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Symptoms of the Long COVID and Related Primary Health Care Implications: Systematic Literature Review

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Abstract

Since the worldwide COVID-19 pandemic, various sources have indicated the long-term symptoms after recovery that is now known as Long COVID (LC). Knowing the damage acute CoV-2 has caused worldwide, it is predicted that LC will have a massive impact on Primary Health Care (PHC). It remains unknown how PHC should cope with such an upcoming burden. The aim is to review studies exploring the most common symptoms as predictors of LC and potential syndrome management challenges in the PHC context. The study undertook a systematic review using Cochrane methodology and PRISMA guidelines. It is known that LC can have numerous nonspecific manifestations; however the main widespread symptoms were chronic fatigue (up to 68.0%), shortness of breath (up to 59.5%), dry cough, chest, and musculoskeletal pain. Most patients reported neurological symptoms, including headache (up to 68.0%), anosmia, partial olfactory dysfunction, and vertigo. LCS usually manifests in psychiatric disorders, such as depression, anxiety, insomnia, and mood changes. Not many clinical trials determined possible risk factors, however, hospitalization in Intensive Care Unit (ICU), intubation, smoking, obesity, and comorbidities such as diabetes and hypertension are some of few confirmed. There is very limited data on LC management specifics regarding PHC context. Although LC remains to be defined, it is necessary to understand its impact and clinical manifestations promptly, so that Family Physicians (FP) would be able to manage the syndrome. There are no predictors which would let a FP predict LC course, severity and recovery. Hence, new strategies and management guidelines of LC need to be established and elaborated for PHC to function thoroughly.

Keywords: COVID-19 • Long COVID • Family medicine • Primary health care • Post COVID-19 condition

Abbreviations: CDC: The Centers for Disease Control and Prevention; EC: European Commission; FP: Family Physician; ICU: Intensive Care Unit; LS: Long COVID; NICE: National Institute for Health and Care Excellence; PHC: Primary health care; PPCS: Persistent Post-COVID Syndrome; WHO: World Health Organization

Introduction

Coronavirus infection, commonly known as CoV-2, is a contagious viral disease caused by infection with the severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2) strain [1]. Clinical manifestation of the disease starts to appear after the incubation period and can range from mild symptoms such as cough, fever, fatigue, and sore throat to severe pneumonia and respiratory failure requiring mechanical ventilation. The treatment of the infection is usually supportive, however effective antiviral treatment that would change the course of the disease is not established yet [2]. Since scientists detected first cases of COVID-19 in December 2019 in Wuhan, China, SARS-CoV-2 has caused worldwide pandemic that resulted in high hospitalization and mortality rates [3]. There are 513 million confirmed cases of CoV-2, including 6.2 million deaths. The World Health Organization (WHO) stated that patients feel the impact of acute CoV-2 infection days and even months after being considered COVID-free [1,4]. CoV-2 may cause various ailments, unrelated and unexplained symptoms, and LC is one of them. 1 out of 10 people still have the remaining symptoms representing LC [1]. However, recent studies have shown that LC may be with much higher incidence. Studies in 2020 showed that LC incidence ranged 10-35% among the patients with acute CoV-2 infection treated at home [5,6]. Among people hospitalized due to CoV-2, the incidence rate could be as high as 80% [5]. In reviewed literature, Huang C, et al. [7] study demonstrated that out of 1655 patients, 76% still had recurring symptoms. Carfi A, et al. [8] showed LC rate being 86.7% and Hermosillo JA, et al. [9] stated that after four weeks, 88.6% of patients experienced symptoms of LC. Townsend L [10] demonstrated that after 12 weeks of follow-up, only 42.2% of the study group felt completely healthy and with no COVID-19 related symptoms.

The early stages of CoV-2 enhanced health care system problems – faulty economic resources distribution, lack of human resources, and inability to cope with patient overload in all health care chains [4]. However, LC can become a new challenge in PHC due to its variability. Knowing the damage acute CoV-2 has caused worldwide, it is predicted that LC will have a massive impact on patient care, and the first responder and help provider to the patient will be a FP. It remains unknown how PHC should cope with such an upcoming burden.

The aim is to review studies exploring the most common symptoms as predictors of LC and potential syndrome management challenges in the PHC context.

Methods

The study undertook a systematic review using Cochrane methodology and PRISMA guidelines.

Search strategy and selection criteria

The literature review was conducted for publications in English indexed in MEDLINE, ScienceDirect, and ClinicalKey databases. Grey literature was searched but restricted to official the United States Centre for Disease Control (CDC) and World Health Organization (WHO) guidelines and presented data. Search terms included terms related to post-COVID condition, known as LC. Search terms were used: "post COVID-19 condition", "Long COVID-19",

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"syndrome", "symptoms", "long haulers". Subsequently, a search was conducted using "Long COVID" combined with "primary health care" and "general practice" to establish any recommendations and trials in PHC context, if possible. Based on lack of literature, all the available studies were included, not only based in PHC to achieve the objectives of this systematic review. Eligibility criteria are presented in Table 1. Reference lists in review articles were identified during this search and the final included articles were checked to identify additional potentially eligible studies. No restrictions were on the study publication date.

Study selection and data extraction

All titles and abstracts were initially screened manually by a single author, then two authors independently screened selected samples. If eligibility criteria were met – the full article was presented for the data extraction. When available, categories of data were extracted from each case study: population of the study and their characteristics (age, sex), symptoms the patients experienced for at least four weeks after considered "COVID-free" and their incidence, potential risk factors, follow up period.

Risk of bias

The study quality was assessed independently by three reviewers. The risk of bias was assessed with the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) tool (Figure 1). One of the review authors undertook quality appraisal, and if any disagreement occurred, it was resolved through discussion.

Results

Our research strategy identified 5976 results. After further inspection, excluding duplicates (n=212), off-topic studies which did not meet inclusion criteria, and our research objectives (n=5680), only 49 were included for evaluation (Figure 2). After thorough full article reading and quality assessment, 15 publications fully met our literature review criteria and were included in the study (Table 2). The study population varies from 100 to 1265 patients, the largest one coming from the Huang C, et al. [7]. The total population sample of our study is 4420 patients. In the studies, the symptoms were considered LC if it occurred 4 weeks after the acute CoV-2 phase (confirmed with RT-PGR or IgG/IgM antibody testing). If possible, risk factors were evaluated [11,12].

LC is a syndrome characterized by the persistence of clinical symptoms beyond four weeks from the onset of acute symptoms [3,13]. The United States CDC has formulated "post COVID-19 condition" to describe health issues and to present their variability - Long COVID (which consists of a wide range of symptoms that can last weeks to months) or Persistent Post-COVID Syndrome (PPCS) [14]. It is unclear how long these symptoms may last. LC can be short-term- experienced for days or weeks, or long-term – persisting for months. Some studies divide post-acute symptoms at 1-month after acute COVID-19 (short term), persisting and new clinical manifestations between 2 and 5 months after infection (intermediate-term), and clinical manifestations that were present at least six months after COVID-19 (long term) [15]. LC would be defined as long term chronic disease if it would last for more than a year, according to CDC [16].

It seems that recent publications show that LC is ubiquitous among patients after acute SARS-CoV-2 infection. LC could emerge as a new hidden pandemic as many patients will seek professional help. The first responders – FP, will be put under pressure to diagnose and treat the LC patients.

Long COVID clinical manifestations

Individuals who have recovered from mild and moderate COVID-19 are also experiencing post COVID-19 symptoms, sometimes with disabling features and inability to return to their everyday life [6].

According to the publications, the most common symptom is chronic fatigue (34.8-68%) which lingers for up to 12-24 weeks after acute CoV-2 infection [6-15]. It can be experienced as exhaustion episodes, cognitive dysfunction, and depression [16]. Another common LC symptom is dyspnea, which occurs in 9.5 to 59.5% of the patients [6-8,11-13,15,17]. Dry cough occurs in 6.6-35.1% of the cases. Worthy of mentioning that respiratory symptoms, such as dyspnea and chest pain, are more familiar to hospitalized patients diagnosed with moderate and severe acute infection [18]. Some patients diagnosed with LC noted muscle and joint pain (9-55%) [6,7,9-11,13-15,19-21].

Most LC patients experience some neurologic symptoms. According to the authors, the most common are anosmia or partial olfactory dysfunction (5-59%), the headache was reported in 68% of patients [6,9,11,12,14,21]. Some even experience vertigos (up to 47%) (Table 3) [21]. These symptoms are usually negligible and related to indirect pathogenetic mechanisms, such as systemic inflammatory response and post-infectious immune response [22].

When a person experiences LC for months, it may manifest in psychiatric disorders-depression, anxiety disorder, mood changes, insomnia. Sleeping disorders were recurrent in LC patients who had comorbidities [10]. These psychologic after-effects were observed for more than 6 months after the SARS-CoV-2 infection [13,17,19]. Potentially, it could be caused by the virus itself, isolation that the infection causes, and stigma surrounding the infected [19]. These patients may demonstrate suicidal thoughts, so FP should take a thorough neurological and psychological exam to prevent potential harm [23]. LC symptoms incidence is presented in Figure 3. Most of the reviewed studies did not obtain a male to female ratio, so conclusions on symptom manifestation differences due to sex cannot be made. Further studies should investigate gender implications on LC as there are data that CoV-2 itself differs in males and females [24].

The syndrome can have numerous manifestations, as seen before - mostly nonspecific. FP is challenged to differentiate whether the problems patients experience are related to the recent acute infection, presence of other diseases, or even reinfection of CoV-2. The National Institute for Health and Care Excellence (NICE) guidelines advice that assessment and management should be tailored to the individual's problems, after excluding any coexisting illness that may be giving rise to the symptoms reported. This would include chest radiography in those with respiratory symptoms, checking for a postural drop in blood pressure in those with dizziness. Red flag symptoms should be excluded by FP as they could indicate the need for emergency care for serious complications of COVID-19. Red flag symptoms include severe, new-onset, or worsening breathlessness or hypoxia, syncope, unexplained chest pain, palpitations or arrhythmias, new delirium, or focal neurological signs or symptoms [1]. If any suspicions of LC occur, FP should consider identifying antibodies against CoV-2 [25-32].

The authors claim that LC incidence is higher in patients with comorbidities such as diabetes mellitus, hypertension, and ischemic coronary disease

Table 1. Eligibility criteria of the study.

Parameters	Inclusion Criteria	Exclusion Criteria
Population	COVID-19 survivors experiencing lasting symptoms	Patients with acute COVID-19 infection, pregnant women. Non- human subjects.
Time	Symptoms lasting more than 4 weeks	>2 weeks after diagnosing COVID-19 (acute phase).
Age	18-65 years	Children under 18 and elderly over 65 years.
Study types	Any study design: would expect to be observational/cohort studies rather than RCT's. Cross-sectional, cohort studies and case-control studies. Randomized controlled trials if the data presented is appropriate	Opinion based reviews, literature reviews, abstracts, one case reports. Studies focusing on special populations (ICU, severe infection) and rehabilitation programmes.
Language	English	Non-English

	Baseline Confounding	Selection of the participants	Intervention measurement	Missing data	Measurement of outcomes	Selective outcome reporting
O. Moreno-Pérez et al. (2021)	⊕	⊕	N/I	⊕	⊕	⊕
C. Huang, L. Huang et al. (2021)	⊕	⊕	⊕	○	⊕	⊕
A. Kashif et al. (2021)	⊕	⊕	○	⊕	⊕	○
D. Menges, T. Ballouz et al. (2021)	⊕	⊕	⊕	○	⊕	⊕
D. L Sykes et al. (2021)	○	○	N/I	⊕	⊕	⊕
T.A. Gaber, A. Ashish, A. Unsworth (2021)	⊕	⊗	N/I	○	N/I	⊗
M. L. Bell et al. (2021)	⊕	⊕	⊕	⊕	⊕	⊕
B. Osikomaiya et al. (2021)	N/I	○	N/I	⊕	⊕	○
Q. Xiong et al. (2021)	N/I	⊕	⊕	⊕	⊕	⊕
A. Carfi et al. (2020)	⊕	⊕	N/I	N/I	○	⊗
L. Townsted et al. (2021)	⊕	⊕	⊕	⊕	⊕	○
C. Carvalho-Schneider et al. (2021)	⊕	⊕	N/I	⊕	⊕	⊕
J. A. Gonzalez-Hermosillo et al. (2021)	N/I	○	⊕	⊕	⊕	⊕
E. L. Graham et al. (2021)	N/I	○	⊕	⊕	⊕	⊕
A. Dennis et al. (2021)	⊕	⊕	N/I	⊕	⊕	○

⊕ - Low risk of bias ○ - Moderate risk of bias
⊗ - High risk of bias N/I – no information

Figure 1. Risk of bias assessment (Adapted from Risk of Bias Assessment tool for Non-randomized Studies (RoBAN) [4].

[19,33]. Moreno-Perez O, et al. [18] state that LC risk is higher among patients hospitalized in ICU, especially those who were intubated and received pulmonary ventilation. Links between lymphopenia, higher ferritin, D-dimer levels, and LC were also observed. Huang C, et al. [7] and Menges D, et al. [26] determined that severity of acute infection, female gender, and smoking are also significant risk factors [17,19]. González-Hermosillo JA [9] linked LCS to obesity [8]. Prolonged symptoms were primarily observed in this 40-60 years age group [6]. According to literature, most of the patients experiencing LC were 50 years old on average and the incidence of LC was much higher when compared to, for example, the patient group under 18 years, where LC rate was observed <1% [34].

Since many authors agree that LC has a cyclical and not progressive course, the patient potentially will come for many appointments, and it could put PHC into an overload if no actions are taken [24,29,35]. There are no predictors which would let a FP predict LC course, severity, and how long it will take the patient to get to total health.

Discussion

More than 513 million CoV-2 infection cases have been diagnosed worldwide up to this day, and the numbers are still growing. According to the available literature, LC incidence may be up to 80%, so it can be assumed that there could be more than 410 million people suffering from LC. However, no clinical trials or statistical data was collected and presented globally about LC prevalence so far.

As established before, LC symptoms are very unspecific and rely primarily on anamnesis. Symptoms such as fatigue, dyspnea, chest, head, and body aches, sleep difficulties, and cognitive disorders may signal many diseases. As this is becoming a challenge for FB, new guidelines and recommendations emerge daily. Some studies suggest approaching diagnosis by ruling out processes unrelated to CoV-2 infection. It may include identifying each and individual system's pre-existing pathologies. If required, follow ups with complimentary testing for other etiologies, may be scheduled, so a FP could identify whether it is persisting post COVID-19 manifestations or not [36]. Delphi study (2021) suggests that the general approach in someone with suspected LC, symptoms of possible non-COVID-19-related issues should be investigated and referred as per local guidelines. Most specialists agreed that carry out a face-to-face assessment including a thorough anamnesis, examination, and tests such as full blood count, C-reactive protein, renal, liver, and thyroid function markers, glycated hemoglobin, vitamins D and B12, folate, ferritin, magnesium, and bone studies should be included [37].

It is important to notice that the symptoms may be debilitating to some individuals and impact their daily life and workability heavily. The prolonged symptoms can make a person unable to work full-time and take sick leaves. Average sick leave length, when diagnosed with LC, remains undetermined. However, in 2021, Sweden's National cohort (n = 11966) presented that more than 13% of the LC patients were forced to take sick leaves, which had a significant economic impact [38]. Some studies show that 84.1% of the patients experienced activity limitation and restrictions in daily life and their workability was heavily impacted [39]. In addition, a recent study, spanning 56 countries, has demonstrated that 45.0% of people who had been sick for over 28 days with cases of COVID-19 reported a reduced work schedule due to ongoing symptoms, and 22.0% not working more than six months after falling sick [40]. Withal, the exact duration of LC is unknown, and people could be disabled from working for extended periods and this could cause major economic implications worldwide. In some countries, PHC specialists are also responsible for issuing sick leave notices both short and long term, which creates an additional administrative and time-consuming challenge for the PHC sector.

Studies show that chronic illnesses such as LC are associated with unemployment and a higher prevalence of psychological disorders, due to

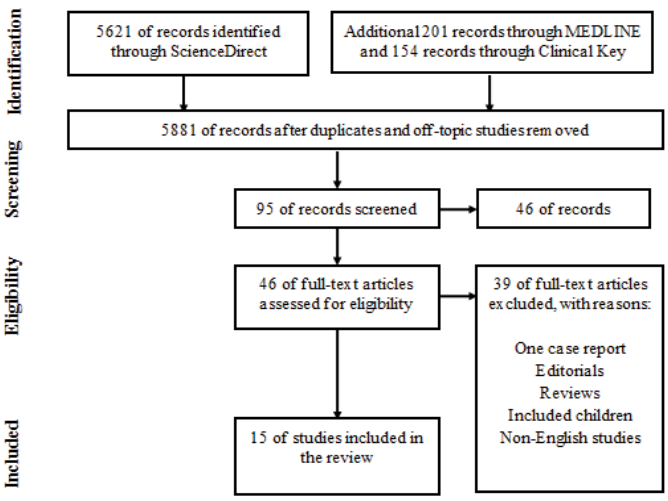

Figure 2. Flow chart of search results (adapted from PRISMA 2009 flow diagram) [5].

Table 2. Overview of the selected studies.

No.	Author (s) and Year	Title of Paper	Methodology	Main Findings/Outcome	Limitations	Country of Origin
1.	O. Moreno-Pérez et al. (2021)	Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study.	A prospective cohort study	A PCS was detected in a half of COVID-19 survivors. Radiological and spirometric changes were mild (less than 25% of patients). No baseline clinical features behaved as independent predictors of PCS.	Undetected pre-COVID abnormalities, the exclusion of some patients with severe comorbidity, the absence of imaging, the lack of study of the diffusion capacity of the lung for carbon monoxide, the relatively small sample size to detect minor associations.	Spain
2.	C. Huang, L. Huang, et al. (2021)	6-month consequences of COVID-19 in patients discharged from hospital: a cohort study	An ambidirectional cohort study	At 6 months after symptom onset, fatigue, muscle weakness, sleep difficulties were the main symptoms of patients who had recovered from COVID-19. Risk of anxiety or depression and impaired pulmonary diffusion capacities were higher in patients with more severe illness.	The baseline data of pulmonary function and 6-min walking distance was unavailable. The data were not stratified further to determine if the symptoms were persistent following COVID-19, worsened after recovery, or occurred post-discharge. Patients with mild COVID-19 symptoms in Fangcang shelter hospitals were not enrolled.	China
3.	A. Kashif et al. (2021)	Follow-up of COVID-19 recovered patients with mild disease	A prospective cohort study	The most common sequelae was fatigue, in mild-COVID-19 recovered patients 3 months after being discharged.	A single-center study with a small sample size and the findings weren't compared with a control group.	Pakistan
4.	D. Menges, T. Ballouz et al. (2021)	Burden of post-COVID-19 syndrome and implications for healthcare service planning: A population-based cohort study	Population-based prospective cohort study	A considerable proportion of SARS-CoV-2 infected individuals experience longer-term consequences and have a relevant demand for healthcare services.	Self-selection bias may have occurred if individuals who are more concerned with their health or experiencing PCS were more likely to participate. Authors did not have a baseline assessment of participants' physical and mental health and did not evaluate the use of specialized medical or diagnostic services in their assessment.	Switzerland
5.	D. L Sykes, L. Holdsworth et al. (2021)	Post-COVID-19 Symptom Burden: What is Long-COVID and How Should We Manage It?	A prospective cohort study	Authors demonstrate an absence of association between symptom burden and radiographic or biochemical abnormality and suggest that the phenomenon of Long-COVID may not be directly attributable to the SARS-CoV-2, but rather the neuropsychiatric insults.	The inability to record any physiological data at follow-up due to the virtual nature of the assessment. Inability to record the severity of each individual symptom.	United Kingdom
6.	T.A. Gaber, A. Ashish, A. Unsworth (2021)	Persistent post-COVID symptoms in healthcare workers	Observational study	About a third of participants were complaining with the symptoms of LCS. The majority of this group was reluctant to neither seek medical advice nor take sick leave.	Authors used subjective descriptions of severity and that made further analysis and categorization difficult. A relatively small number of respondents can naturally increase the risk of selection bias.	United Kingdom
7.	M. L. Bell et al. (2021)	Post-acute sequelae of COVID-19 in a non-hospitalized cohort: Results from the Arizona CoVHORT	A prospective cohort study	The prevalence of post-COVID-19 symptoms amongst individuals who experienced mild-to-moderate COVID-19 were lower than for studies with hospitalized participants.	Low response rate (56%). Characterization of the phenotype is currently limited to 25 symptoms. Data were self-reported. Authors may have been underpowered to detect differences.	United States
8.	B. Osikomaiya et al. (2021)	'Long COVID': persistent COVID-19 symptoms in survivors managed in Lagos State, Nigeria	A retrospective cohort study	Most survivors with persistent symptoms had more than two self-reported symptoms.	The study depended on self-reported persistent COVID-19 symptoms, the sample population was relatively small and some self-reported symptoms might be associated with standard therapeutic agents administered to the patients during isolation.	Nigeria
9.	Q. Xiong et al. (2021)	Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study	A prospective cohort study	The most common early clinical sequelae include physical decline/fatigue postactivity polypnoea, alopecia, some of these sequelae might be related to gender, age and clinical characteristics during hospitalization.	The study may have obtained less accurate information because of the nature of telephone follow-up compared to face-to-face communication. Only a small number of patients were included in the study, and most of them had severe cases.	China
10.	A. Carfi et al. (2020)	Persistent Symptoms in Patients After Acute COVID-19	A prospective cohort study	In patients who had recovered from COVID-19, 87.4% reported persistence of at least one symptom, particularly fatigue and dyspnea.	The lack of information on symptom history before acute COVID-19 illness and the lack of details on symptom severity. Single-center study with a relatively small number of patients and without a control group.	Italy
11.	L. Townsted et al. (2021)	Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection	An observational follow up study	More than half of participants reported persistent fatigue. The association between fatigue and laboratory markers of inflammation or COVID-19 severity was not found.	Study is cross-sectional in nature and only assessed participants at a single timepoint.	Ireland

12.	C. Carvalho-Schneider et al. (2021)	Follow-up of adults with noncritical COVID-19 two months after symptom onset	An observational study	Up to 2 months after symptom onset, two thirds of adults with noncritical COVID-19 had symptoms, mainly anosmia/ageusia, dyspnoea or asthenia.	The evaluation at D30 and D60 was declarative over a phone call, without available physical, biological or imaging assessment. Patients' baseline characteristics were retrospectively collected, data for potentially contributive factors were missing.	France
13.	J. A. Gonzalez-Hermosillo et al. (2021)	Post-Acute COVID-19 Symptoms, a Potential Link with Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: A 6-Month Survey in a Mexican Cohort	A prospective cohort study	91.5% reported at least one symptom. The most common symptoms were fatigue, new-onset dyspnea, sleeping and neurocognitive disturbances, orthostatic intolerance, anxiety, depression, and muscle and joint pain.	The study had relatively small sample size at a tertiary single care center, with telephonic interviews using a binary questionnaire. This investigation was an uncontrolled study. The findings are also limited by the lack of imaging studies. A lack of a reproducible psychological assessment.	Mexico
14.	E. L. Graham et al. (2021)	Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized COVID-19 "long haulers"	A cohort study	Non-hospitalized COVID-19 "long haulers" experienced brain fog and fatigue that affects cognition and quality of life.	Not all participants had the same set of laboratory, imaging, and neurophysiologic testing. Approximately half of the patients were seen through televisits.	United States
15.	A. Dennis et. al (2021)	Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study	Observational study	Individuals at low risk of COVID-19 mortality with ongoing symptoms, 70% have impairment in one or more organs 4 months after initial COVID-19 symptoms, with implications for healthcare and public health	Cardiac MRI protocol excluded gadolinium contrast. For organ impairment, association, not causation was shown. Study population was not ethnically diverse, despite disproportionate COVID-19 impact in non-white individuals. Pulse oximetry, spirometry, MRI assessment of the brain and muscle function were not included from the outset.	United Kingdom

Table 3. Incidence rate of Long COVID symptoms in selected studies.

No.	Source	N	Demographics			LCS Clinical Manifestation and Incidence, % (n)
			Age	Gender		
				Males, % (n)	Females, % (n)	
1.	O. Moreno-Pérez et al., 2021	277 (LCS=141)	Median age 47.3 (42.0-67.5)	52.7 (146/277)	47.3 (131/277)	Fatigue 34.8 (96/277) Dyspnoea 34.4 (95/277) Anosmia/dysgeusia 21.4 (59/277) Cough 21.3 (59/277) Myalgias-arthralgias 19.6 (54/277) Headache 17.8 (49/277)
2.	C. Huang, L. Huang et al., 2021	1733 (LCS=1265)	Median age 57.0 (47.0-65.0)	52 (897/1733)	48 (836/1733)	Fatigue or muscle weakness 63 (1038/1655) Sleep difficulties 26 (437/1655) Hair loss 22 (359/1655) Anosmia 11 (176/1655) Palpitations 9 (154/1655) Joint pain 9 (154/1655) Decreased appetite 8 (138/1655)
3.	A. Kashif et al., 2021	242	N/A	69.4 (168/242)	30.6 (74/242)	Fatigue 41.7 (101/242) Myalgias 35.1 (85/242) Decreased appetite 24 (58/242) Sleep disturbances 21.1 (51/242) Headache 19 (46/242) Low mood 18.2 (44/242) Dizziness 14.5 (35/242) Palpitations 12.4 (30/242) Nausea/vomiting 12 (29/242) Chest pain 10.7 (26/242) Cough 6.6 (16/242)
4.	D. Menges et al., 2021	431	Median age 47 (33-58)	50.3 (217/431)	49.7 (214/431)	Fatigue 55 (233/431) Anxiety 32 (135/431) Depression 26 (111/431) Dyspnoea 25 (96/431) Stress 16 (68/431)
5.	D. L Sykes, L. Holdsworth et al., 2021	134	Mean of age 59.6 ± 14.0 years	65.7 (88/134)	34.3 (46/134)	Breathlessness 59.7 (80/134) Myalgias 51.5 (69/134) Anxiety 47.8 (64/134) Extreme fatigue 39.6 (53/134) Low mood 39.6 (53/134) Memory impairment 37.3 (50/134) Sleep disturbance 35.1 (47/134) Cough 35.1 (47/134) Attention deficit 25.4 (34/134) Pleuritic chest pain 17.9 (24/134) Sore throat 127 (17/134)

6.	T.A. Gaber, A. Ashish, A. Unsworth, 2021	138	N/A	8 (11/138)	92 (127/138)	Sleep disturbance and mood disorders 44 (49/138) Mild-to-moderate shortness of breath 40 (45/138) Moderate-to-severe fatigue 39 (44/138)
7.	M. L. Bell et al., 2021	303 (Follow-up >30 days=208)	Mean of age 43.6 ± 16.6 years	30 (91/303)	70 (212/303)	Fatigue 37.5 (78/208) Shortness of breath 37.5 (78/208) Confusion or brain fog 30.8 (64/208) Stress and/or anxiety 30.8 (64/208) Changes in smell or taste 26.4 (55/208) Body aches or muscle pain 26 (54/208) Insomnia 22.1 (46/208) Headache 20.7 (43/208) Joint pain 20.2 (42/208) Congestion or runny nose 19.2 (40/208)
8.	B. Osikomaiya et al., 2021	274	Mean of age 41.8 ± 11.8 years	66.1 (181/274)	33.9 (93/274)	Fatigability 12.8 (35/274) Headache 12.8 (35/274) Chest pain 9.8 (27/274) Insomnia 9.8 (27/274) Dyspnoea 9.5 (26/274) Cough 9.2 (25/274) Myalgia 8.8 (24/274) Loss of appetite 8.8 (24/274) Palpitations 7.4 (20/274)
9.	Q. Xiong et al., 2021	538	Median age 52.0 (41.0-62.0)	45.5 (245/538)	54.5 (293/538)	Alopecia 28.6 (154/538) Fatigue 28.3 (152/538) Sweating 23.6 (127/538) Post activity polypnea 21.4 (115/538) Somnipathy 17.7 (95/538) Chest distress 14.1 (76/538) Chest pain 12.3 (66/538) Resting heart rate increase 11.2 (60/538)
10.	A. Carfi et al., 2020	143	Mean of age 56.5 ± 14.6 years	62.9 (90/143)	37.1 (53/143)	Fatigue 53.1 Dyspnoea 43.4 Joint pain 27.3 Chest pain 21.7
11.	L. Townsted et al., 2021	128	Mean of age 49.5 ± 15 years	46.1 (59/128)	53.9 (69/128)	Persistent fatigue 52.3 (67/128)
12.	C. Carvalho-Schneider et al., 2021	150	Mean of age 49.0 ± 15 years	44 (66/150)	56 (84/150)	Myalgia, headache and/or asthenia 87 (129/150) Anosmia/ageusia 59 (89/150) Fever 51 (76/150)
13.	J. A. Gonzalez-Hermosillo et al., 2021	130	Mean of age 51.0 ± 14 years	65.4 (85/130)	34.6 (45/130)	Fatigue 53 (69/130) Dyspnoea on effort 50.8 (66/130) Tingling 46.9 (61/130) Short-term memory loss 45.4 (59/130) Sleep disturbance 45.4 (59/130) Muscle pain 40.8 (53/130) Anxiety 39.2 (51/130) Inability to focus vision 38.5 (50/130) Joint pain 38.5 (50/130)
14.	E. L. Graham et al., 2021	100	Mean of age 43.2 ± 11.3 years	30 (30/100)	70 (70/100)	Brain fog 81 (81/100) Headache 68 (68/100) Tingling/numbness 60 (60/100) Dysgeusia 59 (59/100) Anosmia 55 (55/100) Myalgias 55 (55/100) Dizziness 47 (47/100) Pain 43 (43/100) Blurred vision 30 (30/100) Tinnitus 29 (29/100)
15.	A. Dennis et al., 2021	201	Mean of age 44.0 ± 11 years	29.4 (59/201)	70.6 (142/201)	Fatigue 98 (196/201) Shortness of breath 88 (176/201) Muscle ache 86.5 (173/201) Headache 82.5 (165/201) Joint pain 78 (156/201) Chest pain 76 (152/201) Cough 73 (146/201) Fever 72 (144/201) Sore throat 71.5 (143/201) Diarrhoea 59 (118/201) Abnormal pain 54 (108/201) Wheezing 49 (98/201) Inability to walk 40 (80/201)

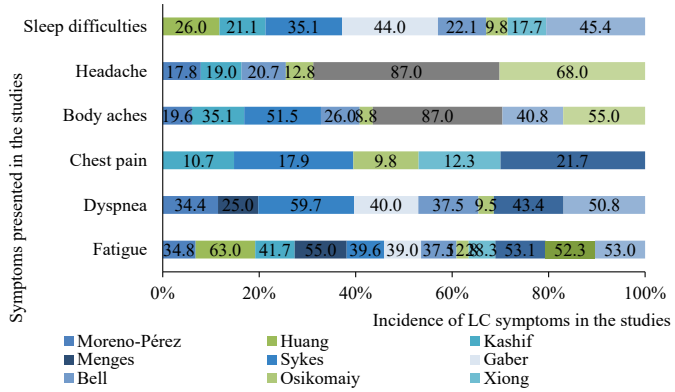

Figure 3. Long COVID symptoms in the selected studies.

workability issues [41]. As the LC population consists primarily of middle-aged people, unemployment may increase, as studies show that as workers get older, the duration of their unemployment lengthens, and the chances of finding a job decline [42]. Rehabilitation and ensuring persons' workability should be a national priority. Furthermore, to help patients with mild to moderate symptoms of LC stay functionally engaged is appropriate workplace accommodations and an adjustment to a job or work environment that makes it possible for a person with a health-related disability to make a timely and safe return to work and to perform their job duties effectively. A FP should advise such accommodations and rehabilitation programs to the patient [43].

New strategies are being developed by the European Commission (EC) to treat LC. It is essential to lecture PHC specialists and provide them with up-to-date information and guidelines about LC as this upcoming burden will become more and more frequent in the primary care chain. To this day, there are no unified guidelines worldwide on how to cope with LC in the PHC chain, only sporadic suggestions. According to some articles, EC will invest 5 million euros at clinical trial safety assessments, another 5 million to map treatments being developed and what supply chains they would need and provide 40 million euros to support the manufacture of remedies for LC. However, this remains uncertain. More and more countries took the matter into their own hands and established post COVID-19 care centers with specialists that help patients with LC. The United States has 44 centers, UK and Italy also have rehabilitation centers, and with certain decisions and guidelines, the centers could potentially help relieve the healthcare system and suffering patients [44,45]. It is crucial to give this upcoming hidden pandemic the attention and prioritize it as the extent of the disease and the damage it could bring devastating results in challenges for many FP as the burden of diagnosing and treating LC patients is entrusted to them.

Few studies explore LC challenges in PHC. Now the only resource of information is NICE guidelines and WHO recommendations, as not many literature reviews or guidelines explore LC in primary care context. A recently published study by Siso-Almirell, et al. suggested local clinical practice guidelines to identify patients with symptoms of LC in primary care through a protocolized diagnostic process and establish an accurate differential diagnosis [36]. In August 2020 first attempts to develop management strategies of LC in PHC occurred even though there was limited evidence, and it was suggested that there was no need to refer or investigate LC cases if the patient is otherwise well [6]. As more significant data about LC emerges, broad, multi-center studies should be initiated to develop diagnostic strategies and management guidelines specifically for FP to follow in the future.

Conclusion

The most common LC symptoms in the selected studies were chronic fatigue, dyspnea, chest pain, muscle and head pain, and neurological and psychological manifestations. Only a few clinical trials determined specific symptoms as possible risk factors for LC development, however, hospitalization in ICU, intubation, smoking, obesity and comorbidities are some of the few confirmed. Currently, there is a substantial lack of universal guidelines or diagnostic protocols that would allow a FP to differentiate LC symptoms from other pathologies. No factors which would help to predict the course and severity of the syndrome, and how long it will take for the patient to recover were defined so far. Further studies investigating LS predictors and PHC management strategies are necessary to correspond to a growing need to provide quality PHC for patients worldwide.

Limitations and Recommendations for Future Studies

There are few systematic literature reviews covering LC sequelae, however, to the authors' knowledge, this is one of the first systematic literature reviews discussing LC in the PHC and its possible impact on patients' workability, and the challenges that the syndrome brings for a FP to diagnose and treat a patient. It provides broad, up-to-date information from the researched literature and even though the topic of Long COVID symptoms has been covered, not many studies discuss the symptoms in on primary healthcare basis and what impact it may have to FP. Most of the studies had a low/moderate risk of bias. The studies identified were all from various countries and are therefore representative of many international contexts. However, more global studies are needed. Many of the included studies used qualitative methods, such as questionnaires, to explore participants' symptoms. Only studies in English were included, however there may be studies in other languages.

A key research priority understands the impact of LC. PHC specialists must become acquainted with LC manifestations and groups at risk to contain them. Evaluations and data should explicitly work towards unified global guidelines as many countries have solitary tries to overcome LC. Further research needs to explore relations between LC and gender, race, comorbidities. Data should be multi-centered. Further predictions can be made based on an unprecedented amount of data collection of this unique pandemic as it would assist unified guidelines and worldwide policies development of LC.

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Conflict of Interest

The authors declare no conflict of interest.

Appendix

Supplementary materials.

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