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## REVIEW

# Long COVID-19 and primary care: Challenges, management and recommendations



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**Abstract** Long COVID-19, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is characterized by persistent symptoms after COVID-19 onset. This article explores the challenges, management strategies, and recommendations for addressing long COVID-19 in primary care settings. The epidemiology of long COVID-19 reveals significant variability, with a substantial portion of COVID-19 survivors experiencing post-acute symptoms. Pathophysiological mechanisms include viral persistence, endothelial dysfunction, autoimmunity, neurological dysregulation, and gastrointestinal dysbiosis. Multiple risk factors, including age, sex, pre-existing comorbidities, smoking, BMI, and acute COVID-19 severity, influence the development of long COVID-19. Effective management requires proactive measures such as vaccination, identification of high-risk populations, public awareness, and post-infection vaccination. Collaboration of primary care physicians with specialists is essential for holistic and individualized patient care. This article underscores the role of primary care physicians in diagnosing, managing, and mitigating the long-term effects of COVID-19.

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## PALABRAS CLAVE

COVID de larga  
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Gestión prolongada  
de la COVID;

## COVID-19 prolongado y atención primaria: desafíos, manejo y recomendaciones

**Resumen** La COVID-19 prolongada, también conocida como secuela postaguda de la infección por SARS-CoV-2, se caracteriza por síntomas persistentes después de la aparición de la COVID-19. Este artículo explora los desafíos, las estrategias de manejo y las recomendaciones para abordar la COVID-19 prolongada en entornos de atención primaria. La epidemiología de la COVID-19 prolongada revela una variabilidad significativa, y una parte sustancial de los

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## Diagnóstico de la COVID prolongada

supervivientes de la COVID-19 experimentan síntomas postagudos. Los mecanismos fisiopatológicos incluyen persistencia viral, disfunción endotelial, autoinmunidad, desregulación neurológica y disbiosis gastrointestinal. Múltiples factores de riesgo, como la edad, el sexo, las comorbilidades preexistentes, el tabaquismo, el IMC y la gravedad aguda de la COVID-19, influyen en el desarrollo de la COVID-19 prolongada. Una gestión eficaz requiere medidas proactivas, como la vacunación, la identificación de poblaciones de alto riesgo, la concienciación pública y la vacunación posterior a la infección. La colaboración de los médicos de atención primaria con los especialistas es esencial para una atención holística e individualizada al paciente. Este artículo subraya el papel de los médicos de atención primaria en el diagnóstico, el tratamiento y la mitigación de los efectos a largo plazo de la COVID-19.

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## Introduction

Post acute sequelae of SARS-CoV-2 infection (PASC), post COVID-19 syndrome, or long COVID-19 is defined by the National Institute for Health and Care Excellence (NICE) as the condition in which the patient suffers from prolonged and persistent symptoms following the acute phase of COVID-19 infection for more than 12 weeks. NICE divides long COVID-19 into two case definitions, which involves the ongoing symptomatic effects of COVID-19 onset from four to twelve weeks and post-COVID 19 syndrome for symptoms that persist for twelve weeks or so after onset.<sup>1</sup>

Long COVID-19 can affect people of all ages and can occur in individuals who had mild, moderate, or severe COVID-19 infections. Symptoms usually occur in the time span of four to twelve weeks post COVID-19 onset,<sup>2</sup> and the current guidance from NICE states the importance of not excluding people from healthcare needs if they give negative SARS-CoV-2 test, because patients experiencing symptoms of long COVID-19 can give false negative results.<sup>1</sup> Patients suffering from long COVID-19, or "long haulers", were not able to receive proper medical care due to lack of accuracy and feasibility of laboratory tests which consequently resulted in drastic conditions. The epidemiology is quite variable due to the variance in the study designs and the methods used, the CDC concluded in June 2022 that one out of five COVID-19 survivors had post acute sequelae of SARS-CoV-2 infection.<sup>3</sup>

In 2022, 70% of the UK population was reported to have been infected by COVID, out of which 41% people had symptoms that persisted for more than 4 months, while 19% reported persistence of symptoms for more than two years.<sup>4</sup> This suggests that a significant population suffers from symptoms that persist for a long time post COVID-19 infection. Furthermore, variability in epidemiology as well as the lack of medical care due to diagnostic inaccuracies can lead to adverse complications. These reasons make it important to discuss various aspects of long COVID-19.

In this review, we discuss the various post acute sequelae, as well as recommendations for proper diagnosis and management of long COVID-19 in primary care settings.

## Pathophysiology

The invasion of the type II alveolar cells occurs by the help of ACE-2 (angiotensin-converting enzyme-2) which helps in the binding of SARS-CoV2 to the nasal epithelium and internalization. ACE-2, when interacted with viruses, can cause many chemical changes leading to the downregulation of the anti-inflammatory effects.<sup>5</sup> A state of immunosuppression is developed in response to the exaggerated acute phase of post COVID-19 syndrome. The virus then stimulates a cytokine storm which attracts neutrophils CD4 and CD8 cells. These cells make an attempt to clear the viral response and consequently cause sequestration in the lungs. This results in acute respiratory distress syndrome (ARDS). Viral replication and viral substances released in the alveolar cells cause apoptosis of type I and II alveolar cells leading to diffuse alveolar damage. The inflammatory response as well as the viral replication lead to ARDS.<sup>6</sup>

## Viral persistence

The viral load is at low levels after the acute phase of COVID-19 has resolved. However, this viral persistence can then lead to further inflammatory processes. There is presence of ongoing inflammation due to increased levels of C-reactive protein and IL-6. Lymphopenia results due to the chronic immune activation and hyperinflammation.<sup>7</sup>

## Endothelial dysfunction

The presence of the virus triggers microthrombi which results in the formation of many clots causing endothelial dysfunction. This dysfunction can lead to further cardiovascular problems causing cardiomyocytes injury, alteration of heart contractility, activated NET (neutrophil extracellular traps), and microangiopathy. These changes are related to chemoattractants, tumor necrosis factor  $\alpha$ , proinflammatory cytokines and G-CSF. It can indirectly affect the autonomic nervous system and resultantly cause regulatory changes in the body. There is pulmonary vascular damage by

the microvascular disorders resulting in lung fibrotic remodeling causing dyspnea.<sup>7</sup>

### Autoimmunity

Autoimmunity can occur due to molecular mimicry following COVID-19 infection. Many individuals have reported autoimmune diseases after COVID-19, but the reasons remain unclear.<sup>8</sup>

### Neurological dysregulation

Neural dysregulation, mainly fatigue in post COVID-19 is a main effect. It affects the daily life of the patient but the reasons causing it remain unclear.<sup>9</sup>

### GI dysbiosis

There is persistence of the virus in the gut microbiota profile further leading to metabolic abnormalities. Elevated *Granulicatella* and *Rothia mucilaginosa* in the gut microbiome of COVID-19 hospitalized patients were reported along with many other microorganisms. The cytokine-induced aftermath of post COVID infection is well explained by the destroyed gut microbiome in stool samples of a hospitalized COVID-19 patient.<sup>10</sup>

### Risk factors of long COVID-19

Multiple risk factors have been identified, including age, sex, smoking, BMI, pre-existing comorbidities, history of depression, and the severity of acute COVID-19.<sup>11-14</sup>

#### Age

It is considered a major factor in the severity of long COVID-19 symptoms. Studies reported increasing age (age > 45 years) is a predictor of severe long COVID-19 and has been associated with prolonged recovery times and a higher likelihood of developing long-term complications.<sup>14,15</sup> However, the conclusion of a study<sup>13</sup> indicates that the impact of age on long COVID-19 is controversial, so the association of age with long COVID-19 needs further investigation.

#### Biological sex

According to most studies, female gender is considered one of the important determinants of long COVID-19.<sup>12,13,16-18</sup> The exact reason for this remains unknown, but it is understood that the difference in expression of ACE-2 and transmembrane protease serine 2 (TMPRSS2) receptors between males and females and various other immunological differences between the two genders are probably involved.<sup>17,18</sup>

#### Pre-existing comorbidities

People with a history of asthma, gastrointestinal issues, rheumatoid arthritis, seasonal allergic flu or other immunologic issues are found to have an increased risk for long

COVID-19. A hypothesis for this risk is that ACE-2 is broken down in these conditions, which is used by SARS-CoV-2 to gain entry into the host cells, and thus results in a rise in inflammatory cytokine and oxidative stress which leads to severe COVID-19 illness.<sup>13</sup>

### Smoking status

Smokers were found more likely to experience persistent symptoms such as fatigue, dyspnea, and musculoskeletal pain compared to non-smokers.<sup>12</sup> But a few researchers have questioned its role as a risk factor.<sup>12,16</sup> Thus, further research may be needed to identify its role as a risk factor for long COVID-19.

### BMI

Symptoms of long COVID-19 were more prevalent in patients with increased BMI and a sedentary lifestyle as compared to people with low BMI and those involved in regular physical activity.<sup>19</sup> A higher BMI may lead to chronic inflammation and metabolic dysregulation, which can exacerbate the persistence of symptoms post-infection.

### Severity of acute COVID-19

Hospitalization during acute COVID-19 is a major threat to symptoms of long COVID-19.<sup>20-22</sup> The correlation between symptoms and long COVID-19 severity is developed by Antonio S Menezes in his observational study.<sup>14</sup> He concluded that patients admitted to the Intensive Care Unit needing mechanical ventilation had more symptoms than those with mild form of the disease, treated at home or in a general ward. Similarly, moderate to severe COVID-19 had prolonged symptoms compared to milder cases. Furthermore, patients with 15 or more COVID-19 symptoms were found more likely to develop severe long COVID-19.

### Management

The CAMFiC long COVID-19 Study Group proposes an approach to management of patients with long COVID-19 in three visits.<sup>23</sup> The first primary care visit is suggested 4 weeks after a confirmed diagnosis, and should include various aspects including personal history, further diagnostic confirmation, physical examination, and laboratory and other relevant testing. They also suggest two more visits, which should be during weeks 8 and week 12 respectively, following the primary diagnosis.

The primary goal in the management of a patient with long COVID-19 is to first establish that the patient had a prior SARS-CoV-2 infection for which a healthy trustful doctor-patient relationship is required.<sup>24</sup> It is important to inquire about the ways in which a person's symptoms have influenced their daily life and activities. This should encompass their professional or educational commitments, their ability to move around, and their level of self-reliance. Demonstrating an open, compassionate, and understanding demeanor can lead to acknowledgment of how the illness has affected their routine.

After evaluation of history of the patient and diagnosis of prior infection, the next equally important goal is to eradicate the initial symptoms. General physicians in primary care should also consult specialists and edify the knowledge about long COVID-19 to the patient. A proper follow-up and monitoring should be required for further evaluation.<sup>24</sup>

A holistic assessment and symptom management is crucial for the improvement of the quality of life of the patient. Some of the main points a clinician should consider for the management of long COVID-19 are cognitive and physical rehabilitation, individualized care plans, screening, and mental health support for the patient.

The association of long COVID-19 with other diseases, as discussed earlier, is also essential for the management of the patient. Accurate diagnosis requires the proper follow-up of the patient in primary care. Comprehending the practical, well-being, and financial impacts of Patient-Centered Care holds significance in discerning the optimal approach for healthcare systems to provide effective care to individuals with PCC (post COVID-19 condition).<sup>25</sup> A worldwide agreement regarding the meaning of PCC is currently absent, given that the WHO interpretation concentrates solely on symptoms emerging post SARS-CoV-2 infection, while the definition from the US Centers for Disease Control and Prevention encompasses both symptoms and newly arising health conditions.<sup>25</sup> Home integrated care for patients is preferred over hospitalized care as it reduces the burden on healthcare.

## Recommendations in primary care settings

In order to curb the threats posed by long COVID-19, as well as reduce its burden on primary care, it is imperative to take proactive measures and manage patients appropriately. Identification of patients is also essential to understand the diverse symptomatology of long COVID. The steps that can be undertaken in line with these two propositions are outlined below.

### Pre-exposure proactive measures

#### 1. Vaccination

In comparison to placebo, most vaccines have been reported to reduce confirmed infection, in addition to reducing the number cases of confirmed symptomatic COVID-19.<sup>26</sup> If the number of symptomatic patients are reduced, it can be assumed that there will be a reduction in the number of patients with infection progressing to long COVID.

Thus, it is clear that the objective of vaccination is twofold: prevention of the infection itself, and reduction of the severity of symptoms.

#### 2. Identification of high risk population

Identification of risk factors can be helpful as individuals can be counseled before time. It is imperative for the high risk population to be aware of the symptomatology and follow up appropriately.

Pre-emptive measures can also be suggested in regards to modifiable risk factors. For example, cessation of smoking can be advised to reduce the risk of long COVID.<sup>12,16</sup>

#### 3. Public awareness

All patients, including those defined as the high risk population, presenting to primary care can be offered advice on diagnosis and management of long COVID-19. This would help reduce burden significantly, as screening would enable primary care physicians to refer patients to specialized care settings, if and when needed.

### Post-exposure measures

#### 1. Identifying miscues

The symptoms of long COVID have been reported to affect multiple systems<sup>27</sup> and have been described in earlier sections. The plethora of symptoms, in addition to a lack of a set diagnostic criteria and the variation in the terms used for the condition, as described in the search of a review,<sup>28</sup> can make it difficult for clinicians to identify and diagnose cases of long COVID.

In addition, diagnosis of non-hospitalised patients can be even more complicated in some cases. One such example is the case of neuropsychiatric symptoms, which have been reported in non-hospitalised patients with long COVID.<sup>29</sup> If a prior diagnosis is not present, patients and healthcare professionals may not be able to associate symptoms with long COVID.

It can easily be concluded that symptoms that are not classically associated with an acute infection, i.e. those other than respiratory symptoms, may not be associated with long COVID. The issue is exacerbated with the absence of a set diagnostic tool and criterion for long COVID.

#### 2. Use of AI for diagnosis

In addition to establishment of diagnostic criteria, the use of AI has been studied and suggested.<sup>30</sup> Use of AI can also help clinicians understand the effects and implications of long COVID on various body systems, and compare the intensity and duration of symptoms to those that are similar but are caused by pathologies unrelated to COVID.

#### 3. Follow up

In the rapid guideline published by NICE on management of the long-term effects of COVID 19, it has been advised that follow up should be tailored to each individual, as a wide array of symptoms have been identified.<sup>1</sup> The guideline also suggests that it is not necessary to limit tests or monitoring to a particular time frame.

## Conclusion

It is essential for primary care physicians to consider risk factors and screening of all patients that present to them. This is imperative due to the nature of the pandemic and the number of people that it affected. Furthermore, a healthy



doctor-patient relationship, as well as liaison with specialists is important for development of effective management strategies for complications associated with long COVID-19.

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## Conflicts of interest

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## References

- National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19; 2021. <https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742> [accessed 31.8.23].
- Koc HC, Xiao J, Liu W, Li Y, Chen G. Long COVID and its management. *Int J Biol Sci.* 2022;18:4768–80, <http://dx.doi.org/10.7150/ijbs.75056>.
- Centers for Disease Control and Prevention. Long COVID or post-COVID conditions; 2023. <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html> [accessed 31.8.23].
- Greenhalgh T, Sivan M, Delaney B, Evans R, Milne R. Long COVID – an update for primary care. *BMJ.* 2022;378:e072117, <http://dx.doi.org/10.1136/bmj-2022-072117>.
- Azer SA. COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics. *New Microbes New Infect.* 2020;37:100738, <http://dx.doi.org/10.1016/j.nmni.2020.100738>.
- Parasher A. COVID-19: current understanding of its pathophysiology, clinical presentation and treatment. *Postgrad Med J.* 2021;97:312–20, <http://dx.doi.org/10.1136/postgradmedj-2020-138577>.
- Mantovani A, Morrone MC, Patrono C, Santoro MG, Schiaffino S, Remuzzi G, et al. Long Covid: where we stand and challenges ahead. *Cell Death Differ.* 2022;29:1891–900, <http://dx.doi.org/10.1038/s41418-022-01052-6>.
- Sharma C, Bayry J. High risk of autoimmune diseases after COVID-19. *Nat Rev Rheumatol.* 2023;19:399–400, <http://dx.doi.org/10.1038/s41584-023-00964-y>.
- Baker AME, Maffitt NJ, Del Vecchio A, McKeating KM, Baker MR, Baker SN, et al. Neural dysregulation in post-COVID fatigue. *Brain Commun.* 2023;5:fcad122, <http://dx.doi.org/10.1093/braincomms/fcad122>.
- Giannos P, Prokopoulos K. Gut dysbiosis and long COVID-19: feeling gutted. *J Med Virol.* 2022;94:2917–8, <http://dx.doi.org/10.1002/jmv.27684>.
- Asadi-Pooya AA, Akbari A, Emami A, Lofti M, Rostami-hosseinkhani M, Nemati H, et al. Risk factors associated with long COVID syndrome: a retrospective study. *Iran J Med Sci.* 2021;46:428–36, <http://dx.doi.org/10.30476/ijms.2021.92080.2326>.
- Barthélémy H, Mougenot E, Duracinsky M, Salmon-Ceron D, Bonini J, Péretz F, et al. Smoking increases the risk of post-acute COVID-19 syndrome: results from a French community-based survey. *Tob Induc Dis.* 2022;20:59, <http://dx.doi.org/10.18332/tid/150295>.
- Notarte KI, de Oliveira MHS, Peligro PJ, Velasco JV, Macaranas I, Ver AT, et al. Age sex and previous comorbidities as risk factors not associated with SARS-CoV-2 infection for long COVID-19: a systematic review and meta-analysis. *J Clin Med.* 2022;11:7314, <http://dx.doi.org/10.3390/jcm11247314>.
- Menezes AS Jr, Botelho SM, Santos LR, Rezende AL. Acute COVID-19 syndrome predicts severe long COVID-19: an observational study. *Cureus.* 2022;14:e29826, <http://dx.doi.org/10.7759/cureus.29826>.
- Thompson EJ, Williams DM, Walker AJ, Mitchell RE, Niedzwiedz CL, Yang TC, et al. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. *Nat Commun.* 2022;13:3528, <http://dx.doi.org/10.1038/s41467-022-30836-0>.
- Wang C, Ramasamy A, Verduzco-Gutierrez M, Brode WM, Melamed E. Acute and post-acute sequelae of SARS-CoV-2 infection: a review of risk factors and social determinants. *Virol J.* 2023;20:124, <http://dx.doi.org/10.1186/s12985-023-02061-8>.
- Fernández-de-Las-Peñas C, Martín-Guerrero JD, Pellicer-Valero ÓJ, Navarro-Pardo E, Gómez-Mayordomo V, Cuadrado ML, et al. Female sex is a risk factor associated with long-term post-COVID related-symptoms but not with COVID-19 symptoms: the LONG-COVID-EXP-CM multicenter study. *J Clin Med.* 2022;11:413, <http://dx.doi.org/10.3390/jcm11020413>.
- Bai F, Tomasoni D, Falcinella C, Barbanotti D, Castoldi R, Mulè G, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. *Clin Microbiol Infect.* 2022;28, <http://dx.doi.org/10.1016/j.cmi.2021.11.002>, 611.e9–e16.
- Muzyka I, Yakhnytska M, Savytska M, Zayachkivska O. Long COVID prevalence and physiology-centered risks: population-based study in Ukraine. *Inflammopharmacology.* 2023;31:597–602, <http://dx.doi.org/10.1007/s10787-023-01177-1>.
- Carfi A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA.* 2020;324:603–5, <http://dx.doi.org/10.1001/jama.2020.12603>.
- Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study [published correction appears in *Lancet.* 2022 May 7;399(10337):1778]. *Lancet.* 2021;398:747–58, [http://dx.doi.org/10.1016/S0140-6736\(21\)01755-4](http://dx.doi.org/10.1016/S0140-6736(21)01755-4).
- Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax.* 2021;76:399–401, <http://dx.doi.org/10.1136/thoraxjnl-2020-216086>.
- Sisó-Almirall A, Brito-Zerón P, Conangla Ferrín L, Kostov B, Moragas Moreno A, Mestres J, et al. Long Covid-19: proposed primary care clinical guidelines for diagnosis and disease management. *Int J Environ Res Public Health.* 2021;18:4350, <http://dx.doi.org/10.3390/ijerph18084350>.
- Perumal R, Shunmugam L, Naidoo K. Long COVID: an approach to clinical assessment and management in primary care. *S Afr Fam Pract (2004).* 2023;65:e1–10, <http://dx.doi.org/10.4102/safp.v65i1.5751>.
- Katz GM, Bach K, Bobos P, Cheung A, Décary S, Goulding S, et al. Understanding how post-COVID-19 condition affects adults and health care systems. *JAMA Health Forum.* 2023;4:e231933, <http://dx.doi.org/10.1001/jamahealthforum.2023.1933>.
- Graña C, Ghosn L, Evrenoglou T, Jarde A, Minozzi S, Begman H, et al. Efficacy and safety of COVID-19 vaccines. *Cochrane Database Syst Rev.* 2022;12:CD015477, <http://dx.doi.org/10.1002/14651858.CD015477>.
- Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine.* 2021;38:101019, <http://dx.doi.org/10.1016/j.eclinm.2021.101019>.

28. Cabrera Martimbianco AL, Pacheco RL, Bagattini ÂM, Riera R. Frequency, signs and symptoms, and criteria adopted for long COVID-19: a systematic review. *Int J Clin Pract.* 2021;75:e14357, <http://dx.doi.org/10.1111/ijcp.14357>.
29. Titze-de-Almeida R, da Cunha TR, Dos Santos Silva LD, Ferreira CS, Silva CP, Ribeiro AP, et al. Persistent, new-onset symptoms and mental health complaints in Long COVID in a Brazilian cohort of non-hospitalized patients. *BMC Infect Dis.* 2022;22:133, <http://dx.doi.org/10.1186/s12879-022-07065-3>.
30. Cau R, Faa G, Nardi V, Balestrieri A, Puig J, Suri JS, et al. Long-COVID diagnosis: from diagnostic to advanced AI-driven models. *Eur J Radiol.* 2022;148:110164, <http://dx.doi.org/10.1016/j.ejrad.2022.110164>.