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Main Sequelae after Covid-19 in Adults

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Abstract

Introduction: During the pandemic, evidence emerged of patients with debilitating symptoms that persisted for weeks and even months after the diagnosis of COVID-19, a fact that is of great concern to the medical community.

Objective: To assess the available evidence of the main sequelae of COVID-19 affecting previously healthy adults.

Mini-Review | Castilho Lopes CC, et al. *Adv Clin Med Res* 2023, 4(4)-64.

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Methods: This study constitutes a systematic review, classified as exploratory and descriptive. The elaboration of the research was bibliographical research in electronic databases on methods associated with RSL (Systematic Literature Review) and SMARTER applications (Simple Multi-Attribute Rating Technique using Exploiting Rankings).

Results: A comprehensive systematic search of the literature yielded a total of 4495 articles referring to the main post-covid sequelae in adult patients. Of these, 38 articles became eligible to compose this systematic review.

Conclusion: The study concluded that future research will be needed for these medium and long-distance patients and also the need to monitor these patients to prevent possible damage to the affected organs and preserve their quality of life.

Keywords

COVID-19; Coronavirus Disease; SARS-CoV-2; Sequelae

Introduction

Corona viruses are a family of viruses that cause illnesses ranging from the common cold to more serious illnesses such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) [1]. The virus causing the pandemic was named as SARS-CoV-2. This new coronavirus generated a disease known as COVID-19, being the agent of a series of cases of pneumonia in the city of Wuhan (China). Until recently, there was no concrete information about the mechanism of action on the disease and, even today, there are no unquestionable measures of effectiveness for the clinical management of cases of human infection with SARS-CoV-2, with many details still to be clarified. The virus has shown to be highly transmissible and causes an acute respiratory syndrome that ranges from mild cases – around 80% – to very severe cases with respiratory failure – between 5% and 10% of cases. Its lethality varies, mainly, according to the age group and associated clinical conditions [2].

During the pandemic, evidence emerged of patients with debilitating symptoms that persisted for weeks and even months after a diagnosis of COVID-19, a fact that is of great concern to the medical community. When observing the size of groups such as the so-called “longhauersCOVID” on social media, it is estimated that the members of such groups add up to thousands of people [3-4]. Several small studies followed recovered cases of COVID-19, with a special focus on severe cases. However, an evidence-based systematic review of the long-term sequelae of COVID-19 in previously healthy adults is needed [3]. This review aims to assess the available evidence of the main sequelae of COVID-19 affecting previously healthy adults.

Methods

This study constitutes a systematic review, classified as exploratory and descriptive. The elaboration of the research was bibliographical research in electronic databases on methods associated with RSL (Systematic Literature Review) and SMARTER applications (Simple Multi-Attribute Rating Technique using Exploiting Rankings). The work carried out is qualitative and quantitative. Qualitative data analysis was performed intuitively and inductively during the survey of the theoretical framework. It is also quantitative using the multicriteria method. In addition, there is also a numerical experimental study in order to simulate an article selection situation based on the observed criteria. Based on bibliographical research, located in the following databases: US National Library of Medicine (Pub Med), Scientific Electronic Library on-line (SCIELO), Latin American Caribbean Health Sciences Information System (LILACS), Science Direct (Elsevier) and Embase. Complementarily, searches were carried out based on bibliographical references of studies that relevantly addressed the topic on the Google Scholar search platform.

The search in the databases was carried out using the terminologies registered in the Health Sciences Descriptors created by the Virtual Health Library developed from the Medical Subject Headings of the US National Library of Medicine, which allows the use of common terminology in Portuguese, English and Spanish. The present study sought to investigate the literature on post-covid sequelae in previously healthy people. For this purpose, the descriptors “COVID-19”, “coronavirus disease 2019”, “SARS-CoV-2”, “sequelae” were used, initially in English, and in a complementary way in Spanish and Portuguese.

As a tool to support the decision in the selection and prioritization of articles, a set of criteria were considered essential to represent the state of the art of the subject object of the research. This method has the following characteristics: (i) rigorous logic allows acceptance of the method as a decision support tool; (ii) simple to understand and apply with easily interpreted results. References from selected papers were also searched for other documents of potential interest. Once qualified for full-text evaluation, articles were included in the qualitative review if they met the following inclusion criteria: a) they contained data on Covid sequelae; b) Covid-19. Articles were excluded if they were reports, banners or conference abstracts. There was no review of confidential health information and the study was non-interventional. Therefore, ethics committee approval was not required. To the end, the result obtained totaled 38 articles that contemplated the desired characteristics for the study.

Three independent researchers extracted data from articles that met the inclusion criteria and recorded them in a “Data Extraction Form” generated in Microsoft Excel on the main post-COVID-19 sequelae in adult subjects. From this form, the authors and year of publication, country, type of study (design), study title, sample size (n) and conclusion of the study, shown below in (table 1), were included.

AUTHORS/YEAR	COUNTRY	KIND OF STUDY	STUDY TITLE	n	CONCLUSION
					The study demonstrated a great loss of health affecting several organs of patients who survived the acute phase of COVID-19.
AL-ALY; XIE; BOWE			High-dimensional characterization of post-acute sequelae of COVID-19		
-2021	USA	Cohort		7435	
					Families will make defensive decisions in spending, consumption, planning and investment. It was evidenced that personal psychological heterogeneity and collective mental programming play a significant role in shaping families' post-pandemic financial intentions.
	North America, Europe, Africa and Latin America – 03 countries		Households' intentions under financial vulnerability conditions: is it likely for the COVID-19 pandemic to leave a permanent scar?		
ALHENAWI; YAZDANPARAST (2022)		Review - Data from a survey		ND	

			Symptom persistence despite improvement in cardiopulmonary health—insights from longitudinal CMR, CPET and lung function testing post-COVID-19	58	Patients with cardiopulmonary problems showed improvement over time, but some measurements remained abnormal relative to controls.
CASSAR et al.	UK	Longitudinal Study			
-2021					
					The symptoms resulting from the involvement of autonomic dysfunction are common in patients who have had COVID-19 and they have a great impact on quality of life both in the short, medium and long term.
CARMONA-TORRE et al. (2022)	56 countries	Critical Narrative Review	Dysautonomia in COVID-19 patients: a narrative review on clinical course, diagnostic and therapeutic strategies		
				3,762	
CROSS			Clinical and immunological aspects of Post-COVID-19 Syndrome		Multifocal rehabilitation is recommended, as well as improving the effects of health facilities
-2022	Brazil	Narrative Review		ND	

					The high mortality at the beginning of the pandemic may have occurred due to the failure of the health services to quickly adapt, demonstrating the great need for more investments to prepare for future pandemics.
CONDURACHE et al.	ND	Revision	Editorial: Post-COVID-19 cardiovascular sequelae		
-2023				ND	
DE MELLO; MORETTI; RODRIGUES			SARS-CoV-2 consequences for mental health: Neuroinflammatory pathways linking COVID-19 to anxiety and depression		Long-term pandemic stress can generate anxiety and depression in infected individuals.
-2022	Brazil	Revision		ND	
			Early experiences of rehabilitation for post-COVID individuals to improve fatigue, breathlessness exercise capacity and cognition—A cohort study		COVID-19 rehabilitation significantly improves clinical outcomes.
DAYNES et al.	UK	observational study		32	
-2021					
					COVID-19 can cause several complications after recovery, such as respiratory, neurological/mental, urinary, cardiovascular,

			What might COVID-19 patients experience after recovery? A comprehensive review	1,46,725	gastrointestinal, musculoskeletal complications, however the main ones were pulmonary sequelae, psychological problems and exercise intolerance.
ELHINY; AL-JUMAILI; YAWUZ (2022)	22 Countries	Revision		In 69 studies	
GREENHALGH et al.					
-2020	UK	Systematic review	Management of post-acute covid-19 in primary care	ND	ND
					Most hospitalized patients reported mental health disorders. Female gender, duration of illness, levels of inflammatory markers, and self-perception of illness severity are all factors that can be used to predict the severity of patients' mental symptoms.
HU et al.			Factors related to mental health of inpatients with COVID-19 in Wuhan, China		
-2020	China	Cross-sectional Research		85	

					Ongoing support by primary care professionals during recovery and rehabilitation is of paramount importance, as patients have demanded credibility regarding their symptoms and that these professionals have understanding and empathy.
KINGSTONE et al.		Qualitative through interviews	Finding the “right” GP: a qualitative study of the experiences of people with long-COVID	24	
-2020	UK				
					Ensuring long-term post-COVID service requires ensuring access to care, reducing the burden of disease, assuming clinical responsibility and providing continuity of care, multidisciplinary rehabilitation, evidence-based research and management, and further development of the knowledge base and services. clinical.
			Persistent symptoms after Covid-19: qualitative study of 114 “long Covid” patients and draft quality principles for services		

LADDS et al.	UK	Social Media through interviews		59	
-2020					
AUTHORS/YEAR	COUNTRY	KIND OF STUDY	STUDY TITLE	n	CONCLUSION
					Persistent symptoms associated with COVID-19 are frustrating for patients and patients should be referred to the COVID-19 care center if available, otherwise referred to specialist.
LEVINER			Recognizing the Clinical Sequelae of COVID-19 in Adults: COVID-19 Long-Haulers		
-2021	USA	Revision		ND	
					To help predict patient progression and future complications, image recognition based on time of infection is required.
LIME	Brazil	Revision	Information about the new coronavirus (COVID-19) Radiologia Brasileira	ND	
-2020					

MANDAL et al.	London		'Long-COVID': a cross-sectional study of persistent symptoms, biomarker and imaging abnormalities following hospitalization for COVID-19		Patients were followed for an average of 54 days after discharge and 53% reported persistent shortness of breath, 34% cough, 69% fatigue and 14.6% depression. 38% of chest X-rays remained abnormal and 9% showed signs of worsening.
-2021		Cross-sectional study		384	
MCINTOSH			COVID-19: Epidemiology, virology, and prevention, 2021		
-2021	USA	Literature review		ND	ND
					Multisystem engagement requires a holistic approach to the long-term management of COVID, and descriptions of cohorts from low- and middle-income countries are eagerly awaited.
MENDELSON et al.	South Africa	Revision	Long-COVID: An evolving problem with an extensive impact	ND	
-2020					
					Even though there is still no universal protocol regarding post-viral autonomic impairment, it should be emphasized that this

MIGLIS et al.	France	ND	Re: 'Post-COVID-19 chronic symptoms' by Davido et al	ND	treatment exists and has the potential to improve the quality of life of these patients.
-2021					
					The article demonstrated the importance of an interprofessional team approach in the management of patients with post-acute COVID-19 syndrome and made several considerations addressing the topic.
NALBANDIAN et al.	India and USA	Revision	Post-acute COVID-19 syndrome	ND	
-2021					
			Long-Term Cardiac Sequelae in Patients Referred into a Diagnostic Post-COVID-19		The study confirmed post-COVID-19 cardiac sequelae, 5 months after remission and that long-term follow-up and therapeutic strategies are needed.
PELÀ et al.	Italy	Single center cohort study	Pathway: The Different Impacts on the Right and Left Ventricles	160	
-2021					
					Several signs and symptoms involve the musculoskeletal system that affect quality of life and may result in a decrease in disability-adjusted life years.
PIRES et al.	Brazil	Systematic review	What Do We Need to Know About Musculoskeletal Manifestations of COVID-19?	ND	

-2022					
					Musculoskeletal disorders are rats compared to extrapulmonary and pulmonary manifestations, these disorders can have dire short- and long-term consequences.
RAMANI et al.	USA	Image Review	Musculoskeletal involvement of COVID-19: review of imaging		
-2021				ND	
RUBIN		Medical news and perspectives	As Their Numbers Grow, COVID-19 "Long Haulers" Stump Experts		
-2020	USA			ND	ND
					Prospective and retrospective studies on cardiovascular impairment, as well as understanding the molecular mechanism, are of utmost importance for the treatment of the SARS-CoV-2 virus, which can mitigate and save humanity around the world from this deadly pandemic.
SAMIDURAI; DAS			Cardiovascular complications associated with COVID-19 and potential therapeutic strategies		
-2020	USA	Revision		ND	
					The included studies suggested that Covid

SCHOU et al.			Psychiatric and neuropsychiatric sequelae of COVID-19—A systematic review	66 studies	survivors are at risk for psychiatric and neuropsychiatric sequelae and that these sequelae are a part of the long-COVID syndrome.
-2021	Denmark	Systematic review			
SEBASTIAN et al.	India	Revision	Postural orthostatic tachycardia syndrome (POTS): an update for clinical practice	ND	The sooner the disease is identified, the better the orientation of patients with suspected postural tachycardia syndrome.
-2022					
AUTHORS/YEAR	COUNTRY	KIND OF STUDY	STUDY TITLE	n	CONCLUSION
					80% of hospitalized patients often had subclinical myocardial dysfunction measured by reduced left

SHMUELI et al.	USA	Retrospective analysis	Left ventricular global longitudinal strain in identifying subclinical myocardial dysfunction among patients hospitalized with COVID-19	589	ventricular global longitudinal tension, whereas left ventricular function parameters, such as reduced ejection fraction and wall motility abnormalities, were less frequent findings.
-2021					
					To improve mental health care, it is necessary to increase awareness of the impact of the pandemic on specific groups, individualized treatment and prevention plans.
SIMON et al.	Germany	Revision	The collateral damage of the COVID-19 outbreak on mental health and psychiatry	ND	
-2021					
			Respiratory sequelae of COVID-19: pulmonary and extrapulmonary origins, and approaches to clinical care and rehabilitation		Physiotherapy as a non-pharmacological option can help reduce shortness of breath in post-Covid patients.
SINGH et al.	England	Revision		ND	
-2023					

			Bidirectional associations between COVID-19 and psychiatric disorder:		Psychiatric diagnosis may be an independent factor of Covid, but survivors of this pathology seem to be at greater risk of psychiatric sequelae.
TAQUET et al.	USA	Cohort	retrospective cohort studies of 62	62,354	
-2021			354 COVID-19 cases in the USA		
			Long-Term Cardiovascular Effects of COVID-19: Emerging Data Relevant to the Cardiovascular Clinician		New data have shown an increase in the incidence of cardiovascular diseases and structural changes in post-Covid patients.
TOBLER et al.	USA	Revision		ND	
-2022					
					Several systems and organs are affected after Covid in the medium and long term, with the main sequelae being carditis, post-infectious fatigue and persistent reduction in lung function.
WILLI et al.	Switzerland	Systematic review	COVID-19 sequelae in adults aged less than 50 years: A systematic review	31	
-2021					
					Some sequelae may be related to age, clinical characteristics during hospitalization and sex. Clinical sequelae were common in patients.
XIONG et al.	China	longitudinal study	Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study	538	
-2021					

			Cardiovascular complications of SARS-CoV-2 infection (COVID-19): a systematic review and meta-analysis	3,044 in 12 studies	Covid survivors had a lower incidence of heart failure and myocardial injury than non-survivors.
ZHAO et al.	China	Systematic Review and Meta-analysis			
-2021					

Table 1: Studies reporting the main sequelae after Covid-19 in adult individuals *ND - nothing described

Results

A comprehensive systematic search of the literature yielded a total of 4495 articles referring to the main post-covid sequelae in adult patients. Of these, 302 studies were excluded due to overlapping data. From there, we choose the SMARTER method (Simple Multi-Attribute Rating Technique using Exploiting Rankings). 393 articles were suitable for full-text screening and 99 articles were included for data extraction, of which 61 were excluded by the exclusion criteria, making 38 articles eligible that were included for systematic review. In (Figure 1), we describe the strategy for selecting articles on the topic in question.

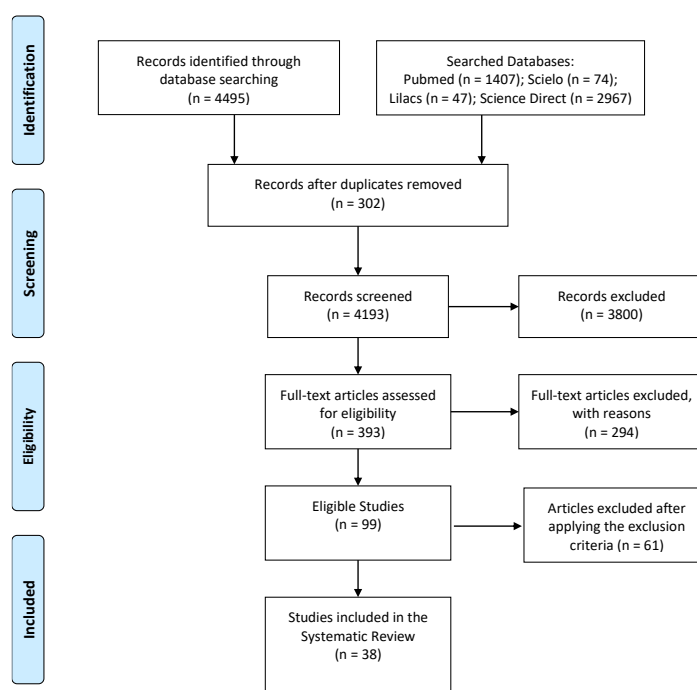


Figure 1: Article search strategy.

Discussion

A study carried out by [21], observed that a subset of individuals with COVID-19 may develop a chronic condition that persists long after the initial presentation, with cognitive slowing, prominent fatigue, and symptoms of autonomic impairment, such as exaggerated postural tachycardia, episodic hyperadrenergic spikes, and orthostatic intolerance. The study entitled “Clinical Sequelae of COVID-19 Survivors in Wuhan, China” conducted by [34], demonstrated that clinical sequelae were common, including general symptoms (49.6%), respiratory symptoms (39%), cardiovascular symptoms (13%), psychosocial symptoms (22.7%) and alopecia (28.6%). The study was carried out with 538 survivors, of which 54.4% were women, with a median age of 52 years and the time from discharge to the first follow-up was an average of 97 days.

Many patients who were diagnosed with the disease ended up not recovering completely, in some cases the symptoms continue to persist, and sometimes increase and sometimes decrease [16-18]. It is believed that around 10% of patients who have had Covid-19 and have mild symptoms will eventually become long-term carriers [14-18]. Patients who have more severe comorbidities or infections with the SARS-CoV-2 virus are those who have a higher incidence of persistent symptoms [18-20]. Although no time period has been established to be identified as persistent symptoms, it is acceptable to say that symptoms that last more than 3 to 4 weeks post diagnosis, and more than six weeks in the case of critical illness, are mild, moderate or severe, it can be considered that they are persistente [18]. Although post-acute sequelae are still not well understood, some people have multiple affected systems that can persist for several months, which ultimately impairs quality of life [14][18][36]. Recovered patients, but with serious complications such as respiratory failure, post-acute thrombosis and cardiac and vascular damage, tend to increase the possibility of future morbidity and mortality. Cohort studies that have investigated these complications are still very limited, for this reason these studies have focused especially on complications that lead to readmission, rather than evaluating post-acute complications [36]. The study carried [5], suggested that Covid-16 infection increases the risk of 6-month mortality.

A study of patients hospitalized for severe post-Covid sequelae showed that they are at greater risk of new hospitalizations than patients who had mild covid. However, in the study it was not clear whether the severe infection increases the risk of mortality in 12 months after the previous episode and there is still a lack of data regarding post-acute sequelae in young patients compared to older patients [36]. Several studies have demonstrated and spoken these days about post Covid sequels. Among these sequels we can mention:

Cardiovascular Sequelae

Studies have shown that these surviving patients are at greater risk of cardiovascular complications, which may include cardiomyopathy, heart failure, acute myocardial infarction and arrhythmias [26-35]. Some of these patients have evidence of myocardial inflammation and ejection fraction of the affected lower left ventricle on cardiac resonance [29-37]. Long-haulers have a higher incidence of thrombosis and coagulopathies and the embolism lung has been described 3 to 4 weeks after the acute illness [22-38].

A study carried out by [23], demonstrated that cardiovascular complications were arrhythmia (10%; ectopic atrial beat n = 10; ventricular arrhythmias n = 2; atrial fibrillation n = 4), followed by venous

thromboembolism (VTE, 8%), hemodynamic instability (defined mainly by hypotension and also the need for pharmacological support with intravenous noradrenaline), deep vein thrombosis (DVT, 2%) and pericarditis (1%). The autonomic nervous system can also be affected by viral diseases, and orthostatic hypotension may be present together with tachycardia in response to changes in position, running the risk of presenting injury due to vasovagal syncope. These symptoms should be well evaluated to rule out other etiologies. Guidance for these patients must be well placed to control symptoms and avoid injuries [8-28].

The available vaccines herald a new phase in the pandemic with a reduction in serious infections and mortality, but it also comes with a lot of concern about their safety, due to the reports of several cases and registry data that have reported myocarditis as a side effect of vaccination against COVID-19 [10]. The complexity of acute cardiovascular diseases caused by SARS-CoV-2 infection is already being well described nowadays, with arrhythmia, myocardial injury, acute coronary syndrome and heart failure as the main ones. Complications that in the long term may require chronic cardiovascular care [33].

Mental health sequelae

Because it is still uncertain, long-term Covid leaves patients feeling helpless about controlling their symptoms [6-30]. Truck drivers went through an interview and said they were frustrated by the lack of assistance from both family members and health professionals [16]. People who before the event were considered healthy and independent, have difficulties with their activities of daily living and have difficulties or have been unable to work because of the symptoms and their limited endurance [17-18]. A cohort study carried out with anonymous data from electronic health records in 54 health institutions in the USA, demonstrated a 5.8% increase in the incidence of psychiatric illnesses, diagnosed 14 to 90 days after diagnosis of the illness, compared to the control group that 2.5 to 3.4% received a new psychiatric diagnosis [32].

These alterations have several etiologies, as a vast number of stressors appeared during the pandemic, such as social and financial isolation and fear and uncertainty regarding the SARS-CoV-2 infection [11]. Acute psychiatric symptoms in patients who had the disease was reported in several studies and that at least 35% of patients demonstrated symptoms of depression and anxiety [15][27].

Musculoskeletal sequelae

Guillain-Barré syndrome (GBS) is a demyelinating polyneuropathy, Acquired nervous system disorder, probably autoimmune in nature, marked by loss of myelin sheath and tendon reflexes, which has been reported with symptoms appearing 3 to 4 weeks after the onset of COVID symptoms, as well as Miller-Fisher syndrome which is a variant of GBS. On magnetic resonance, GBS and its variants demonstrate hyper signal intensity, increase and mild to moderate contrast enhancement of nerve roots/plexuses and cauda equina [25][13], conducted a review study entitled "What might COVID-19 patients experience after recovery?". In this research, twenty-three studies demonstrated musculoskeletal symptoms in Covid-19 survivors, including myalgia and joint pain, which lasted from 35 days to 3 months after discharge. Twelve studies reported that patients experienced fatigue.

Post Covid-19 complications are increasing in survivors in the pandemic years and the musculoskeletal changes cited in these survivors are those that fall in the elderly, increasing mortality after hip fracture, osteoporosis, fibromyalgia, onset of latent muscular dystrophy, urticarial vasculitis with musculoskeletal manifestations, rhabdomyolysis, adhesive capsulitis, Guillain-Barré syndrome, soft tissue abscess, acute sarcopenia, critical illness myopathy, osteonecrosis, muscle denervation atrophy, septic arthritis, myositis, autoimmune necrotizing myositis, and rheumatologic disease [24].

The various signs and symptoms that involve this system end up affecting the quality of life of these patients, as well as reducing the years adjusted for disability, which shows us that the care of the multidisciplinary team, continuing education, preventive measures, is of paramount importance. early diagnosis and treatment [24].

Pulmonary sequelae

Post-covid pulmonary sequelae have been shown for a long time and have been shown to be very important in the post-covid scenario, as they include shortness of breath, breathing pattern disorders. Cough is highly prevalent during acute illness, but with low prevalence post-Covid. The most specific post-Covid sequelae are pulmonary fibrosis and thromboembolic diseases, but these should be evaluated more carefully in order to have a more specific treatment. The combination of extrapulmonary and pulmonary sequelae tend to contribute to persistent and disabling shortness of breath [9]. Regardless of the severity of the illness, long-term Covid survivors report symptoms such as sleep disturbances, headaches, shortness of breath, fatigue and muscle pain [31].

The main complaints of patients are dyspnea, cough and reduced ability to perform exercises [12]. It is believed that lung function tends to improve over time, but the lung symptoms of long-term patients are still unknown. Patients who have acquired pulmonary fibrosis will not improve, as this pathology is irreversible [7].

Final Considerations

Several organs are affected as a result of Covid in patients recovered in the long and medium term, in which we can include post-infectious fatigue, carditis, persistent reduction in lung function, psychiatric and neurological, cardiovascular, musculoskeletal, among others. This reason demonstrates the need for further research and the paramount importance of monitoring these patients over a long distance to prevent possible damage to the affected organs and preserve their quality of life.

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