The immune response in COVID-19 and its outcomes: contribution of risk factors

A resposta imunológica em COVID-19 e seus resultados: contribuição dos fatores de risco

La respuesta inmune en COVID-19 y sus resultados: contribución de los factores de riesgo

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ABSTRACT  
The COVID-19 pandemic, caused by SARS-CoV-2, has resulted in a global health crisis that has highlighted the importance of understanding the host immune response to viral infections. Although the immune system plays a crucial role in controlling viral replication and preventing serious disease, dysregulated immune responses can lead to severe tissue damage and multiple organ failure, as seen in severe cases of COVID-19. In this review, we discuss current knowledge of the immune response to SARS-CoV-2, focusing on the balance between protective and harmful immune responses. We describe the early innate immune response, including the role of interferons and inflammasomes, as well as the adaptive immune response. Furthermore, we discuss the mechanisms of immune dysregulation observed in severe cases of COVID-19, such as cytokine storm and autoimmunity. Finally, we highlight the importance of ongoing research into the host immune response to SARS-CoV-2 in developing effective treatments and vaccines. This article discusses the effects of the immune response to COVID-19 and how risk factors may impact these outcomes.

Keywords: SARS-CoV-2, COVID-19, immune system, immunomodulation, risk factors, pathogenesis.

RESUMO  
A pandemia de COVID-19, causada pelo SARS-CoV-2, resultou numa crise de saúde global que destacou a importância de compreender a resposta imunológica do hospedeiro às infecções virais. Embora o sistema imunológico desempenhe um papel crucial no controlo da replicação viral e na prevenção de doenças graves, as respostas imunes desreguladas podem levar a danos
teciduais graves e à falência de múltiplos órgãos, como observado em casos graves de COVID-19. Nesta revisão, discutimos o conhecimento atual da resposta imune ao SARS-CoV-2, focando no equilíbrio entre as respostas imunes protetoras e prejudiciais. Descrevemos a resposta imune inata precoce, incluindo o papel dos interferons e inflamasomas, bem como a resposta imune adaptativa. Além disso, discutimos os mecanismos de desregulação imunológica observados em casos graves de COVID-19, como tempestade de citocinas e autoimunidade. Finalmente, destacamos a importância da investigação em curso sobre a resposta imune do hospedeiro ao SARS-CoV-2 no desenvolvimento de tratamentos e vacinas eficazes. Este artigo discute os efeitos da resposta imunológica à COVID-19 e como os fatores de risco podem impactar esses resultados.

Palavras-chave: SARS-CoV-2, COVID-19, sistema imunológico, imunomodulação, fatores de risco, patogênese.

1 INTRODUCTION

Infectious diseases represent a major threat to global health, causing considerable economic losses. Therefore, it is essential that they are controlled (Jones et al., 2008). The immune system is vitally important in controlling...
infectious processes involving innate and adaptive immune responses (Janeway et al., 2001). Generally, after the start of an infectious process, microorganisms are detected and quickly annihilated by the mechanisms of innate immunity. If these mechanisms are not efficient enough to contain the infection, the adaptive immune response is initiated to control the pathogen and restore homeostasis (Marshall et al., 2018).

In 2019, in China, a new coronavirus capable of infecting humans emerged: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (HUANG et al., 2020a). SARS-CoV-2 spread quickly across all continents, characterizing a pandemic (reviewed by LI et al., 2021). Currently, as of May 3, 2024, there have been more than 775 million confirmed cases and more than 7 million deaths reported globally in 235 countries and territories (WORLD HEALTH ORGANIZATION, 2024b). However, a study published in The Lancet magazine, still in April 2022, estimated that around 18.2 million people died as a result of the COVID-19 pandemic (measured by excess mortality) between the start of the pandemic (1 January 2020) and at the end of December 2021, about 3 times more deaths than the officially reported number of deaths (WANG et al., 2022).

Although it has a high degree of spread, COVID-19 appears to be a more benign disease than previous coronaviruses (SARS-CoV and MERS-CoV). About 81% of people infected with SARS-CoV-2 appear to be asymptomatic or have mild and moderate forms of the disease and recover without the need for medical treatment. Approximately 14% of those infected develop serious illness, requiring hospitalization, and 5% present critical clinical manifestations, requiring hospitalization in intensive care units (ICU). Elderly people and people of all ages with pre-existing health problems (such as hypertension, heart disease, lung disease, obesity and/or diabetes) appear to develop the serious condition more frequently than others (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2020) who do not have comorbidities. These pre-existing health conditions appear to be associated with intrinsic inflammatory processes. Therefore, understanding how the immune system reacts to SARS-CoV-2 infection seems essential to understanding and treating the entire pathogenesis.
caused by this infection.

In this review we discuss some aspects related to how the immune response against SARS-CoV-2 is orchestrated to result in a cure or worsening of the disease, as well as intervention strategies to modulate the immune response.

2 THE SARS-COV-2 CORONAVIRUS

Coronaviruses (CoVs) are a group of enveloped, positive-sensed, single-stranded RNA viruses (Fig.1).

![Figure 1 – Structure of the SARS-CoV-2 virus.](image)

SARS-CoV-2 (Coronaviridae family) is an enveloped, positive-sense single-stranded RNA virus. The virion has a nucleocapsid containing the genomic RNA and the nucleocapsid protein (N), which is covered by the phospholipid bilayer including the spike glycoprotein (S), the membrane protein (M), and the envelope protein (E). The spike protein allows the virus to enter the host cell by binding to the cell's receptor and membrane fusion. The nucleocapsid protein, on the other hand, regulates the viral replication process.

Due to processes of genetic recombination and mutation, coronaviruses have an excellent ability to adapt to new hosts. These viruses need the RNA-dependent RNA polymerase 5 (RdRp) enzyme to replicate their genome. The
error rate of this enzyme is about 1,000,000 mutations/site/replication, promoting point mutations. Emerging mutations in SARS-CoV-2 have generated worrying variants, especially in relation to virus transmission, pathogenicity and neutralization by natural or vaccine-mediated immunity (SINGH et al., 2021; WORLD HEALTH ORGANIZATION, 2020). Most viral mutations have little or no impact on the ability of the virus to cause infection and disease. But, depending on where the changes are located in the genetic material of the virus, they can affect the properties of a virus, such as transmission or severity. According to aspects of transmissibility and health risk (immunity and severity of infection), the World Health Organization classifies SARS-CoV-2 variants into three distinct categories: variant of concern (VOC), variant of interest (VOI), or variant under monitoring (VUM). VOCs are variants that present changes that can make the virus more transmissible and/or more virulent (Table 1), in addition to interfering with the effectiveness of vaccines, drugs, and diagnostic methods (WORLD HEALTH ORGANIZATION, 2024a).

Table 1 – Anteriorly designated variants of concern (VOCs)

<table>
<thead>
<tr>
<th>WHO LABEL</th>
<th>PANGO LINEAGE*</th>
<th>GISAID CLADE</th>
<th>NEXTSTRAIN CLADE</th>
<th>ADDITIONAL AMINO ACID CHANGES MONITORED°</th>
<th>EARLIEST DOCUMENTED SAMPLES</th>
<th>DATE OF DESIGNATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPHA</td>
<td>B.1.1.7</td>
<td>GRY</td>
<td>20I (V1)</td>
<td>+S:484K +S:452R</td>
<td>UNITED KINGDOM, SEP-2020</td>
<td>18-DEC-2020</td>
</tr>
<tr>
<td>BETA</td>
<td>B.1.351</td>
<td>GH/501Y.V2</td>
<td>20H (V2)</td>
<td>+S:L18F</td>
<td>SOUTH AFRICA, MAY-2020</td>
<td>18-DEC-2020</td>
</tr>
<tr>
<td>GAMMA</td>
<td>P.1</td>
<td>GR/501Y.V3</td>
<td>20J (V3)</td>
<td>+S:681H</td>
<td>BRAZIL, NOV-2020</td>
<td>11-JAN-2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VOC: 11-MAY-2021</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VOC: 26-NOV-2021</td>
</tr>
</tbody>
</table>

* Includes all descendent lineages. See the cov-lineages.org and the Pango network websites for further details.

The variant of concern Omicron promoted the biggest wave of infection seen since the beginning of the pandemic. The number of confirmed cases until mid-March 2022 was approximately 172 million people in the world, mostly caused by the Omicron variant. That number was nearly 84 million in 2020 and surpassed 203 million in 2021 (WORLDMETERS, 2021). Thus, the Omicron infection, in just 2 and a half months, was higher than in the whole year of 2020 and corresponds to more than 84% of the number of confirmed cases until March 2021.

Since February 2022 the Omicron lineage account for ever 98% of the available sequences, showing their sovereignty in the mondial prevalence of SARS-CoV-2 (WORLD HEALTH ORGANIZATION, 2023).

Following the World Health Organization, the currently circulating variants of interest (VOIs) are XBB.1.5, XBB.1.16, EG.5, BA.2.86 and JN (WORLD HEALTH ORGANIZATION, 2024a).

3 THE IMMUNE RESPONSE TO SARS-CoV-2 AND VIRUS PATHOGENESIS:

The first step in the innate immune response to a viral infection is the pathogen recognition through Pattern Recognition Receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) (Ruenjaiman; Hirankarn; Palaga, 2021). The signaling of these receptors in innate immune cells in response to PAMPs from pathogens results in the production of inflammatory cytokines, interferons and chemokines and also in the induction of cell death, in order to carry out viral clearance of infected cells (reviewed by Diamond; Kanneganti, 2022). So far, several PRRs that respond to SARS-CoV-2 have been identified, including Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and inflammasomes, which activate their signaling pathways. Activation of TLR is a common mechanism by which many viruses activate the innate immune system (reviewed by Diamond; Kanneganti, 2022). Furthermore, TLRs show distinct expression in different populations of innate immune cells in
addition to different localizations, such as surface, cytosolic and endosomal (LIU; ZHAO, 2007). Following binding to TLRs, nuclear factor NF-κB, mitogen-activated protein kinases (MAPKs) and interferon (IFN) regulatory factors (IRFs) are activated (Kawai; Akira, 2007). When these molecules are translocated to the cell nucleus, transcriptional activation of several pro-inflammatory cytokines occurs, such as tumor necrosis factor (TNF), IL-6 and IL-1β (reviewed by Diamond; Kanneganti, 2022). Experimental studies indicate that recognition of SARS-CoV-2 occurs mainly by TLR2, although it may also involve the activation of other TLRs (1, 3, 4 and 6) (Choudhury; Mukherjee, 2020; Zheng et al., 2021).

The activation of TLRs (1,2,4,6) via the MyD88 adapter molecule culminates in the activation of NF-κB and IRFs, which are translocated to the cell nucleus, promoting the transcriptional activation of several pro-inflammatory cytokines (Fig. 2). Besides, the transcription of genes that encode other sensors of the innate immune system, for example the NLRP3, the production of IFNs and IFN-stimulated genes (ISGs) also occur (Akira; Takeda, 2004). RLRs, such as MDA5 and RIG-I, can recognize the single-stranded RNA of SARS-CoV-2 within the cell. Once activated by post-translational modifications, RIG-I and MDA5 translocate to the mitochondria, where they bind with the mitochondrial antiviral signaling adapter protein (MAVS) to create a signalosome - a microorganelle that separates intracellular signaling (horner et al., 2011; loo; gale, 2011). The assembly of this complex enables it to move into the nucleus and activate the transcription of genes that produce type I and III IFN (Stark; Darnell, 2012; Wack; Terczyńska-Dyla; Hartmann, 2015). The production and release of IFNs leads to subsequent signaling through IFN receptors (IFNAR1 and/or IFNAR2 for type I IFNs, IFNLR1 and/or IL10Rβ for type III IFNs) in an autocrine and paracrine manner, stimulating the expression of different genes with various antiviral functions, which include inhibition of viral protein synthesis, viral assembly and degradation of RNA viral. Furthermore, NLRs also respond to SARS-CoV-2 infection by inducing the production of type I IFNs and pro-inflammatory cytokines (Christgen; Kanneganti, 2020; Kayagaki et al., 2021) (Fig. 2).
When successful, this response strongly restricts virus replication and cell-to-cell spread of infection (Kell; Gale, 2015). However, many, if not all, viruses have strategies to escape the innate immune response, which can cause disease (Chiang; Davis; Gack, 2014), including SARS-CoV-2 itself. This virus was able to suppress the immune responses of airway epithelial cells more effectively than previous variants, increasing the likelihood of successful transmission (Thorne et al., 2022). In some coronaviruses, such as SARS-CoV, the N protein has an immune system escape function and acts as an antagonist of the host-produced interferon (CUI et al., 2015). Thus, although they are sensitive to these cytokines, IFN-α and IFN-β, SARS-CoV and other coronaviruses remain highly pathogenic (Kopecky-Bromberg et al., 2007; Lu et al., 2011; Spiegel et al., 2005). Some experimental evidence obtained in primary lines of pulmonary epithelium and human alveolar cells suggests this suppressive effect of interferon production also in SARS-CoV-2 (Shuai et al., 2020).
Virus binding to PRR can initiate a signaling cascade that induces cytokine production. Substantial experimental evidence strongly suggests activation of TLR2 by SARS-CoV-2. However, activation of TLR1, 3, 4 and 6 has only been suggested bioinformatically and through associative studies. The activation of TLR (1,2,4,6) via the adapter molecule MyD88 culminates in the activation of the nuclear factor NF-κB and interferon regulatory factors (IRFs), which are translocated to the cell nucleus, promoting transcriptional activation of several
pro-inflammatory cytokines (TNF, IL-6 and IL-1β). Transcription of genes that encode other sensors of the innate immune system, such as NLRP3, occurs, promoting the production of IFNs and IFN-stimulated genes (ISGs). Activation of NLRP3, which is one of the inflammasome sensors, is also triggered in response to PAMPs and DAMPs, leading to caspase-1 activation, IL-1β and IL-18 production and release, and gasdermin D cleavage (GSDM-D). GSDM-D forms pores in the plasma membrane, leading to cell membrane rupture and pyroptotic cell death. The single-stranded RNA of SARS-CoV-2 can also be detected by RLRs within the cell, including MDA5 and RIG-I, which move to the mitochondria, where they interact with the mitochondrial antiviral signaling adapter protein (MAVS) to form a signalosome. Transcription of genes encoding type I and III IFNs occurs. The TLR3 and TLR4 signaling pathway remains inconclusive in SARS-CoV-2 infection, but they can signal, via the TRIF adapter molecule, to activate IRF3 inducing, which, in turn, induce the expression of type I and type III IFNs.

In the cellular aspect, macrophages and dendritic cells (DC) are essential for the immune response to viruses, as they are specialized cells in the capture and presentation of antigens. Dendritic cells are considered a continuum between innate and adaptive immunity, as they are attracted and activated by components of the innate immune response, but also enable the sensitization of T lymphocytes of the adaptive immune response (Cruvinel et al., 2010). There are two main types of dendritic cells: conventional or myeloid, and plasmacytoid dendritic cells. The latter have a large capacity to produce IFN-α and IFN-β and are especially important in innate antiviral responses (Pérez-Gómez et al., 2021). Macrophages, in turn, are immune cells that also mediate innate and adaptive immunity, in addition to participating in physiological and pathological processes, being capable of causing tissue injury or repair. For didactic purposes, they can differentiate into two functional subtypes: i) classically activated macrophages (M1), usually in response to pro-inflammatory cytokines such as IFN-γ, TNF, IL-1, IL-6, IL-12, IL-23, chemokine CCL8 and monocyte chemotactic protein 1 (MCP-1), and ii) alternatively activated macrophages (M2), which occur in
response to cytokines such as IL-4, IL-13, IL-10 and transforming growth factor beta (TGF-\(\beta\)). M1 macrophages actively participate in inflammatory processes, while M2 macrophages reduce inflammation by suppressing effector T cells (Kosyreva et al., 2021). In cases of infection, macrophages detect PAMPs or DAMPs through a range of PRRs, are classically activated, and respond by releasing inflammatory molecules. Macrophages are essentials for containing the infections and, when the initial innate immune response fails to abrogate the infection, for triggering an adaptive immune response. This response is an important determinant of the clinical outcome after infection with SARS-CoV-2 and of the effectiveness of vaccines (Moss, 2022).

The cellular and humoral immune response is part of the adaptive immune response. They are developed by two major lymphocyte types: T cells and B cells (antibody producing cells) (Srinivasan et al., 2013). Both arms of adaptive immunity can be important in protection against viral infections. In the cellular immune response, T cells can be subdivided into cytotoxic T cells (CD8+ T lymphocytes) and helper T cells (CD4+ T lymphocytes which later differentiate into various subpopulations (Manni; Robinson; Alcorn, 2014). TCD8+ lymphocytes have a cytotoxic function and destroy the infected cells by releasing granzimes and perforins. CD4+ T cells secrete cytokines to stimulate plasmocytes (B lymphocytes) to produce specific antibodies against the SARS-CoV-2 by activating T-dependent mechanism, triggering a humoral response. These antibodies can play an important role in combating viral infections by binding to antigens on the surface of extracellular viral particles, preventing the binding and invasion of other cells (neutralizing antibodies) (Fig. 3). Alternatively, antibodies can be adjuvants in the mechanism of antibody-dependent cellular cytotoxicity, by binding to infected cells, allowing the action of NK cells (Duque; Descoteaux, 2014; Machado et al., 2004).

From the moment the SARS-CoV-2 virus penetrates the host's cells through the ACE2 recognition mechanisms (Fig. 3), the viruses begin to use the cellular machinery for its own replication. In the case of SARS-CoV-2, its viral peptides are captured by the MHC class I of infected cells and presented for
recognition by CD8+ T lymphocytes (Jansen et al., 2019; Mistry et al., 2022), which are activated and begin to divide, resulting in effector T lymphocytes and memory T lymphocytes, specific for the same viral antigen. Thus, effector CD8+ T lymphocytes are able to destroy cells infected by SARS-CoV-2 (Azkur et al., 2020). During acute infection, CD4+ T lymphocytes are able to differentiate into effector helper cells, mainly of the Th1 type, with the ability to guide B lymphocytes, support CD8+ T lymphocytes, potentiate the innate immune response, in addition to exerting direct antiviral activities and promote tissue recovery (Fig. 3). IFN-γ is mostly produced by natural killer (NK) cells, but it can be produced by other specialized cells of the immune system, such as T cells, cytotoxic lymphocytes and antigen presenting cells (monocytes/macrophages and dendritic cells). Its production is controlled by positive (IL-12 and IL-18 interleukins) and negative (IL-4, IL-10, TGF-β) regulators secreted by cells (Fig. 3). Thus, in the healthy immune response, the modulation of the inflammatory response is provided by the production of anti-inflammatory cytokines produced by macrophages with M2 profile (IL-10) and by Treg cells (IL-10 and TGF-β). In this way, the inflammation caused during SARS-CoV-2 infection, which results in controlling the infection and preventing the spread of the virus, is modulated and causes little tissue damage.

On the other hand, in some cases the immune response is not adequately modulated and does not resolve the SARS-CoV-2 infection, causing major tissue and systemic damage. When infected lung epithelial and alveolar endothelial cells may enter into apoptosis or promote the activation of the inflammasome (Fig.4), an oligomeric protein complex that initiates an inflammatory cascade through the activation of caspase 1 (MARTINON; BURNS; TSCHOPP, 2002). Then, pro-IL-1β is released, which is cleaved by caspase-1, forming active mature IL-1β, culminating in death from the infected cell by pyroptosis, with the release of DAMPs in the extracellular medium (CONTI et al., 2020) (Fig. 4), including ATP, nucleic acids and ASC oligomers, besides the viral antigens (PAMPs) (YANG et al., 2020). The recognition of DAMPs and PAMPs by TLR of neighboring non-infected cells, such as epithelial cells, endothelial cells and
alveolar macrophages, promotes, again, the formation of inflammasome and the generation of pro-inflammatory cytokines and chemokines. Under the action of cytokines and chemokines, macrophages, neutrophils, dendritic cells and lymphocytes (T [CD4+ and CD8+], B and NK cells) go to the site of infection, promoting further inflammation and establishing a pro-inflammatory feedback loop (TAY et al., 2020) (Fig. 4). Decreased regulatory T cells and hyperactivation can result in the exhaustion of immune cells, where they are unable to respond by producing their pattern of cytokines. The high level of IL-1β could activate (by the autocrine or paracrine way) immune cells that express IL-1R, such as macrophage and NK cells, amplifying the inflammatory process, where macrophages would secrete IL-6, IL-18, TNF and IL-1β and NK cells would secrete IFN-γ (Fig. 4). However, when this response is dysregulated or exacerbated, it contributes to severe clinical signs (Knoll; Schultze; Schulte-Schrepping, 2021). Systemic complications associated with SARS-CoV-2 include severe acute respiratory syndrome (SARS), disseminated intravascular coagulation syndrome, oedema, and pneumonia. These are effects of massive macrophage activation, which is extremely harmful to the host and can lead to Macrophage Activation Syndrome (MAS) (Knoll; Schultze; Schulte-Schrepping, 2021; Kosyreva et al., 2021). There is evidence that the pathogenesis of SARS depends on macrophages, including resident alveolar macrophages and transient monocytes/macrophages recruited from the blood (Johnston et al., 2012; Kosyreva et al., 2021).

Although the activation of the immune system is essential for an infection to be abrogated, an excessive interaction between viruses and cells, along with an imbalance of this response or even a lack of adequate regulation of it can promote an exacerbation of the immune response, generating permanent damage or long-term damages as seen by Gomes and colleagues (2023) (Fig. 4 and 5). In this case, the immune system can change from hero to villain, because an exacerbated inflammatory process can do more harm than cure. This is one of the main explanations for the worsening of the SARS-CoV-2 infection, where the lack of control of the inflammatory response promotes a syndrome of cytokine
storm, culminating in hyper-inflammation, sepsis or multisystemic inflammation syndrome associated with COVID-19 in children or in adults.

Infection of pulmonary epithelial cells by SARS-CoV-2 can promote pyroptosis in these cells (Yang et al., 2020). The same process can occur in the endothelial cells of the alveolar capillaries, also triggering pyroptosis with consequent release of DAMPs and PAMPs and downstream recruitment of inflammatory cells (Teuwen et al., 2020) (Fig. 4). Furthermore, endothelial cells invasion causes changes in the integrity of the vascular barrier, triggering a pro-coagulative state, inducing vascular inflammation (endothelitis) (Fig. 6), mediating, more once, inflammatory cell infiltration (Pober; Sessa, 2007; Varga et al., 2020) and vascular leakage, flooding the alveolus with liquid, a registered trademark of the SARS (Teuwen et al., 2020) (Fig. 4). Varga et al. (2020) showed the presence of viral elements in endothelial cells and the accumulation of inflammatory cells inside the vessels. These data suggest that SARS-CoV-2 infection can induce endothelitis as a consequence of the presence of the virus and of the involvement of the host’s immune response. In addition, the occurrence of apoptosis and, especially, of pyroptosis, helps to promote damage to the endothelium of the alveolar capillaries of patients with COVID-19. The injury promoted in the endothelium allows the exposure of the capillary basement membrane, triggering an uncontrolled coagulation process. There is also the recruitment of additional clotting factors and platelets, which help to form clots (Varga et al., 2020). These clots degrade in the D-dimer (a product of fibrin degradation), causing very high levels of this biomarker in the serum of infected patients (LEI et al., 2020; Matacic, 2020; Zhou et al., 2020) (Fig. 6). D-dimer may be involved in episodes of pulmonary thromboembolism (Mcgonagle et al., 2020; Perrier et al., 1997) or thromboembolism in several organs, promoting the blockage of the blood supply to vital organs, when endothelitis also occurs in these areas (Becker, 2020) (Fig. 6). These changes suggest hyperactivity of the coagulation system participating in organ failure and even death.
Figure 3– Resolutive response to SARS-CoV-2.

1 - After the virus enters the alveolar epithelial cells, type I interferons are released, which prevent the virus spreading by stimulating virus phagocytosis by macrophages and dendritic cells, and destruction of virus-infected cells by NK lymphocytes. 2 - Activation of the inflammasome, with the release of large amounts of IL-1β activates macrophages to produce IL-6, IL-18, IL-1β and TNF, and NK cells to produce IFN-γ. NK cells release granzyme and perforin, killing the virus-infected cells. 3 - Dendritic cells produce IL-12 and present viral Ag to Th0 lymphocytes, which differentiate into IFN-γ-producing Th1 (IFN type II). 4 -IFN-γ induces activation of cytotoxic TCD8 and macrophage M1, and production of neutralizing antibodies by plasma cells. The cytotoxic TCD8 kills infected cells when it recognizes viral antigens presented on class I MHC in the membrane. IFN-γ provided by Th1 cells promotes the production of virus-specific neutralizing antibodies by activating T-dependent B cells. Production of IL-12 and TNF by M1 amplifies Th1 response. 5 - The modulation of the inflammatory response is provided by the production of anti-inflammatory cytokines produced by macrophages with an M2 profile (IL-10) and by Treg cells (IL-10 and TGF-β). In the healthy immune response, the initial inflammation caused by SARS-CoV-2 infection attracts multiple cells including virus-specific T cells to the site of infection, which kill infected cells before the virus spreads and cause minimal damage to the lungs. 6 - Stimulated cells form memory cells, which will be activated in new contact with the virus.
Figure 4 – Non-resolving response to SARS-CoV-2.

1 - Infected lung epithelial cells or alveolar capillary endothelial cells die by pyroptosis, releasing DAMPs and PAMPs, promoting downstream recruitment of inflammatory cells, and the production of type I interferons (α and β) is impaired or insufficient to prevent virus spreading. 2 - Activation of the inflammasome releases large amounts of IL-1β and IL-18, which promote the differentiation of cells with a pro-inflammatory profile, such as macrophages M1, NK, and Th17 lymphocytes. 3 - Dendritic cells produce IL-12, that stimulates the differentiation of Th0 lymphocytes into IFN-γ-producing Th1 lymphocytes and the pro-inflammatory environment helps to amplify and maintain this cell type. The intense production of IFN-γ not only promotes the activation of cytotoxic CD8 T cells that kill virus-infected cells and the induction of virus neutralizing antibody synthesis, but also induces a high activation of M1 macrophages, thus increasing the levels of TNF, IL-1β and IL-12. The exacerbated response to viral infection leads to an overproduction of inflammatory cytokines, called “cytokine storm”. 4 - Decreased regulatory T cells and hyperactivation can result in exhaustion of immune cells, where, even when in large amounts, they are unable to respond by producing their pattern of cytokines. 5 - Activated neutrophils release histones and proteins derived from intracellular granules, forming neutrophil extracellular trap (NET). This NETs formation process is called NETosis and plays a role in controlling pathogens.

Some evidence suggests that neutrophils and the imbalance between the formation and degradation of the neutrophil extracellular trap (NET) may play a central role in the pathophysiology of immunothrombosis, coagulopathy, inflammation and damage to organs that characterize severe cases of COVID-
NETs are structures composed of DNA, histones and proteins derived from intracellular granules released by activated neutrophils (Fig. 6). This NETs formation process is called NETosis and plays a role in controlling pathogens (Fig. 4), but it also has a detrimental effect on cardiovascular and pulmonary diseases (Chang et al., 2006). These findings suggest the possibility of interference from these NETs in the COVID-19 pathogenesis.

Intravascular NETosis in COVID-19 infection may play a role in complications of the vasculature, where thrombotic disease can cause organ damage (Fig. 4, 5, 6). Studies have shown high levels of NET markers, such as cell-free DNA, myeloperoxidase (MPO)-DNA and citrullinated histone H3 (Cit-H3) in serum samples from patients with COVID-19 severe, but not in healthy controls (Li; Bai; Hashikawa, 2020). Arcanjo and colleagues (2020) showed, for the first time, that SARS-CoV-2 is able to activate NETosis in human neutrophils. Their findings indicated that this process is associated with increased levels of intracellular Reactive Oxygen Species (ROS) in neutrophils. It is possible that the activation of NET in the sera from COVID-19 severe patients is due to the presence of active viruses in their blood (Beniac et al., 2006; Nal et al., 2005).
2. Infected lung – Alveolar macrophages internalize the virus, producing inflammatory cytokines and chemokines. Other cells are recruited into the alveoli and increase the production of inflammatory cytokines, which can lead to tissue damage with fibrin production and fluid leakage into the alveoli.
3. Moderate damage – Maintenance of inflammation leads to increased vasodilation, accumulation of cells in the immune system, and a cytokine storm. There is an increase in the entry of liquid into the alveoli and the surfactant begins to decrease, making gas exchange difficult.
4. Severe damage – The exacerbating inflammatory response damages the lung infrastructure, forms scar tissue, sharply reduces the surfactant, impacting gas exchange and leading to an important decrease in oxygen saturation. Additionally, inflammation of the pulmonary vessel endothelium increases fluid leakage into the alveolus and causes changes in the integrity of the vascular barrier, triggering a pro-coagulative state.

These findings point to a critical role for neutrophils in the pathology of the infection. In other serious or persistent viral infections, neutrophil-mediated alveolar damage leads to interstitial oedema, incompatibility of ventilation / perfusion causing respiratory failure. Recent studies have identified neutrophil...
infiltration in pulmonary capillaries in autopsy reports of patients who died as a result of COVID-19 (Chan; Chan, 2013). These data support the hypothesis that neutrophils may have an important role in the gravity of COVID-19 (Fig. 3, 4).

The accumulation of immune cells in the lungs can lead to the production of more pro-inflammatory cytokines, promoting an exacerbated inflammatory response, which eventually damage the lung infrastructure, promoting severe pneumonia, RNAemia, combined with the incidence of ground-glass opacities, and acute cardiac injury (Huang et al., 2020a) (Fig. 5). The SARS-CoV-2-promoted pneumonia is associated with lung damage, lymphopenia and possibly interferon strong inhibition as part of an initial immunosuppression promoted by the virus (Chen et al., 2020a). As above mentioned, the N proteins and some SARS-CoV ORF act as an antagonist to the interferon pathway by regulating IFN-β synthesis and signaling (CUI et al., 2015). IFN-β as well as IFN-γ inhibit the replication of SARS-CoV (SAINZ et al., 2004). This pneumonia can lead to severe acute respiratory syndrome (SARS) in up to 20% of COVID-19 cases (Moore; June, 2020).

The initial development of SARS appears to be induced by secondary hemophagocytic lymphohistiocytosis (sHLH), also seen in patients with SARS-CoV and MERS-CoV (Mehta et al., 2020). sHLH is a syndrome characterized by cytopenia and cytokine release syndrome (CRS), also known as “cytokine storm syndrome”, responsible for triggering the hyperinflammation that leads to organic dysfunction (Crayne et al., 2019) observed in severe cases of COVID-19 (Mcgonagle et al., 2020). In adults, sHLH is most commonly triggered by severe viral infections (Ruan et al., 2020). CRS appears to be promoted by an unbalanced response between Th1 (which produce a profile of inflammatory cytokines involved in cellular immunity) and Th2 (which produce a profile of anti-inflammatory cytokines involved in humoral immunity) lymphocytes (Zheng et al., 2020b) and is the leading cause of morbidity in the cases of SARS-CoV (2002) and MERS-CoV (2012) infections (Channappanavar; Perlman, 2017). Elevated IL-6 serum concentrations, as well as other inflammatory cytokines, are
characteristic of severe MERS-CoV disease (Fehr; Channappanavar; Perlman, 2017).

1- Infection of endothelial cells triggers inflammasome activation and production of IL-18 and IL-1β. 2- Infected endothelial cells enter pyroptosis, releasing large amounts of virus. This process associated with the production of IL-18 and IL-1β induces downstream inflammatory cells leading to damage and inflammation of the alveolar-capillary endothelium. 3- Endothelial damage exposes the basement membrane, induces the recruitment of coagulation factors and platelets, promoting the formation of clots, which degrade into D-dimer (fibrin degradation product). Hyperactivity of the coagulation system leads to thromboembolism, which can contribute to multiple organ failures.

Source: The authors, 2024.
Some authors (Chen et al., 2020a; Ruan et al., 2020) described the frequent presence of CRS in severe COVID-19 patients. In these cases, increase in the IL-6 in blood concentration can be correlated with respiratory failure, SARS and adverse clinical outcomes. C-reactive protein (CRP), an essential marker of inflammatory processes, also functions as a biomarker of severe infection by betacoronavirus. This protein has its expression stimulated by IL-6. Infection of monocytes, macrophages and dendritic cells by betacoronavirus results in the activation of inflammasome, with consequent production of high level of IL-1β, which activates macrophage to produce IL-6 (Kang et al., 2019). Besides IL-1β and IL-6, several cytokines, chemokines and some stimulatory factors are elevated in the most severe cases of COVID-19, indicating the so-called “cytokine storm” (Fig. 4). Among them, we can mention IL-2, IL-7, TNF, GM-CSF (macrophage colony-stimulating factor), MCP-1 (monocyte chemotactic protein-1) (HUANG et al., 2020a), IFN-γ, IL-1ra, IL-2ra, IL-10, IL-18, HGF (hepatocyte growth factor), MCP-3 (monocyte chemotactic protein-3), MIG (IFN-γ induced monocin), G-CSF (granulocyte colony-stimulating factor), MIG-1a (macrophage inflammatory protein 1 alpha), CTACK (cutaneous chemokine that attracts T cells) and IP-10 (protein 10 induced by IFN-γ) (YANG, 2020). In addition, the transcriptomic profile of bronchoalveolar lavage and peripheral blood mononuclear cells from infected patients also revealed high expression of cytokines and chemokines, especially CCL2/MCP-1, CXCL10/IP-10, CCL3/MIP-1α, CCL4/ MIP1-β, CXCL1, CXCL2, CXCL6 and CXCL8 (XIONG et al., 2020). Among patients in need of intensive care, there was an even higher elevation of IL-2, IL-7, GCSF, IP-10, MCP-1, MCP-3, MIP1α, and TNF and the anti-inflammatory cytokines IL-10 and IL-1ra (MOORE; JUNE, 2020; YANG, 2020). Similar Th1-type and Th17-type pro-inflammatory cytokine profiles are observed in patients with MERS and in patients with COVID-19, including elevated levels of IL-17 (Liu et al., 2020; Mahallawi et al., 2018). The correlation of high levels of IL-17 in severe cases of COVID-19 places this cytokine as a possible biomarker of severity and a potential therapeutic target to mitigate the damage to SARS-CoV-2, mainly in the lung (Liu et al., 2020; Wu; Yang, 2020). It is known that IL-
6, together with IL1-β and IL-17, increase adhesion molecules in endothelial cells, allowing leukocyte migration to the inflammatory site, which results in increased production of cytokines and may contribute to the establishment of cytokine storm (Acosta-Rodriguez et al., 2007; Boaventura et al., 2010; Goebel et al., 2000). The correlation of high levels of IL-17 in severe cases of COVID-19 places this cytokine as a possible biomarker of severity and a potential therapeutic target to mitigate the damage to SARS-CoV-2, especially in the lung (Liu et al., 2020; Wu; Yang, 2020).

Histological examination of a patient who died of severe COVID-19 (pulmonary oedema, SARS and cardiac arrest) showed infiltration of lymphocytes in both lungs and liver damage, and mild inflammation of cardiac tissue due to infiltration of mononuclear cells. In addition, their circulating CD4+ and CD8+ T cells, although less than normal, were hyperactivated, with CD4+ T cells presenting a pro-inflammatory Th17 phenotype (probably promoted by IL-1β and IL-6) and CD8+ T highly cytotoxic lymphocytes (XU et al., 2020) (Fig. 4). On the other hand, in a study developed by Moderbacher and colleagues (2020), they found no evidence that the cells of the adaptive immune system were causally involved in the production of the cytokine storm. Among the samples analysed, hospitalized patients had CD8+ T cell response cytokine profiles similar to those of non-hospitalized patients, and the cytokines of Th2 and Th17 response patterns were normal. In fact, what was observed was the opposite effect, where strong SARS-CoV-2 specific CD4+ and CD8+ T cell responses were associated with low disease severity.

The resulting cytokine storm circulates to other organs, causing systemic damage, as seen in the most severe cases of COVID-19 (Guan et al., 2020; Huang et al., 2020a; Xu et al., 2020). The CRS symptoms are generally promoted by an exacerbated immune response. Several affected organic systems promote a variety of symptoms that can lead to death. The cardiovascular system, pulmonary, renal, hepatic and central nervous system are the most affected (Mcgonagle et al., 2020; Together, 2019).
SARS-CoV efficiently infects primary human monocytes and dendritic cells (Chu et al., 2016) and, therefore, it is possible that SARS-CoV-2 is also capable of infecting dendritic cells. Thus, the apoptosis and exhaustion of T cells as a consequence of the damage caused by the dysfunction of infected dendritic cells may contribute to the immunopathogenesis of COVID-19 (Chu et al., 2016; Zheng et al., 2020a) (Fig. 4), promoting the lymphopenia, a vital feature of this disease, generally correlated with clinical severity (Yang, 2020). As with COVID-19, lymphopenia was also a biomarker that correlated with the 2009 influenza A (H1N1) pandemic lethality (Perez-Padilla et al., 2009). In COVID-19 patients, CD4+ and CD8+ T cell counts were negatively associated with the patient survival and with the serum concentrations of IL-6, IL-10 and TNF (Diao et al., 2020), which suggests that an intense activated and inflammatory status may contribute to the depletion and exhaustion of T cell populations.

Independently of the mechanism for lymphopenia, 3 reports (Diao et al., 2020; Moon, 2020; Zheng et al., 2020a) indicated that circulating T and NK cells in patients with COVID-19 acquire an exhausted phenotype, which became more prominent during disease progression. These cells had an overload inhibitory molecule on the cell surface, as well as a reduced ability to produce pro-inflammatory cytokines, such as IL-2, IFN-γ, TNF and cytotoxic factors. It was observed that the NK cell numbers decrease in severe cases of COVID-19, along with increase of NKG2A, an inhibitory receptor which is associated with the exhaustion of cytotoxic NK and T cells (Zheng et al., 2020a). CD8+ T cells, in particular, besides NKG2A expression, exhibit other molecules associated with cellular exhaustion, such as PD-1 and TIM-3 (Diao et al., 2020; Zheng et al., 2020a). COVID-19 patients in intensive care unit presented elevated expression of PD-1 on T cells in comparison with mild patients and healthy donors, suggesting that the disease progression may be characterized by an exhaustion of immune response. Exhaustion is a state in which cells present dysfunction after being fully active, including the ability to produce pro-inflammatory cytokines, such as IFN-γ. Hyperactivation and subsequent exhaustion of effector T cells during the progression of SARS-CoV-2 infection may also be driven by the
decrease in CD4+ regulatory T cells seen in patients with COVID-19, especially those who progress to severe disease (Chen et al., 2020a; Qin et al., 2020) (Fig. 4), which favour an inefficient and dysregulated immune response.

In addition to elevated serum cytokines, high concentrations of ferritin are characteristic of sHLH. Macrophages that express CD163 play an important role in reticuloendothelial signalling of iron and, therefore, are implicated as a source of ferritin, which leads sHLH to be alternatively known as macrophage activation syndrome (MAS) (Moore; June, 2020). A retrospective study of patients with COVID-19 found that elevated ferritin and IL-6 serum concentrations were correlated with cases of non-surviving patients (Ruan et al., 2020). Another explanation for the ferritin level increased in COVID-19 severe cases, is the possibility of SARS-CoV-2 attacks the hemoglobin 1-β chain, capturing the porphyrin to inhibit human heme metabolism. Liu and Li (2020), through analysis of conserved domain, homology modelling and molecular docking, made a comparison between biological roles of novel coronavirus proteins. The authors showed that the ORF8 and surface glycoprotein could bind to the heme, while ORF1ab, ORF10, and ORF3a proteins could coordinate attack to heme on the hemoglobin 1-β chain to promote dissociate the iron, consequently forming porphyrin. In this way, the attack will cause interference with gas transporting resulting in shortness of breath, poisoning and inflammation of the lung cells and, consequently, in ground-glass-like lung images.

In addition, critically ill patients with severe COVID-19 had highly impaired type I interferon response, where no IFN- β production was observed and low IFN-α production and activity were present. This failure to respond to type I IFN was associated with a persistent viral load in the blood and an exacerbated inflammatory response (Hadjadj et al., 2020). Besides, there is also evidence of this escape mechanism in animal models and in lung and serum autopsies from patients with COVID-19 (Blanco-Melo et al., 2020). In this case, an initial response with a failure in the production of α- and β-interferon could contribute to a significant generation of viral particles, favouring an increase in the number of infected cells and allowing the installation of the infection with a high viral load.
(Fig. 4), as has already been observed in the experimental infection of mice (Channappanavar et al., 2016).

4 RISK FACTORS FOR THE AGGRAVATION OF COVID-19

Some studies have shown that male individuals are more susceptible to SARS-CoV-2 than female one (Chen et al., 2020b; Li et al., 2020; Meng et al., 2020; Yang et al., 2020). In this way, male gender is considered a risk factor for severe COVID-19. Male patients with mild to moderate manifestations of COVID-19 symptoms, had higher plasma levels of pro-inflammatory cytokines and chemokines related to the innate immune response including IL-8, IL-18 and CCL5, along with an increase in induction of non-classical monocytes. On the other hand, during SARS-CoV-2 infection female patients presented significantly stronger T-cell activation than male patients, which was maintained in old age. Takahashi and colleagues (2020) showed that a poor T-cell response was negatively correlated with the age of the patients and was predictive of worse disease outcomes in male, but not in female patients. Even so, in general, the most critical cases of COVID-19 are present in patients older than 65 years (Ruan et al., 2020; Wu; Mcgoogan, 2020). Therefore, immunosenescence, the ageing process of the immune system, could be proposed as probably responsible for this aggressive behaviour of SARS-CoV-2 in older individuals.

Ageing is a natural process that involves many complex changes in cellular and molecular mechanisms, which affect the integrity of various tissues, organs and systems, both quantitatively and qualitatively. The immune system is no exception. Ageing promotes a restructuring of the innate and adaptive immune system, decreasing some parameters, unchanging others or even increasing some. This process is characterized by a decrease in the functional activity of dendritic cells, as well as, in the diversity of the T cell repertoire, which generates clinical consequences such as increased susceptibility to respiratory infections, neoplasms, autoimmune and cardiovascular diseases (Torres et al., 2011). Immunosenescence is a secondary process to hormonal decline, stress and the
constant presence of antigenic stimuli and cellular activation that persist throughout the older person's life (Esquenazi, 2008). This phenomenon promotes a decrease in naive T lymphocytes and an increase in memory effector clones. However, the levels of inflammatory cytokines produced by these clones are lower (Alberti et al., 2006), directing the immune system to select clones, which make only potentially less inflammatory responses (Esquenazi, 2008). Looking from this angle, immunosenescence does not seem to be a factor for the complications observed in COVID-19, since, although the resistance of the older people to respiratory viruses decreases, it probably would not trigger the hyperinflammation, so common in critical cases. However, another process still related to aging and quite important for the health and longevity of the older people is the inflammaging, which is defined as a low-grade chronic and systemic inflammatory process that may be present to a lesser or greater extent in the older people. This process is the result of imbalances in organic control between inflammatory and anti-inflammatory mediators, with negative repercussions on the type of response against the most diverse agents, and, therefore, on the ageing process and on the promotion of longevity (Franceschi et al., 2007).

Inflammaging causes an accumulation of chronic injuries. Subclinical infections, accumulation of adipose tissue and smoking contribute to the maintenance of this process (Franceschi et al., 2007), that promotes a constant increase in the basal inflammatory response, represented by increased serum levels of C-reactive protein (CRP), IL-6 and TNF-α. These two cytokines and CRP are implicated in the process of developing chronic degenerative diseases such as neurodegenerative diseases, atherosclerosis, type II diabetes and sarcopenia (Torres et al., 2011), some of which represent important risk factors for the aggravation of COVID-19. High levels of IL-6 and CRP appear to be a predisposing factor to functional disability and increased mortality in older individuals (Jylha et al., 2007). Indeed, some biomarkers of inflammaging increase in the most critical and poorly prognostic cases of COVID-19. In this way, this process could greatly contribute to the worsening of COVID-19 in elderly people.
On the other hand, pediatric patients rarely develop critical illness (Dong et al., 2020; Lu et al., 2020). Dong and colleagues (2020) demonstrated that only 5% of 2,141 children with confirmed COVID-19 had a serious illness and only 0.6% were truly critical. These data differ from those seen in other coronavirus infections (Ogimi et al., 2019), where children and young adults with cancer and immunocompromised patients can progress to greater severity disease (RUAN et al., 2020). In a study of 25 countries with 10,000 children in this possible risk group, of 200 tested for SARS-CoV-2 infection, only nine were positive, eight were asymptomatic or had very mild symptoms, and one had a slightly more severe condition (Hrusak et al., 2020). However, some children around the world have been presented with multisystem inflammatory syndrome (MIS-C), formerly referred to as pediatric inflammatory multisystem syndrome (PIMS), very similar to Kawasaki disease (Couzin-Frankel, 2020). PIMS could be promoted by the direct action of the virus, by deregulation of the immune system after SARS-CoV-2 infection, or by a combination of these two mechanisms. Most cases of this syndrome occur around 4 weeks after infection, with the presence of a high proportion of antibodies against SARS-CoV-2 detected in these patients, compared to viral detection at the time of symptoms (Sood et al., 2021). Thus, the pathogenesis seems to be promoted more by the inadequate activation of the immune system than by the direct action of the virus (Soma; Shust; Ratner, 2021). There is an increase in pro-inflammatory cytokines, such as IL-1, IL-6, IL-18, TNF-α and interferon-γ, and the following symptoms: fever, elevation of inflammatory markers, shock Kawasaki-like, cytokine storm and involvement of several organs. Molecular mimicry generating autoantibodies, expression of viral antigens in infected cells, formation of immune complexes activating the inflammation cascade, and the action of viral superantigens activating the host's immune cells, are among the pathogenic mechanisms proposed for triggering this syndrome (Gruber et al., 2020; Jiang et al., 2020).

Recently, the same multisystem inflammatory syndrome was described in adults (Morris et al., 2020). Thus, the data explained above suggest that people prone to inflammatory processes would be more susceptible to develop the
COVID-19 severe form than people with some type of immunosuppression (Tan et al., 2020). One of the reasons is perhaps that the immunosuppression promotes the decrease in hyperinflammation triggered by the cytokine storm syndrome, since the immune system does not present a response that would be expected.

Thereby, the risk factors for the development of severe COVID-19 include advanced age, male gender and the presence of comorbidities (obesity, diabetes, heart disease, lung disease, kidney disease) (D’antiga, 2020). Therefore, identifying conditions known to be related to inflammation can help stratify the older population’s risks. In the same way, this investigation is also necessary for children who can present pediatric COVID-19-associated multisystem inflammatory syndrome or for more young people that have no present comorbidities involved in the aggravation of COVID-19. Varga and colleagues (Varga et al., 2020), in accordance with their findings of endotheliitis, proposed these people might have undiagnosed autoimmune or clotting disorders, such as rheumatoid arthritis, that amplify the effects of SARS-CoV-2 infection.

Another phenomenon that deserves to be further explored in COVID-19 is the bacterial translocation. In general, symptomatic patients present with fever, dry cough, myalgia, fatigue and dyspnea. However, it is known that extrapulmonary symptoms have also been described in these individuals, such as those related to cardiovascular damage (Huang et al., 2020b), but also of the digestive tract, with gastrointestinal manifestations characterized by nausea, diarrhea and vomiting (Lin et al., 2020). Indeed, some evidence such as the presence of viral RNA in fecal specimens in individuals with SARS-CoV-2 infection, the small intestine enterocytes expressing ACE2 receptors and several membrane-bound serine proteases indicated that the gastrointestinal tract may be involved in colonization by SARS-CoV-2 (Natarajan et al., 2022; Xiao et al., 2020; Zhang; Garrett; Sun, 2021), which may contribute to gastrointestinal symptoms and inflammation susceptibility. It is noteworthy that a recent meta-analysis described that COVID-19 patients with gastrointestinal involvement had a worse disease course (Mao et al., 2020).
This immune disturbance in the mucosa-associated lymphoid tissue, in particular, in the gut, leads to anatomical and functional damage to the intestinal mucosal barrier, and has as a direct consequence for the microbial products translocation into the circulation, as previously described for HIV-1 infection (Brenchley; Price; Douek, 2006; Klatt; Brenchley, 2010). These components induce potent inflammatory responses by activating several receptors present in innate as well as adaptive immune cells, such as TLR and NOD, through their Toll receptor ligands, such as lipopolysaccharide (LPS), flagellin, CPG motifs, acid teichoic and ribosomal RNA (Sandler; Douek, 2012). As described above, these interactions culminate in the activation of the transcriptional factor NF-κB and in the production of inflammatory cytokines such as IL-6, IL-1β, TNF and type I IFN, which in turn will contribute to increase the immune activation.

Considering that patients infected with SARS-Cov-2 have gastrointestinal manifestations along with T lymphocytes impairment and intense activation of the immune system, it is reasonable to accept that microbial translocation from the intestinal lumen to the systemic circulation may be implicated in the pathogenesis and potentiation of the immune activation in SARS-CoV-2 infection. Indeed, high levels of LPS, soluble CD14 (Teixeira et al., 2021), LPB (lipopolysaccharide binding protein) and EndoCab IgM were observed in SARS-CoV-2-infected patients, especially in that admitted in intensive care units (Oliva et al., 2021). Moreover, non-survivors COVID-19 patients presented increased plasmatic concentrations of IL-6, TNF, CCL2/MCP-1 and CCL5/RANTES in concomitance with elevated LPS levels, pointing that such products may potentiate the inflammatory status and contribute to the aggravation of the disease. Severe COVID-19 was associated with plasma markers of disrupted intestinal integrity as zonulin levels, which in turn increase tight junction permeability and microbial translocation. Further studies in this line will be crucial for thinking about new therapeutic strategies in SARS-CoV-2 infection, preventing worse outcomes.

Another hypothesis could be the reactivation of an ancestral virus present in the human genome for about 5 million years, the endogenous human retrovirus of the K family (HERV-K) (Temerozo et al., 2021). This HERV-K is an ancestral
virus that infected the human genome when humans and chimpanzees were dissociating on the evolutionary scale, during speciation (Subramanian et al., 2011). Some of these genetic elements are present in our chromosomes, where they are usually silent for most of our lives. The expression of some genes in this family has been linked to some types of cancer and multiple sclerosis (Xue; Sechi; Kelvin, 2020; Zare et al., 2018). An analysis performed on tracheal aspirates of 25 patients with severe COVID-19, under invasive mechanical ventilation (IMV), showed the presence of HERV-K in these patients. Furthermore, increased HERV-K expression was elicited in primary human monocytes from healthy donors after experimental in vitro infection with SARS-CoV-2. In critically ill patients, higher HERV-K levels were associated with mortality. In addition, in deceased patients, increased expression of this virus was associated with inflammation related to monocyte activation, IL-17 and coagulopathy. Among critically ill patients from COVID-19 who had high levels of HERV-K, the mortality rate reached 50% (Temerozo et al., 2021). Although the mean age of these patients was 57 years old, the presence of reactivation of this virus in younger patients without comorbidities could be a plausible explanation for the worsening of COVID-19 in these cases.

A very important aspect that has been investigated is whether there may be a genetic pattern that may confer susceptibility to the worsening of COVID-19. Since, in several cases, families are observed where several members have worsening of the disease and even death. In a study carried out in Brazil, 20 cases of death from COVID-19 and 10 deaths caused by influenza A H1N1 subtype (H1N1pdm09) were investigated. In this study they evaluated the involvement of single nucleotide polymorphisms (SNPs), which can modify protein expression impacting gene expression, and tissue expression of IL-17A and neutrophils recruitment in post-mortem lung severe samples from patients who died of forms of COVID-19 comparing to those who died by H1N1pdm09. An increase in tissue expression of IL-8/IL-17A and a greater number of neutrophils were observed in samples from the H1N1 group compared to COVID-19 samples, with no statistical difference in the distribution of the genotype in the IL-
17A gene between the groups. However, the G allele (GG and GA) of rs3819025 was correlated with increased tissue expression of IL-17A in the COVID-19 group. In SNP rs3819025 (G/A), the G allele may be considered a risk allele in the patients who died for severe COVID-19 (Azevedo et al., 2021).

In COVID-19, the altered innate immune response is already well documented in terms of disease severity. However, the role of the acquired immune response in the progression of disease severity is not well understood. Recently, Wang and colleagues (2021) described that patients with COVID-19 have a significant increase in autoantibody reactivity when compared to uninfected individuals. Furthermore, among these antibodies there is a high prevalence of autoantibodies against immunomodulatory proteins (including complement components, cell surface proteins, cytokines and chemokines). The authors showed that these autoantibodies disrupt immune function, inhibiting immunoreceptor signaling and changing the composition of peripheral immune cells, which impairs SARS-CoV-2 control. In the mouse model of infection, autoantibodies increase disease severity (Wang et al., 2021).

The study also identified the presence of autoantibodies targeting various tissues in patients with COVID-19. The target cells of these antibodies were present in the skin, vascular tissue, lungs, connective tissue, central nervous system and gastrointestinal system, in addition to identifying antibodies directed towards platelets and coagulation factors. The presence of autoantibodies suggests their direct participation in the severity of COVID-19. Thus, the deregulation of innate immunity would not be the only cause of the worsening of the disease picture, with humoral immunity also participating in the pathogenesis of severe COVID-19 conditions (Wang et al., 2021).

More studies are still needed to understand the immunity acquired in COVID-19, but the discovery of where and how these autoantibodies act and how they influence the patient’s clinical outcome, can help in the development of therapies that seek to act and modulate the immune response, attenuating the harmful effects of autoantibodies.
5 CONCLUSIONS

In this review, we present the central role of the immune response mechanisms for SARS COV-2, which can lead to both the resolution of the infection with little tissue damage, and the hyperinflammation and severity of the disease. The learning of these complex mechanisms can identify biomarkers that allow the prediction of the disease evolution and to perform therapeutic interventions. Several risk factors can be critical for the development of severe COVID-19, as they contribute to the amplification and uncontrolled inflammatory process.

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