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Abstract: Objectives: We aimed to assess the prevalence of long COVID-19 and estimate the average time to its diagnosis and meta-regression for covariates. Methods: We conducted a systematic review, meta-analysis, and meta-regression from 43 studies (367,236 patients) (June 2020–August 2022). With the random-effects model, the pooled prevalence of long COVID-19 was measured. Publication bias was ascertained, and meta-regression analysis was performed on predetermined covariates. The trial was registered with PROSPERO (CRD42022328509). Results: The pooled prevalence of long COVID-19 was 42.5% (95% CI 36% to 49.3%), with 25% and 66% at four and two months, respectively. Mostly, long COVID-19 signs and symptoms occurred at three (54.3%) to six (57%) months (p < 0.0001), further increasing at 12 months (57.9%, p = 0.0148). Hypertension was significantly associated with long COVID-19 at 32% (0.322 (95% CI 0.166, 0.532) (p < 0.001) and hospital re-admission contributed to 17% (Q = 8.70, df = 1, p = 0.0032) (R² = 0.17). All the covariates explained at least some of the variance in effect size on long COVID-19 at 53% (Q = 38.81, df = 19, p = 0.0047) (R² analog = 0.53). Conclusion: The prevalence of long COVID-19 was 42.5% when linked with a cardiovascular disorder. Hospital re-admission majorly predicted the incidence of long COVID-19. Clinical and methodological characteristics in a specific study contributed to over 50% of long COVID-19 events, with most signs and symptoms occurring between 3 and 6 months and increasing at 12 months.

Keywords: long COVID-19; general population; average diagnosis time; meta-regression

1. Introduction

Post-acute sequelae of COVID-19, also known as “long COVID”, is used to describe the long-term symptoms that might be experienced weeks to months after primary infection with SARS-CoV-2, which is the virus that causes COVID-19 [1]. Recent studies in the literature suggest that the syndrome is described by a diverse set of symptoms that persist after a diagnosed COVID-19 infection [2]. This post-acute infection represents a significant challenge for patients, physicians, and society because the causes, patient profile, and even symptom patterns remain difficult to characterize [3]. It may include memory loss, gastrointestinal (GI) distress, fatigue, anosmia, shortness of breath, and other symptoms. Long COVID-19 has been associated with acute disease severity [4]; furthermore, it is suspected to be related to autoimmune factors [5], as well as unresolved viral fragments [6].
Post-COVID conditions are found more often in people who have severe COVID-19 illness, but anyone who has been infected with the virus that causes COVID-19 can experience post-COVID conditions, even people with mild illness or no symptoms from COVID-19 [7]. There is no test to diagnose post-COVID-19 conditions, and people may have a wide variety of symptoms that could come from other health problems. This can make it difficult for healthcare providers to recognize post-COVID-19 conditions. Diagnosis is considered based on health history, including a diagnosis of COVID-19 either by a positive test, symptoms, or exposure, as well as undergoing a health examination [8–10]. Long COVID may be due to persistent immune disturbances [11].

Studies of patients who have recovered from SARS-CoV-2 infection but have persistent symptoms have ranged widely in size, quality, and methodology, leading to confusion about the prevalence and types of persistent symptoms [12]. SARS-CoV-2 can produce short-/long-term sequelae, and reports describing long COVID-19 in the general population are increasing; however, these studies are limited by the lack of a proper pooled average time estimation for diagnosis or occurrence. Therefore, this review aims to assess the prevalence and factors associated with long COVID-19 in our cohort of the general population.

2. Materials and Methods

A standard search strategy was used in PubMed and then later modified according to each specific database to obtain the best relevant results. These included MEDLINE-indexed journals, such as PubMed Central; NCBI Bookshelf; and publishers’ websites. The language was restricted to English, and the search dates were for studies conducted/published between June 2021 and August 2022. The basic search strategy was built based on the research question formulation (i.e., PICO or PICOS) [13]. They were constructed to include free-text terms (e.g., in the title and abstract) and any appropriate subject indexing (e.g., MeSH) expected to retrieve eligible studies with the help of an expert in the review topic field or an information specialist. The summary of search terms was as follows: long COVID-19; long COVID-19 syndrome; post-Coronavirus syndrome; long COVID-19 sequelae; post-acute COVID-19 syndrome; and post-acute COVID-19 condition. Because the study for this topic would be limited, the outcome term (long COVID-19) was not included in the search terms initially in order to capture more studies. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [14] was used. All identified article titles and abstracts were screened independently by two authors, with those meeting the inclusion criteria screened further by a full-text review. On occasions when it was not clear from the abstract if studies were of relevance, the full text of the article was reviewed. A unanimous consensus was met for the inclusion of proposed studies for full-text reviews among the authors. Full-text studies were further evaluated against the inclusion and exclusion criteria. The reference lists of included studies were reviewed to ensure no other relevant studies were overlooked.

2.1. Search Terms and Criteria for Inclusion

The search terms included for PubMed were as follows: (long COVID-19; long COVID-19 syndrome; post-Coronavirus syndrome; post-acute COVID-19 syndrome; post-acute COVID-19 condition) AND (“the study” [Publication Type] OR “study as the topic” [MeSH Terms] OR “study” AND [All Fields]). A search limit for articles published from mid-2020 was applied. The criteria for inclusion were published research articles reporting (1) the rate of prevalence of the long COVID-19 syndrome (at admission or following admission) in the general population and (2) the possible associated clinical parameters. Studies were excluded if they were case reports, review articles, conference abstracts, non-clinical studies, or were not available in the English language.

2.2. Data Extraction

The included studies were evaluated for the authors, the year of study in which it was conducted, title, where it was conducted, study design (prospective, retrospective, or
other), the age and sex of patients, number of patients, number of long COVID-19 patients and the time of diagnosis of long COVID-19 (on admission or following admission with mean/average time to diagnosis in months). A long COVID-19 case was defined as an illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection, usually within three months from the onset of COVID-19, with symptoms and effects that last for at least two months.

2.3. Outcome Measures

The primary objectives were to report the prevalence of long COVID-19 using the most recent data in the general population from mid-2020 and to estimate the average time to diagnosis. Secondary objectives included meta-regressing for any possible and predetermined covariates to ascertain any relationship with long COVID-19.

2.4. Quality Assessment

Using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [15], all included publications were reviewed independently for a potential risk of bias by two authors. The assessment tool used 14 questions to enable the allocation of a score to each article (poor, fair, or good). If there was disagreement regarding the scoring of a study, consensus was met after discussion among both assessors.

2.5. Statistical Analysis

A simple descriptive analysis was performed for the aims of the review. Heterogeneity among the studies was assessed using the chi-squared test and $I^2$; however, due to suspected variation among the studies and associated heterogeneity, the random effects model was used for all meta-analyses [16]. Publication bias was assessed using the Begg and Mazumdar Rank Correlation Test and Egger’s Test of the Intercept, and a precision funnel plot was used to ascertain the publication bias. To account for any possible heterogeneity ($I^2$), sub-group and sensitivity analyses were conducted, and some analyses used fixed-effect model analysis; further to this, meta-regression analysis was run for specific pre-determined covariates. For each outcome variable, 95% confidence intervals (CIs) were presented. A $p$-value < 0.05 was considered statistically significant. The meta-analysis and meta-regression were conducted using Review Manager 5.4 (Cochrane Collaboration, Oxford, UK) [17] and comprehensive meta-analysis version 4 (CMA v4).

3. Results

There were 2197 articles identified in the initial search of databases and reference lists (Figure 1). After the initial screening of titles and abstracts, 197 articles met the inclusion criteria for review. On full-text screening, the number was reduced to 57 studies. Further, 14 studies without clinical outcomes were eliminated. A list of the 43 studies [1,4,18–61] that met the inclusion criteria are provided in Table 1.

Table 1. Summary of the studies used in the analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Study Design</th>
<th>Study Setting</th>
<th>Average Time of Diagnosis (Months)</th>
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3.1. Prevalence of Long COVID-19 Sequelae in General Population

A total of 43 studies \([1,4,18–61]\) \((n = 367,236)\) reported event rates of long COVID-19 sequelae \((n = 183,064)\) in the general population. The prevalence of long COVID-19 ranged from 1.6% to 82%, with a mean of 42.5% \((95\% \text{ CI} \ 36\% \text{ to } 49.3\%)\) \([\text{heterogeneity: } \tau^2 = 0.81; \chi^2 = 24,108.789, \text{df} = 42 \ (p = 0.030); I^2 = 100\%]\) (Figure 2).

The prediction interval demonstrates that the true effects size in 95% of all the comparable populations fell between 0.10 and 0.823, demonstrating that, in some populations, the event rates of long COVID-19 are at one extreme as low as 10% and as high as 82% while the funnel plot of standard error and Egger’s regression intercept test indicated a possible publication bias \((\text{intercept} = -7.13010, 95\% \text{ CI} \ -15.04711, 0.78691), \text{with } t = 1.81881, \text{df} = 41 \text{ and 1-tailed } p = 0.038\) (Figures 3 and 4).

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram for the studies identified and included in the review.
**Figure 2.** A forest plot of the forty-three (43) studies on the prevalence of long COVID-19 sequelae in the general population.

**Figure 3.** The prediction interval demonstrating the true effects size in 95% of all the comparable populations.

**Meta Analysis**

The mean effect size is 0.42 with a 95% confidence interval of 0.36 to 0.49. The true effect size in 95% of all comparable populations falls in the interval 0.10 to 0.82.

**Figure 4.** A funnel plot of standard errors for publication bias assessment.

Sensitivity analysis was performed to explore the impact of excluding or including studies based on the sample size, methodological quality, and variance on the heterogeneity obtained ($I^2 = 100\%$). This, by weight allocation for each study using the scale relative to the maximum, demonstrated that all studies contributed between 2% and 3% of the mean event rate and heterogeneity. To further the robustness of this finding, sensitivity analysis was conducted by removing one study with the highest event rate (82%) [20]; the new mean event rate was 41.4% (95% CI 34.9%, 44.8%), which was a non-significant difference from the original 42.5%. This showed that the mean long COVID-19 event rate estimation was reliable as all the studies depicted a significant $p$-value (Figure 5).
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3.2. Average Time to and Association with Long COVID-19

Of the 43 studies, thirty-five (35) [1,4,22,24–28,30,31,33,34,36–44,46,47,49–51,53–58,60–65] received data for the times at which either a symptom of long COVID-19 was feasible or long COVID-19 was diagnosed, or some clinical parameters were used to ascertain a case of long COVID-19, while eight (8) [18,20,21,23,32,35,45,59] did not have any estimated time to long COVID-19 diagnosis. Using the fixed effect model, the long COVID-19 event rates’ range following sub-group analysis was between 25\% (lowest) at four months in four studies [24,26,43,46] and 66\% (highest) at two months in two studies [50,61]. Generally, using the point estimates with a fixed effect model, the event rates of long COVID-19 were at an average of one month, 44.6\% [31,41], two months, 66\% [50,61], three months, 54.3\% [25,36,37,39,40,49,53,56,58], four months, 25\% [24,26,43,46], five months, 26\% [22,47,54,55], six months, 56.5\% [1,4,27,28,33,57], seven months, 45.1\% [34,60], nine months, 36.3\% [30,44], eleven months, 49.3\% [62] and twelve months, 57.9\% [38,42,51]. It was evident that, majorly, COVID-19 patients developed signs and symptoms of long COVID-19 from three months, as shown by nine studies (at 54.3\%, p = 0.0000) [25,36,37,39,40,49,53,56,58], to six months, as shown by four studies (at 57\%, p = 0.000) [4,27,33,57]; furthermore, up to 12 months, as shown by three studies [38,42,51], long COVID-19 tended to increase up to (57.9\%, p = 0.0148). At an average of two months, however, which was the highest event rate (66\%) in two studies [50,61], there was no significant association with long COVID-19 diagnosis (p = 0.08).
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3.3. Sub-Group and Meta-Regression Analysis

To account for the substantial heterogeneity, it was deemed applicable to better understand whether and which study-level factors drove the measures of effect. A meta-regression analysis was conducted on the prevalence of long COVID-19 in the general population and the average time to long COVID-19 diagnosis.

For the prevalence of long COVID-19 in the general population, seventeen studies [4,21,24–27,30,32,38,41–45,54,58,59], with each detailing a specific leading comorbidity, were used for the analysis to determine their association with long COVID-19 event rates. For this meta-regression collectively, the comorbidities contributed to 14% of the long COVID-19 event rates however, insignificantly (Q = 7.05, df = 8, p = 0.5313) ($R^2 = 0.14$) (Supplementary File S1).

Sub-group analysis on specific comorbidities showed cardiovascular disorder (hypertension) as a strong predictor of long COVID-19 syndrome, contrary to the other conditions.
The 14% proportion depicted as contributing to the comorbidities was majorly a patient who had cardiovascular disease (CVD), more so hypertension, which demonstrated a stand-alone event rate of 32% in the random effects model (0.322 (95% CI 0.166, 0.532) (p = 0.000); \( I^2 = 99\% \)). The chronic obstructive pulmonary disorder and abnormal basal metabolic index had higher event rates (59.8% and 55.9%); however, they were not significantly associated with long COVID-19 (p > 0.05).

Hospital re-admission, on the other hand, contributed to 17% of the long COVID-19 syndrome through meta-regression (\( R^2 \) analog = 0.17) and was significantly associated (Q = 8.70, df = 1, p = 0.0032) (Supplementary File S2). The study design used in a specific study showed that the coefficient for the retrospective study design (Y) was −0.6815, with a 95% confidence interval of −2.5795 to 1.2165. Studies that used this design had a mean effect size of 0.6815 points lower than studies that did not use this design, demonstrating that retrospective study design was probably associated with a smaller effect size on long COVID-19 syndrome. However, there was a significant relationship between the study design and long COVID-19 syndrome (Q = 14.32, df = 3, p = 0.0025) (\( R^2 = 0.26 \)) (Supplementary File S3). The study setting (single-site or multi-site) did not have any effect on long-COVID-19 subject to the year a study was conducted.

Collectively, the combined impact of all covariates in the model was able to explain at least some of the variance in effect size contributing to 53% of the long COVID-19 syndrome (Q = 38.81, df = 19, p = 0.0047) (\( R^2 \) analog = 0.53) (Supplementary File S4).

4. Discussion

This review, meta-analysis, and meta-regression demonstrated the prevalence of long COVID-19 in the general population to be 42.5%, ranging between 1.6% and 82%, and these comorbidities contributed to 14% of the long COVID-19 event rates specifically, including a cardiovascular disorder (hypertension which had a stand-alone event rate of 32%). Chronic obstructive pulmonary disorder and the abnormal basal metabolic index had higher event rates (59.8% and 55.9%); however, they were not significantly associated with long COVID-19. Seventeen percent (17%) of long COVID-19 cases were found to be due to hospital re-admission. Furthermore, there was a significant relationship between the study design and long COVID-19 syndrome, while the study setting and the year the study was conducted did not have any effect on long COVID-19 syndrome. Generally, other covariates related to either methodological or clinical characteristics were able to explain at least some of the variance in effect size contributing to 53% of the long COVID-19 syndrome.

The reported prevalence (42.5%) of long COVID-19 in the current review after index infection with COVID-19 was similar to the findings by a study that looked at global estimated pooled long COVID-19 prevalence derived from the estimates presented in 29 studies as 43% [66]. Primary studies also showed 44.2% prevalence and reported persistent symptoms post primary infection with COVID-19 disease [67]; as seen in yet another study, 49.2% had three or more symptoms of COVID-19 post primary infection [68], and 41% had long COVID-19 with symptoms persisting for more than four weeks [69]. Furthermore, another study established that 36.55% of long COVID-19 occurred between 3 and 6 months, and 57.00% had one or more long-COVID-19 features recorded during the whole 6-month period [57]. Similarly or close to the current findings in this study, another study [70] established that, among 127 patients who had recovered from COVID-19, 52.0% had persistent symptoms, while those with mild COVID-19 were recorded at 49.5%. Again, conforming within the range of post-acute-COVID-19 syndrome in this study (1.6% to 82%), another study established the prevalence of post-COVID-19 to be 72.6% and 46.2% for hospitalized and non-hospitalized patients, respectively [71].

For comorbidities commensurate with this current finding, cardiovascular disease (CVD) emerged as a risk factor for long COVID-19 syndrome, which can affect up to 54% of patients who recover from acute infection [72], which was substantiated further by findings that the presence of certain chronic condition is linked with long COVID-19 [73]. On the other hand, as found in this study at an event rate of 60%, chronic obstructive pulmonary
disorder, though not significantly associated with long COVID-19, was found to be among the comorbidities associated with long COVID-19 presenting with chronic fatigue (1.68, 1.21 to 2.32) [74], and again regarding chronic obstructive pulmonary disorder and the abnormal basal metabolic index, a study established that a high BMI and previous pulmonary disease could be risk factors for long COVID-19 [75]. Furthermore, based on the basal metabolic index, a study concluded that long COVID is more likely to occur in people with a higher body mass index (BMI) [76]. As in this study, subject to comorbidities collectively predicting long COVID-19 at 14%, another study established the overall severity of comorbidities as one the strongest risk factors for long COVID-19 [71].

The finding that hospital re-admission contributes to over 17% of long COVID-19 cases, as per this study, was also shown through similar findings where patients (19.9%) who survived COVID-19 hospitalization were readmitted [77], and for another study, the readmission rate was 13.3% [78].

This study reports that COVID-19 patients develop signs and symptoms of long COVID-19 syndrome at three months (at 54.3%) to six months (at 57%), which tend to increase up to 12 months (at 57.9%). Similar or close to these findings, another study established that, at 3 months of follow-up, 66-7% of participants reported new or persistent COVID-19-related symptoms [49], and another reported that hospitalized and non-hospitalized patients with confirmed or suspected COVID-19 had multiple symptoms present about 3 months after symptom onset [79]. Forty-five percent (45%) of healthcare workers also reported persistent symptoms at three to four months [80]. As regards post-COVID-19 sequelae at six months (6 months), a previous study showed that long COVID-19 prevalence was 50% in adults at 6 months [81], close to the 54% in the current findings. At 12 months, long COVID-19 was reported as (50%) ≥ 1 COVID-19, close to 58%, as per the current findings of this study. This is further substantiated by the findings in a study, where persistent symptoms were highly prevalent, especially fatigue, shortness of breath, headache, brain fog/confusion, and altered taste/smell, which persisted beyond 1 year (12 months) among 56% of patients [82]. Contrary to the current findings though, some studies have reported a decreasing long COVID-19 trend from the sixth to the twelfth month [1,81].

A limitation of the current review was the defined inclusion criteria for a long COVID-19 patient presenting with either one or more suspected signs or symptoms depicting this syndrome. This may have resulted in diverse estimates of the prevalence of post-acute COVID-19 at different times of the event, which were also estimated on an average basis. However, the majority of studies in the current review included a clearly mentioned case of long COVID-19, either as persistent symptoms after primary infection with COVID-19 or a cluster of signs and symptoms post-recovery from index infection with COVID-19. Furthermore, this review focused only on long COVID-19. However, this was even insignificant as the authors intended to ascertain the prevalence and any association with the subject variable, plus a meta-regression was performed to ensure such differential aspects were taken care of.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/covid4070067/s1.


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Data Availability Statement: Data are available on request as this was a systematic review where key information may be retrieved from the included studies, which are already cited.

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