What we already know about the Post-COVID-19 Syndrome: A narrative review

O que já sabemos sobre a Síndrome Pós-COVID-19: Uma revisão narrativa

Lo que ya sabemos sobre el Síndrome Post-COVID-19: Una revisión narrativa

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Abstract
As an increasingly number of patients recover from the acute COVID-19 disease, it has been observed that many face long lasting symptoms, referred as the Post-COVID-19 Syndrome. This article covers the most common signs and symptoms of this syndrome, its general aspects, and important complementary exams related to the disease. The manuscript is a narrative review, gathering new evidence published about the topic. The most common symptoms of the Post-COVID-19 Syndrome are chronic fatigue, breathlessness, depression or anxiety, pain, cough and alopecia, and many of them are still present 6 months after hospital discharge from the acute disease, depending on the gravity of the illness. It is important for patients to maintain medical follow-up to access severity of the symptoms and choose whether further investigation is necessary. There are some treatments available to some minimize the long-lasting burden of the syndrome, and the physician should access the need for treatment with the patient. As a new disease, there is a lot of new evidence being produced rapidly, but no up-to-date protocol has already been published. Even with the vaccinations campaigns, the burden of the pandemic is yet out of sight, as it still killing thousands daily, and those who have recovered from the acute COVID-19 illness can present chronic symptoms. Therefore, we recommend health professionals to continuously up-to-date themselves, as new information is added to make better clinical decisions.
Keywords: COVID-19; SARS-CoV-2; Cough; Fatigue; Chronic disease.

Resumo
Como um número crescente de pacientes que se recuperam da doença aguda COVID-19, tem sido observado que muitos enfrentam sintomas de longa duração, chamados de Síndrome Pós-COVID-19. Este artigo cobre os sinais e sintomas mais comuns desta síndrome, seus aspectos gerais e exames complementares importantes relacionados com a doença. O manuscrito é uma revisão narrativa, reunindo novas evidências publicadas sobre o tema. Os sintomas mais comuns da Síndrome Pós-COVID-19 são fadiga crônica, falta de ar, depressão ou ansiedade, dor, tosse e alopecia, e muitos deles ainda estão presentes 6 meses após a alta hospitalar da doença aguda, dependendo da gravidade da doença. É importante para os pacientes manter um acompanhamento médico para ter acesso à gravidade dos sintomas e escolher se é necessária uma investigação mais aprofundada. Há alguns tratamentos disponíveis para alguns minimizar a carga duradoura da síndrome, e o médico deve ter acesso à necessidade de tratamento com o paciente. Como uma nova doença, há muitas evidências novas sendo produzidas rapidamente, mas nenhum protocolo atualizado já foi publicado. Mesmo com as campanhas de vacinação, o fardo da pandemia ainda está fora de vista,

pois ainda mata milhares diariamente, e aqueles que se recuperaram da doença aguda COVID-19 podem apresentar sintomas crônicos. Portanto, recomendamos aos profissionais de saúde que se atualizem continuamente, pois novas informações são acrescentadas para tomar melhores decisões clínicas.
Palavras-chave: COVID-19; SARS-CoV-2; Tosse; Fadiga; Doença crônica.

Resumen
A medida que aumenta el número de pacientes que se recuperan de la enfermedad aguda por COVID-19, se ha observado que muchos se enfrentan a síntomas duraderos, denominados Síndrome Post-COVID-19. Este artículo abarca los signos y síntomas más comunes de este síndrome, sus aspectos generales y los exámenes complementarios importantes relacionados con la enfermedad. El manuscrito es una revisión narrativa, que recoge las nuevas evidencias publicadas sobre el tema. Los síntomas más comunes del Síndrome Post-COVID-19 son la fatiga crónica, la disnea, la depresión o la ansiedad, el dolor, la tos y la alopecia, y muchos de ellos siguen presentes 6 meses después del alta hospitalaria de la enfermedad aguda, dependiendo de la gravedad de la enfermedad. Es importante que los pacientes mantengan un seguimiento médico para acceder a la gravedad de los síntomas y elegir si es necesario realizar más investigaciones. Hay algunos tratamientos disponibles para minimizar la carga duradera del síndrome, y el médico debe acceder a la necesidad de tratamiento con el paciente. Al tratarse de una enfermedad nueva, se están produciendo muchas pruebas nuevas rápidamente, pero no se ha publicado ningún protocolo actualizado. Incluso con las campañas de vacunación, la carga de la pandemia aún no está a la vista, ya que sigue matando a miles de personas diariamente, y los que se han recuperado de la enfermedad aguda de COVID-19 pueden presentar síntomas crónicos. Por lo tanto, recomendamos a los profesionales de la salud que se actualicen continuamente, a medida que se añade nueva información para tomar mejores decisiones clínicas.
Palabras clave: COVID-19; SARS-CoV-2; Tos; Fatiga; Enfermedad crónica.

1. Introduction

Since the Severe Acute Respiratory Syndrome (SARS) outbreak 18 years ago, many SARS-related coronaviruses (SARSr-CoVs) have been found in their reservoir, the bats. From there on, many studies have shown that some of them can potentially infect humans (Zhou et al., 2020).

Zhou et al. (2020) identified and characterized a new strain of coronavirus, 2019-nCoV. It is also called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) (Xiong et al., 2021). It emerged in Wuhan, China, causing Acute Respiratory Syndrome in humans. In this study, genome sequences were obtained from 5 different patients at an early pandemic stage; those sequences were nearly identical. Furthermore, they shared 79,6% of sequence identity with SARS-CoV and 96% concordance with a bat coronavirus. In addition, Zhou et al. (2020) confirmed that the entry cell receptor used by 2019-nCoV was the same receptor used by SARS-CoV (angiotensin-converting enzyme II – ACE2 – receptor).

Notably, in the attachment phase, ACE2 receptors are critical. They are expressed in the airway epithelial cells, testis, kidneys, and heart. It is that those receptors determine the COVID-19 viral entry into human cells (Teixeira et al., 2021). It is essential to point out that the SARS-CoV-2 mechanism of human cell invasion is unique in a way that has not been seen in any of the other coronaviruses (Zhou et al., 2020).

This new strand has been associated with multi-organ dysfunction through three pathophysiological pathways (Teixeira et al., 2021). The first one is the Cytokine-release Syndrome (CRS), also known as cytokine storm; secondly, there is T-cell dysregulation with a reported decrease in peripheral levels of CD4+ and CD8+. Last, there is hemophagocytic lymphohistiocytosis.

Finally, all those mechanisms combined lead to significant morbidity in COVID-19, representing the cause of many organ-system failure syndromes, for example, Acute Respiratory Distress Syndrome (ARDS) and Acute Kidney Injury (AKI) (Teixeira et al., 2021).

In addition, COVID-19 is associated with persistent and prolonged symptoms in some patients. Those are called the long haulers and were responsible for the description of post-acute COVID-19 (Nalbandian et al., 2021).

According to the United States Center for Disease Control and Prevention (CDC), there are three main subtypes of persistent (more than four weeks) SARS-CoV-2 infection: a) persistent COVID-19; b) multiple organ damage, causing various

symptoms; and c) consequences of COVID-19 treatment or prolonged hospitalization (Carod Artal, 2021; CDC, 2021). Damage to several organ systems was reported, such as pulmonary (e.g., dyspnea, decreased exercise capacity), hematologic (e.g., thromboembolic events), cardiovascular (e.g., palpitations, chest pain), neuropsychiatric (e.g., fatigue, myalgia, headache), and renal (e.g., reduced glomerular filtration rate). Endocrine (e.g., worsening control of existing diabetes mellitus, subacute thyroiditis), Gastrointestinal/hepatobiliary (e.g., altering of the gut's microbiome, making the person prone to opportunistic infections), and dermatologic (e.g., hair loss) repercussions may also happen but are less described in the literature (Nalbandian et al., 2021). More symptoms are elicited in Figure 1.

Even with the global pandemic cooling down due to large vaccination campaigns throughout the world, the burden of the disease is yet unknown, as the number of patients presenting with Post-COVID-19 Syndrome continues to rise. The population and health care workers must be aware of this specific SARS-CoV-2 consequence.

Figure 1. Summary of the multi-systemic impact of the Post-Covid-19 Syndrome.
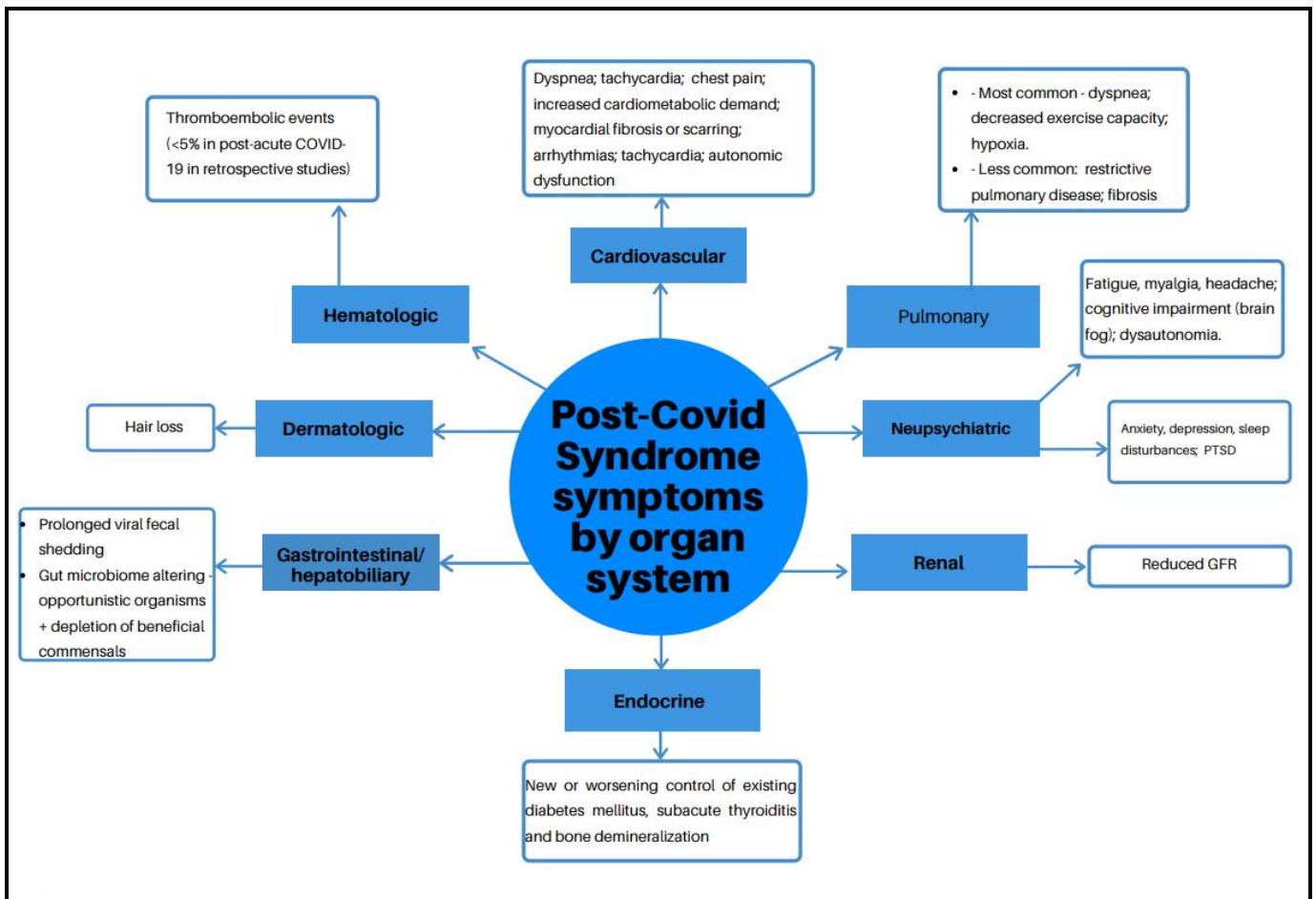
Source: Addapted form Nalbandian et al. (2021).

This manuscript aims to elucidate and bring into evidence information about these long-lasting symptoms, considering the enormous prevalence of them. As a new disease, there is plenty of new evidence being published constantly, and it is important for the health professionals to update yourself so they can take clinical decisions properly. That being said, such as definition, prevalence, treatment and follow-up, in addition to the general aspects of the syndrome and a condensation of the indications and usage of some complementary exams.

2. Methods

A literature review was performed from July 2021 through July 2022 for the medical subject headings and terms used for this search at PubMed (National Library of Medicine), MEDLINE (Medical Literature Analysis and Retrieval System Online) and SciELO (Scientific Electronic Library Online) were: ("Post-COVID" OR "Long COVID") AND ("COVID-19"). The reference lists of all included citations were hand-searched to identify any additional relevant studies. Abstracts were screened for clinical studies and case reports reporting on adult patients (aged ≥18 years). No restrictions were placed on study period or sample size. There was no specificity of language.

3. Theoretical Reference

Experts are calling the Post-Covid-19 Syndrome by several names, such as "chronic COVID-19", "long-COVID," and "post-acute sequelae of SARS-CoV-2 infection". They all refer to the symptoms that surged during or after the acute COVID-19 infection and persisted for longer than four weeks (Bowles et al., 2021). These symptoms are common and are divided into two groups:

• Symptoms experienced during acute illness, classically related to COVID-19 infections, that have chronicled, such as cough, fatigue, dyspnea, and chest pain;

• Additional cognitive, psychological symptoms, common in patients recovering from any critical illness, named "Post-Intensive Care Syndrome (PICS)," including poor memory and concentration, anxiety, and post-traumatic stress disorder (PTSD).

Nonetheless, previous coronavirus outbreaks - SARS and Middle East respiratory syndrome (MERS) - had already shown long-lasting symptoms. Mainly respiratory compromise, PTSD, and reduced Quality of Life persisting up to 12 months after hospital discharge (Ahmed et al., 2020).

3.1 Epidemiology

According to Xiong et al. (2021), who performed a study in Wuhan, 49,6% of recovered COVID-19 patients had long-lasting symptoms, some studies indeed showed that those symptoms could last at least for eight months. As Arnold et al. (2020), stated in a study performed in the United Kingdom, nearly 60% of the recovered patients still reported fatigue.

3.2 Symptoms

The most common symptoms are fatigue and dyspnea. Less commonly, there is cough, muscle/joint pain, neuropsychological symptoms, and headache. Beyond that, more than 20 symptoms were reported, with varying incidences between the studies. Alopecia is a unique feature of the Post-COVID-19 Syndrome, being reported by 14% of patients, almost exclusively by women (Carfì; Bernabei & Landi, 2021; Goërtz et al., 2020). PTSD symptoms are usual components of PICS, relating to various factors such as fear of death, invasive treatment, pain, and are even more intense with the pandemic background (Wade; Hardy & Howell, 2013).

Surprisingly, comparing COVID-19 with community-acquired bacterial pneumonia, the persistence of symptoms in SARS-CoV-2 infection appears to be longer. Wootton et al. (2017), performed a longitudinal study, realizing that patients diagnosed with community-acquired bacterial pneumonia who had not been managed in the ICU recovered 97% of initial symptoms within ten days from hospital discharge.

Below, the most common symptoms associated with post-COVID-19 are better elicited and illustrated.

Cough

The most common symptoms of the acute COVID-19 infection are fever (81% of patients) and cough (58%) (Alimohamadi et al., 2020). At the Post-COVID-19 Syndrome, cough is present in up to 25% of patients 3 months after hospital discharge. (Halpin et al., 2021). Cough presents itself as one of the most common symptoms of upper respiratory tract infections (Dicpinigaitis & Canning, 2020).

According to Barker-Davies et al. (2021), the definition of chronic cough is persistence for at least eight weeks. Until then, if there are no signs of infection or inflammation, the cough can be controlled through breathing exercises and medication. After this period, it is reasonable to evaluate the presence of inflammation through complementary exams (Guan et al., 2020). However, observational studies related to chronic cough in post covid-19 do not indicate a high incidence of this symptom. Moreover, when it is observed, it is reported as not severe and not expressive compared to the other symptoms (Dicpinigaitis & Canning, 2020).

Fatigue

The fatigue, an expressive symptom that have being reported by more than half of Post COVID-10 patients, is understood as a phenomenon involving both cognitive and neuromuscular aspects, and thus the neurological, immunological, and respiratory dysfunctions caused by COVID-19 may trigger the fatigue picture (Ortelli et al., 2021; Oliviero et al., 2020).

Is notorious that fatigue involves several dimensions of the patient's health, although there are not yet publications to show the effectiveness of interventions for this common symptom in Post-COVID-19 patients (Greenhalgh et al., 2020). Thus, pulmonary rehabilitation exercises must be carefully recommended for patients who complain of fatigue. In addition, close monitoring is necessary, extending the investigation if the patient presents with fever, shortness of breath, severe fatigue, or muscle pain. In this process, multidisciplinary work in partnership with the primary care clinician is of great importance for proper management (Greenhalgh et al., 2020).

Dyspnea

Dyspnea is defined by the American Thoracic Society (ATS) (1999), as " a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity ". For them, there is an interaction between physiological, psychological, social and environmental factors that leverage each patient to a symptom intensity.

That symptom often persists after healing from acute COVID-19 illness, and pulse oximeters are helpful to assess it. For patients with dyspnea, self-monitoring of oxygen saturations over three to five days can be performed. According to O'Driscoll et al. (2017), in the British Thoracic Society, the target range for oxygen saturation is between 94 and 98%. For those patients who do not have chronic respiratory failure, supplemental oxygen is required if the reading is 92% or below. The management of these patients should follow a physical exercise schedule with increasing load, accordingly with the patient's capacity, associated with Chest physiotherapy.

Chest Pain

Chest pain is a common symptom in Post-COVID-19, and during a clinical consult, it should be analyzed, differentiating musculoskeletal pain and other non-specific chest pain from severe cardiovascular conditions. As with non-COVID patients reporting chest pain, the clinical evaluation of the post-acute COVID-19 patient with chest pain should be reviewed considering past medical history, risk factors, and a well-conducted physical examination. When the diagnosis is uncertain or the patient is severely unwell, urgent referral to cardiology should be carried out for evaluation and request for specialized tests, such as echocardiography, chest computed tomography, or cardiac magnetic resonance imaging (Barker-

Davies et al., 2020).

Thromboembolism

The severe inflammatory state secondary to infection leads to Disseminated Intravascular Coagulation (DIC), presenting with decreased platelet count, prolonged prothrombin, and thromboplastin partial activated time (PT/APTT), increased fibrin degradation products such as D-dimer, as well as markedly elevated levels of fibrinogen. In fact, about 31% of patients affected by COVID-19 developed some thrombotic disease. Also, the emergence of reactive antiphospholipid antibodies is associated with viral infections, leading to hypercoagulability (Spiezia et al., 2020).

According to Thachil et al. (2020), summarizes the recommendation of the International Society on Thrombosis and Haemostasis that this coagulopathy be followed by laboratory tests for platelet count, fibrinogen and prothrombin time. In certain cases, drugs to inhibit platelet aggregation can be used (Perico et al., 2021).

Pulmonary Embolism (PE)

PEs can occur after cytokine storm in patients with COVID-19, even those in DVT prophylaxis. Studies show that low platelet levels, increased D-dimer, and increasing prothrombin levels in COVID-19 were associated with thromboembolic complications in patients with severe disease (Hadid et al., 2021).

Lack of hydration and mobilization after patients' discharge was likely to explain PE after COVID-19 infection. In addition, incidental RV dysfunction and pulmonary hypertension in a virus-infected patient have also been reported. In this case, an extensive pulmonary disease caused microvascular thrombosis or hypoxemia, leading to pulmonary hypertension and secondary right ventricular tension (Hadid et al., 2021).

According to Tang et al. (2020), in a recent study, they report that patients with severe infection had a high D-dimer and a high score of sepsis-induced coagulopathy (SIC). Among those patients, it was confirmed that anticoagulant therapy reduced mortality. A D-dimer value four times above the reference value, according to the authors, already indicates the need for anticoagulant therapy due to the high risk of DIC induced by sepsis.

The risk of clotting after hospital discharge is still high, and, therefore, it is usually recommended to extend thromboprophylaxis for ten days since it is not yet known how long patients remain hypercoagulable after acute COVID-19 (Greenhalgh et al., 2020). For patients who have been diagnosed with a thrombotic episode during or after hospitalization, care should follow standard guidelines oriented by the National Institute for Health and Care Excellence (2020).

Olfactory and gustatory dysfunctions

Post-COVID-19 symptoms manifest themselves in a broad clinical range. Some are notorious for involving the central nervous system (CNS). Examples of CNS involvement are olfactory (OD) and gustatory dysfunctions (GD).

Studies on these symptoms show significant divergences, and the pathophysiological mechanisms for such alterations in taste and smell are not widely known, but studies highlight the profound negative impact of anosmia and parosmia on the overall quality of life (Scangas & Bleier, 2017).

A study conducted with patients hospitalized for COVID-19 showed that 42% had both smell and taste losses. The mean duration of OD and GD was 18 and 16 days, respectively, and recovery was longer for women (26 days) than it was for men (14 days), being more frequent in men (Meini et al., 2020).

Studies show that olfactory training can help olfactory losses resulting from infections (Damm et al., 2014). It is already known that patients with post-traumatic, post-viral, and idiopathic olfactory dysfunction present an increase in olfactory sensitivity after a 12-week twice-daily exposure to selected odors: phenyl, rose, eucalyptus, lemon, and clove

(Piraccini & Alessandrini, 2014).

Alopecia

Androgenetic alopecia is known to be caused by a progressive reduction in the diameter, length, and pigmentation of hair.

The metabolite effects of dihydrotestosterone (DHT) are pointed out as an impact factor for a reduction in hair thickness resulting from the effect on androgen-sensitive hair follicles. In contrast, Alopecia areata is characterized by nonscarring, autoimmune and inflammatory hair loss in the scalp or body (Wasserman et al., 2007).

Alopecia is one of the prominent symptoms in post-COVID-19. An association between severe manifestations of COVID-19 and androgenetic alopecia is proposed in research by Wambier et al. (2020), which also showed that the prevalence of alopecia due to COVID-19 in women was high, affecting 48.5% of them. In addition, 71% of patients reported that alopecia started after hospital discharge and during hospitalization in the remaining cases.

Treatment for alopecia in patients with COVID-19 should follow the guidelines of non-COVID-19 patients, according to Bowles et al. (2021), which include topical minoxidil, antiandrogen agents, or 5-alpha reductase inhibitors (Piraccini & Alessandrini, 2014).

3.3 Relationship Between Post-COVID-19 Syndrome And Severity Of Acute Infection

Another aspect of Post-COVID-19 Syndrome is its correlation with the severity of the acute infection. Halpin et al. (2021), interviewed 32 patients treated in an Intensive Care Unit (ICU) and another 68 treated in a standard ward hospital without the need for intensive care. They were asked about remaining symptoms that persisted at least two months after discharge. It was observed that overall, the patients in the ICU remained more symptomatic than those treated in a standard ward. Results are better elicited in graphic 1. This study also stated that self-perceived health, measured by an European Quality of Life questionnaire, that showed further decline in perceived health among ICU patients (-15%) compared to standard ward patients (-6%).

Graphic 1. Percentage of patients who declared persistent symptoms after 2 months of hospital discharge, separated by patients who were treated in an Intensive Care Unit or in a common ward.
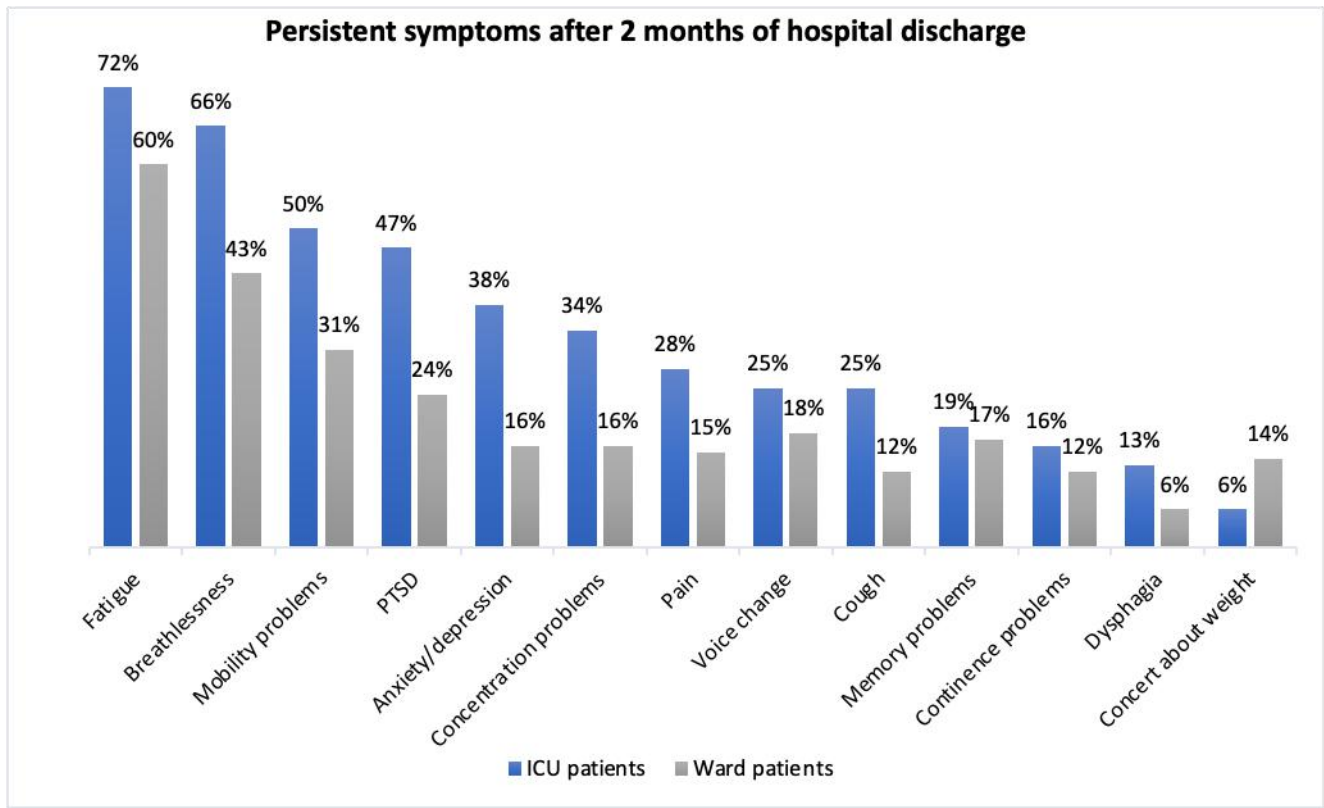
Source: Addapted form Halpin et al. (2021).

3.4 Risk of Rehospitalization

Most patients hospitalized with COVID-19 are successfully discharged, although approximately 10 to 20 percent require rehospitalization within 30 to 60 days (Mikkelsen & Abramoff, 2021). A study performed in New York hospitals found that 83% of readmissions were considered unavoidable and 17% potentially preventable. The authors also concluded that potentially preventable readmissions were from older patients with much shorter periods than nonpreventable readmissions. It was observed that the number of days of rehospitalization was significantly higher than that of the first hospitalization. There was also a strong relationship between the age of patients and the number of days of hospitalization (Durmus & Guneysu, 2020).

To decrease the odds for rehospitalization, it is recommended that patients hospitalized for COVID-19 with or without the need for subsequent post-care, such as inpatient rehabilitation, do a follow-up with the medical team within three weeks after hospital discharge, which can be done online. Even if they have not been hospitalized, older patients or patients with comorbidities are eligible for follow-up three weeks after the end of the Sars- Cov-2 cycle. An evaluation in specialized centers is recommended for patients with persistent symptoms even after 12 weeks of discharge (Mikkelsen & Abramoff, 2021).

Thus, greater attention is suggested when discharging patients with older age and comorbidities. It is also recommended that the health team instructs patients to get in touch if any symptoms recur (Durmus & Guneysu, 2020).

3.5 Laboratory Tests

Blood tests should be ordered selectively and for specific clinical indications after careful history taking and physical exam (Greenhalgh et al., 2020). Even in non-critical patients, radiological and physiological changes are found up to 3 months

after hospital discharge. So, proper exam follow-up allows for the management of emerging or long-term sequelae (Arnold et al., 2021).

The need for laboratory testing in patients who have recovered from acute COVID-19 is determined by the severity and abnormal test results during their acute illness and current symptoms. Thus, for patients with mild acute clinical COVID-19, laboratory tests are not recommended. (Mikkelsen & Abramoff, 2021)

On the other hand, for those who had severe disease, were hospitalized, had difficulty recovering, or have continued symptoms, recommended laboratory workup according to Mikkelsen & Abramoff (2021), are better elucidated at Table 1, shown below.

Table 1: Exams and its indications recommended to be accessed after hospital discharge from COVID-19.

Exam	Indication
Complete blood count	Severe disease
Electrolytes, Blood Urea Nitrogen, Serum creatinine	Severe disease
Liver function studies (including serum albumin)	Severe disease
Brain Natriuretic Peptide (BNP) and troponin	Disease complicated by heart failure/myocarditis or patients with cardiac symptoms covert from myocarditis (dyspnea, chest discomfort, edema)
D-Dimer	Unexplained persistent or new dyspnea, or those with higher risk for thromboembolic events
Thyroid studies	Unexplained fatigue or weakness
Antinuclear Antibody and Creatinine Kinase	Arthralgia, myalgia, or other rheumatologic symptoms

Source: Authors.

It is important to point that coagulation parameters and inflammatory markers are generally not monitored, even though there are divergences in the literature. Troponin and D-dimer tests may be falsely positive, but a negative result can reduce clinical uncertainty. The reason behind D-dimer testing is because it predicts impaired diffusing capacity of the lungs for carbon monoxide (DLCO) after a 3-month discharge period (Greenhalgh et al., 2020).

3.6 Chest Imaging

After 60 and 100 days following a confirmed diagnosis of COVID-19, patients underwent CT scans, and typical radiological pulmonary abnormalities for COVID-19 were found in 77% and 63% of subjects, respectively. Pulmonary involvement was bilateral in 75% of patients, with the lower lobes being the most affected. Prominent abnormalities were ground-glass opacities (GGOs), consolidation, and reticulation. Bronchial dilation was found in a minority of patients. At the second visit, bronchial dilations were almost entirely resolved, and the mean length of GGOs significantly decreased. More than 50% of patients presented residual chest imaging with abnormalities six months after illness onset (Huang et al., 2021).

Chest X-rays for post-COVID-19 patients will depend on the severity of each patient. Those who did not need to undergo the exam during the disease and do not present cardiopulmonary symptoms are not recommended to do it now (Mikkelsen & Abramoff, 2021). The British Thoracic Society protocols propose that patients who had respiratory problems during COVID- 19 should do an x-ray three months after symptom cessation (16). This follow-up is also advised for patients who have had infiltrations or pulmonary abnormalities on chest images during acute COVID-19. To summarize, any patient with new respiratory symptoms or abnormal cardiopulmonary examination should order an x-ray (Mikkelsen & Abramoff, 2021).

3.7 Cardiac Tests

Studies carried out in patients to measure Post-COVID-19 sequelae show that among those who were admitted to the ICU and had persistent symptoms four months after discharge, 10% had a left ventricular ejection fraction of less than 50%, resembling another study in which patients had a high rate of diastolic dysfunction (55%) 100 days after discharge (O'Connor & Franzos, 2021).

Transthoracic echocardiography (TTE) is requested for patients with a history or biochemical evidence of myocardial injury, myocarditis, or patients with dyspnea and other signs and symptoms suggestive of an underlying cardiac disorder. If necessary, cardiopulmonary exercise testing can also be ordered (O'Connor & Franzos, 2021).

On the other hand, evaluating patients with any intermittent or persistent cardiopulmonary symptoms is recommended to perform a 12-lead electrocardiogram. If the electrocardiogram is normal, but the patient remains with persistent cardiac symptoms, particularly palpitations or symptoms of dysautonomia, extended Holter monitoring is recommended (O'Connor & Franzos, 2021).

For athletes who continue to experience activity-limiting dyspnea, it is recommended to perform an initial assessment for myocarditis with ECG, cardiac biomarkers, and an echocardiogram (O'Connor & Franzos, 2021).

3.8 Pulmonary Function Tests

Studies show that pulmonary hypertension and pericardial effusion were detected only in a smaller proportion of patients 100 days after acute COVID-19 infection. However, reduction in forced vital capacity (FVC) and forced expiratory volume in 1s (FEV1) was found in 22% of the patients.

Moreover, a reduction in Total Lung Capacity (TLC) was found in 11% and impairment of Lung Diffusion for Carbon Monoxide (DLCO) in 21% of all patients submitted. In addition, 37% of them had mild or moderate hypoxia at rest (Sonnweber et al., 2021).

A consensus demonstrates that mobilization activities combined with physiotherapy can facilitate and improve patients' long-term pulmonary recovery and functional independence, and if performed while still in hospital, it can shorten the length of accommodation and hospitalization (Rawal; Yadav & Kumar, 2017).

Liu et al. (2020), analyzed that after six weeks of pulmonary rehabilitation, elderly patients with COVID-19 had improvements in their respiratory function, quality of life, and anxiety. Rehabilitation activities were performed once a day for ten minutes and included respiratory muscle training, cough exercises, diaphragm training, stretching exercises, and at-home exercises.

Regarding exams, patients recovering COVID-19 who present persistent, progressive, or new respiratory symptoms or severe pulmonary involvement or COVID-19-related Acute Respiratory Distress Syndrome (ARDS) need to undergo pulmonary function tests (PFTs), including spirometry, lung volumes, and diffusion capacity.

The best timing to perform PFTs is still unclear. Based on studies with patients COVID-19 and non-COVID-19, both with ARDS. It is suggested to request exams at 6 to 12 weeks following hospital discharge. If PFTs abnormalities are detected in patients with COVID-19-related ARDS, follow-up of those tests for six months and then annually for five years is recommended (Mikkelsen & Abramoff, 2021).

3.9 Physical Exercises After Acute COVID-19

Evidence shows that physical fitness may mitigate disease severity among those infected with COVID-19, indicating the need to promote physical fitness during the pandemic.

During lockdown to prevent viral spread, most people had to decrease their aerobic fitness activities. Research made in a Spanish University indicates a moderate reduction of 29.5% in exercises involving a total of 13,754 valid survey responses, a vigorous reduction of 18.3%, and increasingly sedentary time (52.7%) (Rodríguez-Larrad et al., 2021).

Exercise reduction can lead to cardiovascular complications, mainly in athletes, myocarditis, and other myocardial injuries, which may rarely develop without symptoms, exacerbated by exercise weeks after COVID-19 recovery, possibly precipitating sudden cardiac arrest.

It is recommended by authorities to refrain from physical exercises for a minimum of seven days after symptom resolution. The extended period of inactivity may increase the risk for potential injury and cause a degree of detraining. The ideal return time to return exercising after COVID-19 infection is unknown. Athletes who suffered from severe illness may require additional testing and specialist consults before they can resume training (O'Connor & Franzos, 2021).

Red flags that indicate immediate exercise interruption, according to Udelson et al. (2021) are:

- Chest pain or heart palpitations

- Nausea

- Headache

- High heart rate not proportional to exertion level or prolonged heart rate recovery

- Shortness of breath

- Difficulty catching breath or abnormal

- Experiencing tunnel vision or loss of vision

Physicians must be on alert for signs of mental health issues among those athletes, particularly those with known risk factors (e.g., history of depression) (O'Connor & Franzos, 2021).Furthermore, athletes or active individuals who tested positive for COVID-19 should not engage in any physical activity during active disease. It is essential to focus on rest, good hydration, proper nutrition, and following the advice of healthcare providers (Udelson et al., 2021).

4. Final Considerations

COVID-19 affects multiple organs in the human body; furthermore, evidence has shown that it is responsible for acute and chronic diseases. The acute disease has been studied since more than 400 million cases of COVID-19 were reported so far. However, long-COVID is not so well understood. This manuscript aims to elucidate and bring into evidence information about chronic diseases caused by the new coronavirus.

As previously stated, patients who develop COVID-19 infection may present with a chronic symptom state, called by academic professionals long-COVID; chronic COVID-19 and post-acute sequelae of SARS-CoV2 infection. It is defined by the prevailing or arising of symptoms after an acute COVID-19 infection.

Among the most common symptoms of Long-COVID are fatigue, dyspnea, mobility problems, and post-traumatic stress disorder. Less common symptoms include anxiety, depression, concentration problems, pain, voice change, memory problems, continence problems, dysphagia and, worry about weight. Besides reported symptoms, imaging test studies also show evidence of organ damage after an acute COVID-19 infection. It is also essential to address that the prevalence of those symptoms is higher among ICU patients.

Given all the evidence, it is of great importance that every patient infected with COVID-19 undergoes a medical evaluation, especially if there was a need for hospitalization. Considering that the information on long-COVID is relatively new in the medical community, health care workers must continue to up-to-date themselves. We suggest the creation of Post-COVID-19 Syndrome protocols made by medical specialists' associations, focused on clarifying clinical management of the disease, since there are a lot of discrepancies at the scientific literature and fast-changing recommendations. Moreover, the

medical field must expand its research even further to better treat and assess those patients.

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