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## Review Article

# Immunosuppressed Patients and the Risk of COVID-19: A Narrative Review

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ABSTRACT

Immunodeficiency is a disorder of the immune system characterized by the body's inability to establish effective immunity in response to various harmful agents, antigens. It results in an increased susceptibility to infections and can arise as a result of malnutrition, some types of cancer, infections such as HIV, iatrogeny or heredity. The newly discovered coronavirus is responsible for the current pandemic that is plaguing the world population. Most people with some type of immunodeficiency appear to be at greater risk of developing the severe form of the disease, due to its immunomodulatory effect in some patient populations. However, some immunomodulating agents have become the subject of discussion as possible treatments for the disease of the new coronavirus (COVID-19), increasing the importance of understanding its pathophysiological mechanisms and consequent control strategies. The main objective of this review is therefore to present the main global causes of immunodeficiency and their relationship with COVID-19.

## Introduction

Many patients who need to be hospitalized for infection have some type of immunodeficiency. Immunodeficiency can be classified as primary, secondary or acquired. Primary immunodeficiency diseases comprise a genetically heterogeneous group of disorders, mainly childhood disorders affecting distinct components of the innate and adaptive immune system [1, 2]. Secondary immunodeficiencies, which are the most common, are acquired, and often iatrogenic (Figure 1) [3].

The functions of the immune system cells and systemic metabolism are closely related. Changes in the cellular metabolism can influence the cell function of the immune system and, conversely, the cellular immune function determines the metabolic state of cells. The effects of the systemic metabolism or nutritional state on immune cell function and metabolism are less understood, however. Many studies have shown that malnutrition is associated with immunosuppression, leading to increased susceptibility to infection. Meanwhile, overnutrition is associated with chronic inflammations that can increase the risk of metabolic and cardiovascular diseases, promote self-reactivity and disturb protective immunity [4].

Viral infections that attack immune cells can also harm this system. Acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), induces the progressive depletion of a subtype of T lymphocytes [5]. This syndrome is still a major public health challenge worldwide, with millions of people living with the disease. Most do not have access to sufficient therapy and, as such, it is one of the most important causes of immunodeficiency in the world [5, 6]. Age extremes and malignancies are also important causes of immunodeficiency, especially hematopoietic and lymphoid malignancies, as they result in immune dysfunction caused by deficient immune effector cells or a dysfunction of such activities as antibody synthesis [7, 8].

Iatrogenic immunodeficiency results from the extensive use of therapies that cushion the immune system, such as corticosteroids, antineoplastic immunosuppressants, and mono or polyclonal antibodies [9, 10]. Immunosuppressive therapies target inflammatory and immunological pathways and can therefore cause immunodeficiency. Since defending against infection is the main function of the immune system, immunosuppression can lead to severe infections, defined as potentially fatal or requiring hospitalization [11, 12].

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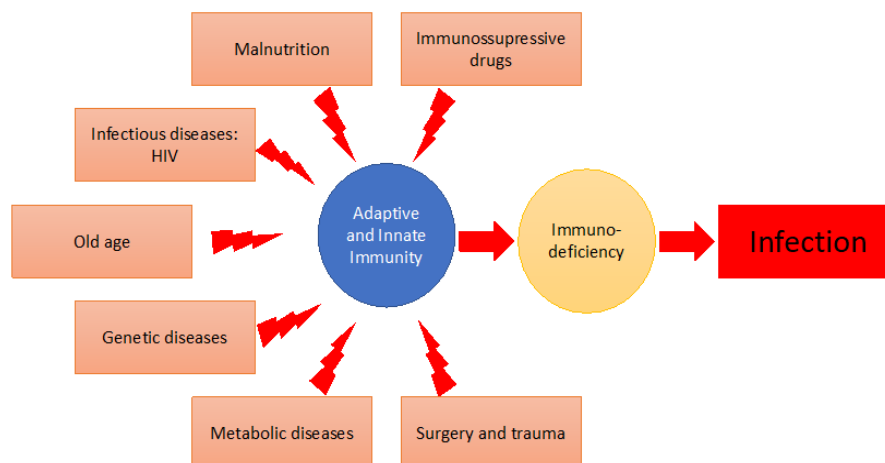
**Figure 1:** Main causes of immunodeficiency.

The current pandemic caused by the new coronavirus has spread throughout the world. On January 30, 2020, the World Health Organization's Emergency Committee declared a global health emergency based on the rising international notification rates. Coronaviruses are single stranded, enveloped RNA viruses that infect humans but also a wide variety of animals. Among the seven subtypes of coronaviruses that can infect humans, the betacoronaviruses can cause anything from a common cold to pneumonia, which can result in acute respiratory distress syndrome, multiple organ failure and death. Elderly patients, immunocompromised patients and patients with comorbidities like hypertension and diabetes, among others, have been consistently reported as belonging to risk groups for an unfavorable prognosis of the disease [13, 14]. The objective of this review is to discuss the most common causes of immunosuppression and its risks related to the infection with the new coronavirus.

## Method

A literature review was conducted to search the PubMed and Medline databases for articles published until June 12, 2020. The following keywords were used: "SARS-CoV-2", "COVID-19", "infection", "immunosuppression", immunodeficiency", "primary", "secondary", "comorbidities", "immunosuppressants", with the Boolean operator interposition "AND". We also retrieved the full text of the relevant cross-references from the research results. In addition, we accessed the currently available scientific literature and the recommendations on the websites of the WHO and U.S. Centers for Disease Control and Prevention (CDC).

## Primary Immunodeficiency

We know that the host's defense against any microorganism depends on the successful integration of all components of the immune system. As such, patients with abnormalities in the cell-mediated immunity typically develop pneumocystis pneumonia, disseminated fungal infections, mucocutaneous candidiasis, chronic or disseminated viral infections, and severe mycobacterial infections. Patients with antibody or complement defects are more often susceptible to pyogenic encapsulated bacterial infections. Patients with phagocytic defects develop bacterial and fungal infections of the skin and reticuloendothelial system [15].

Depending on the type of immune system defect, individuals diagnosed with some primary immunodeficiency (PID) may present a higher risk of infection with the new coronavirus and of a severe secondary respiratory disease. In principle, patients with severe combined immunodeficiency are most at risk, both before and after haematopoietic stem cell transplantation. Patients with PID who were recently subjected to transplantation and/or those who use immunosuppressive drugs for the treatment of autoimmune manifestations are considered at risk for more severe COVID-19 conditions.

However, it should be stressed that, in principle, patients with antibody production defects, the most common PID, do not have a higher risk of infection by the coronavirus or of developing a severe respiratory condition. However, they do present a higher risk of having a bacterial complication after the viral infection, as happens after many other viral infections. Patients who receive immunoglobulin are not more protected from COVID-19 than other individuals, since the antibodies they passively receive were collected from donors' plasma long before this pandemic began. Also, a result of this, the use of human immunoglobulin to transfer antibodies to treat severe COVID-19 in the general population is not yet recommended. Efforts are ongoing to isolate specific antibodies to the coronavirus from people who have recovered from this infection, but they are not yet in use. Patients with PID should therefore be cautious and follow the developments of COVID-19 in their region. Although immunoglobulin replacement therapy provides protection against a wide variety of infections, it is not yet known whether it provides immunity against the new coronavirus [16-20].

## Secondary Immunodeficiency

Secondary immunodeficiencies are those related to other diseases or conditions, or those occurring as a result of treatment for that particular condition. They commonly occur at age extremes, as a consequence of malnutrition, neoplasms and/or their treatment, the prevention and treatment of allograft rejection, the treatment of rheumatologic diseases, metabolic diseases, and other disorders. The degree of immunodeficiency associated with immunosuppressive agents used to treat a variety of conditions will depend on the underlying condition, the doses used and the combinations of agents, which can act synergistically [21-23].

## Malnutrition

Worldwide, protein-calorie malnutrition is the most common cause of immunodeficiency. Malnutrition can result from the limited access to food sources or chronic diseases that induce cachexia, such as neoplastic diseases. Diarrheas caused by infections and respiratory tract infections are common. T-cell production and function decreases proportionally to the severity of hypoproteinemia. Eventually, these immune responses decrease if malnutrition persists. Micronutrient deficiency (e.g., zinc and ascorbic acid) contributes to the increased susceptibility to infections through the weakening of the mucosal barrier, thus facilitating the invasion of pathogens. The correction of nutritional deficiencies usually results in the resolution of these immunological defects [24-27].

Emerging evidence has shown that COVID-19 is associated with negative outcomes in hypoalbuminemic patients. When considered together, the emerging literature on patients with COVID-19 indirectly highlights the relevance of nutrition in the possible determination of its outcomes. Advanced age and the presence of comorbid conditions are almost always associated with compromised nutritional status and sarcopenia, independently of the body mass index. Curiously, a high body mass index seems to be related to a poor prognosis in comorbid patients with COVID-19, which also points to a possible influence of sarcopenic obesity on outcomes. Furthermore, lymphopenia, which is a marker of malnutrition, is a negative prognostic factor in patients with COVID-19. Circulating albumin levels are usually not considered as a nutritional marker, but a recent study pointed out that a low albumin level predicts progression to acute respiratory distress syndrome (ARDS), suggesting that a low nutritional intake may contribute to the outcome of patients with COVID-19. Therefore, the timing of the nutritional intervention may be critical in this group of patients [28-31].

## Infection with the Human Immunodeficiency Virus (HIV)

More than 75 million people worldwide have been infected with the human immunodeficiency virus (HIV), and there are approximately 37 million people living with the infection today. Untreated HIV replication causes progressive loss of CD4 (+) T cells and a wide variety of immune abnormalities, leading to an increased risk of infectious and oncologic complications, especially when the CD4+ T lymphocyte count declines to less than 350 cells per microliter of blood [23]. HIV infection also contributes to cardiovascular disease, bone disease, kidney and liver dysfunction, and various other morbidities [32]. Due to the lack of generalized HIV testing and the costs and toxicity associated with antiretroviral drugs, the majority of the infected population is not receiving effective antiretroviral therapy, making this population susceptible to other infections [33, 34].

Early data from Wuhan, China, suggest that people living with HIV have not shown worse outcomes than others, confirming the World Health Organization's position that people with well-controlled HIV do not appear to be at high risk of infection with the new coronavirus or its serious complications. In addition, the authors suggest that antiretroviral treatment may confer a protective factor on this group of patients and that the compromised immunity may be the reason why patients with HIV / AIDS did not show inflammatory changes and clinical symptoms. In this sense, there is also support for the use of the association of

lopinavir and ritonavir in the prevention or treatment of COVID-19 [35, 36].

## Corticosteroids

Corticosteroids are used to treat a variety of diseases because of their anti-inflammatory and immunosuppressive properties. They have several effects on innate and acquired immunity. Corticosteroids impair neutrophil and monocyte traffic to inflammation sites, inhibit the phagocytic and microbicidal function of macrophages and neutrophils, inhibit the production of almost all known cytokines, sharply reduce the number of circulating dendritic and T cells, and affect the antigen presentation, impairing the effector functions of macrophages and dendritic cells. Their effects on the immune system are dose dependent. At lower doses, T lymphocyte numbers are slightly reduced (CD4 +> CD8 +) and at higher doses they result in the suppression of lymphocyte activation and in the production of antibodies by B cells. Corticosteroids, therefore, also predispose to infection in a dose-dependent manner. The risk of infection is also determined by the underlying disorder and the concomitant treatment with other immunosuppressive agents. Viral (especially herpesvirus), bacterial and fungal infections are more frequently found in patients treated with corticosteroids [37-43].

Patients taking super-physiological doses of glucocorticoids may be more susceptible to COVID-19 as a result of the immunosuppressive effects of steroids, the comorbidities of the underlying immunological disorders for which the steroids have been prescribed, or the immunomodulatory actions of other therapies prescribed in conjunction with glucocorticoids. The reversal of potential adrenal insufficiency as a cause of mortality with parenteral glucocorticoid therapy is relatively simple. In this context, it is important to identify the reason behind the use of glucocorticoids. Previous studies in patients with acute respiratory distress syndrome have shown that glucocorticoid therapy had no confirmed benefit on ventilation and mortality rates, but recent studies in patients with COVID-19 have shown that early administration of dexamethasone reduced mechanical ventilation time and mortality. However, the guidelines of the World Health Organization are still that glucocorticoids should not be prescribed without a precise indication [44-46].

## Chemotherapy

The main toxicities associated with chemotherapy that contribute to the infectious risk are myelosuppression and mucositis. Neutropenia is generally an inevitable consequence of the treatment of the malignancy and significantly increases the patient's risk of infection. This risk increases with the severity of the neutropenia - the highest risk of infection is associated with an absolute neutrophil count of <100 cells/mm$^3$. In addition, chemotherapy results in chemotactic and phagocyte defects in neutrophils, further increasing the risk of severe infection. The source of infection in most patients is the endogenous microbiota of the patient, which are able to translocate through mucocutaneous barriers secondary to the chemotherapy-induced mucosal lesions of the oral cavity and intestinal epithelium, and due to the presence of vascular and urinary catheters [47-51].

A variety of cytotoxic antineoplastic agents are used in combination to treat various malignant diseases. These agents are classified based on the mechanism by which they inhibit cell proliferation. They all cause myelosuppression and most cause some degree of mucositis.

Before starting chemotherapy, physicians should evaluate the evolving epidemic risk of COVID-19. Factors such as the severity of the illness, the potential benefit of treatment, the immunosuppression potential of the drug regimen, patient age, and comorbid conditions should be considered. In adjuvant or neoadjuvant scenarios, physicians should consider the pros and cons of all available treatment options. However, the discussion about postponing cancer treatment is controversial, since the definition of severity is changeable according to the type of cancer and often subjective, in addition to causing other emotional and psychological harm to patients. In Brazil, there are also legal implications with a risk of being accused of willful neglect of duty if the first treatment against cancer in the Public Health System is not started within 60 days from the signing of the pathological report. We should also consider prophylactic interventions once consistent data demonstrate antiviral effects against SARS-CoV-2 in clinical trials, both for patients and their families [52, 53].

**Antilymphocyte Antibody Therapies**

With the continuous progress in the field of molecular immunology, new treatments geared to specific immune cells or mediators are being developed for the treatment of autoimmune diseases, lymphohematologic neoplasms, and other conditions. Therapies with monoclonal antilymphocyte antibodies, or other immunological mediators such as cytokines, belong to the group of therapies known as biological immune response modulators.

These biological immune response modulators are designed to interfere with cytokine function, inhibit T-lymphocyte activation and B-lymphocyte proliferation in order to negatively regulate the pro-inflammatory responses underlying the clinical manifestations of such autoimmune diseases as rheumatologic diseases. The degree of immunosuppression is not as extensive as the one caused by traditional immunosuppressive drugs, but compromising the host's defenses, especially if combined with other immunosuppressive drugs, can result in severe infections. Randomized studies have shown that standard biological drugs combined with disease-modifying antirheumatic drugs like methotrexate are associated with more serious infections than traditional disease-modifying antirheumatic drugs [54-58].

Different viral agents are associated with an increased risk of a more serious progression of the disease and respiratory complications in immunocompromised patients. The recent outbreak of severe acute respiratory disease caused by the new coronavirus, responsible for a severe acute respiratory syndrome (SARS), is a source of concern for the management of patients using immunosuppressants. An Italian study following 320 patients using immunosuppressants found that four were confirmed cases of COVID-19 as identified by rhinopharyngeal swabs.

Another four patients reported symptoms that were highly suggestive of COVID-19. Five patients reported some contact with confirmed COVID-19 patients but remained asymptomatic until the end of the two-week observation period. All patients with infection symptoms temporarily suspended the use of the immunosuppressant at the onset of symptoms. None of the patients with a confirmed COVID-19 diagnosis or with a highly suggestive clinical picture developed severe respiratory complications or died. Only one patient, aged 65, had to be hospitalized. These findings are not surprising, since the severe respiratory complications caused by SARS-Cov-2 are caused by an intense inflammatory response and a cytokine storm perpetuated by the host's immune system. As such, pro-inflammatory interleukin antagonists could be a protective factor. The higher mortality of patients subjected to pharmacological immunosuppression could be due to other underlying comorbidities [59-62].

It is important to emphasize the requirement for continuous surveillance of patients receiving immunosuppressive drugs. In addition, these data can support medical professionals in treating and counseling their patients, avoiding the unsupported preventive withdrawal of immunosuppressants, which could lead to increased risk of relapses and morbidities, and in proposing immunomodulatory strategies for the treatment of COVID-19.

**Diabetes Mellitus**

A relationship between diabetes and infection has been clinically recognized. Infections, particularly influenza and pneumonia, are often common and more severe in older people with type 2 diabetes mellitus (DM2). However, evidence remains controversial as to whether diabetes itself actually increases susceptibility and affects the outcome of infections, or if the cardiovascular and renal comorbidities often associated with diabetes are the main factors involved [63].

Both type 1 and type 2 diabetes mellitus can increase an individual's risk of infection due to the reduced blood supply and denervation of peripheral tissues. Poorly controlled diabetes has been associated with the inhibition of the proliferative response of lymphocytes to different types of stimuli, as well as with impaired monocyte / macrophage and neutrophil functions. The neutrophils of diabetics have a reduction in the expression of adhesion molecules, causing damage in adhesion and chemotaxis. Phagocytosis seems normal, but bactericidal function is impaired. Abnormal delayed-type hypersensitivity reaction and complement activation dysfunction have also been described. These defects lead to predictable infection patterns, with a higher risk of lower respiratory tract, urinary tract, skin and mucosal infections, and a higher risk of recurrence. In addition, patients with diabetes usually have a significant reduction in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), which is associated with increased plasma glucose levels, further worsening any potential pulmonary involvement [64-69].

Diabetes and uncontrolled glycemia were reported as significant predictors of severity and death in patients infected with different viruses, including the pandemic influenza A in 2009 (H1N1), SARS-CoV in 2002, and MERS-CoV in 2012 [70-72]. In the current SARS-CoV-2 pandemic, most studies have shown that elderly patients with chronic diseases, including diabetes, were at higher risk of severe COVID-19 and mortality [73, 74]. Patients with diabetes may experience higher stress conditions, with higher release of hyperglycemic

hormones, e.g., glucocorticoids and catecholamines, leading to increased dysglycemias. It remains largely unknown how exactly the inflammatory and immune response occurs in these patients, and whether hyper or hypoglycemia can alter the virulence of SARS-CoV-2 or whether the virus itself interferes with insulin secretion or glycemic control. In addition, the impact of the usual drug treatment for diabetes on both the outcomes of COVID-19 and the therapeutic approaches of COVID-19 in regulating glucose, are not yet known [72, 75]. At this time, there are no differences between those with type 1 and type 2 diabetes, but people with type 2 diabetes are usually older and have other risk conditions, such as high blood pressure [76].

## Systemic Hypertension (SAH)

The phenotypic manifestations of hypertension involve the central (CNS) and autonomic nervous system (SNA), causing excessive sympathetic activation, kidneys with glomerular damage, a cardiovascular system with heart hypertrophy and vascular damage in the target organ. The immune system plays a significant role in these events, inducing inflammatory processes in all these systems. Studies have shown consistent associations between hypertension, pro-inflammatory cytokines and innate and adaptive immune system cells. The sympathetic nervous system, one of the main determinants of hypertension, innervates the bone marrow, spleen and peripheral lymphatic system and is pro-inflammatory. The neuroimmune synapse is bidirectional because cytokines can increase sympathetic activity through their action on the central nervous system, which in turn increases mobilization, migration and infiltration of immune cells in the terminal organs. The magnitude and extent of the pro-inflammatory immune response may vary in different hypertension mechanisms [77, 78].

Hypertension itself does not cause immunosuppression; on the contrary, the interaction between the sympathetic nervous system and the renin-angiotensin system works in a positive feedback regime with the immune system. However, pathological states that further damage these systems, such as surgical trauma and infections, can make patients with these conditions vulnerable to some complications.

The association of hypertension in patients with COVID-19 is not a surprise, given its high prevalence. However, some studies have observed a correlation between the infection by the new coronavirus and the renin-angiotensin system. The entry of the coronavirus into the cell is facilitated by the spike protein, which uses the angiotensin-converting enzyme 2 (ACE2) and its respective receptor. Studies have shown that the angiotensin II receptor is widely expressed, including in the heart, vascular endothelium, brain and kidneys, as well as in the main target cells of the coronavirus (and site of the dominant lesion), the alveolar epithelial cells of the lung. Under normal conditions, ACE2 levels are low and its functional role in the lungs appears to be relatively minimal, but they may be increased in certain clinical states, such as hypertension, especially in patients using ACE2 inhibitors or angiotensin II receptor blockers (ARBs). However, experimental animal models returned mixed findings regarding the effects of ACE2 inhibitors on ACE2 tissue levels or activity. Similarly, animal models had inconsistent findings regarding the effects of BRAs on ACE2, with some showing increased ACE2 levels in the tissue and others showing no effect.

There is still no evidence that hypertension is related to the outcomes of the new coronavirus, or that the use of ACE2 or BRAs inhibitors is either harmful or beneficial. The use of these agents should be maintained for blood pressure control, and they should not be discontinued, at least not based on current evidence [79-82].

## Elderly Patients

Among the elderly, some individuals have neoplasms and an excessive number of infections caused by viruses and bacteria, reflecting a decrease in immune defenses, especially in the cellular compartment. A decrease in delayed-type cutaneous hypersensitivity reactions and in the proliferative response of lymphocytes to mitogens can be demonstrated in this population of patients. This relative impairment of the immune response has been associated with the development of T cell oligoclonality, together with a limited capacity of the thymus to generate "naive" T cells and, therefore, reduced responses to new antigens. The oligoclonal expansion of CD8+ T cells begins in the seventh decade of life, resulting in the distortion of the T cell repertoire and an increased number of CD8+ T cells with differentiated memory. Similarly, an advanced age is associated with a restricted repertoire of B-cell diversity and, consequently, a limited response to vaccines. Innate immunity may be compromised in the elderly, with increased breakdown of skin and mucous barriers and slow healing processes caused by metabolic and endocrine changes associated with aging.

It is postulated that a decreased production of hematopoietic growth factors occurs in the elderly, resulting in a reduced ability to positively regulate the production and function of macrophages and neutrophils. The progress in understanding the immunological defect associated with aging is important to optimize the protective immunity against avoidable infectious diseases [8, 83]. These individuals are therefore more vulnerable to infections, especially when these immunological defects of senescence are combined with other environmental factors, such as malnutrition or the concomitant presence of chronic inflammation caused by autoimmunity, metabolic disorders, heart disease, cancers, combined with the treatments for these diseases. This makes this group of patients stay longer in intensive care units and, consequently, have a higher mortality [8, 83, 84].

To date, infections with the new coronavirus have been observed to be mild in most people. In the elderly, however, and especially those with comorbidities, it can evolve to pneumonia, acute respiratory distress syndrome (ARDS) and multiple organ dysfunction. These data make this group an important target in SARS-CoV-2 infection prevention strategies [85, 86].

## Chronic Renal Failure

Chronic renal failure (CRF) is associated with a significant increase in morbidity and mortality resulting from cardiovascular diseases and infections, representing 50% and 20% of the total mortality of these patients, respectively. It is possible that these two complications are linked to changes in the immune system that occur in CRF, since uremia is associated with a state of immune dysfunction characterized by immunodepression, which contributes to the high prevalence of infections in these patients, in addition to immunoactivation, which

results in inflammation that may contribute to cardiovascular disease [87].

The following immunological abnormalities have been reported: decreased phagocytic function of granulocytes and macrophages, reduced neutrophil death ability, lower antibody titers, and an inability to maintain adequate antibody titers over time after vaccination and T-cell mediated immunity. This reduction in lymphocytes may result from uremia-induced apoptosis [88, 89].

On the one hand, hypercytokinemia is a typical characteristic of uremia, probably due to the accumulation of pro-inflammatory cytokines as a consequence of decreased renal elimination and/or increased generation after induction by uremic toxins, oxidative stress, volume overload and comorbidities. On the other hand, uremia is associated with immunosuppression due to the impact of the uremic environment and a variety of associated disorders on immunocompetent cells [87, 90].

Chronic renal disease is one of the most prevalent underlying diseases among hospitalized patients with COVID-19 and it seems to be associated with more severe forms of the disease. In addition to a bipolar immune dysfunction, these patients, most of them elderly, have a high prevalence of coexisting diseases like diabetes, hypertension, and lung disease, as well as being submitted to immunosuppressive treatments for their underlying disease; these factors are known to imply a worse prognosis for COVID-19. This group should therefore also be an important target in strategies to prevent SARS-CoV-2 infection [91, 92].

### Liver Failure

Infections are a major complication and one of the leading causes of death in advanced liver disease. The most common infections are bacterial in nature and include spontaneous bacterial peritonitis, pneumonia, bacteremia, urinary tract infections and endocarditis. Many immune abnormalities have been detected in patients with cirrhosis. Low levels of complement and decompensated alcoholic cirrhosis have been associated with an increased risk of infection and mortality. The liver is the primary site of C3 synthesis. As such, the opsonization of bacteria may be impaired in the presence of severe liver failure. The reticuloendothelial system is an important filtration system for blood-borne pathogens. However, due to the activation and mobilization of impaired macrophages in the presence of cirrhosis, this filtering may be impaired. In addition, the portosystemic deviation that occurs in cirrhosis allows the portal blood to reach the systemic circulation without passing through the reticuloendothelial system. This is a suspected etiology of some bacteremia in patients with cirrhosis [93-95].

Patients with cirrhosis often demonstrate anergy and do not respond to vaccination, suggesting delayed-type hypersensitivity and other impaired T-cell dependent functions. This decrease in lymphocyte responsiveness may be due to the effects of the hepatitis C virus on dendritic cells, the antigen-presenting cells essential for the development of an effective immune response. The hepatitis C virus binds to dendritic cells, replicates to a low level in these cells and impairs their maturation. The result is an impaired ability of dendritic cells to stimulate alloreactive T Cell. Similar findings have been reported in patients with chronic hepatitis B virus infection [96-100].

It has been proposed that COVID-19 causes direct liver damage through viral hepatitis, but the liver function impairment appears to be mild. Liver function tests for patients at different stages of the disease point to no evidence that its severe form is associated with increased liver function impairment. What occurs in severe COVID-19 is a liver dysfunction that progresses with increased activation of the coagulation and fibrinolytic pathways, relatively depressed platelet count, increase of the neutrophil count and the neutrophil/lymphocyte ratio and high levels of ferritin. Although these markers are seen as non-specific markers of inflammation, they are believed to fit the paradigm of the disease's severity, coinciding with a failure of innate immune regulation, and which may be worsened by a prior underlying dysfunction. Physicians should therefore not be complacent with the risks of COVID-19 in patients with chronic liver disease and cirrhosis, because these patients have poor immune function and may have worse outcomes for acute respiratory distress syndrome than the rest of the critically ill population [73, 74, 101].

### Organ Transplantation

Immunosuppressive regimens that suppress T-cell immune function are employed to prevent organ rejection and maintain allograft function in the long term. The immunosuppressive regimens employed in various types of organ transplantation are not so different, with cyclosporine or tacrolimus providing the cornerstone of anti-rejection maintenance treatment, along with an antimetabolite, mycophenolate mofetil, possibly a low-dose corticosteroid, azathioprine, monoclonal antibodies against B lymphocytes, among others. As such, the types, pattern and timing of infections found are relatively predictable in the various forms of organ transplantation. The risk of infection is determined primarily by the intensity of exposure to possible pathogens and by the patient's immune suppression status, which depends on the dose, duration and time sequence of the immunosuppressive agents and the presence or absence of infections with immunomodulating viruses (CMV, EBV, hepatitis B or C, and HIV), in addition to other comorbidities [12, 102].

In studies to date, cancer patients are more likely to present the most severe form of COVID-19, despite the evidence that many are elderly and have comorbidities, such as lung disease secondary to smoking, cardiovascular disorders, among others. Unfortunately, a more detailed description of the disease in transplant recipients is not yet available. However, it has been observed that the lymphocyte count was lower in those who needed ICU care and in those who perished. It is not possible to say whether lymphopenia was a manifestation of a more serious form of the disease or if it predisposed to a serious disease; many transplant recipients have medication-induced lymphopenia. For this reason, special attention should be paid to the transplantation of patients with a suspected or confirmed COVID-19 infection, especially lymphopenic patients. They may require special care, such as preventive hospital admission [103, 104].

### Surgical Trauma

The anesthetic-surgical act causes immunosuppression due to the excessive inflammatory and catecholaminergic response followed by a dramatic depression of cell-mediated immunity. The number and function of defense cells drops in the perioperative period and the extent

and duration of this drop is related to the magnitude of the surgery [105, 106].

Regarding the differentiation of lymphocytes into T and B cells, it seems that T lymphocytes are the most affected in the anesthetic-surgical process. In addition to a decrease in the number of T lymphocytes, a change occurs in the balance between immunosuppressive regulator T lymphocytes, immunity promoting auxiliary T cells and cytotoxic T cells. This change results in a predominance of regulatory T cells in the postoperative period, for up to two weeks postoperatively. This impact seems to be proportional to the extent of the surgery, with laparoscopic surgery having a less pronounced effect than conventional open surgery [106-108].

The numbers and functions of Natural Killer (NK) cells are also affected by surgery and this effect is less pronounced in laparoscopic surgery. It is important to note that the activation and cytotoxicity of NK cells increases after the administration of premedication to patients and with the induction of anaesthesia. However, this is followed by a rapid and significant decrease of activity in the postoperative period. The suppression of NK cell cytotoxicity may persist for up to ten days and this once again seems to be related to the size of the surgery and modulated by the type of anaesthesia. Some studies point to the deleterious effects of opioids and inhaled anesthetics, and the protective effects of propofol, regional and systemic local anesthetics, alpha-2 adrenergic agonists and beta-blockers [107, 109-111].

More recent studies also suggest that the immunological effects of the surgical-anesthetic procedure have immediate and medium-term consequences for patients. Perioperative immunosuppression may result in more immediate consequences for patients, including delayed wound healing and other septic events, such as respiratory infections [112].

The epidemic of the new coronavirus has raised another concern for the perioperative setting, since an asymptomatic carrier patient may need some type of surgery. Two recent studies that retrospectively analysed data from 75 patients undergoing elective surgeries during the incubation period, observed that all patients rapidly developed viral pneumonia in the postoperative period. The ICU admission rate was approximately 40% and mortality ranged from 19.5 to 20.5% [113, 114]. Therefore, the current recommendation is that elective surgeries for patients with a suspected or confirmed COVID-19 diagnosis be rescheduled.

**Conclusion**

We can conclude that:
i   The clinical management of COVID-19 is a global medical challenge.
ii  Most patients with impaired immune function seem to be at greater risk of more serious complications of the disease and therefore deserve attention in prevention strategies.
iii Immunomodulatory strategies may be the key to treating this disease, which goes far beyond a viral infection.

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