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Review

Medical sequels of COVID-19☆

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ABSTRACT

COVID-19 pandemic has impacted the world population, with a high rate of morbidity and mortality. While the evidence to date has attempted to describe clinical feature of acute illness, recent reports have also begun to describe persistent symptoms that extend beyond the initial period of illness. Adverse outcomes, in addition to respiratory, have been found to occur at different levels: cardiovascular, neurological, or immunological; skin, gastrointestinal or renal manifestations. The detrimental effect on mental health has also been described, not only in COVID-19 patients. The burden of disease secondary to this pandemic is likely to be enormous and not limited to acute disease alone, thus epidemiological studies are needed to further investigate the long-term impact of this disease. This review summarizes the current evidence on short-term effects and describes the possible long-term sequelae of COVID-19.

Secuelas médicas de la COVID-19

Palabras clave:
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RESUMEN

La pandemia de COVID-19 ha impactado gravemente en la población mundial, con una gran tasa de morbilidad y mortalidad. Si bien la evidencia hasta la fecha ha intentado describir la clínica de la enfermedad aguda, informes recientes también han comenzado a describir síntomas persistentes que se extienden más allá del período inicial de enfermedad. Se ha encontrado que los resultados adversos, además de respiratorios, se presentan a diferentes niveles: cardiovascular, neurológico o inmunológico; manifestaciones cutáneas, gastrointestinales o renales. También se ha descrito el efecto perjudicial sobre la salud mental, no solo en pacientes con COVID-19. Es probable que la carga de enfermedad secundaria a esta pandemia sea enorme y no se limite únicamente a la enfermedad aguda, por lo que se necesitan estudios epidemiológicos que investiguen más a fondo el impacto a largo plazo de esta enfermedad. Esta revisión resume la evidencia actual sobre los efectos a corto plazo y describe las posibles secuelas a largo plazo del COVID-19.

Introduction

The battle against COVID-19 does not seem to end with the detection and treatment of the acute disease. The persistent symptoms described so far by COVID-19 survivors, although heterogeneous, show a high incidence. However, there are still no long-term studies on this subject. Whether these persistent manifestations experienced by patients represent a new syndrome unique to COVID-19 or whether there is an overlap with the recovery phase of similar diseases has not been determined. Much of what has been reported so far is in line with findings from other post-viral syndromes[1] and those found in critically ill (non-COVID) patients who have been discharged from the Intensive Care Unit (ICU) and are still experiencing a wide range of symptoms months

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after hospitalisation, which has been termed post-intensive care syndrome.[2]

The most common physical symptoms described are fatigue, dyspnoea, chest pain or tightness, loss of taste or smell and cough. Other less recurrent sequelae described are headache, arthralgia, anorexia, dizziness, myalgia, insomnia, alopecia, sweating and diarrhoea. The literature maintains that some symptoms resolve more quickly than others. For example, fever, chills, and olfactory/taste symptoms usually resolve within two to four weeks, while fatigue, dyspnoea, chest tightness, cognitive deficits, and psychological effects can last for months[3–7] (Table 1).

The purpose of this review is to describe the existing knowledge on the post-acute-chronic phase of COVID-19 for each of the organs and systems for which we have information and to understand the existing evidence on chronic phase manifestations in order to provide long-term care for these patients.

Material and methods

To carry out this review, international search tools have been used such as: PubMed, Scholar, Embase, Web of Science, and UpToDate. A systematic search of the literature has been carried out, using the following terms as search criteria in different combinations: COVID-19, SARS-CoV-2, coronavirus, respiratory, respiratory function, computed tomography (CT); imaging, fibrosis, decreased carbon monoxide diffusing capacity (DLCO), digestive, diarrhoea, ageusia, anosmia, bradypsychia, neuropathy, anxiety, suicide, Alzheimer's, cardiac output, cardiac function, troponins, athletes, myocarditis, magnetic resonance imaging (MRI); thromboembolic disease, thromboembolism, pulmonary hypertension, autoimmunity, anti-phospholipids, among other terms. More than 200 articles were consulted for this review.

Results

Asthenia

Asthenia is recognized as one of the most common sequelae in people infected with SARS-CoV-2. Despite its high prevalence, there is little detailed literature on this phenomenon. Asthenia lasting six months or more, without an explanation for it, is called chronic fatigue syndrome (CFS) and, although it has been linked to previous coronavirus infections, in the case of COVID-19, the lack of association between its occurrence and the severity of the initial infection has important implications for the potential number of patients who may be affected.[8]

However, it should be noted that asthenia is a feeling and can vary from person to person and we have no test to confirm this diagnosis. Female gender and people with a previous diagnosis of depression or anxiety had a higher risk of fatigue. However, its pathophysiology in patients who have passed COVID-19, as well as its possible associations and predictor values, need to be investigated in long-term longitudinal studies.

Respiratory sequelae

A wide spectrum of pulmonary manifestations has been reported in COVID-19 survivors and are evident on functional and spirometric tests (Table 2). Looking at the subacute period, in a study of 110 hospitalised patients, pulmonary function tests (PFTs) were performed at discharge or one day before.[9] DLCO abnormalities were observed in 47.2% of patients with <80% of predicted capacity, with a higher frequency in those who had experienced a more severe disease.

A meta-analysis by Torres et al.[10] established DLCO as the most common short- to medium-term respiratory function abnormality, occurring in 39% of hospitalised patients. Secondly, the development of a restrictive pattern and an obstructive pattern is described in 15 and 7% of patients, respectively. Huang et al.,[11] after a follow-up of 57 patients 30 days after discharge, show that approximately three quarters developed lung function impairment, with decreased DLCO and decreased forced expiratory volume in the first second/forced vital capacity (FEV1/FVC) ratio again being the most common. In contrast, a more recent study excluding patients who required mechanical ventilation (MV) showed no changes in PFTs at six weeks after admission, except for a minimal decrease in DLCO. This suggests that sequelae described in previous studies are nothing, but a consequence of the effects caused by MV in the short-medium term.[12]

Three month after discharge, Zhao et al.[13] found that these residual lung function abnormalities persisted in 25.4% of patients, mostly in the form of reductions in DLCO, followed by decreases in FEV1, FVC and total lung capacity (TLC), suggestive of fibrotic changes. Moreno et al.,[7] after a follow-up of a Mediterranean cohort for 10–14 weeks, showed that spirometric abnormalities were present in 9.3% of patients, although this time in preference to the obstructive pattern, which was mild in 63.6%. Huang et al.[14] note that, after months, the decrease in diffusion still remains, ranging from 22% for patients who did not require supplemental oxygen during admission to 56% for those who required MV.

The sustained sequelae in respiratory function are compatible with a restrictive pattern secondary to interstitial abnormalities. Various reports describe the existence of residual radiological abnormalities after clinical recovery and discharge, even months later. For instance, Huang et al.[11] show that 30 days after discharge, more than half of the patients still had CT abnormalities, mainly ground glass opacities (GGO) with a peripheral distribution, which had decreased compared to previous CTs. At three months, Zhao et al.[13] found that the typical radiological manifestations of the acute phase such as consolidation and the crazy-paving pattern were practically resolved, but radiological anomalies continue to be maintained (70.91%) despite clinical respiratory improvement, even with fibrosis in the form of interstitial thickening (27.7%). At six months,[14] approximately half of the patients who required hospital admission had at least one pathological finding on the CT scan, with GGO and fibrosis being the most important; with the volume of the lesion being related to the severity of the acute condition. The crazy-paving pattern is minimal at follow-up as a result of that recovery. There are also no lymphadenopathies, a tree-in-bud pattern, masses, mediastinal involvement, pleural effusion, cavitation, or calcifications.

Rogliani et al.[15] describe that radiological abnormalities recover completely during follow-up in mild-moderate cases with no evidence of fibrotic abnormalities. Lung function and exercise capacity were also in the normal range. This provides preliminary evidence to suggest that in hospitalized patients with predominantly mild-moderate forms of COVID-19 the risk of functional and fibrotic sequelae is minimal.

Valuable data in the possible prediction of respiratory sequelae is the information provided by CT scanning, and a relationship has been found between the degree of pulmonary involvement during the initial radiological assessment and the persistence of pulmonary abnormalities in the medium to long term. Tabatabaei et al.[16] observed that there was a relationship between the initial radiological evaluation and the persistence of pulmonary abnormalities in the medium-long term (10.3 ± 5.4 vs. 7.3 ± 4.6; $P = .036$).

Several studies have looked at functional capacity after COVID-19, especially the six-minute walk test (6 MWT).[17] Daher et al.[12] reported that 79% of patients 30 days after discharge had walking

Table 1
Most common symptoms in the post-acute phase of COVID-19.

	Halpin et al.	Carfi et al.	Xiong et al.	Göertz et al.	Moreno-Pérez et al.	Huang et al.
Follow-up	1–2 months after hospital discharge	2 months from symptom onset	3 months	3 months	2–3 months from symptom onset	6 months from symptom onset
Patients	100	143	538	2.159	277	1.733
Age (median [IQR])	70.5 in ward 58.5 in ICU	56.5 (14.6)[a]	52.0 (41.0–62.0)	47.0 (39.0–54.0)	56 (42–67.5)	57 (47–65)
Asthenia (%)	64	53.1	28.3	87	34.8	63
Arthralgia (%)	–	27.3	7.6	22	19.6	9
Headache (%)	–	10	–	38	17.8	2
Dyspnoea (%)	40	43.4	21.4	71	34.4	23
Cough (%)	–	15	7.1	29	21.3	–
Anosmia/Ageusia (%)	–	15	–	12	21.4	7–11
Sleep disorders (%)	–	–	17.7	–	–	26
Anxiety Depression (%)	–	–	5	–	–	23
Post-traumatic stress disorder (%)	31	–	–	–	–	–
Palpitations (%)	–	–	11.2	32	–	9
Chest pain (%)	–	21.7	12.3	44		5
Decreased quality of life (EQ5D-SF36)	Yes	44.1%	–	–	Yes	Yes

IQR: interquartile range; ICU: intensive care unit.
[a] Mean (SD).

Table 2
Prevalence of respiratory and neurological sequelae in patients who have suffered COVID-19.

Respiratory sequelae

	At discharge		1 month		3 months	6 months	
Acute episode severity	Severe	Not severe	Severe	Not severe		Severe	Not severe
DLCO decrease <80% (%)	84.21	38.5	76.5	42.5	16.4	56	22
Restrictive Pattern (%)	10.5–47.3	8.8–19.8	23.5	5–7.5	7.3–10.9	1–11	3
Obstructive Pattern (%)	0	5.5	10.5		–	2–8	8
At least one CT abnormality (%)	–		94.1	37.5	70.91	54	52
6-minute walk test (m [CI])	–		517.43 (472.9–562)	573.52 (535.14–611.9)	–	479 (434.0–515.5)	495.0 (440.0–538)

Neurological sequelae

	6 months	
	Non-hospitalized	ICU
Hemorrhagic stroke (%)	0.31	2.66
Ischemic stroke (%)	0.14	1.05
Guillain barre (%)	0.05	0.33
Neuropathy, plexopathy, radiculopathy (%)	2.69	4.24
Myopathy (%)	0.16	3.35
Encephalitis (%)	0.05	0.35
Delirium (%)	0.35	1.74
	2 months	6 months
Anosmia/ageusia (%)	12–32.6	24

CVA: cerebrovascular accident (stroke); DLCO: decreased diffusion capacity; CI: confidence interval; CT: computed tomography; ICU: Intensive care unit.

distances below their predicted values, of which 46% had figures even below age-adjusted lower normal limits. Three-month values from another study[18] reveal that 22% of patients had a 6MWT < 80% of predicted. 16% of the patients desaturated, showing an association with a decrease in DLCO.

The limitation of patients' physical and functional capacities can be an aggravating factor for their quality of life. Halpin et al.[5] describe a significant drop in the *European Quality of Life - 5 Dimensions* (EQ5D)[19] questionnaire within weeks of discharge in 68.8% of participants requiring ICU and 45.6% of those in the ward group. Van der Sar et al.[20] report that all the items of the SF-36 questionnaire,[21] except for body pain, were significantly lower than the norm, finding an important correlation with the decrease in DLCO. However, this association is weak, indicating that quality of life is determined by more aspects, such as social isolation. These symptoms persist at six months,[14] with greater severity and prevalence for those patients in critical condition during the acute phase, presenting more problems of mobility, pain/discomfort and anxiety/depression.

Cardiac sequelae

With regard to cardiac manifestations, it was initially thought that the frequency of cardiac involvement resulting from SARS-CoV-2 disease was directly associated with the severity of the clinical course of the pathology and the presence of comorbidities. Supporting this theory, a study by Huang et al.[22] in recovered subjects who presented with cardiac symptoms during the acute phase revealed abnormal findings on cardiac magnetic resonance imaging (CMR) in 58% of patients 50 days after the onset of symptoms, notably decreased right ventricular ejection fraction, myocardial oedema suggestive of myocarditis and fibrosis. However, more recent CMR studies of individuals recovered from COVID-19 have shown a high rate of cardiac involvement despite an asymptomatic or benign course of the disease.[23,24]

Puntmann et al.[23] compared the CMR images of 100 patients (49 ± 14 years) with COVID-19 after three months of diagnosis with healthy controls. The participants who had recovered had a lower left ventricular ejection fraction and a considerable proportion had high levels of ultrasensitive troponin T. 78% of the recovered COVID-19 patients had some type of cardiac involvement observable on CMR, such as myocarditis, scarring, or pericardial enhancement. Interestingly, the oligosymptomatic COVID-19 subjects had myocardial inflammation similar to the hospitalized subgroup, which could be related to the age of the study patients and the more common presence of risk factors, as well as previous asymptomatic or undiagnosed lesions.

Rajpal et al.[24] show, after a follow-up (11–53 days) of 26 university athletes, signs of active myocarditis in 15% of them and isolated myocardial fibrosis in an additional 30%. However, in another group of 26 elite athletes who had mostly asymptomatic or mild COVID-19 infection[25] there have been no criteria for the diagnosis of active myocarditis by MRI one or two months after diagnosis, and the findings can be explained by physiological adaptation to exercise (isolated myocardial oedema).

Neurological sequelae

The most common neurological symptoms in COVID-19 are headache, dizziness, anosmia, and ageusia. Other neurological findings include cerebrovascular accidents (CVA), impaired consciousness, seizures, and encephalopathy[26] (Table 2).

Olfactory and/or taste dysfunctions are the most common neurological manifestations after headache, with a prevalence of 52.73% for olfactory dysfunction and 43.93% for taste, reported in a recent meta-analysis.[27] Most patients make a full or near full recovery one month after the acute illness, although in some studies, these symptoms persist longer. In a follow up of 125 patients, Nguyen et al.[28] found that 68.1% recovered their sense of smell and 73% recovered their taste within the first six weeks after the onset of symptoms. A total of 30 patients (24%) reported persistent anosmia/ageusia up to seven months later.

Stroke cases during the acute phase have also been published. The incidence of stroke in hospitalised patients is 1.1%, with the risk of suffering them being related to the greater severity of the acute phase and the previous presence of cardiovascular risk factors.[29] Evidence suggests that stroke associated with COVID-19 disease is more severe than non-associated stroke, with higher mortality and disability rates.[30]

An indirect effect of the COVID-19 pandemic has been a decline in admissions for stroke, with a 40% reduction in admissions compared to the same period last year.[31] Fear of contracting COVID-19 infection may have deterred some patients with milder stroke symptoms from seeking care.

Guillain-Barré syndrome (GBS) has also been described in COVID-19 patients. In a review of 73 post-COVID-19 GBS cases, Abu-Rumeileh et al.[32] report sensory symptoms alone or in combination with paraparesis or tetraparesis, ataxia, and generalized areflexia in these patients. Encephalopathy[33] has been described in people with COVID-19 as a poor prognostic factor, requiring longer hospitalizations, greater functional deterioration at hospital discharge, and a higher 30-day mortality rate.

Neurological sequelae derived from ICU stay have been reported in certain patients; like polyneuropathy[34] and myopathy[35] associated with the disease. However, in a recent study, Daia et al.[36] described cases of these pathologies in individuals who did not require this care during their hospital stay.

In addition to the direct invasion of the central nervous system (CNS) and the induction of inflammatory mediators in the CNS, the effect of sedative strategies, MV, immobilisation and other environmental factors such as social isolation and quarantine have been reported to increase the risk of delirium in these patients.[37]

Table 3
Prevalence of psychiatric and haematological sequelae in patients who have suffered COVID-19.

Psychiatric sequelae		
	3 months	6 months
Mood disorder (%)	2	4.22
Anxiety (%)	4.7	7.11
Psychotic disorder (%)	0.1	0.42
Substance abuse (%)	–	1.92
Insomnia (%)	1.9	2.53
Hematologic sequelae		
	1 month	6 months
Arterial and venous thrombosis (%)	2.5	0
Venous thrombosis (%)	0.6	–
Hemorrhage	3.7	–

Psychiatric sequelae

The pandemic caused by the SARS-CoV-2 virus has been a significant psychological stressor. Fear of illness, death, uncertainty about the future and social isolation resulting from loss of educational and occupational activities threaten to worsen public mental health.[38]

Taquet et al.[39] found that, 90 days after diagnosis, the risk of meeting criteria for a psychiatric illness was twice as high as in patients diagnosed with other non-COVID-19 pathologies, with the highest incidence being for anxiety disorders. Mood disorders and insomnia were also increased. There are also indications that the risk of dementia may double or triple after SARS-CoV-2 infection. In a publication by the same author,[40] 236,379 survivors of COVID-19 undergoing follow-up for six months showed that the risk for a diagnosis of anxiety or mood disorders remained high, although lower than at three months. Substance abuse disorders and insomnia were also more common in COVID-19 survivors than in those who had the flu or other respiratory tract infections. The estimated incidence of neurological or psychiatric diagnosis in the following six months was 33.62%, with 12.84% receiving a first diagnosis of these pathologies (Table 3). In another follow-up of 100 patients with COVID-19,[5] 18% claimed to have suffered memory impairment and 16% concentration impairment between 30–70 days after being discharged; the number was highest among patients admitted to the ICU.

Regarding the indirect effects of COVID-19 on general mental health, there seems to be evidence of an increase in symptoms of depression and anxiety. One study[41] monitored 333 participants during the first wave and after four weeks, initially finding rates of moderate-severe stress in 81%, anxiety in 28.8% and depression in 16.5%. However, no significant reduction was found in any of the three after four weeks, which may suggest a continuation of psychiatric pathology past pandemic control, requiring longer-term studies to provide insight. In a recent meta-analysis[42] of 43 large studies, the prevalence of anxiety disorders in the general population during the onset of the pandemic was estimated to be 25%, three times the pre-pandemic prevalence. On the other hand, in another meta-analysis, Bueno et al.[43] confirmed an increase in the prevalence of depressive disorders seven times higher than those present before the pandemic. Consequently, results from another study indicated substantial COVID-19-related increases in alcohol (23%) and drug (16%) abuse.[44] To this, we must add the detrimental effects fuelled by "infodemic"[45] dissemination across different platforms, stirring up fear and panic through uncontrolled rumours and sensationalism.

Health workers should be considered a highly exposed group, not only to the virus itself, but also to a greater risk of developing psychiatric symptoms; with increased stress, post-traumatic stress disorder, sleep disorders, anxiety and depression having been described in this group.[46]

Thrombotic sequelae

The acute phase of the disease is associated with an exacerbated inflammatory response that accompanies a significant risk of thrombosis, among which acute limb ischemia, acute coronary syndrome, venous thromboembolism (VTE) or stroke, among others, have been described.[47] Given the high rates of thrombosis in hospitalised patients with COVID-19, one would expect this risk to be extended after discharge to the outpatient setting.

However, the long-term risk of post-COVID-19 thromboembolism is poorly defined; a study of 163 patients, of whom 42 (26%) required admission to the ICU, had a cumulative incidence of VTE 30 days after discharge of 0.6%. On the other hand, the cumulative rate at 30 days of bleeding was 3.7%. These rates are comparable to those of VTE, and post-discharge bleeding seen in patients with similar forms of non-COVID-19 acute disease[48] (Table 3). Thus, it appears that hospitalisation for COVID-19 does not increase the risk of VTE after discharge compared to admission for another acute medical illness at discharge.

Therefore, regarding the prophylaxis of VTE after discharge, despite the prothrombotic and pro-inflammatory state observed during hospitalization, the current evidence would go against deviations from standard practice for patients with COVID-19.

Autoimmunity

Although the pathogenesis of autoimmune diseases is not well established, given the pathogenetic mechanisms and clinical-radiological aspects shared between pro-inflammatory diseases and COVID-19, it has been suggested that SARS-CoV-2 could act as a triggering factor for the development of autoimmune dysregulation.[49]

Since the beginning of the pandemic, a significant increase in the number of Kawasaki disease (KD) cases[50] has been observed, which suggests an association between SARS-CoV-2 and this pathology. In addition, cases of atypical or incomplete KD have been described. This condition has been called multisystem inflammatory syndrome in children (MIS-C).[51] Reports record a high incidence of intestinal involvement, myocarditis, cardiac involvement, shock, and macrophage activation in MIS-C, compared to classic KD. This results in affected children being associated with a worse prognosis (myocarditis and coronary involvement) and the need for intensive care.[52]

COVID-19 has been associated with the development of immune thrombocytopenic purpura (ITP). In a systematic review,[53] it was found that certain patients began to show abnormalities even after clinical recovery, up to three weeks after hospitalization. It is important that SARS-CoV-2 infection is part of the differential diagnosis of ITP, although it is necessary to consider the possible concomitance in these patients of other causes of thrombocytopenia, such as different drugs (heparin or beta-lactams), disseminated intravascular coagulation or sepsis.

The development of antiphospholipid antibodies (aPL) secondary to infections has been reported in some patients following SARS-CoV-2 infection.[54] Therefore, the search for aPL should be taken into account in the management of individuals with COVID-19 with vascular manifestations.

Other manifestations

The diabetogenic potential of SARS-CoV-2 has been hypothesized, not only because of the targets used by the virus but also because of the inflammatory stress secondary to the disease. New-onset hyperglycaemia and acute metabolic decompensation from pre-existing diabetes mellitus (DM) are now emerging as complications of COVID-19, especially among hospitalized patients.[55] This new-onset hyperglycaemia is not associated with any other risk factor.

Kidney involvement is also common in patients with COVID-19. The incidence of acute kidney injury (AKI) is as high as 36% in hospitalised subjects[56] and is considered a risk factor for severity and mortality of COVID-19. In a convalescent phase study, Ng et al.[57] reported that 36.9% of patients with AKI during admission still had renal dysfunction at hospital discharge, suggesting prolonged renal dysfunction despite resolution of the acute phase. The only study that has researched long-term glomerular filtration rate[14] describes that 35% of patients with AKI during hospitalisation had a decreased glomerular filtration rate (GFR) ($<$90 mL/min/1.73 m^2) at six months, compared to 13% in patients without AKI.

Discussion

The literature reviewed shows sequelae in different systems and organs, supporting the hypothesis that the adverse health effects were mediated by exaggerated activation of the immune system in response to the virus.

The vast majority of COVID-19 survivor registries have a six-month follow-up period after recovery; therefore, long-term data on these patients is not yet available. Thus, interpretation of results is hampered by unsystematic and short-term assessments, high heterogeneity in relation to age, severity of infection, follow-up and clinical assessment characteristics. Therefore, there is still an important information gap in the scientific literature due to the low level of evidence in the available literature and the lack of publications on the natural history of the disease and the efficacy of different rehabilitation strategies.

Therefore, the preliminary information obtained to date, in combination with data from previous coronavirus epidemics, only allows us to hypothesise about the long-term sequelae and symptomatology in patients who have overcome SARS-CoV-2 infection, as well as the actual extent of this pathology. A consensus is necessary when classifying the manifestations in the post-acute period of COVID-19.

In an attempt to address post-COVID-19 syndrome and facilitate comparison in future series, recent guidelines[58] propose the differentiation of these symptoms into: subacute or continuous, which include abnormalities present four to 12 weeks after acute COVID-19; and chronic or post-COVID-19 syndrome, which includes symptoms that persist or are present beyond 12 weeks from the onset of acute COVID-19 and that are not attributable to alternative diagnoses. Therefore, a key objective is to characterise the disease in each of its phases, to circumscribe its natural history and pathophysiology in order to better understand it.

It is evident that the care of patients with COVID-19 does not end at the time of hospital discharge and that an interdisciplinary vision is needed for the development of future action plans that seek comprehensive care for these individuals in the outpatient setting. In this way, units are already being set up, made up of different specialists (internists, cardiologists, rehabilitation specialists, pulmonologists and psychologists), who assess the patient in a holistic manner.

It is necessary to stress the importance of assessing all patients diagnosed with COVID-19 who experience symptoms beyond the acute phase and not only those who required hospitalisation. In this regard, tools have already been proposed to investigate predictors of post-COVID-19 syndrome in order to identify vulnerable patients, prioritise their care, better assess the impact on the health system and allocate resources appropriately.[59] However, to date there is only low-quality evidence regarding the efficacy of any rehabilitation intervention in these subjects.[60] Given the magnitude of this pandemic, the health care needs of patients with COVID-19 sequelae will continue to increase for the foreseeable future. Addressing this challenge will require the optimisation of healthcare infrastructure, the development of pathology-oriented models of care and multidisciplinary integration to improve the long-term health of COVID-19 survivors.

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The authors declare no conflict of interest.

References

1. O'Sullivan O. Long-term sequelae following previous coronavirus epidemics. Clin Med. 2021;21:e68.
2. Svenningsen H, Langhorn L, Ågård AS, Dreyer P. Post-ICU symptoms, consequences, and follow-up: an integrative review. Nurs Crit Care. 2017;22:212–20.
3. Carfì A, Bernabei R, Landi F, for the Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324:603–5.
4. Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res. 2020;6:542.
5. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J Med Virol. 2021;93:1013–22.
6. Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. Clin Microbiol Infect. 2021;27:89–95.
7. Moreno-Pérez O, Merino E, Leon-Ramirez J, Andrés M, Ramos JM, Arenas-Jiménez J, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: a Mediterranean cohort study. J Infect. 2021;82:378–83.
8. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLOS ONE. 2020;15:e0240784.
9. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020;55:2001217.
10. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, Solis-Navarro L, Burgos F, Puppo H, et al. Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. Pulmonology. 2020:S2531–2.
11. Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res. 2020;21:163.
12. Daher A, Balfanz P, Cornelissen C, Müller A, Bergs I, Marx N, et al. Follow up of patients with severe coronavirus disease 2019 (COVID-19): pulmonary and extrapulmonary disease sequelae. Respir Med. 2020;174:106197.
13. Zhao Y, Shang Y, Song W, Li Q, Xie H, Xu Q, 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.
14. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397:220–32.
15. Rogliani P, Calzetta L, Coppola A, Puxeddu E, Sergiacomi G, D'Amato D, et al. Are there pulmonary sequelae in patients recovering from COVID-19? Respir Res. 2020;21:286.
16. Tabatabaei SMH, Rajebi H, Moghaddas F, Ghasemiadl M, Talari H. Chest CT in COVID-19 pneumonia: what are the findings in mid-term follow-up? Emerg Radiol. 2020;27:711–9.
17. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–7.
18. Van den Borst B, Peters JB, Brink M, Schoon Y, Bleeker-Rovers C, Schers H, et al. Comprehensive health assessment three months after recovery from acute COVID-19. Ann Med. 2020:1–14.
19. Rabin R, Charro F de. EQ-SD: a measure of health status from the EuroQol Group. Ann Med. 2001;33:337–43.
20. Van der Sar - van der Brugge S, Talman S, Boonman-de Winter LJM, de Mol M, Hoefman E, van Etten RW, et al. Pulmonary function and health-related quality of life after COVID-19 pneumonia. Respir Med. 2021;176:106272.
21. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. conceptual framework and item selection. Med Care. 1992;30:473–83.
22. Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. JACC. Cardiovasc Imaging. 2020;13:2330–9.
23. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:1265–73.
24. Rajpal S, Tong MS, Borchers J, Zareba KM, Obarski TP, Simonetti OP, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. JAMA Cardiol. 2021;6:116–8.
25. Małek ŁA, Marczak M, Miłosz-Wieczorek B, Konopka M, Braksator W, Drygas W, et al. Cardiac involvement in consecutive elite athletes recovered from Covid-19: a magnetic resonance study. J Magn Reson Imaging. 2021;53:1723–9, http://dx.doi.org/10.1002/jmri.27513.
26. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol. 2020;77:1018–27.
27. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2020;163:3–11.
28. Nguyen NN, Hoang VT, Lagier J, Raoult D, Gautret P. Long-term persistence of olfactory and gustatory disorders in COVID-19 patients. Clin Microbiol Infect. 2021. S1198–743X:30781–3.
29. Yamakawa M, Kuno T, Mikami T, Takagi H, Gronseth G. Clinical characteristics of stroke with COVID-19: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis. 2020;29:105288.
30. Fuentes B, Alonso de Leciñana M, García-Madrona S, Díaz-Otero F, Aguirre C, Calleja P, et al. Stroke acute management and outcomes during the COVID-19 outbreak: a cohort study from the Madrid Stroke Network. Stroke. 2021;52:552–62.
31. Zhao J, Li H, Kung D, Fisher M, Shen Y, Liu R. Impact of the COVID-19 epidemic on stroke care and potential solutions. Stroke. 2020;51:1996–2001.
32. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain–Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol. 2021;268:1133–70.
33. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol. 2020;7:2221–30.
34. McClafferty B, Umer I, Fye G, Kepko D, Kalayanamitra R, Shahid Z, et al. Approach to critical illness myopathy and polyneuropathy in the older SARS-CoV-2 patients. J Clin Neurosci. 2020;79:241–5.
35. Bagnato S, Boccagni C, Marino G, Prestandrea C, D'Agostino T, Rubino F. Critical illness myopathy after COVID-19. Int J Infect Dis. 2020;99:276–8.
36. Daia C, Scheau C, Neagu G, Andone I, Spanu A, Popescu C, et al. Nerve conduction study and electromyography findings in patients recovering from Covid-19–case report. Int J Infect Dis. 2021;103:420–2.
37. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Critical Care. 2020;24:176.
38. Carvalho PMDM, Moreira MM, de Oliveira MNA, Landim JMM, Neto MLR. The psychiatric impact of the novel coronavirus outbreak. Psychiatry Res. 2020;286:112902.
39. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry. 2021;8:130–40.
40. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021;8:416–27.
41. Wang C, Pan R, Wan X, Tan Y, Xu L, McIntyre RS, et al. A longitudinal study on the mental health of general population during the COVID-19 epidemic in China. Brain Behav Immun. 2020;87:40–8.
42. Santabárbara J, Lasheras I, Lipnicki DM, Bueno-Notivol J, Pérez-Moreno M, López-Antón R, et al. Prevalence of anxiety in the COVID-19 pandemic: an updated meta-analysis of community-based studies. Prog Neuro-Psychopharmacol Biol Psychiatry. 2021;109:110207.
43. Bueno-Notivol J, Gracia-García P, Olaya B, Lasheras I, López-Antón R, Santabárbara J. Prevalence of depression during the COVID-19 outbreak: a meta-analysis of community-based studies. Int J Clin Health Psychol. 2021;21:100196.
44. Taylor S, Paluszek MM, Rachor GS, McKay D, Asmundson GJG. Substance use and abuse, COVID-19-related distress, and disregard for social distancing: a network analysis. Addict Behav. 2021;114:106754.
45. Zarocostas J. How to fight an infodemic. Lancet. 2020;395(10225):676.
46. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open. 2020;3:e203976.
47. Avila J, Long B, Holladay D, Gottlieb M. Thrombotic complications of COVID-19. Am J Emerg Med. 2021;39:213–8.
48. Patell R, Bogue T, Koshy A, Bindal P, Merrill M, Aird WC, et al. Post-discharge thrombosis and hemorrhage in patients with COVID-19. Blood. 2020;136:1342–6.

49. Caso F, Costa L, Ruscitti P, Navarini L, Del Puente A, Giacomelli R, et al. Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? Autoimmun Rev. 2020;19:102524.
50. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771–8.
51. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nature reviews. Nat Rev Rheumatol. 2020;16(8):413–4.
52. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142:429–36.
53. Bhattacharjee S, Banerjee M. Immune thrombocytopenia secondary to COVID-19: a systematic review. SN Compr Clin Med. 2020;19:1–11.
54. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020;382:e38.
55. Singh AK, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diabetes Res Clin Pract. 2020;167:108382.
56. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98:209–18.
57. Ng JH, Hirsch JS, Hazzan A, Wanchoo R, Shah HH, Malieckal DA, et al. Outcomes among patients hospitalized with COVID-19 and acute kidney injury. Am J Kidney Dis. 2021;77:204–15.
58. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of COVID-19: summary of NICE, SIGN, and RCGP rapid guideline. Brit Med J. 2021;372:n136.
59. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. Nat Med. 2021;27:626–31.
60. Ceravolo MG, Arienti C, de Sire A, Andrenelli E, Negrini F, Lazzarini SG, et al. The International Multiprofessional Steering Committee of Cochrane Rehabilitation REH-COVER action. Rehabilitation and COVID-19: the Cochrane Rehabilitation 2020 rapid living systematic review. Eur J Phys Rehabil Med. 2020;56:642–51.