemieniuk RAC, et al. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. Journal of Intensive Care, [S.L.] (Springer Science and Business Media LLC). 24 ago. 2018;**6**(1):1-7. DOI: 10.1186/s40560-018-0321-9. Disponível em: https://jintensivecare.biomedcentral.com/articles/10.1186/s40560-018-0321-9#citeas. Acesso em: 09 fev. 2021

[26] Ko JJ, Wu C, Mehta N, et al. A comparison of methylprednisolone and dexamethasone in intensive care patients

with COVID-19. Journal of Intensive Care Medicine, [S.L.] (SAGE Publications). 25 fev. 2021;**36**(6):673-680. DOI: 10.1177/0885066621994057. Disponível em: https://journals.sagepub.com/doi/10.1177/0885066621994057?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed&. Acesso em: 06 jul. 2021

[27] Paddon-Jones D, Sheffield-Moore M, Cree MG, et al. Atrophy and impaired muscle protein synthesis during prolonged inactivity and stress. The Journal of Clinical Endocrinology & Metabolism, [S.L.] (The Endocrine Society). 1 dez. 2006;**91**(12):4836-4841. DOI: 10.1210/jc.2006-0651. Disponível em: https://academic.oup.com/jcem/article/91/12/4836/2656308. Acesso em: 10 maio 2021

[28] Mayer KP, Bastin MLT, Montgomery-Yates AA. et al. Acute skeletal muscle wear and dysfunction predict physical disability at hospital discharge in patients with critical illness. Critical Care. 2021;**24**(1)

[29] Kirwan R, McCullough D, Butler T, Perez de Heredia F, Davies IG, Stewart C. Sarcopenia during COVID-19 lockdown restrictions: Long-term health effects of short-term muscle loss. GeroScience. 2020;**42**(6):1547-1578. DOI: 10.1007/s11357-020-00272-3

[30] Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial. The Lancet Respiratory Medicine, [S.L.] (Elsevier BV). mar. 2020;**8**(3):267-276. DOI: 10.1016/s2213-2600(19)30417-5. Disponível em: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30417-5/fulltext. Acesso em: 05 mar. 2021

[31] Lheureux O, Prevedello D, Preiser JC. Update on glucose in critical care. Nutrition, [S.L.] (Elsevier BV). mar. 2019;**59**:14-20. DOI: 10.1016/j.nut.2018.06.027. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30415158/. Acesso em: 09 maio 2021

[32] Veiga VC, Prats JA, Farias DL, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: Randomized controlled trial. The BMJ. 2021;**2021**:372

[33] REACT Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19. Jama, [S.L.] (American Medical Association (AMA)). 10 ago. 2021;**326**(6):499-518. DOI: 10.1001/jama.2021.11330. Disponível em: https://jamanetwork.com/journals/jama/fullarticle/2781880#full-text-tab. Acesso em: 10 set. 2021

[34] Tournadre A, Pereira B, Dutheil F, Giraud C, Courteix D, Sapin V, et al. Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. Journal of Cachexia, Sarcopenia and Muscle. 2017;**8**(4):639-646. DOI: 10.1002/jcsm.12189

[35] Tleyjeh IM, Kashour Z, Riaz M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: A living systematic review and meta-analysis, first update. Clinical Microbiology And Infection, [S.L.] (Elsevier BV). ago. 2021;**27**(8):1076-1082. DOI: 10.1016/j.cmi.2021.04.019. Disponível em: https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00204-4/fulltext. Acesso em: 07 maio 2021

[36] Ghosn L, Chaimani A, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: A living systematic

review. Cochrane Database of Systematic Reviews, [S.L.] (Wiley). 18 mar. 2021;**2021**(3). DOI: 10.1002/14651858.cd013881. Disponível em: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013881/full/pt#CD013881-abs-0005. Acesso em: 06 jul. 2021

[37] REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 receptor antagonists in critically Ill patients with Covid-19. The New England Journal of Medicine. 2021;**384**(16):1491-1502. DOI: 10.1056/NEJMoa2100433

[38] Roche. Results of the Ab Cocktail Report (Casirivimab + Imdevimab) in P-III REGN-COV 2069 Covid Symptomatic Infection Assay 19. 2021. Available from: https://pharmashots.com/58368/roche-report-results-of-ab-cocktail-casirivimab-imdevimab-in-p-iii-regncov-2069-trial-for-symptomatic-covid-19-infection/

[39] Weinreich DM, Sivapalasingam S, Norton T. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. New England Journal of Medicine. 2021;**384**(3):238-251

[40] Klok F, Kruip MJ, Van Meer NJ, Arbous MS, Gommers DA, et al. Incidence of thrombotic complications in ICU patients who are seriously ill with COVID-19. Thrombotic Research. 2020;**10**:301

[41] Shi C, Wang C, Wang H, Yang C, Cai F, Zeng F et al. The potential for low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: A retrospective clinical study. medRxiv. 2020;**13**(6):1087-1095

[42] Langford BJ, So M, Raybardhan S, Leung V, Westwood D, Macfadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: Rapid review and live meta-analysis. Clinical microbiology and infection: Official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2020;**26**(12):1622-1629. DOI: 10.1016/j.cmi.2020.07.016

[43] Ranzani OT, Bastos LL, Gelli JGM, et al. Characterisation of the first 250 000 hospital admissions for COVID-19 in Brazil: A retrospective analysis of nationwide data. The Lancet Respiratory Medicine, [S.L.] (Elsevier BV). abr. 2021;**9**(4):407-418. DOI: 10.1016/s2213-2600(20)30560-9. Disponível em: https://www.arca.fiocruz.br/handle/icict/46140. Acesso em: 07 abr. 2021

[44] World Health Organization. Corticosteroids for COVID-19. Living Guidance. 2020. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

[45] Alhazzani W, Evans L, Alshamsi F, et al. Surviving sepsis campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: First update. Critical Care Medicine, [S.L.] (Ovid Technologies (Wolters Kluwer Health)). 28 jan. 2021;**49**(3):219-234. DOI: 10.1097/ccm.0000000000004899. Disponível em: https://journals.lww.com/ccmjournal/Fulltext/2021/03000/Surviving_Sepsis_Campaign_Guidelines_on_the.21.aspx. Acesso em: 05 mar. 2021

[46] Kernick J, Magarey J. What is the evidence for the use of high flow nasal cannula oxygen in adult patients admitted to critical care units? A systematic review. Australian Critical Care, [S.L.] (Elsevier BV). maio 2010;**23**(2):53-70. DOI: 10.1016/j.aucc.2010.01.001. Disponível em: https://www.australiancriticalcare.com/article/S1036-7314(10)00002-0/fulltext. Acesso em: 10 maio 2021

[47] Yuste ME, Moreno O, Narbona S, et al. Efficacy and safety of high-flow nasal cannula oxygen therapy in moderate acute hypercapnic respiratory failure. Revista Brasileira de Terapia Intensiva, [S.L.] (GN1 Genesis Network). 2019;**31**(2):156-163. DOI: 10.5935/0103-507x.20190026. Disponível em: https://www.scielo.br/j/rbti/a/QNGPTVv7w4MwLPhQ8wt97fK/?lang=pt. Acesso em: 10 maio 2021

[48] Dysart K, Miller TL, Wolfson MR, et al. Research in high flow therapy: Mechanisms of action. Respiratory Medicine, [S.L.] (Elsevier BV). out. 2009;**103**(10):1400-1405. DOI: 10.1016/j.rmed.2009.04.007. Disponível em: https://www.resmedjournal.com/article/S0954-6111(09)00132-2/fulltext. Acesso em: 05 maio 2021

[49] Sotello D, Rivas M, Mulkey Z, et al. High-Flow nasal cannula oxygen in adult patients: A narrative review. The American Journal of the Medical Sciences, [S.L.] (Elsevier BV). fev. 2015;**349**(2):179-185. DOI: 10.1097/maj.0000000000000345. Disponível em: https://www.amjmedsci.org/article/S0002-9629(15)30126-9/fulltext. Acesso em: 05 maio 2021

[50] Cai H, Chen Y, Chen Z, et al. Handbook of COVID-19 Prevention an Treatment. The first Affiliated Hospital, Zhejiang University School of Medicine, 2020. Australian and New Zealand Intensive Care Society. ANZICS COVID-19 Guidelines, 2020. Melbourne: ANZICS; 2020

[51] Cordeiro ALL. Manual de Ventilação Mecânica nas Afecções Virais. Salvador: Sanar; 2020. p. 352

[52] Piraino T. Noninvasive respiratory support in acute hypoxemic respiratory failure. Respiratory Care, [S.L.] (Daedalus Enterprises). 20 maio 2019;**64**(6):638-646. DOI: 10.4187/respcare.06735. Disponível em: http://rc.rcjournal.com/content/64/6/638/tab-pdf. Acesso em: 09 maio 2021

[53] Whittle JS, Pavlov I, Sacchetti AD, et al. Respiratory support for adult patients with COVID-19. Journal of the American College of Emergency Physicians Open, [S.L.] (Wiley). abr. 2020;**1**(2):95-101. DOI: 10.1002/emp2.12071. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7228246/. Acesso em: 10 maio 2021

[54] Spadari JAA, Gardenghi G. Aspectos fisiopatológicos do COVID-19 e uso de ventilação não invasiva. É possível? Revista Pesquisa em Fisioterapia, [S.L.] (Escola Bahiana de Medicina e Saude Publica). 4 ago. 2020;**10**(3):372-375. DOI: 10.17267/2238-2704rpf.v10i3.3036. Disponível em: https://www5.bahiana.edu.br/index.php/fisioterapia/article/view/3036. Acesso em: 09 maio 2021

[55] Ranieri VM, Rubenfeld GD, Thompson BT. The ARDS definition task force. Acute respiratory distress syndrome. Jama, [S.L.] (American Medical Association (AMA)). 20 jun. 2012;**307**(23):2526-2533. DOI: 10.1001/jama.2012.5669

[56] Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: Ards or not? Critical Care, [S.L.] (Springer Science and Business Media LLC). 16 abr. 2020;**24**(1):1-3. DOI: 10.1186/s13054-020-02880-z. Disponível em: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-02880-z#citeas. Acesso em: 10 maio 2021

[57] Sarmento GJV. Fisioterapia respiratória de A a Z. Barueri: Manole; 2016

[58] Inoue S, Hatakeyama J, Kondo Y, et al. Post-intensive care syndrome: Its pathophysiology, prevention, and future

directions. Acute Medicine & Surgery, [S.L.] (Wiley). 25 abr. 2019;**6**(3):233-246. DOI: 10.1002/ams2.415. Acesso em: 10 maio 2021

[59] Jones C, Eddleston J, Mccairn A, et al. Improving rehabilitation after critical illness through outpatient physiotherapy classes and essential amino acid supplement: A randomized controlled trial. Journal of Critical Care, [S.L.] (Elsevier BV). out. 2015;**30**(5):901-907. DOI: 10.1016/j.jcrc.2015.05.002. Acesso em: 06 jun. 2021

[60] Bonorino KC, Cani KC. Early mobilization in the time of COVID-19. Revista Brasileira de Terapia Intensiva, [S.L.] (GN1 Genesis Network). 2020;**32**(4):484-486. DOI: 10.5935/0103-507x.20200086. Disponível em: http://rbti.org.br/artigo/detalhes/0103507X-32-4-1. Acesso em: 11 out. 2021

[61] Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;**310**(15):1591-1600. DOI: 10.1001/jama.2013.278481

[62] Costa-Beber LC, Hirsch GE, Heck TG, et al. Companion duality: The role of extracellular and intracellular hsp70 as a biomarker of endothelial dysfunction in the development of atherosclerosis. Archives of Physiology and Biochemistry. 2020;**2020**:1-8

[63] Fraser DD, Cepinskas G, Slessarev M, et al. Inflammation profile of patients with severely ill coronavirus disease 2019. Care Exploration Reviews. 2020;**2**(6):144

[64] Gabay C, Kushner I. Acute phase proteins and other systemic responses to inflammation. New England Journal of Medicine. 1999;**340**(6):448

[65] Guo SC, Xu CW, Liu YQ, et al. Changes in plasmalevels of thrombomodulin and D-dimer in children with different types of mycoplasma pneumoniae pneumonia. Zhongguo Dang Dai Er Ke Za Zhi. 2013;**15**(8):619

[66] Halpern NO, Pastores SM. Critical medicine in the United States 2000-2005: An analysis of bed numbers, occupancy rates, mix of payers and costs. Critical Care Medicine. 2021;**38**(1):65

[67] Heck TG, Ludwig ES, Frizzo MN, et al. Suppressed anti-inflammatory thermal shock response in high-risk covid-19 patients: Basic research lessons (inclusive bats), light on conceivable therapies. Clinical Science. 2020;**134**(15):1991

[68] Herold T, Jurinovic V, Arnreich C, et al. High levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. Journal of Allergy and Clinical Immunology. 2020;**146**(1):128

[69] Hui P, Cook DJ, Lim W, et al. The frequency and clinical significance of thrombocytopenia complicating critical disease. Breast. 2011;**139**(2):271

[70] Jager CPC, Wever PC, Gemen EFA, et al. The neutron-lymphocyte count ratio in patients with community-acquired pneumonia. Plos One. 2012;**7**(10):46561

[71] Jin YH, Cai L, Cheng ZS, et al. A quick guidance of counseling for the diagnosis and treatment of the new coronavirus 2019 (2019-nCoV) infected pneumonia (standard version). Military Medical Research. 2021;**7**(1):1

[72] Letko M, Marzi A, Munster V. Functional evaluation of cell input and receptor use for SARS-CoV-2 and other betacoronavirus B salling. Nature Microbiology. 2021;**5**(4):562-569

[73] Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated

with severe coronavirus disease infections 2019 (COVID-19): A meta-analysis. Clinica Chimica Acta. 2020;**506**:145-148

[74] Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein and procalcitonin in patients with COVID-19. Journal of Clinical Virology. 2020;**127**:104370

[75] Liu J, Liu Y, Xiang P, et al. The neutrophil-lymphocyte relationship predicts patients with critical disease with early-stage coronavirus disease 2019. Journal of Translational Medicine. 2021;**18**:1

[76] Long L, Zeng X, Zhang X, et al. Short-term outcomes of COVID-19 and risk factors for progression. European Respiratory Journal. 2021;**55**:200

[77] Macario AJ, Macario EC. Molecular mechanisms in chapeopathies: Clues to understand histopathological abnormalities and develop new therapies. The Journal of Pathology. 2019;**250**:9

[78] Mitaka C. Clinical laboratory differentiation of infectious versus non-infectious systemic inflammatory response syndrome. Clinica Chimica Acta. 2005;**351**:17

[79] Moore JB, June HC. Cytokine release syndrome in severe COVID-19. Science. 2020;**368**:6490

[80] Paladino L, Vitale AM, Bavisotto DC, et al. The role of molecular companions in virus infection and implications for the understanding and treatment of COVID-19. Journal of Clinical Medicine. 2020;**9**:3518

[81] Qu R, Ling Y, Zhang YH, Wei LY, et al. Platelet--para-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. Journal of Medical Virology. 2020;**92**:1533

[82] Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19 - Preliminary report. medRxiv. 2021;**384**(16):1491-1502

[83] Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on a data analysis of 150 patients from Wuhan, China. Intensive Care Medicine. 2021;**46**:846

[84] Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe covid-19 early. Journal of Medical Virology. 2021a;**92**:856

[85] Tan L, Wang Q, Zhang D, Ding J, Huang Q, et al. The lymphogin predicts the severity of COVID-19 disease: A descriptive and predictive study. Signal Transduction and Directed Therapy. 2021b;**5**:33

[86] Ye W, Chen G, Li X, et al. Dynamic changes in d-dimer and neutrophil-lymphocyte counts as prognostic biomarkers in COVID-19. Respiratory Research. 2021;**21**:169

[87] Zhang M, Tan J, Xu Y, Song R. The neutrophil-lymphocyte relationship predicts patients with critical disease with early-stage coronavirus disease 2019. Journal of Translational Medicine. 2020;**18**:12