Post-acute COVID-19 syndrome

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Shareable abstract (@ERSpublications)
Given the millions of patients infected with SARS-CoV-2 worldwide and the need for multidisciplinary management of the chronic complications, post-acute COVID-19 syndrome will be a major issue for various healthcare providers in the coming months. https://bit.ly/3lBJuXu

Abstract

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19) pandemic that has resulted in millions of deaths and a major strain on health systems worldwide. Medical treatments for COVID-19 (anticoagulants, corticosteroids, anti-inflammatory drugs, oxygenation therapy and ventilation) and vaccination have improved patient outcomes. The majority of patients will recover spontaneously or after acute-phase management, but clinicians are now faced with long-term complications of COVID-19 including a large variety of symptoms, defined as "post-acute COVID-19 syndrome". Most studies have focused on patients hospitalised for severe COVID-19, but acute COVID-19 syndrome is not restricted to these patients and exists in outpatients. Given the diversity of symptoms and the high prevalence of persistent symptoms, the management of these patients requires a multidisciplinary team approach, which will result in the consumption of large amounts of health resources in the coming months. In this review, we discuss the presentation, prevalence, pathophysiology and evolution of respiratory complications and other organ-related injuries associated with post-acute COVID-19 syndrome.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has affected millions of patients worldwide in recent months. The acute symptoms of the disease were reported as early as the spring of 2020. Clinicians quickly realised that the clinical presentation of the infection varied and that it led to asymptomatic forms as well as severe forms, although the latter are infrequent. Multisystem involvement due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been well described.

Beginning in the first worldwide wave of the pandemic, the importance of the cytokine "storm", which affects many organs, including the lungs, heart and brain, raised fears of major sequelae in patients who survived the severe forms. In addition, over time, survivors were frequently observed to present with persistent neurological, respiratory or cardiovascular symptoms, constituting what has been called

"post-acute COVID-19 syndrome" or "long COVID-19" that potentially lasts for weeks or months [1]. These symptoms seem frequent and do not affect only those patients who have experienced the most severe forms of COVID-19.

This topic is important because these symptoms frequently exert a substantial effect on patients' quality of life. Overall, their incidence suggests that a considerable number of patients will be affected.

What are the symptoms of post-acute COVID-19 syndrome? What are their effects? What do we know about their pathogenesis and their risk factors? Do they disappear over time? What assessments should be undertaken in these patients? This synthetic review seeks to answer these questions.

Respiratory disorders
Respiratory symptoms
As part of post-acute COVID-19 syndrome, the persistence of respiratory symptoms, especially dyspnoea and cough, beyond 4 weeks from the onset of symptoms appears to be common. Dyspnoea is the most frequently respiratory reported symptom after COVID-19. Studies reporting respiratory symptoms from 1 to 12 months after COVID-19 show a prevalence of persistent dyspnoea ranging from 5% to 81% after hospitalisation [2–8] and ~14% in non-hospitalised patients with mild COVID-19 [9] (table 1 and figure 1). The persistence of dyspnoea does not seem to be closely related to the initial severity of COVID-19. Indeed, dyspnoea has been reported to be as frequent in patients who initially required initial intensive care unit (ICU) admission as in patients who were initially hospitalised in wards [10] and no correlation has been observed with the number of days on supplemental oxygen [11], despite more frequent pulmonary function test abnormalities in patients initially diagnosed with severe COVID-19 [12]. Dyspnoea exerts a major effect on quality of life [5] and socioeconomic status, as many patients with post-acute COVID-19 syndrome do not return to work for 6 months after COVID-19 [6]. The mechanisms of dyspnoea after COVID-19 are multifactorial, including parenchymal sequelae, dysfunctional breathing, cardiovascular dysfunction and muscular deconditioning [8, 13, 14]. The functional effect of lung parenchymal sequelae is generally limited [8, 10, 11, 15–17] and dyspnoea progressively improves over time even if a subgroup of patients experiences persistent dyspnoea up to 1 year after COVID-19 [2].

Cough seems to be less common than dyspnoea after COVID-19, but it can also persist for weeks or months after SARS-CoV-2 infection and has been reported in 2–42% of patients [3, 5–7, 11, 18, 19]. As reported for dyspnoea, cough potentially alters quality of life [5]. In a large study conducted on patients 11 months after discharge, no clinical or hospitalisation factors were associated with long-term post-COVID-19 cough [19]. In a recent review, Song et al. [18] hypothesised that cough after COVID-19 was due to activation of the vagal sensory nerves, which leads to a cough hypersensitivity state and to neuroinflammatory events in the brain.

| First author or study group [ref.]	Patients, n	Time after discharge	ICU, %	Mechanical ventilation, %	Prevalence of dyspnoea, %	Prevalence of cough, %
Zhao [3]	55	3 months	0	0	15	2
De Lorenzo [4]	185	23 days	2.2	0	31	NA
Jacobs [5]	183	35 days	NA	5	45	42
Bellan [8]	238	4 months	12	9	6	3
Huang [12]	1733	6 months	4	1	26	NA
COMEBAC [7]	478	4 months	30	11	16	5
González [15]	62	3 months	100	63	47	34
Lerum [10]	103	3 months	15	9	54	NA
Ghosn [6]	1137	6 months	29	NA	26	12
Shah [11]	60	3 months	NA	20	20	20
Wu [2]	83	3 months	NA	0	81	NA
		6 months			30	
		9 months			12	
		12 months			5	
Fernández-de-las-Peñas [19]	1950	11 months	7	NA	23	3
Augustin [9]	353	7 months	0	0	14	4

NA: not available.
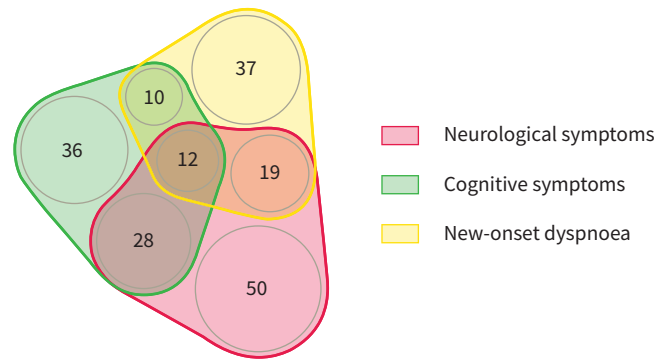
FIGURE 1 Visualisation of symptoms that did not exist before COVID-19 and their overlap in 192 patients (of 478 patients) who presented at least one symptom at teleconsultation. Of note, 52 patients had experienced a new symptom that was not dyspnoea, cognitive or neurological. Reproduced from [7] with permission.

The first 1-year follow-up studies after COVID-19 have recently been published. Wu *et al.* [2] showed that among 83 patients with severe COVID-19 who did not require mechanical ventilation, dyspnoea scores and exercise capacity improved over time. However, a subgroup of patients had persistent physiological and radiographic changes after 1 year [2]. By contrast, Huang *et al.* [20] showed a slight deterioration of dyspnoea scores between 6 and 12 months after COVID-19 and an absence of improvement in exercise capacity and in diffusing capacity of the lung for carbon monoxide (D_{LCO}), while total lung capacity (TLC) and lung imaging abnormalities gradually recovered. Therefore, the precise evolution of respiratory symptoms, of functional and radiological lung damage, remains to be determined in long-term prospective follow-up studies.

Due to the large number of patients with COVID-19 worldwide, the long-term respiratory complications of COVID-19 may lead to the major use of health resources. Physicians should be aware of this condition and of the mechanisms that might lead to persistent dyspnoea and cough in these patients to propose individual management strategies adapted to each condition. Studies reporting respiratory symptoms after COVID-19 are summarised in table 1 and studies reporting pulmonary function tests after COVID-19 are summarised in table 2.

Dysfunctional breathing

Dysfunctional breathing is a term describing a group of breathing disorders resulting in dyspnoea and often non-respiratory symptoms in the absence of or in excess of organic respiratory disease [21]. Hyperventilation syndrome (HVS) is the most frequently studied form of dysfunctional breathing and severely affects quality of life [22]. Since post-COVID-19 dyspnoea can affect patients with even initially mild COVID-19 and no evidence of organ damage at re-evaluation [23], a potentially high prevalence of post-COVID-19 dysfunctional breathing has been suspected early [24]. However, the literature is still scarce. The Nijmegen Questionnaire is a measure of functional respiratory complaints [25, 26] that has been used in our COMEBAC (COnsultation Multi-Expertise de Bicêtre Après COVID-19) cohort study to detect patients with dysfunctional breathing [7]. A positive Nijmegen Questionnaire (score >22 out of 64) was identified in 20.9% of the 177 patients assessed at an ambulatory care visit for persistent symptoms and/or hospitalisation in the ICU [7]. Using cardiopulmonary exercise testing (CPET), Motiejunaite *et al.* [27] reported exercise hyperventilation as a major limiting factor in a case series of eight COVID-19 survivors. Aparisi *et al.* [28] also highlighted ventilatory inefficiency during CPET in patients with post-COVID-19 unexplained dyspnoea, a feature usually observed in patients with HVS. These results were consistent with the study by Taverne *et al.* [29] which reported that 10 out of 147 (7%) patients complained of persistent dyspnoea at 3 months that was unexplained by standard investigations. Six patients had a positive Nijmegen Questionnaire score, hypocapnia at rest and a positive hyperventilation challenge, consistent with the diagnosis of HVS. Interestingly, brain magnetic resonance imaging (MRI) of these patients with HVS was normal [29].

The physiopathology of post-COVID-19 dysfunctional breathing/HVS is poorly understood. Anxiety and depression are common among patients with dysfunctional breathing [30], and some authors have highlighted the role of severe psychological trauma [31]. One may hypothesise that the negative socioeconomic effects of the pandemic on mental health might promote the onset of functional respiratory complaints that are potentially part of a larger post-COVID-19 somatoform disorder. On the other hand,

TABLE 2 Assessment of lung function after COVID-19 reported in the literature

First author [ref.]	Patients, n	Time after discharge	FVC, % pred	TLC, % pred	FEV$_1$, % pred	D_{LCO}, % pred	Lung function abnormalities, n (%)	Low FVC <80% pred, n (%)	Low TLC <80% pred, n (%)	Low FEV$_1$ <80% pred, n (%)	D_{LCO} <70% pred, n (%)
Zhao [3]	55	3 months	NA	NA	NA	NA	14 (25.5)	6 (10.9)	4 (7.3)	NA	9 (16.4)
Bellan [8]	238	4 months	98.5 (90–109)	NA	101 (92–112)	79 (69–89)	NA	NA	NA	NA	113 (51.6)
González [15]	62	3 months	82±17	84±16	89±19	68±13	NA	NA	23 (37.1)	NA	50 (82)
Lerum [10]	103	3 months	94 (76–121)	NA	92 (84–106)	83 (72–92)	NA	7 (7)	NA	11 (11)	24 (24)
Shah [11]	57	3 months	94±16	86±13	93±16	77±16	33 (58)	NA	NA	NA	30 (52)
Wu [2]	83	3 months	92 (81–99)	87 (77–98)	90 (76–100)	77 (67–87)	NA	19 (23)	22 (27)	25 (30)	46 (55)
		6 months	94 (85–104)	91 (82–98)	92 (80–101)	76 (68–90)	NA	13 (16)	16 (19)	20 (24)	45 (54)
		12 months	98 (89–109)	91 (87–100)	96 (85–110)	88 (78–101)	NA	9 (11)	12 (15)	13 (16)	27 (33)
Sonnweber [151]	145	2 months	NA	NA	NA	NA	53 (42)	34 (27)	14 (11)	28 (22)	39 (31)
		4 months	NA	NA	NA	NA	48 (36)	29 (22)	15 (11)	30 (22)	28 (21)
Qin [152]	647	3 months	90±13	99±24	94±11	83±25	NA	17 (21)	NA	5 (6)	31 (38)
Gamberini [153]	178	12 months	97±19	NA	100±17	78±22	NA	NA	NA	NA	NA

Pulmonary function test data are presented as median (interquartile range) or mean±SD. FVC: forced vital capacity; TLC: total lung capacity; FEV$_1$: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; NA: not available.

since the viral receptor angiotensin-converting enzyme 2 (ACE2) is expressed in the brainstem nuclei involved in the regulation of ventilation [32], central interference with the respiratory drive should not be excluded. Data regarding adequate therapeutic strategies are lacking. Management of dysfunctional breathing/HVS usually includes breathing exercises with a physiotherapist (with a low level of evidence) [33].

In conclusion, functional respiratory complaints may impose a significant healthcare burden following COVID-19 and dysfunctional breathing/HVS represents a significant proportion of these symptoms. More studies are needed to evaluate the underlying prevalence, characteristics and pathophysiology of those symptoms, which are complicated by the current absence of both consensus definitions and diagnostic gold standards for dysfunctional breathing/HVS.

Radiological sequelae

Post-COVID-19 radiological sequelae vary widely. High-resolution computed tomography (HRCT) represents the reference examination used for the diagnosis and classification of these sequelae [34]. HRCT allows a fine analysis of the parenchyma and the detection of pulmonary fibrosis, among other lesions. Three main categories of post-COVID-19 sequelae can be distinguished: so-called irreversible lesions, reversible lesions and lesions of undetermined evolution (figure 2).

Post-COVID-19 pulmonary fibrosis is the main irreversible lesion. Histologically, it corresponds to a pathological reconstruction of the alveolar epithelium with an overproduction of the collagenic extracellular matrix associated with destruction of the normal pulmonary architecture. Post-COVID-19 pulmonary fibrosis occurs together with various lesions, such as interstitial abnormalities including reticulation, irregular pleural interfaces, traction bronchiectases or even honeycomb lesions. These lesions are present in 13–27% of patients, depending on the series and the delay in evaluation [3, 7, 15, 35]. The extent of the lesions is small to moderate, frequently involving <25% of the pulmonary parenchyma [7]. LI et al. [36] identified age, body mass index and inflammatory markers (procalcitonin) as the main risk factors for
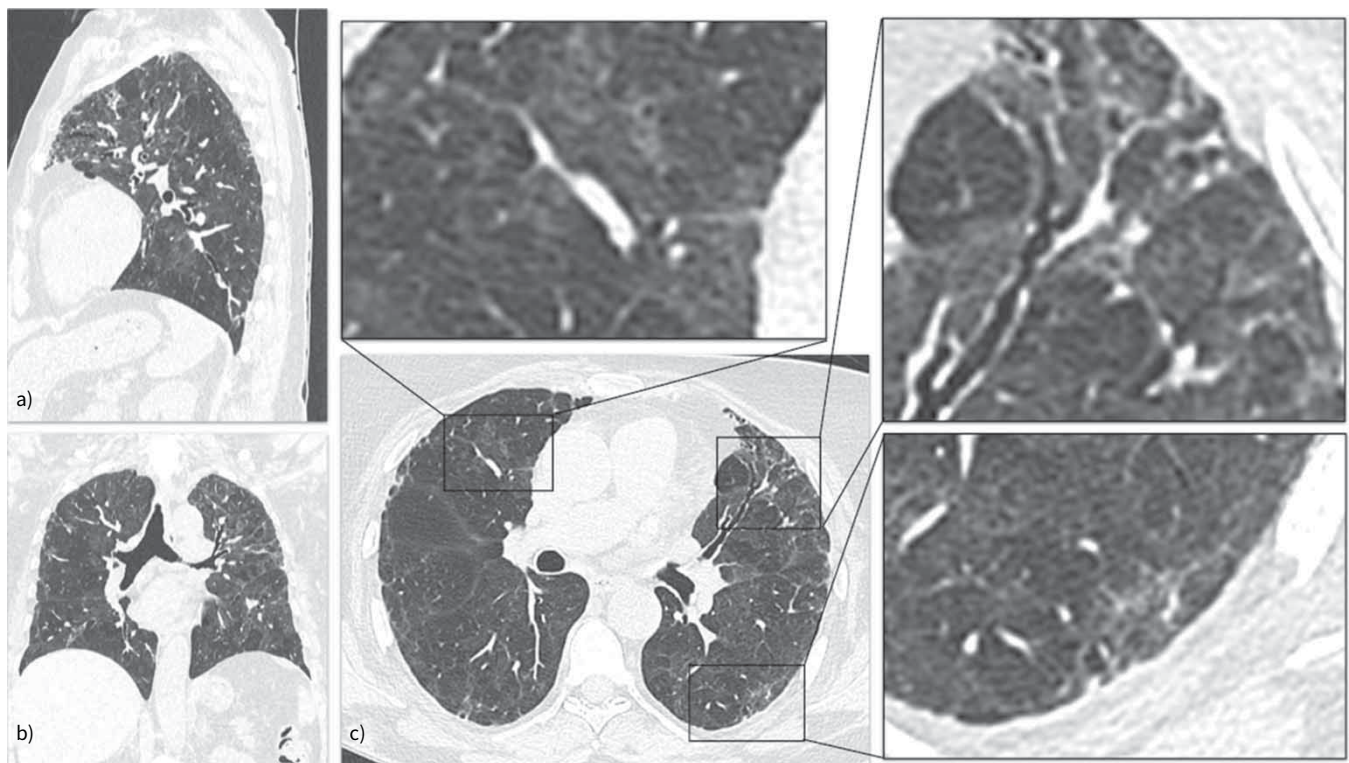

FIGURE 2 a) Sagittal, b) coronal and c) axial multiplanar reconstructions of a thoracic high-resolution computed tomography scan performed at 4 months after COVID-19 showing the sequellar involvement of the pulmonary parenchyma associated with the presence of fibrosing irreversible lesions with traction bronchiectasis (upper right panel, high magnification image from c), reversible lesion ground-glass opacities (upper left panel, high magnification image from c) and subpleural linear lesions with indeterminate evolution (lower right panel, high magnification image from c).

post-COVID-19 pulmonary fibrosis diagnosed from 90 to 150 days. Indeed, these factors are common risk factors for severe forms of COVID-19 [36]. These lesions are thus more readily found in patients who have presented with acute respiratory distress syndrome (ARDS) and those admitted to the ICU, with an incidence that is potentially three times higher for intubated patients than for non-intubated patients [7]. These lesions do not seem to evolve on their own, as follow-up does not show an increase in their incidence [2].

In terms of potential reversible lesions, we consider ground-glass opacity (GGO)-type anomalies. GGOs, which are at the forefront of acute COVID-19, are generally considered the HRCT sign of reversible parenchymal inflammation. Surprisingly, GGOs do not systematically disappear completely at follow-up and have been observed up to 12 months from the initial COVID-19 diagnosis [2]. The incidence varies according to the series and is evaluated to range from 7% to 92%, with a probable effect of the delay between follow-up and the initial infection decreasing over time [2, 7, 12, 35]. Nevertheless, GGOs seem to be associated with altered pulmonary function tests, and their presence might underlie the persistence of residual and autonomous inflammation and might subsequently lead to the development or extension of fibrotic lesions [35].

Finally, lesions with indeterminate status are considered as residual condensations and ventilatory disorders predominantly located in the subpleural portion of the lung, such as curvilinear opacity. Their evolutionary profile is poorly characterised because of the lack of iterative follow-up studies; however, based on the sparse data available, they appear to regress over time [2].

Even if radiological abnormalities are frequently observed during the long-term follow-up of patients with COVID-19, the effect on pulmonary function tests is modest for most patients. In the COMEBAC cohort study, 19.3% of the patients reassessed at the ambulatory care visit had fibrotic lesions (with a lesion extent <25% in 97% of cases) at 4 months [7]. Pulmonary function tests of patients with fibrotic lesions indicated a mild impairment, with TLC 74.1±13.7% predicted and D_{LCO} 73.3±17.9% predicted [7]. WU et al. [2] reported the evolution of pulmonary function tests in a prospective, longitudinal, cohort study of patients admitted to the hospital for severe COVID-19 who did not require mechanical ventilation. The authors found a mild impairment in D_{LCO} and forced vital capacity (FVC) at 3 months (median (interquartile range) 77% (67–87%) predicted and 92% (81–99%) predicted, respectively) with a progressive improvement at 6 months (D_{LCO} 76% (68–90%) predicted and FVC 94% (85–104%) predicted) and 12 months (D_{LCO} 88% (78–101%) predicted and FVC 98% (89–109%) predicted) [2].

Additionally, given the strong association between symptomatic forms of COVID-19 and pulmonary embolism, some teams suggest an assessment of the presence of perfusion disorder at a distance from the initial infection [37, 38]. REMY-JARDIN et al. [39] reported perfusion abnormalities suggestive of widespread microangiopathy in as many as 65.5% of patients. Four patients in the REMY-JARDIN et al. [39] study had normal CT scans and perfusion defects detected using double-energy CT. The risk factors and the evolution of these perfusion disorders are unknown.

In conclusion, the prevalence of radiological abnormalities is much greater than that of objective ventilatory disorders on respiratory functional explorations, with an unclear link between those two abnormalities [7]. Similarly, because most studies lack a control group, the abnormalities observed on HRCT cannot be conclusively identified as being specifically due to SARS-CoV-2 infection or simply the consequence of the diffuse alveolar damage occurring during pulmonary parenchyma infection and/or consecutive ARDS.

Potential sequelae of pulmonary embolism

Pulmonary embolism is a common life-threatening complication of COVID-19, but its precise incidence is poorly known as CT pulmonary angiography (CTPA) was not systematically proposed for the diagnosis of COVID-19. RIYAHI et al. [40] reported a pulmonary embolism incidence of 25% in 413 patients hospitalised with COVID-19 suspected of pulmonary embolism. In a prospective study including 106 consecutive patients with COVID-19 who underwent systematic CTPA, JEVNIKAR et al. [38] reported pulmonary embolism in 15 patients, with an incidence of 14.2% (95% CI 7.5–20.8%). The incidence of thromboembolic events has even been reported to be higher in severe ICU patients (>50% of patients) [41]. This high incidence of pulmonary embolism was confirmed in a large recent meta-analysis of 27 studies including 3342 patients with COVID-19, where the authors reported pooled incidence rates of pulmonary embolism and deep vein thrombosis of 16.5% (95% CI 11.6–22.9%) and 14.8% (95% CI 8.5–24.5%), respectively [42]. The mechanisms of pulmonary embolism in patients with COVID-19 remain a matter of debate but may be at least partially explained by the pulmonary endothelial dysfunction

associated with SARS-CoV-2 infection [43–45]. Based on the high incidence of pulmonary embolism and possible associated endotheliitis of the pulmonary vasculature, one can hypothesise that patients with COVID-19 may be at risk of developing chronic thromboembolic pulmonary hypertension (CTEPH) [46, 47]. Nevertheless, to date, no series of post-COVID-19 CTEPH have been reported. As CTEPH is usually characterised by a so-called honeymoon period after an acute pulmonary embolism, physicians should be aware of this potential complication, which can be easily screened by echocardiography and ventilation/ perfusion lung scans.

Psychiatric symptoms and disorders
Prevalence

After respiratory disorders, psychiatric consequences are the most frequent components of post-COVID-19 syndrome. Understandably, COVID-19 might generate acute psychiatric consequences and symptoms may persist over time after the acute phase. The anxiety-provoking social and media context, the fear of a serious form of the disease, the fear of not being able to benefit from appropriate care, especially in the first weeks of the pandemic, the lack of established curative treatment, the lack of visits from relatives for hospitalised patients, brain damage caused by the virus itself, and inflammatory and immune imbalance have favoured anxiety or depressive symptoms. The traumatic experiences of the acute disease and care, sometimes in degraded conditions, may have favoured the onset of post-traumatic stress. Finally, the persistence of physical disorders for weeks or months after the acute episode may have contributed to psychiatric symptoms and disorder prevalence. What is it truly?

Importantly, symptoms, as assessed using simple questionnaires, and disorders, whose diagnosis requires supervised psychiatric interviews, must be distinguished. The prevalence of psychiatric symptoms in the months following COVID-19 has been reported in several studies based on self-report questionnaires, which provided follow-up for 14 days to 6 months. They consistently reported a high prevalence of insomnia (31–54%), anxiety symptoms (5–46%), depressive symptoms (9–42%) and post-traumatic stress symptoms (10–57%) (supplementary table S1) [7, 8, 12, 48–69]. In the COMEBAC study cohort, we reported insomnia in 54% of patients, anxiety symptoms in 31%, depressive symptoms in 22% and post-traumatic stress symptoms in 14% at 4 months after hospitalisation for COVID-19 [7].

Psychiatric disorders have been less frequently reported because their diagnosis is more difficult to establish. A recent review and meta-analysis estimated that 53 million additional major depressive disorders and 76 million additional anxiety disorders are related to the pandemic worldwide since the beginning of 2020 [70]. Two Italian studies reported a systematic evaluation by qualified psychiatrists of patients after the acute episode of COVID-19 [55, 71]. One study reported the onset of a new mental disorder within 3 months of the acute episode in 12% of patients [71]. In the other study, the prevalence of post-traumatic stress disorder was 30% at 1–3 months after a severe acute episode [55]. However, these studies did not compare these prevalence rates to populations with conditions other than COVID-19.

Two studies performed by TAQUET and co-workers [72, 73] compared psychiatric disorders in patients with and without COVID-19 from very large cohorts (236 379 and 62 354 COVID-19 survivors) based on electronic medical reports. The incidence of mental disorders was higher in patients with COVID-19 than in other populations (influenza, other respiratory infections, skin infections, cholelithiasis, urolithiasis or large bone fractures) [72, 73]. In one of the studies, an anxiety disorder appeared in 7% of patients 6 months after COVID-19 and a mood disorder was observed in 4% [72].

Risk factors

What are the risk factors for presenting persisting psychiatric symptoms or disorders? Typical of psychiatric symptoms and disorders, female sex is associated with higher levels of anxiety, depressive and post-traumatic stress symptoms [49] and disorders [71]. In one study, patients with post-traumatic stress disorder had a more frequent psychiatric history [71]. In another study, younger patients had higher levels of depression and sleep disturbances 1 month after COVID-19 than older patients [49].

Intuitively, psychiatric disorders should be expected in patients with the most severe forms of acute COVID-19. However, no convergent evidence has emerged regarding the association between the prevalence of symptoms or disorders and COVID-19 severity. In one of the large cohorts based on electronic health records, the incidence of these disorders was higher in patients who presented with a severe form of the disease (hospitalisation, admission to ICU and acute encephalopathy) [72]. MAZZA et al. [49] showed that a higher systemic immune-inflammatory index (platelets×neutrophils/lymphocytes) during acute COVID-19 was associated with anxiety and depression symptoms after 1 month and with depressive symptoms after 3 months. However, RAMAN et al. [62] did not replicate these findings. In one of the largest

cohorts of COVID-19 survivors published to date, HUANG et al. [12] reported that psychiatric symptoms were associated with the most severe cases of acute COVID-19 (i.e. high-flow nasal cannula or mechanical ventilation) but not with oxygen dependence. However, this association has not been observed in several other studies [53, 58, 62, 63], including for patients requiring intensive care [12, 63].

Interaction with other post-COVID-19 symptoms

Interestingly, anxiety, depression and post-traumatic stress symptoms have been associated with concomitant dyspnoea in the months following acute COVID-19 [51, 62, 65]. An association of asthenia with gastrointestinal symptoms and cognitive disorders has also been reported [51]. In contrast, no association was observed between neurological symptoms during acute COVID-19 and psychiatric symptoms 6 months later [74]. In another study, patients with post-traumatic stress disorder had more physical symptoms persisting 3 months after the acute infection [71]. A recent study using electronic health records found that psychiatric disorders diagnosed after acute COVID-19 co-occurred more frequently with non-psychiatric symptoms than after influenza [75].

Altogether, the association between COVID-19 acute severity and subsequent psychiatric symptoms remains unclear. The results from well-designed prospective cohort studies are needed.

Cognitive consequences

Symptoms and frequency

During the acute phase of COVID-19, clinical evidence of neurological manifestations of the infection exists. "Impaired consciousness" with somnolence, delirium [76], encephalomyopathy [77], meningitis [78] and strokes [79–81] have been reported as "neuro-COVID" manifestations. Brain MRI has been described as abnormal in up to 56% of these patients and a variety of lesions, including ischaemic strokes, leptomeningeal enhancement and encephalitis, have been observed.

In the post-COVID-19 phase, the issue of neurological sequelae (or de novo manifestations) of the infection has rapidly emerged. In addition to persistent central nervous system (CNS) impairment in patients with strokes or documented encephalopathy beginning in the acute phase, evidence for cognitive dysfunction in patients without acute neuro-COVID-19 and/or with normal brain imaging is increasing. In fact, cognitive complaints have been reported in several studies within 4–5 months after acute COVID-19, with marked similarities among countries impacted by the pandemic. These findings were observed by authors from New York (using the OASIS-D1 mandatory assessment tool) [82], the Netherlands (Cognitive Failure Questionnaire) [53, 58], Italy (self-report questionnaire or Mini Mental State Examination evaluation) [4, 51], France (self-report questionnaire) [83], Germany (Telephone Assessment of Cognitive Status (TICS)) [84], Spain (complete neuropsychological battery) [85], the UK (Montreal Cognitive Assessment) [62], Bangladesh (telephone assessment) [86], Brazil (TICS) [87] and China (complete neuropsychological battery) [88]. One difficulty is the heterogeneity in reporting these outcomes without standardised evaluations. Most studies report the use of screening tools such as the Montreal Cognitive Assessment and the Mini Mental State Examination for a telephone assessment of cognitive complaints. Interestingly, although most of these studies evaluated patients after hospital discharge for COVID-19, some included outpatients with similar cognitive complaints [58].

However, a precise estimation of the exact prevalence of cognitive sequelae is difficult due to the limitations of most of these studies. Many included a limited number of patients, used only self-administered questionnaires or did not include a control population. The population included was sometimes heterogeneous (hospitalised or non-hospitalised patients in the acute phase, initial diagnosis of COVID-19 with or without a positive PCR test).

When considering only the objective cognitive evaluation, a reduced performance has been globally reported in 15–40% of patients. One of the first extended reports on cognitive impairment was published by ALMERIA et al. [85]. They reported on 35 patients from Spain without any prior psychiatric or cognitive history within 35 days after hospital discharge in the first wave of the pandemic during the spring of 2020. All patients underwent a large neuropsychological battery of tests evaluating verbal, visual and working memory, memory coding, attention, process speed, and executive function. Overall, 34% of patients had cognitive complaints, which were notably not associated with cognitive performance. Patients with complaints recorded significantly worse scores on anxiety and depression tests, emphasising the link between cognitive and psychiatric symptoms. Cognitive impairment was associated with headache, anosmia, oxygen therapy during the acute phase and diarrhoea, suggesting roles for severe initial manifestations and persistent symptoms in neuropsychological performance. Reduced sustained attention, executive function, visuospatial processing and memory have been reported compared with controls [84,

85, 89]. SOLDATI *et al.* [87] reported that 13% of patients who recovered from COVID-19 met the criteria for mild cognitive impairment, as observed in patients with other viral infections such as HIV. Notably, some studies enrolled patients with prior alterations in mental health [87], but some studies excluded these patients [85], once again limiting the extrapolation of the conclusions.

Putative mechanisms

Neurological symptoms and cognitive dysfunction might result from virus-related CNS damage and/or non-CNS systemic manifestations such as hypoxia or inflammation [90]. Human coronaviruses are considered potentially neurotrophic. As with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), the virus might directly infect neurons, especially in the olfactory area, through an interaction with ACE2 and then be transported through the axons to the CNS [91]. The temporal region and the hippocampal area seem to be specifically vulnerable in animal models of coronavirus infections [92], as observed in non-coronavirus respiratory infections such as influenza [93], and might be responsible for part of the cognitive dysfunction.

Another indirect role for virus-related CNS dysfunction might be inflammation. Elevated levels of pro-inflammatory cytokines produced during acute COVID-19 can cross the blood–brain barrier and activate astrocytes and microglial cells. They in turn induce the release of interleukin-1β, whose receptors are widely expressed on hippocampal neurons. Additionally, SARS-CoV-2 may decrease ACE2-mediated brain-derived neurotrophic factor activity, which theoretically prevents excessive microglial activation and neuronal inflammation. Lastly, elevated levels of serum markers of axonal injury (neurofilament light chain protein) and astrocytic activation (glial fibrillary acidic protein) have been detected in patients with COVID-19, indicating potential CNS damage during the acute phase that might persist in the aftermath of the infection [94, 95].

Finally, other interrelated factors, such as the severity of the initial infection, might account for some of the symptoms or sequelae. Indeed, profound hypoxaemia and mechanical ventilation [96] or extracorporeal membrane oxygenation procedures for patients admitted to the ICU might be associated with persistent cognitive dysfunction and psychological disturbances in the long term, which are perhaps associated with a risk of cerebral atrophy and ventricular enlargement. The role of the systemic manifestations and the management of long-term CNS consequences of COVID-19 remain to be investigated.

Cardiac consequences

Acute cardiac injury during COVID-19

In contrast to cognitive or psychiatric consequences, post-COVID-19 cardiac symptoms always result from sequelae of acute cardiac injury [97]. Indeed, in the acute phase of COVID-19, cardiovascular involvement is one of the first manifestations of infection [98]. SARS-CoV-2 affects the cardiovascular system through several mechanisms [99]: invasion of cardiomyocytes by the virus *via* ACE2, major systemic inflammation, vascular thrombosis associated with hypercoagulability [100], myocardial ischaemia resulting from the destabilisation of coronary plaques, hypoxaemia and stress cardiopathy [99].

However, the incidence and nature of acute cardiovascular manifestations of COVID-19 are highly variable, ranging from an asymptomatic troponin elevation to fulminant myocarditis resulting in cardiogenic shock [98]. The elevation of troponin levels is found in 20% of patients [101], but it is non-specific since it may result from myocardial ischaemia, myocarditis, pulmonary embolism or renal failure. Moreover, increased troponin levels were reported in a similar proportion in patients with ARDS associated or not with COVID-19 [102]. Cardiac arrhythmias have been reported in 7% of 393 hospitalised patients (and up to 19% of those who were mechanically ventilated) [103].

Long-term consequences

Based on the variability in the type and incidence of acute COVID-19 cardiac symptoms, the finding that long-term sequelae remain largely imprecise is not surprising. Palpitations and chest pain were reported in 9% and 5% of patients, respectively, evaluated at 6 months in a Chinese study [12], but they are of course not specific to any lesions. In the COMEBAC cohort of patients, a left ventricular ejection fraction (LVEF) <50% was detected at 4 months of the acute episode in 5% of non-intubated patients and 18% of patients who had received mechanical ventilation [7], but none had LVEF <40%. However, their previous heart condition was unknown. Interestingly, LVEF <50% was not associated with an increased incidence of persistent dyspnoea. A recent publication from the French COVID cohort study group reported a similar prevalence of LVEF <50% and an impairment of diastolic function (8%) at 6 months following hospitalisation for COVID-19 [104]. However, this diastolic dysfunction was not associated with clinical symptoms. Impairment of diastolic function has also been reported after the acute episode, even in patients

with no history of heart disease who had presented only a mild form of COVID-19 [105]. Although right ventricular systolic dysfunction has been reported in up to 45% of patients admitted for COVID-19 and associated with increased mortality during the acute phase of the disease [106, 107], the prevalence of persistent right ventricular abnormalities and their potential clinical implications remain to be determined.

Several studies, all of relatively small size, reported a cardiac MRI evaluation of the myocardium in patients recovering from COVID-19 [108–111]. They showed the existence of myocardial oedema, necrosis and fibrosis, which are probably sequelae of previous myocarditis. Approximately 40% of these abnormalities were not related to myocardial ischaemia [112]. The incidence of these anomalies varies, ranging from 60% [108] to 30% [109, 110] of the patients studied at 3–4 months following the initial attack. These abnormalities may be present in patients who do not experience acute cardiac manifestations [108]. However, the clinical consequences of these abnormalities are unknown.

In summary, while some patients certainly experience persistent cardiovascular abnormalities 3–6 months after the initial COVID-19 episode, large-scale studies that describe the exact incidence, consequences, risk factors and late evolution of these attacks are lacking.

Olfactory and taste disorders

Acute symptoms

During the first COVID-19 wave, a substantial increase in olfactory and taste disorders (OTD, *i.e.* anosmia, hyposmia and ageusia) was observed and was mainly reported in SARS-CoV-2-infected patients [113]. OTD was thus considered a major diagnostic criterion for COVID-19 [114]. In patients with mild COVID-19, the estimated OTD prevalence ranges from 56.5% to 85.9%, according to the OTD evaluation method [115]. The exact pathophysiology of OTD in patients with COVID-19 remains to be elucidated, but local mucosal inflammation and olfactory epithelial destruction appear to be the main mechanisms [116, 117]. Conversely, COVID-19 only appears to exert a limited effect on olfactory nerves and cerebral areas, at least during the acute phase [118].

Long-term sequelae

OTD long-term follow-up in patients with COVID-19 was studied in several cohorts and predictive factors of smell recovery remain to be identified [119]. In a large European study, 1363 patients with COVID-19 experiencing OTD were asked to report their olfactory function after OTD onset. At 2 and 6 months, 75% and 95% of patients recovered olfaction, respectively. A poor prognosis for olfactory recovery was statistically related to the severity of the baseline olfactory objective evaluation [120]. Smaller studies reported a similar prevalence, although higher rates have been reported in hospitalised patients [121, 122].

Endocrine sequelae

Based on the known presence of coronaviruses in several endocrine glands [123], and ACE2 expression observed in human hypothalamus, pituitary, thyroid, gonads and pancreatic islets [124], researchers have hypothesised that SARS-CoV-2 might affect the endocrine system. Nevertheless, evidence that endocrine disorders may belong to post-COVID-19 syndrome is unclear.

The most obvious consequences of COVID-19 are glucometabolic control. Indeed, several arguments suggest the involvement of SARS-CoV-2 in the occurrence of abnormalities in glucose metabolism [125–127]. New-onset hyperglycaemia, insulin resistance and β-cell hyperstimulation have been reported in one study of patients with COVID-19 without a history of diabetes [128]. In this study, among patients with new-onset hyperglycaemia at hospital admission for COVID-19, ~35% of patients had persistent hyperglycaemia in the next 6 months and overt diabetes was diagnosed in ~2% of patients. Interestingly, continuous glucose monitoring of normoglycaemic patients who recovered from COVID-19 showed a greater duration of glycaemia characterised by a glucose concentration >140 mg·dL^{-1}, higher mean postprandial glycaemia at 120 min, and higher mean blood glucose and higher nadir blood glucose levels compared with healthy controls [128]. Therefore, fasting plasma glucose and haemoglobin A1c levels should be monitored for at least several months after COVID-19 recovery, even in patients without a history of diabetes.

Alterations in thyroid function have been described in the acute phase of COVID-19 with contradictory observations. Overt and subclinical thyrotoxicosis have been reported, mostly due to subacute thyroiditis [129–131]. In a few cases, a clear autoimmune aetiology was found [132]. A non-thyroidal illness pattern characterised by low thyroid-stimulating hormone (TSH), thyroxine and triiodothyronine levels has also been observed [132, 133]. However, to date, data on thyroid function after COVID-19 recovery are not

consistent. In the few studies reporting follow-up (up to 2–3 months), TSH levels had returned to baseline [7, 129, 130, 132].

Currently, no reports of a clear effect of SARS-CoV-2 on the pituitary are available. Corticotropic insufficiency has been hypothesised due to the use of high doses of corticosteroids in the acute phase of COVID-19 and might participate in the fatigue observed in patients with long COVID-19. However, a recent study, in which adrenal function was evaluated with a short Synacthen test (250 μg intravenous bolus), showed no difference in baseline or peak cortisol after Synacthen according to disease severity or history of corticosteroid treatment [134]. Cortisol values and thyroid function tests in this study were not different between patients with persistent fatigue and those without. Finally, since the presence of ACE2 receptors has been reported in the testicles, the effect of SARS-CoV-2 on gonadal function should be evaluated [135].

Miscellaneous

In addition to the currently well-described cardiorespiratory, cognitive or psychiatric manifestations of post-acute COVID, various other clinical manifestations have been described, some persisting symptoms of the acute phase and some other new-onset symptoms. Their mechanisms remain to be determined.

General asthenia may be the most frequent symptom reported by patients after the initial infection. In all the reported series analysing fatigue in the 6 months of the post-acute phase, fatigue has been reported in 40–70% of patients [6, 7, 12, 83, 136, 137]. This evaluation depends on the tool used to evaluate asthenia (e.g. EuroQol EQ-5D-5L in the articles by DAHER et al. [136], GARRIGUES et al. [83] and HUANG et al. [12], Chalder Fatigue Scale used by TOWNSEND et al. [137], and Modified Fatigue Inventory used in the COMEBAC study series [7]). Reasons for persistent fatigue certainly arise from multiple origins. GHOSN et al. [6] reported data from a large French series, and described persistent symptoms at 3 and 6 months
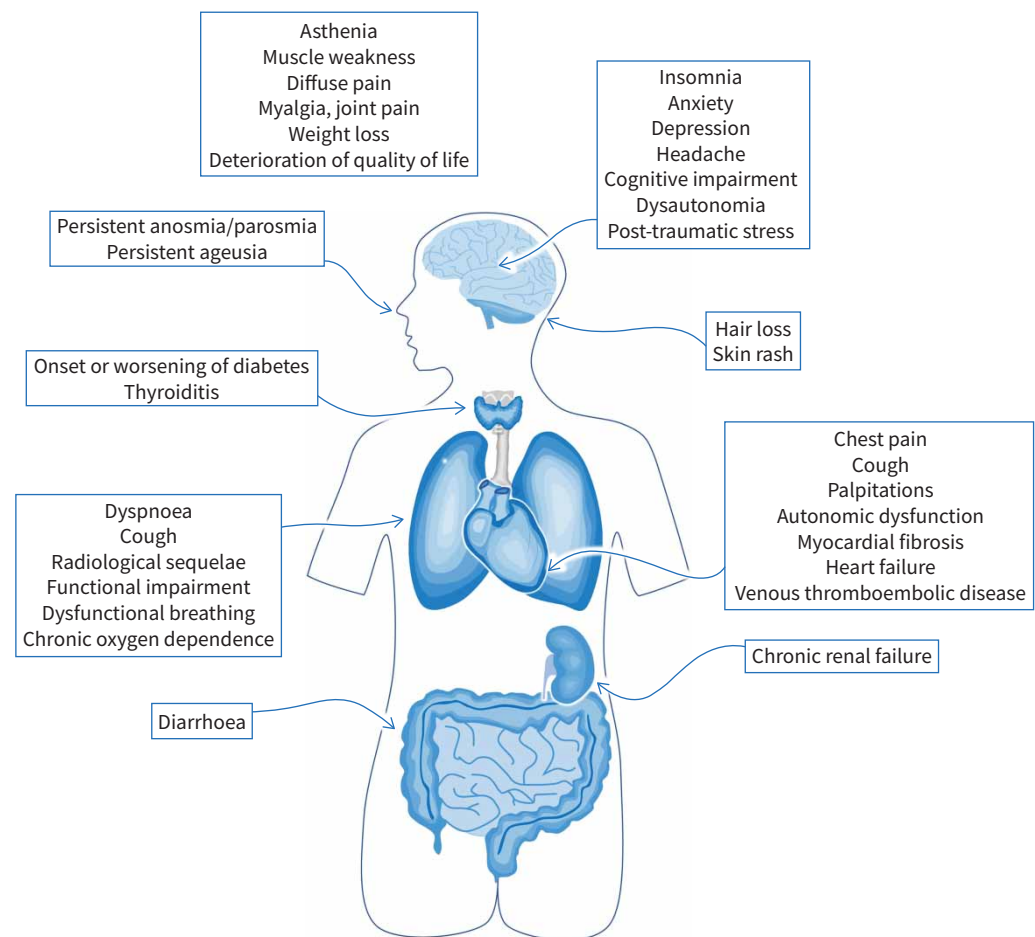

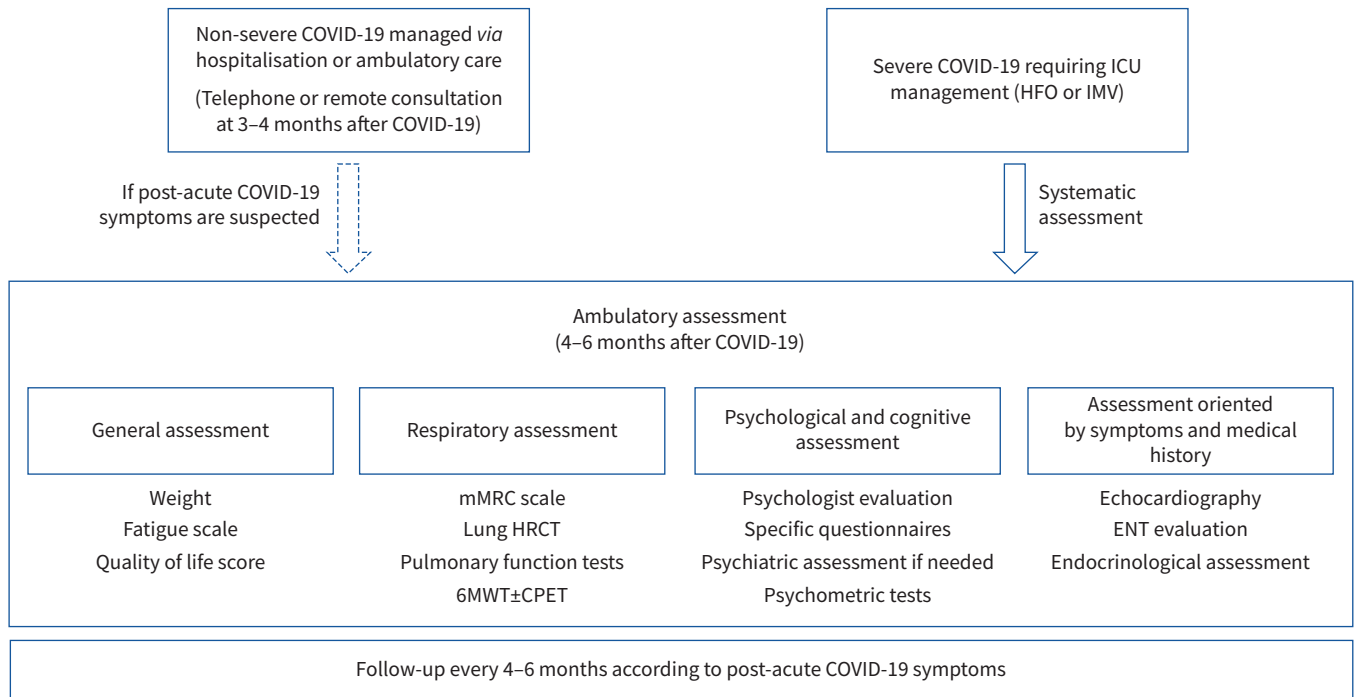FIGURE 3 Schematic summary of post-COVID-19 symptoms.

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┌──────────────────────────────────┐         ┌──────────────────────────────┐
│ Non-severe COVID-19 managed via  │         │ Severe COVID-19 requiring ICU│
│ hospitalisation or ambulatory    │         │ management (HFO or IMV)      │
│ care                             │         │                              │
│ (Telephone or remote consultation│         │                              │
│  at 3–4 months after COVID-19)   │         │                              │
└──────────────────────────────────┘         └──────────────────────────────┘
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If post-acute COVID-19 symptoms are suspected ⤵   Systematic assessment ⤵

Ambulatory assessment
(4–6 months after COVID-19)

General assessment	Respiratory assessment	Psychological and cognitive assessment	Assessment oriented by symptoms and medical history
Weight	mMRC scale	Psychologist evaluation	Echocardiography
Fatigue scale	Lung HRCT	Specific questionnaires	ENT evaluation
Quality of life score	Pulmonary function tests	Psychiatric assessment if needed	Endocrinological assessment
	6MWT±CPET	Psychometric tests	

Follow-up every 4–6 months according to post-acute COVID-19 symptoms

FIGURE 4 Proposal of a multidisciplinary follow-up algorithm for patients after COVID-19. ICU: intensive care unit; HFO: high-flow oxygen; IMV: invasive mechanical ventilation; mMRC: modified Medical Research Council; HRCT: high-resolution computed tomography; 6MWT: 6-min walk test; CPET: cardiopulmonary exercise testing; ENT: ear, nose and throat.

post-infection. The persistence of symptoms (including fatigue) was associated with female sex, ICU management and number of symptoms at admission. However, other studies have reported that both patients with severe and non-severe disease during acute infection may experience persistent fatigue after 6 months [137]. Overall, fatigue is associated with an impaired perception of quality of life, as we and others have reported, as well as with persistent dyspnoea, cognitive complaints and psychiatric symptoms [138].

However, fatigue might be included in a post-infective fatigue syndrome, as already described for herpesviruses [139]. Many viruses (especially Epstein–Barr virus and cytomegalovirus) have been implicated in the emergence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [140, 141]. It has also been described in patients with MERS-CoV infection [142] and SARS-CoV infection [143, 144]. ME/CFS is a poorly understood multisystem disorder that includes severe fatigue, post-exertion malaises and pain, with substantial reductions in functional activity and quality of life. This disorder might explain some symptoms observed after SARS-CoV-2 infection, such as muscle weakness, diffuse pain, myalgia and joint pain, which are reported to various extents in multiple published series [145, 146]. Other functional symptoms, such as urticaria/pruritus, persistent diarrhoea or weight loss, have also been described. These often non-specific symptoms have all been described during post-infective ME/CFS [140].

One major difficulty is that a main hypothesis is lacking to explain these various symptoms. Putative explanations are questioned, such as viral protein persistence in epithelial reservoirs [114], autoimmunity [147], low-level inflammation (as observed in ME/CFS [148]), mitochondrial dysfunction [149] or virus-induced dysautonomia [150], which only partially explain cardiopulmonary deconditioning and persistent dyspnoea. Overall, better knowledge of these persistent symptoms is needed for both physicians and patients to improve care.

Conclusions

The COVID-19 outbreak has been a major challenge for health systems worldwide, requiring the complete mobilisation of health resources. As a result of the successive COVID-19 waves, chronic complications of SARS-CoV-2 infection emerged that were grouped under the term "post-acute COVID-19 syndrome" or "long COVID-19". Patients with post-acute COVID-19 syndrome experience multifactorial dyspnoea and multiple organ involvement, usually with overlapping symptoms, leading to a substantial effect on their

quality of life (figure 3). Notably, these chronic symptoms are not intimately related to the initial severity of COVID-19 and some of them might be included in a multisystem disorder such as CFS. Given the millions of patients infected with SARS-CoV-2 worldwide and the need for multidisciplinary management of these chronic complications, post-acute COVID-19 syndrome will be a major issue for the various healthcare providers in the coming months. Based on the literature and the experience of the COMEBAC study [7], in figure 4 we propose a multidisciplinary screening and follow-up algorithm for patients after COVID-19, based on questionnaires 4–6 months after COVID-19, possibly during a telephone or remote consultation, and then according to the symptoms and severity of the initial COVID-19, an ambulatory multidisciplinary consultation with respiratory, neuropsychological and symptom-oriented assessment. International collaborations are needed to better define the pathophysiology, prevalence, effects of treatments and long-term evolution (after 12 months) of post-acute COVID-19 syndrome.

References

1. Nalbandian A, Sehgal K, Gupta A, *et al.* Post-acute COVID-19 syndrome. *Nat Med* 2021; 27: 601–615.

2. Wu X, Liu X, Zhou Y, *et al.* 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med* 2021; 9: 747–754.

3. Zhao Y-M, Shang Y-M, Song W-B, *et al.* Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; 25: 100463.

4. De Lorenzo R, Conte C, Lanzani C, *et al.* Residual clinical damage after COVID-19: a retrospective and prospective observational cohort study. *PLoS One* 2020; 15: e0239570.

5. Jacobs LG, Gourna Paleoudis E, Lesky-Di Bari D, *et al.* Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. *PLoS One* 2020; 15: e0243882.

6. Ghosn J, Piroth L, Epaulard O, *et al.* Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort. *Clin Microbiol Infect* 2021; 27: 1041.e1–1041.e4.

7. The Writing Committee for the COMEBAC Study Group. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. *JAMA* 2021; 325: 1525–1534.

8. Bellan M, Soddu D, Balbo PE, *et al.* Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. *JAMA Netw Open* 2021; 4: e2036142.

9. Augustin M, Schommers P, Stecher M, *et al.* Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. *Lancet Reg Health Eur* 2021; 6: 100122.

10. Lerum TV, Aaløkken TM, Brønstad E, *et al.* Lung function and CT findings 3 months after hospital admission for COVID-19. *Eur Respir J* 2021; 57: 2003448.

11. Shah AS, Wong AW, Hague CJ, *et al.* A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. *Thorax* 2021; 76: 402–404.

12. Huang C, Huang L, Wang Y, *et al.* 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021; 397: 220–232.

13. Debeaumont D, Boujibar F, Ferrand-Devouge E, *et al.* Cardiopulmonary exercise testing to assess persistent symptoms at 6 months in people with COVID-19 who survived hospitalization: a pilot study. *Phys Ther* 2021; 101: pzab099.

14. Mohr A, Dannerbeck L, Lange TJ, *et al.* Cardiopulmonary exercise pattern in patients with persistent dyspnoea after recovery from COVID-19. *Multidiscip Respir Med* 2021; 16: 732.

15. González J, Benítez ID, Carmona P, *et al.* Pulmonary function and radiologic features in survivors of critical COVID-19: a 3-month prospective cohort. *Chest* 2021; 160: 187–198.

16. van Gassel RJJ, Bels JLM, Raafs A, *et al.* High prevalence of pulmonary sequelae at 3 months after hospital discharge in mechanically ventilated survivors of COVID-19. *Am J Respir Crit Care Med* 2021; 203: 371–374.

17. McGroder CF, Zhang D, Choudhury MA, *et al.* Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length. *Thorax* 2021; 76: 1242–1245.

18. Song W-J, Hui CKM, Hull JH, *et al.* Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. *Lancet Respir Med* 2021; 9: 533–544.

19. Fernández-de-Las-Peñas C, Guijarro C, Plaza-Canteli S, *et al.* Prevalence of post-COVID-19 cough one year after SARS-CoV-2 infection: a multicenter study. *Lung* 2021; 199: 249–253.

20   Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021; 398: 747–758.

21   Boulding R, Stacey R, Niven R, et al. Dysfunctional breathing: a review of the literature and proposal for classification. Eur Respir Rev 2016; 25: 287–294.

22   Chenivesse C, Similowski T, Bautin N, et al. Severely impaired health-related quality of life in chronic hyperventilation patients: exploratory data. Respir Med 2014; 108: 517–523.

23   Goërtz YMJ, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res 2020; 6: 00542–02020.

24   George PM, Barratt SL, Condliffe R, et al. Respiratory follow-up of patients with COVID-19 pneumonia. Thorax 2020; 75: 1009–1016.

25   van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. J Psychosom Res 1985; 29: 199–206.

26   van Dixhoorn J, Folgering H. The Nijmegen Questionnaire and dysfunctional breathing. ERJ Open Res 2015; 1: 00001-02015.

27   Motiejunaite J, Balagny P, Arnoult F, et al. Hyperventilation: a possible explanation for long-lasting exercise intolerance in mild COVID-19 survivors? Front Physiol 2020; 11: 614590.

28   Aparisi Á, Ybarra-Falcón C, García-Gómez M, et al. Exercise ventilatory inefficiency in post-COVID-19 syndrome: insights from a prospective evaluation. J Clin Med 2021; 10: 2591.

29   Taverne J, Salvator H, Leboulch C, et al. High incidence of hyperventilation syndrome after COVID-19. J Thorac Dis 2021; 13: 3918–3922.

30   Howell JB. The hyperventilation syndrome: a syndrome under threat? Thorax 1997; 52: Suppl. 3, S30–S34.

31   Hancox RJ, Morgan J, Dickson N, et al. Rape, asthma and dysfunctional breathing. Eur Respir J 2020; 55: 1902455.

32   Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020; 11: 995–998.

33   Jones M, Harvey A, Marston L, et al. Breathing exercises for dysfunctional breathing/hyperventilation syndrome in adults. Cochrane Database Syst Rev 2013; 5: CD009041.

34   Rubin GD, Ryerson CJ, Haramati LB, et al. The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Radiology 2020; 296: 172–180.

35   Frija-Masson J, Debray M-P, Boussouar S, et al. Residual ground glass opacities three months after Covid-19 pneumonia correlate to alteration of respiratory function: the post Covid M3 study. Respir Med 2021; 184: 106435.

36   Li X, Shen C, Wang L, et al. Pulmonary fibrosis and its related factors in discharged patients with new corona virus pneumonia: a cohort study. Respir Res 2021; 22: 203.

37   Dhawan RT, Gopalan D, Howard L, et al. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. Lancet Respir Med 2021; 9: 107–116.

38   Jevnikar M, Sanchez O, Chocron R, et al. Prevalence of pulmonary embolism in patients with COVID 19 at the time of hospital admission. Eur Respir J 2021; 58: 2100116.

39   Remy-Jardin M, Duthoit L, Perez T, et al. Assessment of pulmonary arterial circulation 3 months after hospitalization for SARS-CoV-2 pneumonia: dual-energy CT (DECT) angiographic study in 55 patients. EClinicalMedicine 2021; 34: 100778.

40   Riyahi S, Dev H, Behzadi A, et al. Pulmonary embolism in hospitalized patients with COVID-19: a multicenter study. Radiology 2021; 301: E426–E433.

41   Mirsadraee S, Gorog DA, Mahon CF, et al. Prevalence of thrombotic complications in ICU-treated patients with coronavirus disease 2019 detected with systematic CT scanning. Crit Care Med 2021; 49: 804–815.

42   Suh YJ, Hong H, Ohana M, et al. Pulmonary embolism and deep vein thrombosis in COVID-19: a systematic review and meta-analysis. Radiology 2021; 298: E70–E80.

43   Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395: 1417–1418.

44   Huertas A, Montani D, Savale L, et al. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? Eur Respir J 2020; 56: 2001634.

45   Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020; 383: 120–128.

46   Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. Eur Respir J 2021; 57: 2002828.

47   Terrigno VR, Ricketti DA, Patel P, et al. Recurrent chronic thromboembolic disease despite optimal anticoagulation in setting of recent COVID-19 infection. BMJ Case Rep 2021; 14: e238733.

48   Poyraz BÇ, Poyraz CA, Olgun Y, et al. Psychiatric morbidity and protracted symptoms after COVID-19. Psychiatry Res 2021; 295: 113604.

49   Mazza MG, De Lorenzo R, Conte C, et al. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. Brain Behav Immun 2020; 89: 594–600.

50   Liu D, Baumeister RF, Veilleux JC, *et al.* Risk factors associated with mental illness in hospital discharged patients infected with COVID-19 in Wuhan, China. *Psychiatry Res* 2020; 292: 113297.

51   Tomasoni D, Bai F, Castoldi R, *et al.* Anxiety and depression symptoms after virological clearance of COVID-19: a cross-sectional study in Milan, Italy. *J Med Virol* 2021; 93: 1175–1179.

52   Méndez R, Balanzá-Martínez V, Luperdi SC, *et al.* Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. *J Intern Med* 2021; 290: 621–631.

53   de Graaf MA, Antoni ML, Ter Kuile MM, *et al.* Short-term outpatient follow-up of COVID-19 patients: a multidisciplinary approach. *EClinicalMedicine* 2021; 32: 100731.

54   Mei Q, Wang F, Bryant A, *et al.* Mental health problems among COVID-19 survivors in Wuhan, China. *World Psychiatry* 2021; 20: 139–140.

55   Mazza MG, Palladini M, De Lorenzo R, *et al.* Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. *Brain Behav Immun* 2021; 94: 138–147.

56   Taylor RR, Trivedi B, Patel N, *et al.* Post-COVID symptoms reported at asynchronous virtual review and stratified follow-up after COVID-19 pneumonia. *Clin Med* 2021; 21: e384–e391.

57   Todt BC, Szlejf C, Duim E, *et al.* Clinical outcomes and quality of life of COVID-19 survivors: a follow-up of 3 months post hospital discharge. *Respir Med* 2021; 184: 106453.

58   van den Borst B, Peters JB, Brink M, *et al.* Comprehensive health assessment three months after recovery from acute COVID-19. *Clin Infect Dis* 2020; 73: e1089–e1098.

59   Wang PR, Oyem PC, Viguera AC. Prevalence of psychiatric morbidity following discharge after COVID-19 hospitalization. *Gen Hosp Psychiatry* 2021; 69: 131–132.

60   Carenzo L, Protti A, Dalla Corte F, *et al.* Short-term health-related quality of life, physical function and psychological consequences of severe COVID-19. *Ann Intensive Care* 2021; 11: 91.

61   Hall J, Myall K, Lam JL, *et al.* Identifying patients at risk of post-discharge complications related to COVID-19 infection. *Thorax* 2021; 76: 408–411.

62   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.

63   Schandl A, Hedman A, Lyngå P, *et al.* Long-term consequences in critically ill COVID-19 patients: a prospective cohort study. *Acta Anaesthesiol Scand* 2021; 65: 1285–1292.

64   Mandal S, Barnett J, Brill SE, *et al.* "Long-COVID": a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2021; 76: 396–398.

65   Naidu SB, Shah AJ, Saigal A, *et al.* The high mental health burden of "Long COVID" and its association with on-going physical and respiratory symptoms in all adults discharged from hospital. *Eur Respir J* 2021; 57: 2004364.

66   Halpin SJ, McIvor C, Whyatt G, *et al.* Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol* 2021; 93: 1013–1022.

67   Yuan Y, Liu Z-H, Zhao Y-J, *et al.* Prevalence of post-traumatic stress symptoms and its associations with quality of life, demographic and clinical characteristics in COVID-19 survivors during the post-COVID-19 era. *Front Psychiatry* 2021; 12: 665507.

68   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: 1275–1287.

69   Latronico N, Peli E, Calza S, *et al.* Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax* 2021; in press [http://doi.org/10.1136/thoraxjnl-2021-218064].

70   COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet* 2021; 398: 1700–1712.

71   Janiri D, Carfì A, Kotzalidis GD, *et al.* Posttraumatic stress disorder in patients after severe COVID-19 infection. *JAMA Psychiatry* 2021; 78: 567–569.

72   Taquet M, Geddes JR, Husain M, *et al.* 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry* 2021; 8: 416–427.

73   Taquet M, Luciano S, Geddes JR, *et al.* Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry* 2021; 8: 130–140.

74   Frontera JA, Yang D, Lewis A, *et al.* A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. *J Neurol Sci* 2021; 426: 117486.

75   Taquet M, Dercon Q, Luciano S, *et al.* Incidence, co-occurrence, and evolution of long-COVID features: a 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med* 2021; 18: e1003773.

76   Mao L, Jin H, Wang M, *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; 77: 683–690.

77   Reichard RR, Kashani KB, Boire NA, *et al.* Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol* 2020; 140: 1–6.

78   Moriguchi T, Harii N, Goto J, *et al.* A first case of meningitis/encephalitis associated with SARS-coronavirus-2. *Int J Infect Dis* 2020; 94: 55–58.

79   Oxley TJ, Mocco J, Majidi S, *et al.* Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 2020; 382: e60.

80   Perry RJ, Smith CJ, Roffe C, *et al.* Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case-control study. *J Neurol Neurosurg Psychiatry* 2021; 92: 242–248.

81   Dhamoon MS, Thaler A, Gururangan K, *et al.* Acute cerebrovascular events with COVID-19 infection. *Stroke* 2021; 52: 48–56.

82   Bowles KH, McDonald M, Barrón Y, *et al.* Surviving COVID-19 after hospital discharge: symptom, functional, and adverse outcomes of home health recipients. *Ann Intern Med* 2021; 174: 316–325.

83   Garrigues E, Janvier P, Kherabi Y, *et al.* Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020; 81: e4–e6.

84   Woo MS, Malsy J, Pöttgen J, *et al.* Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Commun* 2020; 2: fcaa205.

85   Almeria M, Cejudo JC, Sotoca J, *et al.* Cognitive profile following COVID-19 infection: clinical predictors leading to neuropsychological impairment. *Brain Behav Immun Health* 2020; 9: 100163.

86   Mannan A, Mehedi HMH, Chy NUHA, *et al.* A multi-centre, cross-sectional study on coronavirus disease 2019 in Bangladesh: clinical epidemiology and short-term outcomes in recovered individuals. *New Microbes New Infect* 2021; 40: 100838.

87   Soldati AB, Almeida C, Lima M, *et al.* Telephone Screening of Cognitive Status (TICS) in severe COVID-19 patients: utility in the era of social isolation. *eNeurologicalSci* 2021; 22: 100322.

88   Zhou J, Liu C, Sun Y, *et al.* Cognitive disorders associated with hospitalization of COVID-19: results from an observational cohort study. *Brain Behav Immun* 2021; 91: 383–392.

89   Zhou H, Lu S, Chen J, *et al.* The landscape of cognitive function in recovered COVID-19 patients. *J Psychiatr Res* 2020; 129: 98–102.

90   Ritchie K, Chan D, Watermeyer T. The cognitive consequences of the COVID-19 epidemic: collateral damage? *Brain Commun* 2020; 2: fcaa069.

91   Dahm T, Rudolph H, Schwerk C, *et al.* Neuroinvasion and inflammation in viral central nervous system infections. *Mediators Inflamm* 2016; 2016: 8562805.

92   Jacomy H, Fragoso G, Almazan G, *et al.* Human coronavirus OC43 infection induces chronic encephalitis leading to disabilities in BALB/C mice. *Virology* 2006; 349: 335–346.

93   Hosseini S, Wilk E, Michaelsen-Preusse K, *et al.* Long-term neuroinflammation induced by influenza A virus infection and the impact on hippocampal neuron morphology and function. *J Neurosci* 2018; 38: 3060–3080.

94   Ameres M, Brandstetter S, Toncheva AA, *et al.* Association of neuronal injury blood marker neurofilament light chain with mild-to-moderate COVID-19. *J Neurol* 2020; 267: 3476–3478.

95   Kanberg N, Ashton NJ, Andersson L-M, *et al.* Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. *Neurology* 2020; 95: e1754–e1759.

96   Mikkelsen ME, Christie JD, Lanken PN, *et al.* The Adult Respiratory Distress Syndrome Cognitive Outcomes Study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med* 2012; 185: 1307–1315.

97   Bonow RO, O'Gara PT, Yancy CW. Cardiology and COVID-19. *JAMA* 2020; 324: 1131–1132.

98   Bonow RO, Fonarow GC, O'Gara PT, *et al.* Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. *JAMA Cardiol* 2020; 5: 751–753.

99   Rali AS, Ranka S, Shah Z, *et al.* Mechanisms of myocardial injury in coronavirus disease 2019. *Card Fail Rev* 2020; 6: e15.

100   Chung MK, Zidar DA, Bristow MR, *et al.* COVID-19 and cardiovascular disease: from bench to bedside. *Circ Res* 2021; 128: 1214–1236.

101   Prasitlumkum N, Chokesuwattanaskul R, Thongprayoon C, *et al.* Incidence of myocardial injury in COVID-19-infected patients: a systematic review and meta-analysis. *Diseases* 2020; 8: E40.

102   Metkus TS, Sokoll LJ, Barth AS, *et al.* Myocardial injury in severe COVID-19 compared with non-COVID-19 acute respiratory distress syndrome. *Circulation* 2021; 143: 553–565.

103   Goyal P, Choi JJ, Pinheiro LC, *et al.* Clinical characteristics of Covid-19 in New York City. *N Engl J Med* 2020; 382: 2372–2374.

104   Fayol A, Livrozet M, Boutouyrie P, *et al.* Cardiac performance in patients hospitalized with COVID-19: a 6 month follow-up study. *ESC Heart Fail* 2021; 8: 2232–2239.

105   Tudoran C, Tudoran M, Pop GN, *et al.* Associations between the severity of the post-acute COVID-19 syndrome and echocardiographic abnormalities in previously healthy outpatients following infection with SARS-CoV-2. *Biology* 2021; 10: 469.

106   Lassen MCH, Skaarup KG, Lind JN, *et al.* Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. *ESC Heart Fail* 2020; 7: 4189–4197.

107   Rath D, Petersen-Uribe Á, Avdiu A, *et al.* Impaired cardiac function is associated with mortality in patients with acute COVID-19 infection. *Clin Res Cardiol* 2020; 109: 1491–1499.

108   Puntmann VO, Carerj ML, Wieters I, *et al.* Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; 5: 1265–1273.

109   Wang H, Li R, Zhou Z, *et al.* Cardiac involvement in COVID-19 patients: mid-term follow up by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2021; 23: 14.

110   Huang L, Zhao P, Tang D, *et al.* Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging* 2020; 13: 2330–2339.

111   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: 1866–1878.

112   Knight DS, Kotecha T, Razvi Y, *et al.* COVID-19: myocardial injury in survivors. *Circulation* 2020; 142: 1120–1122.

113   Lisan Q, Fieux M, Tran Khai N, *et al.* Prevalence and characteristics of altered sense of smell/taste during Covid-19 first wave: a French nationwide cross-sectional study. *Eur Ann Otorhinolaryngol Head Neck Dis* 2022; 139: 9–12.

114   Salmon Ceron D, Bartier S, Hautefort C, *et al.* Self-reported loss of smell without nasal obstruction to identify COVID-19. The multicenter Coranosmia cohort study. *J Infect* 2020; 81: 614–620.

115   Lechien JR, Chiesa-Estomba CM, Vaira LA, *et al.* Epidemiological, otolaryngological, olfactory and gustatory outcomes according to the severity of COVID-19: a study of 2579 patients. *Eur Arch Otorhinolaryngol* 2021; 278: 2851–2859.

116   Eliezer M, Hamel A-L, Houdart E, *et al.* Loss of smell in patients with COVID-19: MRI data reveal a transient edema of the olfactory clefts. *Neurology* 2020; 95: e3145–e3152.

117   Rafols JA, Getchell TV. Morphological relations between the receptor neurons, sustentacular cells and Schwann cells in the olfactory mucosa of the salamander. *Anat Rec* 1983; 206: 87–101.

118   Niesen M, Trotta N, Noel A, *et al.* Structural and metabolic brain abnormalities in COVID-19 patients with sudden loss of smell. *Eur J Nucl Med Mol Imaging* 2021; 48: 1890–1901.

119   Saussez S, Sharma S, Thiriad A, *et al.* Predictive factors of smell recovery in a clinical series of 288 coronavirus disease 2019 patients with olfactory dysfunction. *Eur J Neurol* 2021; 28: 3702–3711.

120   Lechien JR, Chiesa-Estomba CM, Beckers E, *et al.* Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. *J Intern Med* 2021; 290: 451–461.

121   Petrocelli M, Cutrupi S, Salzano G, *et al.* Six-month smell and taste recovery rates in coronavirus disease 2019 patients: a prospective psychophysical study. *J Laryngol Otol* 2021; 135: 436–441.

122   Maestre-Muñiz MM, Arias Á, Mata-Vázquez E, *et al.* Long-term outcomes of patients with coronavirus disease 2019 at one year after hospital discharge. *J Clin Med* 2021; 10: 2945.

123   Ding Y, He L, Zhang Q, *et al.* Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol* 2004; 203: 622–630.

124   Lazartigues E, Qadir MMF, Mauvais-Jarvis F. Endocrine significance of SARS-CoV-2's reliance on ACE2. *Endocrinology* 2020; 161: bqaa108.

125   Kusmartseva I, Wu W, Syed F, *et al.* Expression of SARS-CoV-2 entry factors in the pancreas of normal organ donors and individuals with COVID-19. *Cell Metab* 2020; 32: 1041–1051.

126   Liu F, Long X, Zhang B, *et al.* ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. *Clin Gastroenterol Hepatol* 2020;18: 2128–2130.

127   Müller JA, Groß R, Conzelmann C, *et al.* SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab* 2021; 3: 149–165.

128   Montefusco L, Ben Nasr M, D'Addio F, *et al.* Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nat Metab* 2021; 3: 774–785.

129   Muller I, Cannavaro D, Dazzi D, *et al.* SARS-CoV-2-related atypical thyroiditis. *Lancet Diabetes Endocrinol* 2020; 8: 739–741.

130   Brancatella A, Ricci D, Cappellani D, *et al.* Is subacute thyroiditis an underestimated manifestation of SARS-CoV-2 infection? Insights from a case series. *J Clin Endocrinol Metab* 2020; 105: dgaa537.

131   Lania A, Sandri MT, Cellini M, *et al.* Thyrotoxicosis in patients with COVID-19: the THYRCOV study. *Eur J Endocrinol* 2020; 183: 381–387.

132   Lui DTW, Lee CH, Chow WS, *et al.* Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with COVID-19. *J Clin Endocrinol Metab* 2021; 106: e926–e935.

133   Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: a retrospective study. *Thyroid* 2021; 31: 8–11.

134   Clarke SA, Phylactou M, Patel B, *et al.* Normal adrenal and thyroid function in patients who survive COVID-19 infection. *J Clin Endocrinol Metab* 2021; 106: 2208–2220.

135   Wang S, Zhou X, Zhang T, *et al.* The need for urogenital tract monitoring in COVID-19. *Nat Rev Urol* 2020; 17: 314–315.

136   Daher A, Balfanz P, Cornelissen C, *et al.* Follow up of patients with severe coronavirus disease 2019 (COVID-19): pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020; 174: 106197.

137   Townsend L, Dyer AH, Jones K, *et al.* Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020; 15: e0240784.

138   Vanderlind WM, Rabinovitz BB, Miao IY, *et al.* A systematic review of neuropsychological and psychiatric sequalae of COVID-19: implications for treatment. *Curr Opin Psychiatry* 2021; 34: 420–433.

139   Cameron B, Flamand L, Juwana H, *et al.* Serological and virological investigation of the role of the herpesviruses EBV, CMV and HHV-6 in post-infective fatigue syndrome. *J Med Virol* 2010; 82: 1684–1688.

140   Hickie I, Davenport T, Wakefield D, *et al.* Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ* 2006; 333: 575.

141   Ariza ME. Myalgic encephalomyelitis/chronic fatigue syndrome: the human herpesviruses are back! *Biomolecules* 2021; 11: 185.

142   Ahn S-H, Kim JL, Kim JR, *et al.* Association between chronic fatigue syndrome and suicidality among survivors of Middle East respiratory syndrome over a 2-year follow-up period. *J Psychiatr Res* 2021; 137: 1–6.

143   Herridge MS, Cheung AM, Tansey CM, *et al.* One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; 348: 683–693.

144   Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurol* 2011; 11: 37.

145   Araja D, Berkis U, Lunga A, *et al.* Shadow burden of undiagnosed myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) on society: retrospective and prospective-in light of COVID-19. *J Clin Med* 2021; 10: 3017.

146   Komaroff AL, Lipkin WI. Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. *Trends Mol Med* 2021; 27: 895–906.

147   Wang EY, Mao T, Klein J, *et al.* Diverse functional autoantibodies in patients with COVID-19. *Nature* 2021; 595: 283–288.

148   Montoya JG, Holmes TH, Anderson JN, *et al.* Cytokine signature associated with disease severity in chronic fatigue syndrome patients. *Proc Natl Acad Sci USA* 2017; 114: E7150–E7158.

149   Ajaz S, McPhail MJ, Singh KK, *et al.* Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19. *Am J Physiol Cell Physiol* 2021; 320: C57–C65.

150   Dani M, Dirksen A, Taraborrelli P, *et al.* Autonomic dysfunction in "long COVID": rationale, physiology and management strategies. *Clin Med* 2021; 21: e63–e67.

151   Sonnweber T, Sahanic S, Pizzini A, *et al.* Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. *Eur Respir J* 2021; 57: 2003481.

152   Qin W, Chen S, Zhang Y, *et al.* Diffusion capacity abnormalities for carbon monoxide in patients with COVID-19 at 3-month follow-up. *Eur Respir J* 2021; 58: 2003677.

153   Gamberini L, Mazzoli CA, Prediletto I, *et al.* Health-related quality of life profiles, trajectories, persistent symptoms and pulmonary function one year after ICU discharge in invasively ventilated COVID-19 patients, a prospective follow-up study. *Respir Med* 2021; 189: 106665.