Post-acute Sequelae of COVID-19 Case Fatality Rate and its Associated Covariates: a Systematic Review, Meta-Analysis and Meta-Regression

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Introduction

Despite several studies describing the case-fatality rate (CFR) of the novel coronavirus disease-2019 (COVID-19) [1-4], there is dearth of information on CFR among those meeting the definition of post-acute sequelae of COVID-19 (PASC). Further, reports have indicated vaccination against COVID-19 disease would mitigate the long-term effects [5.6] including fatalities associated with PASC. Studies have attempted to estimate the CFR in PASC [7-10], but the information is sparse.

PASC occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms of PASC include fatigue, shortness of breath, and cognitive dysfunction among others. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time [11].

PASC is a syndrome characterized by the persistence of clinical symptoms beyond four weeks from the onset of acute symptoms. The Center for Disease Control (CDC) has formulated "post-COVI-19 conditions" to describe health issues that persist more than four weeks after being infected with COVID-19 [12]. Recent reports have described persistent symptoms extending beyond the period of initial illness or hospitalization. Anecdotes of different signs and symptoms occurring after acute infection have also arisen in the lay press [13]. Pulmonary, neuro-psychological, and cardiovascular complications are major findings in most epidemiological studies. However, dysfunctional gastrointestinal, endocrine, and metabolic health are recent findings for which underlying pathophysiological mechanisms are poorly understood [14].

The multisystem nature of PASC compared to previously studied post-acute sequelae of human coronaviruses has raised questions about how to recognize this condition most effectively [15]. Furthermore, regardless of whether they are unique, symptoms frequently reported by patients are not assessed consistently across studies [16]. Based on limited data from multiple studies, patients with PASC who required admission to the intensive care unit and/or ventilatory support were shown to be at increased risk of developing the syndrome [12].

People who have more severe COVID-19 are more likely to experience PASC, but severe acute disease is not a prerequisite. PASC has been found in people with only mild initial illness. The most common symptom is fatigue [17]. More than 6 million people have died from COVID-19 worldwide, including nearly 1 million in the USA [18]. But mortality is not the only adverse consequence of COVID-19. Many survivors of COVID-19 may develop PASC often calls long COVID [17], and presumed to be fatal [19].

People with a history of severe COVID-19 illness are at increased risk of PASC and possible associated death [20]. From January 1, 2020, through June 30, 2022, in United States of America alone, 3,544 COVID-19 deaths mentioned PASC in the death certificate, representing 0.3% of the 1,021,487 deaths

with COVID-19 coded to U07.1 (the ICD–10 code for COVID-19) as an underlying or contributing cause of death in the same time period as per the Vital Statistics Rapid Release.

The purpose of this review was to estimate the reported prevalence of PASC and its associated CFR. Further, it explored covariates that would influence the fatality.

Population and Methods

Search Strategy

A systematic search had been performed using the online databases of PubMed, Science Direct and Google Scholar searcher for relevant publications from June 1, 2020, to August 31, 2022. Advanced search strategy with the following combined text heading as ("long coronavirus" OR "long COVID-19" OR "long novel coronavirus" OR "post-acute SARS-CoV-2 syndrome" OR "2019-nCoV post-acute syndrome" OR "long COVID-19 syndrome") AND ("mortality" OR "death" OR "fatal outcome ") [MeSH Terms] had been used to search the target publications.

Study Eligibility Criteria

We included articles assessing the occurrence of fatalities among patients with PASC as the major outcome of interest. Articles that reported PASC defined by any form and number of presentations were included. Studies that didn't report the prevalence or fatality were excluded and the limitation was basically on all studies accounting for PASC rates and from those, the studies mentioning PASC related fatality, or the occurrence of deaths were used to estimate the CFR due to PASC. For this analysis purpose, studies with any observational study design were used including cross-sectional, case–control and case report study designs. Editorials, systematic review articles, letters to editors and short communication were excluded for this analysis. Studies that included extreme co-infection with other diseases were excluded due to heterogeneous results found among those groups for PASC. Only

articles published in English and only human based studies were included. Published peer reviewed articles including pre-prints were included in the analysis to capture the most recent data. Duplicate articles were found out and deleted.

The studies included had to meet the WHO case definition of PASC [11, 21]. Case fatality in the context of this review was the proportion of deaths among subjects meeting the case definition of PASC.

Data Extraction Process and Assessment of Source of Bias

Two reviewers independently screened full articles after an initial search by title and abstract for inclusion and exclusion criteria. Controversial matters were resolved after discussion. The extracted data included: confirmation of PASC patients, study design, time and place of data collections, author's name, year of publication, country, the total number of reported cases and the total number of fatality cases. The results of this analysis were presented based on the PRISMA checklist and flow diagram [22]. Newcastle–Ottawa technique was used for the assessment source of bias of the included studies [23]. Three major components were utilized to assess the quality of the included studies such as selection procedure of the study patients, assessment of confounding and exposure variables and the article's scoring 5 + points on a scale of 1-9 were considered as high-quality publications [24].

Statistical Analysis

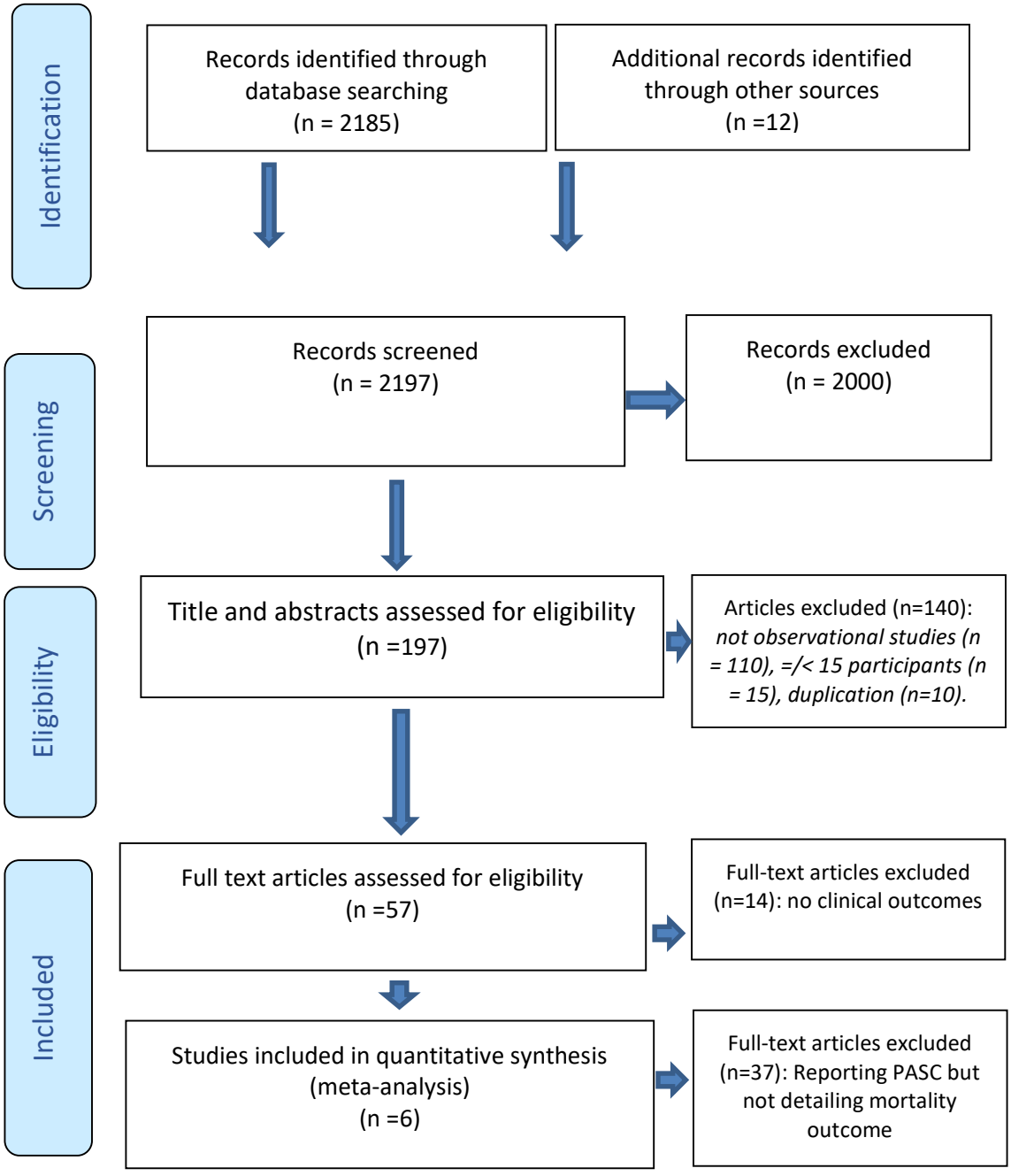
Simple descriptive analyses were performed for the aims of the review. Heterogeneity among the studies was assessed using the chi-squared test and heterogeneity (I^2), however due to suspected variation among the studies and associated heterogeneity random effects models were used for all meta-analyses [25]. PASC events rates were estimated using random-effects model, the estimation of the occurrence of deaths among patients with PASC was statistically assessed using random effects models (DerSimonian and Laird) [26], and event rates (ER) were presented. Publication bias was assessed using the Begg and Mazumdar Rank Correlation Test and the Egger's Test of the Intercept

and a precision funnel plot was used to ascertain this the publication bias status. To account for any possible heterogeneity, sub-group and sensitivity analysis were conducted and in this, some analysis used fixed-effect model analysis, further to these, meta-regression analysis was run for year of publication, hospital re-admission, the study design, the study setting and the region a study as pre-determined covariates. For each outcome variable, 95% confidence intervals (CIs) were presented. A *P*-value < 0.05 was considered statistically significant.

Results

There were 2,197 articles identified in the initial search of databases and reference lists. After initial screening of titles and abstracts 197 articles met the inclusion criteria for review. On full text screening, the number reduced to 57 studies. Further, 14 studies without clinical outcomes were eliminated as shown in Figure 1, which displays the PRISMA flow diagram.

Figure 1. PRISMA flow diagram showing studies identified and included in a systematic meta-analysis



The studies that met the inclusion criteria on PASC from where six studies detailing mortality outcome were retrieved are shown in the Table 1.

Table 1. Summary of the studies used in the analysis of the Prevalence and Case-Fatality of Post-Acute Sequelae of COVID-19, 2022

	Reference #	Continents	Type of Case Series	Study Setting	Average time to PASC diagnosis (months)
1.	27	Africa	Prospective	Single	2
2.	65	Europe	Prospective	Single	3
3.	28	Europe	Retrospective	Multicenter	5
4.	29	America	Prospective	Multicenter	2
5.	30	Europe	Prospective	Single	6
6.	31	Europe	Prospective	Multicenter	12
7.	32	Asia	Prospective	Single	6
8.	33	Europe	Prospective	Multicenter	12
9.	34	Africa	Prospective	Single	3
10.	35	Asia	Retrospective	Single	9
11.	36	Europe	Cross sectional	Single	11
12.	37	Asia	Retrospective	Single	-
13.	38*	America	Prospective	Single	4
14.	39*	Europe	Retrospective	Multicenter	6
15.	40	America	Retrospective	Multicenter	1
16.	41	Asia	Prospective	Multicenter	3
17.	42	Asia	Cross sectional	Multicenter	3
18.	43*	America	Retrospective	Single	-
19.	44	America	Prospective	Single	6
20.	66	America	Cross sectional	Single	-
21.	5*	Europe	Retrospective	Single	12
22.	45	Asia	Prospective	Single	-
23.	46	Europe	Prospective	Multicenter	7
24.	47	Europe	Prospective	Multicenter	3
25.	48	Europe	Prospective	Single	1
26.	49	Asia	Prospective	Single	-
27.	50	Africa	Retrospective	Single	5
28.	51	Africa	Retrospective	Single	5
29.	52	Asia	Prospective	Single	-
30.	53	Europe	Bidirectional	Single	6
31.	67	Europe	Cross sectional	Single	7
32.	54	America	Retrospective	Multicenter	5
33.	55	Europe	Prospective	Single	4
34.	64*	Europe	Retrospective	Multicenter	4
35.	68	Asia	Prospective	Single	3
36.	56*	Europe	Prospective	Multicenter	3
37.	57	America	Retrospective	Single	-
38.	58	America	Retrospective	Multicenter	6

39.	59	Asia	Cross sectional	Single	4
40.	60	Europe	Prospective	Single	3
41.	61	America	Prospective	Multicenter	-
42.	62	Europe	Prospective	Single	3
43.	63	Europe	Retrospective	Single	9

*Indicates the study provided detailed information on deaths due to PASC

Prevalence estimates of PASC and associated case-fatality rate in general population

The prevalence of PASC was 42.5% from total of 43 studies [5, 27-29, 31-68], (n = 367,236) [42.5% (95% CI 36.0% to 49.3%)] with a prediction interval of 10.5 % to 82.3 % [Heterogeneity: Tau^2 = 0.81; Chi^2 = 24108.789, df = 42 (*P* = 0.03); I^2= 100%] (Figure 1).

PASC case-fatality rate

From the 43 studies detailing PASC in general population, six studies [5. 23, 38-39, 43, 57] representing 61,977 cases of PASC on which detailed mortality was reported: the summary estimate was 7.4 % (95% CI 4.9%, 11.2%) [Heterogeneity: Tau^2 = 0.258; Chi^2 = 228.174, df = 5 (*P* < 0.001); I^2 = 97.8%]. Following sensitivity analysis with one study removed [28], it sustained the same CFR at 7.4% (Figure 2).

Figure 1. Pooled prevalence of PASC across 43 studies

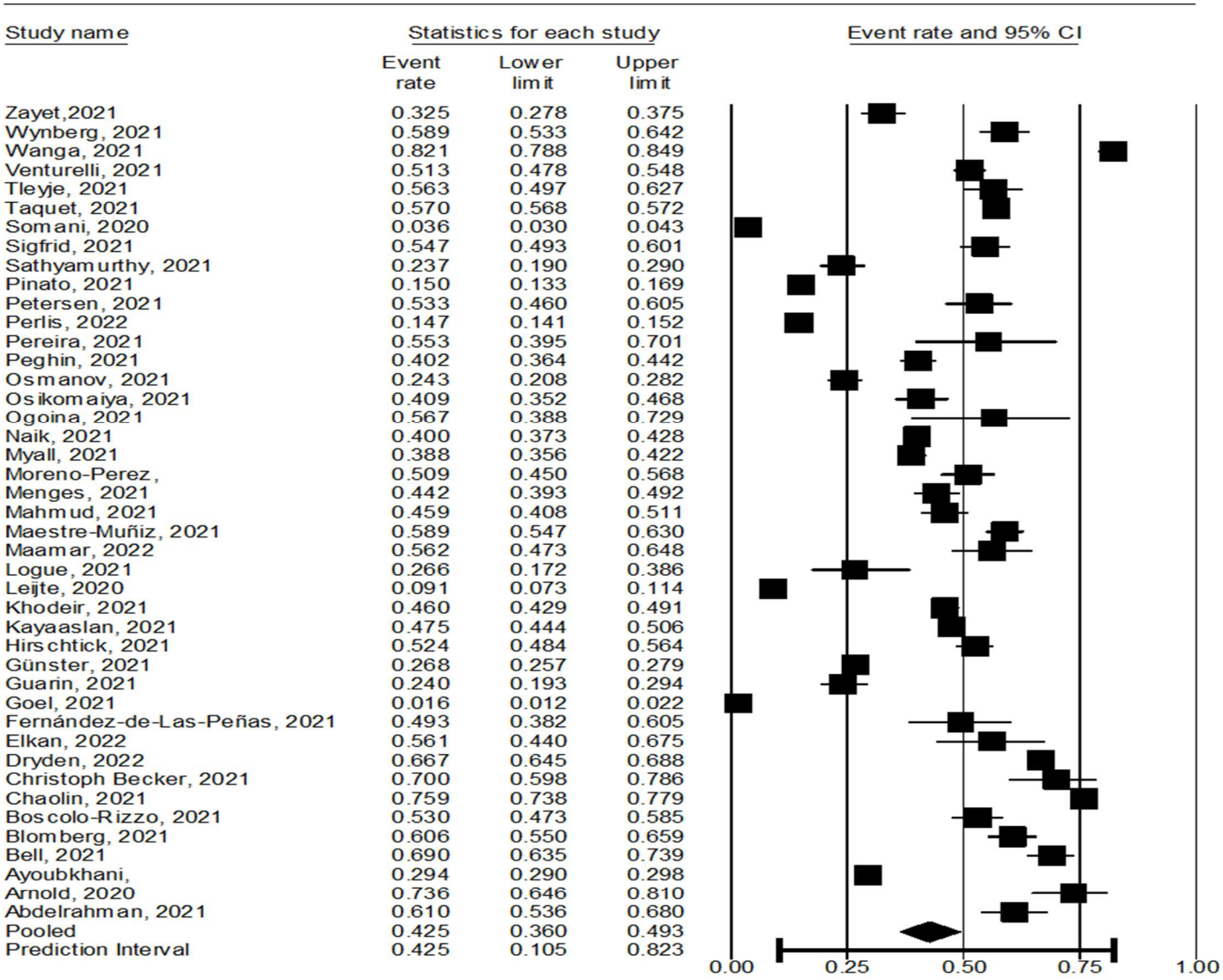
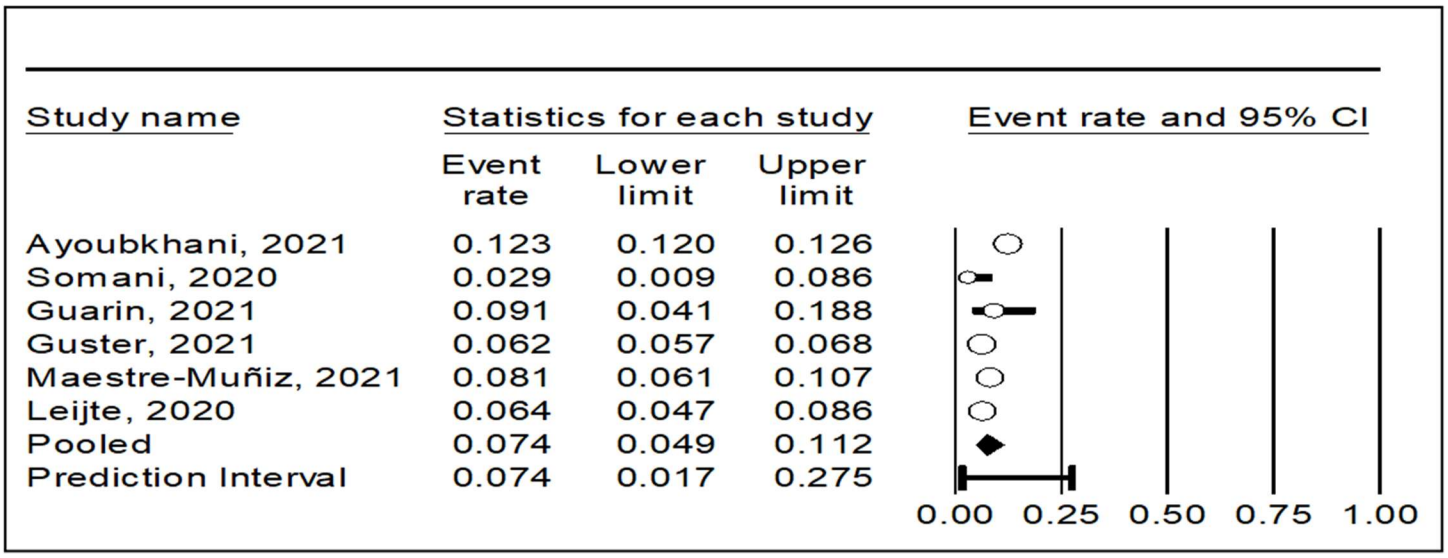


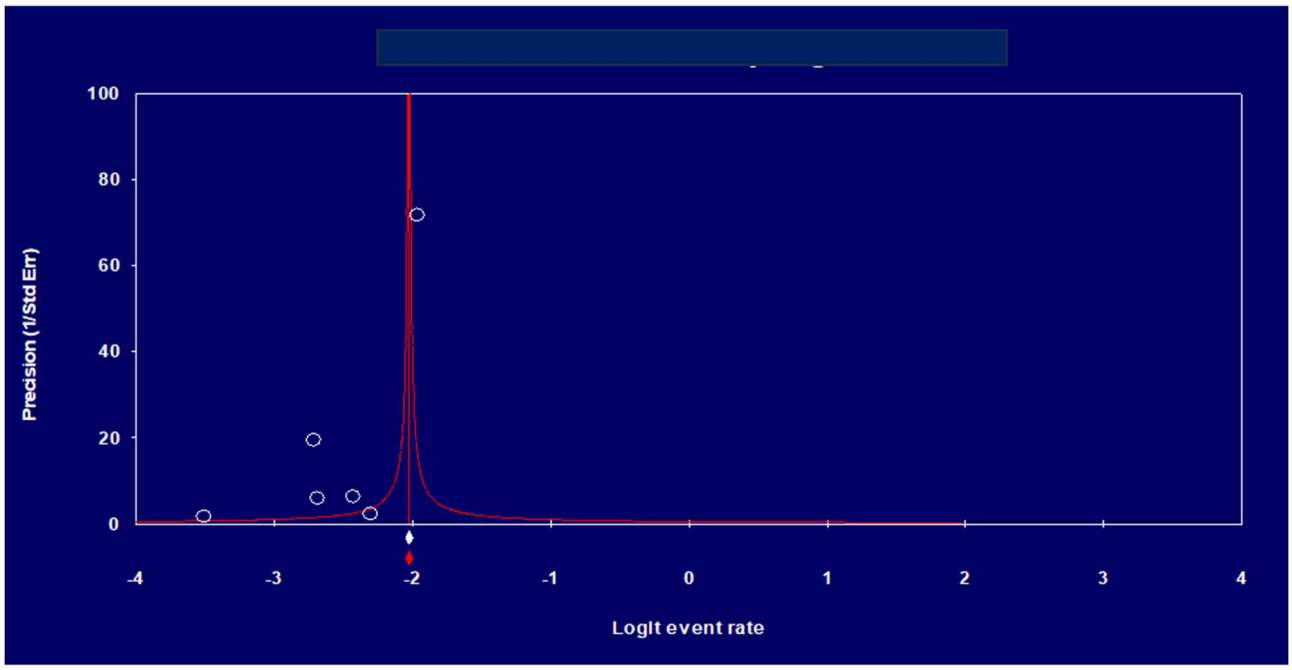
Figure 2. Post Acute Sequelae of COVID-19 Case Fatality in Six Studies 2020-2021



The prediction interval in 95% of all the study populations for the CFR due to PASC was at one extreme as low as 2.0% and as high as 28.0%.

The inspection of the precision plot shows a deficit of small studies (that is with a larger standard error, hence a lower reciprocal of it) on the right side of the plot (Figure 3). The Begg and Mazumdar Rank Correlation Test (Kendall's tau b = 0.0000, *P*-value = 0.5000) does not indicate the presence of publication bias, although the Egger's Test of the Intercept (Intercept = -4.78903, 95% confidence interval (-13.00383, 3.42577), with t=1.61860, df=4. *P*-value = 0.09 suggests some degree of asymmetry, hence evidence of publication bias.

Figure 3. Precision plot to assess publication bias of the six studies of fatality among post-acute sequelae of COVID cases



Meta-regression analysis

For the substantial heterogeneity, meta-regression analysis was conducted including the year a study was conducted, hospital re-admission, the study design, the study setting and the region a study was conducted as the data on covariates available, which would allow us to assess whether and which study-level factors drove these estimates. This meta-regression analysis featured as per the objectives of this meta-analysis on the CFR among PASC diagnosed patients. PASC related mortality was significantly and perfectly correlated with hospital re-admission following meta-regression analysis (Q = 8.58, df = 1, *P* = 0.003) (R^2 analog = 1.00). Further, studies conducted in the year 2021 as opposed to the year 2020 were significantly associated with PASC related CFR at 55.0 % (Q = 4.66, df = 1, *P* = 0.03) (R^2 analog = 0.55).

Discussion

This review, meta-analysis and meta-regression found that across studies, the prevalence of PASC was 42.5% (95% CI = 36.0 % to 49.3%) ranging between 1.6% (lowest) to 82.0% (highest) event rate of PASC in the 43 studies in this current study. Our pooled point estimate of the prevalence of PASC was similar to that of another meta-analysis (43.0% [95% CI: 39.0 %, 46.0%]) [69], while a primary study found demonstrate that the prevalence of long-COVID was 43.6% [70].

CFR from PASC was 7.4%, and although the range of variation (4.9% to 11.2%) might reflect differences in real proportions, our estimate was very consistent with findings relative to PASC CFR across different time-points during the 30 days, 90 days and one-year post-discharge, 7.9%, 7.3%, and 7.1% respectively. The 30-day hospital and further post discharge CFR was 7.9% [71]. This finding was, however, lower than that of one other single study which reported a CFR of 19.0% over 12 months [20].

PASC CFR correlated with hospital readmission. Most hospital readmissions fatalities seem to occur within 30 days after discharge [71], but this may be due to the limited follow-up, as studies with a longer follow-up have found that, COVID-19 patients were more likely to be readmitted or die due to their initial infection (adjusted hazard ratio of 1.4; 95% CI = 1.2 to 1.5, $P < 0.001$) [72-73]. Studies conducted in the year 2021 were strongly correlated with PASC fatality (i.e., explained variance of 55.0 %), which may just reflect a longer follow-up time, and a larger pool of infected persons, at least one year after the onset of infection [21].

A limitation of the current review was the definition of inclusion criteria for a PASC patient, presenting with either one or more suspected signs or symptoms depicting the syndrome, however, a WHO clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021 [11, 74], was used as a guide. Only six studies retrieved detailed PASC deaths and were the only available at the time of

this review. The selection process of the studies included in this review was narrowed to those which only had detailed mortality outcome relative to the PASC which prevented a broad inclusion of all the 43 studies detailing the PASC. Further, another limitation of the review consisted of restricting the studies to those published in English only. However, as at the time of the review, we were unaware of reports published in on other languages. There is some evidence of absence of small studies with estimates of CFR above 12% (i.e., right side of the funnel plot).

The implications for health policy from this study are significant even if the COVID-19 pandemic has ended: the large number of persons affected calls for a continued review of the clinical practice and management of PASC. Further, the study adds new knowledge on CFR due to PASC.

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