Current perspectives on Long-COVID: a brief review of understanding and management

Martínez-Bretón, Paulina[1]; Colonna-Aguirre, Brandon[1]; Zebadúa Rodríguez, Noé[1]; Iñiguez-Luna, María I.[2*]; Cadena-Zamudio, Jorge D.[3*]

[1] Universidad Veracruzana, Facultad de Medicina, C. Agustín de Iturbide S/N, C.P. 91700, Zona Centro, Veracruz.
[2] Grupo Interdisciplinario de Investigación en *Sechium edule* en México, A.C. Agustín Melgar 10 Col. Niños Héroes, Texcoco, Estado de México C.P. 56160.
[3] Instituto Nacional de Investigaciones Forestales, Agrícolas y Pecuarias, Centro Nacional de Recursos Genéticos, Blvd. de la Biodiversidad #400 Rancho las Cruces Tepatitlán de Morelos, C.P. 47600, Jalisco
* Correspondence: eunadimiil@gmail.com; cadena.jorge@inifap.gob.mx

ABSTRACT

Objective: Conduct a retrospective analysis of studies compiled in the literature on the current classification of Long-COVID.

Design/methodology/approach: A search was conducted in medical information platforms using the keywords: COVID-19, Long COVID, COVID.19 sequelae, SARS-CoV 2, prolonged COVID. Articles published in the chronological period between 2020 and 2023 in both English and Spanish were used. Inclusion criteria were a maximum of five years since publication, review articles, systematic reviews, meta-analyses or clinical practice guidelines. The exclusion criteria were that the articles exceeded the time limit, that they were opinion articles, case reports or trials.

Results: There is no homogenized definition or standardized guidelines or norms for the diagnosis of Long-COVID, the epidemiological studies are not completely corroborated and there is a great disparity between the incidence rates estimated in the different research works, same case for treatment.

Limitations on study/implications: The lack of homogeneity in the patterns of symptoms, classification and diagnosis by the literature and health officials.

Findings/conclusions: A multidisciplinary approach is required, where clinical findings, laboratory and imaging studies are integrated, to homogenize information in search of adequate and timely Long-COVID diagnoses and effective treatments for the benefit of patients.

Keywords: SARS-CoV-2, COVID-19, Long-COVID, Viral infection, Sequelae.

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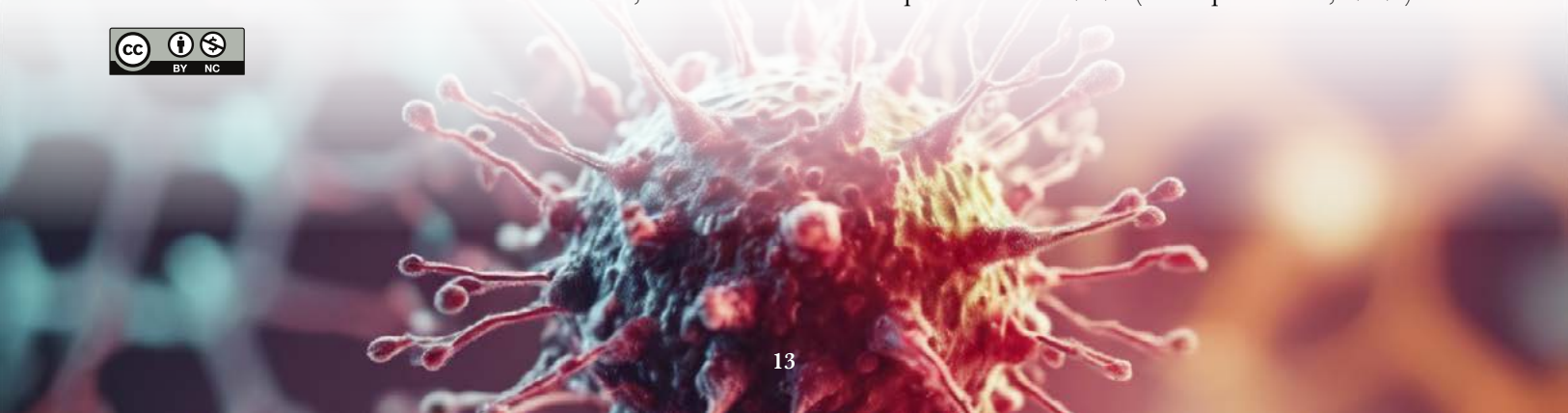
INTRODUCTION

Coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, which emerged in Wuhan, China, has its beginning during December 2019, at the time when cases of pneumonia of unknown cause were detected (Acosta-Morales *et al.*, 2022), which represented the beginning of one of the greatest health challenges of recent times worldwide, as it was declared a pandemic in 2020 (Siddiquea *et al.*, 2021). At



the beginning it was considered as an exclusively respiratory disease, which presented as an influenza picture with alteration of the lower respiratory tract (Gil *et al.*, 2021), however, during the course of this health emergency countless advances in research were made, determining that it is a systemic disease (Anka *et al.*, 2021); where the main extrapulmonary systems affected are the neurological, with symptoms such as anosmia and ageusia, the cardiovascular, with manifestations such as endocarditis and arrhythmias, and the gastrointestinal, with symptoms such as nausea and anorexia (Vázquez *et al.*, 2022).

Today, SARS-CoV-2 disease is recognized as an established and persistent public health problem and no longer as a health emergency (PAHO, 2023), however, it is important to highlight that, after acute infection, a large spectrum of symptoms considered as sequelae of the disease has been reported, the duration of which extends from weeks to months (Raveendran *et al.*, 2021). Some of these symptoms are fatigue, mental fog, myalgia, headache, among others (Ceban *et al.*, 2022; Carfí *et al.*, 2020). The above, takes clinical relevance due to the large number of individuals affected by COVID-19 worldwide, with a total of 774,075,242 reported cases, according to the most current data from the World Health Organization (WHO) (WHO, 2024), where many of these individuals have experienced long-term sequelae associated with SARS-CoV2 infection (Crook *et al.*, 2021). Because of the above, there is still no consensus on appropriate definitions for patient-coined symptomatology referring to the pathological entity whereby persistent symptoms occur in a significant proportion of those who have had COVID-19, whether asymptomatic, mild or severe, persisting beyond the acute phase of infection (Aiyegbusi *et al.*, 2021) or also known as Long-COVID (Long-COVID) (Gonzalez-Hermosillo *et al.*, 2021; Lai *et al.*, 2023).

Because of this lack of standardization in addressing symptoms persisting after acute COVID-19 infection, the aim of the present study focuses on current thinking about Long-COVID, taking into account issues such as definition, epidemiology, clinical manifestations, diagnosis, and treatment.

MATERIALS AND METHODS

A search was performed in the following medical information platforms: Pubmed, Medscape and Google Scholar, where the keywords: COVID-19, Long COVID, COVID.19 sequelae, SARS-CoV 2, prolonged COVID were used and search filters were applied to fit the corresponding inclusion criteria.

Articles published in the chronological period corresponding to the years 2020 to 2023 in both English and Spanish were used; the search for these articles was carried out during the months of December 2023 to February 2024. Different inclusion criteria were used to be considered part of the bibliography, among them are: that they were at least five years old since their publication, that they were review articles, systematic reviews, meta-analyses or clinical practice guidelines. The exclusion criteria were that the articles exceeded the time limit of five years since publication, that they were opinion articles, case reports or trials.

RESULTS AND DISCUSSION

Definition

Prolonged COVID (Long-COVID) was the first term referred to by patients to describe the presence of a set of symptoms, over weeks or months after acquiring SARS-CoV-2 infection, without distinction as to whether the symptoms present are new or are the same symptoms that appeared with the acute illness (Raveendran, 2021). Other terms that can be found in the literature in reference to Long-COVID are: Long-COVID-19, acute post-COVID-19, chronic COVID-19, post-COVID fatigue, post-COVID-19 prolonged carrier, post-COVID-19 neurological syndrome, post-acute sequela of SARS-CoV-2 infection, among others (Gonzalez-Hermosillo *et al.*, 2021; Lai *et al.*, 2023; National Institute of Health (NIH), 2023).

In the same way that there are a large number of terms to try to name this pathology, there are different concepts to try to define it. The WHO defines Long-COVID as a condition characterized by symptoms affecting daily life, such as fatigue, shortness of breath and cognitive dysfunction, which occur after a history of probable or confirmed SARS-CoV-2 infection. Symptoms usually appear three months after the onset of acute COVID-19 symptoms, last at least two months, and cannot be explained by an alternative diagnosis (WHO, 2021). Other studies have concurred in using this three-month time interval in their definitions (Greenhalgh *et al.*, 2020; Chee *et al.*, 2022). Contrary to this, the Center for Disease Control and Prevention (CDC) defines Long-COVID as the development of symptoms that cannot be otherwise explained later than four weeks after acute SARS-CoV-2 infection (CDC, 2023).

Due to the above, establishing a standardized definition has been a matter of debate due to the large number of factors to be considered (Aiyegbusi *et al.*, 2021). Starting with the chronology of the onset of symptoms, which is a relevant point when defining Long-COVID, and as can be noted in the definitions presented above, there is still variation in the range of time that should be considered to speak of this pathology. Also, the set of symptoms that are considered as part of Long-COVID must be defined, as well as the persistence of symptoms due to acute COVID-19 infection. One of the main limitations during the diagnosis of Long-COVID lies in the capacity of viral replication, where its identification is limited to at least three weeks later for its isolation (Terán-Escobar *et al.*, 2023). This becomes relevant in the classification and definition of Long-COVID, since during the clinical assessment it is necessary to clarify whether the symptoms present in the patient are persistent or represent a new symptomatology. In the work of Chent and collaborators, they also emphasize that during the classification of long-COVID it should be categorized as subacute if the symptoms remit in the first 12 weeks, and chronic if they persist beyond that period.

On the other hand, the National Institute for Health and Clinical Excellence of the United Kingdom (NICE), in search of a solution to the problem of the lack of consensus in the definition and terminology of Long-COVID, proposes not to use the terms "chronic" or "persistent" to refer to this entity, because it considers them inadequate. He includes within the term Long-COVID the continuous symptomatic COVID-19 and the post-COVID-19 syndrome. In addition, it suggests using the term acute COVID-19 for signs

and symptoms of COVID-19 for up to four weeks, continuous symptomatic COVID-19 when symptoms last from four to 12 weeks and post-COVID-19 syndrome when they persist for more than 12 weeks in the absence of an alternative diagnosis (NICE, 2021).

NICE's suggestion to avoid certain terms to refer to Long-COVID represents a promising starting point for standardizing the language used in the scientific literature regarding this condition. In addition, its proposal to classify Long-COVID as "continuous symptomatic COVID-19" when symptoms persist between four and 12 weeks, and as "post-COVID-19 syndrome" when they exceed 12 weeks, bears similarity to the CDC definition, which establishes a period after four weeks of acute SARS-CoV-2 infection. On the other hand, the WHO and several investigators consider a three-month period (equivalent to 12 weeks) in their definitions of Long-COVID (Sreelakshmi *et al.*, 2023; Gaspar *et al.*, 2023). The adoption of these NICE recommendations would contribute to a clearer and more uniform definition of Long-COVID in terms of symptom duration. The advantages of standardizing the definition of Long-COVID are to have precise cut-off points to be able to determine from what time point of persistence in clinical manifestations, a patient can be classified as a probable case of Long-COVID; an ambiguous definition brings with it many repercussions for both health care personnel and patients (Figure 1). On the one hand, there would be a bias in the information to be able to talk about this pathology and difficulties in establishing the diagnosis and on the other hand, patients will remain a long time without knowing their diagnosis, with the psychological and medical consequences that this implies (Chater, 2020; Hassan and Jameel, 2023). The limits and challenges for this approval are the lack of experience in the management of this disease and the increasing information that is being published, with diverse epidemiological data and varied incidence rates (Crook *et al.*, 2021).

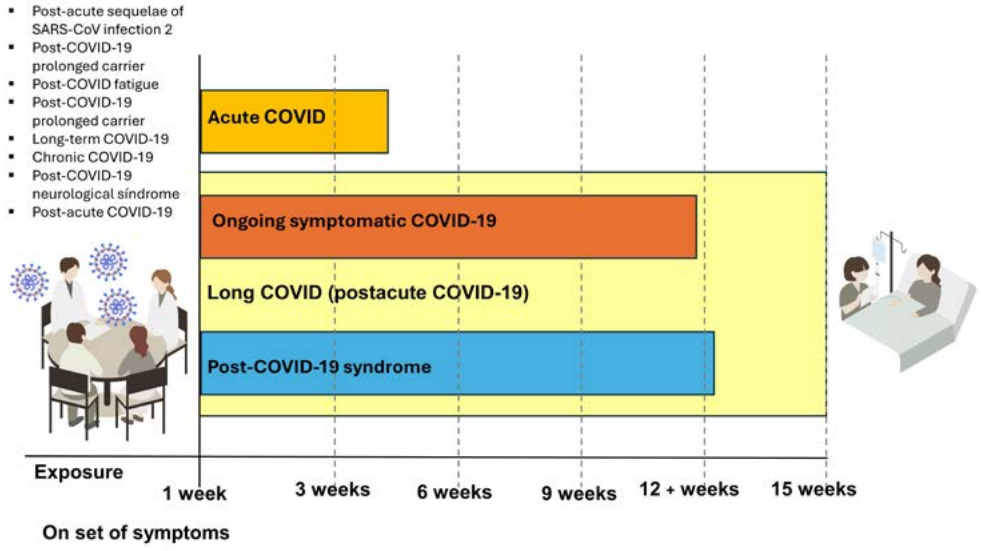


Figure 1. Temporal classification of different definitions of COVID-19 in week. This figure shows the weeks on the data is based on information provided by NICE. 2021. COVID-19 Rapid Guideline: anaging the long-term effects of COVID-19. NICE Guideline [NG188]. https://www.nice.org.uk/guidance/ng188 (Retrieved: January 2024).

Epidemiology

The American literature provides estimates suggesting that between seven and 23 million Americans have developed Long-COVID (McCarthy, 2023); worldwide, the estimated number ranges from five (Yong, 2021) to 65 million people facing Long-COVID (Davis *et al.*, 2023). This heterogeneity is probably due to the aforementioned lack of consensus for the definition of this entity, underdiagnosed cases, the presence or absence of verifiable organic damage, as well as the difficulty in establishing whether a patient's current condition derives from COVID-19 or from another entity (Bouza *et al.*, 2021) (Yong *et al.*, 2021).

Worldwide studies have reported various incidence rates of Long-COVID according to different established times of follow-up examinations of patients after presenting with COVID-19. Identifying an incidence rate of 32.6-87% at 60 days after acute SARS-CoV-2 infection (Carfi *et al.*, 2020; Chopra *et al.*, 2021), 96% at 90 days (Davis *et al.*, 2021) and 76% at six months (Huang *et al.*, 2021).

On the other hand, there are findings that relate the severity of acute infection to the probability of developing late symptoms of the disease (Aiyegbusi *et al.*, 2021). In a study conducted in the Netherlands, they estimate that at least 10% of patients with severe SARS-CoV-2 develop Long-COVID (Ballering *et al.*, 2022). According to other research, in the case of people who suffered COVID-19 and did not require hospitalization, they estimate an incidence rate of 10-30% of developing Long-COVID, 50-70% of developing it in patients who required hospitalization for COVID-19 (Bull *et al.*, 2022; Ceban *et al.*, 2022) and 10-20% in patients who received any vaccine for SARS-CoV-2 (Anka *et al.*, 2021; Al-Aly *et al.*, 2022).

Although the findings on Long-COVID are not fully corroborated and there is great disparity between the incidence rates estimated in different research papers, it is clear that a substantial proportion of people who have had COVID-19 will develop this condition (Crook *et al.*, 2021; Katz *et al.*, 2023; Goodridge *et al.*, 2023). This diversity in incidence estimates worldwide reflects the complexity of Long-COVID, being influenced by factors such as lack of consensus on its definition, underdiagnosed cases, and difficulty in determining whether persistent symptoms are attributable to COVID-19 or other disorders. In addition, an association has been observed between the initial severity of acute infection and the likelihood of developing prolonged symptoms. It is crucial to continue research and provide adequate clinical care recognizing the importance of a more complete understanding of Long-COVID starting with the characterization of the disease by identifying its clinical manifestations and thus being able to improve its management and mitigate its impact on public health (Abrignani *et al.*, 2022; Draud *et al.*, 2023).

Clinical manifestations

Based on evidence from various meta-analyses, 60% of survivors of acute COVID-19 infection will develop at least one post-COVID symptom (Fernandez, 2022). The most commonly encountered symptoms have been: dyspnea, cough, fatigue, mental fog, headache, anxiety, palpitations, muscle pain, joint pain, among others (Ceban *et al.*, 2022; Koc *et al.*, 2022). Fatigue is the most commonly reported clinical manifestation at the time

of medical questioning by patients, especially if this was presented as a severe symptom during acute COVID-19 infection (Bouza *et al.*, 2021; Crook *et al.*, 2021; Mansell *et al.*, 2022).

Separating clinical manifestations by apparatus and systems, it was found that patients who were not hospitalized have a higher probability of presenting neuropsychiatric symptoms, such as anxiety and depression, versus patients who were hospitalized during the acute infection (Premraj *et al.*, 2022). Mental fog is one of the main neurological sequelae occurring in patients and is characterized by problems in memory, executive function and concentration (Carfí *et al.*, 2020). Patients are also reported with loss of smell, reduced ability to detect odors and decreased ability to notice different tastes, which has been related to the severity of symptoms and advanced age of the patient (Mansell *et al.*, 2022; Cau *et al.*, 2022).

Within the studies there is little evidence of gastrointestinal complaints (Yang *et al.*, 2022) reported that 15.3% of patients have bloating after each meal and approximately less than 10% may have poor appetite, constipation, abdominal pain, diarrhea, nausea and vomiting (Lai *et al.*, 2023). Regarding the cardiovascular system, several studies show that, while a considerable number of patients with COVID-19 present with myocarditis and elevated serum troponin levels, these symptoms and signs may persist up to 71 days after diagnosis, as well as angina pectoris (Galarza-Vera *et al.*, 2023). Something similar occurs with thrombosis and its complications, which are pathologies reported upon coronavirus infection, since in subsequent controls of these patients after the acute infection, they present dyspnea and chest pain, and in most of the occasions they present thrombotic phenomena in the vascular tree and alteration of vascular perfusion in the pulmonary bed (Acosta-Morales *et al.*, 2022).

In addition, it has been found that some patients may present dermatological manifestations, especially in children, lesions similar to chickenpox, morbilliform exanthema secondary to lymphocytic vasculitis, and vascular lesions such as livedo reticularis, retiform purpura and necrotic lesions (Gutierrez-Bautista *et al.*, 2021).

The range of clinical manifestations evoked by Long-COVID is, moreover, wide (Figure 2). This is a reflection of the great virulence of this coronavirus, although at the beginning of the pandemic it was considered an exclusive disease of the respiratory system, today the metabolic, cardiovascular, neurological and many other complications have shown that it is not a respiratory virus but a microorganism whose virulence is sufficient to cause a change in the human system that lasts over time, even when there are no viral copies in circulation (Gang *et al.*, 2022; Craddock *et al.*, 2022). Long-COVID unfortunately has no single pattern from which it can be suspected, its presentation is varied in both diversity and severity, however, as reviewed, fatigue, as well as mental fog, headache, anxiety, palpitations, muscle pain, joint pain can be strong indicators of its presence. It is emphasized that Long-COVID can enter the list of differential diagnoses with many other pathologies (Turner *et al.*, 2023), the history of SARS-CoV-2 infection and the ruling out of other diagnostic possibilities play a very important role in the characterization of the clinical picture in the diagnostic process.

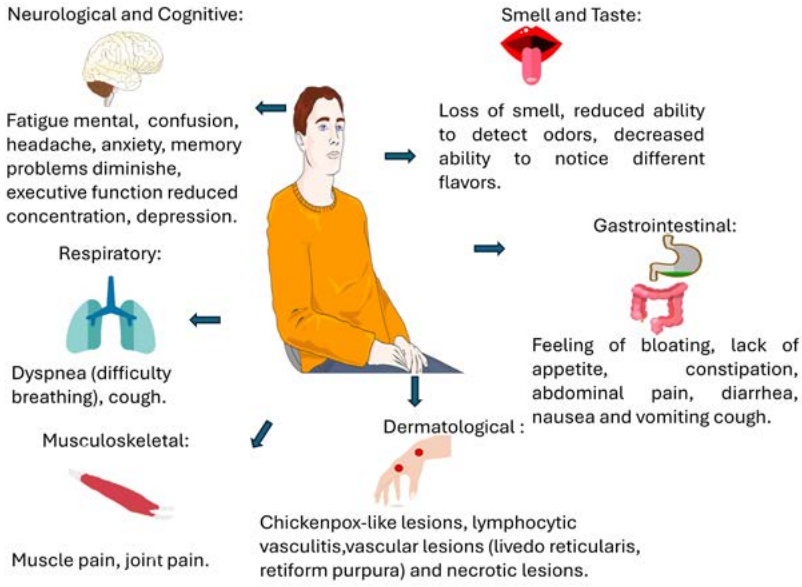


Figure 2. Symptoms and effects associated with a health condition categorized by body systems. This figure represents a visual classification of various symptoms and effects related to a health condition. Symptoms are grouped into specific categories: neurological and cognitive, respiratory, musculoskeletal, gastrointestinal, dermatological, smell and taste.

Diagnosis

Given that the clinical manifestations are broad and involve different devices and systems, there is no single study that establishes the diagnosis of Long-COVID. A multidisciplinary approach is required, where clinical findings, laboratory and imaging studies are integrated (Gogineni *et al.*, 2022; Hardy-Werbin *et al.*, 2023). Clinicians face a challenge in diagnosing Long-COVID, as it involves an overall process of evaluating symptoms and ruling out other conditions to reach a conclusion. This task is complicated by the existence of multiple definitions and diagnostic standards (Srikanth *et al.*, 2023). However, the same problem of lack of homogenization of information on Long-COVID arises in relation to diagnostic tools, most of which are still under development. To date, no specific biomarkers have been identified for this condition, resulting in a paucity of specific guidelines or standards for its diagnosis (Davis *et al.*, 2023; Morello *et al.*, 2023).

There are proposals about the laboratory studies that should be incorporated along with the radiological findings according to the clinical data of each patient. For the respiratory system, an evaluation with respiratory function tests, chest X-ray at 12 weeks and a high-resolution computed tomography (CT) scan are suggested to complete the evaluation (Cau *et al.*, 2022). For the cardiovascular system, noninvasive studies such as echocardiogram, CT or magnetic resonance imaging (MRI), assessment of D-dimer levels, C-reactive protein, doppler ultrasound to rule out thrombotic lower limb vasculopathy, and angiotomography in patients deemed necessary are required (Raman *et al.*, 2022). NICE guidelines suggest screening for anxiety and depression, and other neurological symptoms, as well as considering a CT, MRI or electroencephalogram study to assess nervous system function (Venkatesan, 2021; Premraj *et al.*, 2022).

The wide variety of diagnostic tools proposed to evaluate each body system reflects, firstly, the great capacity of SARS-CoV-2 infection to generate morbidity in the population (Jaros *et al.*, 2023). Secondly, it demonstrates the complexity of the diagnostic approach to a patient with a history of this infection (Davis *et al.*, 2023; Morello *et al.*, 2023). In a patient who has had confirmation of COVID-19 and who four weeks or more after the acute illness reports fatigue or persistence of neurological, respiratory, cardiovascular or digestive symptoms, in the absence of other causal pathology, Long-COVID can be considered (NICE, 2021), using laboratory or laboratory tests for cases in which their use is warranted. The above is secondary to the scarcity of a diagnostic algorithm stipulated by consensus (Platz *et al.*, 2023), undoubtedly this represents a great challenge for the medical community, since the lack of a clinical practice guideline for this disease, which day by day has better characterization, causes a problem for health care measures, leaving a large proportion of cases undiagnosed (Gray *et al.*, 2023) and, consequently, causing an underreporting in the number of real patients to be able to establish an adequate prevalence and incidences on the one hand, and on the other hand, leaving a part of the population without adequate treatment.

Treatment

Approaching treatment in a general way, patients may require multidisciplinary care due to the broad spectrum of manifestations involved in Long-COVID, which involves long-term monitoring of the evolution of symptoms to identify possible complications, clinical intervention, and the need for physical exercise, rehabilitation, mental health care, and social service support (Aiyegbusi *et al.*, 2021) (Figure 4).

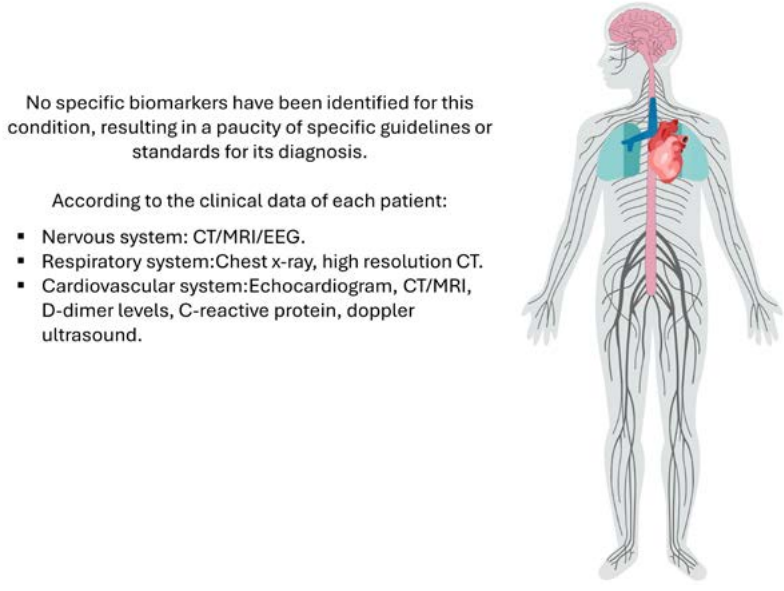


Figure 3. Diagnostic methods for a condition without specific biomarkers identified. This figure shows the different diagnostic methods used to evaluate various body systems in a condition for which no specific biomarkers have been identified, resulting in the paucity of specific guidelines or standards for its diagnosis. According to the clinical data of each patient.

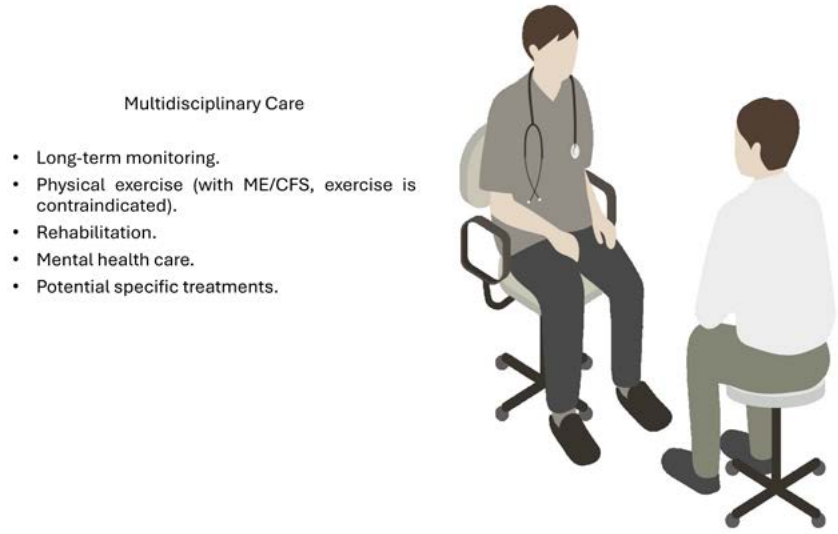


Figure 4. Multidisciplinary care. Comprehensive management of this condition includes long-term monitoring, physical exercise (except in patients with myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS] where exercise is contraindicated), rehabilitation, and mental health care. Additionally, potential specific treatments are considered.

About possible specific treatments for Long-COVID, one case report observed resolution of Long-COVID after treatment with the antiviral nirmatrelvir/ritonavir (Paxlovid) (Geng *et al.*, 2022), and a study investigating treatment of COVID-19 with Paxlovid showed a 25% reduction in the incidence of Long-COVID (Xie *et al.*, 2022); Paxlovid should be further investigated for the prevention and treatment of Long-COVID (McCarthy, 2023). Naltrexone, an opioid antagonist, at low doses has also shown promise in the treatment of Long-COVID (Pitt *et al.*, 2022). Metformin is under investigation for the general prevention of Long-COVID (Yong *et al.*, 2023).

Due to the lack of evidence that any one drug improves or attenuates the Long-COVID symptom cluster in large-scale, controlled cohort studies (Yong, 2021), most current trials focus on individual Long-COVID symptoms, and medical interventions are aimed at treating these symptoms or isolated organ dysfunction, which may be cardiovascular, respiratory, gastrointestinal, neurological, or psychological (Chee *et al.*, 2023). A small trial of sulodexide, a drug that decreases blood clotting, in people with endothelial dysfunction with which a reduction in symptom severity was observed (Charfeddine *et al.*, 2022). Pilot studies of probiotics indicated potential for alleviating gastrointestinal and non-gastrointestinal symptoms (Thomas *et al.*, 2022; Zhang *et al.*, 2022). Systematic reviews and molecular studies have suggested that histamine-1 and histamine-2 antagonists have broad-spectrum antiviral effects; within these, famotidine, a histamine H2-receptor antagonist, has been studied for persistent neuropsychiatric symptoms after acute COVID-19 illness (Alper, 2020; Ishola *et al.*, 2022; Ge *et al.*, 2021).

It has been suggested that drugs used for the management of Long-COVID-like conditions may have the potential to be repurposed for treatment (Yong, 2021). For example, in the case of prolonged fatigue, which is a common manifestation of Long-COVID, due

to the limited availability of specific treatments, the general recommendations made by NICE to manage it are self-care and support (NICE, 2021). However, because myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has been found to be a condition that can overlap with this prolonged fatigue, the treatment algorithm designed to treat ME/CFS may prove useful in the management of Long-COVID (Crook *et al.*, 2021).

On this line of research of Long-COVID patients with ME/CFS, there are several studies. Exercise has been found to be detrimental for this type of patients (Heerdt *et al.*, 2022) and should not be prescribed as treatment in them (WHO, 2021) (CDC, 2021). Rintatolimod, an experimental drug with immunomodulatory and antiviral properties, appears to have modest to high potential as a treatment option (Yong *et al.*, 2023).

Despite the different lines of research that have been carried out, there are no approved treatments to treat Long-COVID (McCarthy, 2023) due to the great problem it raises in the lack of rigor and homogeneity in its definition, the inclusion/exclusion criteria, the characterization of the pathology and the mechanisms underlying it (Aiyegbusi *et al.*, 2021; Ceban *et al.*, 2022).

CONCLUSIONS

This review highlights the long-term implication of SARS-CoV-2 infection in the genesis of various clinical manifestations that impact the quality of life of the population that suffered COVID-19. It is still necessary to expand research on this entity, as well as to systematize and deepen the information currently available. In the absence of a standardized definition, epidemiological studies are not completely corroborated and there is a great disparity between the incidence rates estimated in the different research studies, evidencing the clear underreporting of patients who have been affected by this long-term complication of COVID-19. The same obstacle arises when establishing diagnostic criteria, where no specific guidelines or standards for diagnosis have been determined. A multidisciplinary approach is required, integrating clinical findings, laboratory and imaging studies. This interdisciplinary collaboration will broaden the understanding and allow the homogenization of information in the search for adequate and timely diagnosis of Long-COVID and effective treatments for the benefit of patients.

REFERENCES

Acosta-Morales A.G., Espinosa-Herrera F.V. 2022. Secuelas del COVID-19, un desafío de la salud pública: Revisión bibliográfica. *Revista Vive 5*(15), 889-908. https://doi.org/10.33996/revistavive.v5i15.196

Aiyegbusi O.L., Hughes S.E., Turner G., Rivera S.C., McMullan C., Chandan J.S., Haroon S., Price G., Davies E.H., Nirantharakumar K., et al. 2020. Case Report: Famotidine for Neuropsychiatric Symptoms in COVID-19. *Frontiers in medicine* 7, 614393. https://doi.org/10.3389/fmed.2020.614393

Al-Aly Z., Bowe B., Xie Y. 2022. Long COVID after breakthrough SARS-CoV-2 infection. *Nature Medicine 28*(7), 1461-1467. https://doi.org/10.1038/s41591-022-01840-0

Alper K. (2020). Case Report: Famotidine for Neuropsychiatric Symptoms in COVID-19. Frontiers in medicine 7, 614393. https://doi.org/10.3389/fmed.2020.614393

Anka A.U., Tahir M.I., Abubakar S.D., Alsabbagh M., Zian Z., Hamedifar H., Sabzevari A., Azizi G. 2021. Coronavirus disease 2019 (COVID-19): An overview of the immunopathology, serological diagnosis and management. *Scandinavian journal of immunology 93*(4), e12998. https://doi.org/10.1111/sji.12998

Ballering A. V., van Zon S. K. R., Olde Hartman T. C., Rosmalen J. G. M., Lifelines Corona Research Initiative. 2022. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet (London, England), 400*(10350), 452-461. https://doi.org/10.1016/S0140-6736(22)01214-4

Bouza E., Cantón-Moreno R., de Lucas-Ramos P., García-Botella A., García-Lledó A., Gómez-Pavón J., González-del Castillo J., Hernández-Sampelayo T., Martín-Delgado M. C., Martín-Sánchez F.J., Martínez-Sellés M., Molero-García J.M., Moreno-Guillén, S., Rodríguez-Artalejo F.J., Ruiz-Galiana J., de-Pablo-Brühlmann S., Porta-Etessam J., Santos-Sebastián M. 2021. Post-COVID syndrome: A reflection and opinion paper. *Revista Española de Quimioterapia 34*(4), 269-279. https://doi.org/10.37201/req/023.2021

Bull-Otterson L., Baca S., Saydah S., Boehmer T.K., Adjei S., Gray S., Harris A.M. 2022. Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021. *MMWR. Morbidity and Mortality Weekly Report 71*(21), 713-717. https://doi.org/10.15585/mmwr.mm7121e1

Carfì A., Bernabei R., Landi F. 2020. Persistent Symptoms in Patients After Acute COVID-19. *JAMA 324*(6), 603. https://doi.org/10.1001/jama.2020.12603

Cau R., Faa G., Nardi V., Balestrieri A., Puig J., Suri J.S., SanFilippo R., Saba L. 2022. Long-COVID diagnosis: From diagnostic to advanced AI-driven models. *European Journal of Radiology* 148, 110164. https://doi.org/10.1016/j.ejrad.2022.110164

Ceban F., Ling S., Lui L.M.W., Lee Y., Gill H., Teopiz K.M., Rodrigues N.B., Subramaniapillai M., Di-Vincenzo J. D., Cao B., Lin K., Mansur R.B., Ho R.C., Rosenblat J.D., Miskowiak K.W., Vinberg M., Maletic V., McIntyre R.S. 2022. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain, behavior, and immunity* 101, 93-135. https://doi.org/10.1016/j.bbi.2021.12.020

Centro para el Control y la Prevención de Enfermedades (CDC). 20 de julio de 2023. Long COVID or Pst-COVID conditions. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html (Recuperado: enero 2024)

Centers for disease control and prevention (CDC). 2021. Treatment of ME/CFS | Myalgic encephalomyelitis/chronic fatigue syndrome. https://www.cdc.gov/me-cfs/treatment/index.html (Recuperado: enero 2024)

Charfeddine S., Ibn-Hadjamor H., Torjmen S., Kraiem S., Hammami R., Bahloul A., Kallel N., Moussa N., Touil I., Jdidi J., Abdesselem S., Abid L. 2022. Sulodexide in the treatment of patients with long COVID 19 symptoms and endothelial dysfunction: The results of TUN-EndCOV study. *Archives of Cardiovascular Diseases. Supplements 14*(1), 127. https://doi.org/10.1016/j.acvdsp.2021.10.007

Chee Y.J., Fan B.E., Young B.E., Dalan R., Lye D.C. 2023. Clinical trials on the pharmacological treatment of long COVID: A systematic review. *Journal of medical virology 95*(1), e28289. https://doi.org/10.1002/jmv.28289

Chopra V., Flanders S. A., O'Malley M., Malani A. N., Prescott H. C. 2021. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Annals of internal medicine, 174*(4), 576-578. https://doi.org/10.7326/M20-5661

Crook H., Raza S., Nowell J., Young M., Edison P. 2021. Long covid-mechanisms, risk factors, and management. *BMJ (Clinical research ed.)* 374, n1648. https://doi.org/10.1136/bmj.n1648

Davis H.E., Assaf G.S., McCorkell L., Wei H., Low R.J., Re'em Y., Redfield S., Austin J.P., Akrami A. 2021. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 38, 101019. https://doi.org/10.1016/j.eclinm.2021.101019

Davis H.E., McCorkell L., Vogel J.M., Topol E.J. 2023. Long COVID: major findings, mechanisms and recommendations. *Nature reviews. Microbiology 21*(3), 133-146. https://doi.org/10.1038/s41579-022-00846-2

Fernández-de-las-Peñas C. 2022. Long COVID: current definition. *Infection 50*(1), 285-286. https://doi.org/10.1007/s15010-021-01696-5

Galarza-Vera G.A., Delgado-Zambrano J.C., Alvia-Párraga A.E., Andrade-Zambrano V.A., Franco-Ortega M.E. 2023. Síndrome post-covid-19: manifestaciones clínicas más frecuentes. *Ciencia Latina Revista Científica Multidisciplinar 7*(1), 859-887. https://doi.org/10.37811/cl_rcm.v7i1.4436

Ge S., Wang X., Hou Y., Lv Y., Wang C., He H. 2021. Repositioning of histamine H1 receptor antagonist: Doxepin inhibits viropexis of SARS-CoV-2 Spike pseudovirus by blocking ACE2. *European journal of pharmacology*, 896, 173897. https://doi.org/10.1016/j.ejphar.2021.173897

Geng L. N., Bonilla H. F., Shafer R. W., Miglis M. G., Yang P. C. 2022. Case report of breakthrough long COVID and the use of nirmatrelvir-ritonavir. Preprint at https://www.researchsquare.com/article/rs-1443341/v1

Gil R., Bitar P., Deza C., Dreyse J., Florenzano M., Ibarra C., Jorquera J., Melo J., Olivi H., Parada M. T., *et al.* 2021. CUADRO CLÍNICO DEL COVID-19. *Revista Médica Clínica Las Condes 32*(1), 20-29. https://doi.org/10.1016/j.rmclc.2020.11.004

González-Hermosillo J.A., Martínez-López J.P., Carrillo-Lampón S.A., Ruiz-Ojeda D., Herrera-Ramírez S., Amezcua-Guerra L. M., Martínez-Alvarado M. del R. 2021. Post-Acute COVID-19 Symptoms, a Potential Link with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A 6-Month Survey in a Mexican Cohort. *Brain Sciences 11*(6), 760. https://doi.org/10.3390/brainsci11060760

Greenhalgh T., Knight M., A'Court C., Buxton M., Husain L. 2020. Management of post-acute covid-19 in primary care. *BMJ m3026*. https://doi.org/10.1136/bmj.m3026

Gutiérrez-Bautista D., Wong-Chew R.M., Ángel-Ambrocio A.H., Bautista-Carbajal, P., García-León M.L., Vite-Velázquez X., Cortázar-Maldonado L.A., Díaz-Ramírez J.B., Valadez-González Y., Vásquez-Martínez L.M., et al. 2021. Efectos a largo plazo de la COVID-19: una revisión de la literatura. *Acta Médica Grupo Ángeles 19*(3), 421-428. https://doi.org/10.35366/101741

Heerdt P.M., Shelley B., Singh I. 2022. Impaired systemic oxygen extraction long after mild COVID-19: potential perioperative implications. *British journal of anaesthesia 128*(3), e246-e249. https://doi.org/10.1016/j.bja.2021.12.036

Huang C., Huang L., Wang Y., Li X., Ren L., Gu X., Kang L., Guo L., Liu M., Zhou X., et al. 2021. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet (London, England), 397*(10270), 220-232. https://doi.org/10.1016/S0140-6736(20)32656-8

Ishola A.A., Joshi T., Abdulai S.I., Tijjani H., Pundir H., Chandra S. 2022. Molecular basis for the repurposing of histamine H2-receptor antagonist to treat COVID-19. *Journal of biomolecular structure & dynamics 40*(13), 5785-5802. https://doi.org/10.1080/07391102.2021.1873191

Koc H.C., Xiao J., Liu W., Li Y., Chen, G. 2022. Long COVID and its Management. *International Journal of Biological Sciences 18*(12), 4768-4780. https://doi.org/10.7150/ijbs.75056

Lai C.C., Hsu C.K., Yen M.Y., Lee P.I., Ko W.C., Hsueh P.R. 2023. Long COVID: An inevitable sequela of SARS-CoV-2 infection. *Journal of Microbiology, Immunology and Infection 56*(1), 1-9. https://doi.org/10.1016/j.jmii.2022.10.003

Mansell V., Hall-Dykgraaf S., Kidd M., Goodyear-Smith F. 2022. Long COVID and older people. *The Lancet Healthy Longevity, 3*(12), e849-e854. https://doi.org/10.1016/S2666-7568(22)00245-8

McCarthy M.W. 2023. Paxlovid as a potential treatment for long COVID. *Expert opinion on pharmacotherapy 24*(17), 1839-1843. https://doi.org/10.1080/14656566.2023.2262387

Morello R., Martino L., Buonseno D. 2023. Diagnosis and management of post-COVID (Long COVID) in children: a moving target. *Curr Opin Pediatr. 35*(2).184-192. https://doi.org/10.1097/mop.0000000000001221

Instituto Nacional de Salud (NIH). 28 de septiembre de 2023. Long COVID. https://covid19.nih.gov/covid-19-topics/long-covid. (Recuperado: enero 2024)

NICE. 2021. COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19. NICE Guideline [NG188]. https://www.nice.org.uk/guidance/ng188 (Recuperado: enero 2024)

OMS (Organización Mundial de la Salud). 2024. Number of COVID-19 cases reported to WHO (cumulative total) https://data.who.int/dashboards/covid19/cases?n=c (Recuperado: enero 2024).

OMS (Organización Mundial de la Salud). 2021. Support for Rehabilitation Self-Management After COVID-19 Related Illness. https://www.who.int/publications/m/item/support-for-rehabilitation-self-management-after-covid-19-related-illness (Recuperado: enero 2024)

OPS (Organización Panamericana de la Salud). 2023. Brote de Enfermedad por el coronavirus (covid-19). https://www.paho.org/es/temas/coronavirus/brote-enfermedad-por-coronavirus-covid-19 (Recuperado: enero 2024).

Pitt B., Tate A.M., Gluck D., Rosenson R.S., Goonewardena S.N. 2022. Repurposing low-dose naltrexone for the prevention and treatment of immunothrombosis in COVID-19. *European heart journal. Cardiovascular pharmacotherapy 8*(4), 402-405. https://doi.org/10.1093/ehjcvp/pvac014

Premraj L., Kannapadi N.V., Briggs J., Seal S.M., Battaglini D., Fanning J., Suen J., Robba C., Fraser J., Cho S.M. 2022. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis. *Journal of the Neurological Sciences* 434, 120162. https://doi.org/10.1016/j.jns.2022.120162

Raman B., Bluemke D.A., Lüscher T., Neubauer S. 2022. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *European Heart Journal 43*(14), 1157-1172. https://doi.org/10.1093/eurheartj/ehac031

Raveendran A.V., Jayadevan R, Sashidharan S. 2021. Long COVID: An overview. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15*(3), 869-875. https://doi.org/10.1016/j.dsx.2021.04.007

Siddiquea B.N., Shetty A., Bhattacharya O., Afroz A., Billah B. 2021. Global epidemiology of COVID-19 knowledge, attitude and practice: a systematic review and meta-analysis. *BMJ Open 11*(9), e051447. https://doi.org/10.1136/bmjopen-2021-051447

Srikanth S., Boulos J.,Dover T., Boccuto L., Dean D. 2023. Identification and diagnosis of long COVID-19: A scoping review. *Prog Biophys Mol Biol. 35*(12), 1133-1139. https://doi.org/10.1016%2Fj.pbiomolbio.2023.04.008

Terán-Escobar C.M., Jurado-Melo V.C. 2023. Síndrome post-covid, manifestaciones clínicas, diagnóstico y tratamiento, una revisión bibliográfica desde enero 2020 hasta enero 2022. *Ciencia Latina Revista Científica Multidisciplinar 7*(2), 2381-2393. https://doi.org/10.37811/cl_rcm.v7i2.5494

Thomas R., Williams M., Aldous J., Yanagisawa Y., Kumar R., Forsyth R., Chater A. 2022. A randomised, double-blind, placebo-controlled trial evaluating concentrated phytochemical-rich nutritional capsule in addition to a probiotic capsule on clinical outcomes among individuals with COVID-19 — the UK Phyto-V study. COVID 2 433-449. https://doi.org/10.3390/covid2040031

Vázquez J.B., Menchén D.A., Lloréns M.M.M., Moreno J.S. 2022. Manifestaciones sistémicas y extrapulmonares en la COVID-19. *Medicine - Programa de Formación Médica Continuada Acreditado 13*(55), 3235-3245. https://doi.org/10.1016/j.med.2022.05.004

Venkatesan P. 2021. NICE guideline on long COVID. *The Lancet Respiratory Medicine 9*(2), 129. https://doi.org/10.1016/S2213-2600(21)00031-X

Yong S.J. 2021. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infectious diseases (London, England) 53*(10), 737-754. https://doi.org/10.1080/23744235.2021.1924397

Yong S.J., Halim A., Halim M., Ming L.C., Goh K.W., Alfaresi M., AlShehail B.M., Al-Fares M.A., Alissa M., Sulaiman T., *et al.* 2023. Experimental drugs in randomized controlled trials for long-COVID: what's in the pipeline? A systematic and critical review. *Expert opinion on investigational drugs 32*(7), 655-667. https://doi.org/10.1080/13543784.2023.2242773

Xie Y., Choi T., Al-Aly Z. 2022. Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19. *MedRxiv* 2022.11.03.22281783. https://doi.org/10.1101/2022.11.03.22281783

Zhang L., Xu Z., Mak J.W.Y., Chow K.M., Lui G., Li T.C.M., Wong C.K., Chan P.K.S., Ching J.Y.L., Fujiwara Y., Chan F.K.L., Ng S.C. 2022. Gut microbiota-derived synbiotic formula (SIM01) as a novel adjuvant therapy for COVID-19: An open-label pilot study. *Journal of gastroenterology and hepatology 37*(5), 823-831. https://doi.org/10.1111/jgh.15796

Chater, N. (2020). Facing up to the uncertainties of COVID-19. *Nature human behaviour, 4*(5), 439-439. DOI:https://doi.org/10.1038/s41562-020-0865-2

Hassan, A., & Jameel, A. (2023). The Power of Implicature in Addressing Covid19 as a Global Pandemic. *Al-Adab Journal*, (145), 29-42. DOI: https://doi.org/10.31973/aj.v2i145.4198

Sreelakshmi, P. R., Tandale, B. V., Jadhav, A. V., Vaidya, R. R., Walimbhe, A. M., & Jadhav, S. (2023). A scoping review of persistent symptoms after COVID infection at different follow-up periods. *Indian Journal of Public Health, 67*(2), 292-300. DOI: 10.4103/ijph.ijph_1178_22

Gaspar, P., Dias, M., Parreira, I., Gonçalves, H. D., Parlato, F., Maione, V.& Duarte, L. (2023). Predictors of long-COVID-19 and its impact on quality of life: longitudinal analysis at 3, 6 and 9 months after discharge from a Portuguese Centre. *Acta Médica Portuguesa, 36*(10), 647-660. https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047

Katz, G. M., Bach, K., Bobos, P., Cheung, A., Décary, S., Goulding, S., & Quinn, K. L. (2023, July). Understanding How Post–COVID-19 Condition Affects Adults and Health Care Systems. In JAMA Health Forum (Vol. 4, No. 7, pp. e231933-e231933). American Medical Association.

Goodridge, D., Lowe, T. N., Cai, S., Herriot, F. N., Silverberg, R. V., Heynen, M., & Oyedokun, T. (2023). "We're drowning and we're alone": a qualitative study of the lived experience of people experiencing persistent post-COVID-19 symptoms. *Canadian Medical Association Open Access Journal, 11*(3), E504-E515. DOI: https://doi.org/10.9778/cmajo.20220205

Draud, S., Prado, J., Hass, T., & Ramirez, J. (2023). Long COVID: The Silent Pandemic. *Norton Healthcare Medical Journal, 1*(1). https://doi.org/10.59541/001c.81031

Abrignani, M. G., Maloberti, A., Temporelli, P. L., Binaghi, G., Cesaro, A., Ciccirillo, F., & Colivicchi, F. (2022). Long COVID: nosographic aspects and clinical epidemiology. *Giornale Italiano di Cardiologia (2006), 23*(9), 651-662. DOI: https://doi.org/10.1714/3860.38447

Gang, J., Wang, H., Xue, X., & Zhang, S. (2022). Microbiota and COVID-19: Long-term and complex influencing factors. *Frontiers in Microbiology*, 13, 963488.

Craddock, V., Mahajan, A., Krishnamachary, B., Spikes, L., Chalise, P., & Dhillon, N. K. (2022). Persistent presence of spike protein and viral RNA in the circulation of individuals with post-acute sequelae of COVID-19. *MedRxiv*, 2022-08.

Turner, S., Khan, M. A., Putrino, D., Woodcock, A., Kell, D. B., & Pretorius, E. (2023). Long COVID: pathophysiological factors and abnormalities of coagulation. *Trends in Endocrinology & Metabolism, 34*(6), 321-344.

Hardy-Werbin, M., Maiques, J. M., Busto, M., Cirera, I., Aguirre, A., Garcia-Gisbert, N., ... & Gibert, J. (2023). MultiCOVID: a multi modal Deep Learning approach for COVID-19 diagnosis. *Scientific Reports, 13*(1), 18761.

Gogineni, H., So, W., Mata, K., & Greene, J. N. (2022). Multidisciplinary approach in diagnosis and treatment of COVID-19-associated mucormycosis: a description of current reports. *The Egyptian Journal of Internal Medicine, 34*(1), 58.

Jaros, R. K., Fadason, T., Cameron-Smith, D., Golovina, E., & O'Sullivan, J. M. (2023). Comorbidity genetic risk and pathways impact SARS-CoV-2 infection outcomes. *Scientific Reports, 13*(1), 9879.

Platz, T., Berlit, P., Dohle, C., Fickenscher, H., Guha, M., Köllner, V., ... & Schlitt, A. (2023). S2k-Guideline SARS-CoV-2, COVID-19 and (early) rehabilitation–a consensus-based guideline for Germany. GMS Hygiene and Infection Control, 18.

Gray, P. E., Bartlett, A. W., & Tangye, S. G. (2022). Severe COVID-19 represents an undiagnosed primary immunodeficiency in a high proportion of infected individuals. *Clinical & Translational Immunology, 11*(4), e1365.