Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review ☆,☆☆

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SUMMARY

Objectives: "Long COVID", a term coined by COVID-19 survivors, describes persistent or new symptoms in a subset of patients who have recovered from acute illness. Globally, the population of people infected with SARS-CoV-2 continues to expand rapidly, necessitating the need for a more thorough understanding of the array of potential sequelae of COVID-19.

The multisystemic aspects of acute COVID-19 have been the subject of intense investigation, but the long–term complications remain poorly understood. Emerging data from lay press, social media, commentaries, and emerging scientific reports suggest that some COVID-19 survivors experience organ impairment and/or debilitating chronic symptoms, at times protean in nature, which impact their quality of life.

Methods/Results: In this review, by addressing separately each body system, we describe the pleiotropic manifestations reported post COVID-19, their putative pathophysiology and risk factors, and attempt to offer guidance regarding work-up, follow-up and management strategies. Long term sequelae involve all systems with a negative impact on mental health, well-being and quality of life, while a subset of patients, report debilitating chronic fatigue, with or without other fluctuating or persistent symptoms, such as pain or cognitive dysfunction. Although the pathogenesis is unclear, residual damage from acute infection, persistent immune activation, mental factors, or unmasking of underlying co-morbidities are considered as drivers. Comparing long COVID with other post viral chronic syndromes may help to contextualize the complex somatic and emotional sequalae of acute COVID-19. The pace of recovery of different aspects of the syndrome remains unclear as the pandemic began only a year ago.

Conclusions: Early recognition of long-term effects and thorough follow-up through dedicated multidisciplinary outpatient clinics with a carefully integrated research agenda are essential for treating COVID-19 survivors holistically.

☆ Taking home points

☆☆ • Long term sequelae from COVID-19 may involve the lungs, cardiovascular system, nervous system, blood and immune system, gastrointestinal system and liver, eyes, skin, musculoskeletal and endocrine systems with a negative impact on mental health, well-being and quality of life. • A subset of patients report debilitating chronic fatigue, with or without other fluctuating or persistent symptoms, such as pain or cognitive dysfunction. • Recovery from acute COVID19 is not linear and long-term effects correlate with severity of the acute illness. • The multisystem nature of the disease mandates a holistic approach to research, service provision and community support.

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Introduction

SARS-CoV-2 has spread rapidly with devastating consequences worldwide. Although mortality from acute COVID-19 rivals or exceeds that of influenza,[1,2] 80% of hospitalized patients and 60% of those admitted to intensive care units survive. [1] A more subacute or chronic stage of disease is however increasingly being reported in a portion of COVID-19 survivors (named "COVID-19 long haulers")[3] (Table 1) and has been the subject of considerable interest in lay press, social media and academic centers (Appendix Table 1) catalyzing the creation of several post COVID units in US and overseas.[3–5] The term long COVID was conceived by COVID-19 survivors on social media[3] while in academic literature, terms such as post-acute COVID-19 (defined as presence of symptoms >3 weeks from onset of COVID-19 symptoms) and chronic COVID-19 (symptoms >12 weeks) have been used. [6,7] A discussion on the most appropriate standardized nomenclature for this entity is ongoing.

Recently published cohort studies have reported symptoms from most body systems in following the acute disease phase reflecting its multi-systemic nature[8–23] (Table 1, Appendix Table 2).

The pathogenesis of late sequelae of COVID-19 is undefined.[24] Patients with long COVID comprise a heterogeneous group: those with frailty and organ damage following intensive care unit (ICU) admissions, those with moderate acute phase of COVID-19 but persistent organ damage or patients with a spectrum of lingering, occasionally remitting-relapsing chronic ailments such as fatigue, brain dysfunction (''brain fog"), weakness, or chronic pain, significantly impacting quality of life post-recovery (Table 1, Appendix Table 2). This expanding population of patients, increasingly seek medical advice and stress an already overwhelmed medical system.[25] Currently, there is no evidence-based cost-effective approach and work-up for the care of these patients. Not uncommonly, they undergo expensive, exhaustive work-ups and at the same time are viewed with skepticism ("medical gaslighting").[3]

Fifteen months following the recognition of the pandemic, there is a paucity of reviews on this rapidly evolving and important topic.[26] Herein, we seek to comprehensively review the long-term multisystemic complications that have been described post-acute COVID-19 recovery.

Methods

We conducted a comprehensive literature search (English only) in Ovid-Medline, Ovid-Embase, Pubmed, Scopus, and Google Scholar through April 2021 (see Appendix).

Epidemiology

Observational studies deriving from different populations (USA, Europe and Asia) revealed a variable proportion of persistent symptoms following SARS-CoV-2 infection (Table 1, Appendix Table 2). Early studies provided evidence of persistent COVID sequelae reporting short term outcomes covering the post-acute phase (4–12 weeks) of COVID-19.[8,13,17,19–23,27] Most recent publications present data from larger cohorts with longer follow-up periods (beyond 12 weeks) illustrating the multisystemic manifestations of the so called "long" or "chronic" COVID.[10,12,18]

Eight retrospective and four prospective studies have investigated the post-acute and long COVID sequalae across different populations regarding ethnicity, inpatient/outpatient setting, disease severity (mild, moderate and severe COVID-19 patients). Of these nine studies focused on the post-acute phase with a median follow up ranging from 32 days post discharge up to 83 days (IQR 74–88) after hospital admission. Three studies provided data beyond 12 weeks with a median follow ranging between 97 days (median, IQR 95–102) post discharge and 186 (IQR 175–199) after symptom onset.

The proportion of persistent symptoms varied considerably among studies. The highest proportion of post-acute COVID syndrome, 84.7%, has been reported in an Italian study on 143 hospitalized patients, 20% of them required non-invasive or invasive ventilation.[8] The most common reported symptoms were fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%). A high proportion of persistent symptoms of 74% has been reported in a prospective study from the UK on 110 consecutive hospitalized patients.[28] The most common symptoms included breathlessness, excessive fatigue and limitations in reported physical ability. The largest study reporting on post-acute COVID syndrome included 1409 patients admitted to home health care.[23] The most common symptoms included 42% pain, daily or all the time, 84% dyspnea with any exertion, 50% symptoms of anxiety, 47% confusion. Fatigue was the most common reported symptom across different studies ranging from 30 to 72%, followed by breathlessness/dyspnea cough, confusion/loss of memory, persistent pain, headache, joint pain/arthralgias, chest pain, anosmia/ageusia, palpitations, anxiety/depression, sleep difficulties, GI symptoms and hair loss.

Three studies, two from China and one from France, reported on chronic or long COVID syndrome.[10,12,18] The largest study on 1733 patients after a 6 month follow-up reported in 63% of patients fatigue or muscle weakness, 26% sleep difficulties, 23% anxiety or depression, up to 29% abnormal median 6-min walking distance and importantly, acute kidney injury (AKI) in 13% of patients without AKI at the acute phase.[12] Another study that included 538 patients, 39% of them with critical or severe disease, showed that 49.6% of patients presented at least one symptom during follow up, with 28.3% reporting physical decline or fatigue, 39% respiratory difficulties, 21.4% dyspnea, 14.1% chest distress, 12.3% chest pain, 7.1% cough, 13% cardiovascular complications, 23.6% excessive sweating and 18.6% alopecia.[10]

Obviously, the incidence of reporting symptoms should be considered under the prisma of selection bias, as most studies were retrospective in nature, with small sample sizes and included hospitalized patients with variable degree of COVID-19 severity. Future prospective population-based studies are need in order to provide more reliable estimation on the post-acute or long COVID syndrome on the general population.

Long term COVID-19 manifestations

Respiratory system

The lungs are the organ most likely to sustain serious injury from COVID-19.[29,30] Even mildly symptomatic patients may have lung involvement on CT imaging[31] and persistent alterations of pulmonary function tests (PFTs).[8,18,29,32–38] Abnormal lung function (restrictive abnormalities, reduced diffusion capacity, small airways obstruction) have been identified both early and later (2–12 weeks) after discharge.[29,35,38–42] However, the most severe complication is lung fibrosis (LF) and fibrotic changes have been detected as early as 3 weeks after symptoms onset, regardless of the severity of the acute illness (Appendix Table 2).[37,43–48] LF has also been observed in severe illness caused by other coronaviruses [Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS)] with the same postulated pathobiology (Table 3).[49,50] Potential predictors of LF in COVID-19 include advanced age, severe illness, elevated D-dimers levels, ARDS, history of pulmonary or cardiovascular disease, prolonged mechanical ventilation, smoking, and chronic alcoholism (Table 2).[35,37] The poor

Table 1
Representative studies reporting symptoms of subacute and/or chronic COVID-19 (relevant references can be found in the Appendix Table 4).

Study	Population Age, mean (SD), (years) Sex	Study design	Follow-up Mean (SD), days	% of patients with clinical symptoms indicating late COVID-19
Multisystemic manifestations				
Arnold et al.[s1]	110 consecutive hospitalized pts, median age 60 (IQR 46–73), males 56%	Prospective	83 (IQR 74–88) after hospital admission	74% persistent symptoms (breathlessness and excessive fatigue) and limitations in reported physical ability; 35% clinically significant abnormalities in chest radiograph, exercise tests, blood tests and spirometry
Bowles et al.[s2]	1409 pts admitted to home health care, age 67 (15), 43% younger than 65 years, 36% between 65 and 80 years, and 21% 80 years or older; 51% male	Retrospective	32 (post discharge, home health care stay)	42% pain daily or all the time, 84% dyspnea with any exertion, 50% symptoms of anxiety, 47% confusion
Carfi et al.[s3]	143 pts, age 56.5 (14.6) 63% males BMI 26.3 (4.4) Mean LOS: 13.5 (9.7) days; noninvasive ventilation 21 (15%), invasive ventilation 7 (5%)	Retrospective	60.3 (13.6) (from symptom onset)	87.4% (32.2% with 1 or 2, 55.2% with ≥3) 63% worsened QOL Most common: Fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%), chest pain (21.7%)
Carvalho-Schneider et al.[s4]	130 pts with non- critical COVID-19, age 49 (15), 44% males	Prospective	59.7 (1.7)	10% dyspnea/shortness of breath 17% chest pain 15 28% flulike symptoms 15% digestive disorders 15% weight loss 29% anosmia/ageusia 14% palpitations 21% arthralgia 15% cutaneous signs
Chopra et al.[s5]	488 pts, Median age 62 (50–72) 51.8% males median LOS: 5 (3–8) days Invasive ventilation: 5.9% ICU stay: 13.2%	Retrospective	60 (post discharge)	33% persistent symptoms related to illness (cardiopulmonary), 19% new or worsening symptoms related to illness, 13% continued loss of taste and/or smell, 15% cough, 17% shortness of breath/chest tightness/wheezing, 9% difficulty ambulating due to chest problems, 23% breathlessness walking up stairs, 7% oxygen use, 7% new use of CPAP or other breathing machine when asleep
Garrigues et al.[s6]	120 pts, mean age 63.2 (15.7), 63% males, 80% ward, 20% ICU	Prospective	110 (11.1) (after admission)	Fatigue 55%, dyspnea 42%, loss of memory 34%, loss of concentration 28%, sleep disorders 30.8%, hair loss 20%, cough 17%, chest pain 11%, ageusia 11%, anosmia 13%, 29% mMRC dyspnea scale grade ≥2 No significant difference between ward and ICU pts
Halpin et al.[7]	100 pts, 32 in ICU and 68 in wards, median age 70.5 years for ward and 58.5 for ICU, 54% males	Retrospective Telephone	48 (post discharge)	New fatigue: 63% (72% ICU and 60.3% ward) Breathlessness; 50% (65.6% in ICU group and 42.6% in ward group)
Huang et al.[8]	1733 pts, median age 57(IQR 47–65), 52% males,	prospective	186 (IQR 175–199) (after symptom onset)	63% Fatigue or muscle weakness, 26% sleep difficulties, 23% anxiety or depression, abnormal median 6-min walking distance test: 24% for those at severity scale 3, 22% for severity scale 4, 29% for severity scale 5–6, diffusion impairment: 22% for severity scale 3, 29% for scale 4, and 56% for scale 5–6 median CT scores: 3.0 (IQR 2•0–5•0) for severity scale 3, 4.0 (3.0–5.0) for scale 4, and 5.0 (4.0–6.0) for scale 5–6 13% of pts without AKI and with eGFR 90 mL/min per 1•73 m^2 or more at acute phase had eGFR less than 90 mL/min per 1•73 m^2 at follow-up

(*continued on next page*)

Table 1 (*continued*)

Jacobs et al.[9]	183 pts, median age 57 years, 61.5% male, BMI 30 (IQR 27–33.5) LOS: 7 days (IQR 5–10)	Prospective	35(5) (post discharge)	55% fatigue, 45.3% shortness of breath, 22.8% lack of taste, 50.6% muscular pain, 10.9% diarrhea, 26.2% lack of smell, 44.3% phlegm, 39% headache, 54.7% joint pain, 43.2% confusion, 42.9% eye irritation, 5.3% fever, 20% ulcer
Moreno-Perez et al. [s10]	277 pts, median age 62 years, 52.7% males 19.5% pts without pneumonia, 14.8% with non-severe pneumonia and 65.7% with severe pneumonia	Prospective	77 days (IQR 72–85) after disease onset	50.9% post-acute covid syndrome: 34.8% fatigue, 21.4% anosmia-dysgeusia, 19.6% myalgias-arthralgias, 34.4% dyspnea, 21.3% cough, 17.8% headache, 15.2% amnesic complaints, 10.5% diarrhea, 8.3% skin features, 5.4% visual loss
Raman et al.[s11]	58 pts, Mean age 55(13), 59% males 30 comorbidity-matched controls	Prospective	69 (median, IQR 62–76) (after symptom onset)	64% persistent breathlessness, 55% significant fatigue MRI abnormalities in lungs (60%), heart (26%), liver (10%) and kidneys (29%) Moderate-severe anxiety (35% versus 10% controls, $p = 0.012$), depression (39% versus 17%, $p = 0.036$) and significant impairment in QOL
Rosales-Castillo et al.[s12]	118 pts, 55.9% males, mean age 60.2(15.1), BMI 29.7 (5.8)	Retrospective	50.8 (6) (post discharge)	62.5% reported persistent symptoms: 31.4% dyspnea, 30.5% fatigue, 13% myalgias, 5% cough, 1.7% anosmia, 1% ageusia
Xiong et al.[s13]	538 pts Median age 52 (IQR 41–62), 45.5% males 33.5% severe disease, 5% critical disease, 61.5% general ward	Retrospective	97 (median, IQR 95–102) (post discharge)	49.6% >1, physical decline or fatigue (28.3%), respiratory (39%), dyspnea (21.4%), chest distress (14.1%), chest pain (12.3%), cough (7.1%), excessive sputum (3%), cardiovascular (13%), joint pain (7.6%), throat pain (3.2%), excessive sweating (23.6%), alopecia 18.6% (48.5% in women)

COVID-19: Coronavirus Disease 2019; SD: standard deviation; IQR: interquartile range; pts: patients; BMI: body mass index; LOS: length of in-hospital stay; QOL: quality of life; ICU: intensive care unit; mMRC (Modified Medical Research Council) dyspnea scale; MRI: magnetic resonance imaging; eGFR: estimated glomerular filtration rate.

correlation between imaging and PFT findings makes the evaluation of LF prognosis challenging (Table 2), although persistent lung function abnormalities appear to be more common among patients who had severe acute COVID-19 and high levels of inflammatory markers.[29,35,38,40,51] Long term follow-up studies of SARS and MERS have shown that radiologic abnormalities, pulmonary function impairment and reduced exercise capacity were common, improved over time in most, but persisted for months or years in some patients.[52–54] Additionally, patients hospitalized with severe COVID-19 tend to be older than the ones with MERS or SARS; since age, in addition to COVID-19 severity, is also a risk factor for LF.[37] the burden of this complication after COVID-19 recovery could be substantial. Other potential late COVID-19 complications include pneumothorax, secondary infections, massive hemoptysis, airway strictures, and pulmonary hypertension with or without evidence of thrombosis (Table 2).

There are several mechanisms which may be implicated in acute and long-term damage after COVID-19 including hypoxia-related and mechanical ventilation-related damage, tissue destruction due to uncontrolled cytokine release and immune system activation, direct pneumocyte apoptosis due to ACE2-mediated viral invasion, surfactant inactivation, micro-vascular/thrombotic disease and endothelial dysfunction. Isolated decreased diffusion capacity in several patients also points to the vascular damage induced by SARS-CoV-2; pulmonary hypertension, with or without evidence of thrombosis, has been reported. Polymorphisms in *ACE2*, the entry receptor of SARS-COV-2, may also predispose to lung injury after COVID-19. Although virus persistence in lung tissues is not considered to be a cause, persistence of virally infected cells forming syncytia might play a role. SARS-CoV-2-induced proinflammatory and profibrotic cytokines[55] are overproduced during acute and sub-acute COVID-19, whereas homeostatic mechanisms of lung repair are deregulated leading to the development of LF; the antiviral interferons attenuate lung repair, further increasing disease severity.[56]

It is unknown whether administration of antivirals (remdesivir), corticosteroids or other immunomodulators may affect the risk of long-term post-COVID-19 pulmonary abnormalities. Some guidance has been published for respiratory follow up[57–60] but management of late pulmonary effects is not straightforward. It is unknown if drugs used in idiopathic LF (e.g., pirfenidone, nintedanib) could have a positive effect on the natural history of LF post COVID-19[51].

Cardiovascular system

Accumulating evidence indicates that COVID-19 related cardiac complications (Table 2, Appendix Table 2) may arise or persist weeks or months after resolution of the infection.[61] Among COVID-19 survivors, 5−29% complain of chest pain, dyspnea, or palpitations post- recovery (Table 2, Appendix Table 2), even 6 months after the acute infection.[12] Late cardiac magnetic resonance (CMR) findings indicative of subacute myocarditis[62–66] have been also reported in COVID-19 patients. Although post-recovery persistence of SARS-CoV-2 in myocardial tissue or myocardial inflammation could explain these findings, histological data are lacking. After 24–71 days, CMR studies suggest myocardial inflammation or scarring in 15 to 60% of patients, even those who were asymptomatic or experienced only mild symptoms of acute disease (Appendix Table 2). These findings were correlated with troponin levels[64] and inflammatory markers such as C-reactive protein, white cell count and procalcitonin, indicating a role of inflammation in myocardial tissue abnormalities.[67] Alarmingly, CMR findings consistent with myocarditis were found in 4 out of 26 competitive athletes 11–53 days after recommended quarantine, while in another study CMR

Table 2
Clinical spectrum, risk factors, diagnostic tools, suggested follow up and management of subacute and/or chronic COVID-19 (relevant references can be found in the Appendix Table 4).

Site/organ	Late manifestations	Risk factors	Diagnostic tools	Management
Lung	Lung fibrosis [s1–6] Abnormal PFT[s7–10] Pulmonary vascular disease / pulmonary hypertension[s8,11–18] Bronchiectasis[s19] Spontaneous Pneumothorax[s20–24] Secondary infections[s25] massive hemoptysis[s19] airway strictures[s26]	Older age, male gender, underlying lung disease, intense inflammatory response, elevated BUN, elevated D-dimer levels at admission, length of mechanical ventilation, smoking, chronic alcoholism[s5,7,9,27–29]	Follow up at 4–6 weeks post discharge; Chest X-ray or HRCT at 12 weeks post discharge; Consider 6MWT and/or PFTs as clinically indicated; cardiopulmonary testing in selected cases[s30–33]; CTPA in suspected PVD Bronchoscopy in selected patients (to rule out lung infection)	Although CTs indicate that lung fibrosis tends to stabilize over months in most but not all patients, PFTs suggest persistence of lung dysfunction. Consider referral of selected patients to specialized centers to manage lung fibrosis[s30–33] Consider referral of patients with pulmonary hypertension to dedicated clinics[s34] Consider enrolling pts in ongoing clinical trials
Blood	Hypercoagulation[s35], increased CRP levels[s36], persistent lymphocytopenia[s37], Pulmonary embolism,[s35 38] Left ventricular thrombus, [s35] Acute cardioembolic limb ischemia[s39]	Coagulation profile, comorbidities, severity of index illness, and degree of immobility	Blood, biochemistry and coagulation panel (D-dimers, INR, PT, aPTT, fibrinogen) CT angiography in patients with suspected embolism Cardiac echo	Use thrombotic risk models, consider long-term use of anticoagulants weighting thrombotic vs. bleeding risk Direct oral anticoagulants and low-molecular-weight heparin are preferred over vitamin K antagonists Therapeutic anticoagulation for those with imaging-confirmed VTE is recommended for at least 3 months Consider enrolling pts in ongoing clinical trials
Immune system	Secondary hemophagocytic lymphohistiocytosis[40,41] Arthritis/Skin psoriasis[s42,43] Systemic lupus erythematosus[s44] Grave's disease[s45,46], ITP[s47–50]	Severe disease, elderly pts, low lymphocytes on admission	Autoimmune screening panel based on the acute disease severity and symptoms; Immune immunoglobulins in selected pts; Antiganglioside antibodies	Treat according to each disease-specific guidelines. Consider high dose corticosteroids in selected pts. Consider plasma exchange in selected pts. Consider IVIG treatment in selected pts.
CNS	Headache, vertigo/dizziness,, cognitive impairment[s51,52] Alzheimer's[s53] Parkinsonism, Neuromyelitis optica spectrum disorder[s54] Guillain–Barré[s46,55–58] Multiple sclerosis[s59] Aanosmia/ageusia[s60]	Older age[s61] Preexisting neurodegenerative (Alzheimer. Parkinson)[s62,63] and other neurological disorders (eg multiple sclerosis Prior ARDS/ICU stay COVID-19 severity[s64]	MRI Cognitive screening Lumbar puncture-CSF analysis Electromyogram, Nerve conduction tests if indicated UPST (anosmia screening)	Neuropsychological assessment, neuro-rehabilitation for cognitive deficits. For more complex and persisting complex cognitive/emotional symptoms and/or chronic neuropathy, consider referral to dedicated multidisciplinary rehabilitation clinics (neurologist, physiotherapist, occupational therapist, speech therapist, neuropsychologist, psychologist, psychiatrist) Olfractory training
Cardio-vascular	Myocarditis, myocardial inflammation, [s65–68] chest pain, dyspnea, palpitations, [s69–71] postural tachycardia syndrome[s72]	Largely undefined Hospitalized patients (increased possibility for abnormal Native T1 in CMR) Higher troponin I (TnI) at hospitalization[s73] Previous statin treatment may decrease risk for myocarditis	At 3 weeks post-infection resolution: Initial assessment for diagnosis of persistent cardiac abnormalities and for risk stratification: Troponin, ECG, Echocardiogram In selected pts CMR (based on troponin, ecg or echocardiogram) In selected pts: NT-proBNP, 24 h ECG monitoring, CMR, CT or invasive coronary angiogram	Abstinence from exercise for 2 weeks after first COVID-19 diagnosis and asymptomatic at least 7 days. Duration modified according to 1st post-infection cardiac assessment Slow resumption of activity after resolution of infection Close monitoring for symptoms (first 6 weeks) Guidelines-based drug treatment according to cardiac complication diagnosed Special attention to competitive athletes with evidence of myocarditis (particularly in hospitalized or symptomatic >14 days) Consider enrolling pts in ongoing clinical trials
Kidney	Non recovering Acute kidney Injury - Chronic kidney disease, proteinuria,[s74–76] hematuria[s74,77,78]	Obesity, older age, other comorbidities (eg hypertension, prior renal impairment) genetic factors (high risk APOL1 alleles)[s76]	Regular follow up of renal function (serum creatinine, albumin, assessment of proteinuria, urine protein to creatinine ratio)	As per other renal diseases– no specific guidance Long term follow-up indicated in patients with residual/persisting renal dysfunction. Continue RRT in the small subset of patients who do not recover renal function.
Gastro-intestinal/ liver	Abdominal pain, liver injury (AST, ALT increase)[s36]	Underlying liver disease, obesity, diabetes mellitus	Periodic liver function tests and/ or imaging (abdominal ultrasound or MRI)	Monitoring, avoid drug induced liver toxicity, weight loss, good control of diabetes if present

(*continued on next page*)

Table 2 (*continued*)

Endocrine	Diabetes-like condition, subacute hypothyroiditis, Grave's disease [s79,80] Increased PTH and decreased vitamin D levels[s81]	Preexisting Diabetes or metabolic syndrome (obesity) Lack of sun exposure	Hormonal axis assessment as indicated (symptoms-driven), vitamin D, PTH, TSH, FSH, LH, testosterone, estradiol, Consider serologic testing for type 1 diabetes- associated autoantibodies and repeat post-prandial C-peptide measurements in pts with newly diagnosed diabetes mellitus	If abnormalities, treat appropriately. According to condition-specific guidelines Referral to endocrinologist
Ocular	Subtle retinal changes, ocular induced drug toxicity[s82]	Undefined	Symptoms' monitoring, if available periodical ophthalmology evaluation	Treat appropriately based on symptoms and expert evaluation. Avoid drugs with ocular toxicity Periodical ophthalmology evaluation
Skin	Morbilliform (maculopapular), urticarial, vesicular, pernio/chilblains-like[83], and necrotic/livedoid lesions[s84], hair loss[s85], transverse leukonychia[s86,87]	Undefined	Patient education to report of any abnormal skin lesion.	Treat appropriately with topical or systemic treatment under dermatologic consultation Referral to dermatologist.
Musculo-skeletal	Myalgias, atrophy, sarcopenia, weakness and fatigue,[s88] Myoclonus[s89,90] Myositis[s91] Arthralgias, osteoporosis, progression of osteoarthritis,[s88] osteonecrosis[s92]	ICU Corticosteroids Hydroxychloroquine [s92–94]	CPK Electromyogram Muscle biopsy in selected patients MRI (bone) hip BMD Z-score	Rehabilitation/Physiotherapy Aerobic and resistance exercise program Referral to dietician/nutrition clinic for sarcopenia Close monitoring of pts on corticosteroids Bisphosphonates, extracorporeal shock wave therapy, enoxaparin, and/or lipo-prostaglandin E1[s92]
Fatigue/ Chronic pain[s95–9798–100]	Severe constant or remitting fatigue Chronic constant or fluctuating generalized or limb/joint pain, Joint pain Reduced exercise tolerance	Pre-existing comorbidities, history of chronic pain or previous pain experience history of mental health problems Disadvantaged socioeconomic status Social isolation ICU- related specific factors (prolonged stay, ventilation, proning, sepsis, immobility, neuromuscular block)	Post discharge and at regular intervals screening with: Self-reporting applications and questionnaires (telephone, online) Screening with validated fatigue severity scales; FSS, FAS, CFS-11, PCFS	Rest protocol for most patients with mild or severe symptomatology For severe or persisting symptoms, refer to multidisciplinary rehabilitation services (psychological, occupational therapy, physiotherapy) Peer support groups Consider enrolling pts in ongoing clinical trials
Psychiatric/ Emotional Health and well-being [s101–107,108–110]	Post-traumatic stress disorder (PTSD) Depression Stress/Anxiety Psychosis Mania/Catatonia Somatization Affective disorder Psychosis Increased suicide risk Sleep disorders Hallucinations difficulty to concentrate. Memory lapses Executive function impairment Reduced QoL	Persistent physical symptoms Prior psychiatric comorbidities Social isolation Disadvantaged socioeconomic status. Retirement Female sex Lack of access to healthcare Inconsistent health care advice Younger age or older age group Stigmatization Presence of chronic pain Prior substance abuse Infected family members	Post discharge and at regular intervals screening with validated cognitive assessment tools, validated tools for psychiatric symptoms (PTSD, depression, anxiety), health surveys (SF-36, EQ-5D-3 L), self-reporting applications and questionnaires (telephone, online), QoL assessment tools	Multidisciplinary rehabilitation services (health and social care) Designated COVID-19 follow-up clinics COVID-19-specific rehabilitation pathways/guidelines Mental health care via remote consultation Active screening and monitoring Peer support groups Adapt services to social and cultural context. Consider enrolling pts in ongoing clinical trials

&patients with recurring bacterial infections

PFT: pulmonary function tests; BUN: blood urea nitrogen; HRCT: high resolution computed tomography; CT: computed tomography; 6MWT: 6 min walking test; PVD: pulmonary vascular disease; CRP: C-reactive protein; INR: international normalized ratio; PT: prothrombin time; aPTT: activated partial thromboplastin time; ITP: immune thrombocytopenic purpura; pts: patients; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; PET: positron emission tomography; UPST: University of Pennsylvania Smell Identification Test; CNS: central nervous system; CMR: cardiac magnetic resonance; ECG: electrocardiogram; IL-6: interleukin 6; NT-proBNP: N-terminal pro b-type natriuretic peptide; RRT: renal replacement therapy; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PTH: parathormone; TSH: thyroid stimulating hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; CPK: creatine phosphokinase; BMD: bone mineral density; FSS: fatigue severity scale; FAS: fatigue assessment scale; CFS-11: chalder fatigue scale; PCFS: post-COVID-19 functional status; QoL: quality of life; PTSD: post-traumatic stress disorder; EQ-5D-3L: European Quality of Life with 5 Dimensions.

findings indicative of resolving pericardial inflammation were reported in 19 out of 48 student athletes, after a median of 27 days from diagnosis.[65,68] In contrast, in a more recent case series of 145 competitive student athletes, only 2 (1.4%) presented CMR findings consistent with myocarditis, 15 (range 11 to 195) days after diagnosis, with one of them having increased troponin levels.[69] This finding suggests against routine CMR screening in recovering athletes.[70] Given the lack of histological adjudication, further research with careful follow-up is needed to explore the clinical relevance of persistent myocardial abnormalities by CMR.[59]

Another point of concern is that late cardiovascular complications were found in 80% of children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection.[71] SARS-CoV-2 infection has also been associated with persistently high inflammatory and procoagulant mediators[72,73] and small vessel endothelitis[74] in heart specimens of COVID-19 patients. Given that

Table 3
Similarities and differences of post COVID-19 syndromes with other post viral syndromes (relevant references can be found in the Appendix Table 4).

Organ System	SARS	MERS	Influenza	EBV	Ebola	Zika	Chikungunya
Respiratory	Fibrotic lung changes. Persisting post-recovery CT scan abnormalities, associated with less improvement and worse PFT even at 15 years[s1–6]	Lung fibrosis in up to 33%, associated with a greater number of ICU admission days, older age, higher chest radiographic scores, chest radiographic deterioration patterns and peak LDH levels[s7]	Residual radiologic changes were present at 3 months, some improvement 6 and 12 months but no marked changes later. PFT abnormalities persisted[s8,9]	Severe persisting lung involvement associated with prior EBV infection is rare[s10]	Persistent respiratory symptoms and lung disease are common, and associated with long term mortality[s11,12]	NR	NR
Cardio-vascular	Disturbed lipid metabolism 12 years after infection[s13];35.5% with tachycardia at 3 weeks[s14] Subclinical diastolic impairment, reversible at 30 days[s15]	MERS genome was not detected in heart tissues of postmortem patients[s16]	First 30 days after first infection: Increased risk for acute cardiac injury[s17] Increased risk of myocardial infarction[s18,19] 21 days after infection: Increased cardiovascular disease mortality and ischemic heart disease mortality[s20]	increased inflammatory load and risk of acute myocardial infarction[s21];dilated cardiomyopathy[s22]	Irregular pulse and decreased heart murmur,[s23] chest pain[s24] valvulopathy, tachycardia and cardiopathy Myocarditis[s25]	Persistent myocardial inflammation (assessed by CMR)[s26,27] Arrhythmias (including atrial fibrillation, atrial tachycardia, ventricular arrhythmias), heart failure and pericardial effusion[s27]	Myocarditis and cardiopathy (congestive and constrictive)[s28, 29] Atrial fibrillation with high risk of thromboembolism, ventricular extrasystoles, ventricular fibrillation, sinus bradycardia/ tachycardia, sudden death left ventricular hypertrophy[s29] Decreased ejection fraction eccentric left ventricular hypertrophy and concentric remodeling[s30]
CNS	Encephalopathy, seizures, motor neuropathy[s31] sensory neuropathy, GBS,[s32] PD, MS, ADEM[s33] Cognitive impairment,[s34] POTS[s35]	ADEM, brainstem encephalopathy, neuropathy,[s31] GBS,[s36] Cognitive impairment[s34]	Encephalitis lethargica myelopathy,[s31] post-encephalitic parkinsonism, neurological symptoms relating to PD within a month after the influenza,[s37,38] PD and MS[s39]	Chronic parkinsonism, GBS,[s40] NMOSD,[s41] MS,[s42] Leuko-encephalo pathy[s43]	Seizures, memory loss, headaches, cranial nerve abnormalities, tremor[s44]	Encephalitis/ Encephalomyelitis, motor and cognitive impairment, peripheral neuropathy GBS [s40,45]	GBS[s46,47]
Immune	NR	NR	NR	NR	NR	Remnant inflammation and autoimmune-like relapse with rheumatoid arthritis, arthromyalgia, spondyloarthritis and uveitis[s12,48,49]	Debilitating joint and muscle pain, arthritis (raised levels of immune mediators and infiltration of immune cells in joints and tissues)[s50–52]
Kidney	Persisting renal impairment in 6%[s53,54]	Persisting renal impairment in up to 27% of patients[s55,56]	Up to 33% of hospitalized patients with severe complications developed AKI[s57,58] Long term RRT was required in 6% of survivors,[s59] HUS[s58]	Rare; Acute tubular necrosis, tubulointerstitial nephritis, nephrotic syndrome due to minimal change disease[s60]	Kidney involvement in 20% to 40% of cases associated with high mortality[s61] even among survivors[s11].	Kidney functional or structural lesions not described in patients despite the intense and persistent shredding of zika virus in kidneys and urine[s62]	NR
Gastrointestinal/ liver	Liver impairment[s63]	Liver impairment[s63]	NR	NR	NR	NR	Fulminant hepatitis[s64]
Endocrine	Acute Type I diabetes mellitus like condition,[s65] adrenal insufficiency,[s66] pregnancy failure and irregular menstruation[s67]	NR	Increased the risk of preterm birth and low birth weight irrespective of gestational age[s68]	NR	Pregnancy failure and irregular menstruation[s67]	Zika congenital syndrome[s69]	Neonatal encephalopathy, microcephaly, cerebral palsy[s46,70]

(*continued on next page*)

Table 3 (*continued*)

Ocular	NR	NR	NR	NR	Persistence in ocular fluid, uveitis[s71,72] Visual impairment[s73]	Conjunctivitis (mainly acute)[s74]	NR
Chronic skin lesions	NR	NR	NR	NR	NR	Psoriatic-like lesions[s75]	Palmoplantar dequamation[s76]
Musculo-skeletal	Muscle weakness,[s77] myalgia, reduced exercise capacity[s78]	Muscle weakness reduced exercise capacity[s78]	Myopathy, rhabdomyolysis, myositis[s79] Arthritis[s80]	Generalized muscle weakness, muscle pain, polyarthralgias (without any sign of inflammation)[s81]	Myalgia and arthralgia[s82]	Arthralgia arthritis, myalgia[s83]	NR
Emotional/Well-being	Persistent psychological symptoms even 4 years later (depression, increased suicide rates), sleep disturbances. PTSD, Impaired QoL[s84–86]	PTSD Impaired QoL[s87]	Chronic fatigue Impaired QoL	Memory difficulties	Sleep disturbances PTSD[s12]	NR	Major decreases in QoL[s88,89]
Chronic pain/ Fatigue	Chronic fatigue syndrome /Myalgia Encephalomyelitis[s90]	NR	Chronic fatigue syndrome /Myalgia Encephalomyelitis[s87,91]	Chronic fatigue syndrome /Myalgia Encephalomyelitis[s92,93]	Chronic fatigue syndrome /Myalgia Encephalo-myelitis	NR	Chronic fatigue syndrome /Myalgia Encephalomyelitis[s88,89]

SARS: severe acute respiratory syndrome; MERS: middle east respiratory syndrome; EBV: Epstein-Barr virus; CT: computed tomography; PFT: pulmonary function tests; ICU: intensive care unit; LDH: lactate dehydrogenase; CMR: cardiac magnetic resonance; CNS: central nervous system; GBS: Guillain-Barre syndrome; PD: Parkinson's disease; MS: multiple sclerosis; ADEM: acute disseminated encephalomyelitis; NMOSD: neuromyelitis optica spectrum disorder; AKI: acute kidney injury; RRT: renal replacement therapy; HUS: hemolytic uremic syndrome; NR: not reported; PTSD: post-traumatic stress disorder; QoL: quality of life.

other viral infections may increase atherosclerotic events through increased inflammatory and procoagulant burden,[75] these observations have led to the hypothesis that endothelial dysfunction may play a pivotal role in late COVID-19 cardiovascular complications which is currently under investigation (NCT04468412, NCT04525443, Appendix Table 3).

Despite the relative lack of studies examining the long-term impact of SARS-CoV-2 on cardiovascular system, existing evidence suggests an increased rate of major adverse cardiovascular events in recovered COVID-19 patients after a median follow-up of 140 days.[76] In another study, in accordance with previous data for subacute complications, myocardial injury was detected in 30% of patients at 3-month follow-up after COVID-19 infection.[77] Moreover, postural orthostatic tachycardia syndrome has been observed in recovered patients who still experience significant disability even 6–8 months after acute infection.[78]

Central nervous system (CNS)

There is cumulative evidence that COVID-19 affects brain function and could exacerbate neurodegenerative and neuroimmune disorders.[79–81] CNS and peripheral neural system (PNS) symptoms have been attributed to SARS-CoV-2 neurotropism, post-viral immune-mediated process, or neurological manifestations of systemic and non-specific inflammatory effects.[82,83] The global CNS dysfunction due to microglial activation, persistent neuroinflammation, dysregulated neuro-immunity, and hippocampal atrophy is well recognized in critical illness (e.g., sepsis).[84–86] Prolonged ICU stay, mechanical ventilation, prolonged exposure to sedating medications, sepsis, systemic inflammation, pre-existing cognitive dysfunction, neurological injury, and delirium increase the risk of cognitive decline and neurological complications post-ARDS.[87,88] The long-term sequelae in patients with early neurological complications, such as encephalitis or stroke, in the setting of acute COVID-19 may result in severe lifelong disability, requiring long term rehabilitation[82,89,90] Furthermore, immunomodulatory treatments such as corticosteroids used in the acute phase of COVID-19 frequently have CNS adverse effects, including cognitive and sleep disturbances, delirium, psychiatric manifestations, although symptoms resolve after drug withdrawal.[85] The most common self-reported neurologic symptoms post COVID-19 include headache, vertigo/dizziness, anosmia/ageusia/hypogeusia/dysgeusia, insomnia, memory impairment and inability to concentrate ("brain fog") (Table 2, Appendix Table 2). Less common late manifestations include ischemic stroke, intracranial hemorrhage, encephalitis, encephalopathy, seizures, peripheral neuropathies and autoimmune acute demyelinating encephalomyelitis (Table 2). The CNS damage is not specific to SARS-CoV-2, as several post-acute and long-term neurologic manifestations have been reported during pandemics with influenza and other coronaviruses (SARS, MERS) (Table 3). Direct neuro-invasion, neuronal injury secondary to tissue hypoxia or inflammation, local cytokine network dysregulation, and compromised blood brain barrier integrity with resulting transmigration of infected immune cells have been postulated as pathophysiological mechanisms underlying long-term neurological sequalae after coronavirus infections.[81,91]

A retrospective cohort study among 236,379 patients in the USA showed that the estimated incidence of a neurological or psychiatric diagnosis in the following 6 months post COVID-19 was approximately 33% with 12% of patients diagnosed for the first time with neurological or psychiatric disorders. The estimated incidence was even higher, roughly 46%, for severely ill patients admitted to ICU. Interestingly, most diagnostic categories were more common in COVID-19 patients as compared to patients with influenza.[92] Memory impairment with or without delirium during the acute phase is a common ailment, affecting up to 44% of COVID-19 sur-

vivors,[93] possibly attributed to microthrombi and cerebral structural changes in the hippocampus, insulas, and partial white matter.[81,89,94] Not surprisingly, elderly patients are more prone to long-term neurocognitive complications. Parkinsonism-like symptomatology has been reported as a late manifestation of influenza, SARS, and recently post-COVID-19 in elderly patients (probably due to a-synuclein accumulation and cross-autoimmunity reaction triggered by viral infections),[95–97] raising concerns that COVID-19 might incite a new wave of neuro-degenerative diseases in susceptible patients.[97] Whether COVID-19 predisposes to worsening of preexisting chronic neurodegenerative brain conditions or if chronic COVID-19 sequalae are more common in these patients merits further investigation.[81,95,97]

Additionally, isolated chronic dysfunction of central nerve function (SARS-CoV-2 could invade CNS through the olfractory nerve) such as anosmia, dysgeusia or ageusia, common early symptoms of acute COVID-19, may persist for a long time post-acute infection[86,94,98,99] and have been associated with higher bilateral gray matter volumes in olfactory cortices related to smell loss, as compared with non-COVID-19 volunteers.[94]

Finally, COVID-19 can cause dysautonomia by damaging the vagus nerve and postural orthostatic tachycardia syndrome (POTS)[100] characterized by intermittent tachycardia, fluctuating blood pressure and chronic cough or gastrointestinal complaints, as it has been described in other post viral syndromes (Table 3). The frequency of post COVID-19 POTS is unknown.

Hematopoietic system

The cumulative incidence of thrombosis and hemorrhage at day 30 post discharge were reported to be 2.5 and 3.7% respectively in the USA (Appendix Table 2).[73] Retrospective studies from the UK have shown a similar rate of venous thromboembolism of approximately 3%, whereas it has been estimated that the odds of such events following a hospital discharge are 60% higher in the post-acute COVID-19 setting compared to 2019.[101,102] However, even lower rates of deep vein thrombosis (<1%) assessed by venous ultrasound have been reported in other prospective, post-acute COVID-19 studies conducted in Belgium and China, including a low proportion of patients receiving thromboprophylaxis.[103,104] Severe acute COVID-19 is characterized by lymphopenia, increased inflammatory indices and hypercoagulable state on the grounds of endothelitis, cytokine storm, and thrombotic microangiopathy.[105,106] A prothrombotic state is sustained even at the early chronic COVID-19 setting, e.g. at 4 months post discharge, as documented upon elevated plasma levels of factor VIII and plasminogen-activator inhibitor type 1.[107] In addition, the incidence of lupus anticoagulant positivity was increased in patients with or without thrombosis.[108] Abnormalities in lymphocyte and platelet count tend to normalize over time.[27] However, persistent lymphocytopenia may be evident even at 6 weeks from the onset of initial symptoms, especially among patients with severe acute COVID-19 disease, as compared with healthy controls.[109] This finding is particularly relevant for CD3+, CD4+ and CD8+ lymphocyte subsets.[109] It is unknown whether COVID-19 results in acute or long term hypogammaglobulinemia in some patients. Furthermore, new onset late hematologic events were rarely reported. Lufti et al. reported GSCF-responsive agranulocytosis combined with thrombocytosis occurring one week after resolution of COVID-19 symptoms.[110] Additionally, agents used in acute COVID-19 such is tocilizumab occasionally result in thrombosis and prolonged severe neutropenia, even after the resolution of the acute infection.[111] Regular monitoring of blood abnormalities and evaluating the individualized thrombotic risk based on comorbidities (cancer, immobility, prior thrombosis etc.) and coagulation profile (elevated d-dimers) are considered essential both in the post-acute and chronic COVID-19 (Table 2).[73,112]

Inflammatory, autoimmune, and rheumatological complications

Viruses are known to trigger autoimmune/autoinflammatory diseases. In fact, in addition to aberrant activation of acquired and innate immune responses,[113,114] production of autoantibodies again INF I has been associated with severe COVID-19.[115] Molecular mimicry with induction of autoreactive humoral and/or cell mediated immunity have been postulated as drivers of the immunopathology of a variety of inflammatory/ autoantibody-related autoimmune-disease related conditions (such as scattered cases of Guillain-Barre,[116] neuromyelitis optica, systemic lupus erythematosus, psoriasis, arthritis, myasthenia gravis, and multiple sclerosis) post-acute COVID-19 (Table 2, Appendix Table 2). Delayed onset (3–4 weeks following initial symptoms) immune thrombocytopenic purpura (ITP) has also been reported in the context of COVID-19.[117] Furthermore, a delayed-phase thrombocytopenia of putative immune origin has been reported in 11.8% among 271 patients with COVID-19.[118] Aberrant release of neutrophil extracellular traps (NETs) consisting of myeloperoxidase- and neutrophil elastase-containing granules could be seen in COVID-19.[119] The non-specific action of NETs along with the concomitant release of auto-antigens by apoptotic neutrophils could also stimulate autoimmunity and normal tissue damage.[119] It is not clear whether there is only post-infectious dysregulation of the immune system, as direct injury by the low-grade virus from a sanctuary site or multiorgan dysfunction from persisting systemic inflammation might coexist.

Whether COVID-19 predisposes to flares of preexisting rheumatologic (e.g. SLE) or inflammatory (e.g. multiple sclerosis) conditions or if chronic COVID-19 sequalae are more common in these patients awaits further study. Emerging evidence indicates that SARS-CoV-2 may also lead to autoimmune and autoinflammatory pediatric diseases such as Kawasaki disease, a manifestation of pediatric inflammatory multisystemic syndrome (PIMS)[120,121] Finally, a link between COVID-19 and carcinogenesis has been postulated because of aberrant activation of signaling cascades promoting cell survival (JAK-STAT, MAPK) and deregulation of immune surveillance.[122] Large observational long-term cohorts to evaluate temporal patterns and calculate excess risk are required.

Renal system

Acute kidney injury (AKI) is the most common renal complication in severe COVID-19 and kidney dysfunction after discharge may persist in a group of patients. The rates of in-hospital AKI vary substantially among different series as well as rates of non-recovery of kidney function after convalescence[123,124]; however, given the numbers of patients surviving severe COVID-19, a surge of post-COVID-19 persistent kidney disease may occur. In a large study from Wuhan, 13% of patients without AKI and with normal estimated glomerular filtration rate (eGFR) at the acute phase had decreased eGFR at follow-up, necessitating post-discharge close monitoring of renal function.[12]

Development of AKI is multifactorial, caused by hemodynamic instability, systemic inflammatory response, coagulopathy, and microangiopathy in renal vasculature,[125,126] all of which may lead to chronic renal insufficiency. Furthermore, SARS-CoV-2 directly invades tubular cells and podocytes[127] via binding with ACE2, which is highly expressed in these renal cells, leading to collapsing focal glomerulopathy,[128] tubulo-reticular injury,[129] manifesting as proteinuria, hematuria, renal failure and excess demand for dialysis. Obesity, older age, other comorbidities (including pre-existing renal dysfunction) and genetic factors (collapsing glomerulopathy

FSGS in black patients with high risk APOL1 alleles[130] are additional risk factors (Table 2).

Gastrointestinal system and liver

Patients with acute COVID-19 often present with gastrointestinal symptoms and liver impairment (table 2), attributed to hypoxia-mediated injury, drug-induced hepatitis, veno-occlusive disease and direct invasion by SARS-CoV-2 via ACE2, which is richly expressed in hepatocytes/bile duct cells and enterocytes.[131,132] Pre-existing liver abnormalities, such as hepatic steatosis (seen in patients with obesity and metabolic syndrome) and cirrhosis can exacerbate the COVID-19 induced injury.[133–135] Superior mesenteric artery thrombosis is a rare and atypical manifestation of COVID-19 necessitating long-term recovery.[136] Cases of bowel perforation attributed to tocilizumab were reported.[137]

Acute pancreatitis in COVID-19 patients has been reported, but it is unclear if SARS-CoV-2 can induce chronic pancreatitis. Although long-term outcomes in patients with liver dysfunction in the setting of acute COVID-19 are sparse, liver MRI performed 2–3 months after disease onset revealed signs of fibro-inflammation in 5 out of 52 of such patients.[27] Therefore, follow up for early- and late-onset gastrointestinal symptoms, along with monitoring of liver function tests and abdominal imaging in selected patients should be considered (Table 2). In fact, a SARS-CoV-2 can persist in the gut for weeks following initial COVID-19 diagnosis, even without prominent gastrointestinal symptoms, and this could explain some of the long-term symptoms of some patients, such as dyspepsia and post-infectious manifestations in the spectrum of irritable bowel syndrome.[138,139]

Endocrine and reproductive system

Diabetes mellitus (DM) is a well-identified risk factor for severe acute COVID-19. SARS-CoV-2 induces a proinflammatory state[140] and the cytokine storm is more likely to develop in patients with DM.[141] In addition, direct invasion of SARS-CoV-2 to the pancreas, via ACE2 which is highly expressed in pancreatic tissue, contributes to pancreatic damage and hyperglycemia,[141] which can be further exacerbated by corticosteroids.[142] Long-term follow-up is needed to evaluate for late-onset DM in patients without such history who developed hyperglycemia in the acute phase of COVID-19. The occult effects of SARS-CoV-2 in adrenal, thyroid/parathyroid glands and hypophysis are not well studied. Cases of subacute thyroiditis and emergence of autoimmune disorders including Graves' disease and Hashimoto's thyroiditis have been reported in the post COVID-19 setting.[143,144] Similarly, targeted endocrine work-up, especially in patients with unexplained fatigue and mental impairment post COVID-19 is advisable. Home-isolation during lockdowns might decrease vitamin D levels and impair immunity (Appendix Table 2).[145] Several patients have presented with abnormally low vitamin D and increased parathormone levels 8 weeks post COVID-19 onset, which may also have a clinically relevant impact on bone health (Table 2).[146,147]

The long-term effects of SARS-CoV-2 on the reproductive system are largely unknown. Ovarian function could be affected by autoimmune disorders, whereas testes express ACE2 and can serve as a deposit for SARS-CoV-2.[148] A testicular ultrasound, sperm analysis and FSH/LH/ testosterone measurements should be performed upon clinical indication (Table 2). Although pregnancy itself is not a clear risk factor for severe COVID-19, a meta-analysis indicated an increased risk of premature delivery as a long-term COVID-19 complication.[149]

Musculoskeletal system and skin

Long term musculoskeletal complications are anticipated in patients with COVID-19 as reported previously in patients with SARS and in critically ill, especially post-ICU, patients.[150–152] Proinflammatory effects[150] and deconditioning have been postulated as mechanisms leading to deficits in both muscle strength and endurance. Myositis may also occur as a late complication and has been associated with cytokine storm, hypoxia, thromboembolic events or as a medication-related adverse event.[152] Myositis, muscle atrophy, and weakness can also be induced by long term use of corticosteroids and hydroxychloroquine, a treatment widely used during the first months of the pandemic.[153]

Systemic inflammation and cytokine storm induce osteoclastogenesis and impair osteoblast differentiation resulting to reduction of bone mineral density or even osteonecrosis, both of which can be further exacerbated by corticosteroids[154]. Hypercoagulability, leukocyte aggregation, and vessel inflammation may impair bone microvascular blood flow contributing to osteocytic ischemia and development of osteonecrosis.[155] These preliminary data support that COVID-19 may impair bone metabolism in the long term and invites further investigation.

Skin changes are multiform and among the most frequently patient-reported symptoms, whereas up to 64% emerge in the post-acute setting of the disease.[156–159] However, it seems that COVID-19-related skin rashes do not usually persist in the long-term, as only 3% of the Chinese patients reported a skin rash at 6 months post COVID-19.[103] Interestingly, up to one fifth of the long haulers report hair loss, which might be attributed to telogen effluvium due to direct SARS-CoV-2 infection or/and stress response during COVID-19.[103,160]

Chronic pain/Chronic fatigue

Long-lasting pain is emerging as a frequent and important complication of SARS-CoV-2, in patients with severe illness but also in non-hospitalized patients with mild- to moderate illness. The pain is often poorly characterized and constitutes an important element of the broader long COVID post-viral syndrome (Table 2, Appendix Table 2). Reports place it either in the subacute setting or in the more chronic phase following SARS-CoV-2 infection. It remains unclear how such pain results from the complex and dynamic interactions of viral-associated long-term organ damage, therapeutic-agent induced side-effects, exacerbation of pre-existing pain, and/or cognitive and psychosocial dysfunction.[161] Similarly, it is unknown if SARS-COV-2 infection exacerbates preexisting neuropathies (e.g., diabetic neuropathy)

Long-lasting and disabling fatigue is another frequently reported symptom under the umbrella of long COVID (Table 2, Appendix Table 2).[162,163] Based on recent cohort studies, the frequency of fatigue and/or muscular weakness at 6 months post-symptom onset can reach 60%.[162,164,165] Intensity can fluctuate, it is typically exacerbated by physical or mental effort, it seems to affect mostly young women although exact frequency is hard to ascertain due to reporting bias. Such chronic pain often results leads to a decline in quality of life and sedentary life-styles in previously active people.[166,167] Its pathogenesis remains undefined. Proinflammatory cytokines,[168] low grade endothelitis,[168] and/or autoimmunity and the neurotropism of the SARS-CoV-2 causing dysautonomia may be relevant.[169] Emerging data also support a role for intracortical GABAergic dysfunction.[170] Typically, there is a mismatch between the severity of complaints and the unrevealing clinical and laboratory evaluation. Severe fatigue in combination with "brain fog" and other less defined chronic complaints resemble myalgic encephalomyelitis/chronic fatigue syndrome,[168] which has been described following other post viral syndromes (Table 3).

There are also substantial implications to health economics associated with chronic pain syndromes associated with long COVID, which are the results of frequent health-care visits and expensive investigations. Capturing the magnitude of the problem is paramount for post COVID-19 rehabilitation. Screening tools, early measured intervention with concrete "triggers" for targeted and expanded workups and specialist consultations are needed (Table 2).

Psychiatric/ emotional health and well-being

Beyond physical illness, the current pandemic has created and amplified psychosocial stressors including social isolation, future uncertainty, fear of stigmatization, poor healthcare access, racial and gender biases, lack of social support, and financial strain. Sleeping disorders, anxiety, post-traumatic stress disorder (PTSD), depression, drug and alcohol abuse,[171] impaired quality of life and inability to return to normal daily routine have all been reported among people recovering from an acute infection (Table 1, Appendix Table 2).[172,173] For example, the isolation and lack of ability of family to visit hospitalized patients with acute COVID-19, could amplify feelings of depression and PTSD post discharge. Eighteen to 50% of SARS-CoV-2 survivors screen positive in at least one of the neuropsychiatric domains evaluated in cross-sectional and cohort studies, both in the sub-acute and more long-term setting.[173–175]

Delineating which part of the array of problems are explained by "mechanistic" pathophysiological complications of SARS-CoV-2 and which are secondary to the deep anxiety of a new disease and the bidirectional association between SARS-CoV-2 infection and psychiatric disorders, is difficult.[176,177] Those interactions between physical and psychological symptoms are complex and often referred to as "medically unexplained symptoms".[176] Neuroinflammatory mechanisms implicated in other psychiatric diseases may play a role, triggered by cytokine dysregulation and the neurotropic potential of SARS-CoV-2, possibly inducing autoimmunity and immune dysregulation.[27] GABAergic dysfunction has also been implicated.[178]

Determining which patients are at risk and which will require long-term follow-up is crucial (Table 3). The potential emergence of a "wave" of late-onset neuropsychiatric manifestations remains to be elucidated. There is great need for strategies on screening processes, resource provision, validated care pathways, and multidisciplinary rehabilitation services.[179–181]

Weaknesses of current literature

Our review included studies with significant heterogeneity. These studies had different definitions, follow-up, and investigations (e.g., to rule out concomitant illness); many had an organ-centric approach in measured outcomes (e.g., lungs); and the majority had no case control design or comorbidity adjustments (Table 1, Appendix Table 2). Studies were conducted in different stages of the year during the pandemic (with confounders of different demographics, changing treatment modalities and different degrees of capacity in treating institutions); and had possible referral and reporting biases. Small numbers and a monocentric retrospective nature in most were additional limitations. Importantly, the association of some ill-defined chronic symptoms with prior acute COVID-19 might be problematic with current tests. For example, the presence or absence of a positive SARS-CoV-2 antibody (that can be false positive or false negative due to antibody decay) or the absence (lack of testing, false negative tests) of positivity of SARS-CoV-2 PCR test (that can persist in low titer chronically without reflecting active disease) might correlate poorly with downstream complaints or symptoms. In addition, COVID19 pandemic is being transformed to a series of different "waves" each of which is driven by mutations of the SARS-CoV-2 virus that carry different risks to affect different demographics and cause serious illness. It is unknown if the fluidity in COVID19 epidemiology and if SARS-COV-2 ultimately become endemic in long -term, would be translated to differences in incidence, clinical spectrum and severity of post-acute COVID19.

Conclusions

Given the pandemic spread of COVID-19, the long-term health of millions might be affected. COVID-19 is not always an acutely reversible disease but could have a second act in some patients. Long COVID-19 is a multisystem disease with far-reaching and lingering effects and a complex constellation of symptoms that even if uncommon, could result in significant chronic morbidity. The pace of recovery of the symptoms is non-linear, largely undefined and a complete picture of the natural history and burden of chronic COVID-19 disease might take many months or even years to emerge. At the population level, long COVID-19 rapidly challenges our health care systems and has the potential to aggravate fragmentation of care. Although rapid guidelines started emerging,[182] several research questions exist (Table 4) and are subjects of intense investigation (Appendix Table 3 summarizes ongoing registries and trials regarding long COVID-19). A holistic and evidenced-based approach to medical care and support of the COVID-19 long haulers is needed.

Contributions

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Table 4
Clinical/translational research and care needs in patients with subacute and/or chronic COVID-19.

Uniform definitions and terminology
Development of a uniform diagnostic code of the disease, for better access of patients to clinical care
Epidemiology/Risk factors/Clinical spectrum of the syndrome
Develop robust multi-institutional "holistic" registries and case control studies with appropriate comorbidity matched controls, especially in non-hospitalized COVID-19 patients
How one uses existing databases and big data analysis for granular predictions of late COVID-19 complications?
How to use patient- driven reporting data (e.g., in social media or applications) along with traditional epidemiological studies to capture the spectrum and burden of long COVID-19?
Creation of "living" prediction models based on the evolution of clinical/laboratory imaging data) along with translational readouts (e.g., humoral and cellular immunity and cytokines, microbiome, metabolomics) of the progression from acute to subacute or chronic COVID-19
Do specific patient groups such as those with cancer patients, transplant rheumatologic or inflammatory or neurodegenerative diseases have heightened risk for late and specific complications?
Do patients with other pre-existing somatic or psychologic comorbidities have predilection towards specific organ dysfunction in late COVID-19?
Is the pattern and severity of clinical manifestations in acute COVID-19 as predictor of type and degree of organ dysfunction in late COVID-19?
How the type and sequence of antiviral and/or immunomodulating drugs used in acute COVID-19 affect risk for late onset sequelae
How reversible and when are each of the symptoms?
Etiology
Is long COVID-19 a state of functional immunosuppression vs low grade infection (if so, what is the viral reservoir) vs inflammatory state? Is this organ specific?
Is there an immunogenetic component in long COVID-19?
Do preexisting cross reactive antibodies play a role for late manifestations as in a pattern of antibody-mediated enhancement?
Would an antigenic drift of the SARS-COV-2 (through mutations) influence risk for late complications as we move deeper in the pandemic?
Can some patients with long COVID- 19 have occult reactivation of another virus (e.g., EBV)?
Management
How to approach relatively asymptomatic patients with abnormal imaging (e.g., chest CT, cardiac MRI) suggesting a late post COVID-19 complication?
Do we need routine longitudinal follow up lab testing and imaging in all patients who recovered from mild COVID-19 acute infection?
What interventions are useful to prevent severe sequalae in patients with early organ damage in subacute or chronic COVID-19? (e.g., routine anticoagulation in patients with heart damage, antifibrotic agents in patients with early pulmonary fibrosis, metabolic therapeutics?)
How can we do randomized control trials with adaptive design for therapeutic and/or rehabilitation interventions?
Can prior immune therapies (e.g., IL-6 inhibitors, corticosteroids) ameliorate chronic symptoms?
Can therapies for early COVID19 (e.g., monoclonal antibodies) prevent long COVID through decrease of hospitalizations and ICU admissions?
How safe are vaccines in patients with long COVID-19?
Heath policy issues
How to organize a cost-effective and coordinated model of care delivery and avoid fragmentation of care?
What is the best practice and business model (primary care driven vs specialist -driven vs co-managed model) in patients with long COVID-19?
What is the role of telehealth and how to triage COVID-19 survivors based on pattern and severity of reported symptoms?
How to establish quality criteria for services in long COVID-19?
Best methods to measure the impact of long COVID-19 to social strains, emotional toll and stigmatization of victims
Careful capturing quality of life on long COVID-19
Long COVID-19 in children
Long COVID-19 in health care workers

EBV: Epstein-Barr virus; CT: computed tomography; MRI: magnetic resonance imaging.

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Disclosures

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.05.004.

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