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Extrapulmonary manifestations and complications of severe acute respiratory syndrome coronavirus 2 infection: a systematic review

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ABSTRACT

Introduction: We aimed to describe the extrapulmonary manifestations of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, including their frequency, onset with respect to respiratory symptoms, pathogenesis and association with disease severity.

Methods: We searched the MEDLINE and Embase databases for SARS-CoV-2-related studies. Meta-analysis, observational studies, case series and case reports published in English or Chinese between 1 January and 1 May 2020 were included. Reports with only paediatric or obstetric cases were excluded.

Results: 169 articles were included. Early manifestations (preceding respiratory symptoms until Day 6 of onset) included olfactory and gustatory disturbance (self-reported in up to 68% and 85% of cases, respectively), gastrointestinal symptoms (up to 65.9%) and rash (up to 20.4%). From Day 7 onwards, hypercytokinaemia, paralleled multi-organ complications including acute cardiac injury (pooled incidence of 17.7% in 1,412 patients, mostly with severe disease and 17.4% mortality), kidney and liver injury (up to 17% and 33%, respectively) and thrombocytopenia (up to 30%). Hypercoagulability resulted in venous thromboembolic events in up to 31% of all patients. Uncommon disease presentation and complications comprised Guillain-Barré syndrome, rhabdomyolysis, otitis media, meningoencephalitis and spontaneous pneumomediastinum.

Conclusion: Although the systemic manifestations of SARS-CoV-2 infection are variegated, they are deeply interwoven by shared mechanisms. Two phases of extrapulmonary disease were identified: (a) an early phase with possible gastrointestinal, ocular and cutaneous involvement and (b) a late phase characterised by multiorgan dysfunction and clinical deterioration. A clear, multidisciplinary consensus to define and approach thromboinflammation and cytokine release syndrome in SARS-CoV-2 is needed.

Keywords: complications, COVID-19, extrapulmonary, SARS-CoV-2

INTRODUCTION

As COVID-19 decimates healthcare systems worldwide, our understanding of the disease has extended to manifestations beyond those of the respiratory system. The ubiquitous expression of angiotensin-converting enzyme 2 (ACE-2) receptors in multiple organs, including the lungs, kidneys, endothelium, skin, brain and the gastrointestinal tract,⁽¹⁾ portends the diverse and multifaceted presentation of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Additionally, endocytosis of ACE-2 during viral entry in the lungs has been implicated as a driver of cytokine release syndrome (CRS), with resultant endotheliopathy, thromboinflammation and systemic organ dysfunction.⁽²⁾ As COVID-19 emerges as a complex disease with wide-ranging symptoms, we performed a systematic review with the aim of comprehensively delineating the myriad of extrapulmonary manifestations and complications. In this study, we abstracted the frequency of each manifestation and described their pathogenesis and association with disease severity.

METHODS

We searched the MEDLINE and Embase databases for meta-analyses, observational studies, case series and case reports on laboratory-confirmed or clinically-diagnosed COVID-19 in English or Chinese, published between 1 January and 1 May 2020. We used the search terms ‘COVID-19’, ‘coronavirus infection’, ‘coronavirus disease 2019’ and ‘SARS-CoV-2’. Reports with only paediatric or obstetric cases were excluded. For each manifestation, we abstracted the following: (a) prevalence; (b) description, including onset with respect to respiratory symptoms; (c) correlation with overall disease course; and (d) effect on prognosis.

Two reviewers independently screened studies for inclusion by reading the title and abstract. Each reviewer was blinded to the decision of the other reviewer. The reviewers resolved disagreements by discussion and by reading the full text if necessary. Selected articles were divided among the study team members for Level 2 screening and data extraction. Relevant secondary references were included. Two members of the team cross-checked extracted data. We omitted formal quality assessment, as we aimed to include case reports and case series and to capture the full spectrum of clinical manifestations. However, key limitations of selected studies were highlighted.

The frequency of manifestation was reported as a range across the studies. We abstracted the description of the manifestation from the first study and added information from each subsequent study until saturation was achieved. Effects on the prognosis were reported using estimates for mortality, requirement of intensive care or overall severe disease. Data was extracted and described as per the Synthesis Without Meta-analysis reporting guidelines. This non-funded review has been registered on PROSPERO (registration no. CRD42020184524).

RESULTS

We identified 3,157 articles from the literature search and 49 articles from secondary references. After removing duplicates, 2,797 articles remained for first-level screening. We reviewed the full text of 336 articles, of which 169 were included (Fig. 1). Disease severity was stratified into mild to moderate versus severe and critical, as defined by the WHO-China Joint Mission. The definition of severe disease comprised dyspnoea, respiratory frequency ≥ 30 /minute, blood oxygen saturation $\leq 93\%$, $\text{PaO}_2/\text{FiO}_2$ (arterial oxygen partial pressure/fraction of inspired oxygen) ratio < 300 and/or

lung infiltrates > 50% of the lung field. Critical disease was characterised by respiratory failure, septic shock and/or multiple organ dysfunction.⁽³⁾

Due to a lack of a universally accepted definition of CRS and the lack of routine checks of cytokine levels, the incidence of CRS in SARS-CoV-2 infection remains poorly characterised. Five reports from China (21–452 patients) demonstrated elevated levels of pro-inflammatory cytokines, mainly interleukin-6 (IL-6), interleukin-8, interleukin-10 and interferon- γ , which were associated with indices of inflammation such as leucopenia, lymphopenia, and elevated C-reactive protein (CRP), ferritin and D-dimer levels.^(4–8) Also, in a study of 191 patients, the onset of acute respiratory distress syndrome (ARDS) paralleled an increase in IL-6 on Day 12 of illness.⁽⁹⁾ Interestingly, in a study that performed daily transcriptome studies on a patient, expression of pro-inflammatory genes peaked on Day 6 of illness, but only the expression of IL-1A and IL-1B preceded the peak in oxygen requirement.⁽¹⁰⁾ Hypercytokinaemia was also associated with acute cardiac and liver injury and higher mortality.^(4–8) These findings were corroborated in a meta-analysis of 21 studies including 3,377 patients and 33 laboratory parameters, where elevated IL-6, IL-10 and serum ferritin levels were strong discriminators for severe disease.⁽¹¹⁾ Seven patients displayed laboratory features of hemophagocytic lymphohistiocytosis, based on the H-score in one study.⁽¹²⁾

Underlying immune dysregulation accounting for the hypercytokinaemia was characterised by increased pathogenic T-helper (Th) 1 cells and CD14+CD16+ monocytes⁽¹³⁾ but reduced memory Th (CD3+CD4+CD45RO+) and regulatory (CD3+CD4+CD25+CD127low+) T cells.⁽⁶⁾ Declining absolute CD4+ and CD8+ counts and increased functional exhaustion markers (including PD-1 and Tim-3 expression) portended elevation of IL-6, IL-10 and tumour necrosis factor- α , and the requirement for intensive care unit care.^(14–16)

Haematologic manifestations

Hypercoagulability

As a result of thromboinflammation, thrombotic events occurred at a higher rate in SARS-CoV-2-infected individuals than in matched patients with influenza, particularly in patients with more severe disease.⁽¹⁷⁾ Whole blood thromboelastography of 30 patients with elevated CRP levels demonstrated elevated levels of D-dimer, fibrinogen, factor VIII and von Willebrand factor.⁽¹⁸⁾ In addition, in 16 patients with ARDS, elevation in D-dimer and fibrinogen levels paralleled the rise in IL-6.⁽¹⁹⁾ Another study of 94 patients showed lower antithrombin and higher fibrinogen levels as well as reduced prothrombin and thrombin time in patients with severe disease.⁽²⁰⁾ Other mechanisms for the excess thrombotic risk include endotheliitis via direct viral invasion,^(21,22) complement-mediated endothelial injury⁽²²⁾ and induction of antiphospholipid antibodies.⁽²³⁻²⁵⁾

Venous thromboembolism (VTE) was the most common form of thrombotic complication and afflicts 10%–31% of patients (seven studies, sample size 81–184).^(17,26-31) These events usually presented within the first two weeks of disease^(28,32-36) in spite of prophylactic anticoagulation.^(17,28,29,34,35) Predictors included elevated D-dimer level,^(27,29) age and coagulopathy (defined as spontaneous prolongation of prothrombin time > 3 seconds or activated partial thromboplastin time > 5 seconds).⁽²⁸⁾ VTE and disseminated intravascular coagulation were associated with severe disease and mortality.^(26,30) Other forms of thrombosis, including ischaemic stroke,^(24,25,28,37-42) cerebral venous sinus thrombosis,^(43,44) acute myocardial infarction,^(21,28) systemic arterial embolism,⁽²⁸⁾ arteriosclerosis obliterans,⁽⁴⁵⁾ mesenteric ischaemia,⁽²¹⁾ glomerular fibrin thrombi,⁽⁴⁶⁾ and digital and skin necrosis,^(22,24,47) have been reported. Small fibrinous thrombi were also found in the pulmonary arterioles of ten patients on autopsy.⁽⁴⁸⁾

Blood count anomalies

Lymphopenia was found in 26.1%–85%^(4,9,16,29,49-60) of patients. Low lymphocyte count at baseline, decreasing lymphocyte count over time^(4,9,11,16,54,55,57,61-64) and reduced lymphocyte-to-leucocyte ratio⁽⁶⁵⁾ were associated with severe disease and mortality. A lymphoplasmacytoid subset of reactive lymphocyte population was reported in 69% of patients.⁽⁵⁰⁾ The mechanisms for lymphopenia include: (a) hypercytokinaemia-induced apoptosis;^(6,16) (b) direct viral destruction via ACE-2 receptor;⁽⁶⁶⁾ and (c) translocation into affected organs.⁽⁶⁷⁾ In addition, leucopenia (9%–41%),^(4,9,29,50-53,55,57,64,68,69) leucocytosis (1.9%–44.7%),^(11,51,55-58,63,64,68) neutrophilia (38%–60%)^(4,11,51,57,58,63,65,68) and eosinopenia (52.9%–81.2%)^(11,54,68) were commonly observed. Leucocytosis was associated with severe disease (27.7% vs. 9.3% in mild disease).⁽⁵¹⁾ Thrombocytopenia was seen as a late manifestation in 11.4%–30% of patients, with the nadir observed on Day 15–20 of illness,^(51,70,71) and was associated with mortality.^(70,72)

Neurologic manifestations

Strokes

Based on the literature review censored on 1 May 2020, strokes were reported in 32 patients (27 ischemic strokes, three haemorrhagic strokes and two cerebral venous sinus thrombosis).^(24,25,37-44,73) Strokes occurred synchronously with respiratory symptoms until 33 days after symptom onset. Additionally, strokes have been reported in pre-symptomatic patients (Table I). Although most patients were elderly with cardiovascular risk factors, a case series and one case report described strokes in patients < 50 years old.^(38,43) Positive antiphospholipid antibodies (lupus anticoagulant, anticardiolipin immunoglobulin M [IgM] and immunoglobulin A [IgA], anti-β2-glycoprotein-I IgM, IgA and immunoglobulin G [IgG]) were described in nine patients, eight of

whom suffered multiple cerebral infarcts.⁽²³⁻²⁵⁾ Table I summarises the characteristics of SARS-CoV-2 patients with acute stroke.

Guillain-Barré syndrome and Miller Fisher syndrome

Five Italian patients with Guillain-Barré syndrome (GBS) developed flaccid weakness on Day 5–10 of COVID-19 infection. Electrophysiologic studies revealed a mix of axonal or demyelinating patterns of injury. Antiganglioside antibodies were negative in those who were tested.⁽⁷⁶⁾ One patient developed fever and cough eight days after the GBS diagnosis. The nasopharyngeal swab was positive for SARS-CoV-2. In this study, the authors evoked the possibility of a parainfectious mechanism for GBS that deviated from the usual post-infectious autoimmune aetiology.⁽⁷⁷⁾ Two patients were diagnosed with Miller Fisher syndrome (MFS) on Days 3 and 5 of illness. One carried anti-GD1b IgG antibodies. Both patients reported ageusia that accompanied the typical symptoms of MFS, such as diplopia, ataxia and areflexia.⁽⁷⁸⁾

Seizures and encephalitis

Seizures were uncommon and reported in only four patients in the included studies.^(37,60,79,80) One patient with fever, headache and sore throat suffered generalised seizures nine days later. Brain magnetic resonance (MR) imaging showed right mesial temporal lobe and hippocampal hyperintense signal changes. Lumbar puncture revealed SAR-CoV-2 in the cerebrospinal fluid.⁽⁸⁰⁾ Acute necrotising encephalopathy was reported in another patient three days after the initial fever and cough, and brain MR imaging demonstrated bilateral haemorrhagic rim-enhancing lesions in the thalami and medial temporal lobes.⁽⁸¹⁾

Elevated creatine kinase and rhabdomyolysis

In a meta-analysis of 3,600 patients, elevated creatine kinase (CK) afflicted 28.6% of patients with severe disease, compared to 16.7% of patients with mild disease.⁽⁵¹⁾ Only 0.2% of 1,099 patients suffered rhabdomyolysis in one study.⁽⁴⁹⁾ A case report described a patient with CK of 13,581 U/L who presented with fever and respiratory symptoms.⁽⁸²⁾ Muscle involvement by SARS-CoV-2 could be mediated by viral binding to the skeletal muscle ACE-2 receptor and circulating viral toxins that destroy muscle cell membranes.⁽³⁷⁾

Cardiac manifestations

Acute cardiac injury

The pooled incidence of acute cardiac injury, defined as troponin rise or cardiac dysfunction, was 17.7% from a total of 1,412 COVID-19 patients (ten cohort studies, sample sizes 41–416).^(4,59,62,83-89) In this sample, 70.8% (n = 1,000) had severe disease and 17.4% died. In another meta-analysis of 1,527 patients, 8.0% of patients suffered acute cardiac injury.⁽⁹⁰⁾ Acute cardiac injury was more prevalent in patients with underlying cardiovascular disease^(87,89,90) and non-survivors.^(9,59,62,91) The mean mortality rate was 54.4% (87/150) in patients with acute cardiac injury compared to 9.0% (35/386) in those without.⁽⁸⁷⁻⁸⁹⁾ Patients with acute cardiac injury were at higher risk of malignant arrhythmias⁽⁸⁷⁾ and tended to require intensive care and mechanical ventilation.⁽⁹⁰⁾ There were limited reports on the proportion of patients requiring percutaneous coronary intervention or who developed acute myocardial infarction from atherosclerotic plaque rupture. Postmortem histology of a patient with ST-segment elevation myocardial infarction revealed lymphocytic endotheliitis of the submucosal cardiac vessels.⁽²¹⁾

Heart failure and myocarditis

Heart failure was described in 6.5%–23% of all patients^(9,51,60) and up to 52% of non-survivors.^(9,91) SARS-CoV-2 infection exacerbated pre-existing heart failure in a case series.⁽⁹²⁾ Myocarditis was observed in 12.5% of 112 patients (diagnosis based on raised cardiac enzymes, electrocardiogram and echocardiogram).⁽⁸⁶⁾ Seven patients with viral myocarditis or myopericarditis presented with cardiogenic shock and/or severe left ventricular hypokinesia.⁽⁹³⁻⁹⁹⁾ Cardiac MR imaging demonstrated myocardial oedema and transmural late gadolinium enhancement.^(94,96,99) One patient with acute myocarditis presented with reverse Takotsubo syndrome.⁽⁹⁹⁾ Two patients with myocarditis received endomyocardial biopsy. In the first patient, cytopathic interstitial inflammatory cells containing coronavirus particles were seen on electron microscopy.⁽⁹⁷⁾ In the other patient, T lymphocytes diffusely infiltrated the myocardial interstitium despite the absence of SARS-CoV-2 on molecular analysis.⁽⁹⁹⁾ Pericardial effusion was reported in 18.8% of 112 patients, particularly those with severe disease or myocarditis.^(94,95)

Gastrointestinal manifestations

Gastrointestinal symptoms

Due to heterogeneity in patient populations and symptom definitions, the prevalence of gastrointestinal symptoms in COVID-19 patients ranged widely, from 12.8% to 65.9%.^(65,83,100-105) However, in a meta-analysis that included 4,243 patients, the pooled prevalence of all gastrointestinal symptoms was only 17.6% (anorexia 26.8%, diarrhoea 12.5%, nausea and vomiting 10.2%, abdominal pain 9.2%).⁽¹⁰⁶⁾ Gastrointestinal symptoms were the only presenting symptoms in 28.4% of 74 patients in one study.⁽¹⁰⁷⁾ A patient developed respiratory symptoms only nine days after the onset of haemorrhagic colitis.⁽¹⁰⁸⁾ Interestingly, viral shedding in stools

was reported in up to 48.1% of patients, including patients without diarrhoea.⁽¹⁰⁶⁾ Also, 70.3% of patients continued to have positive stool viral RNA even after demonstrating negative results in respiratory samples.⁽¹⁰⁶⁾ Viral RNA was detected in the oesophagus, stomach, duodenum and rectum in three out of six patients with gastrointestinal symptoms who received endoscopy. One patient bled from multiple herpetic ulcers in the oesophagus.⁽¹⁰⁹⁾ Enteric infection by SARS-CoV-2 occurs via ACE-2 receptors expressed in epithelial cells.⁽¹¹⁰⁾ A postmortem case series reported small bowel endotheliitis in patients with mesenteric ischaemia.⁽²¹⁾

Acute liver injury

Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were observed in 10%–36.6% and 7.7%–33.3% of patients, respectively.^(4,8,49,57,101,104,111-116) Hyperbilirubinaemia was seen in 2.1%–18.2% of patients.^(49,57,111,114,115,117,118) Gross elevation to more than three times the upper limit of normal was reported in 37% of patients for ALT, 20% of patients for AST, and 10% of patients for total bilirubin.⁽¹¹⁹⁾ Rare cases of severe acute hepatitis have also been reported.⁽¹²⁰⁾ Elevation in AST, ALT and bilirubin levels were associated with ARDS, shock and other extrahepatic complications.⁽⁴⁹⁾ Hepatic injury in COVID-19 infection occurs via (a) direct viral cytopathic effect via ACE-2 receptors in biliary and liver epithelial cells; (b) systemic inflammation; and (c) ischaemia from distributive shock.⁽¹²¹⁾ Drug-induced liver injury from the use of lopinavir/ritonavir, remdesivir and tocilizumab should be considered.⁽¹¹⁸⁾ Histological assessment of COVID-19 associated liver injury is non-specific,⁽⁶⁷⁾ although one postmortem examination described lymphocytic endotheliitis in the liver.⁽²¹⁾

Renal manifestations

Acute kidney injury (AKI) was observed 0.5%–7% of all patients and up to 17% of patients in cohorts with higher prevalence of cardiovascular diseases.^(4,9,49,53,57,83,87,104,122) Proteinuria and haematuria were detected in 44% and 27% of patients on admission to hospital, respectively,⁽⁹¹⁾ suggesting renal involvement early in the disease course. AKI is postulated to be driven by a direct viral cytopathic effect, mediated through the ACE-2 receptor and cellular transmembrane serine proteases expressed on podocytes and tubular epithelial cells.⁽¹²³⁾ This was supported by the postmortem renal histopathology of 26 patients, which showed direct viral invasion of the tubular epithelium and podocytes. Erythrocyte aggregation in tubular capillary loops, along with glomerular fibrin thrombi and ischaemic contraction, was also seen.⁽⁴⁶⁾

While the kidneys may be affected early in the course of infection, severe AKI seemed to manifest only later as part of a systemic inflammatory response. In critically ill patients, rates of AKI were increased up to 29%,^(4,49,53,59,83) and AKI was observed in up to 50% of patients who eventually died.^(9,65,68,91) In a study of 191 patients, ARDS developed at a median of 12 days, while the onset of AKI closely followed at a median of 15 days,⁽⁹⁾ suggesting the clustering of AKI at the period of critical illness and mechanical ventilation. The overall rate of renal replacement therapy was 5% in all hospitalised patients, increasing to 17% in the critically ill.^(9,68) Proteinuria, haematuria, elevated baseline serum urea levels, and creatinine and peak serum creatinine levels > 133 $\mu\text{mol/L}$ were associated with mortality.⁽¹²³⁾

Olfactory and gustatory dysfunction

Smell and taste disturbances are early manifestations of SARS-CoV-2 infection and were the presenting symptoms in 11.8%–18.1% of patients.^(124,125) Smell disturbance occurred after 4.4

± 1.9 days of symptom onset among 114 patients. Anosmia lasted a mean of 8.9 ± 6.3 days.⁽¹²⁶⁾ Four studies that captured self-reported symptoms reported smell and taste disturbance in 20%–68% and 24%–85% of patients, respectively.^(126–129) Three other studies that utilised objective measures reported a higher incidence of olfactory and gustatory dysfunction (82.6%–98% and 49.3%–88%, respectively).^(124,125,130) Table II describes the observational studies on smell and taste dysfunction in patients with SARS-CoV-2. Mechanisms for olfactory dysfunction include reactive inflammation of the olfactory cleft causing conductive smell dysfunction^(131,132) and SARS-CoV-2 directly invading ACE-2-expressing olfactory epithelial cells.^(131,132)

Cutaneous manifestations

Cutaneous manifestations were found in up to 20.4% of SARS-CoV-2 infected patients.⁽¹³³⁾ In a study of 375 patients (COVID-19 infection confirmed in 62.4%), five distinct patterns were discerned: (a) maculopapular eruption (47%); (b) urticaria (19%); (c) vesicular eruption (9%); (d) livedoid lesions or necrosis (9%); and (e) chilblain-like lesions (19%).⁽¹³⁴⁾ Maculopapular eruption, vesicular rash and urticaria were also observed in a study of 18 patients⁽¹³³⁾ and eight case series/reports.^(135–142) Variants of maculopapular eruption include widespread confluent lesions of up to 10 cm,⁽¹⁴³⁾ symmetrical drug-related intertriginous and flexural exanthema,⁽¹⁴⁴⁾ petechiae and purpura.^(145–147) Skin histopathology in patients with a maculopapular or vesicular eruption showed varying features including perivascular spongiotic dermatitis, nests of Langerhans cells, eosinophils, lymphocytic vasculitis, microthrombi and dyskeratotic keratinocytes.⁽¹⁴⁸⁾

Most characteristically, chilblain-like lesions that present as erythematous-to-purplish macules and plaques distributed over acral sites ('COVID toes') were reported predominantly in patients who had asymptomatic or mild disease.^(134,149–152) Histopathology showed superficial and

deep lichenoid, perivascular and perieccrine lymphocytic infiltrates with vacuolar interface dermatitis and necrotic keratinocytes.⁽¹⁵⁰⁾ While transient livedo may accompany mild disease,⁽¹⁵³⁾ fixed and necrotic lesions were described in patients with hypercoagulability.^(22,24,45,47) In these patients, skin histopathology demonstrated complement-mediated thrombogenic vasculopathy and epidermal necrosis without vasculitis. Notably, SARS-CoV-2 glycoprotein was found in the skin microvasculature.⁽²²⁾

Other manifestations

Auditory and ocular manifestations of the disease, arthralgia, spontaneous pneumomediastinum and mediastinal lymphadenopathy are described in Table III.

DISCUSSION

We undertook a multidisciplinary approach to systematically consolidate the wide range of manifestations and complications of SARS-CoV-2 infection (Fig. 2 & Table III). Referencing included studies, we assembled a timeline to demonstrate the distribution of these manifestations with respect to the onset of respiratory symptoms (Fig. 3).

While some manifestations occurred early, including olfactory and gustatory disturbance and gastrointestinal symptoms, late manifestations on Day 7–19 were dominated by multiorgan sequelae, mirroring the early ‘viraemic’ and late ‘acute’ phases of disease that were previously described.⁽¹⁸⁰⁾

Multiorgan involvement in SARS-CoV-2 occur via the following key mechanisms: (a) direct cytopathic effect from viral binding to ACE-2 receptors;^(2,66,123) (b) endothelial dysfunction and thromboinflammation;^(19,21,22) and (c) CRS.⁽⁴⁻⁸⁾ Yet, these processes are not separate and exist

on a continuum. Viral entry via ACE-2 receptors presages CRS by increasing angiotensin II and activating NF- κ B and the IL-6 amplifier. IL-1 and IL-6, in turn, promote endotheliopathy and thromboinflammation.^(2,181) Parenchymal injury at various organs occur when circulating leucocytes migrate into the interstitium or when resident histiocytes are activated.⁽¹⁸²⁾ Concurrently, pro-inflammatory cytokines induce the release of ultralarge von Willebrand factor multimers and the overexpression of tissue factor.⁽¹⁸³⁾ As a result, microthromboses, found in the histologic samples in the skin and kidneys of patients with SARS-CoV-2,^(22,46,48) lead to further ischaemic damage.

While immunomodulation in SARS-CoV-2 CRS with IL-6 blockade has been described, patient selection and timing are crucial for safety and success.⁽¹⁸⁴⁾ Extrapulmonary symptoms in the early phase of illness could be attributed to direct viral invasion in sites such as the gastrointestinal tract and conjunctivae. In the later phase, however, multiorgan dysfunction reflects the hypercytokinaemia heralded by endotheliopathy, in which activated leucocytes infiltrate organ interstitium.⁽¹⁸²⁾ Biomarkers that identify patients with early endotheliopathy could inform physicians about the patients who are destined to do poorly, but who could still be intervened upon within this narrow window of opportunity.

Our description of the extrapulmonary manifestations and complications of SARS-CoV-2 has been limited by differences in patient sampling and definitions used for extrapulmonary symptoms in observational studies, resulting in a wide range of incidence of complications quoted in this review. Also, as patients with SARS-CoV-2 were less likely to receive invasive procedures or radiological investigations, many of the manifestations were likely under-reported. In addition, we did not examine the validity of the observational studies, so as to exhaustively describe the range of manifestations. Importantly, after the time of censoring of this review on 1 May 2020,

there have been many important observational studies and meta-analyses of COVID-19-related complications such stroke and AKI that demonstrated a different prevalence or natural history from the reports in this review. In addition, new manifestations, such as thromboembolism in asymptomatic individuals and electrolyte disturbances, have been reported. Unfortunately, these studies were not included based on the design of this review. However, we believe that we have taken the most comprehensive approach to delineate the systemic manifestations and complications of SARS-CoV-2 infection and outline their clinical course.

CONCLUSION

Although the systemic manifestations of SARS-CoV-2 infection are variegated, they are deeply interwoven by shared pathological mechanisms. Two phases of extrapulmonary disease were identified: (a) an early phase with gastrointestinal, ocular and cutaneous involvement and (b) a late phase characterised by multiorgan dysfunction and clinical deterioration. A clear, multidisciplinary consensus to define and approach thromboinflammation and CRS in SARS-CoV-2 is needed to identify patients in need of early intervention.

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TABLES

Table I. Reports of strokes in patients with SARS-CoV-2.

Authors	n	Type of event	Presentation	Radiological anatomy/vascular territory	Time from disease onset (day)	Anti-phospholipid antibody status	Coagulation parameters
Mao et al ⁽³⁷⁾	5	4 ischaemic strokes, 1 haemorrhagic stroke	Not described	Not described	1–18 (median 9)	Not described	Not described
Helms et al ⁽⁴¹⁾	3	All ischaemic strokes	Incidental finding on MR imaging done for encephalopathy	Small hyperintensity lesions on MR imaging	Not described	Not described	Not described
Zhang et al ⁽²⁴⁾	3	All ischaemic strokes	Aged 65–70 yr, headache and digital ischemia	Multifocal infarcts including frontal, parietal, occipital lobes, basal ganglia, brainstem and cerebellum	10, 18, 33	Positive anticardiolipin IgA, anti-β2-glycoprotein-I IgA and IgG in all patients	Elevated PT, aPTT, D-dimer and reduced platelets
Oxley et al ⁽³⁸⁾	5	All ischaemic strokes	Aged 33–49 yr, focal neurological deficits NIHSS score 13–23	1 internal carotid artery, 3 MCA, 1 posterior cerebral artery	Not described	Not described	Prolonged PT or aPTT in 3 patients, elevated D-dimer and fibrinogen in 3 patients
Beyrouiti et al ⁽²⁵⁾	6	All ischaemic strokes	Aged 53–85 yr, acute confusion with focal neurological deficits	5 multifocal infarcts, 2 patients developed ischaemic stroke despite therapeutic anticoagulation	–2 to 24 (median 12.5)	5 patients with lupus anticoagulant, 1 patient with medium-titre IgM anticardiolipin	Prolonged PT or aPTT in 2 patients, elevated fibrinogen in 4 patients, elevated D-dimer in all patients
Avula et al ⁽³⁹⁾	4	All ischaemic strokes	Aged 73–88 yr, focal neurological	2 MCA, 1 frontal lobe, 1 medial temporal lobe	1–3 (median 2)	Not described	Prolonged PT or aPTT in 2 patients, elevated D-dimer in 2 patients

			deficits, NIHSS score 2–36				
Gu et al ⁽⁷⁴⁾	1	Ischaemic stroke	Aged 78 yr with right-sided weakness, NIHSS score 2. A physician involved in treatment contracted COVID-19 three days later	CT brain unremarkable	−2	Not described	Normal PT and aPTT
He et al ⁽⁷⁵⁾	1	Ischaemic stroke with concurrent subarachnoid hemorrhage	Aged 70 yr with anisocoria	Not described	28	Not described	Severe thrombocytopenia and elevated D-dimer
Zhou et al ⁽⁴²⁾	1	Ischaemic stroke	Aged 75 yr with bilateral deep vein thrombosis	Bilateral cerebral infarcts involving the middle and anterior cerebral artery on the right and anterior cerebral artery on the left	15	Not described	Normal coagulation profile, elevated D-dimer
Sharifi-Razavi et al ⁽⁷³⁾	1	Haemorrhagic stroke	Aged 75 yr, drowsiness and extensor plantars	Massive intracerebral haemorrhage in the right hemisphere, accompanied by intraventricular and subarachnoid haemorrhage	3	Not described	Prolonged aPTT, normal platelet count
Hughes et al ⁽⁴⁴⁾	1	Cerebral venous sinus thrombosis	Aged 59 yr with headache and weakness	Cerebral venous sinus thrombosis	Not described	Not described	Not described
Garaci et al ⁽⁴³⁾	1	Cerebral venous sinus thrombosis	Aged 44 yr with drowsiness, aphasia and hemiparesis with	Empty delta sign in the vein of Galen, straight sinus and in the torcular herophili due to dural	14	Absence of anticardiolipin and anti-β2	Severe thrombocytopenia and elevated D-dimer

			concurrent pulmonary embolism	sinus thrombosis with poor representation of left internal cerebral vein		glycoprotein IgM and IgG	
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aPTT: activated partial thromboplastin time; CT: computed tomography; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; MCA: middle cerebral artery; MR: magnetic resonance; NIHSS: National Institutes of Health Stroke Scale; PT: prothrombin time

Table II. Observational studies on olfactory and gustatory dysfunction.

Authors	n	Country	Confirmed SARS-CoV-2 diagnosis (%)	Method of assessing smell and/or taste	Dysfunction (%)		Remarks
					Olfactory	Gustatory	
Lechien et al ⁽¹²⁴⁾	417	12 European hospitals	100	Questionnaires based on the smell and taste component of the National Health and Nutrition Examination Survey and the short version of the Questionnaire of Olfactory Disorders-Negative Statements	85.6	88.0	11.8% had smell dysfunction appearing before other symptoms. Among the 18.2% of patients without nasal obstruction or rhinorrhea, 79.7% were hyposmic or anosmic.
Moein et al ⁽¹³⁰⁾	60	Iran	100	University of Pennsylvania Smell Identification Test	98 (58 severe)	NA	18% smell disturbance in controls
Vaira et al ⁽¹²⁵⁾	72	Italy	100	Odour identification test and the Connecticut Chemosensory Clinical Research Center olfactory test and a standardised test of gustatory function that examined the ability to perceive four primary tastes	82.6 (8.3 severe)	49.3 (22.9 severe)	61.1% subjectively reported olfactory dysfunction
Yan et al ⁽¹²⁷⁾	59	USA	100	Patient-reported via Internet platform	68	71	
Giacomelli et al ⁽¹²⁸⁾	59	Italy	100	Questionnaire about the presence or absence of olfactory and taste disturbance	33.9 with either taste or olfactory disorder, 18.6 with both taste and olfactory disorder		20.3% presented with symptoms of smell or taste disturbance before hospital admission
Klopfenstein et al ⁽¹²⁶⁾	114	France	100	Patient-reported symptoms	47	85	Mean duration of anosmia was 8.9 ± 6.3 days. Duration was ≥ 7 days for 55% and ≥ 14 days for 20%. Tinnitus,

							and hearing loss were uncommon (< 15%)
Bénézit et al ⁽¹²⁹⁾	259	France	26	Web-based questionnaire comprising four questions	20	24	

NA: not applicable; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2

Table III. Summary of extrapulmonary manifestations of SARS-CoV-2.

Manifestation	Described frequency	Day of onset after fever or respiratory symptoms	Pathologic mechanism	Association with severe disease or mortality
Immunologic manifestations				
Cytokine release syndrome	1. Not defined and not precisely described in observational studies 2. Likely mirrors proportion of severe and critical cases (19.9%) ⁽³⁾	Day 7–19 ^(4,9,59,83)	1. Increased pathogenic Th1 cells and CD14+CD16+ monocytes ⁽¹³⁾ 2. Reduced memory Th (CD3+CD4+CD45RO+) and regulatory (CD3+CD4+CD25+CD127low+) T cells ⁽⁶⁾ 3. Depletion of absolute numbers and functional exhaustion of CD4+ and CD8+ T cells ^(14–16)	Not precisely described. ARDS and multiorgan dysfunction accompanies higher mortality, as described below
Induction of antiphospholipid antibodies	3 case reports/series, total n = 9 ^(23–25)	Not reported	1. Unknown for SARS-CoV-2 2. APLs induced by other viruses were related to endothelial exposure of phospholipid-binding viral peptides ⁽¹⁵⁴⁾	Not known
Haematologic manifestations				
Hypercoagulability	Venous thromboembolism in 10%–31% of patients ^(17,26–31)	Although D-dimer increases on Day 5–7, ⁽⁸³⁾ venous thromboembolism was reported on Day 1–21 ^(28,32–36)	1. Thromboinflammation with elevated cytokines, such as IL-6, causing endothelial injury ⁽¹⁹⁾ 2. Direct invasion of endothelial cells by the SARS-CoV-2 virus ⁽²¹⁾ 3. Complement-mediated endothelial injury ⁽²²⁾ 4. Elevations in circulating prothrombotic factors, e.g. factor VIII, fibrinogen,	Disseminated intravascular coagulation was seen in 71.4% of non-survivors vs. 0.6% survivors in one study ⁽²⁶⁾

			prothrombotic microparticles ⁽¹⁸⁻²⁰⁾ 5. Possible role of induced antiphospholipid antibodies ⁽²³⁻²⁵⁾	
Leucocytosis	1.9%–44.7% ^(11,51,55-58,63,64,68)	Peaks on Day 15–17 ⁽⁸³⁾	1. Increased leucocyte mobilisation from hypercytokinaemia 2. Secondary bacterial or fungal infections	1. ICU-admitters had a higher WBC count on admission ⁽⁸³⁾ 2. 46% of non-survivors had leucocytosis vs. 11% of survivors ⁽⁹⁾ 3. In a meta-analysis of 3600 patients, leucocytosis was associated with severe disease (27.7% vs. 9.3% in mild disease) ⁽⁵¹⁾
Lymphopenia	26.1%–85% ^(4,9,16,29,49-60)	Nadir on Day 5–10 ⁽⁸³⁾	1. Apoptosis induced by hypercytokinaemia ^(6,16) 2. Direct viral destruction via ACE-2 receptor ⁽⁶⁶⁾ 3. Translocation into affected organs ⁽⁶⁷⁾	Lymphocyte count at baseline, lymphocyte count over time ^(4,9,11,16,54,55,57,61-64) as well as lymphocyte-to-leucocyte ratio ⁽⁶⁵⁾ were associated with severe disease and mortality
Thrombocytopenia	Thrombocytopenia was seen in 11.4%–30% of patients ^(51,70,71)	Nadir on Day 17–19 ⁽⁷⁰⁾	1. Reduction of platelet production from direct infection of bone marrow or cytokine storm 2. Increased platelet destruction from increased immune clearance 3. Increased platelet consumption from microthrombi or pulmonary damage ⁽¹⁵⁵⁾	In-hospital mortality of 92.1% was observed for patients with a nadir platelet count of $< 50 \times 10^{(70)}$
Eosinopenia	52.9%–81.2% ^(11,54,68)	Not known	Not known	Not predictive of disease severity in a meta-analysis of 294 patients ⁽¹⁵⁶⁾

Neutrophilia	38%–60% (4,11,51,57,58,63,65,68)	Peaks on Day 15–17 ⁽⁸³⁾	1. Increase mobilisation as a result of hypercytokinaemia ⁽¹⁰⁾ 2. Possible secondary bacterial infection	HR 1.14 for death or ARDS in bivariable analysis in one study of 201 patients ⁽⁵⁸⁾
Sickle cell crisis	Case series of 2 patients who presented with painful vaso-occlusive crisis and acute chest syndrome that preceded fever and respiratory symptoms ⁽¹⁵⁷⁾	Days –3 to 1 ⁽¹⁵⁷⁾	Similar process to other viral infections	Not known
Cardiac manifestations				
Acute cardiac injury	1. 17.7% from a total of 1,412 COVID-19 patients (10 cohort studies, sample sizes 41–416). ^(4,59,62,83-89) 2. In another meta-analysis of 1,527 patients, 8.0% of patients suffered acute cardiac injury ⁽⁹⁰⁾	Day 4–21, peaking on Day 15 ⁽⁹⁾	1. Hypercytokinaemia driving increased sympathetic activity and resulting in demand ischaemia ^(7,158) 2. Over-representation of patients with underlying cardiovascular diseases ^(87,89) 3. Myocarditis with direct invasion of ACE-2-expressing myocytes ⁽⁹⁹⁾ 4. Endotheliitis and endotheliopathy impairing perfusion of submucosal cardiac vessels ⁽²¹⁾ 5. Hyperinflammation increasing atherosclerotic plaque vulnerability and rupture ^(21,159) 6. Hypercoagulability leading to pulmonary embolism or microthrombi and right heart strain ^(17,27-29,32)	Mean mortality rate is 54.4% in patients with acute cardiac injury compared to 9.0% in those without ⁽⁸⁷⁻⁸⁹⁾

Heart failure	6.5%–23% of all patients ^(9,51,60)	Not known but likely parallels cardiac injury	<ol style="list-style-type: none"> 1. Ischaemia secondary to endotheliitis and endotheliopathy⁽²¹⁾ 2. Key cytokines implicated in SARS-CoV-2 hypercytokinaemia, such as IL-6, may promote myocardial dysfunction⁽¹⁶⁰⁾ 3. Downregulation of ACE-2 has been demonstrated in SARS-CoV and may reduce cardioprotection by angiotensin 1–7⁽¹⁶¹⁾ 4. Myocarditis 	Seen in 52% of non-survivors vs. 12% of survivors ⁽⁹⁾
Myocarditis	12.5% of 112 patients ⁽⁸⁶⁾ 7 case reports ⁽⁹³⁻⁹⁹⁾	Not known	Direct invasion of myocytes via ACE-2 ⁽⁹⁹⁾	Not known
Arrhythmias	10.9%–16.7% of patients ^(53,83) Rapid ventricular tachycardia and ventricular fibrillation causing haemodynamic instability were seen in 7.0% of 187 patients. ⁽⁸⁷⁾ Reports of transient complete heart block ⁽¹⁶²⁾ and Brugada syndrome ⁽¹⁶³⁾	Not known but likely parallels cardiac injury	<ol style="list-style-type: none"> 1. Acute cardiac injury 2. Myocarditis 3. Electrolyte disturbance from acute kidney injury or diarrhoea 4. Contribution from medications such as hydroxychloroquine 	Seen in 40% of severe cases vs. 1.2% of non-severe cases ⁽⁵³⁾
Gastrointestinal manifestations				
Gastrointestinal symptoms (including nausea, diarrhoea, anorexia and abdominal pain)	<ol style="list-style-type: none"> 1. 12.8%–65.9% of all patients^(65,83,100-105) 2. In a meta-analysis of 4,243 patients, the pooled prevalence of the symptoms was: anorexia 26.8%, 	Predates respiratory symptoms by up to 9 days before, up till 11 days after ^(65,83,100-105)	<ol style="list-style-type: none"> 1. Enteric infection is proposed to be mediated by ACE-2 receptors, which are abundantly expressed in epithelial cells⁽¹¹⁰⁾ 	<ol style="list-style-type: none"> 1. Higher mortality and need for ventilatory support reported in 181 patients with high comorbidity burden⁽¹⁶⁴⁾ 2. No difference in outcomes in another multicentre, cross-

	diarrhoea 12.5%, nausea and vomiting 10.2%, abdominal pain 9.2% ⁽¹⁰⁶⁾		2. Small bowel endotheliitis in patients with mesenteric ischaemia. ⁽²¹⁾	sectional study of 204 patients ⁽¹¹⁰⁾
Acute liver injury	<ol style="list-style-type: none"> 1. Elevated aspartate aminotransferase and alanine aminotransferase were observed in 10%–36.6% and 7.7%–33.3% of patients, respectively.^(4,8,49,57,101,104,111–116) 2. Hyperbilirubinaemia was seen in 2.1%–18.2%.^(49,57,111,114,115,117,118) 	Day 4–11, peak on Day 10 ⁽¹¹⁵⁾	<ol style="list-style-type: none"> 1. Direct virus-induced effect via ACE-2 receptors expressed in biliary, liver epithelial cells or endothelial cells 2. Systemic inflammation and immune injury 3. Sepsis from secondary bacterial infection 4. Ischaemia secondary to hypoxia, heart failure or hypotension 5. Drug-induced liver injury from lopinavir/ritonavir, remdesivir and tocilizumab 	More common in severely ill patients ^(4,49,51)
Neurologic manifestations				
Stroke	<ol style="list-style-type: none"> 1. 5.7% in severely ill patients⁽³⁷⁾ 2. Case series and case reports in Table I 	Day –2 to 33, appear to peak on Day 9–15 (Table I)	Ischaemic strokes may be related to mechanisms of hypercoagulability, endotheliopathy and over-representation of cardiovascular comorbidities, as outlined above	5.7% in severely ill patients vs. 0.8% in mild cases ⁽³⁷⁾
Meningoencephalitis	<ol style="list-style-type: none"> 1. Isolated case reports^(80,81) 2. Leptomeningeal enhancement on brain imaging was reported in 62% of severe patients with 	Diagnosed on Day 3 and Day 9 in 2 case reports ^(80,81)	<ol style="list-style-type: none"> 1. Direct SARS-CoV-2 invasion into CNS⁽⁸⁰⁾ 2. Para-infectious mechanism with blood-brain barrier breakdown due to cytokine storm^(76,80) 	Not known

	ARDS and encephalopathy ⁽⁴¹⁾			
Elevated creatine kinase and rhabdomyolysis	<ol style="list-style-type: none"> 1. 28.6% and 16.7% of patients with severe and mild clinical disease, respectively⁽⁵¹⁾ 2. 0.2% rhabdomyolysis⁽⁴⁹⁾ 	Not known. Reports of rhabdomyolysis as initial presentation ⁽⁸²⁾	<ol style="list-style-type: none"> 1. Direct viral invasion by binding to ACE-2 receptor in skeletal muscle 2. Immune response resulting in cytokine storms and damaging muscle tissues 3. Circulating viral toxins may directly destroy muscle cell membranes^(25,37) 	More common in severely ill patients ⁽⁵¹⁾
Guillain-Barré syndrome and Miller Fisher syndrome	Estimated 0.4-0.5% from an Italian case series of 5 Guillain-Barré syndrome patients, with approximately 1,000–1,200 COVID-19 patients admitted during the study period ⁽⁷⁸⁾	Day 3–10 ^(76,78) (1 report preceding SARS-CoV-2 by 8 days) ⁽⁷⁷⁾	<ol style="list-style-type: none"> 1. Post-infectious autoimmune mechanism with presentation 3–10 days after COVID-19 symptoms^(78,80) 2. Para-infectious mechanism proposed in view of an early presentation of Guillain-Barré syndrome⁽⁷⁷⁾ 	Not known
Non-specific findings including headache, giddiness, delirium and corticospinal tract signs	36.4% of 214 patients in China, including headache (13.1%), giddiness (16.8%) and drowsiness (7.5%). ⁽³⁷⁾ Similarly, in 58 French patients with ARDS, ICU delirium (65%) and corticospinal tract signs (67%) were the main neurological findings. A high incidence of leptomenigeal enhancement and bilateral frontotemporal hypoperfusion was	Not known	Possibly related to general unwell state, systemic inflammation or drugs	Delirium and corticospinal tract signs are common in severely ill patients in ICU ⁽⁴¹⁾

	reported on imaging. SARS-CoV-2 was negative in the CSF of all 7 patients who underwent lumbar puncture. ⁽⁴¹⁾			
Renal manifestations				
Acute kidney injury	0.5%–7% of all patients and up to 17% of patients in cohorts with higher prevalence of cardiovascular diseases ^(4,9,49,53,57,83,87,104,122)	Day 11–17 ⁽⁸³⁾	<ol style="list-style-type: none"> 1. Direct viral cytopathic effect, mediated through the ACE-2 receptor and cellular transmembrane serine proteases expressed on podocytes and tubular epithelial cells.⁽¹²³⁾ 2. Severe AKI in later course of disease in tandem with ARDS and other organ dysfunction, likely related to hypercytokinaemia^(9,83) 	In critically-ill patients, rates of AKI increased up to 29%, ^(4,49,53,59,83) and AKI was observed in up to 50% of patients who eventually died ^(9,65,68,91)
Collapsing glomerulopathy	1 case report in a patient who presented with fever, vomiting and acute renal failure. SARS-CoV-2 was absent in the kidney. ⁽¹⁶⁵⁾	Presented with other symptoms	Patient was homozygous for the <i>APOL1</i> genotype ⁽¹⁶⁵⁾	Not known
Olfactory, gustatory and auditory manifestations				
Olfactory dysfunction	<ol style="list-style-type: none"> 1. Studies using self-reported symptoms: 20%–8% 2. Studies using objective measures: 82.6%–98% (Table II) 	Day 2–7; ⁽¹²⁶⁾ could precede respiratory symptoms	<ol style="list-style-type: none"> 1. Reactive inflammation of the olfactory cleft causing conductive smell dysfunction^(131,132) 2. Direct viral invasion of ACE-2-expressing olfactory epithelial cells^(131,132) 	9% of 54 patients needed ICU care, 4% died ⁽¹²⁶⁾

Gustatory dysfunction	<ol style="list-style-type: none"> 1. Studies using self-reported symptoms: 24%–85% 2. Studies using objective measures: 49.3%–88% (Table II) 	Day 2–7; ⁽¹²⁶⁾ could precede respiratory symptoms	<ol style="list-style-type: none"> 1. Inactivation of ACE-2 receptors in the oral cavity resulting in sodium channel inactivation in the taste receptors⁽¹³²⁾ 2. Viral binding to sialic acid receptors in the taste pores⁽¹³²⁾ 3. Smell dysfunction altering taste perception^(131,132) 	Not known
Cutaneous manifestations				
Maculopapular eruption	47% of cutaneous manifestations ⁽¹³⁴⁾	Day 3–8 ^(135,137,139,141,143,145,147)	Non-specific and could be related to both virus and drugs	12% needed ICU or non-invasive ventilation ⁽¹³⁴⁾
Urticaria	19% of cutaneous manifestations ⁽¹³⁴⁾	Day –2 to 6 ^(136,138,139)	Non-specific and could be related to both virus and drugs	11% needed ICU or invasive ventilation ⁽¹³⁴⁾
Vesicular eruption	9% of cutaneous manifestations ⁽¹³⁴⁾	Day –2 to 12 ⁽¹⁴⁰⁾	Non-specific and could be related to both virus and drugs	<ul style="list-style-type: none"> • 6% of patients needed ICU or invasive ventilation⁽¹³⁴⁾ • 3/22 patients died in one series⁽¹⁴⁰⁾
Livedoid lesions or necrosis	6% of cutaneous manifestations ⁽¹³⁴⁾	<ul style="list-style-type: none"> • Day 7–10 for livedo reticularis⁽¹⁵⁷⁾ • Day 14–21 for skin necrosis⁽²²⁾ 	Endotheliitis, endotheliopathy and hypercoagulability (outlined above). Transient processes may result in livedo, while fulminant intravascular coagulation may lead to fixed necrosis.	33% required ICU or invasive ventilation ⁽¹³⁴⁾
Chilblain-like lesions	19% of cutaneous manifestations ⁽¹³⁴⁾	Day 6–15 (median 10 days) ⁽¹⁵¹⁾	Not known. Likely related to microangiopathic process and a continuous spectrum with livedo	<ul style="list-style-type: none"> • Only 3% required ICU or invasive ventilation.⁽¹³⁴⁾ • Case reports of generally well patients.^(149,150,152)
Other manifestations				
Conjunctivitis	19 patients (1 observation study and 3 case series/reports) ⁽¹⁶⁶⁻¹⁶⁹⁾	Was the only symptom in 7 patients and often preceded other symptoms ⁽¹⁶⁶⁻¹⁶⁹⁾	Viral invasion of conjunctival cells that express ACE-2	Not known. Observed in asymptomatic as well as critically ill patients

	Symptoms included conjunctival hyperaemia, chemosis, epiphora and increased secretions ⁽¹⁶⁸⁾			
Mediastinal lymphadenopathy	1%–6% of patients who received chest computed tomography in 2 small observational studies (described to be subcarinal and voluminous) ^(170,171)	Not clear and depended on time of imaging	Likely similar to other infection-associated lymphadenopathy	Not known
Spontaneous pneumomediastinum	3 case reports in patients with bilateral pneumonia (one received positive pressure ventilation) ⁽¹⁷²⁻¹⁷⁴⁾	Day 10–12 ⁽¹⁷²⁻¹⁷⁴⁾	Not known	Not known
Arthralgia	2 case reports, one in a patient with fever and thrombocytopenia, ⁽¹⁷⁵⁾ another in a patient with urticaria ⁽¹³⁶⁾	Presenting symptom in both patients	<ol style="list-style-type: none"> 1. Not known for SARS-CoV-2 2. Possibly similar to other viral arthritides: mechanisms include complement activation and infiltration of inflammatory cells into synovium 3. Key cytokines in the cytokine release of SARS-CoV-2 (e.g. IL-6 and MCP1) have been implicated in pathogenesis of acute arthritis for other viruses⁽¹⁷⁶⁾ 	Not known
Auditory manifestations	Tinnitus (11%) and hearing loss (4%) were	Not known for tinnitus and hearing loss.	Postulated to be due to direct viral damage to the hair cells,	Not known

	reported among 54 patients with anosmia. ⁽¹²⁶⁾ A study showed that the high frequency pure-tone threshold and the transient evoked otoacoustic emissions amplitudes were significantly worse in a group of 20 young patients with confirmed SARS-CoV-2 who were asymptomatic. ⁽¹⁷⁷⁾ One patient with otitis media presented with otalgia along with bilateral pneumonia ⁽¹⁷⁸⁾	Report of otitis media was synchronous with other symptoms ⁽¹⁷⁸⁾	organ of Corti, stria vascularis, or spiral ganglion ⁽¹⁷⁷⁾	
Testicular pain	One patient presented with stabbing testicular pain and fever ⁽¹⁷⁹⁾	Same as other symptoms	Not known	Not known

ACE-2: Angiotensin-converting enzyme 2; AKI: acute kidney injury; APL: anti-phospholipid antibodies; ARDS: acute respiratory distress syndrome; CNS: central nervous system; CSF: cerebrospinal fluid; HR: hazard ratio; ICU: intensive care unit; IL-6: interleukin-6; MCP1: monocyte chemoattractant protein-1; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; Th1: T-helper 1; WBC: white blood cell count

FIGURES

Fig. 1 PRISMA flow diagram shows the inclusion process for the study.

Fig. 2 Illustration shows extrapulmonary manifestations and complications of SARS-CoV-2 infection. *Manifestations described only in case series or case reports.

Fig. 3 Time course of extrapulmonary manifestations of SARS-CoV-2 infection with respect to respiratory symptoms shows early manifestations (blue bars), late manifestations (orange bars) and single day events (green bars). Some manifestations (*) were only from case series/reports.