



# Immunology of COVID-19: Mechanisms, clinical outcome, diagnostics, and perspectives—A report of the European Academy of Allergy and Clinical Immunology (EAACI)

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#### Abstract

With the worldwide spread of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) resulting in declaration of a pandemic by the World Health Organization (WHO) on March 11, 2020, the SARS-CoV-2-induced coronavirus disease-19 (COVID-19) has become one of the main challenges of our times. The high infection rate and the severe disease course led to major safety and social restriction measures worldwide. There is an urgent need of unbiased expert knowledge guiding the development of efficient treatment and prevention strategies. This report summarizes current immunological data on mechanisms associated with the SARS-CoV-2 infection and COVID-19 development and progression to the most severe forms. We characterize the differences between adequate innate and adaptive immune response in mild disease and the deep immune dysfunction in the severe multiorgan disease. The similarities of the human immune response to SARS-CoV-2 and the SARS-CoV and MERS-CoV are underlined. We also summarize known and potential SARS-CoV-2 receptors on epithelial barriers, immune cells, endothelium and clinically involved organs such as lung, gut, kidney, cardiovascular, and neuronal system. Finally, we discuss the known and potential mechanisms underlying the involvement of comorbidities, gender, and age in development of COVID-19. Consequently, we highlight the knowledge gaps and urgent research requirements to provide a quick roadmap for ongoing and needed COVID-19 studies.

#### KEYWORDS

COVID-19 comorbidity, COVID-19 immunity, COVID-19 multimorbidity, COVID-19 prevention, COVID-19 treatment, SARS, SARS-CoV-2 receptors

## 1 | INTRODUCTION

Infections with the novel coronavirus SARS-CoV-2 resulting in COVID-19 development represent the major medical and scientific

challenges of our time. Knowledge on SARS-CoV-2 infection pathways and mechanisms associated with immune defense or immunopathology is growing exponentially, as it is indispensable to design the proper diagnostic and therapeutic strategies. However, there

**TABLE 1** Summary of knowledge gaps and research needs pertaining to SARS-CoV-2 and COVID-19 (as of May 20, 2020)

Knowledge Gaps	Research Needs
Origin and evolution SARS-CoV-2	To shed light on the origin of SARS-CoV-2 via studies of genomic epidemiology and evolutionary dynamics
COVID-19 diagnosis	To develop rapid and specific point-of-care diagnostic test for COVID-19 and to validate existing serological tests
Zoonotic transmission and exhaustive characterization of human SARS-CoV-2 transmission	To elucidate mechanisms of SARS-CoV-2 transmission from animals to humans and vice versa. To determine how demographic factors and severity of COVID-19 patients affect SARS-CoV-2 transmission as well as how infectious are asymptomatic or pre-symptomatic infected people
Route of SARS-CoV-2 transmission	To ascertain the role of fecal-oral transmission in COVID-19 and better define the presence and duration of SARS-CoV-2 in oral and respiratory secretions, in fecal samples and in serum.
Natural history of asymptomatic and mild SARS-CoV-2 infection in humans	To identify SARS-CoV-2 a-/oligosymptomatic carriers to track their viral loads, clinical presentations and immune response (antibody titers, immune phenotyping, etc) over time
Pathogenicity of SARS-CoV-2	To investigate mechanisms of and changes in SARS-CoV-2 pathogenicity (as compared to SARS-CoV) to provide the basis for the identification of novel therapeutic targets
Spectrum of COVID-19 severity	To characterize the heterogeneity of COVID-19 severity to aid in directing management and treatment of COVID-19 patients
Risk factors and biomarkers associated with severe illness or mortality in COVID-19	To identify COVID-19 sensitive groups and determine the causes underlying disease severity to reinforce prevention strategies and treatment of high-risk groups
COVID-19 treatment	To screen new pharmaceuticals, small molecule compounds, biologics, and other agents that have potent anti-SARS-CoV-2 to empower current COVID-19 treatments
Vaccine development for SARS-CoV-2	To develop SARS-CoV-2 vaccines for prevention and ultimate eradication of SARS-CoV-2. Particular attention should be placed to investigate potential antibody-dependent enhancement of viral infection in vaccine candidates
Pre-clinical models for SARS-CoV-2 and COVID-19 research	To develop animal models for SARS-CoV-2 research (mechanisms of infection, pathogenesis, treatments, etc)
Para-/postinfectious syndromes in SARS-CoV-2 infection	To understand COVID-19-associated Kawasaki-like syndrome/TSS in children and rare para-/postinfectious symptoms in adults.
Long-term sequelae of COVID-19	Follow-up of COVID-19 patients to detect potential long-term consequences of COVID-19 pneumonia (eg, pulmonary fibrosis, early COPD) and other manifestations (eg, renal impairment, cardiac/vascular dysfunction, increased risk of thrombosis/ sepsis (due to endothelial dysfunction))
Individual protection after SARS-CoV-2 infections	To understand why development of protective antibodies is not seen in all infected patients and whether this might be related to severity of SARS-CoV-2 infection

are several knowledge gaps and urgent unmet research needs in our understating of the current pandemics (Table 1). A group of experts in basic and clinical immunology has joined forces under the umbrella of the European Academy of Allergy and Clinical Immunology (EAACI) to provide a consensus report on the basic molecular and immune mechanisms associated with susceptibility, clinical presentations and severity of COVID-19.

## 2 | SARS-COV-2 RECEPTORS: PROVEN AND POTENTIAL INTERACTION PARTNERS

On the basis of sequence homology, all human coronaviruses have animal origins: SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-NL63, and HCoV-229E are considered to have originated from bats,<sup>1</sup> whereas HCoV-OC43 and HKU1 likely originated from rodents (Figure 1).<sup>2</sup> SARS-CoV-2 has a significant structural similarity to SARS-CoV and MERS-CoV and other human and animal

coronaviruses.<sup>3,4</sup> It has been quickly determined that SARS-CoV-2, similarly to SARS-CoV, utilizes the membrane bound form of angiotensin-converting enzyme 2 (ACE2) to enter human cells via its spike protein (S).<sup>5</sup> After SARS-CoV-2 has bound ACE2, ACE2 will be internalized and its membrane expression decreased. Whereas ACE2 is an important regulator of bradykinin, its reduced expression in the lung environment results in local vascular leakage leading to angioedema in the affected lung tissue.<sup>6</sup> The host serine protease TMPRSS2 cleaves spike protein into S1 and S2 fragments, which enables fusion with the cellular membrane, entrance to the cell, and start of the replication process.<sup>7</sup> In addition to TMPRSS2, other proteins such as furin or human endosomal cysteine proteases are potentially capable of cleaving S, such as cathepsin L (CTSL) and cathepsin B (CTSB).<sup>8,9</sup> ACE2 is highly expressed in the lungs, small intestine, kidney, and heart, but it is not expressed on innate and adaptive immune cells.<sup>10-13</sup> As recently shown, SARS-CoV-2 can also use CD147 (also called basigin (BSG) or extracellular matrix metalloproteinase inducer (EMMPRIN)), to enter cells of

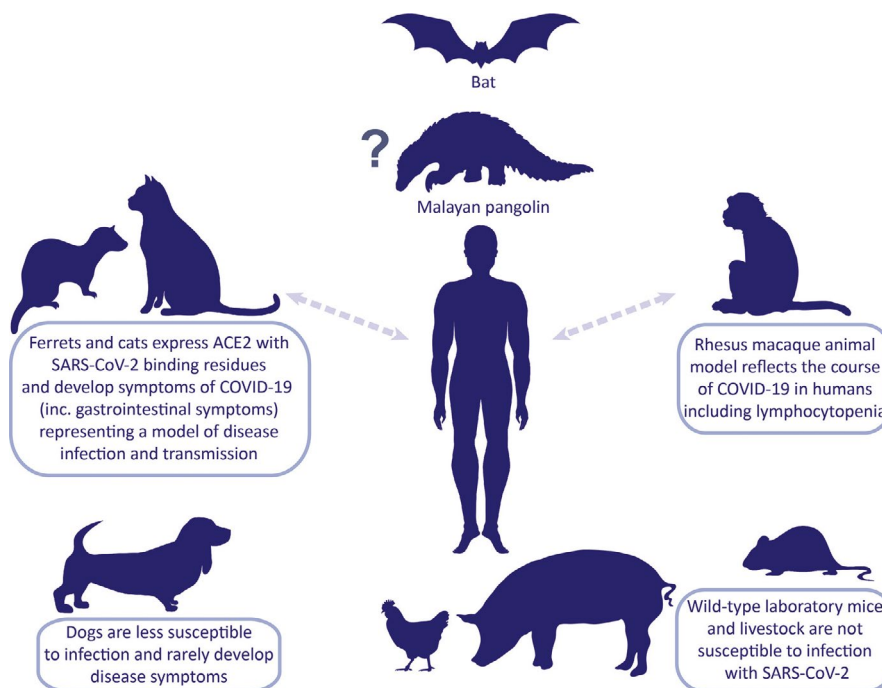
epithelial origin, but it is not yet clear if then virus can efficiently replicate or it leads to the cell death<sup>14</sup> CD147 is utilized as a receptor by other viruses including SARS-CoV and HIV-1, as well as by malaria to enter erythrocytes.<sup>15-17</sup> It is, however, not yet clear if SARS-CoV-2 can replicate inside immune cells or just infects them and causes cell death. CD147 is a transmembrane immunoglobulin-like receptor, which also exists in a secreted form.<sup>13,18</sup> At the cellular membrane, it is activated by several extracellular ligands such as cyclophilins A and B (PPIA and PPIB), S100A9 or platelet glycoprotein VI (GP6).<sup>19-22</sup> Its extracellular glycosylation sites bind to complex proteoglycans such as syndecan-1.<sup>23</sup> CD147 often creates membrane complexes with CD44, one of the receptors for hyaluronan, an extracellular matrix component.<sup>24</sup> Coronaviruses incorporate host cyclophilins during their cellular replication cycle, which further enables them to bind to CD147.<sup>25,26</sup> CD147 is expressed in human airway and kidney epithelium, as well as in innate cells (granulocytes, macrophages, dendritic cells (DC), innate lymphoid cells (ILCs), and lymphocytes).<sup>10</sup> Other receptors potentially utilized by SARS-CoV-2 are CD26 (encoded by *DPP4*; a receptor for MERS-CoV), an important T cell and also epithelial cell receptor, amino peptidase N (ANPEP; a receptor for human and porcine coronaviruses),<sup>13,27</sup> ENPEP and a glutamyl aminopeptidase,<sup>28</sup> as well as DC-SIGN<sup>29</sup> (Figure 2).

### 3 | ENTRANCE OF THE VIRUS THROUGH EPITHELIAL BARRIERS: COVID-19 PATHOPHYSIOLOGY

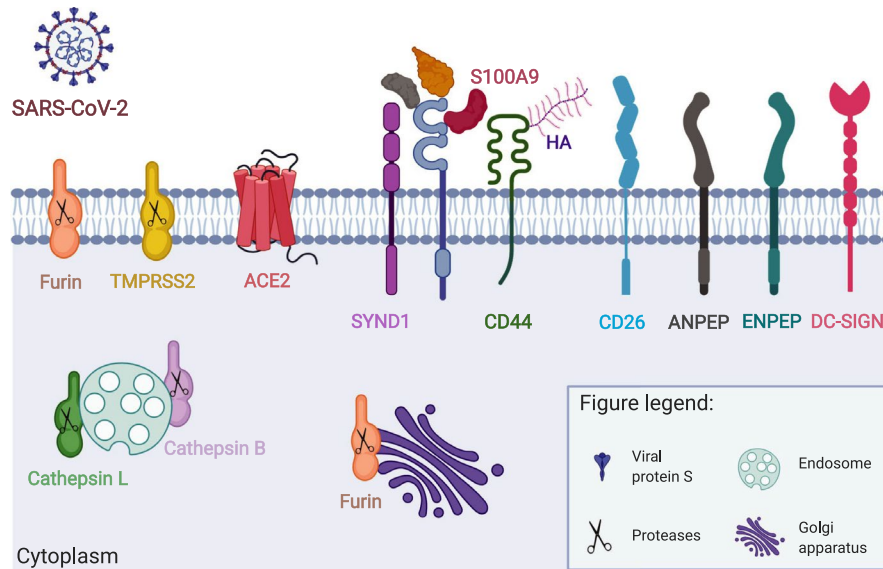
#### 3.1 | Airway epithelium: hotspot for disease development

In the upper and lower airways ACE2 and TMPRSS2 are highly co-expressed,<sup>10-13</sup> but there is no expression of SLC6A19, which potentially blocks the access of TMPRSS2 to ACE2 and subsequently reduces active infection.<sup>30,31</sup> In the nasal and the pharyngeal epithelium, in goblet and ciliated cell, ACE2 is expressed at high levels and co-expressed with TMPRSS2 representing the sites of initial viral replication and a main source of infectious particles.<sup>10-13,30</sup> The lower airways, bronchial epithelium and type II pneumocytes (AT2 cells) highly express ACE2 and TMPRSS2, which may provide virus entrance to the lung and lead to COVID-19 pneumonia. Moreover, CD147, CD26, ANPEP, and ENPEP are also expressed in the airway epithelium, as well as in many innate and adaptive immune cells,<sup>10,13</sup> both in bronchoalveolar lavage (BAL) and peripheral blood (Figure 3A).

Once the virus enters the host cell, it releases its RNA into the cytoplasm and uses the host translation machinery to translate its



**FIGURE 1** SARS-CoV-2 on the animal-human interphase. Animal models that resemble clinical and pathological features of COVID-19 are essential to investigate pathogenesis, transmission, and therapeutic strategies. SARS-CoV-2 shares 96.2% of its genome sequence with the bat CoV RaTG13 posing the bat as the most probable natural host of virus origin. SARS-CoV-2-related coronaviruses have been identified in Malayan pangolins, which is considered as an intermediate host between bats and humans. ACE2, a critical SARS-CoV-2 receptor, in wild-type mice differs from the human one; therefore, transgenic mice models with recombinant hACE2 are necessary. To this date, Rhesus macaques, with ACE2 identical to human's, have been used to study the natural course of the disease and the effectiveness of therapeutic intervention with intravenous immunoglobulins. Ferrets and cats have been shown susceptible to SARS-CoV-2 infection and to develop COVID-19 symptoms including respiratory and gastrointestinal manifestations. Limited facilities and expertise in handling nonmurine species may hamper usage of the aforementioned models. Transmission between humans and animals has not been unequivocally confirmed



**FIGURE 2** Cellular distribution of confirmed and potential SARS-CoV-2 receptors and interaction partners. Entry of SARS-CoV-2 into the host cells depends on expression of i) adequate receptors and ii) cellular proteases. The two-step infection process is mediated by the viral Spike (S) protein. Its binding to the receptor and cleavage by proteases assures virus internalization. ACE2 and TMPRSS2 are critical complex for SARS-CoV-2 infection. CD147 and its extracellular (Cyclophilin A, Cyclophilin B, Platelet glycoprotein VI, S100A9, Hyaluronic acid) and transmembrane (CD44, Syndecan-1) interaction partners can be also used for SARS-CoV-2 entry and/or modulation of immune responses to the virus. It has been suggested for SARS-CoV-2 and shown in case of other *Coronaviridae* family members that they can also exploit other cell surface receptors (CD26, ANPEP, ENPEP, DC-SIGN) and proteases (Furin, Cathepsin L, Cathepsin) to enter human cells. CypA, Cyclophilin A; CypB, Cyclophilin B; GPVI, Platelet glycoprotein VI; HA, Hyaluronic acid; SYND1, Syndecan-1. This figure is modified from the original publication by Radzikowska, Ding, et al, presenting the distribution of these receptors in various human tissues and immune cells in healthy children and adults, and in patients with COVID-19 comorbidities and risk factors (ref). Created with Biorender.com

polyproteins pp1a and pp1b, also known as replicases and viral essential proteases 3CLpro and PLpro. These proteases cleave polyprotein complex into several nonstructural proteins (Nsp), which together with the viral RNA-dependent RNA polymerase form the replication complex, where the negative strand and mRNA for structural proteins (S, nucleocapsid (N), envelope (E), and membrane (M)) and accessory proteins for the virus are created.<sup>2,32,33</sup> After protein translation, they traffic through the ER to the Golgi apparatus, where the mature virions are assembled in budding vesicles and are exocytosed from the cell. Inside infected cells, there are several innate immune mechanisms responsible for recognizing the virus at different stages of its replication and leading to the production of interferons type I (IFN $\alpha$  and  $\beta$ ), type III, and pro-inflammatory cytokines.<sup>34</sup> Genes encoding these interferons form the type-1 (E1) epithelial response profile. Also, ACE2 is a typical E1 gene.<sup>35</sup> This response also includes mechanisms such as the expression of helicases or cytidine deaminases targeting viral RNAs (Figure 3A).

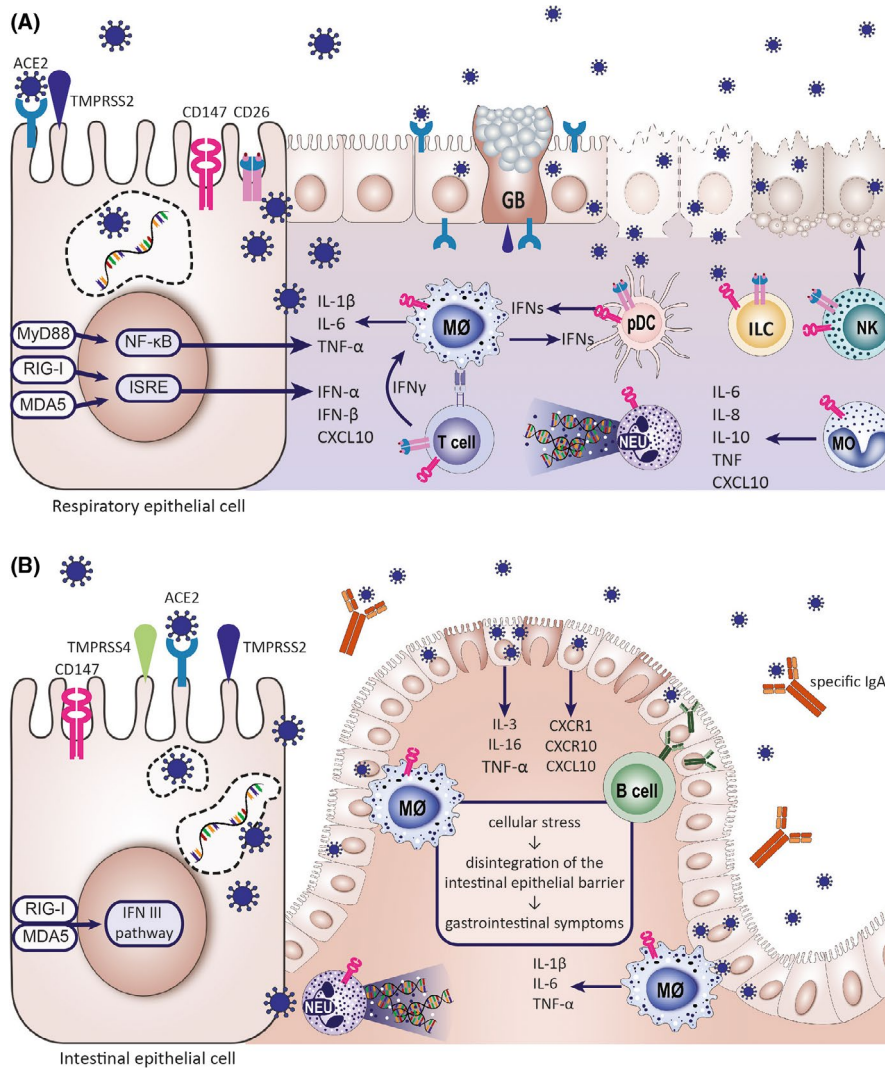
Viruses use various strategies to evade those mechanisms.<sup>36</sup> Yet, little is known about SARS-CoV-2 antiviral responses and evasion strategies of this virus, but likely much can be extrapolated from the SARS-CoV and MERS-CoV-based knowledge.<sup>34,37</sup> Viral single-stranded RNA (ssRNA), double-stranded RNA (dsRNA), and proteins are recognized by cytosolic pattern recognition receptors (PRR), mainly RIG-I/MDA5 and toll-like receptors (mainly TLR7/8). This recognition leads to recruitment of MAVS, MyD88, and/or TRIF, respectively. Eventually, IRF3 and IRF7 transcription factors

are activated leading to the production of type I interferons (IFN- $\alpha$  and IFN- $\beta$ ), whereas NF- $\kappa$ B and AP-1 transcription factors lead to the production of pro-inflammatory cytokines such as IL-6, IL-8, IL-1 $\beta$ , CXCL10, and CCL2.<sup>37</sup>

Epithelial cells produce type I and type III IFNs upon viral infection. Type I IFN act through receptors expressed in a vast number of cells. In contrast, type III IFNs seem to exert their effect mostly on epithelial cells, are less inflammatory, and are activated faster than type I IFN.<sup>38,39</sup> IFNs are one of the most potent antiviral components of the innate immune response. They work on various levels, that is, blocking viral attachment, entry, trafficking, protein production, and genome amplification and also viral assembly and egress.<sup>38</sup> Moreover, IFNs also activate other innate and adaptive immune responses. However, in case of COVID-19 these responses seem to be diminished<sup>40</sup> or dysregulated.<sup>41</sup>

SARS-CoV and MERS-CoV inhibit IFN signaling on various levels.<sup>42</sup> The nsp 16 mediated 2'O methylation of viral mRNA cap structure prevents coronaviruses recognition by MDA5.<sup>43</sup> The sequestration of viral dsRNA within double membrane vesicles (DMVs) also protects coronaviruses from detection through cytosolic PRRs.<sup>44</sup> Moreover, coronaviruses produce many non-structural proteins which inhibit induction of IFNs (inhibition of IRF3 and IRF 7), and/or interferon signaling (inhibition of STAT 1 signaling).<sup>42</sup> A reduced antiviral response via IFN pathway inhibition, together with an ongoing pro-inflammatory response, presumably heightened by increased viral load, may lead to excessive





**FIGURE 3** Epithelial barriers are susceptible for the SARS-CoV-2 infection. (A) Epithelial cells of the respiratory system are the primary site of SARS-CoV-2 infection. The respiratory epithelium is equipped with the receptors and other host proteins allowing viral entry: ACE2, TMPRSS2, CD147, and CD26. The highest expression of ACE2 is found in the nasopharynx. The virus was found to propagate in the lower respiratory tract as well, especially in type II alveolar cells. The effects of the virus on the respiratory epithelial barrier include cell membrane fusion and syncytium formation (which represents a mechanism of viral spread), apoptosis and virus-mediated cell lysis leading to the loss of barrier function. Upon infection, epithelial cells release interferons, chemokines, and cytokines promoting tissue infiltration by innate immune cells, such as monocytes, NK cells, neutrophils, and, with time, inflammatory macrophages and virus-specific lymphocytes. Immune cells express putative SARS-CoV-2 receptors, CD147, and CD26. (B) Gastrointestinal symptoms are seen in a substantial percentage of COVID-19 patients. The intestinal tissue has a high expression of ACE2 receptor, TMPRSS2, and TMPRSS4 proteases. Their expression increases with intestinal epithelial cell differentiation. ACE2 expression in intestinal epithelium decreases with inflammation and shows a negative correlation with IL-1 $\beta$  levels. SARS-CoV-2 infection results in disintegration of the intestinal epithelial barrier. Virus-specific IgA have been found in the gastrointestinal tract. Noninfectious SARS-CoV-2 RNA is found in stool after negative nasal swab tests. CXCL10, C-X-C motif chemokine 10; CXCR1, C-X-C motif chemokine receptor 1; CXCR10, C-X-C motif chemokine receptor 10; GB, goblet cell; ILC, innate lymphoid cell; IL, interleukin; IFN, interferon; M0, macrophage; MO, monocyte; NEU, neutrophil; NK, natural killer cell; pDC, plasmacytoid dendritic cell; TNF, tumor necrosis factor

inflammation<sup>41</sup> and worsening of the disease. In an animal model of SARS-CoV, a delayed type I interferon response resulted in accumulation of inflammatory monocytes/macrophages, leading to elevated lung cytokine/chemokine levels, vascular leakage, and impaired virus-specific T-cell responses.<sup>41</sup> A recent study in humans showed that SARS-CoV-2 infection induces weak IFN responses from infected pneumocytes, even weaker than in SARS-CoV

infection.<sup>40</sup> Interestingly, ACE2 has been recently shown to be an interferon-stimulated gene.<sup>12</sup> ACE2 is also known to protect mice against acute lung injury. Therefore, it needs to be determined whether upregulation of ACE2 after the initial antiviral response is used by SARS-CoV-2 to enhance infection, but also if the delay of IFN responses potentially leads to impairment of ACE2-related protection against lung injury.

### 3.2 | From oral to rectal mucosa: What we know about the involvement of the gastrointestinal tract in COVID-19

Based on the current knowledge of SARS-CoV-2 receptors' expression on the epithelial barrier sites, the gastrointestinal tract requires special attention. Human ACE2 is homogeneously distributed on the brush border of enterocytes across the small intestine and in the lung epithelium.<sup>45,46</sup> In the oral mucosa, the basal layer of nonkeratinized, squamous epithelial cells were reported to be ACE2-positive, while stomach epithelial cells and colon enterocytes remained negative.<sup>45</sup> TMPRSS2 and TMPRSS4 mediate infection of small intestinal epithelial cells.<sup>47</sup> These enzymes might additionally be an interesting target for therapeutic intervention, since a clinically approved protease inhibitor is available.<sup>7</sup> Less is known regarding the gastrointestinal distribution of CD147.<sup>14</sup> Enteric CD147 seems to play a role in carcinogenesis and inflammation,<sup>48</sup> which might shed a new light on patients' group at risk for severe SARS-CoV-2 infections and needs further attention. Of note, CD26 expression was reported to be high in ileum and jejunum, low in duodenal samples and not detectable in colon epithelial cells (Figure 3B).<sup>49</sup>

Gastrointestinal symptoms like vomiting and diarrhea in COVID-19 are gaining attention.<sup>50</sup> In the previous SARS outbreak and in MERS patients, gastrointestinal complaints were found in approximately 30% of patients. In SARS-CoV-2 infections, diarrhea, and abdominal pain occur in 20%-50% of COVID-19 patients and might even precede onset of respiratory symptoms.<sup>51,52</sup> SARS-CoV active replication was detected in small intestinal enterocytes<sup>53</sup> and enteroids derived from human ileum and colon in case of SARS-CoV-2.<sup>47</sup> This is highly relevant as viral excretion was detected in fecal samples and anal swabs of COVID-19 patients.<sup>54</sup> While first evidence is available that human colonic fluids might rapidly inactivate SARS-CoV-2 *in vitro*,<sup>46</sup> MERS-CoV was found to resist gastrointestinal fluids simulating conditions with elevated pH levels after food ingestion, while the virus rapidly lost infectivity when exposed to an acidic gastric fluid simulating fasted state.<sup>55</sup> These reports might explain, at least partially, the fact that even though SARS-CoV-2 RNA was detected in stool samples from patients, the isolates were not infective.<sup>56</sup> Thus, it remains unclear whether the fecal-oral-route might propagate disease transmission especially in reduced hygienic conditions.<sup>57</sup>

Further understanding of the relationship between disease and the digestive tract is essential to prevent transmission and disease progression as well as to design efficient treatment of COVID-19.

### 3.3 | Skin barrier: more than just matter of wearing protective equipment

Recent reports indicate that in COVID-19 the skin might also be affected. An Italian and a French study reported that 20.4% to 50% of COVID-19 cases, respectively developed nonpruritic, erythematous rashes, urticaria or varicella-like lesions affecting the trunk and sometimes the limbs.<sup>58,59</sup> In general, the rashes occurred 3 days

after development of COVID-19 symptoms and the median duration was 8 days.<sup>60</sup> In addition, acrolated ischemic, self-healing lesions at toes, and fingers have been observed mainly in children and young adults shortly before COVID-19 symptom appearance.<sup>61</sup> To put otherwise, healthy kids in quarantine upon detection of these lesions might help to prevent infection from spreading. Apparently, cutaneous manifestations of COVID-19 are similar to skin rashes observed in other common viral infections. There is no evidence that they are related to the severity of the disease or an indication that the virus can replicate in the skin.

Unfortunately, the few studies available so far did not detect SARS-CoV-2 presence in skin lesions, which questions if the skin manifestations are indeed infectious or para-infectious driven. Given that ACE2 and TMPRSS2, the receptors for SARS-CoV-2 entry into human cells, are absent or weakly expressed in the skin,<sup>11</sup> para-infectious events seem to be more likely. Furthermore, the possibility of adverse drug reactions as causative for skin manifestations in COVID-19 is being strongly considered in certain cases.

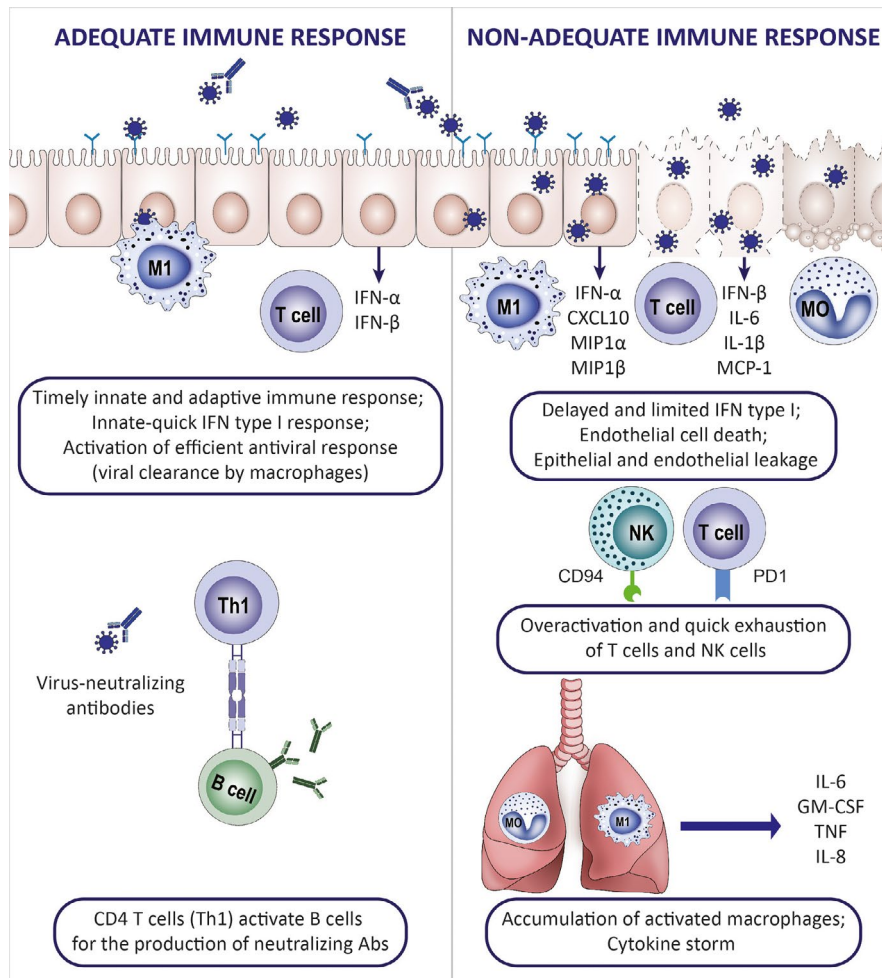
Some of the protective measures taken during the SARS-CoV-2 pandemic (use of gloves, masks or goggles) can affect the skin. Masks and goggles often induce pressure injury due to not properly fitted material, and a study in Chinese health care workers indicated that 71% suffer from skin barrier damage such as dryness, scales, papules or erythema.<sup>62</sup> Causative is the inevitable hand hygiene procedure—66.1% stated to wash their hands more than 10 times per day and only 22.1% used appropriate skin care products afterward. Moreover, long-term usage of gloves over 6 hours per day is common in health care workers leading to overhydration and dysbiosis with damage to the stratum corneum and subsequent skin infection or sensitization.<sup>63</sup> Thus, proper education regarding the use of skin care products after the hand hygiene procedure is essential to protect the skin barrier and prevent further skin complications.

## 4 | DEVELOPMENT AND FAILURE OF AN ADEQUATE IMMUNE RESPONSE

### 4.1 | Innate Immunity

#### 4.1.1 | DCs and macrophages

Monocytes/macrophages and DCs play a crucial role in anti-viral responses by linking innate and adaptive immunity. Peripheral activation and accumulation of activated pro-inflammatory monocytes/macrophages within lungs has become one hallmark of symptomatic SARS-CoV-2 infection.<sup>41,64-66</sup> In contrast, the exact role of interactions between DCs and SARS-CoV-2 has not been determined yet. Previous *in vitro* experiments showed that different human coronaviruses display either high (229E) or poor (OC43) capacities to infect macrophages.<sup>67</sup> The efficiency of macrophage infection by coronaviruses was negatively correlated with IFN- $\alpha$  production.<sup>67</sup> In COVID-19 patients, ACE2 expression was detected on both lymph node-associated CD68 + macrophages and tissue-resident CD169 + macrophages.<sup>68</sup> It needs to be



**FIGURE 4** Immunology of adequate and nonadequate response to SARS-CoV-2 infection. The clinical course of the SARS-CoV-2 infection varies from an asymptomatic to a severe, life-threatening syndrome. The number of asymptomatic carriers is unknown, and virus detection is often accidental. Data on the immune characteristics in this group are lacking. Patients who experience mild symptoms are characterized by a transient, slight decrease in lymphocyte counts and an increase in neutrophil counts in the peripheral blood. Viral clearance in this group is convergent in time with the specific antibody production. Delayed and limited IFN type I response in combination with the overactivation of pro-inflammatory cytokine response has been suggested as a possible mechanistic explanation of hyperinflammatory syndrome in COVID-19 patients presenting with severe clinical manifestations: respiratory insufficiency, kidney failure, thromboembolic, and other complications. Severe COVID-19 is characterized by a systemic cytokine release syndrome (CRS), increased levels of LDH and CRP, hypoalbuminemia, deepening decrease in lymphocyte counts and immune exhaustion of T cells

addressed, however, whether other proven and potential SARS-CoV-2 receptors, such as CD147 or CD209 (DC-SIGN), both being expressed by monocytes/macrophages and DCs can facilitate viral entry to these cells.<sup>14,29,69,70</sup> Recently, SARS-CoV-2 particles were found in macrophages, but it remains elusive whether these findings were an effect of active cellular infection or just the consequences of physiological phagocytosis. It is tempting to speculate that SARS-CoV-2, similarly to HIV, can use macrophages as a Trojan horse contributing to viral spread.<sup>68,71</sup> Regardless of the exact mechanism of viral entry, both previously described coronaviruses and the new SARS-CoV-2 can trigger NLRP3 inflammasome activation in monocytes/macrophages, production of high levels of pro-inflammatory mediators such as IL-6, GM-CSF, IL-1 $\beta$ , TNF, CXCL-8, CCL-3, and enhanced cell death. Subsequently, it may lead to the cytokine storm also known as cytokine release syndrome (CRS) (Figure 4).<sup>72</sup> Some of these cytokines (ie, IL-6) are mainly

secreted by macrophages,<sup>66,73-76</sup> and the evidence of macrophage activation syndrome has been reported.<sup>77</sup> Thus, beneficial effects of anti-IL-6R treatment on COVID-19 outcomes indicate that therapies targeting macrophage-related activities can become promising means to inhibit the inflammatory storm in the course of coronavirus disease.<sup>78</sup> Overloaded, activated and subsequently dying macrophages might contribute to an increase in the levels of plasma ferritin and profound dysregulation of iron metabolism.<sup>79,80</sup> High ferritin levels are common clinical findings in patients with severe COVID-19.<sup>81</sup>

#### 4.1.2 | Neutrophils and eosinophils

Neutrophils are one of the predominant lung infiltrating leukocytes in severe SARS-CoV-2 infection, and neutrophilia predicts poor clinical



outcome.<sup>82</sup> Postmortem analysis of lung samples from COVID-19 patients showed neutrophil infiltration in pulmonary capillaries and neutrophil extravasation into the alveolar space.<sup>83,84</sup> Under neutrophil-activating conditions, such as those occurring during systemic inflammation (CRS), neutrophil extracellular traps (NETs) can be released. Although this is a way to ensnare pathogens, NET formation is linked to pulmonary diseases, particularly acute respiratory distress syndrome (ARDS). Severe COVID-19 conditions with uncontrollable progressive inflammation presumably induce an intense crosstalk between neutrophils releasing NETs and IL-1 $\beta$  secretion from macrophages, which is the driving force in further complications.<sup>83</sup>

Although eosinophils have protective effects in different viral infections, the eosinophil response toward SARS-CoV-2 is incompletely understood.<sup>85</sup> A significant amount of COVID-19 patients present eosinopenia,<sup>86,87</sup> although it is not reported in all cohorts.<sup>88</sup> The pathophysiological mechanism of eosinopenia in COVID-19 patients is not clear but may be related to increased apoptosis, less eosinophilopoiesis, and decreased eosinophil egression from the bone marrow.<sup>89</sup> Increased tissue migration is unlikely because eosinophils infiltration was not found in pulmonary tissue of COVID-19 patients,<sup>90</sup> but further research is needed.

#### 4.1.3 | ILC and NK cells

ILC are effector cells that respond to environmental cytokines and regulate immune responses.<sup>91,92</sup> Type 1 ILC include IFN- $\gamma$  producing subtypes and natural killer (NK) cells. Limited data are available on the role of ILC in relation to COVID-19, but it has been shown that ILC1-ILC3 express CD26, CD147, cyclophilins and their interaction partners.<sup>10</sup> Data on the numbers of NK cells in patients with COVID-19 are varied. Some studies reported no differences in NK cell counts compared with healthy controls,<sup>93,94</sup> while one study found increased numbers of NK cells and suggested a role for NK cells in the CRS.<sup>95</sup> In contrast, other studies showed low<sup>96</sup> or considerably decreased numbers of NK cells in patients with SARS-CoV-2 infection, which was more prominent in severe cases.<sup>97-99</sup> After successful treatment, the numbers of NK cells restored to the normal levels with reduced expression of NKG2A.<sup>99</sup>

Functional exhaustion of NK cells and CD8<sup>+</sup> T cells was described in relation to severe SARS-CoV-2 infection (Figure 4). Exhausted NK and CD8<sup>+</sup> T cells expressed CD94/NK group 2 member A (NKG2A), which functions as an inhibitory receptor, and showed diminished production of CD107a, IFN- $\gamma$ , IL-2, granzyme B, and TNF- $\alpha$ .<sup>99</sup> During infection, IFN- $\gamma$  induce expression of the nonclassical human leukocyte antigen E (HLA-E).<sup>100</sup> HLA-E is the ligand of NKG2A, which is expressed on epithelial cells. NKG2A blockade with monoclonal antibodies (Monalizumab) prevents the binding of HLA-E, which may be a target for COVID-19 therapy.

#### 4.1.4 | Complement and SARS-CoV-2

The complement system is engaged in both coagulation and inflammatory pathways. Histologic and immunohistochemical analysis of lung

and skin have been conducted in patients with COVID-19-induced ARDS. The typical pulmonary findings for ARDS were accompanied with significant deposits of terminal complement components C5b-9 (membrane attack complex), C4d, and mannose binding lectin (MBL)-associated serine protease (MASP)2, in the microvasculature.<sup>101</sup> The biopsies of both damaged and normally appearing skin revealed a pauci-inflammatory thrombogenic vasculopathy, with deposition of complement products C5b-9 and C4d.<sup>101</sup> The authors conclude that a subset of sustained, severe COVID-19 patients may be defined by a type of catastrophic microvascular injury syndrome mediated by activation of complement pathways and an associated procoagulant state. Further, C3-deficient mice developed significantly less respiratory dysfunction despite viral loads deposited in the lung. These data indicate that SARS-CoV-mediated disease is largely immune driven and complement activation regulates a systemic pro-inflammatory response to SARS-CoV infection.<sup>102</sup> Most recently, the placentas from 5 healthy newborns (all negative for viral RNA and spike protein) of COVID-19 positive mothers revealed vascular thrombosis without complement deposition, supporting COVID-19's systemic procoagulant effects unrelated to systemic complement activation.<sup>103</sup>

#### 4.1.5 | Trained immunity

Stimulation of innate immune cells with specific microbial antigens induces long-lasting epigenetic and metabolic re-programming leading to enhanced responses upon a second challenge by the same or unrelated microbial insults, a process coined as "trained innate immunity."<sup>104,105</sup> As a consequence, trained immunity-based vaccines (TibV) able to induce potent responses against both specific and nonspecific antigens contained in the formulation has emerged as a novel concept in vaccinology.<sup>105</sup> TibV might be especially relevant when conventional vaccines are not available, as it is the case for SARS-CoV-2. One of the best examples about trained immunity is the influence of BCG vaccination on unrelated pathogens.<sup>104</sup> BCG seems to induce nonspecific responsiveness to infections both at the level of trained immunity and prolonged heterologous Th1/Th17 responses.<sup>106</sup> BCG-vaccinated infants have significantly increased production of pro-inflammatory cytokines, increased protection against infections and reduced mortality.<sup>107</sup> Increased expression of PRRs in monocytes isolated from peripheral blood mononuclear cells (PBMCs) of healthy individuals 1 year after BCG vaccination has marked the importance of trained immunity.<sup>106</sup> Although further studies are required, lower number of cases and deaths per population during COVID-19 pandemic seem to be reported in countries with BCG vaccination programs than those that did not have or ceased it, which could be attributed to potential BCG vaccination-induced trained immunity effects.<sup>108,109</sup> Trials assessing the efficacy of BCG vaccination in populations at high risk of infection or with a high risk of mortality, such as hospital staff working in close contact with COVID-19 patients or older individuals, are currently being performed in the Netherlands, Australia and Greece.<sup>110</sup> Future research and clinical trials are needed to demonstrate whether novel TibV

might represent a suitable strategy for the prevention and treatment of SARS-CoV-2 infection.

## 4.2 | Adaptive immunity

### 4.2.1 | T cell-related mechanisms: lymphopenia, T-cell over-activation and T-cell exhaustion

Cytotoxic CD8<sup>+</sup> T cells directly neutralize infected cells, and CD4<sup>+</sup> T cells aid B cells to initiate humoral responses (Figure 4).<sup>111</sup> T cells are instrumental in developing immunological memory in the form of virus-specific CD8<sup>+</sup> and CD4<sup>+</sup> T cells as shown in case of SARS-CoV.<sup>112-114</sup> In fact, SARS-CoV-specific CD8<sup>+</sup> T cells have been detected in humans up to 11 years postinfection, which is longer than the specific antibodies.<sup>114</sup> SARS-CoV-2-specific CD8<sup>+</sup> and CD4<sup>+</sup> T cells were also recently identified in ~70% and 100% of COVID-19 convalescent patients, respectively. CD4<sup>+</sup> T cells responded to spike (S) protein, which correlated with the magnitude of the anti-SARS-CoV-2 IgG and IgA titers. Importantly, SARS-CoV-2 reactive CD4<sup>+</sup> T cells were also detected in ~40%-60% of unexposed individuals, suggesting cross-reactive T-cell recognition between circulating "common cold" coronaviruses and SARS-CoV-2,<sup>115</sup> which was confirmed by others.<sup>116</sup> Profound lymphopenia, with the subsequent shifts in the T-cell subsets composition, is often reported in SARS-CoV-2 infection, similarly to SARS-CoV and some other viruses.<sup>94,98,117</sup> Total numbers of CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells are below normal levels in most COVID-19 patients, with the lowest numbers in the severe cases. Moreover, the number of Treg cells is also decreased,<sup>98</sup> whereas a recent case report of nonsevere COVID-19 showed a progressive increase in the proportion of CD4<sup>+</sup>CXCR5<sup>+</sup>ICOS<sup>+</sup>PD-1<sup>+</sup> circulating follicular helper T (T<sub>FH</sub>) cells.<sup>96</sup> Delayed development of adaptive responses, together with prolonged virus clearance, has been reported in cases of severe SARS-CoV-2 infection (Figure 4).<sup>118</sup> Unfortunately, the mechanisms involved in the lymphocytopenia are still not known in SARS-CoV and SARS-CoV-2 patients. T cells can be infected through highly expressed CD147<sup>14,15</sup> or potentially through CD26, as ACE2 expression on lymphocytes is very low,<sup>10</sup> except in certain tissue-derived T cells.<sup>119</sup> It is yet unclear whether such infection is the reason of the death of infected T cells. Secondly, as in the case of SARS-CoV, an alteration in the antigen-presenting cells (APCs) function and subsequent impairment of T-cell priming might lead to an inefficient/delayed formation of virus-specific T cells.<sup>120-122</sup> Finally, also a high cytokine response from the infected cells might induce apoptosis of T cells.<sup>123</sup> The causes of lymphopenia need to be extensively studied, as it correlates with the higher risk of severe disease and increased length of hospitalization.<sup>124,125</sup> In addition to decrease in numbers, there are also other defects reported in the function of T-cell subsets in SARS-CoV-2 infection. In severe pneumonia in COVID-19 patients, it has also been shown that highly cytotoxic, activated CD8<sup>+</sup> T cells and Th17 cells, can also participate in the CRS, together with macrophages and epithelial cells.<sup>117</sup> Highly activated T cells participating in viral infection often acquire

an exhausted phenotype. Surviving T cells appear functionally exhausted with elevated levels of PD-1.<sup>126</sup> The increased expression of PD-1 and Tim-3 on CD8<sup>+</sup> T cells was found to progress with the infection. T-cell exhaustion is a reversible process where a decrease in antigen availability, achieved either through the gradual resolution of the infection or intervention strategy, has led to exhausted T cells regaining their functions.<sup>127</sup>

### 4.2.2 | B cell-related mechanisms and antibody-responses

Human SARS-CoV-2 infection activates mechanisms of B- and T-cell immunity that result in the generation of neutralizing antibodies.<sup>96</sup> Initially, B cells appear to recognize SARS-CoV-2 through the nucleocapsid protein, which induces their activation and subsequent interaction with cognate CD4<sup>+</sup> T cells. The antibody response is mounted 4-8 days after the onset COVID-19 symptoms and dominated by IgM.<sup>128</sup> This initial IgM-response is followed by IgA and then IgG production (10-18 days).

The development of mucosal IgA likely prevents SARS-CoV-2 re-infection while circulatory IgA may contribute to systemic SARS-CoV-2 neutralization and to dampen inflammation during active infection (Figure 4).<sup>129</sup> The extent and quality of the IgG response to neutralize SARS-CoV-2 is critical. Based on previous SARS-CoV infection reports, SARS-CoV-2-neutralizing IgG antibodies should be specific for the S protein and detected in serum at 2-3 weeks post-infection.<sup>130,131</sup> For that reason, human convalescent serum transfer has been proposed for the prevention and treatment of COVID-19 patients.<sup>132</sup> In fact, and a number of clinical trials have recently reported its therapeutic value in COVID-19.<sup>51,54,133,134</sup> However, low affinity or suboptimal IgG levels may enhance viral entry into Fcγ receptor-expressing cells through IgG binding. This mechanism may induce the release of inflammatory cytokines and contribute to the CRS reported in some severe COVID-19 patients.<sup>135</sup>

In a recent *pre-print* study, single-cell RNA sequencing (scRNA-seq) of PBMCs of 7 patients hospitalized with confirmed COVID-19 and 6 healthy controls was performed.<sup>136</sup> Heterogeneous interferon-stimulated gene (ISG) signature, HLA class II downregulation, and a novel B cell-derived granulocyte population were reported in patients with acute respiratory failure requiring mechanical ventilation. The putative contribution of this intriguing B-cell population to COVID-19 pathology remains to be elucidated.

A central issue of B-cell immunity to SARS-CoV-2 is the duration of the antibody (IgG) response once the infection is cleared, as well as the ability for SARS-CoV-2 specific memory B cells to expand, or replenish, the plasma cell compartment upon re-infection. Given that long-lived plasma cells and high-affinity memory B cells are thought to be germinal center-dependent,<sup>137</sup> it is important to characterize the antibody and B-cell memory repertoire (affinity, number of mutations, clonal origin, etc) of asymptomatic patients and patients that have recovered from COVID-19. The rapid peak of viral load detected in COVID-19 patients,<sup>138,139</sup> as compared to SARS-CoV, may

accelerate plasma cell differentiation,<sup>140</sup> thus limiting the germinal center phase and the degree of long-term immunity protection.

### 4.3 | Multiorgan involvement in severe COVID-19

#### 4.3.1 | Lung pathologies in COVID-19

It has yet to be determined whether SARS-CoV-2 shows significantly more pronounced lung tropism than other respiratory viruses. COVID-19-associated viral pneumonia is relatively frequently complicated by ARDS. Lung CT images of COVID-19 pneumonia patients revealed mostly diffuse patchy ground-glass opacities under the pleura with partial consolidation which, in clinically improving individuals, can be further absorbed and followed by formation of fibrotic tissue.<sup>141</sup> Postmortem analysis of COVID-19 patients revealed extensive alveolar damage complicated by the formation of hyaline membranes, diffuse remodeling of alveolar wall and accumulation of immune cells (mostly macrophages) infiltrating air spaces.<sup>117,142</sup> Macrophages accumulating in lungs secrete type I and type III IFNs that enhance local antiviral defenses in surrounding epithelial cells. Lung-associated macrophages contribute to development of CRS by producing IL-6 and IL-1 $\beta$ , cytokines promoting further recruitment of cytotoxic T cells and neutrophils. In consequence, activated neutrophils produce reactive oxygen species and leukotrienes that directly contribute to acute lung injury.<sup>143</sup> Even successful eradication of the virus does not prevent from continuous lung damage, development of frequently progressive and irreversible fibrotic consequences.<sup>144</sup> At this relatively early phase of the pandemic, the exact fraction of COVID-19 patients burdened with persistent fibrotic interstitial lung disease cannot be precisely determined. Nevertheless, available and novel anti-fibrotic therapies should also be considered as candidate strategies to manage post-COVID-19 long-term lung fibrosis.<sup>145</sup>

#### 4.3.2 | Myocardial and endothelial damage: an immunological perspective on cardiac presentation of COVID-19

Cardiac injury is a prominent feature in COVID-19 developed by a considerable proportion of patients and is associated with an increased mortality.<sup>146</sup> The pathogenesis of COVID-19 in the cardiovascular system likely results from a combination of several mechanisms such as direct viral toxicity, systemic CRS-mediated and stress-related injury. These mechanisms promote cardiomyocyte and endothelial apoptosis, endothelial shedding, plaque destabilization, and increase wall shear stress, leading to myocarditis, endotheliitis, ischemia, cardiac arrhythmias, and hypercoagulability. ACE2 is highly expressed on cardiomyocytes and endothelial cells, possibly facilitating direct viral damage. However, it is unknown whether vascular derangements in COVID-19 patients are due to endothelial cell involvement by the virus. A recent study found that endothelial cells can be infected by SARS-Cov-2, as postmortem analysis of kidney

by electron microscopy revealed viral inclusion structures within endothelial cells.<sup>147</sup> The postmortem histology from patients with multiorgan failure in COVID-19 showed endotheliitis in the lung, heart, kidney, liver, and small intestine, with an accumulation of inflammatory cells associated with endothelium.<sup>147</sup> These findings suggest that the endotheliitis may be a combination of direct consequence of the viral involvement (ie, presence of intracellular viral bodies) and the host inflammatory response (Figure 5).

In cardiomyocytes, SARS-CoV-2 appears to downregulate ACE2 and diminish its cardioprotective role, promoting left ventricular failure and hypertrophy, as well as pro-thrombotic and pro-oxidant pathways.<sup>148</sup> Few cases documented myocarditis with diffuse T-lymphocytic inflammatory infiltrates with interstitial edema and without fibrosis, suggesting an acute inflammatory process. A recent study presenting data from autopsy series also demonstrated SARS-CoV-2 viral load in heart tissue.<sup>149–151</sup> Since SARS-CoV-2 may predispose patients to coagulopathies with clinical manifestations ranging from arterial and venous embolisms to disseminated intravascular coagulation, with very poor prognosis, early prophylactic anticoagulation in hospitalized patients is recommended.<sup>152</sup> Taken together, direct viral involvement, imbalanced host immune response, and systemic inflammation are proposed as important mechanisms of myocardial/endothelial injury.

#### 4.3.3 | Coagulation parameters in COVID-19 patients

Abnormal coagulation parameters such as mild thrombocytopenia, prolonged prothrombin time, disseminated intravascular coagulation,<sup>153–155</sup> and elevated D-dimers are seen in 36% to 43% of COVID-19 patients.<sup>154,156</sup> In a meta-analysis of 4 published studies, higher D-dimers were found in patients with more severe COVID-19.<sup>156</sup> Also, thrombocytopenia was reported to be associated with more severe COVID-19 and increased risk of death (Figure 5).<sup>155,157</sup> In a trial of severe COVID patients (n = 99), anticoagulant therapy (eg, low molecular weight heparin) was associated with better prognosis.<sup>158</sup>

Activation of endothelium, platelets, and leukocytes leads to enhanced local and systemic production of thrombin, which in turn leads to deposition of fibrin, microangiopathy, and eventual organ damage. Both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) initiate these processes.<sup>159</sup> In 16 patients with severe COVID-19, a correlation between IL-6 and fibrinogen levels was found, supporting a link between hyperinflammation and increased venous thromboembolism (VTE) risk.<sup>160</sup>

Although thrombocytopenia has been implicated in patients infected with SARS-CoV-2, the association between platelets and the disease mortality is not clear. In COVID-19 patients from Wuhan, China, platelet count increase was an independent risk factor reversely associated with in-hospital mortality, as an increase of 50x10<sup>9</sup>/L platelets was associated with a 40% decrease

in mortality.<sup>155</sup> Another study of 548 patients from China found that while platelet levels were decreased when hospitalization for COVID-19, platelet levels increased in survivors over time, but maintained lower levels or dropped significantly over time in nonsurvivors.<sup>161</sup> Thus, baseline platelet levels and changes over time appear to be associated with subsequent mortality and monitoring platelet levels is important in predicting prognosis of patients with SARS-CoV-2 infection.

#### 4.3.4 | Neurological disease presentation

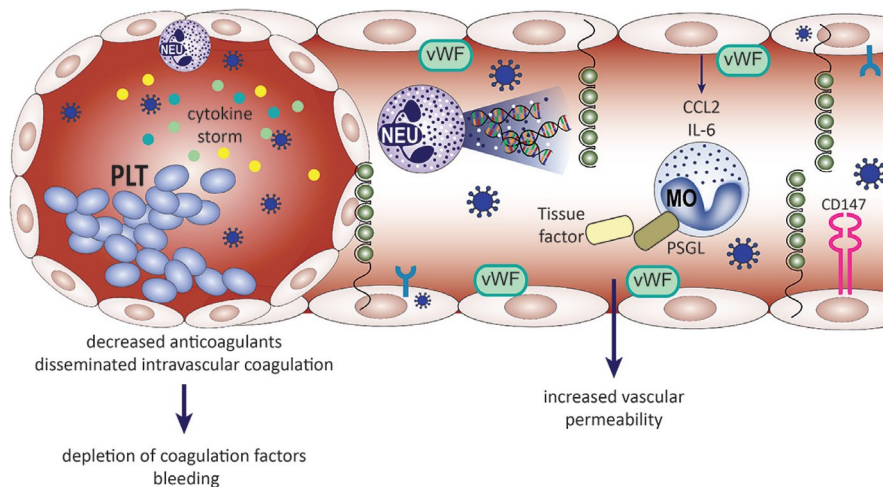
Together with the choroid plexus, the blood-brain barrier protects the brain from invading microorganisms.<sup>162</sup> Nevertheless, several pathogens, including viruses, are still able to traverse the barriers,<sup>163</sup> especially in cases of systemic inflammation<sup>164</sup> causing potential alterations of the central nervous system (CNS). In particular, coronaviruses might exhibit neurotropic properties,<sup>165</sup> and SARS-CoV was detected in human brain.<sup>166,167</sup> Of interest, ACE2 is expressed in the human brain.<sup>45</sup> Based on the knowledge from animals studies, SARS-CoV can enter the brain via the olfactory nerve leading to a rapid, transneuronal spread to connected areas of the brain.<sup>168</sup> As SARS-CoV infects immune cells, the virus might penetrate the CNS also via the hematogenous route.<sup>167</sup>

In the current COVID-19 outbreak, a few case reports described meningitis/encephalitis or COVID-19-associated acute necrotizing hemorrhagic encephalopathy with or without SARS-CoV-2 RNA detected in the cerebrospinal fluid.<sup>169,170</sup> Moreover, autopsies of patients with COVID-19 showed cerebral hyperemia and edema with

degeneration of some neurons.<sup>171</sup> In a study on COVID-19 patients from Wuhan hospitals, 78 out of 214 patients had neurological manifestations especially in severe infections. Some patients had only neurological manifestation without typical COVID-19 symptoms.<sup>172</sup> In addition, olfactory and gustatory dysfunctions are often reported in patients with COVID-19,<sup>173-175</sup> which might be due to direct effects on the nervous system.

#### 4.3.5 | COVID-19-related kidney failure

Recent evidence indicates that kidney injury occurring during SARS-CoV-2 infection can result not only from CRS and ongoing sepsis but also from direct virus-induced impairment.<sup>176,177</sup> In fact, ACE2 is highly expressed on renal tubular cells.<sup>178</sup> Clinical observations of COVID-19-related kidney damage have been confirmed by an elegant experiment demonstrating that SARS-CoV-2 can directly infect human kidney organoids.<sup>179</sup> Moreover, this infection led to further efficient shedding of progeny viruses capable of infecting Vero E6 cells. This finding suggests that kidneys are an active player in the process of viral spread rather than only a site of virus-induced tissue damage. The process of kidney infection by SARS-CoV-2 was significantly, but not completely inhibited by human recombinant soluble ACE2, which indicates that there might be other than ACE2 receptors accounting for the entry of SARS-CoV-2 to kidney cells.<sup>179</sup> The putative candidate can be CD147 being highly expressed on proximal tubular epithelium. CD147 together with one of its ligands, cyclophilin, plays a crucial role in renal inflammation and renal fibrosis.<sup>180</sup> Moreover, cyclophilins efficiently control the process of



**FIGURE 5** Involvement of endothelium in COVID-19 progression. SARS-CoV-2 viremia is seen approximately 1 wk after the onset of illness, accompanied by an abundance of circulating pro-inflammatory cytokines. Endothelial cells express ACE2 receptor and can be infected by the SARS-CoV-2. Direct viral influence on the endothelial cells, as well as systemic inflammation (depicted by activated neutrophils and extensive NET-osis) and cytokine storm, can lead to endotheliitis, disseminated intravascular coagulation, and coagulopathy, described in severely affected COVID-19 patients. Activated endothelial cells upregulate the expression of adhesion molecules (P-selectin) and coagulation factors (vWF), secrete immune mediators (CCL2, IL-6). Monocytes respond to these by releasing tissue factor and upregulate the expression of PSGL. Simultaneously, platelet activation and aggregation occurs. Increased numbers of neutrophils and monocytes in the peripheral blood correlate with severe disease course and fatalities. CCL2, CC-chemokine ligand; IL-6, interleukin 6; MO, monocyte; NEU, neutrophil; NET, neutrophil extracellular traps; PLT, platelets; PSGL, P-selectin glycoprotein ligand 1; vWF von Willebrand factor.



coronavirus replication.<sup>181</sup> Thus, therapeutic strategies could aim at breaking the CD147-cyclophilins.

#### 4.4 | Multi-morbidities as a risk factor for severe COVID-19

Multi-morbidities are associated with the severe course of COVID-19. A meta-analysis including 1,558 patients with COVID-19 showed as independent risk factors chronic obstructive pulmonary disease (COPD) (OR: 5.97), cerebrovascular disease (OR:3.89), type 2 diabetes mellitus (T2DM) (OR: 2.47), and hypertension (OR: 2.29).<sup>182,183</sup> In the nation-wide report from China including 1590 patients with COVID-19, one comorbidity was present in 25.1% and two or more comorbidities in 130 8.2% patients (Figure 6).<sup>184</sup>

Several mechanisms directly linked to the underlying pathological condition can contribute to the unfavorable clinical outcome. A recent study suggested that hypertension and diabetes resulted in delayed clearance of SARS-CoV-2.<sup>185</sup> The relationship between the immune dysfunction in patients with multi-morbidities and infection with SARS-CoV-2 was not specifically evaluated. A transgenic diabetic mouse model expressing human CD26 had more severe

disease together with a dysregulated immune response following infection. A delayed and decreased recruitment of CD4<sup>+</sup> T cells and inflammatory monocytes and macrophages into the lung tissue and a more prominent Th17 response was observed.<sup>186</sup> Interestingly, obesity is changing the expression profile of SARS-CoV-2 receptors.<sup>10</sup>

Metabolic induced low-grade systemic inflammation, as in obese patients,<sup>187</sup> facilitates an enhanced release of cytokines upon an acute trigger such as viral infection. As the human endocrine pancreas expresses ACE2, the coronavirus might enter islets and cause acute  $\beta$ -cell dysfunction, leading to acute hyperglycemia and transient T2DM.<sup>188</sup> A mathematical model showed that the insulin resistance, advanced glycan end product (AGE)-Receptor of AGE (RAGE) signaling pathway in diabetic complications and the adipocytokine signaling pathway were found in all fatal comorbidities of COVID-19.<sup>189</sup> In addition, AGEs can induce monocyte CD147 expression, an effect mediated by inflammatory pathways and RAGE.<sup>190</sup> CD147 is highly expressed in patients with diabetic complications such as nephropathy, retinal neuropathy, and vasculopathy and was associated with chronic renal failure of other causes.

COPD and ongoing smoking contribute to COVID-19 severity.<sup>191</sup> COPD and active smokers had significantly increased expression of ACE2 and its gene expression inversely related to the lung function, suggesting a dose-dependent response.<sup>192</sup>

**FIGURE 6** Age, gender, and comorbidities modify the onset and progression of COVID-19. Epidemiological observations show clear differences in the course of SARS-CoV-2 infection between children and adults. It seems that children are less susceptible to the infection and develop less typical symptoms of the disease. Consequences of the infection on physiological development of children are unknown. Clinical data and age-related rhesus macaque model of COVID-19 reveal that obesity, diabetes, hypertension, smoking, chronic respiratory diseases, male gender, and older age are the most common risk factors for development of severe COVID-19. Older age is associated with higher incidence of multimorbidity and state of low-grade systemic inflammation. Immunosenescence could influence the adequacy of the host's response to the infection



- Th-2 skewed immunity
- Higher susceptibility to infections with lower tendency to cytokine storm
- More often asymptomatic and silent carriers
- Less comorbidities
- Rare severe complications (acute pediatric hyperinflammatory syndrome)

- Immunosenescence: reduced ability to respond to new antigens and poor post-vaccination immune response
- Compromised response to cellular and metabolic stress
- Frequent multimorbidity
- Chronic low-grade systemic inflammation facilitating cytokine release upon viral infection



Multimorbidity is also associated with elevated levels of plasminogen. Plasmin, and other proteases, may cleave a newly inserted furin site in the S protein of SARS-CoV-2, extracellularly, which increases its infectivity and virulence. Hyperfibrinolysis associated with plasmin leads to elevated D-dimer in severe patients. Thus, the plasminogen system may prove a promising therapeutic target in COVID-19.<sup>193</sup>

#### 4.5 | Sex and aging as a risk factor for COVID-19 course

The increased vulnerability of males compared with females to severe COVID-19 has been reported during the pandemic. A direct endocrine link is involved as androgen receptor activity is required for the transcription of TMPRSS2 gene.<sup>194,195</sup> Male vulnerability may be further enhanced by X-linked inheritance of genetic polymorphisms as both the androgen receptor, and the ACE2 genes loci are on chromosome X.

Old age was also associated with an increased risk of infection and worse outcome (Figure 6). Frailty is characterized by multisystem dysregulation leading to reduced physiologic reserve. Although not formally assessed in the COVID-19 trials, frailty may be linked to infectious disease through common pathways that reduce immunity.<sup>196,197</sup> Frailty has also been shown to be associated with poor postvaccination immune response.<sup>196</sup> The aged immune system is characterized by a low-grade chronic systemic inflammatory state marked by elevated inflammatory markers such as IL-6 and C-reactive protein and an increased susceptibility to infection.<sup>198</sup> The expression of ACE2 and TMPRSS2 genes in the type II alveolar cells of elderly and young patients is comparable. Therefore, it does not seem to be responsible for the worse outcomes observed in COVID-19 affected elderly, but the expression of other receptors is age-dependent.<sup>10</sup>

#### 4.6 | Allergy-related risk for COVID-19

Drug hypersensitivity (11.4%) and urticaria (1.4%) were self-reported by patients with COVID-19.<sup>86</sup> In contrast, respiratory allergies and asthma were not reported as risk factors for SARS-CoV-2 infection.<sup>82,86,199–202</sup> However, a report from the CDC of US hospitalizations described contradicting findings in adults with asthma. Among hospitalized patients with COVID-19, 27.3% of 18–49 year old adults had asthma, 13.2% of 50–64 years, and 12.9% of those of 65 years or older.<sup>203</sup> Currently, patients with allergic rhinitis and patients treated with allergen-specific immunotherapy are advised to continue their therapies.<sup>204–206</sup>

Another study elucidated the impact of comorbid respiratory allergy or asthma on COVID-19 susceptibility and disease severity.<sup>207</sup> Children with asthma and moderate to severe allergic sensitization showed reduced ACE2 gene expression compared with children with nonatopic asthma. An additional trial including 23 patients with asthma confirmed reduced ACE2 expression in lower airway epithelial cells postallergen challenge. Finally, *in vitro* experiments using

nasal and bronchial airway epithelium showed that IL-13 reduced the ACE2 expression.<sup>207</sup> However, adult patients with asthma seem to have higher expression of TMPRSS2 and CD44, which forms a functional complex with CD147 in bronchial epithelium.<sup>10</sup>

### 5 | IMMUNOLOGICAL BIOMARKER PROFILING OF COVID-19 FOR PREDICTION OF DISEASE SEVERITY

The development of serious complications and even fatal outcome in SARS-CoV-2 infection is strongly linked to the patients' immune response resulting in CRS.<sup>208</sup> There is an urgent need for biomarkers that predict patients developing severe complications.<sup>209</sup> To date, there is limited information on the biomarkers associated with, or even predicting severe complications in COVID-19. However, there is much similarity on the biomarkers that have been described before for MERS-CoV and SARS-CoV, also  $\beta$ -coronaviruses, but also with sepsis. Many markers have been demonstrated to be increased in SARS-CoV-2-infected individuals. These markers are related to innate as well as adaptive immunity, endothelial cell activation, thrombocyte activation, and leukocyte infiltration.<sup>201</sup> The list of markers related to severe disease, ICU, and even lethality is more limited. In ICU-admitted COVID-19 patients, significant increases of D-dimer, ferritin, LDH, IL-6, high sensitivity cardiac troponin, IL-2, IL-7, G-CSF, MCP-1, MIP-1 $\alpha$ , and TNF- $\alpha$  were reported.<sup>201</sup> An even more restricted group of markers (IL-10, MCP-3, IL-1ra) were increased in severe and lethal cases.<sup>210</sup> Differences in the biomarkers described are most probably due to the different sampling time during disease and the large heterogeneity between the patients.<sup>201</sup>

Most likely, single biomarkers will not be predictive. On the other hand, a combination of markers (a biosignature) will help in patient stratification and may even guide patients-tailored therapy.

### 6 | URGENT RESEARCH NEEDS FOR MECHANISTIC, DIAGNOSTIC APPROACHES, THERAPEUTIC, AND PREVENTIVE INSIGHT

#### 6.1 | Kids versus adults: Mechanisms explaining the clinical differences

Children experience milder COVID-19 as compared to adults, and a larger proportion of children remains asymptomatic (Figure 6).<sup>203</sup> Data from the USA show a strikingly low number of pediatric hospitalizations (5.7%) and very limited ICU admissions in young age.<sup>203</sup> Of note, children show similar chest CT results as compared to adults, with subpleural ground-glass opacities even when having few symptoms.<sup>211</sup> While children may be asymptomatic, they are shedding viral particles and can therefore still be contagious with comparable virus loads.<sup>212</sup> ACE2 receptors are upregulated by type 1 IFNs,<sup>12</sup> but downregulated by IL-13, indicating that Th1/Th2 balance may significantly influence course of SARS-CoV-2 infection.<sup>207</sup> Therefore, type 1 IFNs driving

anti-viral immunity may paradoxically promote SARS-CoV-2 expansion by upregulating ACE2 expression. Inflammatory responses differ throughout life, for example, pre-existing chronic inflammation is common in elderly while absent in children. In addition, children have less potent PAMP activation, suboptimal, and Th2-skewed cytokine production, all resulting a hypo-inflammatory immune response.<sup>213</sup> This confers decreased protection against infections, but seem beneficial in preventing a CRS in SARS-CoV-2 infection. Hence, preferential Th2-skewed cytokine production observed in children is presumably protective (Figure 6). Additionally, children have less often comorbidities such as hypertension, diabetes, and COPD. However, in rare cases, a severe hyperinflammatory shock syndrome with features of atypical Kawasaki disease or toxic shock syndrome was reported in pediatric COVID-19 patients,<sup>214</sup> which is currently intensively investigated.<sup>215</sup> Data are lacking on evidence surrounding transmission rates of the virus by children. The China/World Health Organization joint commission found that infected children were largely identified through contact tracing in households of adults.<sup>216</sup> However, no significantly different virus levels in the respiratory tract were recently reported across age groups, thus having the potential for similar transmission rates.<sup>56</sup> Understanding the mechanisms underlying different prognosis in children is essential for designing targeted therapies for COVID-19.

## 6.2 | Immunological diagnosis of SARS-CoV-2 infection: challenges of current approaches

PCR tests are useful for detecting SARS-CoV-2 RNA in an upper respiratory (preferably a nasopharyngeal) specimens. In addition, a number of diagnostic procedures to assess immunity built against SARS-CoV-2 are still being developed, validated, and optimized.

Antibody testing is evolving, and the market is flooded with test kits (both ELISA and rapid tests in the form of lateral flow immunoassays). However, only a small number of these kits are certified, and the results need to be interpreted with caution. Preliminary data indicate that COVID-19 presents with a classical antibody response consisting of early induction of IgM, followed by IgA and IgG antibodies (Figure 7).<sup>128</sup> IgG seems to appear early in the course of clinical presentation probably due to the relatively long incubation period. However, there is not yet enough evidence with regard to the development of long-term protective immunity. Antibody testing is so far more valuable in mapping the situation in individual populations, as planned by the WHO in the Solidarity II project.<sup>217</sup> Test kits for the assessment of SARS-CoV-2-specific T-cell responses for diagnostic use are currently not available.

## 6.3 | Immunological treatment approaches: biologicals, small molecules and beyond

Current evidence on the role of biologicals, small molecules, and passive immunizations in the treatment of COVID-19 was assessed conducting a systematic literature search (see online Supporting information).

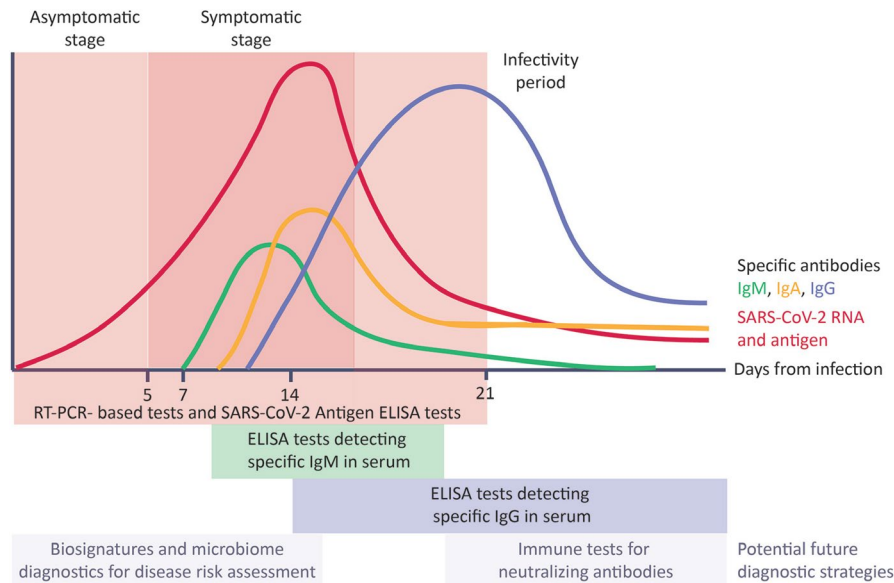
By May 15, 2020, case series and nonrandomized, small, open-label studies report on the treatment of SARS-CoV-2 infections were assessed. Results from controlled, randomized or placebo-controlled, randomized trials are still lacking. Approaches include either targeting the CRS and hyperinflammatory status of lung destruction via anti-IL-6R antibodies,<sup>218-237</sup> IL-1R antagonists,<sup>238-240</sup> JAK-STAT inhibitors,<sup>241</sup> or inhibition of entrance by anti CD147 antibodies<sup>237</sup> and destruction of the virus via protective antibody delivered with convalescent plasma<sup>51,54,66,133,134,242</sup> (Table 2). Eculizumab targets complement protein C5 preventing activation of complement terminal complex, which was used off label in patients with SARS-CoV-2 infection and severe pneumonia or ARDS and is now evaluated in an ongoing trial (SOLID-C19).<sup>243</sup> Additionally, clinical trials with type I and III interferons in COVID-19 are currently conducted.<sup>244,245</sup> Targeting T-cell exhaustion to reverse the dysfunctional state and restore immune responses can be achieved by anti-PD-1 and LAG-3 therapies,<sup>246,247</sup> revealing novel therapeutic opportunities for persisting infections. In conclusion, prospective, randomized, and placebo-controlled trials are needed to elucidate the clinical potential of immunomodulatory or passive immunization therapies.

## 6.4 | Virome interactions with commensal communities: future prevention and treatment strategies for SARS-CoV-2 infections?

Mucosal anti-viral immunity can be regulated by the microbiota via multiple mechanisms. The immune response to microbes is a form of host defense and entails a variety of intimate interactions with important symbiotic physiological effects on the host.<sup>248</sup> Specific bacterial components and specific metabolites can promote immune maturation and polarization, which ensures appropriate defense against occasional pathogens, while strongly promoting immune tolerance networks that dampen aberrant inflammatory responses.<sup>249,250</sup> The composition of the gut and lung microbiome is strongly associated with the induction of polarized immune responses within the human lung.<sup>187,250</sup> Bacterial-derived metabolites such as short chain fatty acids (SCFAs) promote anti-viral responses in the lungs, while also reducing inflammation.<sup>251,252</sup> Composition and metabolic activity of the gut microbiome has been associated with blood proteomic biomarkers predictive of severe COVID-19.<sup>253</sup> The integration of microbial diagnostics with traditional immunological biomarkers will improve patient's stratification and prognosis. In addition, the combination of microbial-derived therapeutics with immune modifying drugs, such as biologicals, will enhance response to treatment and better protect from damaging inflammatory processes.

## 6.5 | Future pandemic prevention strategies based on immunological knowledge

Apart from the well-known measures of social distancing, washing hands, and disinfection, which have proven to limit the SARS-CoV-2 spread, several prevention strategies can be considered



**FIGURE 7** Clinical stages of COVID-19 and their virology and immunological assessment. The success of restraining SARS-CoV-2 transmission depends on accurate and timely diagnostics. Asymptomatic patients transmit SARS-CoV-2. RT-PCR-based test detecting the SARS-CoV-2 RNA in posterior conchae nasal swabs are currently the golden standard in the initial phase of the infection. Viral antigens can be detected in patients' blood by means of ELISA tests. ELISA tests allow for detection of virus-specific antibodies in patients' serum. The production of specific IgM starts after about a week from infection and IgM levels decrease with the production of specific IgG (after about 2 wks from infection). Novel diagnostic and risk-stratification strategies could include microbiome profiling and tests detecting neutralizing antibodies

from an immunological point of view. The WHO Strategic and Technical Advisory Group for Infectious Hazards (STAG-IH) regularly reviews and updates its risk assessment of COVID-19 to make recommendations.<sup>254</sup>

For the future, it is essential to define the actual prevalence of COVID-19 in the population. Confirmation of infection at present consists of PCR for acute infection and serological tests to identify antibodies.<sup>255</sup> However, this may not be sufficient. The implementation of immune tests detecting neutralizing antibodies is key to define protection against SARS-CoV-2 (Figure 7). This can only be achieved by implementing massive testing. Moreover, multiple vaccines are under development with the aim of preventing infection, reducing disease severity, and viral shedding. A complete and continually updated list is available from the WHO.<sup>256,257</sup>

Zoonotic infectious diseases have been an important concern to humankind for more than 10 000 years. Today, approximately 75% of newly emerging infectious diseases (EIDs) are zoonoses that result from various anthropogenic, genetic, ecologic, socioeconomic, and climatic factors. The COVID-19 pandemic is an extreme reminder of the role which animal reservoirs play in public health. Also, it reinforces the urgent need for globally operationalizing a One Health approach focusing on a broad surveillance for SARS-CoV-2 among different animals, and the possibility of reverse zoonosis.<sup>258</sup> Moreover, the current pandemic highlights the essential need for a broad understanding of immunological mechanisms underlying infectious diseases to design suitable therapeutic and preventive strategies.

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TABLE 2 Novel immunological treatment options for COVID-19 (as of May 15, 2020)

Treatment	Type of Drug	Mode of Action	Clinical Manifestations	Age, Gender	Intervention	Key Information (type of trial, sample size, effect)	Reference
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	17/21 (severe); 4/21 (critical) 6 days postonset (median) Heterogenous clinical presentations and comorbidities	56.8 ± 16.5 (25-88) 18M, 3F	400mg once iv (in addition to lopinavir)	n = 21, prospective, open-label, nonrandomized single-arm, interventional trial Normalization body tempin 24h Improvement of clinical symptoms: 15/21 lower oxygen demand; 1/21 no oxygen demand improvement CT (19/21), 19/21 discharge at 13.5 d after treatment start no AE related to drug reported	Xu et al <sup>230</sup>
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	All critical in ICU Heterogenous clinical presentations and comorbidities	64 (IQR 59-72), 50-76; 30M, 3F	27/33 lopinavir/ritonavir; 26/33 hydroxychloroquine; 28/33 dexamethasone; 4/33 tocilizumab	n = 4/33 tocilizumab treatment, single-center prospective observational cohort 9/33 discharged ICU, 1 died, 23 in ICU Outcome of Tocilizumab-treated patients not disclosed	Piva S et al <sup>227</sup>
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	All post-solid organ transplantation 22/90 mild, 41/90 moderate; 27/90 severe; heterogenous clinical presentations and comorbidities All of moderate-severe group had abnormal chest radiographs None on ECMO, 13 no oxygen	57y (46-68); 53M, 37F	Heterogenous uses hydroxychloroquine (61), azithromycin (45), bolus steroids (16) Tocilizumab n = 14 N = 9 1 dose 400mg or 8mg/kg up to 800mg iv; n = 4 - 2 doses; n = 1 - 3 doses.	n = 14/68 hospitalized received tocilizumab, retrospective study, 6/41 and 8/27 received tocilizumab 3/14 died, 4/14 remain ICU, 5 improvement, 2 discharged. No adverse events linked to tocilizumab	Pereira et al <sup>226</sup>
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	#1 12d flu-like symptoms, dyspnea; hypertension, respiratory distress progressing #2; fever, dyspnea, chest pain	1; 71y/M 2; 45y/M	D12 Lopinavir/ritonavir + hydroxychloroquine d10: 2 doses tocilizumab 12h apart Day 1 Lopinavir/ritonavir + hydroxychloroquine Day 5 tocilizumab: 2 doses 12h apart	n = 3, case report #1 d12 hospitalization, d21 deterioration and application of tocilizumab 3d fever resolution case report #2 Initial improvement, then worsening dyspnea until d5 when tocilizumab was applied d7 fever resolution, clinical improvement	Di Giambenedetto et al <sup>221</sup>

(Continues)

TABLE 2 (Continued)

Treatment	Type of Drug	Mode of Action	Clinical Manifestations	Age, Gender	Intervention	Key Information (type of trial, sample size, effect)	Reference
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	#3; flu-like symptoms, pneumonia 6/15 (severe); 7/15 (critical); 2/15 (moderate); 10 had comorbidity	3; 53y/M 73y (62-70) 12M, 3F	Day 1 Lopinavir/ritonavir + hydroxychloroquine Day 3 started, 3 doses In 8, Tocilizumab (80 to 600mg) with methylprednisolone (20mg to 80 b.i.d.); In n = 5, 2 or more doses	case report #3 respiratory symptoms worsened d2 d3 tocilizumab given progressive resolution of the symptoms day 9) n = 15, pilot study; retrospective observational study Outcomes: 3/4 (critical receiving one dose) died, 4th persistence of CRP elevation over weeks IL-6 decreased in 10/15 patients, increased in 4 critical and 1 severe. n = 2 disease aggravation n = 1 disease improvement n = 9 disease stabilization	Luo et al <sup>224</sup>
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	Kidney-transplanted individuals Heterogenous clinical presentations and comorbidities, All presented with fever.	59 (IQR 51-64) 16M, 4F	Medication adjusted according to renal function. d1- 7: lopinavir/ritonavir (400/100 mg bid) -hydroxychloroquine 200 mg bid if GFR > 30 ml/min 200 mg/day GFR > 15 ml/min and < 30 ml/min 200 mg every other day if GFR < 15 ml/min Longer in case of deterioration Dexamethasone (20mg/d for 5 days followed by 10mg/d for 5 days) Tocilizumab (up to 2 infusions at intervals of 12 to 24 hours; 8 mg/kg (max 800 mg)	n = 6 TCZ /20, single-center observational study n = 1 death n = 2 discharged n = 3 inpatient Chest X-ray improvement after 3-11 days on tocilizumab: n = 3 no improvement n = 2 improvement n = 1 n/a	Alberici et al <sup>218</sup>
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	COVID-19-related pneumonia and respiratory failure, not needing mechanical ventilation. Included if satisfying at least one criteria: respiratory rate $\geq$ 30/min, SaO <sub>2</sub> $\leq$ 93% or PaO <sub>2</sub> /FiO <sub>2</sub> $\leq$ 300 mmHg.	65y (IQR 54.5-73); 64 M 21F (75%)	Standard therapy (ST, N = 23): hydroxychloroquine (400 mg daily) and lopinavir (800 mg daily) plus ritonavir 200 mg daily Tocilizumab treatment (TCZ) started within 4 days of admission single administration, 400mg/iv	n = 62 TCZ/Co, single-center, retrospective, observational study Survival rate significantly higher in tocilizumab-treated patients (60/62) as compared to controls (12/23) (HR 0.035) 92% of discharged patients recovered in Tocilizumab. Respiratory function improved in 64.8% 42% of discharged patients in control group recovered. Respiratory function worsened in all the patients; mechanical ventilation needed.	Capra et al <sup>219</sup>

(Continues)



TABLE 2 (Continued)

Treatment	Type of Drug	Mode of Action	Clinical Manifestations	Age, Gender	Intervention	Key Information (type of trial, sample size, effect)	Reference
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	SMACORE is the cohort of patients with confirmed diagnosis of COVID-19 disease referred to the IRCCS Policlinico San Matteo Hospital of Pavia enrolled March 14th-27th TCZ + SOC vs. standard of care (SOC) TCZ criteria: CRP > 5 mg/dl, Procalcitonin < 0.5 ng/mL, arterial partial pressure of oxygen/fractional inspired oxygen (fIO2) (PF ratio) < 300 ALT < 500 U/L.	SOC 63.74 (IQR 16.32) 63M 28F TCZ 16.32), 62.33 (IQR 18,68) 19M 2F	Standard of care (200 mg bid), azithromycin (500 mg once), prophylactic dose of low weight heparin, and methylprednisolone (a tapered dose of 1 mg/kg up to a maximum of 80 mg) for 10 days	N = 91 SOC vs. N = 21 TCZ Retrospective registry analysis No difference regarding mortality d7 and ICU admissions (major outcomes)	Colaneri et al <sup>220</sup>
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	Heterogenous clinical presentations and comorbidities; all critically ill with oxygen needed	76.8 (52-93) ± 11; 9M, 11F 70.7 (33-96) ± 15; 6M, 19F	Standard of care n = 20; antivirals, oxygen, antibiotics with occasional corticosteroids; 1 or 2 doses of TCZ average d7 from admission n = 25, same as above, no TCZ	n = 45, retrospective case-control study: n = 20 (TCZ, off label) to n = 25 (no TCZ) P = .002; 25% vs 72% combined death and/or ICU admission endpoint; P < .001; 0% vs 44% ICU admission for n = 20	Klopfen-stein et al <sup>223</sup>
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	Dyspnea, cough, fever with prior hypercholesterolemia Fever, cough, tachypnea with prior comorbidities Fever, dyspnea, needing Venturi; multiple comorbidities	61y/F 57y/F 56y/M	d2 sc. 162mg single dose; with antibiotics; previously on antivirals d6 sc. 162mg single dose; d1 antivirals d1 antivirals, d2 antibiotics for pneumonia, d8 sc. 162mg single dose	n = 3, case series All with IL-6 decrease and CT improvement; no adverse effects #1 fever resolved in 2 days and oxygen high flow nasal cannula progressive decrease, stopped d12 #2 worsening SpO <sub>2</sub> lead to Venturi mask d2. d8 fever gone and oxygen stopped #3 fever resolved d8, reduction of oxygen to 4L/min from 15L/min.	Mazzitelli et al <sup>225</sup>

(Continues)

TABLE 2 (Continued)

Treatment	Type of Drug	Mode of Action	Clinical Manifestations	Age, Gender	Intervention	Key Information (type of trial, sample size, effect)	Reference
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	Hospitalized adult patients with severe COVID-19 Inclusion criteria: a) PCR-confirmed COVID-19; b) SaO <sub>2</sub> < 93% at ambient air, or tPao <sub>2</sub> / Fio <sub>2</sub> < 300 mm Hg c) at least 3 of the following: CRP > 10-fold normal ferritin > 1000 ng/ml D-dimer x 10 normal values; LDH x 2 the upper normal limits.	62.6y (±12.5); 56M 7 F	Tocilizumab treatment tocilizumab iv (8 mg/kg) or s.c. (324 mg); a second administration within 24 h was given in 52/63 patients. Route of administration disposed according to the drug availability Concomitant treatment with antivirals in 63/63 patients (100%): Lopinavir/ritonavir in 45/63 patients (71.4%) Darunavir/cobicistat in 18/63 (28.6%)	Pilot prospective open, single-arm multicentre study. Patients were prospectively followed for, at least, 14 days after admission. Route of administration did not significantly affect mortality: 12.9% (4/31) and 10.3% (3/29) in the tocilizumab iv and s.c. groups, OR 1.16). Tocilizumab treatment within 6 days from admission was associated with an increased likelihood of survival ad d14(HR 2.2 95%CI 1.3-6.7).	Sciascia et al, <sup>228</sup>
Tocilizumab	Hum. mAb IgG1	IL-6R blockade	All patients receiving noninvasive ventilation (NIV) n = 57 BCRSS = 3 or mechanical ventilation with tracheal intubation (BCRSS score > 3) n = 43 all patients: lymphopenia, high-level inflammatory markers,	62y (57-71 IQR) 88 M 12 F	Lopinavir + ritonavir 400mg bid + 100mg bid or remdesivir 100mg/d antibiotic prophylaxis hydroxychloroquine 400mg/d Dexamethasone 20mg/d NIV or Mechanical ventilation TCZ 8mg/kg (max 800mg) two infusion 12 hours apart and a third optional 24h	N = 100 consecutive patients receiving tocilizumab; uncontrolled, single-center observation, 58% clinical and resp. improvement within 24-72h 37% stable; 5 worsened (4 deceased) D10: Improvement or stabilization 77%; 15% discharged 23% worsening 20% died N = 43 in ICU with mechanical ventilation, 32 (74%) improved 17 off ventilator 1 (2%) remained stable (BCRSS class 5) 10 (24%) died (all BCRSS ≥ 7 before TCZ).	Toniati et al <sup>229</sup>
Tocilizumab or Sarilumab	Hum. mAb IgG1	IL-6R blockade	All critical disease on ECMO, heterogeneous clinical presentations and comorbidities	52.41y, ±12.49; 22M, 10F	4/5 iv steroids, 3/5 antivirals, 2/5 tocilizumab or sarilumab, 1/5 hydroxychloroquine	n = 3/32, report, real-time cohort study 17 remain on ECMO, 10 died prior or shortly after decannulation, 5 extubated, 1 of the 5 discharged (9 doses remdesivir). All 5 only on vv. ECMO 2/3 on Tocilizumab weaned from ECMO, 1 died	Jacobs, et al ASAIO. 2020 <sup>222</sup>

(Continues)

TABLE 2 (Continued)

Treatment	Type of Drug	Mode of Action	Clinical Manifestations	Age, Gender	Intervention	Key Information (type of trial, sample size, effect)	Reference
Convalescent Plasma	N/A	Passive immunity	Severe disease 16.5 d (IQR 11-19.3) since onset to CP transfusion Heterogenous clinical presentations and comorbidities Ventilation: none (n = 3) low flow nasal cannula (n = 2), high flow nasal cannula (n = 3), mechanical ventilation (n = 2) (3/10 SARS-CoV-2 negative at application Donor: >3w postonset, >4d postdischarge	52.5y (IQR 45-59.5y) 6 M 4 F	Different co-medication (anti-viral 10/10; anti-fungal 2/10; antibiotics 8/10) steroids 6/10 iv methylprednisolone. 200 ml convalescent plasma with a neutralizing antibody titers of > 1:640	n = 10, pilot study; open-label prospective, nonrandomized, single-arm study with a retrospective control group 10/10: SARS-CoV-2 RNA load negative serum neutralizing antibodies 9/10 1:640 (all 9 had pre-existing neutralizing antibodies); 1/10 unavailable Compared to historic control: CP group: 3/10 discharged 7/10 improved status Control group: 3/10 deceased, 6/10 stabilized, 1/10 improved	Duan et al <sup>51</sup>
Convalescent Plasma	N/A	Passive immunity	Critical disease on mechanical ventilation, 1/5 ECMO 10, 19, 20, 20 and 22 days postonset of symptoms	36-65y 3 M 2 F	All on Antivirals and methylprednisolone, N = 3 on interferon alpha 1b 400ml convalescent plasma with SARS-CoV-2 specific ELISA titer > 1:1000 and neutralizing titer > 40	n = 5, case series ARDS resolved in 4/5 within 12d 3 dismissed (51-55 d postinfusion) 2 stable, on mechanical ventilation (d37 postinfusion) 5/5: SARS-CoV-2 RNA load negative d12	Shen et al <sup>133</sup>
Convalescent Plasma	N/A	Passive immunity	N = 5 moderate-critical disease 31-58d postonset of symptoms CT-chest abnormalities Critically ill with deterioration after standard treatment (arbidol) 4/5 required oxygen N = 1 asymptomatic postdischarge SARS-CoV-2 positive.	56-75; 3M, 3F	All on Antivirals and methylprednisolone, N = 3 on interferon alpha 1b 200 ml convalescent plasma up to three times	n = 6, case series 5/6 radiological improvement and symptom improvement 1/6 asymptomatic at enrollment	Ye et al <sup>242</sup>

(Continues)

TABLE 2 (Continued)

Treatment	Type of Drug	Mode of Action	Clinical Manifestations	Age, Gender	Intervention	Key Information (type of trial, sample size, effect)	Reference
Convalescent Plasma	N/A	Passive immunity	Critically ill SARS-Cov-2 infected patients requiring different types of ventilation	31-69 2M, 2F	All started Antiviral treatment 3/4 interferon alpha-2b treatment 200-400mL CP (1-8 transfusions) transfusion from 9d -12d after admission	n = 4, case series (including a pregnant woman) d11-18 all 4 recovered. N = 3 discharged d24-33 after first CP application. N = 1 discharged from ICU d35 after first CP application Not clear whether effect relates to CP or supportive care.	Zhang et al <sup>154</sup>
Convalescent Plasma	N/A	Passive immunity	Severe pneumonia, ARDS, ventilation CT-chest abnormalities Critically ill with deterioration after standard treatment	71y male; 67y female	All on antivirals, methylprednisolone iv, and antibiotics 2 doses 250ml convalescent. plasma 12 h apart	n = 2, case reports #1 d22 CP #2 d7 CP No adverse reaction to plasma, radiological and symptom improvement # 1 tracheostomy, off ventilation now, SARS-CoV-2 RNA load negative d26; #2 1 discharged d24 postinfusion; SARS-CoV-2 RNA load negative d20	Ahn JY et al <sup>134</sup>
Baricitinib	SMO	JAK1/2 pathway inhibition	moderate (>2 of the following symptoms: fever, cough, myalgia, fatigue AND evidence of radiological pneumonia); 6 days of onset (IQR 4-6.25)	63.5y (IQR 57.7-72.20y) 10M, 2F	4mg/day for 14 days; orally in combination with lopinavir-ritonavir	n = 12, pilot study; open-label prospective, nonrandomized, single-arm study with a retrospective control group (n = 12 lopinavir-ritonavir, hydroxychloroquine) Outcomes: resolution of cough, dyspnea, within 14 days vs 9/12 and 8/12 in control group discharge from hospital 7/12 vs 1/12 in control group	Cantini et al <sup>241</sup>

(Continues)

TABLE 2 (Continued)

Treatment	Type of Drug	Mode of Action	Clinical Manifestations	Age, Gender	Intervention	Key Information (type of trial, sample size, effect)	Reference
Mepplazumab	Hum. mAb IgG2	CD147 blockade	Severity in treatment group: 4/17 (common); 6/17 (severe); 7/17 (critical); 4/11 (common); Severity in control group: 4/11 (common) 4/11 (severe); 3/11 (critical) 27/28 had fever as symptom? (16/17 in treatment group and 11/11 in control group) Comorbidities in 9 (treatment) and 4 (control)	51y (IQR 49-67y) 11M, 6F	16/17 glucocorticoid, all 17 antibiotics; 7/11 glucocorticoid; 10/11 antibiotic 10mg days 1,2,5 iv for 11 patients, 6 had 2 doses only.	n = 17, clinical trial; open-label prospective, concurrent controlled (n = 11) for 28 days All previously treated with lopinavir/ritonavir and $\alpha$ -2b. Outcomes: shorter time to discharge treatment vs control (P = .006); case severity improved (P = .021); shorter time to virus negative (P = .014). No adverse effect with treatment	Bian et al <sup>259</sup>
Anakinra	Recombinant human anti-IL-1R $\alpha$	IL-1R blockade	Consecutive patients with SARS-CoV-2 pneumonia with high risk of worsening chest CT compatible with COVID-19-pneumonia, hospitalized in a non-ICU, oxygen flow of $\leq$ 6 L/min, CRP $\geq$ 50 mg/L. Days since onset of symptoms 8 (median) Oxygen therapy 4.5d (median)	46-62y 8M, 1F	sc. 100 mg/every 12h d1-d3 sc. 100 mg/every 24h d4-d10.	N = 9 case series; prospective, observational, nonrandomized N = 1 acute resp. failure 6h after first dose (authors found no evidence of linkage to Anakinra) and stopped thereafter and ICU admission. Slow reduction of CRP over time and normalization in 5/8 at day 11 8/11 no fever d3 Reduction of affected areas in CT scan (d5-8) 7/9 no oxygen demand d11	Aouba et al <sup>238</sup>
Anakinra	Recombinant human anti-IL-1R $\alpha$	IL-1R blockade	n = 8; secondary hemophagocytic lymphohistiocytosis, severe; acute respiratory failure; heterogeneous clinical presentations and comorbidities n = 1 no ICU; n = 7 ICU admission	n = 7; 51-84y/M n = 1; 71y/F	n = 7; iv 200mg every 8h/7 days started after ventilation with hydroxychloroquine, azithromycin n = 1; d9 300mg q.d., iv 4 days, then 100mg q.d. All on antibiotics	n = 8, case series, nonrandomized, no placebo 3 died from refractory shock (no evidence of linkage to anakinra) n = 1, ventilation prevented, discharged d18 All with respiratory function improved, reduction of CRP, ferritin, D-dimers, and PCT.	Dimopoulos G. et al <sup>240</sup>

(Continues)



TABLE 2 (Continued)

Treatment	Type of Drug	Mode of Action	Clinical Manifestations	Age, Gender	Intervention	Key Information (type of trial, sample size, effect)	Reference
Anakinra	Recombinant human anti-IL-1R $\alpha$	IL-1R blockade	moderate to severe ARDS + hyperinflammation (CRP $\geq$ 100mg/L and/or Ferritin $\geq$ 900ng/ml) CPAP	HDA: 62y (IQR 55-74) LDA: 68y (IQR 51-73) ST: 70y IQR (64-78)	N = 29 high-dose Anakinra (HDA) 5mg/kg iv. Bid until sustained benefit then 3d low-dose therapy + standard treatment N = 7 low-dose Anakinra (LDA) 100mg sc. Bid until sustained benefit + standard treatment N = 16 standard treatment (ST) 200mg hydroxychloroquine 400mg lopinavir with ritonavir 100mg bid	N = 16/29/7 (ST/LDA/HAD) Retrospective cohort analysis HDA vs ST: Survival rate d21 high-dose Anakinra significantly higher (90% vs 56%) HDA vs ST: Mechanical ventilation free survival rate d21 (72% vs 50%; not significant) HDA: n = 7 discontinuation for adverse events d9 (IQR 8-10) N = 4 (vs ST n = 2) Bacteremia N = 3 (vs ST n = 5) Increased serum liver enzymes Causes of death: HDA: thromboembolism, respiratory insufficiency, and multiorgan failure (n = 1 for each). ST: respiratory insufficiency (n = 3), multiorgan failure (n = 3), and pulmonary thromboembolism (n = 1).	Cavalli et al <sup>239</sup>



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#### AUTHORS' CONTRIBUTIONS

SM drafted the manuscript. SM, JJ, and PSI contributed to "SARS-CoV-2 receptors: proven virus interaction partners and structural considerations." SM, MJ, SWCB, and SJ wrote "Airway epithelium: hotspot for disease development." SM, SWCB, and SMH contributed to "T cell-related mechanisms: lymphopenia, T-cells over-activation, and T-cell exhaustion." LZ designed the figures and wrote the figure legends. AI and KKI wrote "Multi-morbidities as a risk factor for COVID-19 course," "Sex and aging as a risk factor for COVID-19 course" and "Allergy-related risk for COVID-19." AI, SA, and vdWW contributed "Immunological diagnosis of SARS-CoV-2 infections: challenges of current approaches." AI and GCC contributed to "Future pandemic prevention strategies based on immunological knowledge." ACA and ES wrote "Skin barrier: more than just matter of wearing protective equipment." AD contributed "Myocardial and endothelial damage: an immunological perspective on cardiovascular presentation of COVID-19." AM, SA, JSR, and vdWW wrote "B cell-related mechanisms and antibody-responses." BW and PF contributed "Neurological disease presentation." BH, FW, MH, and TG wrote "Kids versus adults: mechanisms explaining the clinical differences." ET, JM, KA, and PO contributed "Immunological treatment approaches: biologicals, small molecules and beyond." CO and PO wrote "Trained immunity." EA wrote "Dendritic cells and macrophages" together with MM and PO. HSK and UE contributed "From oral to rectal mucosa: what do we know about the involvement of the gastrointestinal tract in COVID-19." JSR and KA provided the tables. KEF wrote "Neutrophils and eosinophils" and "Immunological biomarker profiling of COVID-19 for prediction of disease severity." KKI wrote "ILC and NK cells" with MH. LZ and OML wrote "Virome interactions with commensal communities: future prevention and treatment strategies for SARS-CoV-2 infections?". MM wrote "Lung pathologies in COVID-19" and "COVID-19-related kidney failure." NK and PM contributed "Complement and SARS-CoV-2" and "Coagulation parameters in COVID-19 patients." SM and UE orchestrated the whole process and conducted the final editing. UE and SM wrote the Introduction and Abstract. All authors contributed to the manuscript, revised, and edited.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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