PERSPECTIVE
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Immune determinants of COVID-19 disease presentation and severity

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COVID-19, caused by SARS-CoV-2 infection, is mild to moderate in the majority of previously healthy individuals, but can cause life-threatening disease or persistent debilitating symptoms in some cases. The most important determinant of disease severity is age, with individuals over 65 years having the greatest risk of requiring intensive care, and men are more susceptible than women. In contrast to other respiratory viral infections, young children seem to be less severely affected. It is now clear that mild to severe acute infection is not the only outcome of COVID-19, and long-lasting symptoms are also possible. In contrast to severe acute COVID-19, such 'long COVID' is seemingly more likely in women than in men. Also, postinfectious hyperinflammatory disease has been described as an additional outcome after SARS-CoV-2 infection. Here I discuss our current understanding of the immunological determinants of COVID-19 disease presentation and severity and relate this to known immune-system differences between young and old people and between men and women, and other factors associated with different disease presentations and severity.

The SARS-CoV-2 virus infects humans via droplets, and to some extent, aerosols[1]. In symptomatic adults, the disease typically presents after 2–14 days of incubation as a respiratory illness with fever, cough, headache, myalgia and in some cases intestinal symptoms[2]. A growing number of studies are pointing toward asymptomatic infection in a significant fraction of individuals[3], and as many as half of all transmission events occur from presymptomatic and asymptomatic individuals[4].

In this Perspective, I discuss what we know about the immune response to SARS-CoV-2 infection and how this might explain different disease presentations and disease severity by considering known immunological differences between the groups that are most commonly affected.

COVID-19 disease courses

Mild and severe acute COVID-19. It is clear that the outcome of infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) varies broadly, with the majority of young individuals experiencing mild disease[5]. Also, sex is an important; men are over-represented among patients with severe disease, presumably due to differences in the elicited immune responses[6]. Comorbidities such as obesity, hypertensive disease, chronic obstructive pulmonary disease and cardiovascular disease are all associated with severe COVID-19 disease[2]. Higher SARS-CoV-2 copy numbers at diagnosis have been reported in patients with severe COVID-19 than in those with mild COVID-19 (ref. [7]). Smoking is yet another risk factor: cigarette smoke induces expression of angiotensin-converting enzyme 2 (ACE2), which allows SARS-CoV-2 to enter cells, and could possibly influence viral invasion[8] beyond its negative effects on overall lung function.

Despite the increased risk of severe disease with increased age, a minor subset of young and middle-aged individuals present with severe COVID-19 disease characterized by poor oxygen saturation and massive inflammatory responses in the lung. Such cases need urgent management and intensive care, and several studies have attempted to unravel the mediators of such hyperinflammatory disease presentation[9–13].

Long COVID. Apart from the differences in severity among patients with acute COVID-19, it is now clear that a number of other outcomes are possible after an initial infection with SARS-CoV-2. After a long period of intensive care and mechanical ventilation, general anesthesia and severe illness, it is not surprising that long rehabilitation periods are needed[14]. However, it is now also clear that some individuals with milder initial symptoms of COVID-19 can suffer from variable and debilitating symptoms for many months after the initial infection[15,16]. This condition is popularly referred to as long COVID. An exact definition is lacking, but typically symptoms with a duration >2 months are considered long COVID. The condition involves a range of symptoms such as persistent fatigue, myalgia, autonomic dysregulation manifested as postural orthostatic tachycardia syndrome, abnormal thermoregulation, intestinal disturbances and skin manifestations[17]. This post-COVID syndrome bears resemblance to postinfectious syndromes that followed outbreaks of chikungunya[18] and Ebola[19], for example, and selected symptoms overlap with myalgic encephalomyelitis, a disease that is also often triggered by infection and immune activation[20] and manifests as a dysregulated autonomic nervous system and perturbed immune parameters[21]. More research is needed to understand the pathogenesis of all of these postinfectious conditions, and long COVID offers a unique opportunity to perform such studies in larger numbers of individuals, all infected by the same virus during a limited time frame.

Multisystem inflammatory syndrome associated with COVID-19. Another rare and serious postinfectious condition that can occur 2–6 weeks after SARS-CoV-2 infection is the multisystem inflammatory syndrome associated with COVID-19, first described in children (MIS-C)[22–24], and more recently in young adults (MIS-A)[25]. This hyperinflammatory syndrome shares clinical features with Kawasaki disease[26], but affects children who are older than the typical patient with Kawasaki disease and who more often present with intestinal involvement and myocardial failure and shock. There is also significant clinical overlap in presentation with toxic shock syndrome[22] or septic shock. Subgroups of children affected by MIS-C

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are being described[27], and optimal management is being worked out by collaborative networks of pediatricians. Most MIS-C patients are treated with strong immunomodulatory regimens such as high-dose steroids, intravenous immunoglobulins and anti-cytokine therapies coupled with anti-coagulation to counter the microangiopathy and activation of both complement and coagulation cascades during the hyperinflammatory disease phase[28,29]. The pathogenesis of MIS-C is unknown, but a delay of 2–6 weeks from initial SARS-CoV-2 infection indicates a role for adaptive immune responses and specific autoantibodies have been proposed[30,31].

Viral recognition and innate immune responses

Viral entry. SARs-CoV-2 infects cells by attaching to the principal viral entry receptor, ACE2 (ref. [32]). The expression of this receptor has been reported in single-cell messenger-RNA-sequencing data on epithelial cells in the oral mucosa[33], liver, kidney, intestine and heart[34], and at the protein level in alveolar epithelial cells[35], although the tissue distribution of protein expression differs to some extent[36]. Several reports have shown abundant expression of ACE2 in the intestinal epithelium leading to viral shedding via feces[37], while ACE2 does not seem to be expressed by cells of the immune system[38].

Innate immune responses. SARS-CoV-2, like the related SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), is a single-stranded RNA virus. After entering a target cell, the virus is recognized by pattern recognition receptors such as Toll-like receptors 3, 7, 8 and 9 and viral-infection sensors RIG-I and MDA5 (ref. [39]), and viral recognition induces the type I interferon (IFN) response program and IFN-stimulated genes[40] (Fig. 1a). The TLR3 response triggers transcription of the NLR family pyrin domain containing 3 (*NLRP3*) gene, which together with other cellular responses to viral infection—such as the formation of reactive oxidative species, calcium flux from cytoplasmic storages, protein aggregation and the release of danger-associated patterns—contributes to the activation of the NLRP3 inflamasome[41] and likely other inflammasome complexes. The NLRP3 inflammasome induces caspase-1-dependent cleavage and release of key proinflammatory cytokines interleukin-1β (IL-1β) and IL-18, and triggers gasdermin D-mediated pyroptotic cell death. The extent of NLRP3 activation correlates with COVID-19 disease severity[42] (Fig. 1b). As a result of pyroptotic cell death, the enzyme lactate dehydrogenase (LDH) is released. Elevated LDH levels have been observed in the blood of patients with COVID-19, and levels of this enzyme correlate with disease severity[2]. Together, these data suggest that inflammasome activation is an important feature of COVID-19 (ref. [43]) (Fig. 1b). This pathway also triggers the coagulation cascade, for example via the extracellular release of gasdermin D[44], and coagulopathy and severe thrombotic events are common in patients with severe COVID-19 (ref. [45]). A similar activation of the coagulation cascade and elevated LDH levels are also seen in patients with MIS-C[22], but not in patients with long COVID[46], indicating differences in the underlying pathogenesis.

A characteristic feature of SARS-CoV and MERS-CoV viruses is their ability to inhibit and delay the induction of type I IFN by infected cells, which contributes to the immunopathology associated with such infections[47,48]. Also, SARS-CoV-2 is able to inhibit the type I IFN responses in infected cells, leading to delayed or overall suppressed type I IFN responses[49,50]. This allows the virus to replicate and induce more tissue damage, and triggers a more exuberant immune response as the immune system struggles to limit viral replication and to manage dying and dead cells. Immune pathology continues as inflammatory cells flow into the lung and produce large amounts of proinflammatory cytokines, further escalating the situation (Fig. 1c). Such imbalanced immune responses, caused in part by the impaired early type I IFN responses, are the most likely determinant of the overall severity of acute COVID-19 (refs. [50–53]). This is further emphasized by recent results from the COVID Human Genetic Effort[54] (https://www.covidhge.com/), which found that inborn errors in the type I IFN pathway[55], or the presence of neutralizing autoantibodies to type I IFNs[56], were strongly over-represented among individuals who developed life-threatening COVID-19. Whether imbalanced or impaired innate responses also contribute to the development of other disease manifestations such as MIS-C and long COVID remains to be determined.

Adaptive immune responses

Serological tests for SARS-CoV-2 have been the subject of much discussion and conflicting results during the course of this pandemic so far. However, with time it has become apparent that the adaptive immune responses induced by SARS-CoV-2 infection largely follow the expected patterns based on what is known from other comparable viral infections, with >90% of infected individuals seroconverting a few weeks after initial infection[57,58]. Presence of anti-spike IgG antibodies were associated with protection from reinfection in a UK cohort of health-care workers at high risk of exposure[59].

T cell responses to the SARS-CoV-2 spike protein correlate with B cell responses to the same protein and are detectable in nearly all convalescent patients with COVID-19 (ref. [60]). T cell reactivity to SARS-CoV-2 can also be detected in unexposed individuals, presumably due to cross-reactive immunity to common-cold coronaviruses[60] or to other antigens, as has been shown for other virus-specific T cells[61]. Another study has reported SARS-CoV-2-reactive T cells in patients who survived the SARS epidemic in 2003, but also in unexposed individuals; interestingly, such responses preferentially targeted epitopes different from the ones in convalescent patients with COVID-19, and were not homologous with common-cold coronaviruses, but conserved among animal coronaviruses[62].

Antibody-dependent enhancement (ADE), a phenomenon that has been described for infections with viruses such as dengue[63], has been proposed as a possible mechanism of severe COVID-19. ADE occurs when antibodies target a virus without neutralizing it, for example if the antibody is raised against a different serotype of the virus or when the antibody fails to block viral entry. Then, the antibody might facilitate Fc-receptor-mediated endocytosis of the virus and enhanced viral replication, and massive inflammatory responses. This has been described to occur for MERS[64], but no clear evidence of ADE as a cause of severe SARS-CoV-2 infection has been communicated. Reinfections have been reported, and in a few instances, the second infection was more severe than the first, but serological responses suggest that patients never seroconverted after initial infection and ADE is a less likely cause of a more severe second infection[65].

The role of pre-existing immunity to common-cold coronaviruses is another possible determinant of COVID-19 disease severity[66]. T cell reactivity is found in unexposed individuals and has been linked to prior exposures to common-cold coronaviruses[67]. Also, IgG that is specific to SARS-CoV-2 spike protein has been found in unexposed individuals, particularly in children and young adults, and some of these had neutralizing activity against SARS-CoV-2, indicating a potentially protective effect against severe COVID-19 (ref. [68]). Another study also identified such antibodies but found no evidence for a protective effect against COVID-19 (ref. [69]). Cross-reactive antibodies are also more frequently found in serum samples collected in sub-Saharan Africa prior to the COVID-19 pandemic[70], indicating a possible explanation for the surprisingly low number of severe COVID-19 cases seen on this continent. Whether there is a role for cross-reactive antibodies or T cells, or the absence of such features, in determining other disease manifestations, such as MIS-C or long COVID, remains to be seen. Children who develop MIS-C have detectable IgG responses without obvious differences from convalescent children without MIS-C[29,71,72],

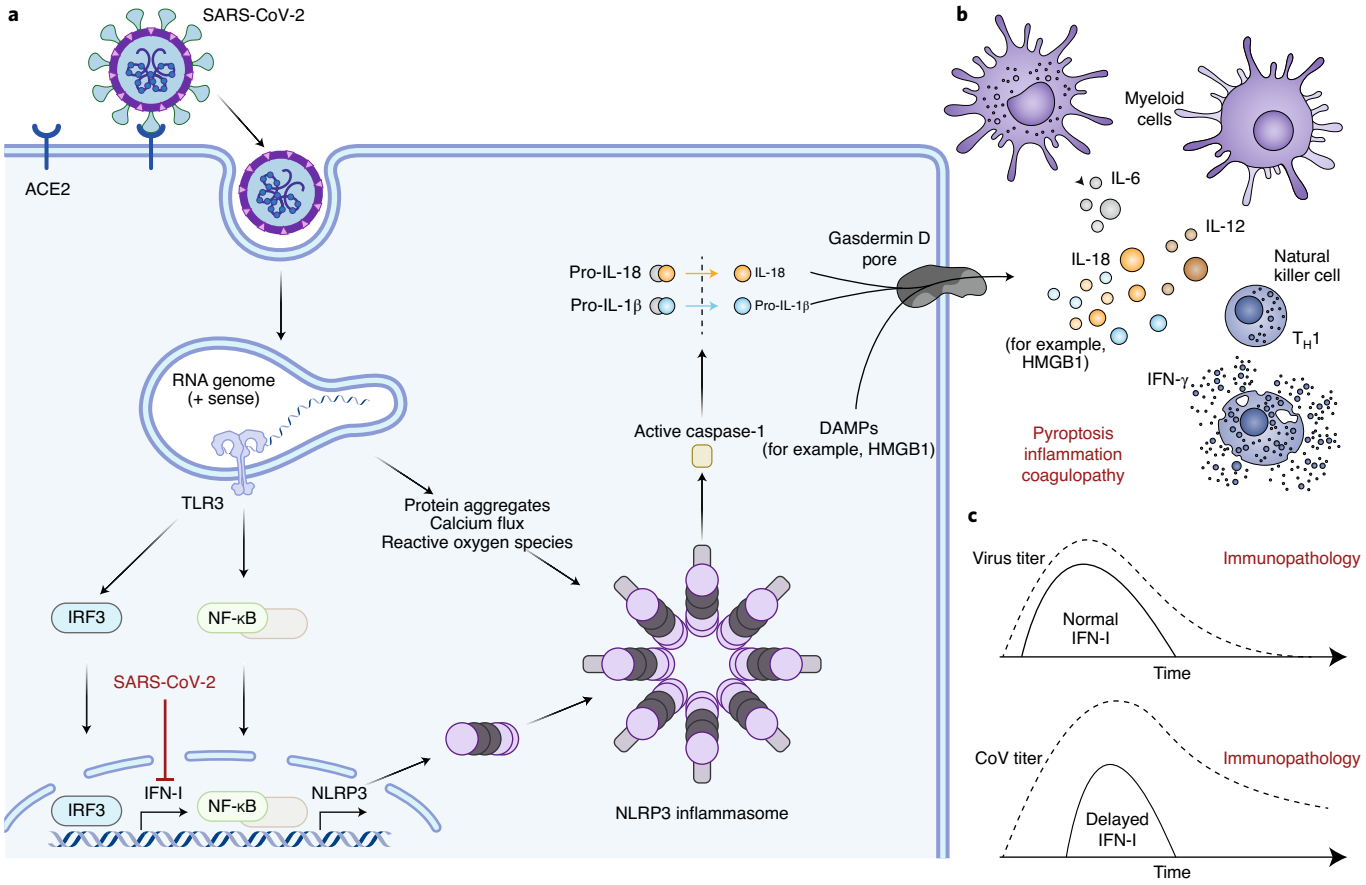

Fig. 1 | Coronavirus recognition and immune response. a, SARS-CoV-2 viruses bind to the ACE2 receptor for cell entry. Viral RNA is recognized by TLR3, which triggers transcriptional responses and cytoplasmic changes that activate the NLRP3 inflammasome. This leads to cleavage of precursor IL-1β (pro-IL-1β), pro-IL-18 and gasdermin D, allowing secretion of IL-1β and IL-18. These changes collectively induce pyroptosis, inflammation and coagulopathy. **b**, Secreted IL-18 together with IL-12 from myeloid cells stimulate T_H1 immunity and natural killer cells to secrete IFN-γ. **c**, A key feature of coronaviruses (MERS-CoV, SARS-CoV) is a capability to inhibit and delay the type I IFN response, leading to increased viral replication and severe immunopathology.

although one study indicated subtle IgG-subclass and functional differences between children with MIS-C and those without MIS-C[73].

Known immunological differences between high- and low-risk individuals

The risk of developing severe COVID-19 increases steeply above age 70, and also with the severity of obesity and other risk factors. Men have a much greater risk of severe acute COVID-19 than women, whereas women are over-represented among patients who develop long COVID[15]. The infection differs from many other respiratory infections in that children are seemingly able to cope, even in the very first years of life, without developing severe respiratory disease except in a few rare cases. The known immunological differences between young and old people and between men and women should help us further unravel the immunological mechanisms behind disease presentation and severity.

Sex differences. As mentioned above, type I IFN responses are critical determinants of disease severity during acute SARS-CoV-2 infection, and the virus has developed methods for subverting these responses. Women elicit stronger type I IFN responses upon stimulation with TLR7 ligands[74] and develop stronger vaccine responses[75], but also more side effects, and have better survival rates for a number of acute infections than do men[76]. These sex differences are seen even in boys and girls before puberty—pointing towards genetic, rather than hormonal, differences. It is worth noting that a common sensor of viruses, TLR7, is expressed on the X chromosome, providing a possible difference in gene-dosage effect between men and women[77]. Interestingly, the neutralizing autoantibodies to type I IFN found in patients with severe COVID-19 were much more abundant in men than in women, but the reasons for this are elusive[56]. Immune-response differences have also been reported between male and female patients with COVID-19 (ref. [6]), and collectively these sex differences could explain the overall susceptibility of male patients to developing severe acute COVID-19. MIS-C is quite evenly distributed between boys and girls[22], whereas long COVID is more prevalent in female patients[15,16]. It is also important to consider whether social factors and differing exposure play a part in sex differences.

Age differences. If type I IFN responses were the sole determinants of COVID-19 severity, one would expect young children to be highly susceptible because both newborn and young children produce lower amounts of type I IFN upon stimulation through various viral-sensing pathways[78]. The low risk of severe SARS-CoV-2 disease in young children also differs from that of other respiratory viral infections like the flu[79], and points toward other protective mechanisms in young children. The immune systems of young children are accustomed to facing novel challenges, whereas older individuals rely more on memory responses. The thymus decreases its output of naive T cells and involutes at a rate of about 3% per year, and some data indicate more rapid involution in boys than in

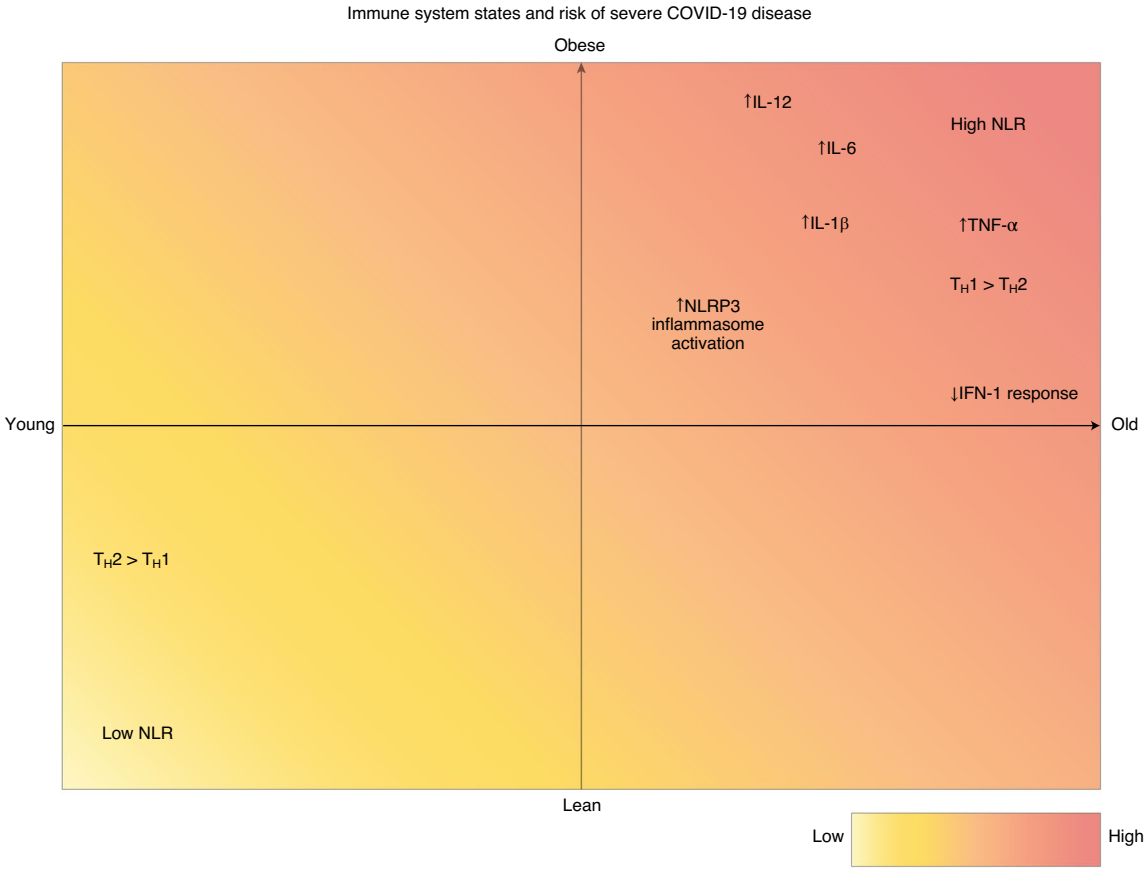

Fig. 2 | Immune-system parameters associated with obesity, aging and severe COVID-19. The gradient illustrates the risk of developing severe COVID-19 in relation to known immune system changes with age (*x* axis) and obesity (*y* axis).

girls[80]. Cross-reactive antibodies to common-cold coronaviruses are one possible explanation; another possibility is that constitutive differences in immune system states between young and old people are of importance. One example could be the skewing of T cells from T helper type 1 (T_H1) toward more T_H2 in young children[81] (Fig. 2).

Disease severity in COVID-19 also correlates with neutrophil-to-lymphocyte ratio (NLR)[82], a metric reflecting immune-cell composition that is frequently studied across populations and disease conditions as a surrogate marker of systemic inflammation. The NLR ratio positively correlates with advancing age[83] and with the degree of obesity, especially in the context of metabolic syndromes and type 2 diabetes[84]. As such, the NLR ratio is indicative of low-grade inflammation, 'inflammaging' and obesity-associated inflammation, and is a poor prognostic factor in COVID-19 (Fig. 2). This observation indicates that individuals with such underlying immune-system conditions either fail to develop productive antiviral immune responses or are more prone to develop uncontrolled, exuberant responses upon infection, leading to hyperinflammation and acute respiratory distress syndrome, characteristic of severe COVID-19 (Fig. 2). Older individuals typically produce weaker type I IFN responses upon viral infection, which further worsen the situation[85]. Also, additional markers of inflammaging and obesity-associated inflammation have been shown to be predictive of a severe COVID-19 course, such as NLRP3 activation[43], IL-6, IL-12 and IL-1β secretion[86] and danger-associated molecular patterns, including high mobility group box 1 (HMGB1)[87] (Fig. 2).

Immunodeficiencies. Since the beginning of the pandemic, there have been grave concerns over the risk of developing severe COVID-19 for individuals with immunodeficiencies or those taking immunosuppressive therapies. One systematic review found no statistically significant increased risk of severe COVID-19 in immunosuppressed patients[88], but other studies have shown an increased risk for patients with solid-organ transplants and some patients with cancer[89]. Patients with cancer treated with checkpoint inhibitors are at particularly high risk of severe COVID-19, according to another recent report[90]. It is important to note that type and degree of immunosuppression likely varies substantially among heterogeneous patient groups, and more detailed subset analyses are needed. This is also highlighted by an Italian study of patients with different forms of primary antibody deficiencies, in which patients with combined variable immunodeficiency, often associated with low-grade inflammation, developed severe COVID-19, while patients with similarly low antibody levels due to other forms of inborn errors of immunity generally experienced milder course of disease[91].

Future directions. In summary, COVID-19 can develop into a life-threatening hyperinflammatory disease in rare cases, and global efforts are ongoing to better understand productive immune responses against the SARS-CoV-2 virus and the immunopathological mechanisms underlying severe disease. At the same time, additional disease outcomes, such as MIS-C, MIS-A and long COVID, are becoming increasingly known. By considering known differences between high- and low-risk individuals for each of these conditions, we will be able to design optimal studies contrasting such patient groups and their immune responses. The origin of the different disease trajectories upon SARS-CoV-2 infection can likely be traced back to the early stages of infection, as illustrated by the essential role for type I IFN responses during acute COVID. With this Perspective, I hope to open up a discussion on the different

disease manifestations, their shared and distinguishing features and affected populations and immunological features.

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