INVITED REVIEW

COVID-19: immunopathology, pathophysiological mechanisms, and treatment options

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread globally despite the worldwide implementation of preventive measures to combat the disease. Although most COVID-19 cases are characterised by a mild, self-limiting disease course, a considerable subset of patients develop a more severe condition, varying from pneumonia and acute respiratory distress syndrome (ARDS) to multi-organ failure (MOF). Progression of COVID-19 is thought to occur as a result of a complex interplay between multiple pathophysiological mechanisms, all of which may orchestrate SARS-CoV-2 infection and contribute to organ-specific tissue damage. In this respect, dissecting currently available knowledge of COVID-19 immunopathogenesis is crucially important, not only to improve our understanding of its pathophysiology but also to fuel the rationale of both novel and repurposed treatment modalities. Various immune-mediated pathways during SARS-CoV-2 infection are relevant in this context, which relate to innate immunity, adaptive immunity, and autoimmunity. Pathological findings in tissue specimens of patients with COVID-19 provide valuable information with regard to our understanding of pathophysiology as well as the development of evidence-based treatment regimens. This review provides an updated overview of the main pathological changes observed in COVID-19 within the most commonly affected organ systems, with special emphasis on immunopathology. Current management strategies for COVID-19 include supportive care and the use of repurposed or symptomatic drugs, such as dexamethasone, remdesivir, and anticoagulants. Ultimately, prevention is key to combat COVID-19, and this requires appropriate measures to attenuate its spread and, above all, the development and implementation of effective vaccines.
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Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread globally despite the extensive implementation of preventive health measures. As of 24 January 2021, the pandemic has accumulated over 98 million confirmed cases, including more than 2.1 million deaths [1]. While most SARS-CoV-2 infections cause mild, self-limiting upper respiratory complaints, a notable subset of patients require hospitalisation upon progression to severe disease, varying from lower respiratory tract infection to acute respiratory distress syndrome (ARDS) and multi-organ failure (MOF) [2]. This is accompanied by abnormal laboratory parameters, including lymphopaenia and elevated levels of C-reactive protein (CRP), D-dimers, ferritin, and lactate dehydrogenase (LDH) [3]. Individuals particularly at risk for severe disease include the elderly, males, and those with comorbidities such as cardiovascular disease, diabetes, obesity, chronic respiratory disease, and immunocompromising conditions [4].

The complex pathophysiology of COVID-19 seems to consist of multiple mechanisms, of which the immunopathological response to SARS-CoV-2 infection became a major area of interest. While a well-regulated immune response is essential in controlling SARS-CoV-2 infection, a hyperinflammatory innate immune response along with an inadequate adaptive response may elicit extensive local and systemic tissue injury. In addition, recent reports demonstrate that SARS-CoV-2 infection may trigger autoimmune (adaptive immunity) and autoinflammatory (innate immunity) conditions, and several reactive autoantibodies have been found (see below). A profound understanding of the immune responses that lead to recovery instead of worsening disease is essential for developing effective treatment options for COVID-19. To date, there are no specific treatment regimens to combat the disease, and current management revolves around supportive treatment and the use of (repurposed) drugs, such as dexamethasone, remdesivir, and anticoagulants. As for prevention of COVID-19, several measures are held in place (e.g. social distancing, quarantine, wearing face masks, frequent handwashing) and emergency use authorisations have been issued for various vaccines, resulting in the implementation of large-scale vaccination programmes. In this review, we elaborate on the various pathways and systems involved in the pathophysiology and immunopathogenesis of COVID-19. Furthermore, we discuss the rationale and outcome of the use of several repurposed treatment modalities employed to combat SARS-CoV-2.

Proposed pathophysiological mechanisms underlying COVID-19

COVID-19 progression is considered to result from a complex interplay of multiple pathophysiological mechanisms, including (1) direct cytopathic effects of SARS-CoV-2; (2) angiotensin-converting enzyme 2 (ACE2) downregulation with subsequent renin–angiotensin–aldosterone system (RAAS) disbalance and decreased inactivation of des-Arg^9-bradykinin; (3) a dysregulated immune response featuring a 'cytokine storm'; (4) coagulopathy associated with exocytosis of procoagulatory factors, thrombotic microangiopathy – probably caused by virus-induced endothelial injury, complement activation, and cytokine effects – and uncontrolled localised and/or systemic 'immunothrombosis'; and (5) autoimmunity [5,6]. The relative contributions and interactions of these intertwined mechanisms to COVID-19-associated organ dysfunction remain undetermined, with the possibility of immunopathology being a hallmark of severe disease. Herein, we outline the various routes involved in the immunopathology of COVID-19 based on a narrative review of the literature.

Immunopathology and immune defects

Innate immune response

The innate immune system provides the first line of immunological defence against SARS-CoV-2 infection. Following binding of the spike (S) protein to ACE2, SARS-CoV-2 may enter the cell either via endocytosis and cathepsin L (CTSL)-dependent viral escape from the endosome – which is augmented by transmembrane serine protease 2 (TMPRSS2) – or by TMPRSS2-dependent direct fusion of the viral envelope with the cell membrane (Figure 1) [7–9]. Unlike SARS-CoV, cell entry of SARS-CoV-2 can also be facilitated by furin and neuropilin-1 [10,11]. Upon infection, viral pathogen-associated molecular patterns (PAMPs) are sensed by endosomal pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs). This results in intracellular signalling cascades, which involve activation of transcription factors such as nuclear factor-kappa B (NF-κB) and interferon regulatory factors (IRFs) [12]. These events ultimately lead to the production of type I interferons (IFNs) and pro-inflammatory cytokines (Figure 1).

An adequate IFN response normally induces an antiviral immune state in infected cells that limits viral replication and induces apoptosis to protect the host from viral dissemination. However, multiple SARS-CoV-2 proteins [e.g. open reading frame 6 (ORF6) and ORF3b] have been shown to suppress antiviral type I IFN (IFN-I) production and signalling [13–15]. The initial delay of the IFN-I response is followed by unrestrained viral replication and dissemination in the infected host, thereby promoting an eventual increase of IFN-I that can exacerbate hyperinflammation in the progression to severe disease [16]. Transcriptome profiling of respiratory cell types showed that SARS-CoV-2 infection elicited exceptionally low IFN levels, while inducing a robust pro-inflammatory cytokine response [17]. In this study, there was also a significant induction of monocyte and
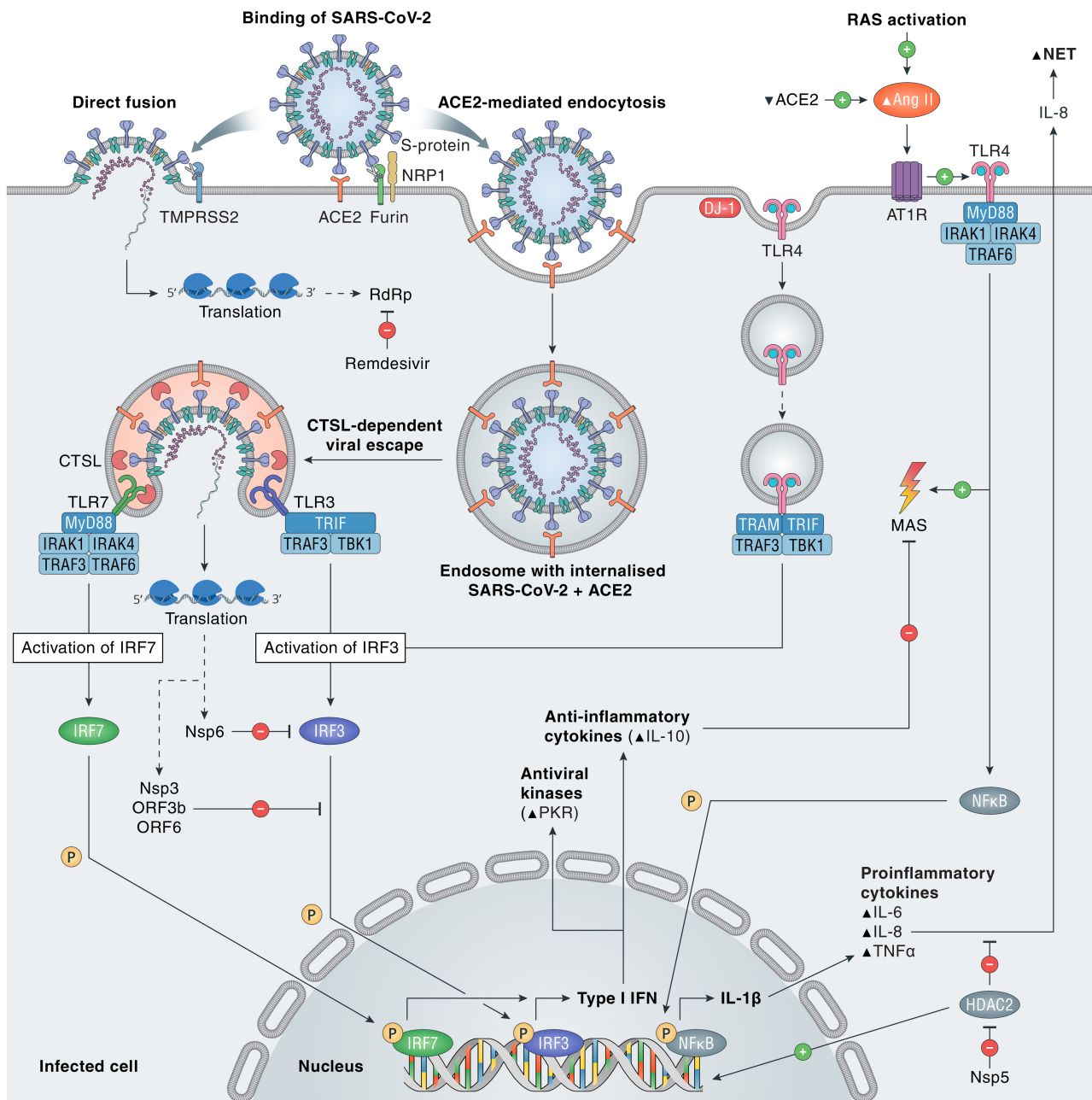
Figure 1. SARS-CoV-2 entry and immune activation. SARS-CoV-2 needs to bind to ACE2 to enter the cell, either by TMPRSS2-dependent direct fusion of the viral envelope to the cell membrane or by TMPRSS2-enhanced endocytosis. Furin and NRP1 can also facilitate viral entry. Viral escape by fusion to the endosomal membrane is CTSL-dependent, as is activation of TLR7, which is essential in the recognition of single-stranded RNA viruses and induction of type I IFN via IRF7. Activation of RAS by viral infection, via Ang II and AT1R, induces the TLR4/MyD88/NFκB pathway to increase pro-inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α. After DJ-1-induced endocytosis of TLR4, type I IFN, antiviral kinases, and the anti-inflammatory cytokine IL-10 are activated. Nsp3 and -6 of SARS-CoV-2 inhibit IFN activation via the IRF3 pathway. Nsp5 blocks HDAC2, preventing it from decreasing IL-8, a pro-inflammatory cytokine with a role in NET formation. MAS is stimulated by the pro-inflammatory TLR4/MyD88-dependent pathway and inhibited by the anti-inflammatory cytokine IL-10. ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II; AT1R, angiotensin II type 1 receptor; CTSL, cathepsin L; HDAC2, histone deacetylase 2; IL, interleukin-1β/6/8/10; IRAK1/4, interleukin 1 receptor associated kinase 1/4; IRF3/7, interferon regulatory factor 3/7; MAS, macrophage activation syndrome; MyD88, myeloid differentiation primary response 88; NET, neutrophil extracellular trap; NFκB, nuclear factor kappa B; NRP1, neuropilin 1; Nsp3/5/6, nonstructural protein 3/5/6; ORF3b/6, open reading frame 3b/6; P, phosphate; PKR, double-stranded (ds)RNA-dependent protein kinase; RAS, renin–angiotensin system; RdRp, RNA-dependent RNA polymerase; TBK1, TANK binding kinase 1; TLR, toll-like receptor 3/4/7; TMPRSS2, transmembrane serine protease 2; TNFα, tumour necrosis factor α; TRAF6, tumour necrosis factor receptor-associated factor 6; TRAM, TRIF-related adaptor molecule; TRIF, Toll-IL-1 receptor domain-containing adaptor inducing IFN-β; type I IFN, type I interferon.

neutrophil chemoattractants, in line with the commonly observed lung infiltration of macrophages and polymorphonuclear leukocytes in autopsied COVID-19 cases [18–20]. Similar to other viral infections, inter-individual

variability in IFN responses may contribute to the heterogeneity of disease manifestations in COVID-19. In a Dutch case series including four young male patients from two unrelated families admitted to the intensive

care unit (ICU), rare genetic variants in the *TLR7* gene were identified and associated with impaired IFN-I and IFN-II responses [21]. These findings may partially explain the discouraging results of the TLR7-antagonising antimalarial drugs hydroxychloroquine and chloroquine [22,23], whereas the TLR7-agonist imiquimod may serve as suitable treatment option in some COVID-19 patients [24]. Recently, two paired studies also reported specific underlying defects of IFN-I signalling in life-threatening COVID-19, including inborn errors of TLR3- and IRF7-dependent IFN-I immunity [25], and the presence of neutralising autoantibodies against IFN-I [26]. The latter study demonstrated that neutralising autoantibodies against IFN-I were present in 10.2% of 987 patients with life-threatening COVID-19 pneumonia, ~15-fold higher than the general population, and showed a male preponderance. These findings provide a rationale for the use of IFN-based treatments in the early stage of COVID-19 when only mild symptoms are present. Previously, some concerns were raised that conditions associated with IFN elevations could induce ACE2 expression – thereby promoting SARS-CoV-2 entry – since ACE2 was considered to be an interferon-stimulated gene (ISG) [27]. However, a recent study discovered a novel truncated isoform of ACE2 – so-called deltaACE2 – which was demonstrated to be an ISG as opposed to ACE2. DeltaACE2 neither acts as a receptor for SARS-CoV-2 nor acts as a carboxypeptidase for angiotensin II (Ang II) and des-Arg^9-bradykinin [28]. Therefore, IFN-induced deltaACE2 does not promote SARS-CoV-2 infection. Importantly, whereas the immune response is initially suppressed, an eventual overactivation of immune responses contributes to hyperinflammation and organ damage [16]. Hypercytokinaemia has been reported in severe COVID-19 on several occasions. This condition is often referred to as a 'cytokine storm', being reminiscent of the macrophage activation syndrome (MAS) [29]. However, the role of a cytokine storm in COVID-19 pathogenesis has been questioned recently, since the degree of pro-inflammatory cytokinaemia in COVID-19 has been shown to be profoundly less than in archetypical conditions associated with MAS [30].

Another key player in the innate immune response is the complement system, acting as a rapid immune surveillance system against invading pathogens, bridging innate and adaptive immunity [31]. In the case of COVID-19, complement activation is overwhelming, which results in harmful acute and chronic inflammation, endothelial cell dysfunction, and intravascular coagulation [32]. Indeed, strong complement activation has been demonstrated in the systemic circulation [33,34] as well as locally in various organs of COVID-19 patients (see below) [34–36], providing a rationale for the use of complement inhibition as therapy in COVID-19.

Finally, the innate immune system interacts with coagulation – a process known as 'immunothrombosis' – that is thought to be dysregulated in severe COVID-19,

leading to localised and/or systemic coagulopathy [37]. The detection of PAMPs and damage-associated molecular patterns (DAMPs) by PRR-expressing monocytes results in their enhanced expression of tissue factor (TF), which in turn activates the extrinsic pathway of coagulation [38]. In addition, activated neutrophils release neutrophil extracellular traps (NETs) – lattices composed of neutrophil-derived DNA and acetylated histones – which trap and kill invading pathogens but may also induce a strong procoagulant response [38]. NETs can promote activation of the intrinsic coagulation pathway by activation of factor XII but can also bind TF to activate the extrinsic coagulation pathway [38]. NETs have been frequently demonstrated in COVID-19, sometimes forming aggregates with platelets [39,40], and they may be drivers of disease severity [41]. An overview of SARS-CoV-2 effects on the innate immune response is depicted in Figure 1.

Adaptive immune response

The adaptive immune system plays a pivotal role in SARS-CoV-2 clearance via activated cytotoxic T-cells that destroy infected cells and through B-cells that produce neutralising antibodies against virus-specific antigens (Figure 2). A key feature of COVID-19 is blood lymphopaenia, with reduced numbers of CD4$^+$ T-cells, CD8$^+$ T-cells, and B-cells [42]. Lymphopaenia may be partially explained by an abnormal innate immune response featuring low IFN-I, considering its essential role in the assembly of viral material for antigen presentation and the subsequent induction of adaptive immunity [43]. Other mechanisms that potentially contribute to COVID-19-associated lymphopaenia include direct SARS-CoV-2 infection of T-cells [44], cytokine-induced apoptosis and pyroptosis of lymphocytes [45], MAS-related haemophagocytosis, lymphocyte sequestration in the lungs or other organs [46], reduced bone marrow haematopoiesis [47], and virus-induced tissue damage of lymphatic organs [48,49]. Notably, both spleen and lymph nodes showed the presence of SARS-CoV-2 [49], and pathological alterations (e.g. splenic white pulp atrophy and lymph node structure disruption) have been reported [48,49], suggesting that direct SARS-CoV-2 cytotoxicity in lymphatic organs may impair the adaptive immune response in COVID-19.

Loss of germinal centre formation in both spleen and lymph nodes provides a potential explanation for suboptimal humoral immunity, with the possibility of reinfection in certain individuals [50,51]. Nevertheless, the vast majority of COVID-19 patients with mild-to-moderate disease experience a robust adaptive immune response consisting of T-cells (against S-protein- and nucleoprotein/membrane protein-derived antigens) and neutralising antibodies (against S-protein-derived antigens), which persists for months after primary infection [52,53]. Overall, coordinated SARS-CoV-2-specific adaptive immune responses are associated with milder
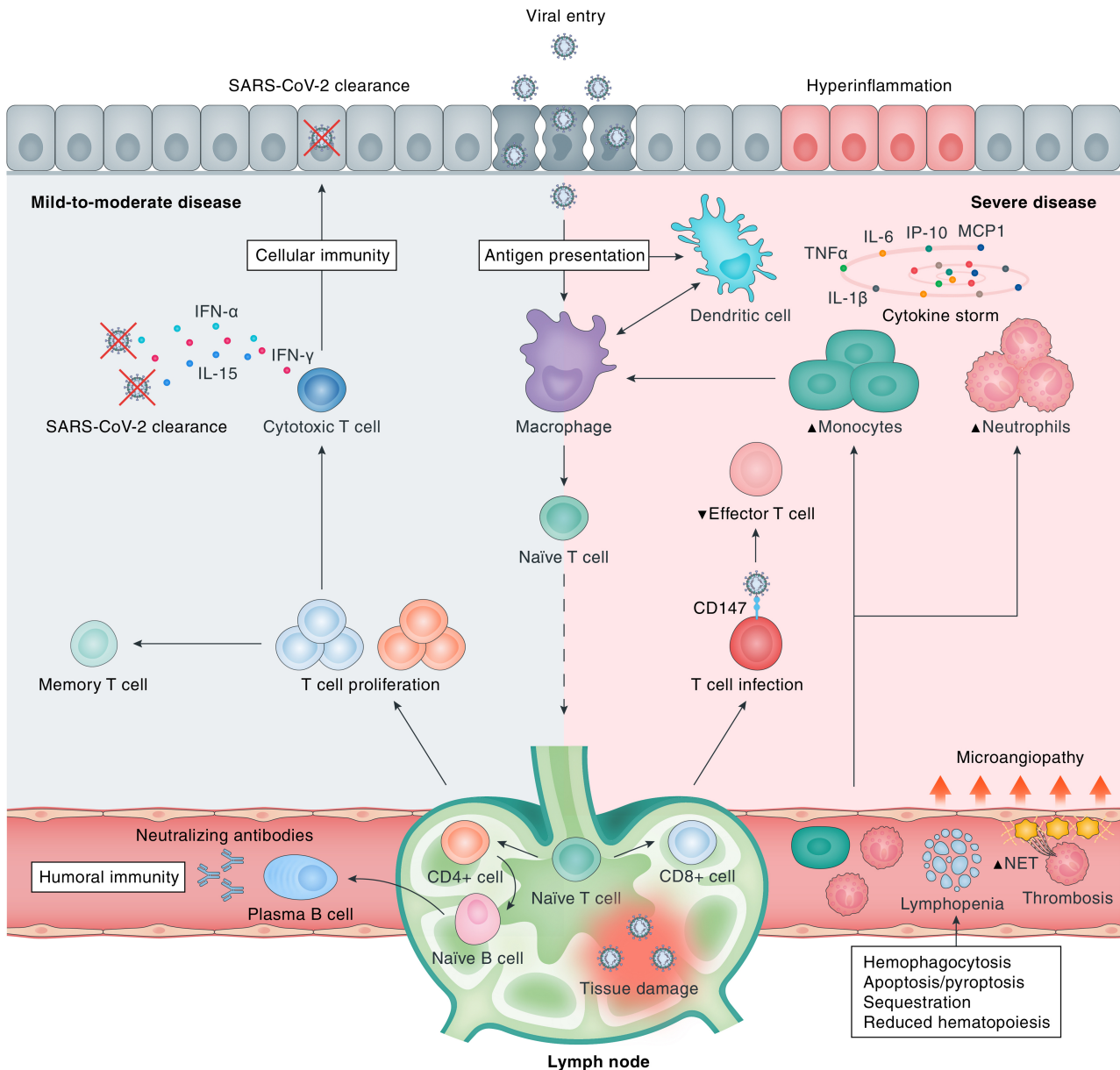
Figure 2. Immunological response to SARS-CoV-2 infection. Upon viral cell entry, SARS-CoV-2 antigens are processed by the innate immune system through antigen-presenting cells (APCs), e.g. epithelial cells, macrophages, and/or dendritic cells. Subsequently, the adaptive immune system is activated by migration of APCs to the lymphoid system. Upon antigen recognition, T-lymphocytes proliferate and differentiate into CD4^{+} and CD8^{+} T-lymphocytes that are responsible for sequential events including cytokine production, activation of naïve B-lymphocytes, and clearance of infected cells (CD8^{+} cytotoxic T-lymphocytes). B-lymphocytes proliferate and differentiate into plasma cells that produce large numbers of neutralising antibodies, representing humoral immunity. A bulk of cytokines is induced upon SARS-CoV-2 infection, most of which contribute to hyperinflammation as constituents of the 'cytokine storm' in severe disease (e.g. IL-6, TNF-α, IL-1β, IP-10, MCP-1, CSFs, and IL-17A), whereas others are particularly important for viral clearance (e.g. IL-15, IFN-α, IL-12, IL-21, and IFN-γ) in mild-to-moderate disease. Severe COVID-19 is marked by dysfunction of certain immune cells, with relatively increased abundances of neutrophils and monocytes and decreased levels of effector T-lymphocytes. In addition, multiple downstream pathophysiological processes are activated, including an increased thrombogenic state [microangiopathy, formation of neutrophil extracellular traps (NETs)], haemophagocytosis, reduced haematopoiesis, and increased apoptosis/pyroptosis. CD147, cluster of differentiation 147; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

disease and are therefore essential for optimally controlling viral infection [54].

Autoimmunity and autoinflammation

Recent research has highlighted the potential role of autoimmunity and autoinflammation in COVID-19 (Figure 3). Dysregulation of TLRs has been discussed above. TLR7 recognises single-stranded RNA of pathogens in order to initiate an immune response. To prevent the induction of an immune response against endogenous RNA, TLRs contain a self-recognition mechanism, failure of which can lead to autoreactivity [55,56]. During the course of the pandemic, cases of multisystem
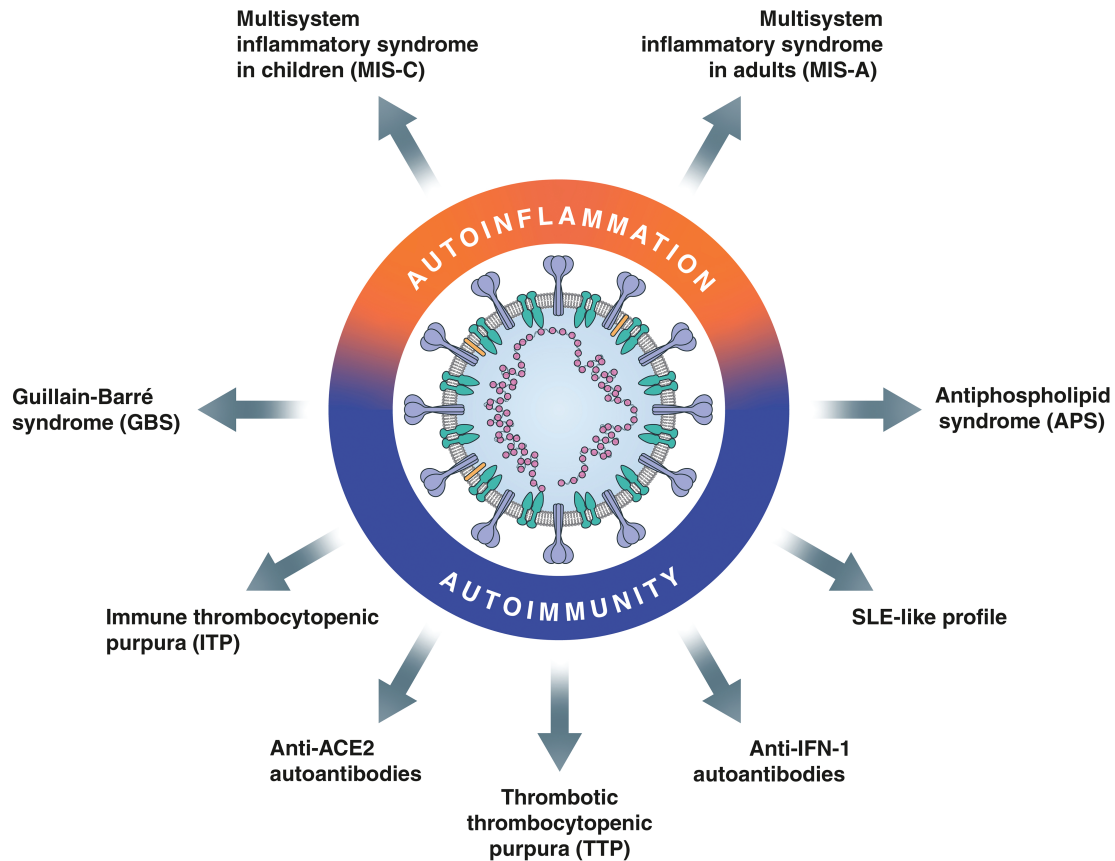
Figure 3. Autoimmunity and autoinflammation in COVID–19. ACE2, angiotensin-converting enzyme 2; IFN, interferon; SLE, systemic lupus erythematosus.

inflammatory syndrome in children (MIS-C) have been repeatedly reported [57]. MIS-C is an immunopathogenic illness consisting of systemic hyperinflammation and MOF, which may clinically resemble Kawasaki disease or toxic shock syndrome [58,59]. While its pathogenesis in COVID-19 is incompletely understood, MIS-C represents an immune-mediated post-infectious process featuring autoantibodies, with several specificities likely being involved [60,61]. Furthermore, a case report was published describing adult COVID-19 patients with a disease state resembling MIS-C, termed MIS in adults (MIS-A) [62].

Autoimmune conditions that are potentially associated with COVID-19 in selected cases comprise Guillain–Barré syndrome and its variants: immune thrombocytopenic purpura [63,64]; antiphospholipid syndrome (APS), including its severe form catastrophic antiphospholipid syndrome (CAPS) [65,66]; and thrombotic thrombocytopenic purpura (TTP) [67]. APS is an autoimmune disorder with formation of antiphospholipid antibodies (aPLs) causing an increased risk of (micro)vascular thrombosis [68]. Its severe variant CAPS is characterised by rapidly developing multiorgan thrombotic injury [69], which may be linked to the hypercoagulability observed in severe COVID-19. The presence of aPLs has been frequently reported in COVID-19 patients [65,70–72], although their association with thrombotic risk in this disease is still

controversial [71,73]. Interestingly, aPLs induce activation of pro-inflammatory NF-κB and increase the expression of TLR7, which may lead to overactivation of the pro-inflammatory cytokine response [74]. Various viral infections have been shown to induce the production of autoantibodies against a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) – a von Willebrand factor-cleaving metalloprotease – leading to TTP, a condition that shares clinical similarities with COVID-19, considering the frequent presence of endothelial cell injury and thrombotic microangiopathy [67,75]. Furthermore, extrafollicular B-cell responses in critically ill COVID-19 patients have been associated with poor clinical outcomes [76]. Of note, the extrafollicular B-cell signatures showed high similarity to those in autoimmune settings, especially systemic lupus erythematosus (SLE), suggesting that the antibodies were pathogenic due to autoreactivity [76]. Finally, a pre-print study reported the presence of IgM autoantibodies against ACE2, which was strongly associated with severe clinical outcome in COVID-19 patients [77]. The persistence of autoreactive antibodies may contribute to the post-acute sequelae observed in a substantial proportion of symptomatic COVID-19 patients – colloquially known as 'long-COVID' [78–80]. These findings provide convincing evidence for the involvement of autoinflammation and autoimmunity in COVID-19.

Host–specific factors determining disease course

Inter-individual differences in the adequacy of host defence mechanisms constitute a plausible explanation for the heterogeneity of disease course among infected individuals (Figure 4) [81]. Uncoordinated responses of adaptive immunity are associated with ageing and frequently precede disease control failure [54]. This can be explained by the concept of 'immunosenescence', which involves the age-related decline in immune function with defects in both innate and adaptive immune responses, such as impaired pathogen recognition and chronic involution of the thymus [82,83]. Other age-related contributors include a chronic state of low-grade systemic inflammation in the elderly ('inflammaging'), an increased incidence of comorbidities in the elderly, and moderate to severe frailty [84]. Sex-related variability in immune responses against SARS-CoV-2 may potentially underlie the increased disease vulnerability of males. In a study analysing sex differences in immune phenotypes, male patients showed a more robust innate immune response with higher plasma cytokine levels, whereas female patients had more robust T-cell activation [85]. A poor T-cell response against SARS-CoV-2 correlated with worse disease outcome in males, whereas higher levels of cytokines were associated with worsening of disease course in females, underscoring the potential rationale for sex-specific treatment options. Apart from the aforementioned genetic variants in IFN-related immunity [21,25], additional undiscovered genetic immune variations may contribute to the variation in disease course, as well as pre-existing T-cell and B-cell immune memory with antibody cross-reactivity between seasonal coronaviruses and SARS-CoV-2 [86–89].

Individuals with multiple underlying morbidities or with severe single disease are at increased risk of developing severe COVID-19, including those with cardiovascular disease, hypertension, diabetes, pulmonary disease, neurodegenerative disorders, immunodeficiencies, renal disease, liver damage, and obesity, among others [4]. Visceral fat, measured as abdominal adiposity, is associated with severe COVID-19 disease [90]. Interestingly, a Dutch study on ICU-admitted COVID-19 patients found that serum leptin levels were increased in SARS-CoV-2-infected patients compared with control patients with a similar body mass index (BMI) [91]. The authors hypothesised that this increase in leptin production, induced by SARS-CoV-2 infection of ACE2-expressing adipocytes in visceral fat, led to activation of pulmonary leptin receptors resulting in enhanced local inflammation, thereby adding to the already existent chronic inflammatory state of obese patients. Treatment with resveratrol may be beneficial in this regard, considering its inhibitory effect on leptin secretion from adipocytes in addition to direct antiviral effects [92].

Furthermore, variations in ACE2 expression and activity among individuals are thought to affect the vulnerability to disease progression in COVID-19. Paradoxically, increased membrane-bound ACE2 may allow for more opportunities for SARS-CoV-2 to invade host cells, whereas downregulation of ACE2 (due to SARS-CoV-2-induced endocytosis) precipitates tissue injury by (1) decreasing inactivation of des-Arg^9-bradykinin, which potentiates the formation of pulmonary angioedema [93]; and (2) dysregulating the RAAS by causing a lack of conversion of Ang II into angiotensin(1–7) [94]. Interestingly, Ang II stimulates a disintegrin and metalloproteinase 17 (ADAM17), resulting in the release of cytokines [e.g. tumour necrosis factor alpha (TNF-α)], thereby exacerbating inflammation, especially in individuals with pre-existent chronically activated RAAS with high Ang II levels [95]. In addition, ADAM17 is a sheddase for ACE2, resulting in a soluble form of ACE2 (sACE2) [96]. Cardiovascular conditions and other COVID-19 risk factors (e.g. male gender, older age, higher BMI) have been associated with increased levels of sACE2 [97–99]. A recent study showed a 97-fold higher sACE2 activity in recovered SARS-CoV-2 patients compared with healthy controls, although its clinical significance is still a subject of debate [100]. Increased sACE2 may be deleterious by acting as an antigen (bound to SARS-CoV-2), thereby inducing autoimmunity against ACE2 [77,101]. On the contrary, sACE2 may have beneficial effects as a competitive interceptor by preventing SARS-CoV-2 binding to membrane-anchored ACE2 for host cell entry, a theory that has received experimental support from an *in vitro* study in which SARS-CoV-2 infection of human organoids could be inhibited by the administration of human recombinant sACE2 [102], in addition to favourable results from a single case study [103]. Finally, several other host factors are thought to determine COVID-19 disease course, such as epigenetic mechanisms, malnutrition status, and ABO blood group status [104–106].

Pathology

COVID-19 is a disease in which multiple organ systems can be involved. The main pathological alterations detected in the most commonly affected organ systems are discussed in the following paragraphs, with particular emphasis on immunopathology.

Respiratory system

SARS-CoV-2 primarily affects the respiratory system, with viral entry into upper and lower respiratory epithelial cells, causing influenza-like clinical manifestations, such as fever, cough, and dyspnoea [107,108]. The ensuing immune response is suppressed in some individuals, leading to unrestrained viral replication that facilitates progression to a pulmonary phase with pneumonia [109]. In late-stage disease, hyperactivation of immune responses contributes to widespread hyperinflammation with the development of severe disease, including ARDS [109]. Histological examinations showed various
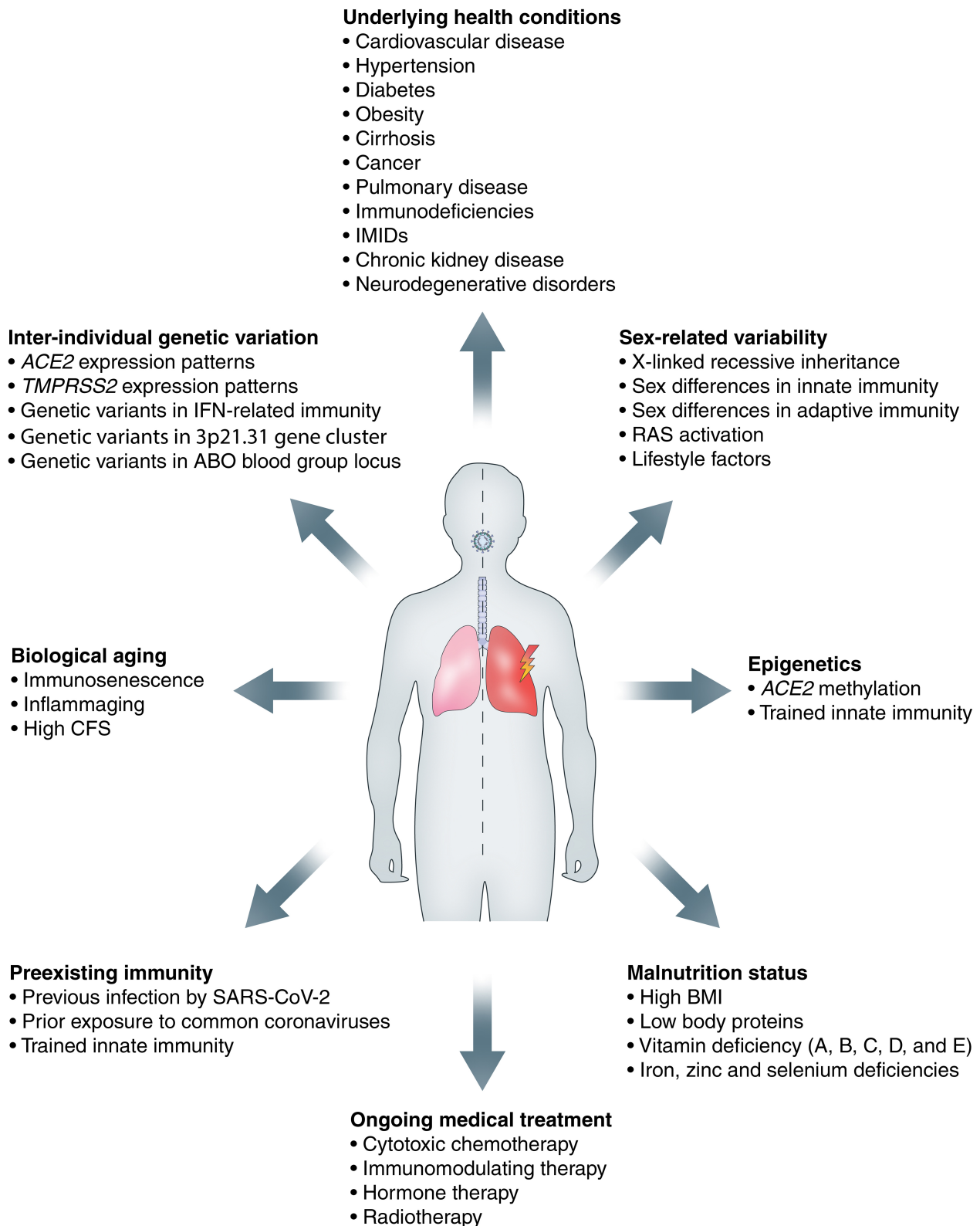
Underlying health conditions
• Cardiovascular disease
• Hypertension
• Diabetes
• Obesity
• Cirrhosis
• Cancer
• Pulmonary disease
• Immunodeficiencies
• IMIDs
• Chronic kidney disease
• Neurodegenerative disorders

Inter-individual genetic variation
• *ACE2* expression patterns
• *TMPRSS2* expression patterns
• Genetic variants in IFN-related immunity
• Genetic variants in 3p21.31 gene cluster
• Genetic variants in ABO blood group locus

Sex-related variability
• X-linked recessive inheritance
• Sex differences in innate immunity
• Sex differences in adaptive immunity
• RAS activation
• Lifestyle factors

Biological aging
• Immunosenescence
• Inflammaging
• High CFS

Epigenetics
• *ACE2* methylation
• Trained innate immunity

Preexisting immunity
• Previous infection by SARS-CoV-2
• Prior exposure to common coronaviruses
• Trained innate immunity

Malnutrition status
• High BMI
• Low body proteins
• Vitamin deficiency (A, B, C, D, and E)
• Iron, zinc and selenium deficiencies

Ongoing medical treatment
• Cytotoxic chemotherapy
• Immunomodulating therapy
• Hormone therapy
• Radiotherapy

Figure 4. Host-specific factors determining disease course. ACE2, angiotensin-converting enzyme 2; BMI, body mass index; CFS, clinical frailty score; IFN, interferon; IMIDs, immune mediated inflammatory diseases; RAS, renin–angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2.

patterns of diffuse alveolar damage (DAD) with interstitial T-cell infiltration [40,49,110] (Figure 5). In some cases, an even more severe form of DAD could be observed, namely acute fibrinoid and organising pneumonia [111]. Typical features of DAD, with hyaline membrane formation and type II pneumocyte hyperplasia, were frequently encountered [110,112]. Interestingly, abundant presence of SARS-CoV-2 has been
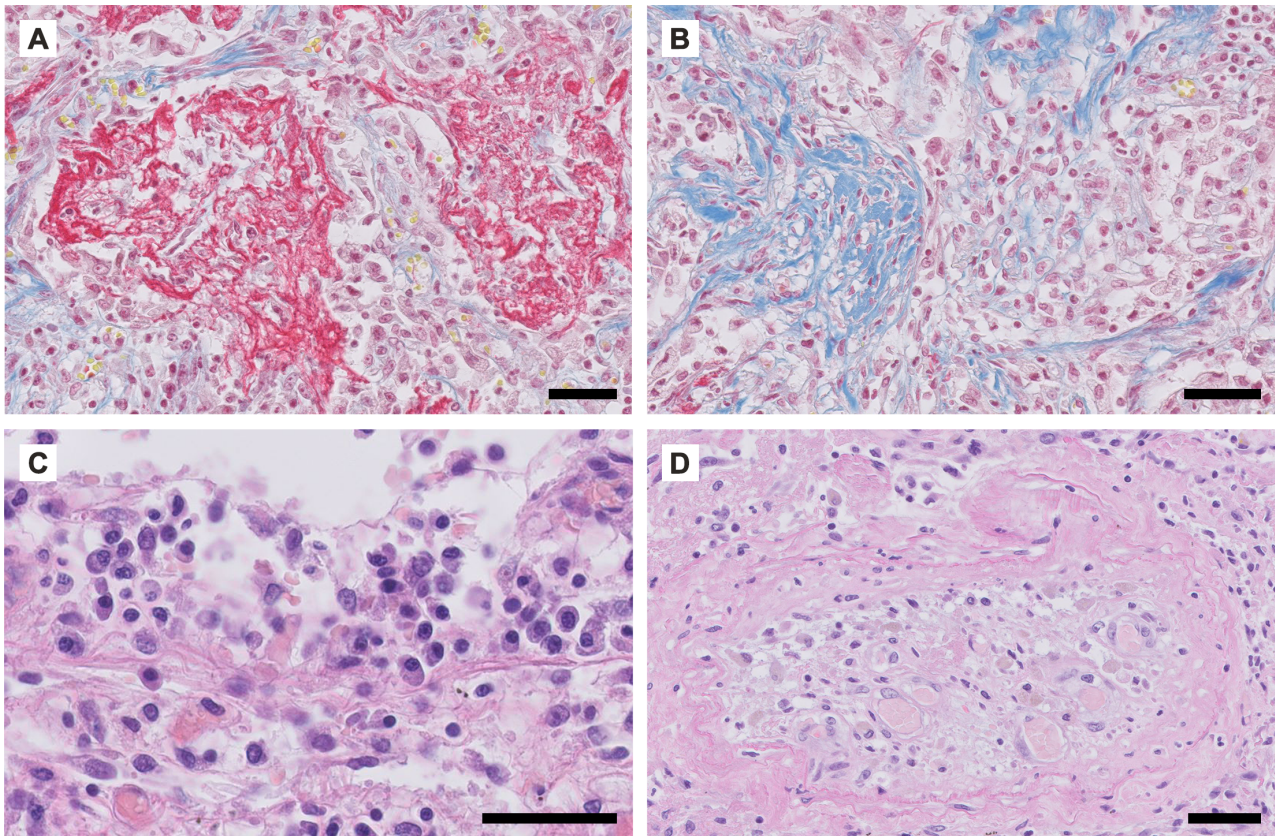
Figure 5. Representative examples of COVID-19-associated lung pathology. Panels A, B, and D show photomicrographs of the lung tissue of a 55-year-old male who died of COVID-19 4–5 weeks after admission to the intensive care unit (ICU) of the University Medical Center Groningen. Panel C is from a 63-year-old male who died 2.5 weeks after admission to the ICU. (A) Alveolar spaces are filled with fibrin, stained in red. (B) Organising pneumonia is observed with fibrosis in blue; fibroblast proliferation can be observed on the right hand side. (C) Lymphoplasmocytic infiltration. (D) Occluded artery (thrombosis) with recanalization. (A, B) Martius scarlet blue; (C, D) H&E. Scale bar = 50 μm.

demonstrated early in the disease course, whereas virus-infected cells were only sporadically present at later stages of COVID-19 [40,46,113]. The decrease in viral presence may be attributed to prompt immune activation, as demonstrated by extensive alveolar and interstitial inflammation [40] (Figure 6). In line with this, a recent autopsy study discovered two distinct immunopathological reaction patterns in the lungs of deceased COVID-19 patients: in the first subgroup, patients died early after hospitalisation with high viral load and relatively limited pulmonary pathology, implying extrapulmonary factors as contributors to lethal outcome, while patients in the second subgroup had a longer disease course and low viral load, yet prominent DAD, which was associated with marked immune cell infiltration and local complement activation [46]. The disconnection between viral presence and pulmonary inflammation highlights the contribution of immunopathology in causing severe COVID-19 [114].

Other main findings of fatal COVID-19 pneumonia were vascular alterations, including the presence of thrombi and microthrombi, intussusceptive angiogenesis, and severe endothelial injury [115]. SARS-CoV-2-mediated endothelial injury and endotheliitis can give rise to dysregulated local immunothrombosis, culminating in microvascular dysfunction and the formation of microthrombi [115–117]. In a recent post-mortem study, neutrophil accumulation (Figure 6) was demonstrated in lung parenchyma and vasculature, with the formation of NETs, indicating a role for a maladaptive immune response in causing pulmonary coagulopathy [40,118]. Furthermore, vigorous and dysregulated respiratory effort may also contribute to the progression of lung damage in COVID-19, a phenomenon known as 'patient self-inflicted lung injury' [119].

Cardiovascular system

Myocardial injury, reflected by increased blood troponin levels, has been reported frequently in COVID-19 [120]. Pre-existing cardiovascular disease is associated with poor prognosis [121], whereas COVID-19 itself can induce cardiovascular complications, such as acute heart failure, arrhythmias, acute coronary syndrome, and myocarditis [120]. The latter has raised particular concern, with multiple case studies reporting on COVID-19-associated myocarditis [122–124] and studies demonstrating ongoing myocardial inflammation after recovery from COVID-19 [125,126]. Myocarditis may result from direct cardiotoxic effects of SARS-CoV-2 infection or from indirect effects, either via cytokine-mediated cardiotoxicity or by triggering an
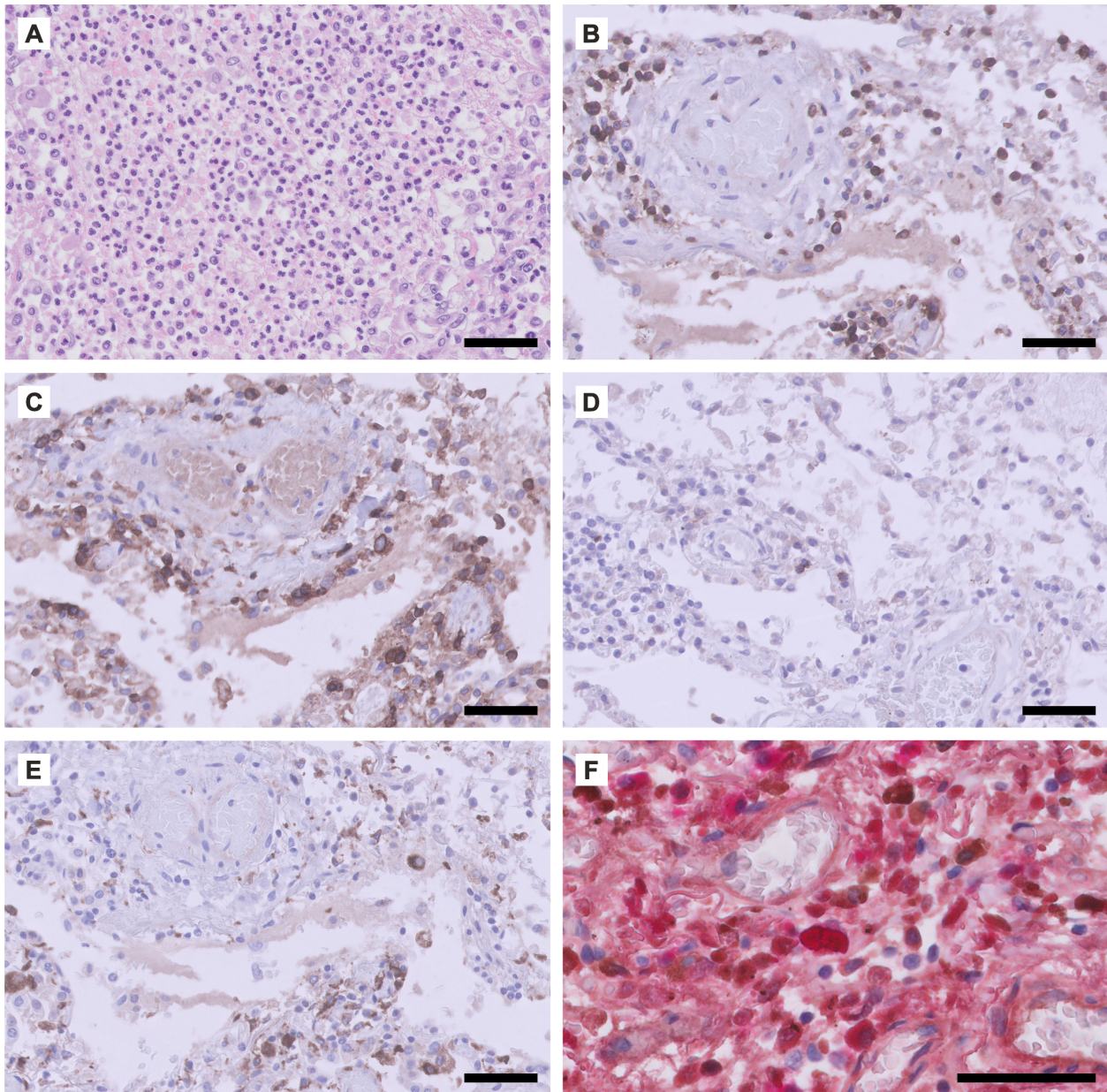
Figure 6. Phenotype of the inflammatory response observed in COVID-19-associated lung pathology. Panel A shows the lung tissue of a patient (male, 55 years) who died of COVID-19 4–5 weeks after admission to the intensive care unit (ICU) of the University Medical Center Groningen. Panels B–F are from a male (63 years) who died 2.5 weeks after admission to the ICU. (A) Diffuse neutrophilic infiltrate in the alveolar spaces. Immunohistochemical staining for (B) CD3 (T-cells), (C) CD4 (CD4+ T-cells and macrophages), (D) CD8 (CD8+ T-cells), (E) CD68 (macrophages), and (F) immunoglobulin kappa (brown) and lambda (red) light chains (double labelling). Scale bar = 50 μm.

autoimmune response against cardiac components [127]. In line with expression of ACE2 on different cell types in the human heart [128], SARS-CoV-2 has been detected in a variety of cells in myocardial tissue, including interstitial inflammatory cells [129,130], cardiomyocytes [40,124], and capillary endothelial cells [124]. These findings indicate that SARS-CoV-2 may directly infiltrate the heart via the bloodstream – consistent with the finding of cardiac endotheliitis [116] – or indirectly via immune cell transmigration. An autopsy study demonstrated that the presence of SARS-CoV-2 in myocardial tissue was not associated with a cardiac inflammatory response consistent with myocarditis

[129]. Instead, COVID-19-associated myocarditis may rather result from secondary reactions to disease.

Cardiac inflammation has been described in several other reports [40,131]. In a study analysing post-mortem heart tissue from 20 COVID-19 patients, epicarditis and endocarditis were present in all patients, whereas myocarditis was found in 55%, characterised by the presence of histiocytes, T-cells, and neutrophils [40]. However, the presence of myocarditis showed no association with the type of myocardial injury and was inconsistent with clinical ECG observations and the presence of SARS-CoV-2 in the heart [40]. Another autopsy study including 21 patients who succumbed to COVID-19

demonstrated that 18 patients had widespread interstitial macrophage infiltration without a clear association with myocardial injury, whereas multifocal lymphocytic myocarditis was found in three patients [131]. Besides cardiac inflammation, other forms of myocardial injury may be involved in COVID-19, such as right ventricular strain injury secondary to lung pathology [131,132], microvascular thrombi [40,131], hypoxic injury [133], and pre-existing injury compatible with underlying disease [40,134].

Nervous system

Neurological manifestations have frequently been described in patients suffering from COVID-19, ranging from anosmia, dysgeusia, headache, and 'brain-fog' to severe conditions including ischaemic stroke and encephalopathy/encephalitis [135,136]. Furthermore, cognitive deficits have been reported even after recovery, which is probably partly related to incident delirium in many cases [137]. The neurological manifestations may result from direct cytopathic effects of SARS-CoV-2 infection or from superimposed disease factors, including hypoxia-induced damage [40,138,139], drug-related changes, and harmful immune responses. The presence of SARS-CoV-2 has been demonstrated in the cerebrospinal fluid (CSF) [140–142] and post-mortem brain tissues [138,143–145] from COVID-19 patients, indicating its neurotropic potential. The virus may enter the central nervous system (CNS) via the haematogenous pathway – involving immune cell transmigration or penetration of the blood–brain barrier – as well as via the neuronal pathway [146]. The identification of viral particles in the olfactory bulb [147], together with the common occurrence of anosmia [148], point to the olfactory pathway as a plausible route of neuroinvasion by SARS-CoV-2. On the other hand, ACE2 and TMPRSS2 have been found in microvillar cells, olfactory horizontal basal cells, and olfactory sustentacular cells but not in olfactory neuronal extensions. Therefore, the olfactory entry route into the CNS remains a conundrum [149]. Next to nervous and olfactory involvement, SARS-CoV-2 protein has recently been demonstrated intracellularly in the ocular tissues of a patient previously infected with this virus [150].

To date, the contribution of SARS-CoV-2 neuroinvasion to the pathogenesis of neurological manifestations in COVID-19 remains undetermined. A study of SARS-CoV in mice indicated that direct neuronal infection in vital brain regions (e.g. cardiorespiratory centres in the medulla oblongata) induces neuronal death and likely contributes to severe disease [151]. In human COVID-19 autopsy studies, microglial activation and cytotoxic T-cell infiltration were indeed most pronounced in the brainstem and cerebellum (Figure 7) [40,145]. However, these studies also indicated that the role of neurotropism in causing COVID-19-related brain pathology may be rather limited. Autopsy series of COVID-19 patients demonstrated the presence of SARS-CoV-2 in 53% of the brains investigated but

showed no association with the severity of neuropathological alterations [145]. Instead, other factors are likely involved in the neuropathology observed in COVID-19, such as an overstimulated immune response. An autopsy study of brain tissues from nine deceased COVID-19 patients reported on extensive neuroinflammation, involving T-cell infiltration and massive activation of microglia with formation of nodules, while SARS-CoV-2 RNA could not be detected [40]. This could indicate rapid viral clearance or widespread neuroinflammatory activation in response to serious SARS-CoV-2 infection elsewhere in the body. A disrupted blood–CSF barrier through SARS-CoV-2-induced choroid plexus damage may also contribute to neuroinflammation by allowing entry of immune cells and cytokines [152]. An extensive inflammatory response was most notable in the olfactory bulbs – possibly leading to anosmia – as well as in the medulla oblongata, in which the primary respiratory control centre is located, and could therefore contribute to respiratory failure in COVID-19 patients [40]. Another autopsy study found comparable neuroinflammatory findings [145]. Furthermore, the observation of neutrophilic plugs with NET formation in post-mortem brain tissues indicates a role for immunothrombosis in thrombotic brain injury [40]. Finally, SARS-CoV-2 potentially acts as a trigger of neurodegenerative proteinopathies, such as Parkinson's disease and Alzheimer's disease, partly due to intracellular responses to inflammation that could lead to protein misfolding and aggregation [153–155]. Longitudinal studies should further clarify whether the COVID-19 pandemic will lead to an increased burden of neurodegenerative and autoimmune conditions among COVID-19 survivors.

Kidneys

Development of acute kidney injury (AKI) is common in COVID-19 patients and is associated with poor clinical outcome [156]. COVID-19 could affect renal tubular, glomerular, and vascular tissues, leading to conditions such as acute tubular injury, collapsing glomerulopathy, and thrombotic microangiopathy [157]. Potential mechanisms underlying AKI range from direct SARS-CoV-2 infection via ACE2, which is expressed in proximal tubular cells and glomerular epithelial cells [158], to indirect effects resulting from RAAS dysregulation, coagulopathy, haemodynamic instability, systemic inflammation, MOF, and iatrogenic injury [159]. A direct cytopathic effect of SARS-CoV-2 in the kidney is currently a subject of debate. Electron microscopy studies demonstrated viral particles within podocytes, proximal tubular epithelium, and endothelium [160–162], although careful interpretation is warranted as various cytoplasmic structures exhibit viral-like morphology [163,164]. Nevertheless, SARS-CoV-2 was detected in the renal parenchyma by alternative methodologies, which corroborated the concept of direct SARS-CoV-2 infection [40,143,162]. An autopsy study including 63 patients who had SARS-CoV-2 respiratory infection
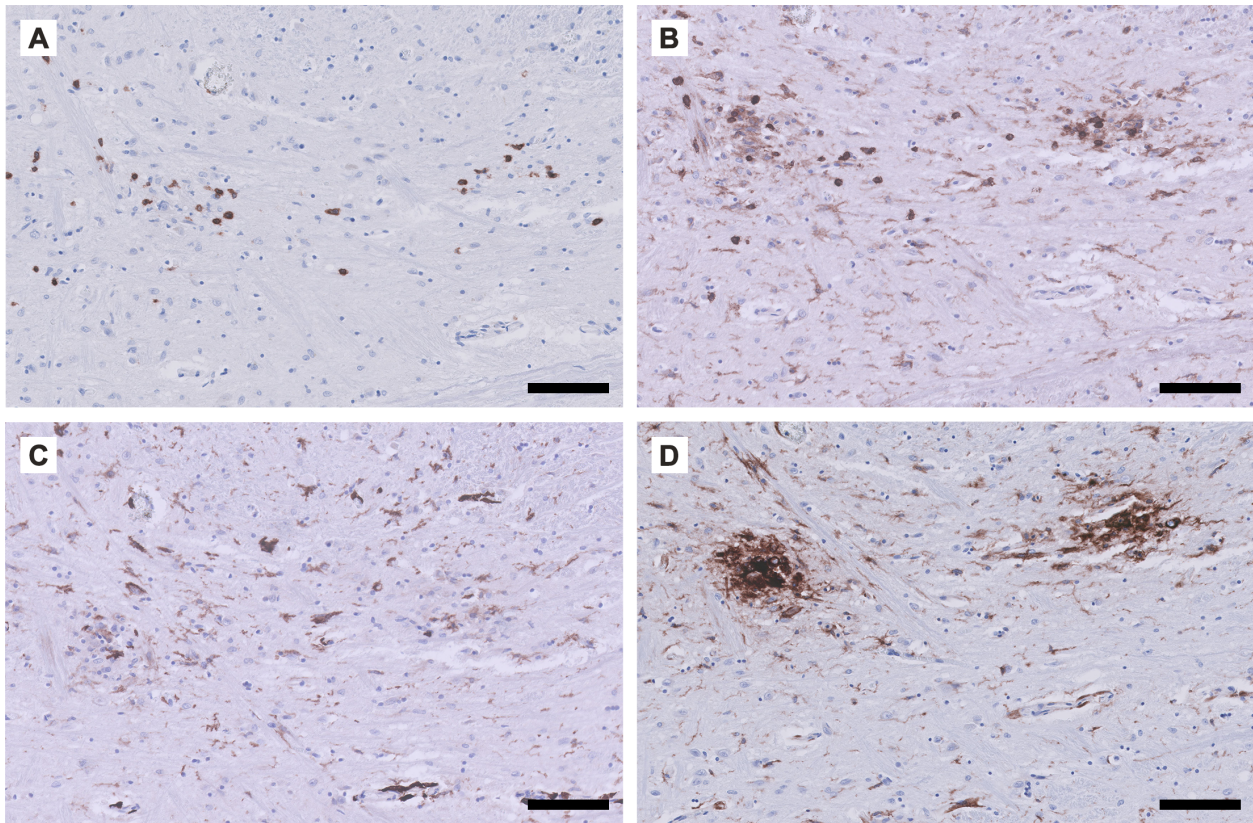
Figure 7. Phenotype of the inflammatory response observed in COVID-19-associated brain pathology. Detailed micrographs from the tegmental area of the medulla oblongata in a patient (male, 63 years) who died 2.5 weeks after admission to the ICU. Immunohistochemical staining for (A) CD3 (T-cells), (B) CD45 (leukocytes including microglia), (C) CD163 (scavenger receptor, activated microglia), and (D) HLA-DR (MHC class II, activated microglia). The T-cell infiltrate (A) co-localises with activated microglia (C and D). Scale bar = 100 μm.

demonstrated an association between SARS-CoV-2 renal tropism with development of AKI and shorter patient survival time [165]. Interestingly, a characteristic post-mortem finding in COVID-19 patients was proximal tubular vacuolisation, which correlated with the presence of SARS-CoV-2-like particles in renal tubular epithelial cells; this may therefore be indicative of a direct cytopathic effect of SARS-CoV-2 infection [40,160,162]. These findings are in contrast to multiple other studies in COVID-19 patients with AKI that found no evidence of significant SARS-CoV-2 presence in renal tissue [157,166–168].

Dysregulated immune responses in COVID-19 probably play a role in the pathological tubular, glomerular, and vascular alterations in the kidney [157,166]. AKI in COVID-19 has been linked to sepsis-associated AKI, partly due to the frequent observation of acute tubular necrosis, in which ischaemia and nephrotoxicity play a critical role [167]. Reports on COVID-19-associated collapsing glomerulopathy in primarily black patients suggested a role for cytokine-mediated kidney disease in individuals with high-risk apolipoprotein L1 genotypes with SARS-CoV-2 infection, as occurs with other forms of viral-mediated collapsing glomerulopathy [166,169–171]. Vascular pathology has been described sporadically in the kidneys of COVID-19 patients and comprises vasculitis, thrombotic microangiopathy, and microthrombi [40,157,162], which may result from

COVID-19-induced endothelial dysfunction, coagulopathy, and complement activation [157]. Figure 8 shows representative micrographs of the composition of the lymphocytic infiltrate present predominantly in the tubulointerstitial compartment.

Gastrointestinal system

Gastrointestinal (GI) symptoms of COVID-19 (e.g. anorexia, diarrhoea, abdominal pain) occur commonly and have been associated with more severe disease [172,173]. Several lines of evidence support the GI tract as a potential site for active SARS-CoV-2 infection and replication. ACE2 was found to be abundantly present on the brush border of absorptive enterocytes in both the small and the large intestine, providing a prerequisite for SARS-CoV-2 infection and a potential route of faecal–oral transmission [158]. Furthermore, single-cell transcriptomics revealed high co-expression of ACE2 and TMPRSS2 in absorptive enterocytes along the entire GI tract [174]. Enterotropism of SARS-CoV-2 has been demonstrated *in vitro* by using human small intestinal organoids [175–177], *in vivo* in non-human primate models [178,179], and in human gastrointestinal tissue [180]. Apart from the intestinal epithelium, marked ACE2 expression has been observed within the intestinal endothelium and in smooth muscle cells of the intestinal muscular layers, suggesting a secondary, indirect possibility of intestinal transfection
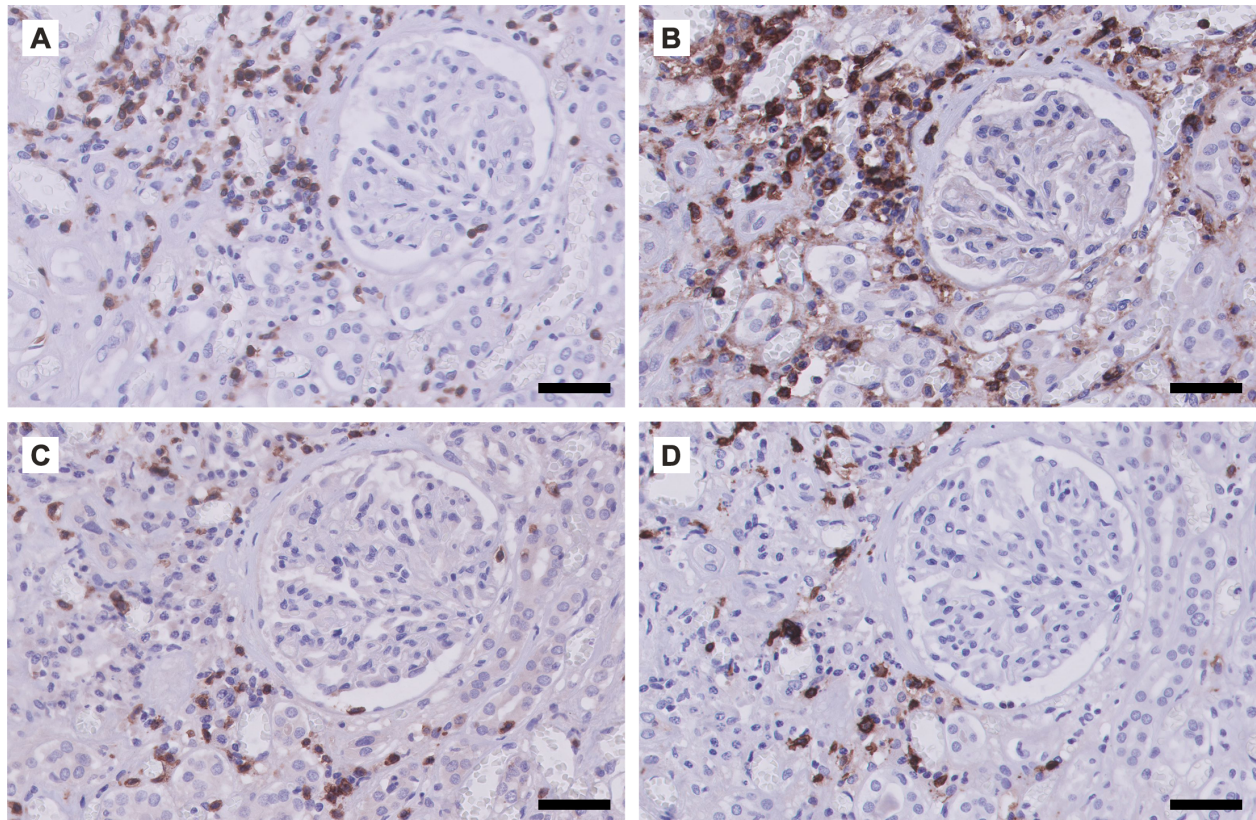
Figure 8. Phenotype of the inflammatory response observed in COVID-19-associated renal pathology. Micrographs of the renal cortical tissue from a patient (male, 65 years) who died of COVID-19 5 weeks after appearance of the first symptoms. Immunohistochemical staining for (A) CD3 (T-cells), (B) CD4 (CD4^{+} T-cells and macrophages), (C) CD8 (CD8^{+} T-cells), and (D) CD20 (B-cells). The lymphocytic infiltrate is located mainly in the tubulointerstitium. Scale bar = 50 μm.

[108,158]. Further evidence of viral GI infection is provided by prolonged presence of SARS-CoV-2 RNA in faecal samples of infected patients [181]. In some cases, RNA positivity persisted in faecal samples even after it vanished from respiratory tract samples [180,181], which may be explained by the composition and functionality of the gut microbiota, which shows considerable inter-individual diversity and diversifying responses of host immunity [182].

Previous autopsy studies revealed distinct histopathological features in GI tissues of patients with COVID-19. Along different parts of the GI tract, interstitial oedema within the lamina propria and concurrent infiltration, mainly with lymphocytes, monocytes, and plasma cells, have been reported [180,183]. Although the location and numbers of intestinal epithelial cells may have a natural appearance, they are sometimes accompanied by inflammatory infiltrates. Mucosal changes of the GI tract vary, from disruption of epithelial architecture, dilated and congested capillaries within the lamina propria and submucosa, and immune cell infiltration, to necrosis and shedding of the entire mucosa [184,185].

Hepatic and biliary system

Patients with COVID-19 are at risk of developing liver injury, manifested by increased liver transaminases with subtle hyperbilirubinaemia [186]. Pathological findings of liver injury have been reported most commonly in individuals with moderate-to-severe COVID-19 [187]. Hepatic invasion by SARS-CoV-2 may be possible via constitutively expressed ACE2, mainly on cholangiocytes and, to a lesser extent, hepatocytes [188]. Thus, it has been hypothesised that SARS-CoV-2-induced liver damage primarily results from biliary tract infection through cholangiocytes, with secondary injury to and compensatory proliferation of hepatocytes [108,189]. In contrast to the endothelial linings of other organs, ACE2 expression of the hepatic sinusoidal endothelium is very limited [158]. Microscopically, pathological features of COVID-19 in the liver include moderate macrovesicular steatosis, mild lobular and portal (mainly lymphocytic) infiltration, patchy hepatic necrosis, and both periportal and centrilobular sinusoidal dilatation [190,191]. Apart from direct viral hepatic infection, liver damage may arise from immune-mediated inflammation, drug toxicity, pre-existing chronic liver disease, or concomitant hepatic infections [185,192]. Finally, mild cases of COVID-19 are not accompanied by signs of liver damage, and, if so, this injury is often transient and eventually shows spontaneous recovery [193].

Reproductive system and pregnancy

Concern has been raised about involvement of the reproductive system in COVID-19, as this may affect fertility

and poses a potential risk of sexual transmission. SARS-CoV-2 has been demonstrated in the semen of men with COVID-19 in both the acute and the recovering stage of viral infection [194]. In line with this, ACE2 is highly expressed in the testis and epididymis – more specifically, in the spermatogonia, Leydig cells, and Sertoli cells [195,196]. An autopsy study examining 12 testes from patients who succumbed to COVID-19 showed significant damage to seminiferous tubules with ballooning of Sertoli cells, reduced numbers of Leydig cells, and a mild interstitial infiltration of predominantly T-cells [197]. In this study, SARS-CoV-2 RNA was absent in 90% of patients, and no viral particles were demonstrated by electron microscopy, suggesting that viral presence had already been cleared by the immune response or that other factors were involved.

As for the female reproductive system, only few data are available on its association with SARS-CoV-2 infection. In a cohort of ten female patients with COVID-19, no evidence of viral infection in vaginal fluids was reported [198], while another study did report on the presence of SARS-CoV-2 RNA in vaginal fluid [199]. Considering the well-established functions of ACE2 within the female reproductive system and its ubiquitous expression in these organs, people have been concerned about the potential harm of COVID-19 on female fertility and pregnancy-related outcomes [200]. Although rare, transplacental transmission is possible, with subsequent significant placental inflammation and neonatal SARS-CoV-2 infection [201,202]. Nevertheless, pregnancy outcomes in COVID-19 are generally good [203].

Integumentary system

A diversity of dermatological manifestations have been described in patients suffering from COVID-19. These include morbilliform rashes, pernio-like acral lesions, urticaria, macular erythemas, vesicular eruptions, papulosquamous eruptions, and retiform purpura [204]. Many of these manifestations are non-specific, although some may be secondary to COVID-19-related immune and inflammatory reactions [204]. Pernio (chilblain)-like acral lesions in COVID-19 – colloquially known as 'COVID toes' – typically present after the onset of COVID-19 symptoms and are associated with a relatively mild disease course [204]. The underlying mechanism is thought to be primarily inflammatory with histopathological findings similar to those observed in idiopathic and autoimmune-related pernio, including vacuolar interface damage with epidermal necrotic keratinocytes, perivascular and peri-eccrine lymphocytic infiltration, and dermal oedema [204–206]. Interestingly, in the skin of COVID-19 patients with pernio-like lesions, SARS-CoV-2 was found in vascular endothelial cells and in epithelial cells of eccrine sweat glands [206], implying direct SARS-CoV-2 infection as a potential aetiopathogenic mechanism. In addition, a robust antiviral IFN response may be involved in causing pernio-like lesions, thereby providing an explanation for the mild disease course observed in patients with pernio [207]. On the other hand, critically ill COVID-19 patients may present with retiform purpura, livedo racemosa, and acral ischaemia, which are distinct from pernio with histopathological features of non-inflammatory to pauci-inflammatory thrombogenic vasculopathy [35,204,208]. Skin biopsies from COVID-19 patients demonstrated the involvement of complement activation in the pathogenesis of cutaneous thrombosis, sometimes with co-localisation of the SARS-CoV-2 S-protein [35,208].

Treatment

Current management strategies for COVID-19 comprise the implementation of preventive (social) measures and vaccination to control viral dissemination, the implementation of supportive care when indicated, and the use of (repurposed) drugs. Considering that *de novo* development of specific anti-SARS-CoV-2 drugs and vaccines takes time, clinical investigations have focused on drug repurposing. The efficacy and safety of many repurposed treatment modalities have been tested in preclinical studies and/or clinical trials, often with mixed results, and many trials are still ongoing.

During the course of the pandemic, progress has been made with regard to patient treatment. Successful treatment may depend on the correct timing of repurposed drugs, which requires an understanding of their mode of action, COVID-19 pathophysiology, and disease stages. Drugs that inhibit viral entry and replication (i.e. antivirals) may hold more promise when applied early in the disease course, whereas immunomodulating therapy (including corticosteroids and anti-cytokine antibodies) may have the greatest impact on the hyperinflammatory state in more advanced disease and can even be harmful during the initial stage, when an adequate immune reaction is indispensable for viral clearance. In keeping with this, a useful timeline was recently provided, demonstrating the potential contribution of each repurposed drug class to the treatment of the consecutive stages of COVID-19 [93]. Immunomodulators have been widely used during the pandemic and will probably continue to play an important role. They are thought to act through several key mechanisms: (1) glucocorticoid-mediated inhibition of pro-inflammatory signals and activation of anti-inflammatory signals; (2) inhibition of cytokines; (3) strengthening of antiviral defence by supplementation of IFN; (4) inhibition of the TLR-signalling pathway; and (5) inhibition of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway.

Based on the aforementioned pathophysiological and immunopathological considerations, we provide a detailed overview of currently advocated repurposed

Table 1. Overview of (repurposed) drugs for COVID-19, based on the described pathophysiological and immunopathological mechanisms.

Drug class	Drug names	Proposed mode of action	Clinical effectiveness	References
Antivirals	Remdesivir	Inhibition of RdRp	Reduces recovery time; halts progression to severe disease; no effect on survival	[209, 210]
	Lopinavir/ritonavir	Inhibition of 3CL^{pro}	Probably ineffective	[211]
	Ivermectin	Inhibition of the IMP α/β receptor responsible for viral protein transmission into host cell nucleus Inhibition of LPS-induced inflammation	Inconclusive	[212–219]
	Ribavirin	Inhibition of viral RNA synthesis/mRNA capping	Unrealistic dosing requirement	[220]
	Favipiravir	Inhibition of RdRp	Unrealistic dosing requirement	[221–223]
	Umifenovir	Impeding trimerization of SARS-CoV-2 S-protein	Probably ineffective	[224]
	Zinc	Inhibition of RdRp	Uncertain	[225]
Anticoagulants	LMWH (e.g. nadroparin)	Potentiation of antithrombin-mediated inhibition of coagulation factors Xa and IIa Conformational change of spike S1 receptor binding domain, possibly impeding binding to ACE2	Established	[226]
	Unfractionated heparin	Reducing viral entry by interacting with S-protein Heparanase inhibition (associated with COVID-19 severity) Neutralisation of chemokines and cytokines, and extracellular histones Interference of leukocyte trafficking through interaction with leukocyte surface ligands, preventing leukocyte attachment and extravasation Potentiation of antithrombin-mediated inhibition of coagulation factors Xa and IIa		[227, 228]
Immunomodulators – corticosteroids	Dexamethasone	Glucocorticoid-mediated effects; inhibition of pro-inflammatory signals and activation of anti-inflammatory signals; mechanisms include lipocortin-mediated PLA$_2$ suppression (decreased arachidonic acid as precursor of prostaglandins, leukotrienes, and thromboxanes), COX inhibition (decreased prostaglandin synthesis), and inhibition of NF-κB signalling, among others	Established	[229–232]
	Methylprednisolone	Similar to dexamethasone	Uncertain	[232–234]
	Hydrocortisone	Similar to dexamethasone	Uncertain	[235]
Immunomodulators – biologicals	IFN β-1a	Supplementation of interferon for antiviral defence	Uncertain ACTT-3 trial ongoing	[236, 237]
	IL-6R-antagonists (e.g. tocilizumab)	Inhibition of the pro-inflammatory action of IL-6	Improves outcome in critical COVID-19	[238]
	IL-1R antagonists (e.g. anakinra)	Inhibition of the pro-inflammatory action of IL-1	Uncertain in severe disease; no improved outcomes in mild-to-moderate COVID-19	[239, 240]
	TNF-α inhibitors (e.g. adalimumab)	Inhibition of the pro-inflammatory cytokine TNF-α	Uncertain	[241–243]
	BTK inhibitors (e.g. ibrutinib)	Inhibition of the TLR signalling pathway and thereby decreased cytokine production	Uncertain	[244]
	JAK inhibitors (e.g. baricitinib, fedratinib)	Inhibition of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, a signalling cascade mediating cellular responses to multiple cytokines, growth factors, and other ligands (such as Ang II) after binding to their respective receptors Inhibition of upstream regulators of ACE2-mediated endocytosis of SARS-CoV-2, including AAK1 and GAK	Possible	[245–247]
	Calcineurin inhibitors (e.g. cyclosporine, tacrolimus)	Inhibition of IL-2 production and IL2-R expression, leading to decreased T-lymphocyte activation Potential antiviral activity by inhibiting viral replication, based on previous preclinical evidence for other coronaviruses (including SARS-CoV)	Uncertain	[248–253]

(Continues)

Table 1. Continued

Drug class	Drug names	Proposed mode of action	Clinical effectiveness	References
Complement inhibitors	Eculizumab	Terminal complement inhibitor that binds to C5 complement protein and blocks the generation of pro-inflammatory C5a and the membrane attack complex (C5b-9)	Uncertain	[32, 254, 255] Clinicaltrials.gov NCT04355494
Kinin–kallikrein pathway inhibitors	Lanadelumab	Inhibition of plasma kallikrein	Uncertain	Clinicaltrials.gov NCT04422509
	Icatibant	Selective antagonist of bradykinin receptor type 2	Uncertain	[256]
Angiotensin inhibitors	Angiotensin receptor blockers	Prevention of Ang II binding to AT1R, thereby counteracting vasoconstriction, proliferation, fibrosis, thrombosis, and inflammation Prevention of ACE2 downregulation by endocytosis	Uncertain	[108, 257, 258]
	ACE inhibitors	Prevention of Ang II formation	Uncertain	[108, 257, 258]
	Recombinant human ACE2 (rhACE2)	Binding of the viral spike protein and thereby neutralisation of SARS-CoV-2 Minimising COVID-19-associated organ damage as a result of RAAS hyperactivation/increased Ang II levels	Uncertain	[103]
SERPINs	C1 esterase inhibitor	Inhibition of the complement cascade by binding to C1r and C1s Inhibition of the contact activation system (intrinsic coagulation and kinin–kallikrein pathways) by binding to FXIIa and kallikrein	Uncertain	Clinicaltrials.gov NCT04530136 [259]
	Camostat mesylate	Inhibition of TMPRSS2	Uncertain	[7]
	Nafamostat mesylate	Inhibition of various serine proteases: thrombin, FXII, TMPRSS2, and kallikrein	Uncertain	[260]
Antimalarials	Hydroxychloroquine (HCQ)/chloroquine (CQ)	Inhibition of viral entry and endosome fusion/ uncoating, reduction of cytokine production, and inhibition of platelet aggregation	Probably ineffective	[22, 23, 261–264]
Blood–derived products	Convalescent plasma	Neutralising antibodies from recuperated COVID-19 patients	Probably ineffective	[265–268]
	Hyperimmune immunoglobulin	Neutralising SARS-CoV-2 viral antigens by administering antibodies from recuperated COVID-19 patients with high antibody titres	Uncertain	[269]
	REGN-COV2	Cocktail of two neutralising antibodies against SARS-CoV-2 spike protein receptor binding domain	Uncertain	[270]
	Bamlanivimab	Anti-spike neutralising IgG1 monoclonal antibody initially derived from a recovered COVID-19 patient, intended for the treatment of mild to moderate COVID-19	Promising	[271, 272]
Miscellaneous	Colchicine	Anti-inflammation: inhibition of tubulin polymerisation, with effects on the inflammasome, cellular adhesion molecules, and inflammatory chemokines	Promising	[273]
	Vitamin D	Supports innate and adaptive immunity Inhibition of ADAM17 Counteracting NADPH oxidase activity resulting in decreased ROS production, thereby enhancing NO bioavailability Enhancing antioxidant enzymes that can scavenge free radicals Suppression of NF-κB signalling and production of pro-inflammatory cytokines	Vitamin D deficiency associated with COVID-19; effect of supplementation inconclusive	[274, 275]
	Azithromycin	Potential antiviral activity, based on evidence from other RNA viruses	Uncertain	[276–279]
	Sirolimus	Inhibition of mTOR pathway, which plays a role in pro-inflammatory T-cell differentiation	Uncertain	[280]
	Resveratrol	Reduction of leptin levels Suppression of Ang II Antioxidant effects Direct antiviral activity by inhibiting viral replication	Uncertain	[92, 281–283]

(Continues)

Table 1. Continued

Drug class	Drug names	Proposed mode of action	Clinical effectiveness	References
Heterologous vaccines	Influenza vaccine	Stimulation of trained innate immunity	Uncertain	[284, 285]
	BCG	Stimulation of trained innate immunity	Uncertain; no significant effect in frail elderly	[286–288]
	Measles vaccine	Stimulation of trained innate immunity	Uncertain	[289]

drug therapies with accompanying modes of action and clinical efficacy in Table 1. For an exhaustive list of experimental treatments, the reader is referred to the landscape document of the WHO [290]; the latest recommendations can be found in the living WHO guideline on drugs for COVID-19 [291].

Vaccine development

The fight against COVID-19 initiated a worldwide endeavour to develop a safe and effective vaccine. This has resulted in more than 230 vaccine candidates currently under development, 63 of which reached phase 1–3 clinical evaluation as of 26 January 2021 [292]. Several vaccines have already been authorised and used in vaccination programmes around the world. Currently, some of the most promising vaccine candidates include Pfizer–BioNTech (mRNA vaccine, efficacy 95.0%) [293], Moderna (mRNA vaccine, efficacy 94.1%) [294], Oxford–AstraZeneca (adenoviral vector vaccine, efficacy 70.4%) [295], Johnson and Johnson (adenoviral vector vaccine, efficacy 66%) [296], Novavax (protein subunit vaccine, efficacy 89.3%) [297], Sinopharm (inactivated vaccine, efficacy 79.3%) [298], Sinovac (inactivated vaccine, efficacy 50.4%) [299], and Sputnik V (adenoviral vector vaccine, efficacy 91.6%) [300]. However, it is important to note that the hitherto reported efficacy and safety results are based on interim analyses, as phase 3 trials for all of these candidates are still ongoing; more definite results and real-world evidence are anxiously anticipated. Recently, concern has been raised about the emergence of three mutations of SARS-CoV-2 – the UK, South Africa, and Brazil variants – which may potentially hamper viral epitope recognition by induced antibodies. Other potential vaccine-related limitations include insufficient immunogenicity (e.g. in the elderly), development of antibody-dependent enhancement [301], failure of long-lasting immunity, rapid vaccine development potentially compromising evaluation of long-term effects, and vaccination hesitancy in the general population [302]. An extensive discussion on vaccine development in COVID-19 is beyond the scope of this review and a comprehensive overview of current vaccine candidates can be found in the landscape document of the WHO [292]. Finally, some promising results were demonstrated with the use of heterologous vaccines, including influenza vaccine, bacillus Calmette-Guérin (BCG) vaccine, and measles vaccines, which are incorporated in Table 1.

Conclusion

COVID-19 progression is considered to result from a complex interplay of multiple pathophysiological mechanisms, among which the immunopathological response to SARS-CoV-2 infection is a key player in determining disease course, involving dysregulated innate and adaptive immunity as well as autoimmunity. Whereas the immune response is suppressed in the early stages of the disease, resulting in unrestrained viral replication and dissemination in infected host cells, an eventual increase of immune responses contributes to hyperinflammation and organ damage. Inter-individual differences in failure of host defence mechanisms, along with other host-specific factors, likely determine whether an individual progresses to severe disease. The multi-faceted nature of the pathophysiology of COVID-19, with its various disease stages, provides a basis for the use of various treatment regimens, ranging from antivirals early in disease when mild symptoms are present, to immunomodulating, antioxidant, and antithrombotic therapy in more advanced disease. Overall, COVID-19 pathophysiology is complex with multiple interacting mechanisms being involved; approaching a single pathway would be insufficient for disease containment. Instead, a multilevel approach targeting multiple facets of the pathophysiology is required to tackle the COVID-19 pandemic.

Ethics statement

Use of patient material was permitted according to regulations of the national 'Code for Good Use of Patient Material'.

Abbreviations

ACE2	angiotensin-converting enzyme 2
AKI	acute kidney injury
Ang II	angiotensin II
aPls	antiphospholipid antibodies
APS	antiphospholipid syndrome

ARDS	acute respiratory distress syndrome
CAPS	catastrophic antiphospholipid syndrome
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CSF	cerebrospinal fluid
CTSL	cathepsin L
DAD	diffuse alveolar damage
DAMP	damage-associated molecular pattern
ICU	intensive care unit
ISG	interferon-stimulated gene
LDH	lactate dehydrogenase
MAS	macrophage activation syndrome
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
MOF	multi-organ failure
NET	neutrophil extracellular trap
PAMP	pathogen-associated molecular pattern
PRR	pattern recognition receptor
RAAS	renin–angiotensin–aldosterone system
RAS	renin–angiotensin system
sACE2	soluble ACE2
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TF	tissue factor
TMPRSS2	transmembrane serine protease 2
TTP	thrombotic thrombocytopenic purpura

Author contributions statement

All the authors were involved in the conceptualisation of this review. LEvE, MB, ARB, AEA, AKO and HvG designed the outline of the review. LEvE, MB and HvG wrote the first draft. ARB and AKO wrote sections of the review. All the authors contributed to manuscript revision and approved the submitted final version.

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