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PREVALENCE, CLINICAL MANIFESTATIONS, AND ASSOCIATED FACTORS OF LONG COVID-19

PREVALENCIA, MANIFESTACIONES CLÍNICAS Y FACTORES ASOCIADOS AL COVID-19 DE LARGA DURACIÓN

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REVIEW ARTICLE

ABSTRACT

Objective: The objective was to describe the prevalence, clinical manifestations, and associated factors of long the COVID-19. **Methods:** A bibliographic search of systematic reviews and meta-analyses on long COVID-19 was carried out in MEDLINE (via PubMed) up to April seven th, 2022. 37 articles were found and three were included. **Results:** The quality of the evidence was evaluated through AMSTAR 2 criteria. The reported prevalence of long COVID-19 was 43% (95% CI: 39% – 46%). The main clinical manifestations were weakness (41% [95% CI: 25% - 59%]), malaise (33% [95% CI: 15% - 57%]), fatigue (31% [95% CI: 24% - 39% %]), changes in concentration (26% [95% CI: 21% – 32%]) and shortness of breath (25% [95% CI: 18% – 34%]). **Conclusion:** Factors associated with long COVID-19 include female gender, the severity of initial symptoms, age, and the presence of comorbidities.

RESUMEN

Objetivo: El objetivo fue describir la prevalencia, las manifestaciones clínicas y los factores asociados de COVID-19 de larga duración. **Métodos:** Se realizó una búsqueda bibliográfica de revisiones sistemáticas y metaanálisis sobre COVID-19 de larga duración en MEDLINE (vía PubMed) hasta el siete de abril de 2022. Se encontraron 37 artículos y se incluyeron tres. La calidad de la evidencia fue evaluada a través de los criterios de AMSTAR 2. **Resultados:** La prevalencia reportada de COVID-19 de larga duración fue 43% (IC95%: 39% – 46%). Las principales manifestaciones clínicas fueron debilidad (41% [IC95%: 25% – 59%]), malestar general (33% [IC95%: 15% – 57%]), fatiga (31% [IC95%: 24% – 39%]), alteración en la concentración (26% [IC95%: 21% – 32%]) y sensación de falta de aire (25% [IC95%: 18% – 34%]). **Conclusión:** Los factores asociados a COVID de larga duración incluyeron sexo femenino, severidad de cuadro inicial, edad y presencia de comorbilidades.

Palabras clave: COVID-19, síndrome de COVID-19 post-agudo, COVID-19 de larga duración. (Fuente: DeCS BIREME)

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INTRODUCTION

COVID-19 has been characterized by its acute clinical manifestations, including fever, cough, dyspnea, and fatigue [1,2]; As the disease progresses, approximately 10% of patients require intensive care [3]. Although it is true that most people who contract COVID-19 fully recover, there is a proportion that reported persistence of symptoms in the medium and long term [4-6], this picture is called by some researchers COVID-19 of long duration (long COVID) [4,7,8].

Despite the existence of cases of people with persistent symptoms after SARS-CoV-2 infection, there is still no clear consensus on the definition of long the COVID-19. On the one hand, there is research evaluating the sequelae of the COVID-19 [1,9], on the other hand, others define it as post-acute COVID-19 syndrome or PACS [10,11], as well as there is also a definition of the post-COVID syndrome [12,13]. Such differences result in different estimates of prevalence, as well as different clinical implications. In this sense, the WHO defined long COVID-19 as "the disease contracted by people with a history of probable or confirmed SARS-CoV-2 infection; usually within three months of the onset of COVID-19 and with symptoms or effects lasting at least two months" [14].

Research has considered different definitions, outcomes, and follow-up times, so the state of knowledge about long COVID-19 is still insufficient. Our objective was to synthesize the available scientific information from systematic reviews regarding the prevalence, clinical manifestations, and associated factors of long COVID-19. The information presented was part of the evidence synthesis report prepared by the National Health Institute at the request of the Peruvian Ministry of Health [15].

METHODOLOGY

Question formulation

Two clinical questions were formulated: in adults with a history of SARS-CoV-2 infection, what is the prevalence of long COVID-19 and the frequency of long COVID-19 symptoms? And, in adults with a history of SARS-CoV-2 infection, what are the factors associated with the presentation of long COVID-19?

Search and selection of evidence

The bibliographic search was carried out in MEDLINE (via PubMed), through a search strategy that included free terms and controlled language descriptors for long COVID-19 (Supplementary material one: search strategy), the search was carried out until April seven th, 2022.

The selection of the articles was carried out individually by the authors, considering an initial phase of reading the titles and abstracts through the Rayyan platform (www.rayyan.ai) and a phase of reading the full text of the potentially relevant publications to determine their eligibility. The inclusion criteria were:

1) systematic reviews and meta-analyses of cohort, case-control, or cross-sectional studies that report results for outcomes of interest, evaluated at least three months from the onset of COVID-19 in adults; 2) reviews published in English and Spanish. If more than one systematic review was identified, the one with the best methodological quality was chosen. The following were excluded: 1) systematic reviews that had not assessed the risk of bias or the methodologic quality of the included studies; 2) systematic reviews focused on determining the prevalence of symptoms of a single organ or system and 3) letters to the editor, narrative reviews, preclinical studies (studies in vitro or animal models), and opinion articles.

Data extraction

The data was extracted in a standardized form that included the following information: author, year of publication, number of studies included in the review, number of participants, design, place, population characteristics, prevalence outcomes, associated factors, and assessment tool. risk of bias assessment and AMSTAR 2 score.

Assessment of methodological quality and risk of bias

The AMSTAR 2 tool[16] was used to assess the methodological quality of identified systematic reviews. The evaluation was carried out by four authors (FHR, DG, DR, MCR) in a paired and independent manner and discrepancies were resolved by consensus. The risk of bias in the included studies was considered from the reviews with the best AMSTAR 2 score.

RESULTS

37 articles were identified in the bibliographic search.

After reading the titles and abstracts, 17 articles were selected for full-text reading. Finally, after verifying eligibility criteria and applying the AMSTAR 2 criteria, 3 systematic reviews were selected for data synthesis (Figure 1), one of them was peer-reviewed and published after the search, considering the information provided by this latest version[9]. Excluded articles and reasons for exclusion are described in Supplementary Material.

2. The main characteristics of the selected systematic reviews are summarized in Table 1.

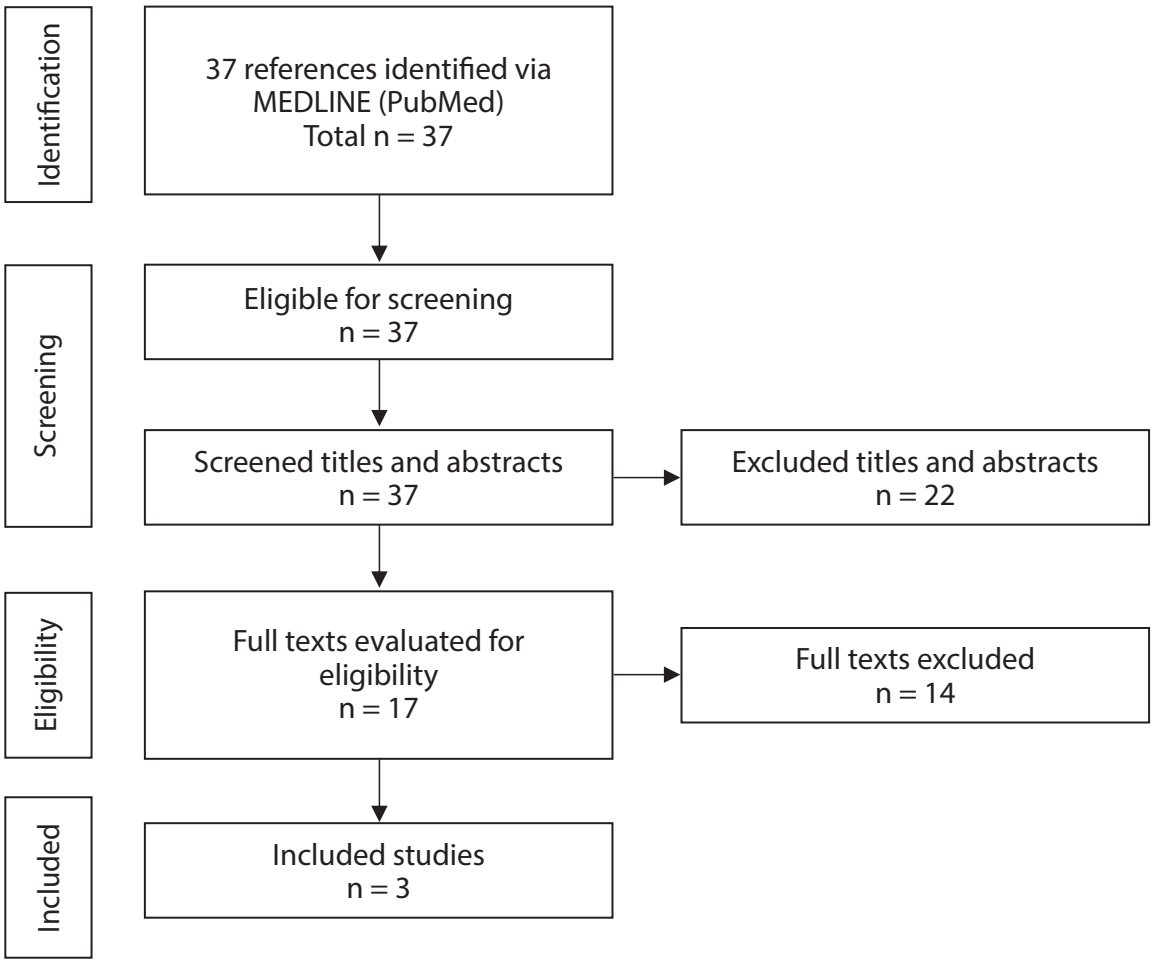

Figure 1. PRISMA diagram for study selection.

Table 1. Characteristics of the selected systematic reviews.

Author and year	Number of studies/ participants	Design	Place / Region	Population characteristics	Reported Prevalence Outcomes	Evaluated factors	Risk of study bias	Score AMSTAR 2 of the RS
Chen 2021	50 studies 1,680,003 people	- Prospective cohorts (n=28) - Retrospective cohorts (n=7) - Bidirectional cohorts (n=6) - Transversal (n=9)	- Europe: 22/50 - North America: 11/50 - South America: 1/40 - Asia: 13/50 - International: 3/50	- Not hospitalized: 4165 (5 studies) - Hospitalized: 67,161 (22 studies) - 1,608,677 positive COVID-19 patients, regardless of their hospitalization condition	Prevalence in positive COVID-19 patients Hospitalized prevalence Prevalence 90 days Prevalence of general symptoms: - Fatigue - Dyspnea - Sleeping problems - Memory problems	- Sex - Presence of asthma	- 39 studies scored 6/9 or 7/9 - 1 study got 9/9	12/16 2 critical weaknesses Critically low confidence
Michelen 2021	39 studies 10 951 people	- Cohort (n=32) - Transversal (n=6) - Case-control (n=1)	12 countries - Europe: 24/39 - Asia: 9/39	- People diagnosed with COVID-19 with symptoms ≥ 12 weeks, after the onset of COVID-19	Prevalence of signs and symptoms - Systemic - Cardiopulmonary - Upper respiratory - Gastrointestinal - Musculoskeletal	- Sex - Age - Severity of the initial disease - Presence of	- High risk (n=12) - Moderate risk (n=22) - Low risk (n=5)	13/16 1 critical weaknesses
			- United States: 3/39 - Middle East: 3/39	- Age: 90% adults only - Female sex: 48% - Hospitalization during acute COVID-19: 78%	- Neurological and Neuromuscular - Psychological and social - Neurocognitive - Others (skin rash, hair loss, conjunctivitis)	comorbidities		low confidence
Maglietta 2022	20 studies 13 340 people	- Prospective cohorts (n=8) - Ambidirectional (cohorts, descriptive n=12)	- Europe: 11/20 - China: 8/20 - South America: 1/20	- Adults discharged from hospitalization for COVID-19 with prospective follow-up ≥ 12 weeks - Female sex: 48%	Not rated	- Sex - Severity of the initial disease	- High risk (n=11) - Moderate risk (n=9)	13/16 1 critical weaknesses low confidence

95% CI: 95% confidence interval, OR: Odds ratio, SR: systematic review

Characteristics of the studies

The study by Chen et al.[9] was a systematic review and meta-analysis that aimed to examine the prevalence of post-acute sequelae of the COVID-19 around the world [9]. The databases consulted were PubMed, Embase, and iSearch for studies without peer review (preprints) of medRxiv, bioRxiv, Social Science Research Network (SSRN), and others (search performed on July 5, 2021, with an extension to March 13 of 2022). Studies in English that evaluated long the COVID-19, defined as conditions that persist for at least 28 days after diagnosis or recovery from SARS-CoV-2 infection, were selected. The outcomes evaluated were prevalence, risk factors, duration, or associated symptoms.

The search identified 5 125 studies, from which 40 were included for qualitative synthesis, and 33 for meta-analysis (number of participants: 886 388). The selected studies were of the prospective cohort type (n = 23), retrospective cohort (n = 6), bidirectional cohort (n = 3), and cross-sectional studies (n = 8).

The risk of bias assessment was carried out using the Joanna Briggs Institute tool for studies with prevalence results, for which they added the total responses classified as "Yes" concerning nine questions of the tool (score from zero to nine) where Aspects such as the representativeness of the population included (sampling framework, sampling), the size of the sample, the description of the population and the environment, the methods to evaluate the study condition, the

statistical analysis and the percentage of response of the participants [17]. After updating the search to March 13, 2022, an additional ten studies were included for qualitative synthesis, of which eight were included in the meta-analysis. The selected studies were of the prospective cohort type (n = 5), retrospective cohort (n = 1), bidirectional cohort (n = 3), and cross-sectional studies (n = 1).

The total number of participants after the new systematic search was 1,680,003. The characteristics of the participants were: non-hospitalized participants (4,165 of 5 studies), hospitalized participants (67,161 of 22 studies), and any the COVID-19 positive patient, regardless of their hospitalization status (1,608,677 of 23 studies). According to the risk of bias assessment with the Joanna Briggs Institute tool, the most frequent methodological limitations were: sampling was not adequate (16 of 50 studies), a valid method was not used to identify the study condition (15 of 50 studies), the sampling frame was not appropriate to address the target population (seven of 50 studies) and the data analysis was not performed with sufficient coverage of the identified sample (seven of 50 studies).

The study by Michelen et al. [8] aimed to synthesize the evidence on the characteristics of long-lasting COVID-19 [8]. The study design was of the living systematic review type. The authors performed the systematic search in the MEDLINE, CINAHL, Global Health (Ovid), WHO Global Research on the COVID-19, LitCOVID, and Google Scholar databases (search period from January one, 2002, to March 17, 2021). The outcomes evaluated were the prevalence of signs and symptoms and associated factors. A total of 39 studies were selected (cohort studies: 32; cross-sectional studies: six; case-control studies: one).

The total number of participants was 10 951 (48% women) from 12 countries. The main finding was the estimation of the prevalence of symptoms of long COVID, in addition, a qualitative synthesis was carried out on diagnostic imaging (13 of 39; diagnostic methods included tomography, ultrasound, and artificial intelligence) and functional tests (ten of 39; methods included spirometry, diffusing capacity, lung volume, and exercise tests). The risk of bias was evaluated with the instrument developed by Hoy et al. [18], which is a validated tool for bias assessment in prevalence studies. The studies had a low risk of bias (4/39), moderate risk (23/39), and high risk (12/39). The domains that presented more studies with a high risk of bias were: 1) representation of the national population (21 of 39 studies), 2) true sampling frame or close representation of the target population (24 of 39) and 3) random selection used for sample selection (32 of 39 studies).

The study by Maglietta et al. [12] aimed to identify, in patients who had been hospitalized for the COVID-19, which factors were already present or emerging during hospitalization, It was associated with a higher risk of presenting new or persistent symptoms [12]. The study design was a systematic review and a bibliographic search was carried out in two databases (MEDLINE and Web of Science) until September 20, 2021, including observational studies in English, with 12 weeks or more of prospective follow-up. Odds ratios were estimated for each assessed factor using unadjusted data. They also performed a random effects meta-analysis, using the Paule and Mandel method for estimating variance between studies [19,20]. The confidence intervals for the global effect of the factors of interest were adjusted by applying the Hartung-Knapp-Sidik-Jonkman (HKSJ) approach, which takes into account the uncertainty in the variance of the estimates [21].

Risk of bias assessment was performed using the QUIPS tool [22]. This review provides evidence based on 20 observational studies and association measures for the factors of gender and severity of the initial condition concerning outcomes such as any symptoms, respiratory symptoms, mental health symptoms, and fatigue. Most studies (11 of 20) were rated as high risk of bias in at least one domain of the QUIPS tool and

included: loss of participants to follow up (ten studies), the study sample was not representative of the population of interest (four studies), limitations in statistical analysis and reporting of results (three studies), and potential confounders not adequately addressed (one study). The remaining studies (nine of 20) were at moderate risk of bias.

Prevalence of Long COVID-19

According to Chen et al.[9], the overall prevalence of post-acute COVID-19 syndrome was 0.43 (95% CI: 0.39 – 0.46) (I2 = 100%; p < 0.001). The authors stratified the analysis according to sex, region, hospitalization, and follow-up time. According to sex, the prevalence of PACS in men was 0.37 (95% CI: 0.24 – 0.51) and in women, 0.49 (95% CI: 0.35 – 0.63); while, by region, the highest prevalence was found in Asia (0.51 [95% CI: 0.37 – 0.65]), followed by Europe (0.44 [95% CI: 0.32 – 0.56]) and the United States (0.31 [95% CI: 0.21 – 0.43]); According to the history of hospitalization, the prevalence in hospitalized the COVID-19 patients was 0.54 (95% CI: 0.44 - 0.63), in the non-hospitalized group it was 0.34 (95% CI: 0.25 - 0.36), and in the mixed group between hospitalized and non-hospitalized was 0.33 (95% CI: 0.29 – 0.37).

According to the follow-up time, the prevalence of PACS after 90 days was 0.32 (95% CI: 0.14 – 0.57), while the prevalence after 120 days was 0.49 (95% CI: 0.40 – 0.59).

Prevalence of long-term clinical manifestations of COVID-19

According to Chen et al.[9], the most frequent clinical manifestations of PACS were: fatigue (prevalence: 0.23 [95% CI: 0.17 – 0.30]), memory problems (0.14 [95% CI: 0.10 – 0.19]), dyspnea (0.13 [95% CI: 0.11 – 0.15]), insomnia (0.11 [95% CI: 0.05 – 0.23]), and joint pain (0.10 [95% CI: 0.04 – 0.22]).

On the other hand, according to Michelen et al.[8], the most frequent clinical manifestations were weakness (prevalence: 41% [95% CI: 25.43 - 59.01]), malaise (33% [95% CI: 14.91 - 57.36]), fatigue (31% [95% CI: 23.91 – 39.03]), altered concentration (26% [95% CI: 20.96 – 31.73]), and shortness of breath (25% [95% CI: 17.86 – 33.97]). The list of signs and symptoms is described in Table 2.

Table 2. Prevalence of signs and symptoms of long COVID-19, according to the meta-analysis by Michelen (2021)

	Number of studies	Proportion (95 % CI)	Heterogeneity I2 (%)
Neurological and neuromuscular			
Headache	11	4.88 (2.30 – 10.06)	94.88
Tremor	3	3.53 (0.30 – 30.63)	89.14
Seizures	1	1.33 (0.49 – 2.87)	NA
Bradykinesia	1	5.19 (2.11 – 10.39)	NA
Dissymmetry	1	1.48 (0.18 – 5.25)	NA
Muscular atrophy	1	6.67 (3.09 – 12.28)	NA
Altered muscle tone	1	4.44 (1.65 – 9.42)	NA
Altered gait or posture	3	4.20 (2.02 – 8.53)	0
Taste disturbance	17	13.52 (8.96 – 19.89)	96.75
Alteration of smell	19	15.17 (10.75 – 20.97)	96.2
Hearing disturbance	1	1.11 (0.36 – 2.57)	NA
Vision disturbance	2	4.78 (3.32 – 6.83)	26.01

	Nº estudios	Proporción (IC95%)	Heterogeneidad I2 (%)
Dysarthria/speech difficulty	1	2.22 (0.46 – 6.36)	NA
Sensation of decreased sensitivity	2	10.90 (6.71 – 17.22)	71.76
Paresthesia	2	9.12 (2.21 – 30.87)	93.07
Trigeminal neuralgia	1	3.28 (0.90 – 8.18)	NA
Impaired reflexes	1	22.96 (16.17 – 30.98)	NA
Others	1	14.81 (9.29 – 21.95)	NA
Psychological and social			
Anxiety	7	18.73 (8.89 – 35.35)	97.2
Depression	6	8.06 (4.14 – 15.10)	97.45
Sleep disturbance	9	18.15 (9.61 – 31.63)	93.87
Post-traumatic stress disorder	6	9.14 (3.66 – 21.04)	96.44
Dysphoria	3	1.79 (0.00 – 98.74)	97.83
Reduced quality of life	3	36.76 (18.43 – 59.83)	91.07
Care dependency	3	5.89 (0.46 – 45.96)	98.37
Neurocognitive			
Memory disturbance	5	17.94 (5.26 – 46.25)	95.08
Altered concentration	2	25.98 (20.96 – 31.73)	0
Confusion	2	2.71 (1.93 – 3.79)	0
Frontal Release Signs	1	14.81 (9.29 – 21.95)	NA
Others	3	17.77 (0.08 – 98.23)	98.68
Others			
Skin rash	4	2.83 (0.95 – 8.16)	80.76
Hair loss	5	14.34 (5.33 – 33.23)	94.64
Conjunctivitis	1	1.77 (0.77 – 3.47)	NA

A stratification was performed according to hospitalization status for the COVID-19 and it was found that the prevalence of clinical manifestations was significantly higher in hospitalized patients, compared to non-hospitalized patients with fatigue (hospitalized: 37.10% [95% CI: 26.54 – 49.06]; not hospitalized: 24.6% [95% CI: 20.11 – 29.72]; p = 0.012), shortness of breath (hospitalized: 28.7% [95% CI: 18.48 – 41.64]; no hospitalized: 13.7% [95% CI: 8.51 – 21.37]; p = 0.003), weight loss (hospitalized: 37.31% [95% CI: 29.55 – 45.79]; non-hospitalized: 10.83% [95% CI: 8.23 – 14.12]; p < 0.001), and memory alterations (hospitalized: 34.8% [95% CI: 23.64 – 47.88]; non-hospitalized: 15.6% [95% CI: 9.64 – 24.32]; p = 0.001). The alteration in smell was significantly higher in non-hospitalized patients (hospitalized: 12.2% [95% CI: 7.96 – 18.10]; non-hospitalized: 22.19% [95% CI: 11.69 – 38.04]; p = 0.035).

In both studies, limitations focused on the heterogeneity of the selected investigations in aspects such as design, population, measurement of the disease (heterogeneity in access to diagnostic tests), measurement of outcomes (self-diagnosis and differences in access to health), and follow-up period. In addition, there were inconsistencies in the terms used to describe symptoms, as well as limitations in the details and stratification of pre-existing comorbidities, the severity of the COVID-19, and treatment methods. Also, the geographical distribution of the participants was another limitation. For example, few studies on long the COVID-19 in low- or middle-income countries were identified, no studies were found in the pediatric population, and analyses stratified by ethnicity were also not performed. Other factors that can affect the measurement of prevalence are the type of predominant variant; thus, the Omicron variant (B.1.1.529) is related to mild acute symptoms in the vaccinated population; furthermore, the selection of articles in the English language excludes other important studies published in different languages.

Associated factors

The evidence came mainly from studies on people with a history of hospitalization for the COVID-19, included in the systematic review by Michelen et al.[8] y Maglietta et al.[12] . There was high heterogeneity between the studies included in the reviews, given the different operational definitions for the prognostic factors evaluated and the outcomes of interest (Table 3).

Table 3. Factors associated with long COVID-19.

Factor	Outcome	Number of studies	OR (CI95%)	Heterogeneity I2 (%)
	Any symptom	8	OR: 1.52 (1.27 – 1.82)	68%
	Respiratory symptoms	12	OR: 1.20 (1.00 – 1.45)	65%
	Any respiratory symptoms	2	OR: 1.10 (0.83 – 1.47)	63%
	Cough	3	OR: 0.99 (0.75 – 1.31)	34%
Female Sex	DLCO<80%	4	OR: 2.28 (0.99 – 5.27)	71%
	Dyspnea	4	OR: 1.07 (0.70 – 1.65)	87%
	Difficulty breathing	2	OR: 1.12 (0.73 – 1.71)	63%
	Odynophagia	3	OR: 1.40 (0.94 – 2.07)	0%
	Mental health symptoms	7	OR: 1.67 (1.21 – 2.29)	58%
	Anxiety	3	OR: 1.95 (1.52 – 2.49)	8%
Severity of	PTSD	3	OR: 2.78 (0.63 – 12.22)	76%
the initial disease	Sleeping difficulties	3	OR: 1.26 (0.98 – 1.63)	32.5%
	Others	3	OR: 1.72 (1.14 – 2.60)	41%
	Fatigue	7	OR: 1.54 (1.32 – 1.79)	49%
	Respiratory symptoms	9	OR: 1.66 (1.03 – 2.68)	71%
	Cough	2	OR: 1.78 (1.05 – 3.03)	0%
	DLCO<80%	6	OR: 2.05 (1.06 – 3.96)	49%
	Dyspnea	1	OR: 1.53 (0.66 – 3.54)	NA
Age	Difficulty breathing	2	OR: 1.12 (0.73 – 1.71)	63%
Age > 60 years	Fatigue	5	OR: 1.23 (0.73 – 2.07)	71%
Age	Olfactory dysfunction	1	OR: 0.42 (0.19 – 0.91)	
	Limitations in functional status (grade II to IV on the Post-COVID Functional Status Scale)	1	OR: 2.60 (1.19 – 5.67)	NA

Factor	Outcome	Number of studies	OR (CI95%)	Heterogeneity I2 (%)
Age ≥ 60 years	Low Quality of Life scores	1	OR: 2.44 (1.33 – 4.47) vs 0-17 years: p=0.003	NA
Age 50-66 years vs younger age	Persistence of symptoms (at 125 days)	1	vs 18-34 years: p=0.001	
Comorbidities Previous psychiatric diagnosis	Persistence of depressive symptoms	1	P=0.006	
1 comorbidity	Olfactory dysfunction	1	OR: 0.39 (0.16–0.91)	
2 comorbidities≥	Symptoms at follow-up	1	OR: 0.33 (0.19–0.99) OR: 2.52 (1.58 – 4.02)	
2 comorbidities Cardiovascular disease (CVD) and diabetes	Spirometric abnormalities 3 months after discharge	1	Reduced FEV1: ECV: 34.2% vs 9.4% Diabetes: 28.9% vs 12% Reduced FVC: ECV: 29.7% vs 11%	NA

DLCO: Carbon monoxide diffusing capacity; FVC: Forced Vital Capacity; FEV1: Forced Expired Volume in the first second; PTSD: post-traumatic stress disorder.

Female gender was associated with the presence of any long-lasting the COVID-19 symptoms (eight studies; OR: 1.5 [95% CI: 1.27 – 1.82]; I2 = 68%), with the presence of mental health symptoms, such as anxiety, post-traumatic stress disorder, insomnia, among others. (seven studies; OR: 1.7 [95% CI: 1.21 – 2.29]; I2 = 58%), and with fatigue (seven studies; OR: 1.5 [95% CI: 1.32 – 1.79]; I2 = 49%). However, no association was found between the female gender and respiratory symptoms (12 studies; OR: 1.20 [95% CI: 1.00 – 1.45]; I2 = 65%).

The severity of the initial symptoms of the COVID-19 was associated with the persistence of respiratory symptoms (nine studies; OR: 1.66 [95% CI: 1.03 – 2.68]; I2 = 71%). In the analysis by symptom, the severity of the initial symptoms was associated with the persistence of cough (two studies; OR: 1.78 [CI95%: 1.05 – 3.03]; I2 = 0%), and with the diffusing capacity of carbon monoxide (DLCO) < 80% (six studies; OR: 2.05 [95% CI: 1.06 – 3.96]; I2 = 49%). No statistically significant association was found with the presence of fatigue (five studies; OR: 1.23 [95% CI: 0.73 – 2.07]; I^2 = 71%).

In the review by Michelen et al.[8], age was not included in the meta-analysis due to the high variability of the definitions for this variable and the different outcomes. Age ≥ 50-60 years was associated with a higher frequency of low quality of life scores (1 study), the persistence of symptoms assessed at 125 days of follow-up (one study), and a lower frequency of olfactory dysfunction (one study). Likewise, as age increased, an increased risk of deterioration in functional status measured by the post-the COVID-19 functional status scale was observed (one study).

Michelen et al.[8] narratively synthesized the assessment of the presence of comorbidities and their association with the long-term persistence of the COVID-19 symptoms. Having a previous diagnosis of psychiatric illness was significantly associated with the persistence of depressive symptoms (one study). Likewise, having two or more comorbidities were risk factors for the persistence of symptoms during follow-up (one study). An additional study identified that the presence of spirometric abnormalities three months after hospital discharge was more frequent among those with a history of cardiovascular disease and diabetes.

Methodological quality of the included systematic reviews

The quality assessment of the reviews included with AMSTAR 2 is presented in Table 4. Two of the reviews [8,12]

had low confidence due to the presence of a critical weakness (item seven: list of items not provided). excluded studies and ustification for exclusions), and jconfidence was very low in a further review due to two critical weaknesses (item two: lack of an explicit statement of the existence of a protocol and item seven already noted).

Table 4. Assessment of methodological quality according to AMSTAR 2

Ítem	Criteria	Michelen 2021	Magliett a 2022	Chen 2022
1	Do the research questions and inclusion criteria for the review include the PICO components? (YES/NO)	YES	YES	YES
2	Does the report contain an explicit statement that the review methods had been established before the review was conducted and did it justify any significant deviations from the protocol? (YES / YES PARTIAL / NO)	YES	YES	NO
3	Did the authors explain the selection of study designs to include in the review? (YES/NO)	YES	YES	YES
4	Did the authors use a comprehensive literature search strategy? (YES / YES PARTIAL / NO)	YES	YES PARTIAL	YES PARTIAL
5	Did the authors perform the study selection in duplicate? (YES/NO)YES	YES	YES	YES
6	Did the authors perform data extraction in duplicate? (YES/NO)	NO	YES	YES
7	Did the authors provide a list of excluded studies and justify the exclusions? (YES / YES PARTIAL / NO)	NO	NO	NO
8	Did the authors describe the included studies in	YES	YES PARTIAL	YES
9	Did the authors use a satisfactory technique to assess the risk of bias in the individual studies that were included in the review? (YES / YES PARTIAL / NO)	YES	YES	YES
10	Did the authors report funding sources for the studies included in the review? (YES/NO)	YES	NO	NO
11	If they performed a meta-analysis, did the authors use appropriate methods for statistical pooling of results? (YES/ NO/ NO META-ANALYSIS)	YES	YES	YES
12	Did the authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis? (YES/ NO/ NO META-ANALYSIS)	YES	NO	NO
13	Did the authors account for the risk of bias in individual studies when interpreting/discussing the results of the review? (YES/NO)	YES	YES	YES
14	Did the review authors provide a satisfactory explanation and discussion of any observed heterogeneity in the review results? (BUT)	YES	YES	YES
15	Did the authors conduct an adequate investigation of publication bias and discuss its possible impact on the results of the review? (YES/ NO/ NO META-ANALYSIS)	YES	YES	YES
16	Did the authors disclose possible sources of conflict of interest, including the funding they received to conduct the review? (YES/NO)YES	YES	YES	YES
Score		13/16	13/16	12/16
Number of critical weaknesses		1 (ítem 7)	1 (ítem 7)	2 (ítems 2 y 7)

Ítem		Michelen 2021	Magliett a 2022	Chen 2022
Overall Confidence		Low	Low	Critically low

	Critical domains

CONCLUSIONS

Long COVID-19 is a problem that persists despite patients recovering from SARS-CoV-2 infection. According to the findings, the prevalence is greater than 40%, the most frequent clinical manifestations are weakness, malaise, fatigue, impaired concentration, and shortness of breath. Female sex, greater severity of the initial condition, increasing age, and the presence of comorbidities were found to be associated with long-lasting COVID-19 symptoms. Both in the assessment of prevalence and the analysis of associated factors, the findings came from studies with a moderate to high risk of bias.

This review has limitations to consider, such as the restriction to systematic reviews in Spanish or English, the search was limited to PubMed, and the selection and extraction of da However, considering the results of systematic reviews with better methodological quality, an overview of the best evidence available to date on this condition is provided and the need for better quality research for an adequate characterization of COVID-19 has been identified. of long duration and identification of its risk factors.

REVIEW ARTICLE

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