

## REVIEW

# Coronavirus infection: An immunologists' perspective

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## Abstract

Coronavirus infections are frequent viral infections in several species. As soon as the severe acute respiratory syndrome (SARS) appeared in the early 2000s, most of the research focused on pulmonary disease. However, disorders in immune response and organ dysfunctions have been documented. Elderly individuals with comorbidities exhibit worse outcomes in all the coronavirus that cause SARS. Disease severity in SARS-CoV-2 infection is related to severe inflammation and tissue injury, and effective immune response against the virus is still under analysis. ACE2 receptor expression and polymorphism, age, gender and immune genetics are factors that also play an essential role in patients' clinical features and immune responses and have been partially discussed. The present report aims to review the physiopathology of SARS-CoV-2 infection and propose new research topics to understand the complex mechanisms of viral infection and viral clearance.

## 1 | INTRODUCTION

Coronaviruses (CoVs) are a collection of enveloped viruses with non-segmented, positive-sense single-stranded RNA genomes with distinctive crown-like spikes that protrude from the capsid of helical symmetry.<sup>1</sup> They have a remarkably long RNA genome and a particular replication strategy. In this complex family, several members attack different species causing several diseases that can end up in death. In November 2002, in China, a severe acute respiratory syndrome coronavirus (SARS-CoV) was identified. It promptly spread to other countries. There were around 8000 confirmed cases, and the mortality rate was 9.6%.<sup>2</sup> Then, another member of

the family, Middle East respiratory syndrome coronavirus (MERS-CoV), appeared in Saudi Arabia in 2012 and later emerged in South Korea in 2015. The confirmed cases of MERS-CoV exceeded 2000, with a mortality rate of ~35%.<sup>2</sup> In 2019, another member of the family was identified, SARS-CoV-2.<sup>3</sup> The number of infected people and the mortality rate still grow continuously. Infected elderly individuals with comorbidities exhibit the worst outcomes. There are now several vaccines against SARS-CoV-2 approved for emergency use by the regulatory offices of different countries.

The coronavirus genome is formed by 2 UTR sites, 5' and 3', the replicase, the spike (Spike), the envelope E (Envelope), the M (Membrane), the N (Nucleocapsid) and

the poly (A) tail. There are additional genes at the end of the genome. The S protein is highly glycosylated, and it is required for infection.<sup>4</sup> Even though the S protein is very similar to SARS (94% nucleotide sequence), a protease-sensitive site in the SARS-CoV-2 is absent in the previous one.<sup>4</sup> The membrane protein and the accessory proteins are non-essential for replication; however, they have essential viral assembly and pathogenesis roles. Other non-structural genes, open reading frame (ORF), ORF1ab, ORF3a, ORF6, ORF7a, ORF10 and ORF8, are also transcribed.<sup>5</sup> These proteins' function in the infection, viral replication and host response are still controversial.<sup>6,7</sup>

The primary transmission is airborne, close and direct human-to-human contact, droplets from saliva, sneeze or cough. A less prevalent infection occurs by direct skin contact, faeces or contaminated objects.<sup>8,9</sup> The incubation period range is from 2 to 14 days, and the infected person can be asymptomatic during this period.<sup>8-10</sup> SARS-CoV-2 has an R0 of 2.2-2.6, implying that each infected individual has the potential to infect 2.2 other people.<sup>8-10</sup> One key issue is that the virus is detectable by molecular biology early in the nostrils and saliva; however, antigens are reported later at the onset of symptoms.<sup>11</sup> The lag time in detectable antigen can be critical in the pathogenesis and multiorgan infection. Even though most SARS-CoV-2-infected persons are asymptomatic, around 20% of the patients may have severe manifestations, and 5 to 10% require intensive care.<sup>8-10</sup> The severe cases with associated mortality are generally older adults with comorbidities; however, severe forms of infection have been detected in all ages.<sup>12</sup> Moreover, virus variants also impact the rate of infection, disease severity and lethality.<sup>13</sup>

The coronavirus infection causes hypoxemia, from mild to severe (SARS), skin rash, fever, anosmia, fatigue, pain chest, muscle, articular and unexpected hyperglycaemia or increase in blood pressure. The virus affects microcirculation; it generates endothelial cell damage, capillary damage and micro thrombosis.<sup>14</sup> The immune response against the virus and the virus's cytopathic effect induces the activation of the innate immune system, protein and cells, which may generate a massive inflammatory reaction (cytokine storm). The hypoxia induces hypoxia transcription-inducing factor I (HIF-I), amplifying the inflammatory response by activating myeloid cells and enhancing transcription of proinflammatory cells and oxidative enzymes.<sup>14</sup> Even though it is still controversial, increased BMI has been considered a risk factor for COVID infection.<sup>15,16</sup> More studies are required to ascertain the relationship between metabolic syndrome, a subclinical proinflammatory condition and HIF-I as the triggering factor for massive neutrophil lung recruitment and cytokine storm in SARS-CoV-2-infected patients.

It is unclear how the virus causes neurological effects, and some authors have proposed direct cytopathic effects.<sup>17</sup> Gastrointestinal manifestations, cardiac, kidney and hepatic

dysfunctions are observed in human and animals infected by a coronavirus.<sup>1,3</sup> Skin manifestations reveal immune complex deposition as it has been recorded in other viral diseases, and it is age-independent.<sup>18</sup> In a general analysis, Mason<sup>19</sup> described three phases of SARS-CoV-2 viral infection. The first phase is the asymptomatic phase since the infection mostly is present in the nose and on the buccal cavity. In the nose, the immune system involves local antibodies' and innate immune cells that may elicit an adaptative immune response.<sup>19</sup> The induction of the adaptative immune response depends on antigen expression, which is low at the early stages of the viral infection.<sup>11</sup> In the oropharyngeal cavity, the innate immune response is prevalent, complement, neutrophils and macrophages, and antibodies, essentially IgA, bactericidal peptides and enzymes that control mostly bacterial infections.<sup>19</sup> There, the virus elicits a minimal innate immune response. In the moderate symptomatic phase, the virus is primarily present in the larger airways' pseudostratified epithelium.<sup>19</sup> There is an excellent innate immune response in these areas with the recruitment of cells and proteins, which may cause damage and obstruction of the airway. However, the damaged epithelial cells can be removed and replenished with basal cells.<sup>7,19</sup> There is a more severe disease in the bronchioles where the club cells are usually infected and affect surfactant production and other secretory products.<sup>7,19</sup> In severe cases, the alveoli are compromised; the virus targets the epithelial type II cells that express ACE.<sup>15,19</sup> The decrease in viable epithelial type II cells is responsible for respiratory insufficiency. The lack of lung surfactant, alveolar flooding and loss of the extracellular matrix generating more viral infection affects the pulmonary parenchyma's standard repair and the inflammation's resolution.<sup>19</sup> The typical active resorption of alveolar fluid and electrolytes is also hampered, resulting in hypokalaemia.<sup>19</sup> Impaired endothelial cells lead to transudation of plasma protein of inflammatory origin and an irregular formation of hyaline membranes.<sup>7,19</sup> Residual fibrosis may result after viral infection due to the low resolution of the inflammatory response.<sup>19</sup>

The evidence of lung tissue destruction came from an exciting study analysing proteins of organs of autopsies by HPLC/MS.<sup>20</sup> The authors were able to identify high amounts of cathepsin L1, an enzyme involved in intracellular protein catabolism.<sup>20,21</sup> The increase in cathepsin L1 is related to extracellular matrix degradation critical in viral infection and release.<sup>19,21</sup>

Significant alterations in blood electrolytes have been described in hypertensive patients infected with SARS-CoV-2, hypokalaemia, hyponatraemia and hypocalcaemia.<sup>22,23</sup> Nonetheless, few studies have dealt with the mechanism involving electrolyte imbalance with neural, cardiovascular, gastrointestinal and renal dysfunctions due to either the general renin-angiotensin system or the virus's cytopathic effect as it occurs in the lung.<sup>22</sup> Electrolyte imbalance induces

inflammasome activation and, consequently, exacerbates the inflammatory response;<sup>24</sup> then, multiorgan dysfunction in severe COVID patients may result from multiorgan-induced inflammatory reaction.

## 2 | ANGIOTENSIN-CONVERTING ENZYME 2 AND THE SARS-COV-2 RECEPTOR

SARS-CoV-2 uses the complex angiotensin-converting enzyme 2 receptor (ACE2), a glycosylated transmembrane protein, to infect and invade the target cell.<sup>25,26</sup> Two differentially spliced forms of ACE2 are known and have different substrate specificities.<sup>25,26</sup> The maximum expression of ACE2 is observed in the respiratory epithelium, lungs, kidneys, intestines, testis (Sertoli and Leydig cells), uterus, vagina, endothelium and the heart.<sup>25-27</sup> The spike protein protease-sensitive site is cleaved by a specific transmembrane serine protease 2 (TMPRSS2) and divides the protein in two. The S 1 unit (S1) of the virus binds to the ACE2 as the target receptor.<sup>25-27</sup> Then, it uses the host serine protease TMPRSS2 for S cleavage, allowing the union of viral and cellular membranes and, consequently, viral entry into the cell.<sup>25-28</sup> The binding of the virus and its internalization leaves the cells without an active ACE2 enzyme. Soluble ACE2 that lacks membrane anchor is found in low levels in the blood.<sup>29</sup> The impact of a small amount of active ACE2 and its role in cardiovascular physiology and SARS-CoV-2 physiopathology is still debatable.

Battle and collaborators<sup>29</sup> proposed that soluble ACE2 could act as a competitive receptor of SARS-CoV and other coronaviruses by avoiding binding the viral particle to the surface-bound, full-length ACE2. Therefore, the provision of the recombinant human soluble protein ACE2 could be beneficial as a novel biological therapy to limit the infection's progression caused by coronaviruses that use ACE2 as a receptor. Hoffmann et al<sup>30</sup> presented a study demonstrating that binding the virus to the cell can be inhibited by blocking the cellular serine protease protein TMPRSS2. As aforementioned, the S1 protein/ACE2/ACE receptor complex is responsible for infection and internalization. According to the authors,<sup>30</sup> antibodies may inhibit the binding of S1 to the complex leading to a possible therapeutic target. Johnson et al<sup>31</sup> were able to show that mutation in the furin site in the S protein of the SARS-CoV-2 virus is essential in viral pathogenesis. In the animal models, exposure to the mutated virus prevents the infection with the typical virus suggesting a possible role of the mutated protein in therapeutic responses.

Studies involving monoclonal antibodies to decrease viral burden have been published<sup>32,33</sup> and several regulatory agencies' have approved its use. However, only a combination of

monoclonal antibodies against different S protein domains was shown to be more effective, bamlanivimab and etesevimab.<sup>32</sup> Antibodies and B cells from convalescent patients were used to construct recombinant antibodies; the trials' results are promising.<sup>33</sup> There are, however, some limitations on the use of the therapy as expected. A general question arises from the fact that IVIG has also been shown to be partially protective.<sup>34</sup> In risk populations with initial exposition to the virus, early IVIG therapy could be beneficial to prevent severe disease.

The ACE2 receptor gene is located in the X chromosome, and TMPRSS2 gene is situated in chromosome 21.<sup>35</sup> The ACE2 gene's location may provide an advantage to females (2 copies in duplicate of the same gene); on the other hand, TMPRSS2 is an androgenic stimulated gene.<sup>35</sup> In post-menopause, as expected, due to the lack of hormones, this protection is less effective.

Zhen and Cao<sup>36</sup> provided evidence of gene polymorphisms of ACE2 in different populations and its importance in SARS-CoV-2 infection. In Italy, Asselta et al<sup>37</sup> analysed the Italian population generating an analysis of the critical polymorphism and the role of gender. Most ACE2 genetic variants, although involved in increased hypertension susceptibility, have a similar binding affinity for SARS-CoV-2 S protein. Hussain et al<sup>38</sup> were able to demonstrate that ACE2 alleles, rs73635825 (S19P) and rs143936283 (E329G), had a lower affinity to the S1 protein. The relevance of these polymorphisms and their impact on ethical genetic analysis was not demonstrated.<sup>39</sup> It is suggested that admix populations may have an advantage as compared to closed populations. More research is required to ascertain TMPRSS2 allelic variants' role, gene and post-transcriptional regulation, and the role of furin in SARS-CoV-2 infection.

Ziegler et al<sup>40</sup> were able to show that ACE2 is an interferon-stimulated gene in human cells and tissue; the regulation is not observed in simian or mouse samples. Upon activation of the immune response, more expression of the enzyme on the cell surface may enhance virus infection. Even though these results would suggest limitations of animal models in SARS-CoV-2 studies, the models can still be suitable to study immune response against the virus.

## 3 | VIRAL RECOGNITION AND CELL METABOLISM

The immune response to respiratory viral infection has several steps: one humoral component with antibodies and complement, the cellular part that comprises cells that require no antigen presentation (innate response) and the antigen-specific cells that belong to the adaptive response component.<sup>7,41-43</sup> Nevertheless, besides interferons and inflammatory cytokines, the immune response depends upon

intracellular transport of pathogen, miRNA from virus and the host, host-derived machinery and the genetic and metabolic response to the infection.<sup>41</sup>

Pattern recognition receptors (PRRs) are cellular membrane and cytoplasmic receptors that recognize viral proteins and nucleic acids.<sup>41,42</sup> For example, double-stranded RNA (dsRNA) or single-stranded RNA (ssRNA) with a 5'-triphosphate are sensed by the retinoic acid-inducible gene I (RIG-I) cytoplasmic protein.<sup>41-43</sup> These types of RNA are viral replication products not found in the cytoplasm of healthy cells. When RIG-I recognizes these viral RNAs, cells are activated and start synthesizing interferon and proinflammatory cytokines.<sup>41-43</sup>

Other virus detectors are Toll-like receptors (TLRs), which detect viral dsRNA, ssRNA, CpG sequences and viral glycoproteins.<sup>41-43</sup> Viral genomic RNA and/or replication intermediates (dsRNA) are identified by RIG-I/MDA and the endosomal RNA receptors, TLR3 and TLR7.<sup>41-43</sup> These events generate the activation of NF- $\kappa$ B and IRF1, IRF2, IRF5, IRF7, IRF8, IRF9 signalling cascades which induce the transcription and expression of type I interferon (IFN- $\alpha$ , IFN- $\beta$ , IFN- $\delta$ ).<sup>43-45</sup> In turn, IFN type I binds to its receptor and triggers the JAK-STAT pathway, JAK1 and TYK2 kinases phosphorylate STAT1 and STAT2, which then forms a complex with IRF9-inducing transcription of IFN-stimulated genes (ISGs) under the control of IFN-stimulated response element (ISRE)-containing promoters.<sup>43,44</sup>

IFN pathway is essential in cell viral response since mutations affecting the cascade are related to the Mendelian predisposition to viral infections.<sup>46-48</sup> Several immune deficiencies have unravelled the importance of several proteins involved in the IFN pathway crucial to antiviral response.<sup>46,47</sup> Wang et al<sup>48</sup> described the different proteins involved in the antiviral function of interferon. SARS-CoV and MERS inhibit IRF3, IRF7 and IRF9 proteins confirmed for SARS-CoV-2 infection.<sup>44,49</sup> Proteins induced by IFN like the interferon-induced transmembrane protein 3 (IFITM3) and interferon-stimulated protein (IFIT1) could interfere with a viral infection of the neighbouring cells.<sup>44,48</sup> The blocking effect should be parallel to the impact on cyclin-dependent kinases (Cdks) on cell proliferation.

Several proteins of SARS-CoV-2 have been shown to inhibit IFN signalling. Lei et al<sup>49</sup> screened 23 viral proteins. They found that SARS-CoV-2 NSP1, NSP3, NSP12, NSP13, NSP14, ORF3, ORF6 and M protein can inhibit IFN- $\beta$  induced Sendai virus promoter activation, suggesting that they may downregulate the production of the cytokine that impedes SARS-CoV-2 viral replication. ORF-3b is a potent interferon antagonist,<sup>50</sup> and ORF6 may also disrupt the IFN type I signal and STAT nuclear import.<sup>51</sup> Protein M (membrane) has also been shown to be a potent inhibitor of interferon type I and III.<sup>52</sup> Interestingly, proteins S and NSP of the virus appear to promote the IFN signal.<sup>49-51</sup>

In a genetic study, Zhang et al<sup>53</sup> were able to identify that inborn genetic errors of TLR3 and IRF7, IFN I-dependent immunity were more susceptible to the virus and may have the worst outcome. New mutations in STAT2 and IFN- $\gamma$  have also been reported.<sup>54</sup> These patients could be more susceptible to viral infections and severe disease.

Anti-IFN antibodies were detected in severe COVID-19-infected patients.<sup>55</sup> Autoantibodies would decrease the immune response against the virus and predispose to a higher viral replication and an impaired immune response. Interestingly, the presence of autoantibodies is more frequent in men than in women.<sup>55</sup> The reason for the gender difference is unknown.

In silico and bioinformatics assessments revealed several host binding microRNA (miRNA).<sup>56-63</sup> Several host miRNA (15b-5p, 15a-5p, 197-5p, 548c-5p, 548d-5p, 409-3p, 30b-5p and 505-3p) may be involved blocking viral replication.<sup>56,57</sup> Also, viral miRNA is shared with cells miRNA (8066, 5197, 3611, 3934-3p, 1307-3p, 3691-3p, 1468-5p), which may modulate cell response facilitating SARS-CoV-2 infection.<sup>58</sup> Among the different virus escape mechanisms, inhibition of host miRNA maturation, viral miRNA control of the cellular process and metabolic pathways, and viral miRNA sponges are crucial for viral escape.<sup>56-61</sup> IFN pathway is inhibited or downregulated, and TGF- $\beta$  signalling, involved in cell suppression, is enhanced.<sup>49,53,54</sup> The IFN pathway inhibition affects viral RNA recognition by Toll receptors and RIG.<sup>43-49</sup> Nonetheless, extracellular vesicles containing non-coding RNA could be important in controlling viral replication and enhancing an effective immune response.<sup>49</sup>

Nersisyan et al,<sup>61</sup> using bioinformatic analysis, identified six hot miRNAs able to bind viral sequences (miR-21-3p, miR-195-5p, miR-16-5p, miR-3065-5p, miR-424-5p and miR-421). In the mouse model, miR-21-3p is upregulated during SARS-CoV infection suggesting that it may have an essential role in viral pathogenesis. In the ovalbumin asthma mouse model, miR-21 was related to M2 macrophage polarization and lung hyperresponsiveness.<sup>62</sup> Thus, miR-21 is involved in remodelling, which may be crucial for viral infection replication.

An important issue arises concerning the role of miRNA in ACE2 and TMPRSS2 transcripts. There is a controlling system containing let-7e/miR-125a/miR-200 families, histone demethylase JARID1B that regulates ACE2 expression; hsa-miR-200c-3p and hsa-miR-141-3p can bind 3' UTR of ACE2 mRNA and, in consequence, modulate the transcription of the gene.<sup>51,61,63</sup> Paniri et al<sup>64</sup> proposed that polymorphisms of miR rs3746444 for hsa-miR-499a-3p, rs113808830 for hsa-miR-4532, rs3751304 for hsa-miR-6763-3p and hsa-miR-26b-5p were strongly hybridized with ACE2 mRNA and might stimulate its expression.

Recently, Wyler et al,<sup>65</sup> through the analysis of in vitro infection and miRNA, showed that heat-shock protein (HSP)

90 is crucial in SARS-CoV-2 infection. Inhibition of HSP 90 resulted in decreased viral replication and reduced transcription of cytokines. These results generate new research areas and therapeutic options involving chaperone proteins, protein degradation and presentation, which may be necessary to understand viral infection and the immune response against it.

The miRNA reports generate vital information about virus infection and pathogenesis, host immune and metabolic response to infection. This new knowledge can be explored to produce successful therapies for appropriate pharmaceutical intervention.

## 4 | METABOLIC CHANGES IN SARS-COV-2 INFECTION

As expected in the hyperinflammatory response, glucose and fatty acid metabolism changes are observed in non-diabetic patients. The increase in blood glucose may parallel with C-reactive protein, procalcitonin and lactate suggesting a high metabolic regulation.<sup>66</sup> Most severe cases are observed in the obese and elderly infected patients, presumably due to the subclinical inflammatory condition, which may be prone to generate a deregulated immune response and cytokine storm. Several authors<sup>67,68</sup> have suggested that adipokines are responsible for patients' metabolic response against the SARS-CoV-2 virus, which, in turn, induces inflammasome NLP3 activation. The inhibition of fatty acid synthase by orlistat and the AMP-activated protein kinase (AMPK) activator metformin seem to reduce viral replication of the coronavirus along with a decrease in systemic inflammation.<sup>68</sup> These findings and the genetic predisposition of severe SARS-CoV-2 infection in Apo E e4/e4 homozygotes<sup>69</sup> suggest that host metabolism may be critical in the response against the virus.

Lipidomic changes are also observed upon IFN stimulation in order to protect cells from viral entry. The changes involve modifications at the membrane levels.<sup>70</sup> IFN promotes the increase in cholesterol membrane content. The plasma membrane becomes more rigid, decreasing the possibility of viral infection.<sup>70</sup> Moreover, changes in glycerophospholipids and sphingolipids are also observed upon IFN production.<sup>66-68</sup> Membrane arachidonic acid is augmented, leading to its metabolites' marked production.<sup>70-72</sup> Yan et al<sup>71</sup> reported that arachidonic acid and linoleic acid metabolism are amplified in vitro in HCoV-229E-infected epithelial cells, suggesting that the cell response upon viral infection may be combined with the IFN-induced response. Shen et al<sup>72</sup> reported that arachidonic acid levels in the serum of SARS-CoV-2 patients decrease depending on the disease's severity. Phospholipases A2 (secreted, cytosol and membrane) are then the pathway's critical enzymes.<sup>70,71</sup> Arachidonic acid and its metabolites could be significant predictors of viral infection

and/or replication. An extensive scale lipid plasma analysis reported that two phosphatidylcholine species, 14:0–22:6 and 16:1–22:6, one phosphatidylethanolamine species, 18:1–20:4, plasma triglycerides values, and plasma free fatty acid values, especially arachidonic acid and oleic acid, were positively correlated with SARS-CoV-2 infection.<sup>73</sup> Moreover, a more detailed analysis revealed that adiponectin, IL-26 and ceramides are also involved.<sup>74</sup> Ceramides are essential players of lung inflammation.<sup>75</sup>

Assessment of ceramides in several diseases has provided significant evidence of tissue destruction and resolution.<sup>75</sup> In lung inflammation, sphingosine-1-phosphate (S1P) has been a substantial marker of resolution of lung inflammation, while ceramide 1 P (C1P) has been the contrary.<sup>76</sup> Prakash et al<sup>77</sup> have proposed that possible treatment with S1 analogue would hamper immune response in SARS, and consequently, C1P can be used to decrease viral replication and enhance T cell response.<sup>77</sup> Furthermore, it has been shown that acid sphingomyelinase activity blockage prevents the uptake of SARS-CoV-2 by epithelial cells in vitro.<sup>78</sup> The modification of extracellular matrix and heparan sulphate may also help modulate different enzyme activities that would favour but not necessarily be essential in virus entrance or cytopathogenesis.

Several studies have illustrated ApoE polymorphism's (e4/e4) importance and relevance in virus neurotropism.<sup>69</sup> However, more lipidomic data are required to evaluate the role of Apo E protein and gene polymorphisms and the role of other apolipoproteins, particularly A1 as anti-inflammatory, in SARS-CoV-2 viral infection and resolution.

## 5 | INNATE IMMUNITY

### 5.1 | Complement

Complement is a critical system of the innate immune response. In SARS-CoV-2 infection, the activation of complement can be mediated by the lectin pathway and the alternative pathway. The lectin pathway involves the interaction of collectin 11, mannose-binding protein (MBP) and ficolin, which is associated with the mannose-binding lectin-associated serine protease (MASP). MASP activates the coagulation system since it is a serine protease. The alternative pathway involves factor B.<sup>79</sup> Upon tissue destruction with pathogen and danger signals, PAMPs and DAMPs, classical activation of the complement is possible, rendering massive protein-mediated tissue destruction.<sup>79</sup>

Fang et al<sup>80</sup> reported a relationship between C3 levels and patient prognosis. The lower the values, the worse is the outcome. In SARS-CoV-2-infected patients, complement activation is detected on circulating neutrophils, as evidenced by cell surface C3 fragment deposition.<sup>80-82</sup> The activation of C3

requires factor B and Fc $\gamma$  receptors but not C4.<sup>81</sup> C3 convertase is activated upon priming of neutrophils with immune complex via Fc $\gamma$  receptors.<sup>81</sup> Moreover, C3 is also involved in NETosis, amplifying neutrophil death and immune response.<sup>82</sup> These two processes were observed studying SARS using the C3 KO mouse.<sup>83</sup>

Lin et al<sup>84</sup> and Cugno et al<sup>85</sup> were able to detect increased complement activation during the progression of COVID-19. This activation is decreased during remission. An association between C3 levels and biomarkers of endothelial damage, soluble von Willebrand factor VIII, tissue injury markers and lower clearance of the virus was observed. On a large scale, multiple analyses performed,<sup>86</sup> complement proteins were found to be overexpressed in COVID-19 infection, and in severe patients, the levels were the highest. The increase in complement proteins is combined with a decreased apo-A, and HDL synthesis increased B lymphocyte activation and increased lipoprotein metabolism.<sup>86</sup> The increase in acute-phase proteins can be partially accounted for the changes; however, their participation in enhancing proinflammatory pathways may generate cytokine storm and, consequently, a dysfunctional immune response.

Intracellular complement 3 has also been involved in protecting airway epithelial cell from pathogen infection and stress.<sup>87</sup> Its content in the lung increases upon inflammation and inflammatory cytokines, and consequently, lung levels of C3 are increased in patients with lung diseases.<sup>87</sup> As expected, SARS-CoV-2-infected patients with lung illness have a higher risk to progress to severe disease and die.<sup>88</sup> Since C3 is involved in airway disease and emphysema,<sup>89</sup> COPD patients with high levels of C3 and infected with SARS-CoV-2 may be more susceptible to develop a severe disease that stable COPD patients without exacerbations and treated with anti-inflammatory therapy.<sup>90</sup>

Polycarpou et al<sup>91</sup> have an exciting approach to managing complement and the deleterious effect of the innate immune response in COVID-19 patients. The goal is to decrease innate cell activation by C3a and C5a; both activated proteins attract and activate immune cells in the inflammatory site. Mastellos et al,<sup>92</sup> treating patients with eculizumab that targets C5 and AMY-101 that target C3, were able to show a decrease in the inflammatory response in treated patients with a marked reduction in IL-6 and C-reactive protein levels an improvement of lung function and then a resolution of the distress syndrome. Interestingly, factor D inhibitor ACH145951 can suppress the complement cascade's activation induced by the virus's S protein; besides, factor H enhanced this inhibition.<sup>93</sup> Besides complement, macrophages' tissue factor upon neutrophil cell death plays a role in distress syndrome.<sup>94</sup> These results suggest that there are still important questions to answer in this field of complement activation and pulmonary distress syndrome.

Holter et al<sup>95</sup> associated the activation of complement to respiratory failure in a hospital screening. The authors were able to show a direct association of sC5b-9 values with respiratory failure. Interestingly, mannose lectin-binding protein (MLB) was not altered in patients than controls.<sup>95</sup> The low amount of samples and the lack of MLB deficiencies in the cohort could be responsible for the lack of association. More studies should ascertain the role of collectins, ficolins and MLB in an antibody-free environment as the first line of defence against SARS-CoV-2.

The genetics of complement protein has also been a matter of discussion in the SARS-CoV-2 infection. Polymorphisms of the MBP codon 54 variant (A/B) and CCL2 predispose to the severe acute respiratory syndrome in SARS.<sup>96</sup> The antiviral interferon-induced product myxovirus resistance protein 1 (MxA) may also be involved.<sup>97</sup> Analysis of the chromosome 3p21.31 multigene gene cluster and the ABO blood group revealed that the variant rs11385949 G>GA predisposes to severe infection since it is associated with enhanced complement activation of C5 and terminal activation complex in the non O blood group.<sup>98</sup> These results suggest that both C3 and C5 are involved in the exacerbated immune response.

In conclusion, complement therapeutic may be considered essential in patients with severe disease. Published reports using anti-C3 and anti-C5, alone or in combination, in SARS infection have given vital information to design clinical trials.<sup>92,98-100</sup> Considering the differences between the convertases C3 and C5, the approach to blocking both pathways or just C5 to prevent terminal activation seems logical. Inhibition of factor D<sup>93</sup> could give an extra advantage of blocking C3b amplification induced by the cell debris generated in the death of neutrophils in the infection and avoid jeopardizing the complement cascade from any opportunistic infection. However, up to date, there are no clinical reports to confirm this hypothesis. More research is needed to generate therapeutic tools to modulate complement protein function.

## 5.2 | Neutrophils, eosinophils, mast cells, macrophages and dendritic cells

Respiratory viruses do not infect neutrophils, yet neutrophils can phagocytose virions, viral particles and apoptotic bodies containing viruses. In the process, neutrophils are recruited by proteins of the complement systems and chemokines to the inflammation site.<sup>7</sup> Activated neutrophils secrete cytokines, antimicrobial peptides and a variety of enzymes.<sup>7</sup> They also produce oxygen radicals and other mediators to kill pathogens.<sup>7</sup>

Recruited neutrophils are activated in the lungs and can form and release extracellular traps, neutrophil extracellular traps (NETs), composed of proteases, antimicrobial proteins,

and decondensed chromatin, and histones, which, in principle, restrains pathogens and inhibits further dissemination.<sup>101</sup> NETosis, the common apoptotic death of neutrophils, is generally cleared by macrophages, a process that may also hamper local immune response against pathogens.<sup>101</sup> In severe SARS-CoV-2-infected patients, there is an increase in circulating neutrophils in the simple haematological analysis. These neutrophils have been shown as dysfunctional.<sup>102</sup> In essence, the myeloid cells are essential markers of IFN signal with an increase in monocyte HLA-DR, CD11c and CD16.<sup>102</sup> Remnants of NETs were identified in patients.<sup>101-104</sup> These remnants contain cell-free DNA, myeloperoxidase-DNA complexes, citrullinated histone H3 and calprotectin neutrophil-derived S100A8/A9.<sup>104,105</sup> Consequently, there is an increased risk of hypercoagulability. Lung microbiota controlled by the immune system now, in severe patients, represents a threat for the individual.<sup>104-106</sup> Consequently, the excessive activation of neutrophils may cause damage to the respiratory epithelium amplifying local inflammatory response and decreasing lung function.<sup>103-106</sup>

One of the remarkable yet partially explored findings in leukocyte analysis of SARS-CoV-2 patients is the marked decrease in the haemogram's eosinophil cell population.<sup>107,108</sup> The reduction in eosinophil number has not been analysed thoroughly. Eosinophils do not seem to be openly involved in human response to respiratory viruses as in other animal species; consequently, they are not considered to be directly involved in SARS pathogenesis.<sup>107,108</sup> Since in SARS-CoV-2-infected patients, there is no exacerbation of atopic disease, many researchers discarded its role in the viral infection.<sup>107</sup> However, the number of circulating eosinophils was a significant factor associated with a subprophylactic amount of anti-factor Xa inhibitor,<sup>109</sup> suggesting that these cells may be involved in tissue destruction or remodelling as a result of the viral infection. Several drugs used to decrease eosinophil migration to the airways in asthma may be useful as palliative treatment in this viral infection.

In post-mortem studies of patients who have died from SARS-CoV-2 infection, an enhanced concentration of perivascular and septal mast cells and a high density of mast cell progenitors recruited in the alveolar were described septa.<sup>110</sup> Mast cell recruitment into the alveolar septa may be a consequence of the initial endothelial and epithelial cell damage of the alveolar septa. However, complement activation may be the key factor involving mast cell migration to the airways and the generation of mast cell extracellular traps generated upon activation.<sup>83,84</sup> Also, the degranulation of tryptase and chymase may contribute to more cell death and, consequently, the destruction of lung parenchyma architecture, favouring virus invasion.<sup>83,84</sup> In summary, NETosis, mast extracellular traps and the attraction of other non-neutrophilic cells along with inflammatory cytokines enhanced activation of complement and coagulation cascades.

Interestingly, the use of antihistamine receptors as adjuvant therapy for SARS-CoV-2 patients in the initial schemes seems to have decreased and may have protected patients from the deleterious effect of mast cell activation.<sup>111</sup> Tissue destruction and cell attraction in the inflammatory site may potentiate the cytokine storm observed in SARS-CoV-2 patients. Most probably, the use of histamine receptor inhibitors indirectly would protect patients from this event as it has been proposed.<sup>111</sup>

Alveolar macrophages are, along with dendritic cells (DC), the lung's sentinels, and their activation is crucial to limit bacterial and viral infections and recruit immune cells to the tissue.<sup>112</sup> Monocytes and macrophages are targets of the SARS-CoV-2 virus,<sup>113</sup> and they become nonfunctional after infection; the virus infects but not replicates in these cells.<sup>114</sup> The increase in suppressive myeloid cells with a decrease in normal and inflammatory monocytes and dendritic cells has been reported in COVID patients.<sup>115</sup> The suppressive cells may be crucial in the lack of an effective immune response to the virus.

Inflamed age macrophage is a derived term for alveolar macrophage that distinguish the low responsible macrophage in lung tissue from elderly individuals, which is less active and consequently less prone to eliminate bacterial or viral infections.<sup>113,114</sup> These non-effective cells increase in smokers as compared to non-smokers suggesting that the impaired response leads to severe lung diseases in these patients.<sup>113-115</sup> Lung microbiota is also vital in SARS-CoV-2-infected patients since dysfunctional myeloid cells may give rise to bacterial co-infection.<sup>102,106</sup>

Mature DCs (mDCs) can efficiently activate T cells and maintain specific immune responses, and immature dendritic cells (imDCs) can relocate in different tissues.<sup>116,117</sup> Thus, in the absence of mDCs, the adaptive immune response is impaired.<sup>116,117</sup> MHC class I and II molecules are immediately regulated with antigens and costimulatory molecules when DC cells are infected with viruses.<sup>118</sup> This activation leads to a prompt and potent stimulation of T lymphocytes activity.<sup>117,118</sup> Plasmacytoid dendritic cells (pDC) produce type I IFN and are critical for antiviral response to fight infections.<sup>118</sup> Even though DC cells' role is still debatable in SARS-CoV-2 infection by some authors,<sup>119</sup> the viral infection has been shown to modulate DC subclasses and activate pDC in early stages.<sup>120</sup> There is a redistribution of CD1<sup>+</sup> cDC cells in severe cases in the infection, along with critical changes in other subpopulations and myeloid suppressor cells.<sup>114,115</sup> Thus, it is clear that dysfunctional macrophages and DC affect T activation since proper antigen presentation or activating IFN response is produced. The decrease of co-receptors as CD40, crucial for DC or macrophage interactions, is not fully expressed.<sup>120,121</sup> DC cells' role in the immune response generated by vaccines against SARS-CoV-2 will be critical to analyse, especially in those using the attenuated virus..<sup>114-119</sup>

### 5.3 | Inflammasomes and cytokine storm (CS)

Upon cell injury or infection, inflammasomes trigger proinflammatory cytokine production, mainly IL-1 $\beta$  and IL-18.<sup>122</sup> PRR receptors, including nucleotide-binding oligomerization domain-like receptors (NLR), are critical for inflammasome activation. Excessive activation of inflammasomes may induce cell death (pyroptosis).<sup>122-125</sup>

In several autoinflammatory conditions, the NALP3 inflammasome is uncontrolled.<sup>124,125</sup> The balance between beneficial versus detrimental activation of the inflammasome is challenging.<sup>123-125</sup> The inflammasome activity is critical to the host response and microbial pathogens, also vaccine adjuvants, since the production of cytokines by the innate immune system serves to outline the adaptive immune response.<sup>122-125</sup> The stimulated inflammasomes activate caspase 1, which is involved in the release of bioactive IL-1 $\beta$  and IL-18.<sup>122-125</sup> IL-1, IL-1 $\alpha$  and IL-1 $\beta$  then induce robust proinflammatory activities and play an essential role against harmful exogenous or endogenous stimuli.<sup>123</sup> The production of IL-1 is then critical for the stimulation of the transcription and secretion of other proinflammatory cytokines as IL-6, TNF- $\alpha$ , IL-33, all involved in inflammatory response against pathogens. In genetic hereditary autoinflammatory disorders, there is an uncontrolled production of IL-1, which is usually treated with biological therapy.<sup>122-125</sup> There are several therapeutic approaches to modulate inflammasome activation currently available.<sup>124-126</sup>

Cytokines and particularly chemokines play an essential role in a robust immune response against coronavirus infections.<sup>83,87</sup> However, they are also involved in the immunopathology generated by them.<sup>83,87</sup> Even though a fast and coordinated innate immune response is the first line of defence against viral infections, unregulated and disproportional responses may be responsible for disease severity. Several genetic haplotypes have been related to it, although chronic inflammation may predispose a more severe cytokine storm (CS).<sup>124,125</sup> Rodrigues et al<sup>126</sup> were able to show the activation of inflammasomes in response to SARS-CoV-2 infection and relate the activation to the severity of the disease. As expected, lethality upon virus infection dramatically increases.<sup>127</sup>

Several studies have changed our mechanistic understanding of inflammasome genetics, signalling, cell death decisions and cytokine activation and secretion.<sup>128-133</sup> In severe infections, even mild genetic mutations of proteins of the inflammasome affect its activation and regulation. Several mutations have been described that either delay activation or dysregulate its activity.<sup>129</sup> Therefore, activation of the inflammasome cannot be considered destructive, and the therapeutic mechanism of inhibition must be understood to regulate innate immune response properly.<sup>128-133</sup> CS is a

common complication in SARS-CoV-2, SARS, MERS and other viral respiratory infections. IRF3 and NF- $\kappa$ B are activated by viral RNA, which induces the transcription of IFN and inflammatory cytokines.<sup>133</sup> Figure 1 illustrates the pathological cytokine storm in SARS-CoV-2 infection.

In older adults and patients with comorbidities, including obesity, severe reactions to SARS-CoV-2 due to CS activation is observed; inflammaging and subclinical inflammation have been related to severe and worst outcome.<sup>12,68,131-133</sup> A less developed immune response produces lower levels of inflammation-driving cytokines.<sup>134</sup> The best model of CS is a severe lung infection and sepsis. Sepsis is characterized by persistent hypotension, hyper- or hypothermia, leukocytosis or leukopenia, and thrombocytopenia. Severe lung damage associated with CS resembles sepsis.<sup>126,127</sup>

Regulatory cytokines present a two-sided coin in respiratory infection, limiting immunopathology and, at the same time, compromising viral clearance.<sup>135,136</sup> The balance between proinflammatory and regulatory cytokines is related to clearance and tolerance of the respiratory infection. Pathogens can modify host regulatory cytokines to promote their persistence, as shown for IL-10 in *Mycobacterium tuberculosis* infection and TGF- $\beta$  in influenza virus infection.<sup>136</sup>

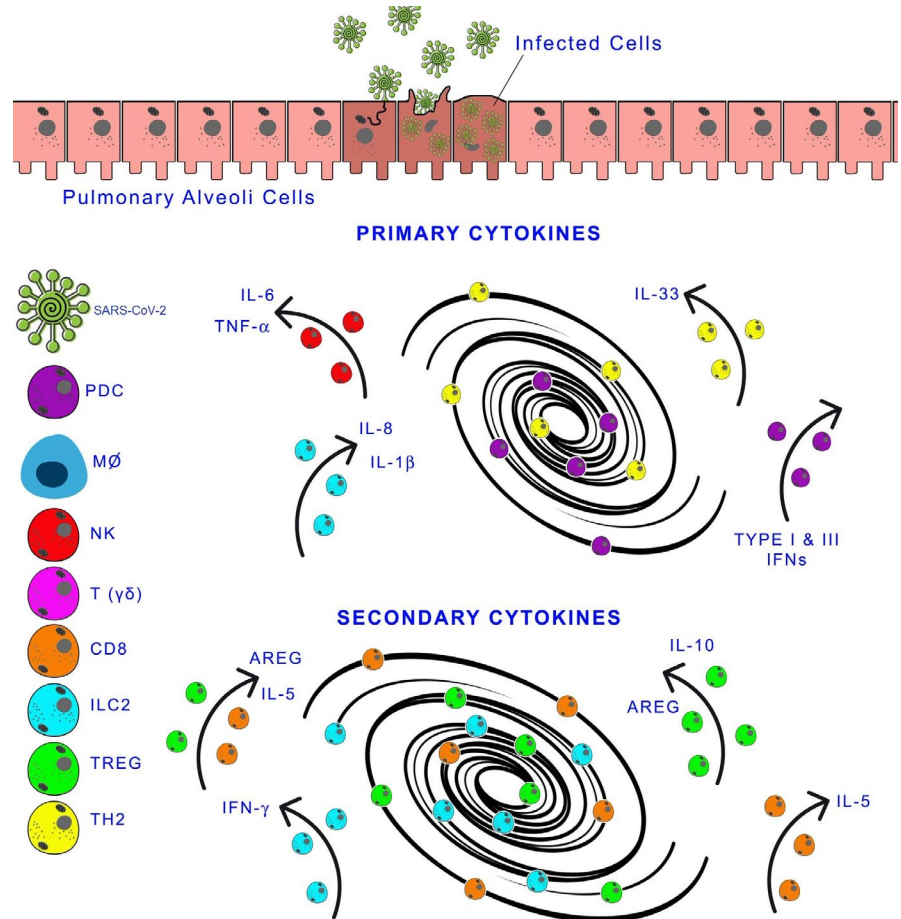
Hyper- and hyporesponders to bacterial components are distinguishable in the healthy population.<sup>137-139</sup> The response is partly explained by genetic polymorphisms that affect the structure and function of Toll-like receptors (TLR).<sup>137</sup> Wurfel et al,<sup>138</sup> in a group of septic patients infected with Gram-positive bacteria, were able to identify a specific hypermorphic single nucleotide genetic polymorphism of TLR1. This mutation was significantly related to the exacerbated immune response and multiple organ failure and death. TLR2 polymorphism, IL-4 rs2070874 and the chemokine (C-C motif) ligand 2 gene (CCL2) also seem to be involved in this phenomenon.<sup>139</sup>

In addition to the polymorphisms of PRRs and cytokines, adaptor proteins may be involved in T cells' response upon cytokine storm-generated in viral infection.<sup>139</sup> The adhesion and degranulation-promoting adapter protein (ADAP), involved in T cell antigen response and survival, is crucial in controlling influenza in the murine model.<sup>139</sup> Little is known about the importance of more critical proteins of the TLR pathway and inflammasome pathways, modulated by several factors, including ageing.<sup>139,140</sup>

Cytokine storm appears to affect patients in severe conditions; lymphocytopenia and exhaustion or anergic responses are often reported in critical patients with COVID-19.<sup>141</sup> Patients who eventually enter the intensive care unit (ICU) have significantly higher plasma levels of IL-6, and IL-10, non-necessarily TNF $\alpha$  and fewer circulating CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes, NK, and B lymphocytes.<sup>141-144</sup> CD8 and NK cells exhaustion markers indicate progression and prognosis of the viral infection,<sup>142-144</sup> and IL-6 appears to be the



**FIGURE 1** Cytokine Storm and SARS-CoV-2 Infection. After infection of the lower respiratory tract's epithelial cells by SARS-Cov-2, the innate immune response is initiated by recruiting cells that produce inflammatory cytokines. If the immune response is successful, there is a resolution. On the contrary, an exaggerated inflammatory process is amplified and damages the tissue. In the left-side panel: SARS-CoV-2 and immune cells. In the centre of the figure are the primary and secondary cytokines (players participating in the storm). AREG, amphiregulin; CD8, CD8+T cells; IFN, interferon; IL, interleukin; ILC2, type 2 innate lymphoid cells; MΦ, macrophages; NK, natural killer cells; pDC, plasmacytoid dendritic cells; T(γδ), T gamma delta cells; TH2, helper cells; TREG, regulatory T cells



crucial cytokine in the inflammatory process.<sup>144</sup> In animal studies, CS also impaired the development of adequate adaptive immunity against SARS-CoV infection.<sup>145</sup> Primarily, 14-month-old BALB/C mice infected with SARS had a higher inflammatory response (higher biphasic transcription of IL-6, TNF- $\alpha$ , CCL2, CCL3, CXCL10 and IFN- $\gamma$  genes), without resolution of the infection as compared to 8-week-old young mice.<sup>145</sup> Molecular analysis showed a wide variety of gene transcription between old and young infected mice,<sup>146,147</sup> suggesting that these two different entities cannot be managed with the same therapy.

#### 5.4 | NK, NKT, T $\gamma\delta$ cells and Mucosa-associated invariant T (MAIT) cells

In several viral infections, NK cells, NKT cells and T gamma delta cells may generate a specific memory against the pathogen in a mechanism that differs from adaptive immunity.<sup>148-153</sup> Circulating NK and NKT cells levels were shown to be in very low numbers in both active and severe patients with SARS-CoV-2.<sup>148-153</sup> In SARS infection, V $\gamma$ 9V $\delta$ 2 T cells were shown to be protective, and this subpopulation showed a memory cell response to the virus.<sup>149</sup> Higher immunoglobulin G anti-SARS-CoV titres were recorded when memory

V $\gamma$ 9V $\delta$ 2 T cells were identified.<sup>149</sup> Moreover, stimulated V $\gamma$ 9V $\delta$ 2 T cells, in vitro, secreted interferon- $\gamma$ , could activate cytotoxic cells to kill SARS-CoV-infected cells.<sup>149,150</sup> Chen et al<sup>150</sup> encountered a significant inverse correlation between the increase in peripheral nonfunctional immature neutrophils with the circulating numbers of CD8 T and T $\gamma\delta$  cells. Alterations in T $\gamma\delta$  were also recorded by Jouan et al,<sup>151</sup> which demonstrated the importance of CD69 activation marker in patients recovering from the infection. These results suggest that the impaired immune response observed in severe cases is due to the lack of protective antiviral immune response. Any opportunistic pathogen may easily overcome the protective immune response. Following the lack of proper innate immune response, Carissimo et al<sup>152</sup> reported the presence of immature neutrophils, and the ratio of immature neutrophils to VD2  $\gamma\delta$  T cells CD8 accurately predicted pneumonia and hypoxia onset.

Maucourant et al<sup>153</sup> analysed different NK populations in infected patients. The authors were able to show that NK cell subpopulations and functions were related to the clinical con the patients. Two critical markers were found: NKG2C, an activation marker, and Ksp37, a secretory protein related to cytotoxicity. In recovered patients, these two markers were important.<sup>153</sup> Nonetheless, a decrease in the expression of the inhibitory receptor CD158b, KIR2DL2/L3 was reported in

SARS-infected patients that recover from the infection.<sup>153,154</sup> In animal models, the ligand interaction NKG2D (CD314) protects the animals from neurologic and hepatic damage induced by the coronavirus.<sup>154</sup> Blocking NKG2D made mice more susceptible to tissue damage, suggesting that the receptor may be necessary for immune surveillance.<sup>154</sup> Future studies should assess the importance of killing and KIR receptors and their ligands in this viral disease. More research is required in this field.

The innate immune response is crucial to defining COVID patients' outcome, resolution and viral clearance, severity and chronicity.<sup>18,155,156</sup> Immune senescence could be a critical issue in generating an effective immune response.<sup>157</sup> An impaired immune response can also be observed in patients infected with other viral infection (influenza, cytomegalovirus) or bacterial infection decreasing immune surveillance and effective antiviral response.

Mucosa-associated invariant T (MAIT) cells are distinctive innate-like T cells that facilitate the interaction between innate and adaptive immunity and consequently are important in defence against bacterial and viral infections.<sup>158</sup> MAIT cells express CD8 CD45RO CD161 and can be easily identified by the use of 5-(2-oxopropylideneamino)-6-D-ribityl amino uracil (neoantigen of bacterial origin) in tetramers.<sup>158</sup> Tissue activation of MAIT cells predisposes neutrophil attraction which enhances the inflammatory milieu.<sup>158</sup> Recently, it was shown that these cells decrease in peripheral circulation in SARS-CoV-2.<sup>159</sup> However, the circulating cells are activated, and high expression of CD69 and low CXCR3 seems to be related to poor clinical outcome. In convalescence, the number of MAIT cells increases, suggesting a direct relationship with the viral infection resolution.<sup>159</sup> These cells' roles in SARS-Cov-2 pathogenesis and other innate lymphoid cells (ILC1, ILC2 and ILC3) are still under investigation since they may be crucial in resolving the viral infection. The use of animal models will improve our vision of these cells in the viral infection.

Multisystemic inflammatory syndrome associated with SARS-CoV-2 infection is a new syndrome described in children characterized by fever, rash, conjunctivitis, mucocutaneous involvement and cardiac complications along with gastrointestinal symptoms and coagulopathy.<sup>160</sup> Interestingly, the syndrome affects more Black than Asian descent children suggesting that there may be a genetical relationship related to HLA. In children, the syndrome involves activation of T $\gamma$  $\delta$  and CD4<sup>+</sup>CCR7<sup>+</sup> T cells, high expression of CD64 on neutrophils and monocytes, and a decrease amount of conventional monocytes and antigen-presenting cells which have low expression of HLA-DR and CD86.<sup>160,161</sup> Some children with a high incidence of respiratory infectious diseases may present temporary hypogammaglobulinaemia or low IgA levels.<sup>162</sup> These patients may be more at risk to develop severe illness from SARS-CoV-2 infection. Patients with absent

humoral immunity respond well to remdesivir<sup>163</sup> and IL-6R biological therapy.<sup>160,161</sup> Noteworthy, Naito et al<sup>164</sup> proposed an association between IgA deficiency with SARS-CoV-2 infection and severity based on the incidence of reported IgA immunodeficiency. It can be concluded that the IgA response induced through MAIT cells can be crucial in an effective and protective response against SARS-CoV-2.

## 6 | ANTIGEN PRESENTATION AND ADAPTIVE IMMUNE RESPONSE VIRUS ESCAPE

Antigen presentation in SARS-CoV-2 infection has not been well studied as the other members of the coronavirus family SARS and MERS.<sup>165</sup> DC and chemokines such as IP-10 and MP1 play an essential role in antigen presentation and T cell activation.<sup>165,166</sup> Also, antigen presentation by DC is preferential via MHC class I and then class II suggesting that CD8 response may be an earlier event.<sup>116,117</sup> Macrophages also present viral antigens that can be obtained by 1) an effective RIG-TLR dependent response against the virus, 2) the uptake of killed virus-infected cells or 3) through immune complex binding to Fc receptors as described by other viral diseases<sup>167</sup> and suggested in the data obtained from the analysis of patients' samples.<sup>114,115</sup> The presence of non-typical monocytes recorded and the decrease in HLA-DR indicate that one mechanism of viral escape could be through HLA molecules' low expression.<sup>165,166</sup> The use of chloroquine as initial treatment in SARS-CoV-2 patients may be responsible for decreasing antigen expression and the short-lasting antibody response in some cases.<sup>168</sup>

Both HLA molecules, class I and class II, can bind SARS-CoV-2 S peptides with different affinities.<sup>169-171</sup> Sanchez-Mazas<sup>171</sup> reviewed the link between genetic variability among MHC class I genes (A, B and C) that may affect the predisposition and severity of acute respiratory distress syndrome in coronavirus infection. They found similarities in the previous SARS infection, MERS and SARS-CoV-2. In the three reports,<sup>169-171</sup> HLA-B \* 46:01 (a haplotype usually encountered in eastern Asia) had the lowest predicted binding score for S1 peptides, suggesting that people with this allele may be more susceptible to infection, analogous to what occurs in SARS infections. Other alleles encountered HLA-B\*07:03, DRB1\*03:01, DRB1 \*12:02 are also related to SARS susceptibility.<sup>171</sup> HLA-B \* 15:03 and HLA A 02\*01 showed the highest scores for binding highly S peptides and other common human coronaviruses. These results suggest that several HLA haplotypes are associated with different diseases' susceptibilities.<sup>169-173</sup> Based on the incidence of SARS-CoV-2 infections and death in Africa, Iesa et al<sup>173</sup> encountered common immunodominant regions of *Plasmodium falciparum*, explaining the lower infection rates. Even though

CD8 cells could be responsible for the postulated protective immune response, antibodies that cross-react against similar epitopes of both pathogens have to be analysed carefully. It is also interesting to examine the effect of hydroxychloroquine treatment on malaria patients exposed to the SARS-CoV-2 virus.<sup>168</sup>

In a complete and detailed analysis performed with data provided by 98 countries, Leite et al<sup>174</sup> were identified several interesting loci related to mortality. Besides the strong association of polymorphisms of the cytokines IL-6, IL-10 and IL-12B, the authors reported HLA-B\*13:01 as a protective allele. This allele is expressed preferentially in Asiatic populations, and it is linked to dapson-induced hypersensitivity reactions.<sup>175</sup> Dapsone was proposed as a potential treatment to decrease cytokine storm induced by SARS-CoV-2 infection.

Bruchez et al<sup>176</sup> analysed class II presentation in Ebola infections found that CIIA, an MHC II transactivator, can be crucial for host defence against viruses. CD74 p41 blocks the coronavirus endosomal entry pathway, a process essential for SARS-CoV-2 replication. Interestingly, statins suppress CIIA transcription induced by IFN  $\gamma$ <sup>177</sup> and probably affect the mentioned mechanism of protection. More research is required to ascertain the role of MHC and CIIA in viral entry and antigen presentation.

Analysing the changes in circulating cells in SARS-CoV-2-infected patients, García,<sup>156</sup> in a review, outlined the difference between protective immunity and immune dysregulation. In severe patients, the expression of exhaustion markers or inhibitory markers is significant, suggesting that CD8 circulating cells are non-responsive or anergic.<sup>156</sup> However, other unsolved issues arise from the changes in circulating cells during the infection, the generation of antibodies, cytokine changes and viral clearance. The induction of specific CD8 cells against the virus can be essential to decrease the viral burden. Vibholm et al<sup>178</sup> were able to show that SARS-CoV-2 virus persistence was depended on CD8 responses based on a nucleotide-based screening test. However, the lack of an effective CD8 response is dependent on innate immune cells and MAIT cells.<sup>179-181</sup> Viral shedding, the lack of viral RNA recognition and the impaired generation of IFN I and III production and pathways generated by them are related to viral persistence and chronicity.<sup>179-182</sup> The adaptive immune response can be long lasting,<sup>181,182</sup> suggesting that chronicity may be replaced by an effective innate immune response in the airways for T cells, CD4 and CD8, and B cells.<sup>181,182</sup>

Chen et al,<sup>183</sup> in BALB/c SARS model, were able to show that the T cell CD4<sup>+</sup> population is critical for a viral response as opposed to T cytotoxic CD8<sup>+</sup> cells. Antibody response seems to be essential in viral clearance. Likewise, in severely infected patients, IFN- $\gamma$  production by CD4<sup>+</sup> T cells is significantly lower than controls,<sup>142,143,156,157</sup> and the circulating B lymphocyte number is deficient. The decrease

in TH1 and B cells impairs antibody production in these patients.<sup>156,157</sup> Wang et al<sup>184</sup> established that post-treatment, a significant reduction of CD8<sup>+</sup> T cells and B cells, and a higher CD4<sup>+</sup>/CD8<sup>+</sup> ratio were markers of unresponsiveness to therapy worse outcome. In a series of experiments ex vivo to understand virus involvement in cell activation, mononuclear cells from patients were stimulated with a mixture of *E coli* and *Candida albicans*.<sup>184</sup> The cells secreted more IL-6 than TNF $\alpha$  and IL-1 $\beta$ , and the same ratio was observed in the sera.<sup>184</sup> Plasma from patients decreased HLA-DR expression in stimulated cells, an effect that tocilizumab, anti-IL-6R, blocked.<sup>184</sup> It is clear then the dependence of innate immunity and acute-phase proteins in the infection's adaptive immune response. Once the hyperinflammation is controlled therapeutically, an effective immune response is achieved.

Several bioinformatics studies on COVID-19 and T and B cell paratopes have been published.<sup>185-187</sup> Two linear epitopes on the SARS-CoV-2 spike protein elicit neutralizing antibodies in COVID-19 patients.<sup>186</sup> Liu et al<sup>187</sup> found potent and neutralizing antibodies against multiple epitopes. Nonetheless, the number of epitopes and the antibody responses of convalescent plasma does not match with the role of CD8 in cell recruitment and cytotoxic response. This paradigm can probably be explained by the longitudinal modulation of T and B cell responses described by Niu et al.<sup>188</sup> The authors showed a diminished TCR repertoire at the beginning of the infection but increased convalescence and recovery. In B cells, clonal expansion occurs in convalescence with a dramatic expansion of IgA positive B cells, and then, other B cells start producing IgG antibodies with neutralizing ability. This process is probably hampered in elderly patients.<sup>189</sup> Nonetheless, important questions also arise in patients with IgA immunodeficiency or mild immunodeficiencies and patients with IgA nephropathy even though they respond to remdesivir therapy.<sup>163</sup>

Strong antibody responses against the SARS-CoV-2 virus were detected in patients that quickly recover from the infection.<sup>190</sup> In these individuals, the authors were able to detect virus-specific memory B cells and circulating activated CD4 T cells suggesting that a memory response was responsible for the effective response. In concordance with these studies, in a flow cytometry assessment in our laboratory,<sup>191</sup> we observed that circulating memory T cells do not decrease in infected patients with moderate infection, suggesting a possible response to previous coronavirus infection.

Ferreti et al<sup>192</sup> analysed, doing a genome-wide screening, the specific antigens recognized by memory CD8 cells against the virus. They identified the epitopes that would bind to the 6 most prevalent MHC class I in the population. Interestingly, of the 29 shared epitopes, only 3 were located in the spike protein. The other epitopes were located in the ORF1ab or in the nucleocapsid protein.<sup>192</sup> The memory response does not seem to be related to other coronaviruses,

suggesting that an effective innate response against the virus was crucial in developing CD8 specific T cells.<sup>192</sup>

Several studies aiming to analyse the differences between responders and non-responders to SARS-CoV-2 infection have addressed as if there was a protective immune response before infection.<sup>193-196</sup> It has been shown that there are memory T cell responses against other coronaviruses, which protect from SARS-CoV-2 infection.<sup>193-196</sup> This protection is often encountered in children exposed to other coronaviruses. Eventually, the generation of memory cells and protective antibodies by immunization against other viruses can occur.<sup>196</sup> The protection mechanism may depend on similar epitopes presented by the vaccine or even an induction or immune response stimulation like the BCG vaccine.<sup>197</sup> The vaccine was shown to decrease mortality by activating immune response to activation of innate lymphoid cells (T $\gamma$  $\delta$ , NKT, ILC).

Conti and Younes<sup>198</sup> hypothesized (in an editorial) that the difference in the immune response against coronavirus infection between genders is due to several issues: (a) men are more susceptible to viral infections because men produce a lower amount of antibodies; (b) the amount of circulating T CD4<sup>+</sup> cells is smaller in man as compared to women, (c) men produce higher amounts of IL-6, and consequently, cytokine storm is most probable. In a recent revision, Rahimi et al<sup>199</sup> analyse the different immune responses dependent on gender and the various trials associated with SARS-CoV-2. The detailed analysis favours the proposal of several new therapies; however, more research needs to be performed based on virus variations, gender, ethnicity and age.<sup>12,13</sup>

A relationship between gene clusters and COVID-19 severity has been postulated since the beginning of the pandemic. Karaderi et al<sup>200</sup> were able to show in an interesting analysis of gene mortality the importance of chromosome 3 cluster and other clusters. In the cluster in chromosome 3.21, six genes, CCR9, CXCR6, FYCO1, LZTFL1, SLC6A20, XCR1, have been associated with severity. The group consists of chemokine receptors, CCR9, CXCR6, XCE1, a protein related to vesicle transport and autophagosome maturation, FYCO1, the leucine zipper transcription factor-like protein 1 related with ciliary function, LZTFL1, and a sodium and chloride-dependent transporter, SLC6A20. An additional cluster involved in the viral immune response is the 2'-5'-oligoadenylate synthetase 1 cluster, OAS. In this cluster, another six genes are involved: the receptor interferon  $\alpha\beta$ 2, IFNAR2, two chemokine receptors CCR2, CCR3, HLA-G, a regulator of mRNA, coiled-coil alpha-helical rod protein 1, CCHCR1 and NOTCH4. Two independent genes were associated with the finding; the serine protease dipeptidyl peptidase 9 (DPP9) and the kinase TYK2, associated with the IFN  $\alpha$  signal. Also, there is an association with ABO genes in various ethnic groups. As stated in the complement section of the review,<sup>98</sup> the chromosome 3 variant rs11385942

is involved in complement activation and makes this cluster a candidate for genetic, biochemical and immunological analysis. Thus, chemokine receptors and IFN receptors are related to the SARS-CoV-2 viral infection and therapy response, as has been illustrated through the review. The role of transports involved in electrolyte balance should not be overlooked in patients infected with SARS-CoV-2.

In general, we consider that innate immunity, complement, memory T cells, CD4 and CD8 and B cells are crucial to generate an effective immune response against the viral infection independently of ethnicity, gender or ageing. In a proinflammatory environment (inflammaging and metabolic syndrome), the generation of memory cells may be impaired, yet it can be boosted with immune therapy, vaccines or other therapies.

## 7 | CONCLUSIONS

The SARS-CoV-2 infection goes through multiple phases. The initial stage involves viral replication, often paired with relatively mild symptoms and innate immune response activation. Subsequently, adaptive immunity is activated, and either the virus is cleared, the infection is solved, or it becomes severe or chronic. The clinical spectrum may vary depending on the viral load and immune status of the patient. Immunocompromised patients or patients with several comorbidities are more susceptible to develop severe disease. Severe pulmonary distress syndrome is often observed in these patients with a long recovery rate. In some patients, lung fibrosis may occur. Young patients with high exposure to the virus may have the same outcome, that is, infected health care personnel.

Clinicians and researchers have learned that severe hyperinflammation (cytokine storm) should be avoided. Genetic polymorphisms and mutations may affect the immune response and viral clearance, essentially IL-6, IL-10, IL-12, chemokine receptors and IFN type I and III response. The role of complement in the disease's immunopathology has provided new insights for treatment and clinical management. The mechanism of the specific generation of memory T CD4 and CD8 cells against the virus seems essential in the production of protective antibodies and virus elimination. The role of NK, NKT, T $\gamma$  $\delta$  and innate cells (MAIT and ILC) on the viral infection is still under scrutiny, although they may play an essential role in the initial infection. Most probably in vaccine studies, their immune vigilance role against the virus could be ascertained in detail. Long-term memory is the final goal.

Genetic polymorphism and mutations may hamper an effective antiviral immune response, and more research should be done in this area. Even though healthy children are less

prone to have severe disease, medical counselling, including up to date vaccine schedule, may help protect this population from SARS infections. Virus infections, common in elders, may also contribute to the impaired response in this population and should be carefully screened. To avoid severity in risk populations, viral and antigen screening should be performed on a large scale. Moreover, continuous screening of recovered patients with comorbidities should be performed to avoid a second infection.

Finally, even though this evolving disease's progress is very fast, the immunologist's role in ascertaining an effective immune response mechanism is still needed.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

JBDS, AG and DM were involved in the review and literature search. The manuscript writing was completed by JBDS, AG and DM and editing by JBDS, AG, DM and MH. MH is responsible for funding.

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