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Post-acute sequelae of COVID-19: understanding and addressing the burden of multisystem manifestations

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Individuals with SARS-CoV-2 infection can develop symptoms that persist well beyond the acute phase of COVID-19 or emerge after the acute phase, lasting for weeks or months after the initial acute illness. The post-acute sequelae of COVID-19, which include physical, cognitive, and mental health impairments, are known collectively as long COVID or post-COVID-19 condition. The substantial burden of this multisystem condition is felt at individual, health-care system, and socioeconomic levels, on an unprecedented scale. Survivors of COVID-19-related critical illness are at risk of the well known sequelae of acute respiratory distress syndrome, sepsis, and chronic critical illness, and these multidimensional morbidities might be difficult to differentiate from the specific effects of SARS-CoV-2 and COVID-19. We provide an overview of the manifestations of post-COVID-19 condition after critical illness in adults. We explore the effects on various organ systems, describe potential pathophysiological mechanisms, and consider the challenges of providing clinical care and support for survivors of critical illness with multisystem manifestations. Research is needed to reduce the incidence of post-acute sequelae of COVID-19-related critical illness and to optimise therapeutic and rehabilitative care and support for patients.

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This is the third in a Series of three papers about the post-acute sequelae of COVID-19 All papers in the Series are available at www.thelancet.com/series/post-acute-sequelae-of-COVID-19

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Introduction

Many individuals with SARS-CoV-2 infection have symptoms that persist well beyond the acute phase or emerge after the acute phase, lasting for weeks, months, or even years after the initial acute illness.[1] Various terms have been proposed to describe this collection of symptoms, which span physical, cognitive, and mental health domains and multiple organ systems, including long COVID, post-acute sequelae of SARS-CoV-2 infection or COVID-19, or post-COVID-19 syndrome. In 2021, WHO conducted a multidisciplinary expert consensus process and adopted the term post-COVID-19 condition, which they defined as a "condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis".[2–4]

The proportion of patients affected by post-COVID-19 condition might be in the range of 10–30% of those infected with SARS-CoV-2, although understanding of this condition is still evolving. Many individuals are therefore presenting with this new and complex systemic condition, and there is an urgent need to identify individuals at risk, the overlapping contribution of various factors (other than the direct effects of, and the host response to, SARS-CoV-2) to the post-acute sequelae of COVID-19 (eg, the consequences of critical illness), and potential approaches to clinical care and support. Patients who are critically ill and admitted to the intensive care unit (ICU) with acute COVID-19 might be at an increased risk of a range of post-acute sequelae.

In this Series paper, we provide an overview of the multisystem manifestations of the post-COVID-19 condition, with a primary focus on adult survivors of critical illness. The first paper[5] in this Series reviewed pulmonary and extrapulmonary origins of respiratory symptoms after acute COVID-19 and considered approaches to clinical care and rehabilitation. The second paper[6] focused on the pressing need to mitigate neurological, cognitive, and psychiatric sequelae of COVID-19-related critical illness. We consider the multisystem, longitudinal effects of endothelial dysfunction and immune system dysfunction before reviewing organ system sequelae of COVID-19, which are summarised in table 1. We highlight the challenges of providing appropriate care and support for patients with a novel, heterogeneous, multisystem condition and outline priorities for research.

Epidemiology and impact of post-COVID-19 condition

Long-term consequences of respiratory viral infections are not unique to SARS-CoV-2. A variety of persistent symptoms were described in survivors of SARS-CoV infection in 2003 and in survivors of Middle East respiratory syndrome (MERS) in 2012, including reduced exercise capacity, mental health complications, and worsened health-related quality of life.[17–21] However, it remains unclear whether the incidence, nature, and trajectory of the long-term clinical consequences of COVID-19 are similar to those of SARS and MERS. Given the very high prevalence of COVID-19, the impact on individuals, health-care systems, communities, and society at large could be overwhelming. Several million individuals (conservative figures indicate at least 65 million people worldwide) are estimated to be affected by persistent symptoms at present.[22,23]

A retrospective analysis from a large electronic health record database of adults in the USA showed that

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For more on the **post-COVID-19 condition** see https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition

Key messages

- Many individuals with SARS-CoV-2 infection have symptoms that persist well beyond or develop after the acute phase; these sequelae of COVID-19, known collectively as long COVID or post-COVID-19 condition, can last for weeks, months, or years after the acute illness
- The post-COVID-19 condition is systemic, with most organ systems in the body potentially affected; potential mechanisms include pathophysiological changes related to virus-specific effects, immunological and inflammatory dysregulation damage in response to the acute infection, and expected sequelae of critical illness
- Challenges that must be addressed in providing therapeutic and rehabilitative care and support for people with multisystem post-COVID-19 condition include the novelty of the condition, the overwhelming number of individuals affected, the need to coordinate multidisciplinary expertise, and the need to reach vulnerable and neglected populations; models of care have been proposed, drawing on previous experiences with survivors of critical illness
- The intersection of socioeconomic factors, pre-existing comorbidities, support and health-care access, and the consequences of critical illness is complex and might contribute to disparities in presentation, experiences, and outcomes of post-COVID-19 condition for patients and caregivers
- Research is needed to understand the causes and pathophysiological mechanisms of post-COVID-19 condition, to distinguish the effects of COVID-19 from those of critical illness per se, to develop specific preventive and therapeutic interventions for post-acute sequelae of COVID-19-related critical illness, and to understand and meet the needs of all those affected

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COVID-19 survivors were significantly more likely to have incident conditions than were matched controls without evidence of COVID-19.[24] This study found that 20% of COVID-19 survivors aged 18–64 years and 25% of those aged ≥65 years had at least one persistent symptom or organ dysfunction that might be attributable to previous COVID-19.[24] A Canadian study showed that nearly 15% of adults in Canada with suspected or confirmed SARS-CoV-2 infection had symptoms beyond 3 months; persistent symptoms were more frequently reported by women (18·0%) than by men (11·6%).[25] A prospective, population-based observational cohort study in the Netherlands assessed symptom severity before and after SARS-CoV-2 infection in participants with COVID-19 and compared it with symptom severity in matched, COVID-19-negative controls.[22] 12·7% of participants with COVID-19 reported persistent symptoms 3–5 months after infection that could be attributed to COVID-19.[22]

Many individuals with post-COVID-19 condition are unable to return to full-time work at 1 year after infection. A longitudinal cohort study involving 1192 people who were admitted to hospital in Wuhan, China, and who survived COVID-19 showed that 11% of those who were previously employed had not returned to work after 2 years.[13] In Canada, more than one in five adults who survived COVID-19 reported persisting limitations to their daily activities, ranging from 2·5% for adults with no initial symptoms to 36·4% for adults with severe initial symptoms.[25] The post-COVID-19 condition affects individuals at low risk of COVID-19 mortality, including young adults with no pre-existing comorbidities. A UK community-based, prospective study assessed individuals older than 18 years with persistent symptoms after recovery from acute SARS-CoV-2 infection and age-matched healthy controls, and showed that 70% of individuals with ongoing symptoms had impairment in one or more organs 4 months after initial infection.[26]

A study of 6-month outcomes in survivors of critical illness included 254 patients from two prospective observational studies in Australia and reported no difference in new disability, severity of disability, psychological function, cognitive function, or health-related quality of life in patients requiring mechanical ventilation for COVID-19-related versus non-COVID-19-related acute respiratory failure.[27] However, the study had limitations: patients were not matched, with some baseline differences, baseline function was retrospectively assessed, and functional outcome data for patients unable or unwilling to participate in the follow-up interviews were missing.[27] A study in Scotland exploring outcomes among confirmed cases and a matched comparison group reported that severe acute COVID-19 was significantly associated with long-term sequelae.[28] Other factors associated with incomplete recovery after COVID-19 included older age, female sex, deprivation, White ethnicity, and pre-existing health conditions, including respiratory disease and depression.[28] Similarly, the multicentre, long-term Post-hospitalisation COVID-19 study (PHOSP-COVID) in the UK identified female sex, middle age (40–59 years), two or more comorbidities, and acute severe illness as factors related to poor recovery after hospital admission with COVID-19 at 6 months after discharge.[29]

The reported 1-year and 2-year outcomes in survivors of COVID-19-related critical illness[1,13] share many of the same multidimensional morbidities already documented in the past 20–30 years in long-term (≥8 years) survivors of acute respiratory distress syndrome (ARDS), sepsis, and chronic critical illness.[30–32] These outcomes have led to overlapping syndromic constructs for each of these conditions, in addition to the post-intensive care syndrome (PICS; original and extended definitions).[33,34] The nature and impact of these post-acute conditions have been discussed in detail, together with the effects of critical illness on family caregivers, children, and professional caregivers.[35] Survivors of COVID-19-related critical illness are at risk of acquired or exacerbated organ

	Complications	Onset and course
Endothelium (multisystem)	Altered arterial stiffness, vascular reactivity, and capillary morphology; thromboembolic disease; elevated risk of atherosclerosis in the long term	Onset in the acute phase, persisting for 6 months after acute illness, possibly longer;[7–9] course of recovery unclear
Immune system	Dysregulated immune responses with raised cytokines concentrations; immune system alterations (eg, loss of memory lymphocyte subsets, lymphocyte exhaustion markers, and epigenetic changes)	Onset in the acute phase, persisting for 8 months after acute illness, possibly longer;[10] course of recovery unclear
CNS and peripheral nervous system	Cerebrovascular disorders (eg, stroke and transient ischaemic attack); neurodegenerative disease such as Alzheimer's disease and Parkinson's-like disease; peripheral nervous system changes; long-term anxiety, depression, and stress disorders; myalgic encephalomyelitis/chronic fatigue syndrome	Origins and symptom onset in the acute and post-acute phases, with symptoms potentially persisting or progressing for months to years after initial infection;[6] further research needed to understand the long-term course of various sequelae
Cardiac	Major cardiovascular adverse events (eg, myocardial ischaemia); decreased ventricular (right or left) function; myocarditis and myocardial scarring; pericardial effusion; impaired chronotropic response and exercise intolerance	Origins and symptom onset in the acute and post-acute phases, with symptoms persisting or progressing up to 1 year (and potentially longer) after initial infection;[11] further research needed to understand the long-term course of cardiac function and associated symptoms
Respiratory	Breathlessness and limited exercise tolerance; persistent radiological alterations suggestive of lung fibrosis; chronic microvascular and macrovascular thrombi in the pulmonary circulation	Origins and symptom onset in the acute and post-acute phases, with symptoms lasting up to 1 year (and potentially longer) after initial infection;[5] further research needed to understand the course of lung disease and long-term outcomes
Renal	Progressive decline in renal function; chronic kidney disease and dialysis dependence	Origins in the acute and post-acute phases, with symptoms lasting up to 1 year (and potentially longer) after initial infection;[12] further research needed to understand the longer-term course of kidney function
Musculoskeletal	Myopathy; muscular atrophy; joint stiffness and frozen joints	Onset in the acute phase, persisting up to 2 years after initial infection;[13,14] further research needed to understand the course of recovery
Gastrointestinal	Gastroenteritis; pancreatitis; elevation of liver enzyme concentrations; long-lasting and severe cholestasis	Onset in the acute phase, persisting up to 6 months after initial infection;[15,16] further research needed to understand the course of recovery

Table 1: **Organ system complications associated with the post-COVID-19 condition**

dysfunction, as described in these other non-COVID-19 conditions, and the additive multisystem impact of COVID-19 (figure 1). In individuals who are more severely critically ill, identifying sequelae that are distinctly related to COVID-19 might be difficult; as patient outcomes and the results of translational studies continue to emerge, new data on this question will hopefully accrue.

The post-COVID-19 condition is systemic, with most organ systems potentially affected (table 1; figure 1).[36] The clinical features and clinical course of post-COVID-19 condition might reflect the severity and management of acute disease (figure 2), but its pathophysiology is complex and our current understanding is far from complete. Moreover, the effects of different SARS-CoV-2 variants and of reinfection remain incompletely characterised at present.[23] Potential contributing mechanisms include pathophysiological changes related to SARS-CoV-2-specific effects; immunological and inflammatory dysregulation in response to the acute infection; effects of in-hospital and ICU care; and expected sequelae of critical illness.[21] The intersection of socioeconomic factors, pre-existing comorbidities, support and health-care access, and the consequences of critical illness is complex and might contribute to disparities in presentation, experiences, and outcomes of post-COVID-19 condition for patients and caregivers alike.[37]

Endothelial dysfunction

One unique manifestation of COVID-19 and COVID-19-related critical illness that was observed early in the pandemic is endotheliitis and its multisystem and longitudinal impact. The endothelium is a single layer of cells lining every blood vessel, and forms a physiological barrier between the circulation and the vessel wall and tissue compartment. The endothelium is crucial for maintenance of an antithrombotic surface, regulation of inflammation and oxidative stress, governance of vascular tone, synthesis of growth factors and cell matrix, and regulation of cellular metabolism, ageing, and cell death.[38,39] Control of these functions is meticulous and reflects the capacity of this cellular layer to respond to dynamic events such as injury, infection, and noxious stimuli. In this way, the endothelium is a gateway to health and disease.

Effects of acute SARS-CoV-2 infection on endothelial functions

The endothelium is dysfunctional in several diseases and physiological states, such as diabetes, hypertension, cardiovascular disease, and obesity. The vulnerability of these patient populations was noted early in the COVID-19 pandemic[40] and provided a clue that the endothelium was vulnerable to SARS-CoV-2 infection.[41,42] Circulating markers of endothelial injury provided additional clues (eg, elevated P-selectin concentrations, von Willebrand factor activity, and soluble thrombomodulin concentrations).[43] Varga and colleagues[44] and Ackermann and colleagues[45] reported endotheliitis and widespread vascular damage in post-mortem analyses of several tissues. Subsequent studies showed that endothelial dysfunction is a unifying thread in the multiorgan injury associated with SARS-CoV-2 infection,[46] including excessive inflammation (as a cause or consequence of endothelial activation), extensive

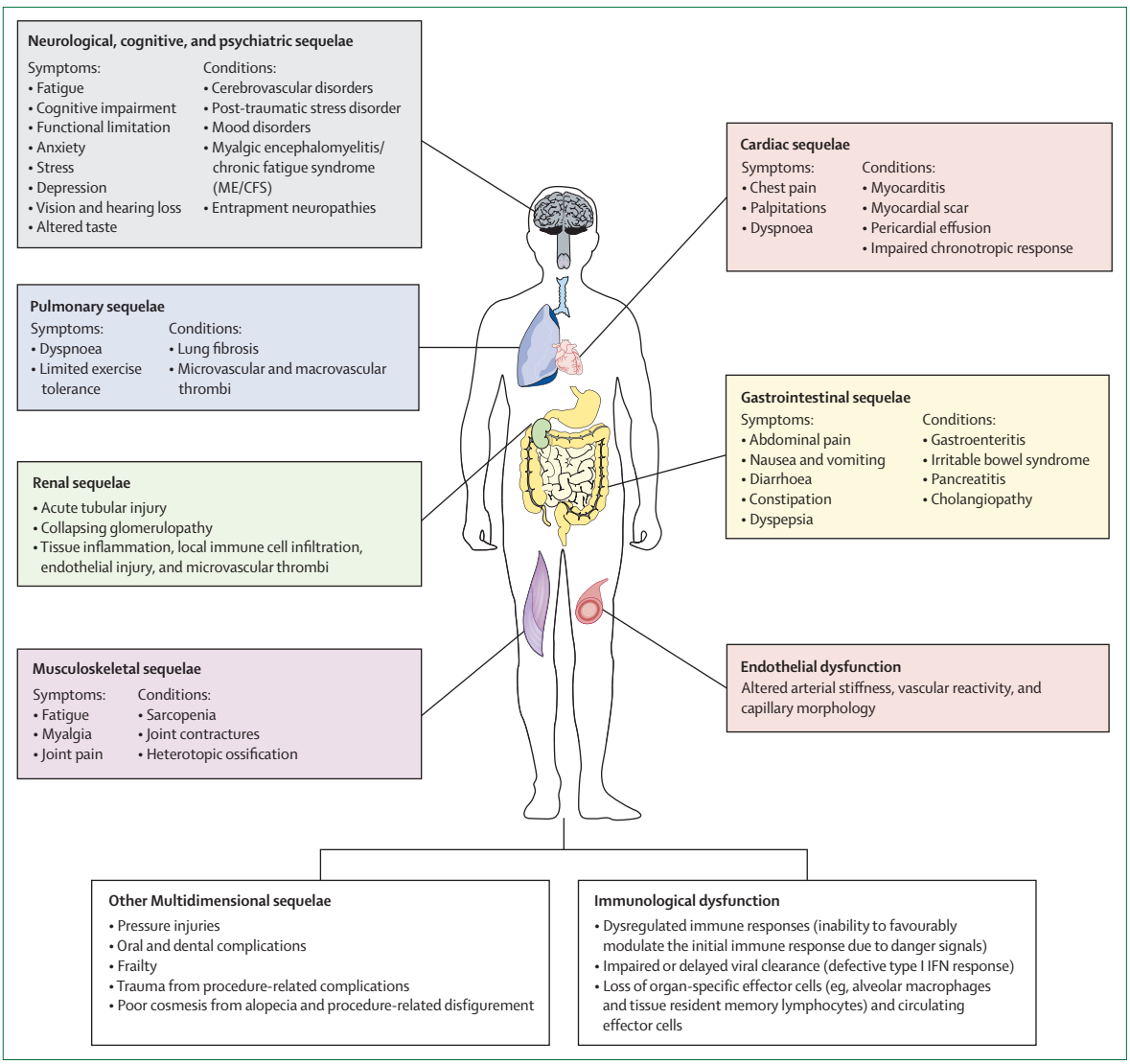

Figure 1: **Multisystem morbidities in survivors of COVID-19-related critical illness**
The post-COVID-19 condition is systemic, with most organ systems in the body potentially affected. Sequelae of COVID-19-related critical illness might overlap with those of non-COVID-19-related critical illness and less severe acute COVID-19.

thrombosis, neutrophil extracellular trap formation, endothelial barrier dysfunction, and oxidative stress.[47–49] Clinically, these pathophysiological changes manifest as a hypercoagulable state in both the venous and arterial macrovascular systems, with pulmonary and extra-pulmonary events such as acute myocardial infarction and ischaemic stroke,[50] venous thromboembolism,[51] superior mesenteric artery thrombosis with acute intestinal ischaemia,[52] intraluminal carotid thrombosis causing stroke,[53] and free-floating aortic thrombi causing limb ischaemia.[54] Multiomics analysis showed persistent upregulation of gene expression signatures related to vascular and clotting pathways several months after infection, elucidating the biological underpinnings of the long-lasting pro-thrombotic state associated with COVID-19.[55] The microvascular system can also be affected. Histopathology of paediatric chilblains (also referred to as COVID toes) has shown SARS-CoV-2 in the cytoplasm of endothelial cells from skin biopsies with lymphocytic vasculitis ranging in severity from endotheliitis to overt thrombosis.[56] Standard therapies for SARS-CoV-2 infection that improve outcomes include heparin in non-critically ill patients[38] and tocilizumab in hospitalised patients with COVID-19 who have hypoxia and systemic inflammation;[57,58] both treatments directly target endothelial dysfunction.

Endothelial dysfunction in COVID-19 survivors

Physiologically, endothelial dysfunction is measured with the well established metric of brachial flow-mediated

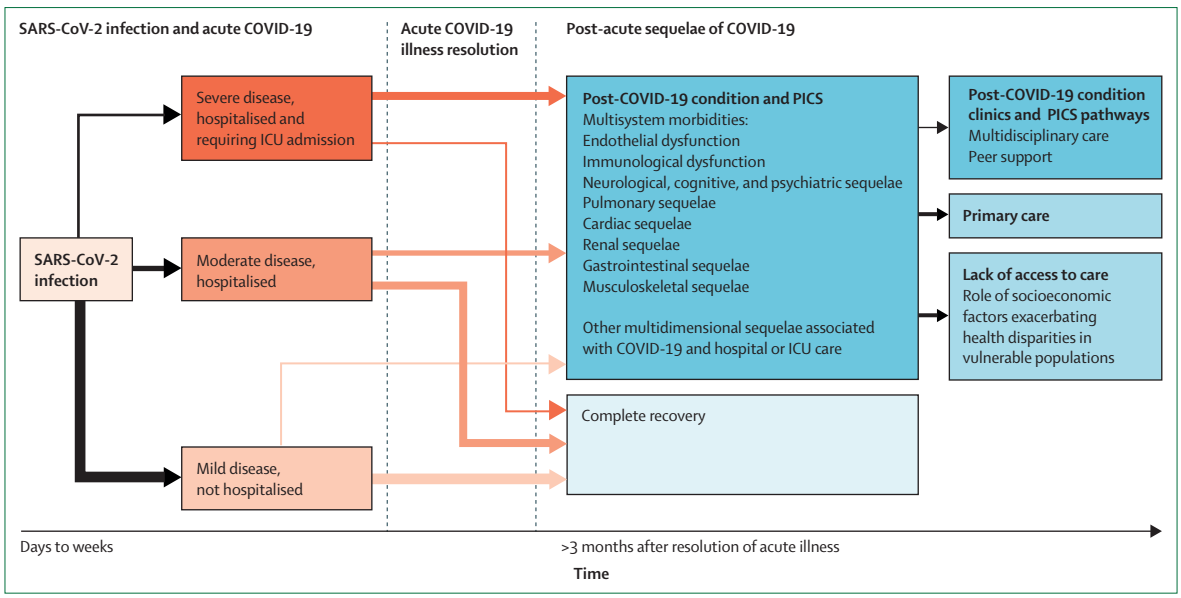

Figure 2: **Potential trajectories for survivors of acute COVID-19**
The differential weights of the arrows are intended to illustrate potential proportions of patients. Further research is needed to better characterise these trajectories and the proportion of patients affected. ICU=intensive care unit. PICS=post-intensive care syndrome.

dilatation. In a study of 400 individuals with SARS-CoV-2 infection, low brachial flow-mediated dilatation predicted worse prognosis (ICU admission or in-hospital death).[59] Survivors of SARS-CoV-2 infection have ongoing endothelial dysfunction, as shown by substantial impairment of brachial flow-mediated dilatation—initially worse in patients in the ICU compared with those on a medical ward—which persists at 1 month and 6 months after discharge.[7] Ongoing endothelial dysfunction (with or without elevated proinflammatory cytokines) might be associated with increased risk of atherosclerosis in the long term,[8] which warrants careful prospective assessment. Clinically, evidence suggests that changes in the endothelium are lasting, with altered arterial stiffness, vascular reactivity, and capillary morphology.[9]

The post-COVID-19 condition encompasses lasting multiorgan effects, with manifestations in the CNS (eg, anosmia and cognitive impairment), respiratory system (eg, breathlessness and poor exercise tolerance), cardiovascular system (eg, arrhythmias), gastrointestinal system (eg, diarrhoea), and musculoskeletal system (eg, ICU-acquired weakness and myalgias), and in the symptoms of depression and fatigue.[60,61] These multisystem effects probably reflect the complex interplay of the dysfunctional endothelium, altered immunity, and the stress response after severe illness. To fully understand the long-term effects of COVID-19, there is an overt need to consider the lasting impact of endothelial dysfunction in the context of ageing, endothelial senescence, brain–endothelium crosstalk, and a cycle of chronic inflammation from lessons already learned from SARS-CoV.[62]

Immune system dysfunction

The profound and protean immunological perturbations in COVID-19-related critical illness are similar to those associated with sepsis-related critical illness and other infectious insults. Post-acute, long-term immunological sequelae are inevitable in survivors of COVID-19-related critical illness. Immunological sequelae contribute to adverse outcomes in survivors of sepsis[63] and other post-infection syndromes;[64] therefore, understanding the acute and post-acute immunological perturbations of COVID-19-related critical illness could inform better follow-up care and lead to better outcomes.

Immunological perturbations reflect a combination of the inability of the host to mount timely, appropriate antimicrobial (antiviral) responses and the inability to favourably modulate the initial immune response due to danger signals (from a pathogen and from tissue damage due to the pathogen), which are key features of sepsis pathobiology[65,66] and COVID-19.[67]

COVID-19-related critical illness is characterised by activation, dysfunction, or depletion of key effector cell subsets from the innate and the adaptive immune systems.[68] Impaired and delayed viral clearance (with detectable serum SARS-CoV-2 viral load, or RNAaemia, as surrogate[69]) from defective type 1 interferon response—often seen in individuals with COVID-19-related critical illness—is associated with emergency myelopoiesis resulting in immature monocytes, neutrophils, and myeloid progenitors in peripheral blood.[69] This myelopoiesis is often associated with loss of organ-specific effector cells (eg, alveolar macrophages and tissue-resident memory lymphocytes) and circulating effector cells (eg, lymphocyte subsets and dendritic

cells).[69] Substantial polyreactive plasmablast expansion also occurs, as indicated by low rates of somatic mutations. Immunopathology is also driven by the presence of antibodies targeting self-antigens (eg, nuclear antigens, phospholipids, T-cell antigens, B-cell antigens, chemokines, and cytokines), functional afucosylated anti-SARS-CoV-2 IgG1 with enhanced affinity for the activation of FcγRIIIa (which generates more inflammation), and cytokine excess.[70–74]

In survivors of sepsis, long-term adverse sequelae associated with immunological perturbations occur either from non-resolution of the dysregulated immune responses in acute illness, with persisting elevated cytokines, or from immune system alterations such as loss of memory lymphocyte subsets, lymphocyte exhaustion markers, and epigenetic changes.[75–78] Emerging literature suggests that similar long-term adverse sequelae occur in survivors of COVID-19-related critical illness, resulting from a combination of, and interaction between, immune dysregulation, microbiota disruption, autoimmunity, and endothelial dysfunction.[23] Studies of post-acute immune responses at the proteomic, cellular, and transcriptomics levels in survivors of COVID-19 support these findings. Long-term sequelae in COVID-19 survivors might include $CD4^+$ T-cell and $CD8^+$ T-cell activation and exhaustion, as indicated by concurrent, increased expression of activation markers (eg, CD69, OX40, HLA-DR, and CD154) and checkpoint molecules (eg, PD-L1 and TIGIT), in addition to B-cell activation and exhaustion, as indicated by elevated expression of CD95, CD69, and PD-1.[79] Patients with symptomatic post-COVID-19 condition had highly activated innate immune cells and elevated type 1 and type 3 interferon for up to 8 months after initial infection.[10] Patients also had reduced lymphocyte subsets.[10,79] Additionally, elevated concentrations of cytokines (eg, interleukin-1β, interleukin-6, TNF, and IP10)[80] and autoantibodies (eg, anti-interferon and anti-nuclear autoantibodies)[80] were associated with symptomatic post-COVID-19 condition.

Given the immunological similarities between critical illness in general and COVID-19, many of the long-term sequelae reported in individuals with critical illness are likely to occur in survivors of COVID-19. Indeed, a systematic review highlighted that about 80% of COVID-19 survivors had one or more post-acute symptoms, with fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnoea (24%) being the most common.[81] These symptoms have similarities to those seen in sepsis survivors[1,23] and ARDS survivors,[82] and are associated with long-term clinical sequelae,[63,75,81] including residual organ dysfunction, new morbidity, re-hospitalisation, and increased long-term risk of death.[83–85]

Neurological, cognitive, and psychiatric sequelae

Neurological, cognitive, and psychiatric sequelae of COVID-19-related critical illness are explored in detail in the second paper in this Series, by Pandharipande and colleagues.[6] These sequelae are common in survivors of COVID-19-related critical illness and overlap with the features of PICS. Compared with controls who did not have COVID-19, survivors of COVID-19-related critical illness are reported to have increased risks of cerebrovascular disorders such as stroke and transient ischaemic attack, as well as diagnosis of neurodegenerative diseases such as Alzheimer's disease, Parkinson's-like disease, and peripheral nervous system changes. Long-term anxiety and depressive and stress disorders are also more frequently reported in hospitalised and non-hospitalised patients with COVID-19, although the risks are higher for hospitalised patients. Myalgic encephalomyelitis/chronic fatigue syndrome—a chronic, multisystem, neuroimmune illness characterised by chronic fatigue, post-exertional malaise, and cognitive impairment—is estimated to affect one in two individuals with post-COVID-19 condition.[6]

Pulmonary sequelae

Pulmonary sequelae are explored in detail in the first paper in this Series, by Singh and colleagues.[5] Breathlessness and limited exercise tolerance are commonly seen after COVID-19. Although extrapulmonary factors (eg, decreased muscle mass and strength) contribute to these symptoms, long-term pulmonary disease might affect a substantial proportion of patients after COVID-19-related critical illness. Persistent radiological abnormalities suggestive of lung fibrosis have been described, and studies are underway to establish their prevalence.[86] Chronic microvascular and macrovascular thrombi could also contribute to long-term pulmonary symptoms.[5]

Cardiac sequelae

In addition to severe respiratory symptoms, cardiovascular manifestations of COVID-19-related critical illness might contribute to high mortality for patients with COVID-19 in the ICU, mainly from arrhythmias, myocarditis, acute heart failure, or thromboembolic complications. Several cardiovascular disease-related factors independently contribute to in-hospital mortality, including myocardial injury,[87] atherosclerotic risk factors,[88] and atrial fibrillation.[89]

Long-term cardiovascular sequelae

In the post-COVID-19 condition, the main cardiovascular symptoms—such as chest pain, palpitations, and dyspnoea—are similar between hospitalised and non-hospitalised individuals.[90] Additionally, some persisting symptoms might be due to progression of pre-existing comorbidities or might be difficult to separate from other organ system dysfunction, such as post-exertional malaise or stress-induced chest pain of non-cardiac origin.

In critically ill patients, multiple cardiovascular risk factors and comorbidities have been identified that contribute to high morbidity and increased rates of hospital re-admission and mortality at long-term

follow-up. In a study by Weber and colleagues,[91] mortality rates for patients with cardiac injury (high-sensitivity cardiac troponin T ≥14 ng/L) were 28·6% during hospitalisation, 32·2% at 6-month follow-up, and 33·2% at 12-month follow-up. By contrast, patients with positive but low concentrations of high-sensitivity cardiac troponin T had mortality rates of 4·1% during hospitalisation, 4·9% at 6-month follow-up, and 4·9% at 12-month follow-up.[91] In a different study, myocardial injury was associated with a 270-day mortality rate of 21·3%.[92]

The long-term cardiovascular sequelae of COVID-19-related critical illness are frequent and complex (table 2). Studies have shown that approximately 5% of patients admitted to hospital with COVID-19 had major adverse cardiac events within a 5-month follow-up,[93] and cardiovascular events affected 14% of patients with COVID-19-related critical illness at 9 months of follow-up.[94] Ventricular (right or left) dysfunction was noted in 3% of patients at 2 months after initial infection,[95] and abnormalities on cardiac MRI were detected in 54% of patients.[96] Myocarditis (12%) and myocardial scars (30%) were also reported,[98,99] and impaired chronotropic response and exercise intolerance have been described.[97]

Xie and colleagues[11] compared the 1-year cardiovascular complications of 153 760 individuals with COVID-19 (5388 of whom were admitted to ICU) with two control cohorts: a contemporary cohort of 5 637 647 individuals with no evidence of SARS-CoV-2 infection and a historical cohort of 5 859 411 individuals whose information predated the COVID-19 pandemic. The authors found a higher risk of incident cardiovascular disease, compared with contemporary controls, in patients with COVID-19 who were admitted to the ICU than in individuals with COVID-19 who were not hospitalised, including major adverse cardiac events (hazard ratio 4·36 [95% CI 3·87–4·91] *vs* 1·26 [1·22–1·30]), cerebrovascular disorders (4·00 [3·19–5·02] *vs* 1·30 [1·22–1·37]), dysrhythmia (7·93 [7·00–8·98] *vs* 1·33 [1·29–1·38]), ischaemic heart disease (5·65 [4·75–6·72] *vs* 1·24 [1·18–1·31]), myocarditis (35·57 [13·56–93·26] *vs* 3·47 [2·25–5·35]), heart failure (6·05 [5·18–7·07] *vs* 1·37 [1·31–1·44]), and thromboembolic disorders (14·51 [12·30–17·13] *vs* 1·74 [1·64–1·84]).[11] Differences in risk between individuals with COVID-19 who were admitted to the ICU and historical controls are shown in table 3.

Pathophysiology of cardiac injury from SARS-CoV-2

SARS-CoV-2 exerts direct and indirect effects on the myocardium and the cardiovascular system.[100] Evidence exists for multiple mechanisms of direct injury. SARS-CoV-2 might be internalised in the cardiomyocyte through direct entry via the angiotensin-converting enzyme 2 (ACE2) receptor. Post-mortem histology studies have shown the presence of interstitial viral particles in myocardial tissue with associated neutrophil and lymphocytic infiltration.[101] Intracellular infection of vascular endothelial cells leads to vasculitis and

	Study type and setting	Participants	Follow-up time	Incidence
Re-hospitalisation, major adverse cardiac events, or death	Retrospective cohort study in NHS hospitals in England, UK[93]	47 780 patients (mean age 65 years, 55% men) hospitalised with COVID-19 until Sept 30, 2020	140 days	Re-hospitalisation 29·4%; major adverse cardiac events 4·8%; death 12·3%
Any cardiovascular event*	Retrospective cohort study of a claims database in the USA[94]	21 069 patients (mean age 54 years, 48% men) admitted to the ICU of 1 357 518 patients diagnosed with COVID-19 between April 1, 2020, and May 31, 2021	9 months	14%
Endothelial dysfunction	Single-centre, prospective cohort study in Greece[8]	27 patients (mean age 68 years, 74% men) admitted to the ICU of 73 patients hospitalised with COVID-19 between Nov 20, 2020, and March 31, 2021	6 months	NR
Right or left ventricular dysfunction	Single-centre, retrospective cohort study in England, UK[95]	29 patients (mean age 64 years, 83% men) hospitalised with COVID-19 until April 30, 2020	1–2 months	3%
At least one MRI-derived cardiac alteration, MRI myocarditis, or MRI myocardial scar	Multicentre, prospective study across six acute hospitals in England, UK[96]	148 patients (mean age 64 years, 70% men) hospitalised with COVID-19 and elevated troponin concentrations, discharged from hospital up until June 20, 2020	2 months	At least one MRI-derived cardiac alteration 54%; MRI myocarditis 8%; MRI myocardial scar 44%
Pericarditis	Single-centre, prospective cohort study in Italy[92]	701 patients (mean age 66 years, 60% men) hospitalised with COVID-19 from March, 2021, to January, 2022	9 months	1·4%
Impaired chronotropic response, exercise intolerance	Single-centre, cross-sectional study within a randomised controlled trial of exercise intervention in survivors of severe COVID-19 in Brazil[97]	35 (mean age 59 years, 63% men) admitted to the ICU with COVID-19	3–6 months	NR

ICU=intensive care unit. NHS=National Health Service. NR=not reported. *First occurrence of dysrhythmia, ischaemic heart disease, thrombotic disorders, cerebrovascular accident (ie, stroke or transient ischemic attack), or other cardiac disorders (eg, heart failure and myocarditis).

Table 2: **Long-term cardiovascular disorders in patients with COVID-19 admitted to the ICU**

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	Hazard ratio (95% CI)
Combined cerebrovascular events	3·9 (3·1–4·89)
Stroke	4·26 (3·31–5·48)
Combined dysrhythmia	7·35 (6·49–8·33)
Atrial fibrillation	7·29 (6·20–8·56)
Combined inflammatory heart disease	10·28 (5·87–17·98)
Myocarditis	58·11 (22·08–152·93)
Combined ischaemic heart disease	5·19 (4·37–6·17)
Myocardial infarction	8·44 (6·82–10·44)
Heart failure	5·56 (4·76–6·50)
Cardiac arrest	30·53 (20·68–45·07)
Cardiogenic shock	18·28 (12·37–27·03)
Combined thrombotic disorders	16·20 (13·72–19·12)
Pulmonary embolism	27·61 (22·10–34·50)
Deep vein thrombosis	9·80 (7·59–12·64)
Major adverse cardiac events	4·51 (4·01–5·08)
Any cardiovascular outcome	6·00 (5·44–6·63)

Hazard ratios of 5388 patients admitted to the ICU in the acute phase of COVID-19 who survived the first 30 days of COVID-19, compared with a historical cohort (predating the COVID-19 pandemic) consisting of 5 859 411 non-SARS-CoV-2-infected users of the US Veterans Health Administration system, 2017.[11] ICU=intensive care unit.

Table 3: **12-month disease burden in ICU-treated patients compared with historical controls**

endotheliopathy. Matrix remodelling of the myocardial tissue might lead to electromechanical dissociation and conduction abnormalities; local vascular thromboembolism, coagulopathy, and development of neutrophil extracellular traps have also been observed.[101]

In addition to direct effects, the cardiovascular system could be injured indirectly through many mechanisms: systemic inflammation, cytokine storm, and disseminated intravascular coagulopathy resulting from sepsis; systemic hypoxaemia due to ARDS; organ crosstalk from viral interaction with ACE2 receptors in other organs and systems (eg, in the gastrointestinal tract, affecting the gut–heart axis, with alterations of the gut microbiome potentially contributing to cardiovascular disease,[102] or through viral cerebral invasion, affecting the brain–heart axis by causing autonomic imbalance, alterations in the neural cardiovascular control, or other effects);[103] and activation of chronic inflammatory processes such as rheumatic disorders.

Several other immune factors have been associated with development of the cardiovascular post-COVID-19 syndrome,[104] despite limited understanding of the exact mechanism. These observed cellular and molecular contributors involve cellular pathomechanisms—including diverse immune cells (B cells, T cells, monocytes, and mastocytes), circulating endothelial cells, persistent autoantibodies, and autoantigens—protracted immunosuppression by latent reactivation of different viruses, and molecular pathomechanisms including mitochondrial dysfunction.[104]

Renal sequelae

Acute kidney injury (AKI) and renal dysfunction are common complications of COVID-19, associated with increased mortality, especially when renal replacement therapy is required.[105,106] Up to a third of inpatients and 46–77% of patients with COVID-19-related critical illness in the ICU develop AKI, although this incidence might have declined after the first wave of the pandemic.[107,108] According to the report of the Acute Disease Quality Initiative working group, 20% of hospitalised patients with COVID-19 and more than 50% of critically ill patients develop AKI.[109] Large observational studies and meta-analyses report an incidence of 28–34% in all inpatients and 46–77% among patients in the ICU.[107]

Long-term sequelae of renal dysfunction

The association of AKI with post-acute kidney function among COVID-19 survivors has been noted. In a study looking at the association between AKI and 1-year outcome of renal function in survivors who were hospitalised with COVID-19, development of AKI during the acute phase of COVID-19 was closely related to a longitudinal decline in kidney function even 1 year after the onset of symptoms.[12] Progressive decline in renal function leading to chronic kidney disease in individuals with COVID-19 is probably due to multiple factors, including ongoing inflammation, kidney fibrosis, tubular injury, or maladaptive repair, among other pathways. In a study describing outcomes of patients with AKI after ICU discharge, stage progression of chronic kidney disease was associated with AKI lasting longer than 7 days and with more severe AKI (Kidney Disease Improving Global Outcomes stage 3), although it was not associated with baseline renal function.[110] Stockmann and colleagues[111] described the outcomes of 74 patients admitted to the ICU who developed severe AKI and required renal replacement therapy. After a median follow-up of 5 months, three surviving patients (8%) of 37 patients who survived to hospital discharge were dialysis-dependent, whereas the remaining 34 (92%) patients had variable degrees of renal recovery, including 23 (62%) with full renal recovery.[111] New kidney-specific plasma and urine biomarkers (eg, MCP-1 [also known as CCL2], uromodulin, and YKL-40 [also known as CHI3L1]) might help to identify underlying aetiologies and patients at high risk of chronic kidney disease after COVID-19 hospitalisation.[112] Earlier and more intense patient surveillance for kidney function might be beneficial in COVID-19 survivors.

Pathophysiology of renal injury from SARS-CoV-2

Histopathological findings have highlighted both similarities and differences in AKI between patients with COVID-19-related and those with non-COVID-19-related sepsis.[113] A high incidence of thrombi and intravascular coagulation in individuals with COVID-19 has been reported as one striking difference.[114] Tissue

inflammation, local immune cell infiltration, endothelial injury, and microvascular thrombi are common in COVID-19 and might have an important role in AKI.[113] Acute tubular injury appears to be most common in patients with COVID-19 and AKI. Analyses of post-mortem kidney samples from patients with stage 2 or 3 AKI and COVID-19 have shown acute tubular injury characterised by mild, focal, acute tubular necrosis, despite severely altered kidney function.[115,116] Collapsing glomerulopathy, described as COVID-19-associated nephropathy—occurring mostly in people without severe respiratory symptoms of COVID-19 and isolated AKI—has also been reported.[117] An impaired type 1 interferon response has also been noted in patients with severe COVID-19 and AKI.[113]

Musculoskeletal sequelae

Musculoskeletal symptoms are among the most prevalent and persistent symptoms in people with post-COVID-19 condition. Joint stiffness, joint pain, and myalgia are frequently reported and usually associated with an impact on activities of daily living.[14] Additionally, musculoskeletal symptoms might be the most clinically significant manifestation of the post-COVID-19 condition for patients and their caregivers because they limit physical and functional performance and impede return to work.

Long-term musculoskeletal sequelae

In the longitudinal cohort study describing health outcomes 2 years after hospitalisation with COVID-19 in Wuhan, China, muscle weakness or fatigue were the most common sequelae, affecting 30% of survivors.[13] Among 246 ICU survivors in the Netherlands, four musculoskeletal conditions (joint stiffness, joint pain, muscle weakness, and myalgia) were among the five most common new physical problems at 1 year after infection, with an incidence ranging from 21·3% to 26·3%.[14] Among 280 survivors who were hospitalised with acute COVID-19 in Mexico (168 [60%] of whom required invasive mechanical ventilation for an average of 15 days), musculoskeletal conditions were present in 94 (34%) patients, with fatigue being the most common symptom (41%), followed by paraesthesia and neuralgia (26%), myalgia (21%), and joint pain (12%) up to 6 months after hospital discharge.[118] Neuromuscular involvement was more common among patients who had received invasive mechanical ventilation, even after adjustment for confounding factors (adjusted odds ratio [OR] 1·95 [95% CI 1·06–3·59]).[118] In a cohort of 1864 survivors of hospitalisation with COVID-19 in China, fatigue was still the most frequent symptom at the 2-year follow-up, as both a persistent and a new-onset symptom, with a prevalence of 10·3%.[119]

Pain of musculoskeletal origin was another commonly reported symptom after COVID-19-related critical illness. In a systematic review of 33 studies, the prevalence of myalgia in hospitalised patients was 22% (95% CI 9–44; seven studies) at 90 days of follow-up and 10% (4–22; seven studies) at 180 or more days of follow-up, compared with 14% (8–24; five studies) and 12% (8–20; seven studies) in individuals who were not hospitalised.[120] The prevalence of joint pain in hospitalised patients was 11% (2–22; three studies) at 90 days of follow-up and 8% (2–31; three studies) at 180 or more days of follow-up, compared with 13% (9–19; four studies) and 7% (1–30; four studies) in non-hospitalised individuals with COVID-19.[120] Although the direct comparison between hospitalised and non-hospitalised individuals is not straightforward because of differences in age, comorbidities, and other factors, the higher prevalence of pain of musculoskeletal origin in hospitalised patients seems to occur mainly within the first months of follow-up. Impairment in bone mass and arthralgia have also been described.[121]

Pathophysiology of musculoskeletal injury from SARS-CoV-2

The pathophysiology of musculoskeletal impairment after COVID-19-related critical illness is multifactorial and still not completely understood. Direct cellular injury due to SARS-CoV-2, the proinflammatory response, and oxidative stress—coupled with potential autoimmunity and microthrombi—are the main mechanisms invoked in musculoskeletal dysfunction.[122] Mitochondrial damage, immobility, and hypoxaemia, particularly leading to sarcopenia, are other purported mechanisms.[123] There are some shared mechanisms for critical illness myopathy between individuals with post-COVID-19 condition and those with non-COVID-19 ARDS. However, unique features have been noted in COVID-19 survivors, including viral infiltration and reduced recovery of muscle function.[122] These differences could explain, in part, the accentuated symptoms of muscle weakness and exercise intolerance observed in individuals with post-COVID-19 condition, including in those with mild acute infection.[122]

Gastrointestinal sequelae

Gastrointestinal manifestations are common during acute SARS-CoV-2 infection, affecting up to 50% of patients, including those with mild initial disease and those who develop critical illness.[124] These manifestations include gastroenteritis, pancreatitis, increased concentrations of liver enzymes, long-lasting and severe cholestasis (described as post-COVID-19 cholangiopathy), and malnutrition.[15,124,125] Symptoms such as abdominal pain, nausea and vomiting, and diarrhoea are frequently reported[15] and resolve within 3–6 months after the original infection in approximately 90% of individuals, although malnutrition remains prevalent and is probably multifactorial.[124] New-onset constipation, irritable bowel syndrome, and dyspepsia have been described in individuals with post-COVID-19 condition.[15,16]

Similar to the effects observed in other systems, gastrointestinal manifestations in individuals with

post-COVID-19 condition might be related to direct viral toxicity, endothelial damage, and persistent inflammation.[126] Viral antigen persistence has been observed for months after initial infection in the gastrointestinal system, and faecal viral shedding has been described for longer periods of time than oropharyngeal shedding.[127] Additionally, alterations of the gut microbiome (dysbiosis) are present and persist for months after infection, promoting continued inflammation and potential invasion by opportunistic microorganisms.[128]

Multidimensional sequelae of critical illness

Survivors of COVID-19-related critical illness might share many of the multidimensional consequences of critical illness with survivors of ARDS, sepsis, and chronic critical illness, including muscle injury, impaired cognition and mood disorders, and pulmonary sequelae, as described previously and in the first and second papers in this Series.[5,6] Shared sequelae of critical illness also encompass pressure injuries, oral and dental complications, frailty, vision and hearing loss, ageusia or dysgeusia, trauma from procedure-related complications, joint contractures, heterotopic ossification, entrapment neuropathies, and poor cosmesis from alopecia and procedure-related disfigurement.[35]

In a systematic review of hospital-acquired pressure injuries in patients with COVID-19, risk factors included male sex, prolonged hospitalisation, absence of a wound care team, and prone positioning.[129] The ubiquity of prone positioning in the management of COVID-19 has highlighted how injurious this intervention can be in terms of facial pressure injury and neuropraxia, most commonly involving the brachial plexus.[130]

Oral health is central to overall health status. The Canadian-led CHORAL study established the importance of oral hygiene in critically ill patients and linked the implementation of an oral care bundle to improved oral health outcomes.[131] In a different study, poor oral health status was prevalent in individuals with COVID-19 and was an important risk factor for COVID-19-related critical illness and death.[132]

Frailty is both a risk factor for severe COVID-19 and an important patient-centred outcome measure after COVID-19-related critical illness.[133] In a Brazilian study, newly acquired frailty was noted in 31% of patients at 90 days after hospital discharge, and the number of disabilities (eg, decreased mobility and need for help from others in activities of daily living such as bathing and dressing) also increased compared with estimates of baseline condition 2–4 weeks before COVID-19, occurring mainly in those who were not frail before their COVID-19 illness.[134]

Prioritisation of reports of cosmetic concerns are gaining momentum as their impact on health, wellness, and global quality of life are validated. These aforementioned, multidimensional outcomes are increasingly included as part of large, granular follow-up studies.[29] A precise understanding of the wide range of multidimensional sequelae of COVID-19-related critical illness would help to identify potential preventive measures, inform decision making aligned with patient and family values, and plan specific care needs, allowing appropriate access to care and resource allocation.

Vulnerability to perioperative complications

Many individuals require surgery each year, with estimates of more than 300 million procedures performed each year worldwide,[135] and an average of more than nine surgeries over a lifetime for individuals living in high-income countries.[136] The COVID-19 pandemic has affected the care of these individuals, partly because of disruption to health-care systems due to the large number of hospital admissions and the related decrease in scheduled surgeries. Patients with COVID-19 who require surgery have an increased risk of perioperative morbidity, critical illness, and mortality. This risk persists for some time after recovery, with pathophysiological mechanisms not yet fully elucidated.

Large, prospective international datasets have found that, in patients with a preoperative COVID-19 diagnosis, perioperative mortality was significantly increased compared with baseline risk (ie, without COVID-19) when surgery occurred within 0–2 weeks (OR 4·1 [95% CI 3·3–4·8]), 3–4 weeks (3·9 [2·6–5·1]), and 5–6 weeks (3·6 [2·0–5·2]) of the diagnosis.[137] The mortality risk returned to baseline levels for patients whose surgery occurred 7 weeks or more after a COVID-19 diagnosis (OR 1·5 [95% CI 0·9–2·1]).[137] However, higher mortality was noted for individuals who continued to have symptoms and underwent surgery more than 7 weeks after a COVID-19 diagnosis (6·0% [95% CI 3·2–8·7]) than for those whose symptoms had resolved (2·4% [1·4–3·4]) or who had been asymptomatic (1·3% [0·6–2·0]).[137] Furthermore, individuals with SARS-CoV-2 infection were found to be at increased risk of postoperative pulmonary complications, venous thromboembolism, cardiac arrest, and AKI compared with individuals with no history of infection.[138,139]

In consideration of these findings, several international scientific societies have issued recommendations to postpone elective surgeries to more than 7–8 weeks after SARS-CoV-2 infection, and to consider a longer wait period if symptoms persist.[140] Some data on low-risk surgeries suggest that previous vaccination might confer some protection; however, more data are needed.[141] The impact of different virus variants remains unclear too. A revised multidisciplinary consensus statement on behalf of the Association of Anaesthetists, the Federation of Surgical Specialty Associations, the Royal College of Anaesthetists, and the Royal College of Surgeons of England was recently released.[142] The new recommendations advise that after 2 weeks and up to 7 weeks after SARS-CoV-2 infection, surgery can proceed if the patient and surgery are deemed to be low risk. The

increased vulnerability to perioperative complications as a long-lingering consequence of COVID-19 is not completely understood and, at present, no preventive or specific treatment measures have been identified. Such vulnerability could have an adverse impact—in particular, in patients whose conditions require urgent and emergent surgery, or in those not considered to be at low risk. In such circumstances, risk–benefit assessments should be made on a case-by-case basis.[141,142]

Family caregivers

There is a robust literature on family outcomes after critical illness that has accrued in the past 25 years. Family and loved ones have a challenging parallel experience during critical illness, which is also injurious and associated with long-term mood disorders including anxiety, depressive symptoms, post-traumatic stress disorder, suicidality, and substance misuse.[35] The COVID-19 pandemic has similarly shown the burden on family and the effect that the absence of family at the bedside has had on patients during their ICU stay.

In their study of the lived experiences of families of patients with severe COVID-19 who died in the ICU, Kentish-Barnes and colleagues[143] highlighted families' inability to build a relationship with the ICU team and the sense of powerlessness, abandonment, and unreality as they experienced complete disruption of their relationship with their loved one. They also described the "stolen moments"[143] resulting from disruption of end-of-life practices.

Families of patients with COVID-19-related ARDS were found to be at increased risk of post-traumatic stress disorder (prevalence 35%) compared with those of patients with non-COVID-19 ARDS (19%).[144] In a multivariable analysis, COVID-19 ARDS was an independent risk factor for post-traumatic stress disorder.[144] De-adoption of the ABCDEF (A2F) bundle and best practice during the COVID-19 pandemic also contributed to adverse clinical outcomes for patients.[145] Absence of family presence at the ICU bedside resulted in an increased risk of delirium and a cascade of longer-term deleterious consequences for patients.[146] The Canadian COVID-19 Prospective Cohort Study (CANCOV) is a platform observational study that will provide a comprehensive evaluation of early to 2-year outcomes in patients with COVID-19 and their family caregivers.

Provision of therapeutic and rehabilitative care and support

Providing clinical care and support for people with multisystem manifestations of the post-COVID-19 condition, including those recovering from critical illness (figure 2), presents several challenges. Many individuals will present to primary care providers with a range of symptoms. Apart from the novelty of the condition and incomplete understanding of pathogenesis and natural history, the multisystem involvement in post-COVID-19 condition—and its heterogeneous nature, non-specific symptoms, and the lack of clear diagnostics—could leave clinicians at a loss.[147] Approaches to the management of common and potentially modifiable symptoms have been suggested, including acknowledging the patient's experience—"Say it out loud. They need to hear it"[147]—and understanding the impact of their symptoms on daily living; addressing fatigue with tailored, structured activity and energy conservation strategies; using interventions for mental health complications informed by guidelines; providing comprehensive sleep counselling for people with sleep disturbances; and using specific existing guidelines for the treatment of palpitations and tachycardia with particular causes.[148] Survivors of COVID-19-related critical illness are also at risk of PICS. The complexity of treating such conditions in ambulatory care requires coordinated efforts, and approaches to the design of multidisciplinary clinics for post-COVID-19 care after severe disease have been described.[149,150] Socioeconomic factors probably have a substantial role in access to care for post-COVID-19 condition, and could further exacerbate health disparities in vulnerable populations, underserved communities, and populations in low-income and middle-income countries. Peer support, applicable in various settings and models, might also be a valuable tool in post-COVID-19 condition, and experiences in PICS could help to inform this approach.[151] The physical and mental health needs of family members should also be considered, and the involvement of primary care providers might be fundamental in this regard.

Conclusions and future directions

The COVID-19 pandemic has shown the consequences of a dysregulated endothelium, an exuberant inflammatory response, and an altered immune system in the acute setting, with nearly 7 million deaths globally as of June 30, 2023. Importantly, in COVID-19 survivors, residual dysfunction of the endothelium and the immune system continues, with a complex interplay that manifests in many of the multisystem sequelae that we describe in this Series paper. As every organ system is reliant on homoeostasis of the endothelium and appropriate immune responses, it is perhaps unsurprising that multisystem dysfunction ensues for many individuals. COVID-19 survivors are a large proportion of the global population, and timely discussion of the data available is needed to address the burden of post-acute sequelae, acknowledging that much remains to be learnt about the biological and clinical consequences of COVID-19.

The post-COVID-19 condition is systemic, affecting various organ systems. It results in increased use of health-care resources, decreased quality of life, and increased susceptibility to subsequent viral or bacterial infection, and leads to heightened vulnerability to perioperative morbidity and mortality for individuals who require a surgical procedure for any (unrelated)

For **WHO's up-to-date COVID-19 dashboard** see https://covid19.who.int/

For more on **CANCOV** see https://cancov.net/

Panel: Future developments to support individuals with post-COVID-19 condition after critical illness

- The complex, multisystem nature of post-COVID-19 condition requires a coordinated, multidisciplinary approach to care and support; dedicated clinics have been proposed to care for patients with the condition and models of care (informed by experiences with PICS) have been described
- Identifying patients with post-acute sequelae of COVID-19 who are in need of care might be challenging; multidisciplinary health professionals, including primary care providers, will have an important role in the screening, complex diagnosis, and referral to specialised care (including dedicated clinics, where available) when required; rapid dissemination of research findings and targeted, broad educational initiatives will be fundamental to ensuring accurate identification of affected individuals
- Post-COVID-19 condition or PICS clinics could provide a platform for high-quality research; multi-institutional networks with shared, standardised definitions and metrics could help to drive progress in understanding and addressing the post-acute sequelae of COVID-19
- Research priorities include understanding of the causes and risk factors, pathophysiological mechanisms, trajectories and relationships of individual sequelae, and natural history of the condition; identification and validation of diagnostic, prognostic, and theranostic biomarkers; and development of preventive and therapeutic interventions and models of care
- Research should aim to identify vulnerable populations and the needs of people in LMICs; studies should be inclusive of vulnerable individuals, underserved communities, and LMIC populations to reflect and respond to the global burden of post-COVID-19 condition

LMICs=low-income and middle-income countries. PICS=post-intensive care syndrome.

Search strategy and selection criteria

We searched PubMed for articles published in English from March 1, 2020, to April 30, 2023, using the terms "COVID", "SARS-CoV-2", "critically ill", "long term outcomes", "long COVID", and "post COVID-19 condition". We also identified relevant articles through searches in the authors' personal files, in Google Scholar, and from the reference lists of selected papers, including articles published before 2020.

indication. With a large and growing global population of survivors of COVID-19, the impact on individuals, health-care systems, communities, and society is likely to be substantial.

The post-COVID-19 condition might be explained partly by pathophysiological changes related to virus-specific effects, immunological and inflammatory dysregulation damage in response to the acute infection, and expected sequelae of post-critical illness. However, understanding of causes and risk factors, underlying pathophysiological mechanisms, and the course of biological and clinical features of post-COVID-19 condition remains incomplete and continues to evolve. Better characterisation of the specific consequences of SARS-CoV-2 infection and COVID-19 versus the effects of critical illness per se is needed (panel). Many survivors of COVID-19-related critical illness have persistent weakness, which is probably related to ICU-acquired weakness from severe illness, immobility, paralytics, or deep coma. A central issue to elucidate is the way in which reported symptoms relate to organ dysfunction or chronic disease in the post-acute phase.

Identifying steps that can be taken during the acute phase of COVID-19 to prevent or reduce the range and severity of post-acute sequelae—based on an understanding of causes, risk factors, aetiology and pathophysiology—is a priority for clinicians, researchers, patients, and other stakeholders. At present, there are no specific treatments for post-COVID-19-condition. Health-care teams should assess for potentially modifiable symptoms and consider treatments for similar conditions in individuals without COVID-19 that might offer benefit in this population.[148,152] Progress in understanding of aetiology and pathophysiology will provide a foundation for the development of specific, targeted treatments for the post-acute sequelae of COVID-19.

Socioeconomic factors are fundamental determinants of health after COVID-19. Individuals from low-income and middle-income countries, those from marginalised communities, and those who are socially disadvantaged are probably disproportionately affected; however, these groups are systematically under-represented in research studies owing to several contributing factors (insufficient local resources, compromised access to health care, poor education, poor health advocacy and literacy, institutional racism, and poverty),[153] which limits understanding of intersectionality in COVID-19 and leaves an important global health knowledge gap to fill (panel).[154]

Overall, the burden of post-COVID-19 condition has important individual, health-care system, and socioeconomic implications on an unprecedented scale. A substantial proportion of survivors of COVID-19-related critical illness are affected by multisystem involvement, with a degree of overlap with PICS. Further research will help to characterise the nature of and risk factors for post-COVID-19 condition, to develop potential preventive and therapeutic treatments and models of care and support, and to address the needs of vulnerable populations and patients in low-income and middle-income countries.

Contributors

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Declaration of interests
We declare no competing interests.

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References

1 Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021; **398:** 747–58.
2 WHO. A clinical case definition of post COVID-19 condition by a Delphi consensus. Oct 6, 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 (accessed March 3, 2023).
3 Munblit D, Nicholson T, Akrami A, et al. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. *Lancet Respir Med* 2022; **10:** 715–24.
4 Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis* 2022; **22:** e102–07.
5 Singh SJ, Baldwin MM, Daynes E, et a. Respiratory sequelae of COVID-19: pulmonary and extrapulmonary origins, and approaches to clinical care and rehabilitation. *Lancet Respir Med* 2023; published online May 19. https://doi.org/10.1016/S2213-2600(23)00159-5.
6 Pandharipande P, Williams Roberson S, Harrison FE, Wilson JE, Bastarache JA, Ely EW. Mitigating neurological, cognitive, and psychiatric sequelae of COVID-19-related critical illness. *Lancet Respir Med* 2023; published online July 17. https://doi.org/10.1016/S2213-2600(23)00238-2.
7 Bianconi V, Mannarino MR, Figorilli F, et al. Low brachial artery flow-mediated dilation predicts worse prognosis in hospitalized patients with COVID-19. *J Clin Med* 2021; **10:** 5456.
8 Oikonomou E, Souvaliotis N, Lampsas S, et al. Endothelial dysfunction in acute and long standing COVID-19: a prospective cohort study. *Vascul Pharmacol* 2022; **144:** 106975.
9 Gao YP, Zhou W, Huang PN, et al. Persistent endothelial dysfunction in coronavirus disease-2019 survivors late after recovery. *Front Med (Lausanne)* 2022; **9:** 809033.
10 Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol* 2022; **23:** 210–16.
11 Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022; **28:** 583–90.
12 Gu X, Huang L, Cui D, et al. Association of acute kidney injury with 1-year outcome of kidney function in hospital survivors with COVID-19: a cohort study. *EBioMedicine* 2022; **76:** 103817.
13 Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med* 2022; **10:** 863–76.
14 Heesakkers H, van der Hoeven JG, Corsten S, et al. Clinical outcomes among patients with 1-year survival following intensive care unit treatment for COVID-19. *JAMA* 2022; **327:** 559–65.
15 Rizvi A, Ziv Y, Crawford JM, Trindade AJ. Gastrointestinal and hepatobiliary symptoms and disorders with long (chronic) COVID infection. *Gastroenterol Clin North Am* 2023; **52:** 139–56.
16 Blackett JW, Wainberg M, Elkind MSV, Freedberg DE. Potential long coronavirus disease 2019 gastrointestinal symptoms 6 months after coronavirus infection are associated with mental health symptoms. *Gastroenterology* 2022; **162:** 648–50.
17 Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 2005; **60:** 401–09.
18 Tansey CM, Louie M, Loeb M, et al. One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome. *Arch Intern Med* 2007; **167:** 1312–20.
19 Lam MH-B, Wing Y-K, Yu MW-M, et al. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. *Arch Intern Med* 2009; **169:** 2142–47.
20 Ahmed H, Patel K, Greenwood DC, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. *J Rehabil Med* 2020; **52:** jrm00063.
21 Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med* 2021; **27:** 601–15.
22 Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet* 2022; **400:** 452–61.
23 Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023; **21:** 133–46.
24 Bull-Otterson L, Baca S, Saydah S, et al. Post-COVID conditions among adult COVID-19 survivors aged 18–64 and ≥65 years—United States, March 2020–November 2021. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 713–17.
25 Government of Canada. Frequency and impact of longer-term symptoms following COVID-19 in Canadian adults. 2022. https://health-infobase.canada.ca/covid-19/post-covid-condition/fall-2022-report.html (accessed March 3, 2023).
26 Dennis A, Wamil M, Alberts J, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* 2021; **11:** e048391.
27 Hodgson CL, Higgins AM, Bailey MJ, et al. Comparison of 6-month outcomes of survivors of COVID-19 versus non-COVID-19 critical illness. *Am J Respir Crit Care Med* 2022; **205:** 1159–68.
28 Hastie CE, Lowe DJ, McAuley A, et al. Outcomes among confirmed cases and a matched comparison group in the Long-COVID in Scotland study. *Nat Commun* 2022; **13:** 5663.
29 Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med* 2021; **9:** 1275–87.
30 Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364:** 1293–304.
31 Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010; **304:** 1787–94.
32 Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. *Am J Respir Crit Care Med* 2010; **182:** 446–54.
33 Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012; **40:** 502–09.
34 Rousseau A-F, Prescott HC, Brett SJ, et al. Long-term outcomes after critical illness: recent insights. *Crit Care* 2021; **25:** 108.
35 Herridge MS, Azoulay É. Outcomes after critical illness. *N Engl J Med* 2023; **388:** 913–24.
36 Quinn KL, Razak F, Cheung AM. Diagnosing post-COVID-19 condition (long COVID) in adults. *CMAJ* 2023; **195:** E78–79.
37 Jung A-S, Haldane V, Neill R, et al. From dichotomisation towards intersectionality in addressing COVID-19. *BMJ* 2021; **375:** e067500.
38 Gimbrone MA Jr, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res* 2016; **118:** 620–36.
39 Cahill PA, Redmond EM. Vascular endothelium—gatekeeper of vessel health. *Atherosclerosis* 2016; **248:** 97–109.

40 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395:** 1054–62.

41 Gustafson D, Raju S, Wu R, et al. Overcoming barriers: the endothelium as a linchpin of coronavirus disease 2019 pathogenesis? *Arterioscler Thromb Vasc Biol* 2020; **40:** 1818–29.

42 Teuwen L-A, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol* 2020; **20:** 389–91.

43 Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol* 2020; **7:** e575–82.

44 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395:** 1417–18.

45 Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med* 2020; **383:** 120–28.

46 Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J* 2020; **41:** 3038–44.

47 Montiel V, Lobysheva I, Gérard L, et al. Oxidative stress-induced endothelial dysfunction and decreased vascular nitric oxide in COVID-19 patients. *EBioMedicine* 2022; **77:** 103893.

48 Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol* 2021; **17:** 46–64.

49 Zuo Y, Zuo M, Yalavarthi S, et al. Neutrophil extracellular traps and thrombosis in COVID-19. *J Thromb Thrombolysis* 2021; **51:** 446–53.

50 Modin D, Claggett B, Sindet-Pedersen C, et al. Acute COVID-19 and the incidence of ischemic stroke and acute myocardial infarction. *Circulation* 2020; **142:** 2080–82.

51 Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. *Semin Thromb Hemost* 2020; **46:** 763–71.

52 Cheung S, Quiwa JC, Pillai A, Onwu C, Tharayil ZJ, Gupta R. Superior mesenteric artery thrombosis and acute intestinal ischemia as a consequence of COVID-19 infection. *Am J Case Rep* 2020; **21:** e925753.

53 Hamouda D, Jillella DV, Bhatt N, Koneru S, Frankel MR, Nogueira RG. Intraluminal carotid thrombosis and acute ischemic stroke associated with COVID-19. *J Neurol* 2021; **268:** 4443–47.

54 Kashi M, Jacquin A, Dakhil B, et al. Severe arterial thrombosis associated with COVID-19 infection. *Thromb Res* 2020; **192:** 75–77.

55 Gisby JS, Buang NB, Papadaki A, et al. Multi-omics identify falling LRRC15 as a COVID-19 severity marker and persistent pro-thrombotic signals in convalescence. *Nat Commun* 2022; **13:** 7775.

56 Colmenero I, Santonja C, Alonso-Riaño M, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. *Br J Dermatol* 2020; **183:** 729–37.

57 The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. *N Engl J Med* 2021; **385:** 790–802.

58 RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 1637–45.

59 Writing Committee for the REMAP-CAP Investigators. Long-term (180-Day) outcomes in critically ill patients with COVID-19 in the REMAP-CAP randomized clinical trial. *JAMA* 2023; **329:** 39–51.

60 Jud P, Gressenberger P, Muster V, et al. Evaluation of endothelial dysfunction and inflammatory vasculopathy after SARS-CoV-2 infection—a cross-sectional study. *Front Cardiovasc Med* 2021; **8:** 750887.

61 Crook H, Raza S, Nowell J, Young M, Edison P. Long COVID—mechanisms, risk factors, and management. *BMJ* 2021; **374:** n1648.

62 Wang C, Yu C, Jing H, et al. Long COVID: the nature of thrombotic sequelae determines the necessity of early anticoagulation. *Front Cell Infect Microbiol* 2022; **12:** 861703.

63 Higgins V, Sohaei D, Diamandis EP, Prassas I. COVID-19: from an acute to chronic disease? Potential long-term health consequences. *Crit Rev Clin Lab Sci* 2021; **58:** 297–310.

64 Prescott HC, Angus DC. Enhancing recovery from sepsis: a review. *JAMA* 2018; **319:** 62–75.

65 Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. *Nat Med* 2022; **28:** 911–23.

66 van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis. *Immunity* 2021; **54:** 2450–64.

67 Bauer M, Shankar-Hari M, Thomas-Rüddel DO, Wetzker R. Towards an ecological definition of sepsis: a viewpoint. *Intensive Care Med Exp* 2021; **9:** 63.

68 Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med* 2021; **9:** 622–42.

69 Merad M, Blish CA, Sallusto F, Iwasaki A. The immunology and immunopathology of COVID-19. *Science* 2022; **375:** 1122–27.

70 Gutmann C, Takov K, Burnap SA, et al. SARS-CoV-2 RNAemia and proteomic trajectories inform prognostication in COVID-19 patients admitted to intensive care. *Nat Commun* 2021; **12:** 3406.

71 Lucas C, Wong P, Klein J, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020; **584:** 463–69.

72 Park A, Iwasaki A. Type I and type III interferons—induction, signaling, evasion, and application to combat COVID-19. *Cell Host Microbe* 2020; **27:** 870–78.

73 Fish M, Rynne J, Jennings A, et al. Coronavirus disease 2019 subphenotypes and differential treatment response to convalescent plasma in critically ill adults: secondary analyses of a randomized clinical trial. *Intensive Care Med* 2022; **48:** 1525–38.

74 Mathew D, Giles JR, Baxter AE, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science* 2020; **369:** eabc8511.

75 Kuri-Cervantes L, Pampena MB, Meng W, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. *Sci Immunol* 2020; **5:** eabd7114.

76 Shankar-Hari M, Rubenfeld GD. Understanding long-term outcomes following sepsis: implications and challenges. *Curr Infect Dis Rep* 2016; **18:** 37.

77 Yende S, Kellum JA, Talisa VB, et al. Long-term host immune response trajectories among hospitalized patients with sepsis. *JAMA Netw Open* 2019; **2:** e198686.

78 Arens C, Bajwa SA, Koch C, et al. Sepsis-induced long-term immune paralysis—results of a descriptive, explorative study. *Crit Care* 2016; **20:** 93.

79 Files JK, Boppana S, Perez MD, et al. Sustained cellular immune dysregulation in individuals recovering from SARS-CoV-2 infection. *J Clin Invest* 2021; **131:** e140491.

80 Glynne P, Tahmasebi N, Gant V, Gupta R. Long COVID following mild SARS-CoV-2 infection: characteristic T cell alterations and response to antihistamines. *J Investig Med* 2022; **70:** 61–67.

81 Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021; **11:** 16144.

82 Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 2022; **185:** 881–95.

83 Herridge MS. Fifty years of research in ARDS. Long-term follow-up after acute respiratory distress syndrome. Insights for managing medical complexity after critical illness. *Am J Respir Crit Care Med* 2017; **196:** 1380–84.

84 Jovanoski N, Chen X, Becker U, et al. Severity of COVID-19 and adverse long-term outcomes: a retrospective cohort study based on a US electronic health record database. *BMJ Open* 2021; **11:** e056284.

85 Wulf Hanson S, Abbafati C, Aerts JG, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. *JAMA* 2022; **328:** 1604–15.

86 Wild JM, Porter JC, Molyneaux PL, et al. Understanding the burden of interstitial lung disease post-COVID-19: the UK Interstitial Lung Disease-Long COVID Study (UKILD-Long COVID). *BMJ Open Respir Res* 2021; **8:** e001049.

87 Zwaenepoel B, Dhont S, Hoste E, Gevaert S, Schaubroeck H. The prognostic value of cardiac biomarkers and echocardiography in critical COVID-19. *Front Cardiovasc Med* 2021; **8:** 752237.

88 Al Mutair A, Elhazmi A, Alhumaid S, et al. Examining the clinical prognosis of critically ill patients with COVID-19 admitted to intensive care units: a nationwide Saudi study. *Medicina (Kaunas)* 2021; **57:** 878.

89 Ip RJ, Ali A, Baloch ZQ, et al. Atrial fibrillation as a predictor of mortality in high risk COVID-19 patients: a multicentre study of 171 patients. *Heart Lung Circ* 2021; **30:** 1151–56.

90 Katsarou M-S, Iasonidou E, Osarogue A, et al. The Greek collaborative long COVID study: non-hospitalized and hospitalized patients share similar symptom patterns. *J Pers Med* 2022; **12:** 987.

91 Weber B, Siddiqi H, Zhou G, et al. Relationship between myocardial injury during index hospitalization for SARS-CoV-2 infection and longer-term outcomes. *J Am Heart Assoc* 2022; **11:** e022010.

92 Rinaldi R, Basile M, Salzillo C, et al. Myocardial injury portends a higher risk of mortality and long-term cardiovascular sequelae after hospital discharge in COVID-19 survivors. *J Clin Med* 2022; **11:** 5964.

93 Ayoubkhani D, Khunti K, Nafilyan V, et al. Post-COVID syndrome in individuals admitted to hospital with COVID-19: retrospective cohort study. *BMJ* 2021; **372:** n693.

94 Wiemken TL, McGrath LJ, Andersen KM, et al. Coronavirus disease 2019 severity and risk of subsequent cardiovascular events. *Clin Infect Dis* 2023; **76:** e42–50.

95 Knight DS, Kotecha T, Razvi Y, et al. COVID-19: myocardial injury in survivors. *Circulation* 2020; **142:** 1120–22.

96 Kotecha T, Knight DS, Razvi Y, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J* 2021; **42:** 1866–78.

97 Longobardi I, do Prado DML, Goessler KF, et al. Oxygen uptake kinetics and chronotropic responses to exercise are impaired in survivors of severe COVID-19. *Am J Physiol Heart Circ Physiol* 2022; **323:** H569–76.

98 Raman B, Cassar MP, Tunnicliffe EM, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine* 2021; **31:** 100683.

99 Cassar MP, Tunnicliffe EM, Petousi N, et al. Symptom persistence despite improvement in cardiopulmonary health—insights from longitudinal CMR, CPET and lung function testing post-COVID-19. *EClinicalMedicine* 2021; **41:** 101159.

100 Pesce M, Agostoni P, Bøtker HE, et al. COVID-19-related cardiac complications from clinical evidences to basic mechanisms: opinion paper of the ESC Working Group on Cellular Biology of the Heart. *Cardiovasc Res* 2021; **117:** 2148–60.

101 Zhang Q, Zhang H, Yan X, et al. Neutrophil infiltration and myocarditis in patients with severe COVID-19: a post-mortem study. *Front Cardiovasc Med* 2022; **9:** 1026866.

102 Zhou D, Wang Q, Liu H. Coronavirus disease 2019 and the gut-lung axis. *Int J Infect Dis* 2021; **113:** 300–07.

103 Lionetti V, Bollini S, Coppini R, et al. Understanding the heart–brain axis response in COVID-19 patients: a suggestive perspective for therapeutic development. *Pharmacol Res* 2021; **168:** 105581.

104 Gyöngyösi M, Alcaide P, Asselbergs FW, et al. Long COVID and the cardiovascular system—elucidating causes and cellular mechanisms in order to develop targeted diagnostic and therapeutic strategies: a joint Scientific Statement of the ESC Working Groups on Cellular Biology of the Heart and Myocardial and Pericardial Diseases. *Cardiovasc Res* 2023; **119:** 336–56.

105 Chan L, Chaudhary K, Saha A, et al. AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol* 2021; **32:** 151–60.

106 Gupta S, Coca SG, Chan L, et al. AKI treated with renal replacement therapy in critically ill patients with COVID-19. *J Am Soc Nephrol* 2021; **32:** 161–76.

107 Matsumoto K, Prowle JR. COVID-19-associated AKI. *Curr Opin Crit Care* 2022; **28:** 630–37.

108 Hoogenboom WS, Pham A, Anand H, et al. Clinical characteristics of the first and second COVID-19 waves in the Bronx, New York: a retrospective cohort study. *Lancet Reg Health Am* 2021; **3:** 100041.

109 Nadim MK, Forni LG, Mehta RL, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. *Nat Rev Nephrol* 2020; **16:** 747–64.

110 Hultström M, Lipcsey M, Wallin E, Larsson I-M, Larsson A, Frithiof R. Severe acute kidney injury associated with progression of chronic kidney disease after critical COVID-19. *Crit Care* 2021; **25:** 37.

111 Stockmann H, Hardenberg J-HB, Aigner A, et al. High rates of long-term renal recovery in survivors of coronavirus disease 2019-associated acute kidney injury requiring kidney replacement therapy. *Kidney Int* 2021; **99:** 1021–22.

112 Puthumana J, Thiessen-Philbrook H, Xu L, et al. Biomarkers of inflammation and repair in kidney disease progression. *J Clin Invest* 2021; **131:** e139927.

113 Legrand M, Bell S, Forni L, et al. Pathophysiology of COVID-19-associated acute kidney injury. *Nat Rev Nephrol* 2021; **17:** 751–64.

114 Akilesh S, Nast CC, Yamashita M, et al. Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. *Am J Kidney Dis* 2021; **77:** 82–93.

115 Golmai P, Larsen CP, DeVita MV, et al. Histopathologic and ultrastructural findings in postmortem kidney biopsy material in 12 patients with AKI and COVID-19. *J Am Soc Nephrol* 2020; **31:** 1944–47.

116 Schurink B, Roos E, Radonic T, et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe* 2020; **1:** e290–99.

117 Wu H, Larsen CP, Hernandez-Arroyo CF, et al. AKI and collapsing glomerulopathy associated with COVID-19 and *APOL 1* high-risk genotype. *J Am Soc Nephrol* 2020; **31:** 1688–95.

118 Irisson-Mora I, Salgado-Cordero AM, Reyes-Varón E, et al. Comparison between the persistence of post COVID-19 symptoms on critical patients requiring invasive mechanical ventilation and non-critical patients. *PLoS One* 2022; **17:** e0273041.

119 Yang X, Hou C, Shen Y, et al. Two-year health outcomes in hospitalized COVID-19 survivors in China. *JAMA Netw Open* 2022; **5:** e2231790.

120 Fernández-de-Las-Peñas C, Navarro-Santana M, Plaza-Manzano G, Palacios-Ceña D, Arendt-Nielsen L. Time course prevalence of post-COVID pain symptoms of musculoskeletal origin in patients who had survived severe acute respiratory syndrome coronavirus 2 infection: a systematic review and meta-analysis. *Pain* 2022; **163:** 1220–31.

121 Awosanya OD, Dadwal UC, Imel EA, Yu Q, Kacena MA. The impacts of COVID-19 on musculoskeletal health. *Curr Osteoporos Rep* 2022; **20:** 213–25.

122 Soares MN, Eggelbusch M, Naddaf E, et al. Skeletal muscle alterations in patients with acute COVID-19 and post-acute sequelae of COVID-19. *J Cachexia Sarcopenia Muscle* 2022; **13:** 11–22.

123 Di Girolamo FG, Fiotti N, Sisto UG, et al. Skeletal muscle in hypoxia and inflammation: insights on the COVID-19 pandemic. *Front Nutr* 2022; **9:** 865402.

124 Rizvi A, Patel Z, Liu Y, Satapathy SK, Sultan K, Trindade AJ. Gastrointestinal sequelae 3 and 6 months after hospitalization for coronavirus disease 2019. *Clin Gastroenterol Hepatol* 2021; **19:** 2438–40.

125 Roth NC, Kim A, Vitkovski T, et al. Post-COVID-19 cholangiopathy: a novel entity. *Am J Gastroenterol* 2021; **116:** 1077–82.

126 Ghoshal UC, Ghoshal U, Rahman MM, et al. Post-infection functional gastrointestinal disorders following coronavirus disease-19: a case-control study. *J Gastroenterol Hepatol* 2022; **37:** 489–98.

127 Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. *Gastroenterology* 2020; **159:** 81–95.

128 Ren Z, Wang H, Cui G, et al. Alterations in the human oral and gut microbiomes and lipidomics in COVID-19. *Gut* 2021; **70:** 1253–65.

129 Bourkas AN, Zaman M, Sibbald RG. COVID-19 and hospital-acquired pressure injuries: a systematic review. *Adv Skin Wound Care* 2023; published online Jan 27. https://doi.org/10.1097/01.ASW.0000919408.20614.61.

130 Elmer N, Reißhauer A, Brehm K, Vockeroth C, Liebl ME. Long-term complications of prone position ventilation with relevance for acute and postacute rehabilitation: a systematic review of the literature. *Eur J Phys Rehabil Med* 2023; **59:** 111–21.

131 Dale CM, Rose L, Carbone S, et al. Effect of oral chlorhexidine de-adoption and implementation of an oral care bundle on mortality for mechanically ventilated patients in the intensive care unit (CHORAL): a multi-center stepped wedge cluster-randomized controlled trial. *Intensive Care Med* 2021; **47:** 1295–302.

132 Costa CA, Vilela ACS, Oliveira SA, et al. Poor oral health status and adverse COVID-19 outcomes: a preliminary study in hospitalized patients. *J Periodontol* 2022; **93:** 1889–901.

133 Ma Y, Hou L, Yang X, et al. The association between frailty and severe disease among COVID-19 patients aged over 60 years in China: a prospective cohort study. *BMC Med* 2020; **18:** 274.

134 Taniguchi LU, Avelino-Silva TJ, Dias MB, Jacob-Filho W, Aliberti MJR. Patient-centered outcomes following COVID-19: frailty and disability transitions in critical care survivors. *Crit Care Med* 2022; **50:** 955–63.

135 Rose J, Weiser TG, Hider P, Wilson L, Gruen RL, Bickler SW. Estimated need for surgery worldwide based on prevalence of diseases: a modelling strategy for the WHO Global Health Estimate. *Lancet Glob Health* 2015; **3** (suppl 2)**:** S13–20.

136 Lee PHU, Gawande AA. The number of surgical procedures in an American lifetime in 3 states. *J Am Coll Surg* 2008; **207:** S75.

137 COVIDSurg Collaborative, GlobalSurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. *Anaesthesia* 2021; **76:** 748–58.

138 Knisely A, Zhou ZN, Wu J, et al. Perioperative morbidity and mortality of patients with COVID-19 who undergo urgent and emergent surgical procedures. *Ann Surg* 2021; **273:** 34–40.

139 COVIDSurg Collaborative, GlobalSurg Collaborative. SARS-CoV-2 infection and venous thromboembolism after surgery: an international prospective cohort study. *Anaesthesia* 2022; **77:** 28–39.

140 El-Boghdadly K, Cook TM, Goodacre T, et al. Timing of elective surgery and risk assessment after SARS-CoV-2 infection: an update: a multidisciplinary consensus statement on behalf of the Association of Anaesthetists, Centre for Perioperative Care, Federation of Surgical Specialty Associations, Royal College of Anaesthetists, Royal College of Surgeons of England. *Anaesthesia* 2022; **77:** 580–87.

141 Le ST, Kipnis P, Cohn B, Liu VX. COVID-19 vaccination and the timing of surgery following COVID-19 infection. *Ann Surg* 2022; **276:** e265–72.

142 El-Boghdadly K, Cook TM, Goodacre T, et al. Timing of elective surgery and risk assessment after SARS-CoV-2 infection: 2023 update: a multidisciplinary consensus statement on behalf of the Association of Anaesthetists, Federation of Surgical Specialty Associations, Royal College of Anaesthetists and Royal College of Surgeons of England. *Anaesthesia* 2023; published online June 19. https://doi.org/10.1111/anae.16061.

143 Kentish-Barnes N, Cohen-Solal Z, Morin L, Souppart V, Pochard F, Azoulay E. Lived experiences of family members of patients with severe COVID-19 who died in intensive care units in France. *JAMA Netw Open* 2021; **4:** e2113355.

144 Azoulay E, Resche-Rigon M, Megarbane B, et al. Association of COVID-19 acute respiratory distress syndrome with symptoms of posttraumatic stress disorder in family members after ICU discharge. *JAMA* 2022; **327:** 1042–50.

145 Liu K, Nakamura K, Katsukawa H, et al. ABCDEF bundle and supportive ICU practices for patients with coronavirus disease 2019 infection: an international point prevalence study. *Crit Care Explor* 2021; **3:** e0353.

146 Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med* 2021; **9:** 239–50.

147 Landhuis EW. How primary care physicians can recognize and treat long COVID. *JAMA* 2023; **329:** 1727–29.

148 Quinn KL, Cheung AM, Razak F. Treating common and potentially modifiable symptoms of post-COVID-19 condition (long COVID) in adults. *CMAJ* 2023; **195:** E80–81.

149 Santhosh L, Block B, Kim SY, et al. Rapid design and implementation of post-COVID-19 clinics. *Chest* 2021; **160:** 671–77.

150 Parker AM, Brigham E, Connolly B, et al. Addressing the post-acute sequelae of SARS-CoV-2 infection: a multidisciplinary model of care. *Lancet Respir Med* 2021; **9:** 1328–41.

151 Haines KJ. Peer support to improve recovery after critical care for COVID-19. *J Physiother* 2022; **68:** 83–85.

152 Quinn KL, Razak F, Cheung AM. Assessing common and potentially modifiable symptoms of post-COVID-19 condition (long COVID) in adults. *CMAJ* 2023; **195:** E76–77.

153 Herridge MS, Azoulay É. The COVID-19 continuum of illness. *Lancet Respir Med* 2022; **10:** 630–31.

154 Kapilashrami A, Hankivsky O. Intersectionality and why it matters to global health. *Lancet* 2018; **391:** 2589–91.