Research Article

Long COVID Syndrome: A Systematic Review of Persistent Symptoms Post-Pandemic

Cristina Ruas[1], Ana Luiza Gonzaga Ferreira Figueiredo[1], Amanda Pacheco de Alencar[1], Samuel de Souza Melo[1], Natália Virtude Carobin[1], Melina Aparecida Cordeiro[1], Adriano de Paula Sabino[1]

1. Federal Institute of Minas Gerais, Belo Horizonte, Brazil

The manifestation of persistent symptoms following COVID-19 infection, also known as Long COVID, is recognized by the World Health Organization. However, uncertainties remain regarding the symptoms, definitions of this condition, and its manifestation in the population. Therefore, this systematic review aims to provide an overview of the centrally published reviews describing persistent symptoms and critically analyze existing studies to identify gaps and propose new research perspectives. Initially, relevant studies were researched, followed by selection based on the titles and abstracts of articles obtained from the PubMed electronic database up to May 2023. Subsequently, the selected studies underwent a thorough analysis and interpretation of results, and pre-defined inclusion and exclusion criteria were considered. The inclusion criteria considered only English articles that conducted systematic reviews and meta-analyses of primary studies on persistent symptoms following SARS-CoV-2 infection. To maintain the generalizability of the results, studies that restricted the age of participants or considered samples with specific clinical conditions (comorbidities) were excluded. A total of 10 articles published between 2021 and 2022 were identified, encompassing a sample ranging from 4,664 to 257,348 adult patients, predominantly from the northern hemisphere. The studies focus on identifying the prevalence of symptoms following acute infection in individuals who tested positive for COVID-19, regardless of hospitalization status. Only one article offered a comparative perspective between positive and negative groups. The post-acute phase range varied from short periods (14 days) to long-term (over one year). The prevalence of symptoms varied over time. The most prevalent symptoms of Long COVID, regardless of the post-acute phase time range, were fatigue and dyspnea. A knowledge gap was identified in this research field, necessitating further investigation and the search for solid evidence to understand the persistent symptoms associated with COVID-19.

Cristina Mariano Ruas[1], **Ana Luiza Gonzaga Ferreira Figueiredo**[2], **Amanda Pacheco de Alencar**[2], **Samuel de Souza Melo**[3], **Natália Virtude Carobin**[4], and **Melina Aparecida Cordeiro**[4], **Adriano de Paula Sabino**[4]

[1]*Department of Social Pharmacy, School of Pharmacy, Federal University of Minas Gerais, Belo Horizonte, Brazil.*

[2]*Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil.*

[3]*Faculty of Pharmacy, Federal University of Minas Gerais, Belo Horizonte, Brazil.*

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[4]*Department of Clinical and Toxicological Analysis, School of Pharmacy, Federal University of Minas Gerais, Belo Horizonte, Brazil.*

[a] ORCID iD: 0000-0003-0275-8416

[b] ORCID iD: 0009-0002-7856-7106

[c] ORCID iD: 0009-0004-7301-8233

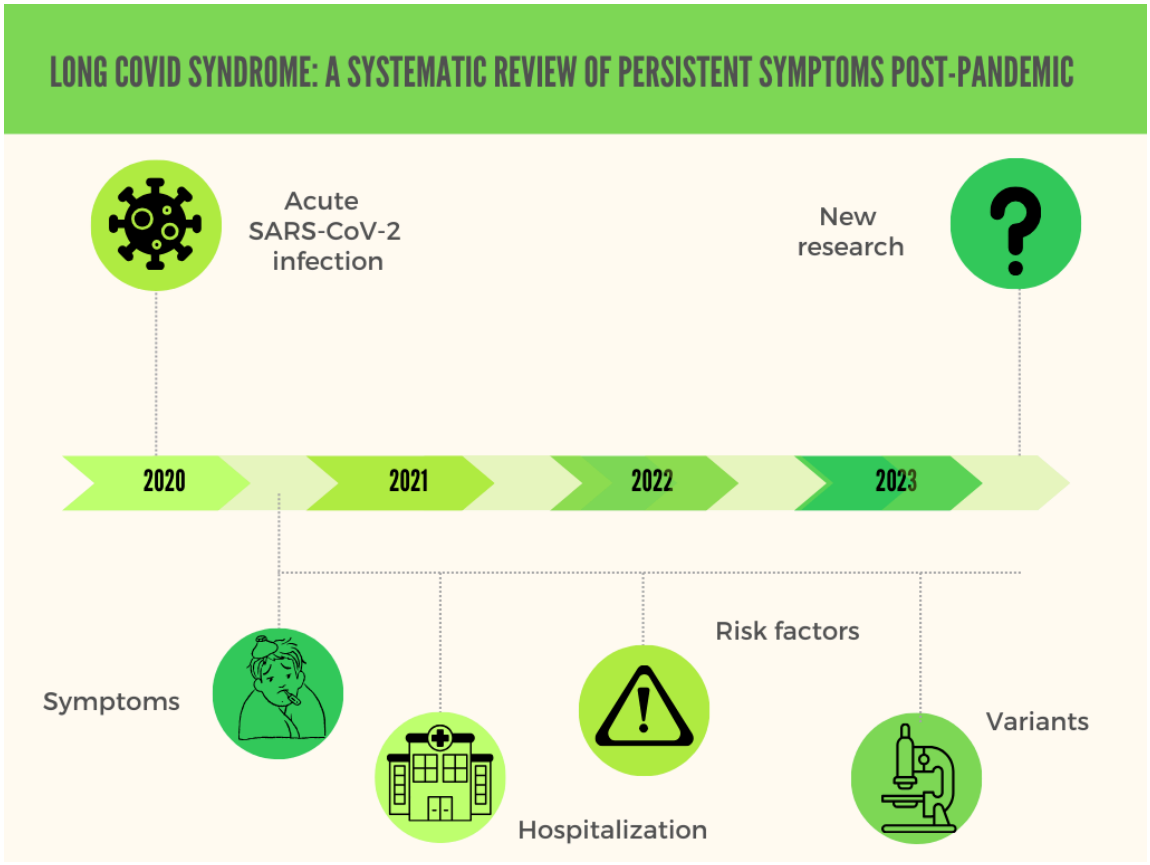
[d] ORCID iD: 0009-0003-9268-9350

[e] ORCID iD: 0000-0002-3830-2640

[f] ORCID iD: 0009-0006-0581-7126

[g] ORCID iD: 0000-0001-8562-8689

*Correspondence: crisruasufmg@gmail.com



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Introduction

The World Health Organization (WHO) defines Long COVID as the perpetuation and manifestation of symptoms three months after the initial SARS-CoV-2 infection, without a specific cause [1]. The symptoms include fatigue, dyspnea, decreased concentration, sleep disturbances, myalgia, depression, anxiety, and loss of smell and taste [2]. Due to no specificity of them, it is not clear the causal relationships.

Fatigue is the primary complaint in up to 20% of cases seeking primary care in Germany. Its prevalence increases with age and affects women [3]. Musculoskeletal pain affects mid 13.5% and 47.0% and has risk factors associated with age, sex, lifestyle habits, emotional state, and sleep disturbances [4]. According to the American Thoracic Society, dyspnea constitutes 50% of hospitalizations in the tertiary health system and 25% of ambulatory cases [5]. Anxiety and depression are present in 25% of cases in general clinical practice, often presenting as comorbid symptoms [6]. In 2017, the Global Burden of Disease reported 792 million people with mental disorders, representing a ratio of one in ten people globally (10.7%) [7].

After experiencing crises, as occurred during the COVID-19 pandemic, an increase in these symptoms is common. However, a study conducted in the Netherlands among individuals with and without depression, anxiety, and obsessive-compulsive disorder showed a significant increase in mental disorder symptoms in the general population during the SARS-CoV-2 pandemic [8].

Considering the occurrence of these symptoms in the general population and their potential association with COVID, this study aims to provide insights into the relationship between the clinical manifestations presented and SARS-CoV-2 viral infection. Understanding the magnitude of the problem is essential for healthcare services, which must address both daily demands and those related to Long COVID.

Methods

This text provides a comprehensive overview of systematic reviews on enduring manifestations after the acute COVID infection. The authors followed the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [9].

The PubMed electronic database was used, prioritizing articles in English until March 2024. The keywords and terms used in combination were: Long COVID Syndrome, Long COVID, post-COVID condition, long-term sequel COVID-19, systematic review, and outcomes.

To select the article, two researchers sequentially screened titles, abstracts, and complete articles, with a third evaluator of expertise intervening to ensure and oversee the caliber of the articles. The references and hyperlinks were methodically arranged within a document, and the researchers executed manual processes to eliminate duplicates and exclude articles that did not align with the predetermined inclusion criteria. It included reviews describing long COVID symptoms in the general population, and systematic reviews, while excluding articles that

focused on specific symptoms or groups (age range or healthcare professionals), primary studies, and only time post-COVID less than 6 months. The selected references were grouped according to study type and central theme for synthesis.

A total of 521 articles were identified in the database. Duplicates or more repetitions (n=73), inaccessible articles (n=1), observational studies with a time post-COVID of less than 6 months (n=43), analyzes limited to specific groups (such as comorbidities or specific age ranges) (n=29), studies that did not provide data on Long COVID manifestations or were unrelated to this research focus (n=319) and studies that were not reviewed (n=56) were excluded. In total, 13 articles were selected for this overview.

Results

Included Studies

The results of the thirteen studies were reported (Table 1). Two studies consisted of a scoping review, two presented the manifestations of Long COVID in different variants, and eight described prevalence results, comparing before and after. The studies were conducted in Europe, North America, and Asia. The unique Latin country that participated in this review was Mexico. One study used studies from South Africa. The most prevalent symptoms are described in Tables 2, 3, and 4.

Study/year	Time after Covid	Location	Methods	Severity	Included items	n	Age
Akbarialiabad et al (2021)[10]	< 2 w >186 d	Europe, North America and Central Asia	Scoping Review	Hospitalized and non-hospitalized	Total of 120 67 original studies: 22 cohort and 28 cross-sectional studies	> 3.000	Not specified
Sreelakshmi et al (2023)[11]	3-12 m	European, American, Western Pacific, South-East Asia, Eastern Mediterranean and African regions.	Scoping Review	All categories of severity, and hospitalized pacients.	Cohort/longitudinal/follow up studies	303.375	Average age between 37 and 65 years
Du et al (2022)[12]	6 -12 w > 12 m	Spain, Italy e China.	Systematic review and meta-analysis	Covid positive for different viral variants.	51meta-analysis	33.573	Not specified
Fernández-de-las-Peñas et al (2022)[13]	1-6 m	Japan, Italy, United States, United Kingdom, India and Spain	Systematic review	Different viral variants. Hospitalized and non-hospitalized	6 articles and 1 preprint	100.832	Mean age of 50.1 years
Ma et al (2022)[14]	≥ 6 m	Multicentric, highlights China and Europe	Systematic review	Critical, severe, moderate and mild	40 Cohort study	10.945	Not specified
Alkodaymi et al (2022)[15]	<6 m 6 -9 m 9 -12 m ≥12 m	North America, Asia and Europe	Meta-analysis	Severe acute infection	57 Cohort study and 6 cross section	257.348	Not specified
Lopez-Leon et al (2021)[16]	14 -110 d	United States, United Kingdom,	Systematic review and	acute infection	15 cross-sectional, cohort and case-control studies	47.910	between 17 and

Study/year	Time after Covid	Location	Methods	Severity	Included items	n	Age
		Europe, Australia, China, Egypt and Mexico	meta-analysis				87 years old
Qing Han et al (2022)[17]	12 m	China, Italy, Spain and Germany	Meta-analysis	Acute infection	18 cohort, cross-sectional and case series reports	8.591	Between 42 and 71 years old
Sanchez-Ramirez et al (2021)[18]	3-6 m	Canada, Italy, China, France, Switzerland, United States, Norway, Austria, Netherlands, Iran and United Kingdom	Systematic review and meta-analysis	After onset of symptoms in acute infection or after hospital discharge	24 articles from cohort and cross-sectional studies	5.323	Mean age of 55.2 years (± 8.1)
Nasserie et al (2021)[19]	>2 m	United Kingdom, Italy, France, China, Spain, United States, Netherlands and Germany, Belgium, Norway, Canada, Austria, England, Turkey and Ireland	Systematic review	SARS-CoV-2 infection	45 cohort studies	9.751	Average age between 50 and 60 years
Rochmawati et al (2022)[20]	< 12 m	Europe, Asia, North America and South Africa.	Systematic review	Hospitalized and non-hospitalized patients	16 observational studys	8.756	Not specified

Study/year	Time after Covid	Location	Methods	Severity	Included items	n	Age
Rahmati et al (2023)[21]	> 2 y	USA, Australia, UK, Spain, Bulgaria, India, Malaysia, Taiwan, China and France	Systematic review and meta-analysis	SARS-CoV-2 infection	Cohort studies	1.289.044	Median age ranged from 40 to 61 years
Abdel-Gawad et al (2022)[22]	14-90 d	Italy, Bangladesh, Israel, United States, United Kingdom, Netherlands, Belgium and Egypt	Systematic review	SARS-CoV-2 infection	12 Cross-sectional, case-controlobservational, retrospective analysis, cohort and questionnaire studies	4.664	Between 2.9 to 93 years old

Table 1. Descriptive characteristics of the included studies about Long covid manifestations (n=13)

d: day; w: week; m: month; y: year

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Selected Reviews	Prevalent symptoms
Akbarialiabad et al (2021)[10]	The most prevalent symptoms were fatigue, loss of smell and taste, myalgia, dyspnea, cough, sleep disturbance, anxiety, and depression.
Du et al (2022)[12]	• Wild type strain: Computed Tomography abnormalities (60.5%; 95% CI: 40.4%, 80.6%) in 11 studies. • Alpha variant: Combination of symptoms fatigue, cough, and dyspnea were 65.8% (95% CI: 47.7%, 83.9%) for three studies, 66.1% (95% CI: 42.2%, 89.9%) for three studies, 34.2% (95% CI: 8.3%, 60.1%) for two studies, and 23.7% (95% CI: 2.0%, 45.5%) for two studies. • Delta variant: Difficulty sleeping (2.5%; 95% CI: 0.2%, 4.9%) in two studies. • Omicron variant: Difficulty sleeping (3082/16211; 18.7%; 95% CI: 1.0%, 36.5%) and fatigue (3457/15848; 18.1%; 95% CI: 0.4%, 35.8%).
Fernández-de-las-Peñas et al (2022)[13]	Fatigue was the most prevalent symptom regardless of the SARS-CoV-2 variant. Dyspnea, memory loss, cough, and sleep disturbance became less frequent with each new viral variant.

Table 2. Primary manifestations of long COVID in studies involving variants and scoping reviews (n=3)

Selected Reviews	Prevalent symptoms
S. Lopez-Leon et al (2021)[16]	14 to 110 days after infection 1. Fatigue (58.0%, 95.0% CI, 42.0–73.0%) 2. Headache (44.0%, 95.0% CI, 13.0–78.0%) 3. Attention disorder (27.0%, 95.0% CI, 19.0–36.0%) 4. Hair loss (25.0%, 95.0% CI, 17.0–34.0%) 5. Shortness of breath (24.0%, 95.0% CI, 14.0–36.0%) 6. Loss of taste (23.0%, 95.0% CI, 14.0–33.0%) 7. Post-exertional polypnea (21.0%, 95.0% CI, 18.0–25.0%) 8. Loss of smell (21.0%, 95.0% CI, 12.0–32.0%) 9. Persistent cough (19.0%, 95.0% CI, 7.0–34.0%) 10. Joint pain (19.0%, 95.0% CI, 7.0–34.0%) 11. Night sweats (17.0%, 95.0% CI, 6.0–30.0%) 12. Memory loss (16.0%, 95.0% CI, 0–55.0%) 13. Ear ringing or hearing loss (15.0%, 95.0% CI, 10.0–20.0%)
Qing Han et al (2022)[17]	Starting from 1 year after the acute phase of COVID: 1. Fatigue and weakness (28.0%, 95.0% CI, 18.0-39.0%) 2. Arthromyalgia (26.0%, 95.0% CI, 8.0–44.0) 3. Depression (23.0%, 95.0% CI, 12.0–34.0) 4. Anxiety (22.0%, 95.0% CI, 15.0–29.0) 5. Memory loss (19.0%, 95.0% CI, 7.0–31.0) 6. Dyspnea (18.0%, 95.0% CI, 13.0–24.0) 7. Difficulty concentrating (18.0%, 95.0% CI, 2.0–35.0) 8. Insomnia (12.0%, 95.0% CI, 7.0–17.0)

Selected Reviews	Prevalent symptoms
Sanchez-Ramirez et al (2021)[18]	> 3 months post-acute phase: 1. Abnormalities in lung tomography (59.0%, 95.0% CI, 44.0-73.0) 2. Abnormal lung function test (39.0%, 95.0% CI, 24.0-55.0) 3. Fatigue (38.0%, 95.0% CI, 27.0-49.0) 4. Dyspnea (32.0%, 95.0% CI, 24.0-40.0) 5. Chest pain (16.0%, 95.0% CI, 12.0-21.0) 6. Cough (13.0%, 95.0% CI, 9.0-17.0) 7. Expectoration (12.0%, 95.0% CI, 3.0-21.0) 8. Throat inflammation (4.0%, 95.0% CI, 2.0-7.0)
Nasserie et al (2021)[19]	> 60 days after diagnosis or > 30 days after hospital discharge post-acute phase of Covid 1. Fatigue or exhaustion (40%, IQR, 31.0–57.0) 2. Shortness of breath (36%, IQR, 27.6–50.0) 3. Memory loss (28.3%, IQR, 18.6–35.8) 4. Loss of smell in the acute phase (23.6%, IQR, 12.4–40.7) 5. Anxiety (22.1%, IQR, 10.0–29.6) 6. Cognitive deficit (17.6%, IQR, 15.0–21.6) 7. Cough (16.9%, IQR, 14.4–25.1) 8. Loss or alteration of taste (15.6%, IQR, 10.1–23.9) 9. Depression (14.9%, IQR, 11.0–18.0) 10. Atypical chest pain (13.1%, IQR, 10.8–18.0) 11. Fever (1.0%, IQR, 0%–3.0%)
Rochmawati et al (2022)[21]	Time record up to 1 year after the acute phase of infection. 1. Fatigue and dyspnea (42.0%, 95.0% CI, 27.0-58.0) 2. Sleep disturbance (28.0%, 95.0% CI, 14.0–45.0) 3. Anxiety and depression (27.0%, 95.0% CI, 8.0-53) 4. Cough (25.0%, 95.0% CI, 10.0–44.0) 5. Loss of smell and taste (24.0%, 95.0% CI, 7.0–47.0) 6. Fever (21.0%, 95.0% CI, 4.0–47.0) 7. Myalgia (17.0%, 95.0% CI, 2.0–41.0) 8. Chest pain (11.0%, 95.0% CI, 5.0–20.0) 9. Headache (9.0%, 95.0% CI, 2.0–20.0)
Abdel-Gawad et al (2022)[22]	14 days to 90 days after acute infection phase: The most prevalent symptoms were fatigue, dyspnea, neurological disorder, and chronic pain.

Selected Reviews	Prevalent symptoms
	Specific post-COVID manifestations: Kawasaki-like cardiac affection, acute myocardial infarction, retinal vascular affection, thromboembolism, and hemorrhagic manifestations.

Table 3. Prevalent symptoms found in long COVID review studies without time specification

Selected Reviews	<6 months	6 to 12 months	> 12 months
Sreelakshmi et al (2023)[11]	**Up to 3 months** 1. Fatigue 29.0% (20.0-37.0%) 2. Shortness of breath 23.0% (16.0-30.0%) 3. Hair fall 22.0% (11.0-34.0%) 4. Cognitive impairment 18.0% (14.0-22.0%) 5. Headache 9.0% (4.0-15.0%) **4-6 months** 1. Fatigue 32.0% (16.0-48.0%) 2. Shortness of breath 28.0% (19.0-36.0%) 3. Hair fall 13.0% (5.0-22.0%) 4. Cognitive impairment 12.0% (9.0-15.0%) 5. Headache 8.0% (6.0-11.0%)	**7-9 months** 1. Fatigue 39.0% (9.0-69.0%) 2. Shortness of breath 20.0% (14.0-25.0%) 3. Hair fall 3.0% (1.0-4.0%) 4. Cognitive impairment 34.0% (15.0-82.0%) 5. Headache 32.0% (7.0-71.0%) **11-12 months** 1. Fatigue 27.0% (19.0-35.0%) 2. Shortness of breath 18.0% (10.0-27.0%) 3. Hair fall 16.0% (9.0-23.0%) 4. Cognitive impairment 20.0% (9.0-32.0%) 5. Headache 7.0% (4.0-9.0%)	
Ma et al (2022)[14]	-	1.Muscle aches or weakness (54.21%,95%CI,45.16–63.27%) 2. Fatigue (30.94%, 95%CI, 20.21–41.66%) 3. Shortness of breath (27.06%,95%CI,18.67–35.44%) 4. Anxiety (25.19%, 95%CI, 13.88–36.49%) 5. Difficulty sleeping (24.11%,95%CI,14.67–33.56%)	1. Myalgia or joint pain (34.52%,95%CI, 9.01–60.02%) 2. Fatigue (34.22%, 95% CI, 23.75–44.70%) 3. Respiratory symptoms (32.7%, 95% CI, 3.97–61.43%) 4. Runny nose (30.93%, 95% CI, 11.60–50.26%) 5. Anxiety (29.78%, 95% CI, 16.29–43.27%) 6. Difficulty concentrating (29.47%, 95%CI, 19.80–39.14%)

Selected Reviews	<6 months	6 to 12 months	> 12 months
		6.Difficulty concentrating (22.47%,95%CI,4.49–40.44%) 7. Limited mobility (21.81%,95%CI,4.17–47.78%) 8. Chest tightness (21.18%, 95% CI, 4.94–37.43%) 9. Depression (20.16%, 95% CI, 10.36–29.97%).	7. Difficulty sleeping (26.31%,95%CI,15.73–36.89%).
Alkodaymi et al (2022)[15]	1. Fatigue (32%,95% CI, 22%–44%) 2. Shortness of breath (25%,95%CI,17%–34%) 3. Sleep disturbance (24%,95%CI,8%–44%) 4. -Difficulty concentrating (22%, 95% CI, 15%–31%)	1. Exercise intolerance (45%,95%CI,25%–67) 2. Fatigue (36%, 95% CI, 27%–46%) 3. Sleep disturbance (29%,95%CI,15%–45%) 4. Shortness of breath (25%,95%CI,20%–30%) **9 to 12 months** 1. Fatigue (37%,95% CI, 16%–62%) 2. Shortness of breath (21%,95%CI,14%–28%)	1. Fatigue (41%, 95% CI: 30%–53%, number of studies = 4, sample size = 1246)
Rahmati et al (2023)[21]	-	•	**2 years** 1. Fatigue 27.4% (17.0–40.9.0%) 1. Sleep difficulties 25.1% (22.4–27.9%) 1. DLCO < 80 of predicted 24.6% (10.8–46.9%)

Selected Reviews	<6 months	6 to 12 months	> 12 months
			1. RV < 80 of predicted 13.0% (0.4–8.5%) 1. Hair loss 10.2% (7.3–14.2%) 1. Dyspnea 10.1% (4.3–21.9%) 1. Anxiety 9% (5.1–15.4%) 1. Difficulty focusing 8.1% (5.3–12.2%) 1. Headache 6.9% (2.7–16.4%) 1. TLC < 80 of predicted 6.8% (0.8–4.1%) 1. Depression 6.6% (5.5–8.0%) 1. Myalgia 5.8% (2.5–13.1%) 1. FEV1 < 80 of predicted 5.5% (3.4–8.8%) 1. Chest pain 5.1% (2.1–11.7%) 1. Memory loss 5.1% (0.4–44.3%)

Selected Reviews	<6 months	6 to 12 months	> 12 months
			1. Smell loss 4.5% (1.6–12.1%) 1. Cough 4.4% (1.4–13%) 1. FVC/FEV1 < 80 of predicted 4.2% (1.4–11.8%) 1. FVC < 80 of predicted 3.8% (2.3–6.4%) 1. Expectoration 3.7% (0.4–28.5%) 1. Taste lost 3.5% (1.2–9.8%) 1. Dizziness 3% (0.4–18.6%) 1. Palpitation 2.5% (0.5–12.3%) 1. Rashes 2.5% (1.9–3.4%) 1. Sore throat 2.1% (0.9–4.7%) 1. Nausea 1.2% (0.4–3.4%) 1. Diarrhea 0.8% (0.5–1.4%) 1. Vomiting 0.8% (0.1–7.7%)

Selected Reviews	<6 months	6 to 12 months	> 12 months
Caspersen et al., 2022[25]	1. Olfactory and taste alterations 89.9% (72.7-111.1%) 2. Myocarditis 42.3% (4.5-396%*****) 3. Decreased lung function 22.5% (15.5-32.5%) 4. Dyspnea 13.9% (11.3-17.1%) 5. Chest pain 7.5% (5.2-10.7%)	**11 and 12 months** 1. Alterations in smell and taste 51.4% (36.0-73.5%) 2. Decreased lung function 24.9% (14.6-42.7%) 3. Dyspnea 8.7% (5.7-13.3%) 4. Chest pain 6.7% (3.6-12.7%) 5. Memory loss 5.3% (3.8-7.3%)	-

Table 4. Main symptoms found in long COVID review studies, stratified by period

Abbreviations: CI, confidence interval; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

Principal Insights

One scoping review included 120 studies, which had varied follow-up times for hospitalized and non-hospitalized patients after the acute phase of COVID-19, including short (<2 weeks) and long (>186 days) time intervals. Among the selected research, there was a predominance of reporting at least one symptom after the acute phase of COVID, whether in the short or long term. Furthermore, there were reports of continuous symptoms after the acute phase of SARS-CoV-2 infection, which were similar across the selected studies, with emphasis on fatigue, loss of smell and taste, myalgia, dyspnea, cough, sleep disorders, anxiety, and depression [10].

The scoping study by Sreelakshmi et al. (2023) examined 48 studies that identified persistent Covid-19 symptoms persisting for a period of 3 to 12 months after the acute phase of the disease. The most commonly reported symptoms included fatigue, shortness of breath, headache, hair loss and impaired cognitive function. Fatigue emerged as the most prevalent symptom of long-standing Covid, with an increasing prevalence over time, rising from 29% after 3 months to 39% after 6 months, and remaining high even after 12 months of follow-up. In addition, longer-term studies have identified neurological problems, psychological issues such as depression and dermatological problems as predominant symptoms. Late manifestations such as alopecia, memory impairment,

disorientation, and sleep disturbances appeared during the chronic phase of Covid-19, highlighting the complexity and variety of persistent symptoms associated with the disease [11].

A systematic review and meta-analysis were conducted based on 51 studies (33,573 patients) examining the characteristics of Long COVID caused by different variants of SARS-CoV-2 six months after the initial infection. Fatigue was more prevalent in Alpha variant infections (66.1%), followed by the wild-type strain (26.3%), and Omicron (18.1%), with $p<0.05$. The symptom of myalgia was more prevalent among patients infected with the Omicron variant (11.7%). Sleep disturbance had a higher prevalence in the wild-type strain (24.5%) and the Omicron variant (18.7%). This study identified different virulence associated with SARS-CoV-2 variants and a wide range of respiratory system damage, observed through abnormalities in lung imaging in 62.2% of the total cases. Overall, all strains were associated with Long COVID [12].

A systematic review based on 430 studies (100,832 patients) compared the prevalence of Long COVID symptoms according to the historical, Alpha, Delta, and Omicron variants of the SARS-CoV-2 virus. The sample consisted of those who had contracted COVID-19 and were followed up for variable periods of 1 to 6 months after infection. There was no statistical synthesis of the data, only a description of the direction findings. Among the prevalent general symptoms across the variants, fatigue was the main clinical manifestation regardless of the strain, while dyspnea, memory loss, cough, and sleep disturbances were less frequent with each new viral variant. One of the hypotheses explaining these findings and their evolution is related to the fact that the initial contact with the virus generates a more severe response, followed by the development of immunity and vaccination over time, coinciding with the emergence of new strains [13].

Systematic review and meta-analysis with 40 cohort studies (10,945 patients) described the long-term consequences of COVID-19 six months after infection. Among all patients, 63.9% reported at least one symptom after the initial six months. Between the sixth- and twelfth-month post-infection, symptoms with a prevalence more significant than 20% were fatigue, muscle weakness, dyspnea, anxiety, difficulty sleeping, limited mobility, chest pain, and depression [14].

The systematic review based on 63 studies evaluated the prevalent symptoms of Long COVID (257,248 individuals). The most prevalent symptoms were fatigue (32.0%), dyspnea (25.0%), sleep disturbances (24.0%), and difficulty concentrating (22.0%), three to six months after acute infection. In the six to nine-month interval, low exercise tolerance (45.0%), fatigue (36.0%), sleep disturbances (29.0%), and dyspnea (25.0%) were the most common. After one year following the infection, the persistent symptoms reported were fatigue (41.0%), dyspnea (31.0%), sleep disturbances (30.0%), and myalgia (22.0%) [15].

Systematic review with meta-analysis of 15 observational studies examined the long-term effects of COVID-19. The review included data from 47,910 patients aged 17-87 years, followed for 14 to 110 days after infection. A prevalence of 80.0% for the development of long-term symptoms was estimated. The study identified more than

50 persistent manifestations after acute infection, with the five most common symptoms being fatigue (58.0%), headache (44.0%), attention disorder (27.0%), hair loss (25.0%), and dyspnea (24.0%) [16].

Meta-analysis of 18 studies was conducted. A total of 8,591 patients, with mean ages ranging from 42-71 years, were followed for one year after SARS-CoV-2 infection. The most prevalent symptoms were fatigue and weakness (28.0%), arthralgia (26.0%), depression (23.0%), and anxiety (22.0%). There was a higher likelihood of developing post-COVID-19 symptoms in women, patients with greater severity of initial infection and hospitalization during the acute phase, and individuals with high body mass index. Additionally, age showed inconsistent associations, with some studies indicating a positive association and higher prevalence in middle-aged individuals (40-54 years), while others found a negative association or no association with age [17].

Systematic review with meta-analysis of 24 studies was conducted to explore the prevalent effects of COVID-19 infection. A total of 5,323 patients, with a mean age of 55.2±8.1 years, were observed between three and six months after symptom onset or hospital discharge. The analyzed manifestations were abnormal lung computed tomography (59.0%), abnormal lung function test (39.0%), fatigue (38.0%), and dyspnea (32.0%). Additionally, functional capacity loss was identified in 36.0%, primarily associated with work productivity and physical activity [18].

A systematic review of 45 cohort studies determined the prevalence of persistent symptoms in individuals infected with SARS-CoV-2. Among 9,751 patients, with mean ages ranging from 50 to 60 years and a follow-up period of at least 2 months, the most prevalent symptoms were dyspnea fatigue or exhaustion (40%), shortness of breath (36%), memory loss (28.3%), loss of smell in the acute phase (23.6%), and anxiety (22.1%) [19].

A systematic review with meta-analysis of 16 observational studies provided an overview of the prevalence and duration of persistent symptoms in 8,756 patients. Within 12 months after infection, the most prevalent symptoms were fatigue and dyspnea (42.0%), sleep disturbances (28.0%), anxiety and depression (27.0%), cough (25.0%), loss of smell and taste (24.0%), and fever (21.0%) [20].

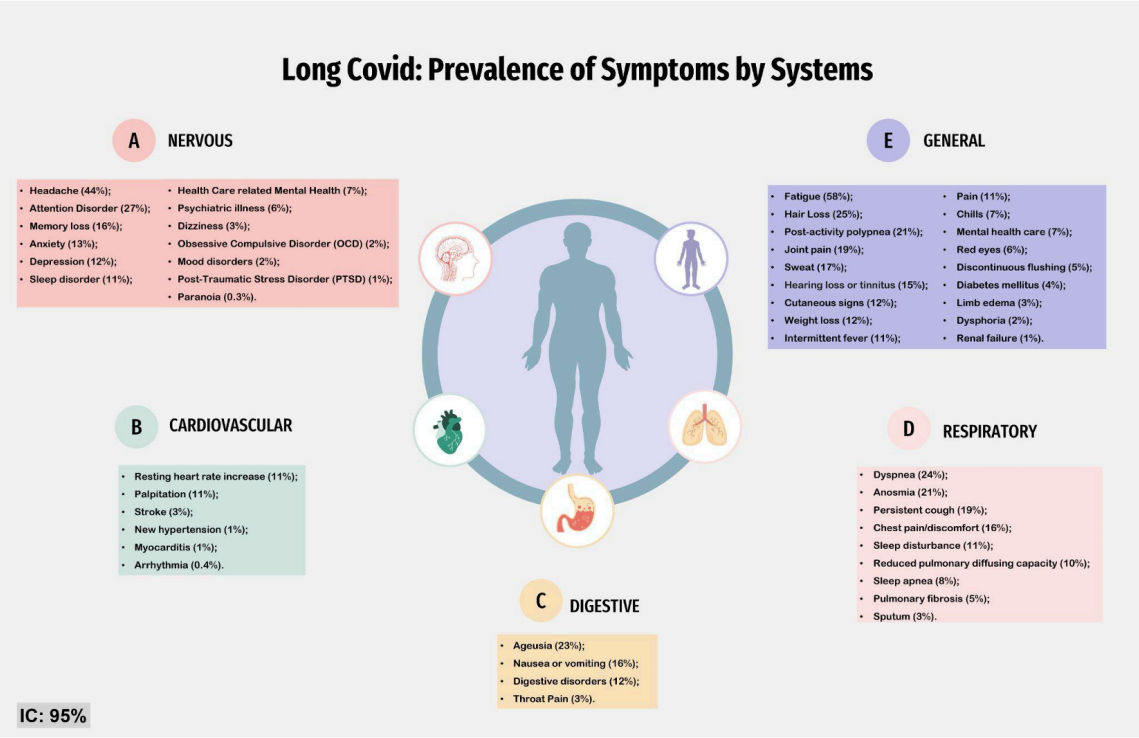
Rahmati et al described the prevalence of long COVID symptoms 2 years after acute COVID-19 infection in a total of 1.289.044 patients, with median age ranging from 40 to 61 years and including North America, Europe and Asian studies. In this meta-analysis, the prevalence of at least one unresolved symptom 2-year after SARS-CoV-2 infection was 41.70% (95% CI, 40.10%-43.20%) and the prevalence of the most common residual symptoms were fatigue (27.40%), sleep difficulties (25.10%), alopecia (11.00%), dyspnea (9.60%), anxiety (9.00%), brain fog (8.10%) and headache (6.90%). Rahmati et al also identified several predictors of long COVID symptoms, such as older age, female gender, higher BMI, pre-existing comorbidities, severe COVID-19, symptom burden, and elevated levels of inflammatory markers [21].

Systematic review of 12 observational studies with 4,664 patients, aged 2.9-93 years, and a follow-up period of 14 to 90 days, found the prevalence of Long COVID manifestations ranged from 35.0% to 90.5% in 7 out of 12 studies. Fatigue was a symptom present in almost all studies. One article mentioned a 30-fold increase in the development

of Kawasaki disease after SARS-CoV-2 infection compared to the previous 5 years. Another one associated the infection with a higher occurrence of peripheral venous, pulmonary, cardiac, and arterial thromboembolic events. Overall, fatigue, dyspnea, neuropsychological disorders, and pain were the most frequent post-COVID-19 manifestations in patients [22].

Overall Results

In general, fatigue has been identified as the most prevalent symptom, present in almost all studies, followed by manifestations such as headache, dyspnea, and sleep disturbances. Furthermore, other neurological, respiratory, gastrointestinal, and psychological symptoms have also been reported consistently (Infographic 1)



Infographic 1.

Discussion

Based on this overview, eleven systematic reviews were identified, covering between 4,664 and 257,348 patients, A wide range of persistent symptoms associated with Long COVID has been described, with variations among them. The results and prevalence of disease symptoms were influenced by several factors, including age, sex, severity of infection, and follow-up time of patients, which contribute to the heterogeneity of clinical manifestations.

Gender-Specific Prevalence

Most research shows a greater persistence of post-COVID symptoms in females. Bai et al. [23] showed a three times greater risk of women manifesting long-term COVID (adjusted odds ratio (AOR) 95%CI: 3.32 (1.78-6.17), p<0.0001). On the other hand, Zeng et al. [24] identified preliminary studies that showed a higher prevalence of fatigue and other symptoms in females, while other investigations found no associations between clinical conditions and gender. The authors also reported that there is an influence on female hormones in the perpetuation of the hyperinflammatory state, even after the acute phase of the disease. A greater amount of SARS-COV-2 IgG antibodies was detected in women after 2 to 4 weeks of the acute (severe) phase and in the initial period of infection, a relevant fact to determine the symptomatology both during and after COVID.

Covid Variant

Among the different variants, a greater association between Long COVID Syndrome and the historical strain was reported, with the possibility of symptomatic manifestation up to 2 years after the initial infection. On the other hand, Omicron had a prevalence of less than 25% and was associated with lower risks of developing the syndrome when compared to previous strains [12]. In the same study, fatigue was the most prevalent symptom, regardless of the strains.

Intensity in The Acute Stage

Regarding the severity of the disease, patients who had mild and moderate cases of infection showed less persistence of long-term COVID symptoms compared to those with greater severity in the acute phase. Research conducted by Caspersen et al. [25] observed a higher prevalence of symptoms in severe cases compared to mild cases, such as the prevalence of mental fog (18.1% vs. 9.2%), dyspnea (19.5% vs. 6.9%), and alterations in smell and taste (23.5% vs. 16.0%).

Among the hospitalized groups, there were greater long-term consequences for the mental health of patients, justified by the stress and concerns correlated and intensified by the illness process within this environment. However, in the same review, other studies diverged on the idea that hospitalization minimized the context of social isolation for patients, as it was associated with contact with the healthcare team, resulting in an inverse proportion between the duration of hospitalization and the consequences for mental health [10].

Post-Covid Timeframe

The post-COVID time frame covered in the selected reviews ranged from 14 days to over 12 months. The studies by Abdel-Gawad et al. [22] and Lopez-Leon et al. [15] presented a short panorama of the post-acute phase, specifically 14 days, despite the WHO definition (2022) [2] that determines Long COVID as symptoms persisting after 3 months of infection. In general, studies comparing different post-COVID periods observed a progressive reduction in

symptoms over time, both in terms of the absolute number and the type of symptom. Fatigue was consistently present throughout all post-infection moments, persisting even after one year. Sleep disturbances, dyspnea, difficulty concentrating, and psychological symptoms also persisted for up to 12 months [11][14,][16].

Long Covid Symptoms

The most frequent symptoms of Long COVID were identified as fatigue and dyspnea. This finding has led to discussions about the development of chronic fatigue syndrome after SARS-CoV-2 infection. The intense fatigue resulting from this clinical condition has caused significant physical, occupational, and psychosocial impacts. Studies carried out by Miranda et al. [26] point out that infections caused by the SARS and MERS viruses also have persistent symptoms, such as chronic fatigue, myalgia, insomnia, depression, and anxiety. Considering that SARS-CoV-2 has some similarities with these viruses, it is possible to predict that, after the COVID-19 pandemic, survivors will also have to deal with prolonged manifestations of these symptoms.

Long COVID has been associated with a range of symptoms in a patient's mental health, such as anxiety and depression. Although the prior mental health conditions of those affected are unknown, there is evidence of a slight association between SARS-COV-2 infection and the development of these disorders [27]. In addition, several factors related to the pandemic, such as social isolation, fear of illness, restrictions, and the economic crisis, have directly impacted the mental health of the general population [25]. Additional studies suggest that the observed symptoms may be associated with stressful situations, traumatic events, hormonal issues, and cortical limbic stimuli [8]. In short, there is a clear need to better understand the symptoms associated with viral infection, differentiating them from the diverse factors that can affect the emotional health of the general population.

Guo et al. [28] explored cognitive differences among those with COVID-19 infection. They identified a consistent link between COVID-19 and reduced memory performance, particularly in individuals with ongoing symptoms. The study suggests that self-reported memory issues correspond to measurable memory declines, emphasizing the importance of broader access to neurological and neuropsychological assessments for Long COVID patients reporting cognitive deficits.

Risk Factors

Educational, sociodemographic, and occupational conditions constitute social determinants of health and are important to define the probability of infection of the disease and, consequently, for later manifestations. In this way, the Long COVID Syndrome presents itself disproportionately in different realities and contexts. Studies commonly highlight the high rates of infection by COVID, as well as high mortality rates in individuals with social vulnerability [29]. In this overview, few studies addressed the follow-up of patients from the global south, and it is not possible to assess whether the occurrence of post-COVID symptoms is higher in the population living in underdeveloped or developing countries, compared to the global north. In addition, the majority of studies did not

assess the social, economic, and cultural profile of the sample, which is fundamental to understand the manifestation of long-term COVID in different population segments. Another point is that the pre-existence of other health conditions such as hypertension, diabetes, obesity, and cardiovascular diseases is important to understand whether comorbidities are risk factors for the Long COVID Syndrome. This is because the prior impairment of the organism makes it more susceptible to a physiological response that contributes to the persistence of symptoms.

Worldwide Consequences for Public Health

With the COVID-19 pandemic, new clinical manifestations were seen in primary, secondary, and tertiary care settings around the world. Even with the absence of scientific knowledge that explained the causes, mechanisms, effects, and sequelae of the disease, health systems had to organize themselves to the population demand from March 2020. The varied and frequent nature of persistent post-COVID conditions has led to care challenges. Specialized clinics are being established to serve patients with post-acute sequelae of SARS-CoV-2. While many post-COVID conditions can be improved through comprehensive rehabilitation plans, different clinical settings may require diverse coordinated care models. Achieving recovery requires a multidisciplinary team with physiatry involvement to address the unique needs of post-acute sequelae of SARS-CoV-2 patients. Additionally, ensuring equitable access and institutional commitment to allocate resources for these programs is essential [30]. Other strategies include primary care reference guides for health professionals, with guidance for systematic assessment of symptoms and correct treatment [31] and teleconsultation, using communication technologies to monitor and assist patients remotely [32].

Research Projects Under Consideration

Longitudinal comparative studies are best suited to establish a causal relationship between COVID infection and persistent symptoms. In this sense, Caspersen et al. [25] followed a cohort of 70,000 adults with and without COVID-19, in Norway, for a period of up to 12 months. Based on the relative risk present between previously infected and non-infected, the studies resulted in the association of 13 of the 22 symptoms reported by the participants as related to the SARS-CoV-2 virus. In general, clinical manifestations that were strongly related to the viral infection were highlighted, such as loss of smell and taste, with a relative risk of 51.4%, in periods of 11-12 months post-infection, being a more prevalent symptom among women. Fatigue (4.8%), and dyspnea (8.7%) were other symptoms that presented a higher risk of association with the disease. Emotional factors such as depression had no statistically significant association with COVID-19, with a relative risk of 1.5% [25].

We can observe that the appearance and development of specific symptoms may be associated with several "triggers" experienced by patients that are not, necessarily and directly, related to the virus. Factors such as sex, age, life habits, physical activity, sleep quality, emotional state, stress, and trauma are identified as possible triggers of Long COVID. Socioeconomic and demographic conditions can also interfere with health status and

individual manifestations. In addition, understanding the symptoms that already exist in the population and the factors associated with it is necessary for the definition and differential diagnosis of Long COVID Syndrome. The WHO recognizes that knowledge about the Long COVID Syndrome is limited. Thus, it emphasizes the need to seek new data and results to improve the approach to the health condition [33].

Limitation

The main limitation of the analyzed studies was the population used and the selected study design. Most of them were prevalence studies focused solely on patients with COVID-19. The primary limitation relates to the predominant study trial, which mainly relied on prevalence studies, which are not ideal for establishing causal relationships. Another limitation is the exclusive selection of English-language articles and the absence of studies from developing countries which may have led to a limited view and potential language bias in the obtained results.

Conclusions

Long COVID has considerable relevance to global health, considering the high prevalence of individuals who have contracted COVID-19. Major studies included in this review were conducted in the Northern Hemisphere, including Europe, Asia, and North America. Most studies have focused on analyzing the prevalence of symptoms in individuals who tested positive for COVID-19, whether hospitalized or not — one study compared Long COVID symptoms in positive and negative populations. The post-acute phase time interval varied from short periods (14 days) to long-term (over one year). The prevalence of symptoms varied over time. The most prevalent Long COVID symptoms, regardless of the post-acute phase time interval, were fatigue and dyspnea.

Statements and Declarations

Funding

The research received funding from the Minas Gerais State Research Support Foundation (FAPEMIG), the National Council for Scientific and Technological Development (CNPq) and Financiadora de Projetos (FINEP), providing financial support for the study. The resources were used to cover the costs related to data collection and the acquisition of necessary tools for conducting the research. It is important to note that FAPEMIG, CNPq and FINEP did not influence the research design, analysis of results, or writing of this article.

Conflict of Interests

There were no conflicts of interest among the authors or other parties involved in this study. A comprehensive analysis of the researchers' financial, personal, and academic connections revealed no relationships that could compromise the objectivity of the results presented. This statement doesn't rule out the potential for unconscious

bias or indirect influence on the study's conclusions. Nevertheless, there were rigorous measures to maintain impartiality and result integrity and the funding sources were disclosed. Throughout the research and writing process were maintained transparency and adherence to scientific ethics.

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Declarations

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