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Risk Factors Associated With Post–COVID-19 Condition
A Systematic Review and Meta-analysis

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IMPORTANCE Post–COVID-19 condition (PCC) is a complex heterogeneous disorder that has affected the lives of millions of people globally. Identification of potential risk factors to better understand who is at risk of developing PCC is important because it would allow for early and appropriate clinical support.

OBJECTIVE To evaluate the demographic characteristics and comorbidities that have been found to be associated with an increased risk of developing PCC.

DATA SOURCES Medline and Embase databases were systematically searched from inception to December 5, 2022.

STUDY SELECTION The meta-analysis included all published studies that investigated the risk factors and/or predictors of PCC in adult (≥18 years) patients.

DATA EXTRACTION AND SYNTHESIS Odds ratios (ORs) for each risk factor were pooled from the selected studies. For each potential risk factor, the random-effects model was used to compare the risk of developing PCC between individuals with and without the risk factor. Data analyses were performed from December 5, 2022, to February 10, 2023.

MAIN OUTCOMES AND MEASURES The risk factors for PCC included patient age; sex; body mass index, calculated as weight in kilograms divided by height in meters squared; smoking status; comorbidities, including anxiety and/or depression, asthma, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, immunosuppression, and ischemic heart disease; previous hospitalization or ICU (intensive care unit) admission with COVID-19; and previous vaccination against COVID-19.

RESULTS The initial search yielded 5334 records of which 255 articles underwent full-text evaluation, which identified 41 articles and a total of 860 783 patients that were included. The findings of the meta-analysis showed that female sex (OR, 1.56; 95% CI, 1.41-1.73), age (OR, 1.21; 95% CI, 1.11-1.33), high BMI (OR, 1.15; 95% CI, 1.08-1.23), and smoking (OR, 1.10; 95% CI, 1.07-1.13) were associated with an increased risk of developing PCC. In addition, the presence of comorbidities and previous hospitalization or ICU admission were found to be associated with high risk of PCC (OR, 2.48; 95% CI, 1.97-3.13 and OR, 2.37; 95% CI, 2.18-2.56, respectively). Patients who had been vaccinated against COVID-19 with 2 doses had a significantly lower risk of developing PCC compared with patients who were not vaccinated (OR, 0.57; 95% CI, 0.43-0.76).

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis demonstrated that certain demographic characteristics (eg, age and sex), comorbidities, and severe COVID-19 were associated with an increased risk of PCC, whereas vaccination had a protective role against developing PCC sequelae. These findings may enable a better understanding of who may develop PCC and provide additional evidence for the benefits of vaccination.

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Editor's Note

Supplemental content

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Since the first SARS-CoV-2 infections were identified in December 2019, the COVID-19 pandemic has significantly increased morbidity and mortality around the world.[1] Previous epidemics of viruses from the coronavirus family, such as SARS-CoV and the Middle East Respiratory Syndrome coronavirus (MERS-CoV), have developed into persistent symptoms in infected individuals, including severe fatigue, decreased quality of life (QOL), and shortness of breath, as well as behavioral and psychological problems.[1] These persistent postviral symptoms have been associated with a substantial burden to health care systems.

Similarly, a constellation of various clinical symptoms has been described in a subset of patients who have survived the acute phase of SARS-CoV-2–induced COVID-19.[1] This constellation of symptoms has received many labels, including *post-acute COVID-19 syndrome*, *persistent post-COVID-19 syndrome*, and *Long COVID-19*. These terms have been used interchangeably for several years. The UK National Institute for Health and Care Excellence proposed *Long COVID* to describe the presence of symptoms that persist for 4 or more weeks after acute COVID-19 infection.[2] The World Health Organization (WHO) defined *post–COVID-19 condition* (PCC) as having symptoms usually 3 months from the onset of COVID-19 with a duration of at least 2 months.[3] Typical clinical symptoms include dyspnea, fatigue, autonomic dysfunction, headache, and persistent loss of smell and/or taste—although a wide range of symptoms has been described.[1,4] Given that individuals with PCC may need long-term clinical support,[4] the economic consequences have been estimated to be substantial.[5]

Not only is it important to recognize which individuals may be at high risk of developing PCC and to offer follow-up care; it is imperative to plan population-level public health measures. Several studies have been published investigating clinical and epidemiologic risk factors and/or predictors of PCC.[5-8] However, these studies often had relatively few patients. Furthermore, wide discrepancy exists among published data, yielding uncertainty on the clinical utility of their findings. Therefore, the aim of this study was to search the available literature for published studies that found clinical and epidemiologic risk factors associated with the development of PCC and to pool their results.

Key Points

Question Which individuals are at risk of developing post–COVID-19 condition (PCC)?

Findings This systematic review and meta-analysis of 41 studies including 860 783 patients found that female sex, older age, higher body mass index, smoking, preexisting comorbidities, and previous hospitalization or ICU admission were risk factors significantly associated with developing PCC, and that SARS-CoV-2 vaccination with 2 doses was associated with lower risk of PCC.

Meanings The findings of this systematic review and meta-analysis provide a profile of the characteristics associated with increased risk of developing PCC and suggest that vaccination may be protective against PCC.

Methods

This study was exempt from ethics review because it used only previously published data; informed consent was also waived for this reason. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[9]

Search Strategy and Selection Criteria

MEDLINE and Embase databases were systematically searched for studies investigating the risk factors or clinical predictors for PCC in patients diagnosed with COVID-19, from inception to December 5, 2022. Search terms included "long-COVID-19," "post-COVID-19," and "chronic COVID-19," as well as the corresponding MeSH (Medical Subjects Heading) terms. Only peer-reviewed articles were included; preprints were excluded. The full search strategy is available in the eMethods in Supplement 1.

Data Extraction

Search results were imported for abstract screening; duplicates and irrelevant studies were removed based on predetermined inclusion and exclusion criteria. All studies that investigated the risk factors or predictors of PCC, as defined by the WHO definition (≥1 symptom for ≥3 months), in a cohort of adult (≥18 years) patients were included. The risk factors evaluated for this meta-analysis were: age; biological sex; body mass index (BMI), calculated as weight in kilograms divided by height in meters squared; smoking status; comorbidities including anxiety and/or depression, asthma, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes, immunosuppression, and ischemic heart disease (IHD); and COVID-19 vaccination status. Studies were excluded if they investigated persistent COVID-19 symptoms of less than 3 months duration; did not provide data for any of the risk factors listed; or used only univariate regression because we wanted to identify independent risk factor association.

Subsequently, full texts of studies were retrieved and scrutinized against the criteria. The relevant data from the included studies were independently extracted by 2 authors (H.E., V.T.) who were blinded to the authors and institutions involved. Any disagreements were resolved by discussion with the senior author (V.V.). Some cohorts were studied and/or published more than once, for example, neurological PCC and respiratory PCC were evaluated in the same cohort in some studies.[10-12] To avoid double-counting patients of these cohorts, we initially meta-analyzed all the PCC symptoms and produced a single odds ratio (OR) for the specific cohort; this OR was then used in the meta-analysis. The Newcastle-Ottawa Scale,[13] a 9-point measure assessing the quality of cohort studies and case-control studies or case series, was used to evaluate the observational studies included.

Statistical Analysis

Quantitative synthesis of included studies was performed using RStudio 2022.07.1 + 554 and R, version 4.0.5 (The R Foundation for Statistical Computing). The ORs for each risk factor

were pooled with the random-effects model. This was deemed more appropriate than the fixed-effects model because the studies included in this meta-analysis represented samples from different populations. For studies reporting rate ratios, those were converted to ORs using the methods defined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[14] Summary statistics were expressed as ORs and 95% CIs. Prediction intervals were also reported. Statistical heterogeneity was assessed using the I^2statistic. Publication bias was assessed qualitatively by visual inspection of inverted funnel plot asymmetry and Egger test was performed to assess small study effects. Statistical tests were 2-tailed, and the statistical significance threshold was $P < .05$. Data analyses were performed from December 5, 2022, to February 10, 2023.

Results

The search of MEDLINE and Embase databases yielded a total of 5334 records. After removal of duplicates, 3363 were screened at title and abstract level, and 255 studies underwent full-text evaluation. Of those, 41 records with a total of 860 783 patients met the inclusion criteria and were included in the meta-analysis. The PRISMA flowchart for study selection is available in eFigure 1 in Supplement 1. The **Table** summarizes the population cohorts and the study design characteristics of all the included studies.[10-12,15-61] Of the 41 observational studies, 30 were ranked as high quality and 11 moderate quality on the Newcastle-Ottawa Scale (eTable 1 in Supplement 1).

All previously identified risk factors for PCC were evaluated, including patient age, sex, BMI, smoking status, comorbidities (ie, anxiety/depression, asthma, CKD, COPD, diabetes, immunosuppression, IHD), and hospitalization or ICU admission for COVID-19. In addition, the role of vaccination as a risk factor for PCC was evaluated. Funnel plots for all the meta-analyses are shown in eFigure 2 in Supplement 1. Race and ethnicity were not evaluated as this information was not provided consistently across the included studies.

Patient Sex

Of the 41 studies, 38 studies including a total of 727 630 patients investigated sex as a risk factor for PCC. Overall, the pooled ORs showed that female sex was significantly associated with PCC (OR, 1.56; 95% CI, 1.41 to 1.73; I^2 = 94%; **Figure 1**). However, the 95% prediction interval (95% PI, 0.94 to 2.61) suggested that this may not be demonstrated in all future studies. To investigate this further, we undertook subgroup analysis separating the studies that included only hospitalized patients from those that included only nonhospitalized and those that included a mixture of hospitalized and nonhospitalized patients (eFigure 3 in Supplement 1). This showed that heterogeneity was lower in studies that included only hospitalized or only nonhospitalized patients compared with those that included patients from both settings (58%, 24%, and 97%, respectively), with the correlation remaining significant and the prediction intervals showing evidence supporting this significance for future studies. Subgroup analysis was also performed by study quality (high vs moderate) per the Newcastle-Ottawa Scale, with no significant between-group differences demonstrated (eFigure 4 in Supplement 1). Meta-regression analysis by study size showed no significance (effect size = 0.0001; 95% CI, −0.0001 to 0.0001; $P = .26$). Egger test for small study effects was not significant (intercept = 0.36, 95% CI, 0.21 to 0.50; $P = .15$).

Patient Age

Of the 41 studies, 9 studies including a total of 324 950 patients investigated age as a risk factor for PCC. For the meta-analysis, the risk of PCC among 3 age groups (40-69 years and ≥70 years vs 18-40 years) was analyzed. We found that patients in both of the older groups had a significantly higher risk of PCC when compared with adult patients younger than 40 years, with no significant between-group differences (OR, 1.21; 95% CI, 1.11 to 1.33; I^2 = 95%; **Figure 2**). However, this may not be demonstrated in all future studies (95% PI, 0.84-1.76). Subgroup analysis by study size demonstrated a high rate of heterogeneity in the group of large studies (eFigure 5 in Supplement 1). Meta-regression analysis by study size was significant (effect size = −0.0001; 95% CI, −0.0002 to −0.0001; $P = .02$) indicating that study size may have influenced the results (eFigure 6 in Supplement 1). Egger test for small study effects was not significant (intercept = 0.20; 95% CI, 0.06 to 0.50; $P = .34$). Subgroup analysis by study population (not hospitalized patients vs combined settings) showed no significant between-group differences (eFigure 7 in Supplement 1), whereas sensitivity analysis by study quality demonstrated that high quality studies have higher heterogeneity (eFigure 8 in Supplement 1).

Body Mass Index

Of 41 studies, 16 studies including a total of 701 807 patients investigated obesity (high BMI, defined as ≥30) as a risk factor for PCC. Obesity was found to be significantly associated with PCC (OR, 1.15; 95% CI, 1.08 to 1.23; I^2 = 91%; eFigure 9 in Supplement 1). However, this significant correlation may not be shown in all future studies (95% PI, 0.94 to 1.42). Subgroup analysis by study population (hospitalized vs nonhospitalized vs combined) showed that the correlation remained significant in all 3 subgroups; however, the studies of nonhospitalized patients had the lowest heterogeneity (eFigure 10 in Supplement 1). Subgroup analysis by study quality showed that the significant correlation between obesity and PCC was evident only in high quality studies (eFigure 11 in Supplement 1). Egger test was found to be significant (intercept = .06; 95% CI, −0.02 to 0.15; $P < .001$), suggesting publication bias as shown in the funnel plot (eFigure 2C in Supplement 1). Meta-regression analysis by study size was not significant (effect size = −0.0001; 95% CI −0.00001 to 0.0001; $P = .86$).

Smoking Status

Of the 41 studies, 20 studies including a total of 455 204 patients investigated whether current smokers had higher risk of developing PCC compared with nonsmokers. Overall, the pooled ORs showed that smoking was significantly associated with PCC (OR, 1.10; 95% CI, 1.07 to 1.13; I^2 = 0%; **Figure 3**).

Table. Characteristics of Included Studies of Risk Factors Associated With Post–COVID-19 Condition (PCC), 2021 to 2022

Source and study design	Population	COVID-19 test type	Aims/parameter	Follow-up	Main findings	Analysis methods
Abdelrahman et al[10]						
Prospective cohort study	172 Hospitalized and nonhospitalized patients	Positive SARS-CoV-2 test	Telephone interview	8-10 mo	Age was a risk factor for persistent symptoms	Multivariate logistic regression analysis to detect potential risk factors associated with persistence of symptoms
Aranda et al[15]						
Multicenter prospective cohort study	150 Hospitalized patients	RT-PCR-proven SARS-CoV-2 infection	Clinical assessment	12 mo	Female sex, COPD, smoking were independent risk factors for persistent dyspnea	Multivariate logistic models to identify factors associated with persistent dyspnea
Asadi-Pooya et al[16]						
Observational cohort study	2696 Hospitalized patients	RT-PCR-proven SARS-CoV-2 infection	Interview, questionnaire	≥3 mo Postacute illness	Female sex, respiratory problems at onset, ICU admission were significantly associated with PCC "brain fog"	Significant variables from univariate analyses entered into the logistic regression analysis model
Augustin et al[17]						
Longitudinal prospective analysis	958 Nonhospitalized patients with mild COVID-19	RT-PCR-proven SARS-CoV-2 infection	Persistent symptoms (anosmia, ageusia, fatigue, shortness of breath)	4 mo and 7 mo Postinfection	Sex not correlated with PCC risk. Lower baseline level of SARS-CoV-2 associated with higher risk of developing PCC. Anosmia and diarrhea in acute COVID-19 were independent predictors for PCC after 7 mo	Unadjusted and adjusted ORs with 95% CIs from logistic regression reported for various baseline clinical data and patient characteristics
Ayoubkhani et al[18]						
Cross-sectional study	3090 Nonhospitalized patients	RT-PCR-proven SARS-CoV-2 infection or positive swab test in national testing programs	PCC incidence by vaccination status, UK COVID-19 Infection Survey	≥12 wk Postinfection	Unvaccinated individuals had higher risk of developing PCC	Double-vaccinated and unvaccinated participants, 1:1 propensity score matched for single year of age, sex, ethnicity, country/region of residence, area deprivation quintile group, and preexisting health/disability status
Baruch et al[19]						
National cross-sectional survey	2665 Hospitalized and nonhospitalized patients	RT-PCR-proven SARS-CoV-2 infection	Online questionnaire	3-6 mo Postpositive test	Female sex, hospitalization, and initial symptoms were associated with higher odds of fatigue, shortness of breath, cough, anxiety, sadness, memory loss	Logistic regression. Age, sex, wave number, health care worker status, initial symptoms, and hospitalization for COVID-19 were used as covariates
Bellan et al[20]						
Prospective cohort study	238 Hospitalized patients	232 RT-PCR positive swab, 1 bronchoalveolar lavage positive, 5 SARS-CoV-2 antibodies, suggestive radiologic findings	Pulmonary function, physical performance, psychological symptoms tests	4 mo Posthospital discharge	No significant association between sex, age, diabetes, CAD, obesity, CKD, COPD, and functional impairment	Univariate analysis to identify associations with different end points. All associations with $P < .20$ were included in logistic regression model
Blomberg et al[21]						
Prospective cohort study	312 Hospitalized and nonhospitalized (home-isolated) patients	Positive SARS-CoV-2 antigen or antibody test	Collection of demographic and clinical data and blood samples	6 mo Postinfection	At 6 mo, 61% (189/312) of all patients had persistent symptoms independently associated with severity of initial illness, increased convalescent antibody titers, and preexisting chronic lung disease	Multivariable analysis was performed by binary logistic regression for dichotomous outcome variables. Negative binomial regression to analyze factors associated with numeric outcome variables
Chudzik et al[22]						
Retrospective observational study (STOP COVID registry)	2218 Hospitalized and nonhospitalized patients	Positive RT-PCR test and/or antigen test	Clinical assessment	3 mo Postinfection	Female sex, severe acute COVID-19 infection, dyspnea, chest pain were risk factors for developing PCC	Multivariate logistic regression models (explanatory variables were duration and number of symptoms, severity of COVID-19 infection, blood pressure, diarrhea, arthralgia, headache, leg pain, hearing dysfunction)

(continued)

Table. Characteristics of Included Studies of Risk Factors Associated With Post–COVID-19 Condition (PCC), 2021 to 2022 (continued)

Source and study design	Population	COVID-19 test type	Aims/parameter	Follow-up	Main findings	Analysis methods
Daitch et al[23]						
Multicenter prospective cohort study	2333 Hospitalized patients	Positive RT-PCR test	Clinic review, history, physical examination, spirometry	5 mo Postdisease onset (median)	Independent risk factors for PCC fatigue and dyspnea were female sex, obesity, and closer proximity to COVID-19 diagnosis	Multivariable analysis
Debski et al[24]						
Cross-sectional study	1487 Hospitalized and nonhospitalized patients	Positive RT-PCR test	Data collection/analysis from NHS digital databases	Persistent symptoms ≥12 wk	Female sex, BMI were risk factors significantly associated with PCC	Multivariable logistic regression analysis. Full model with all covariates was assessed. Backward variable selection used to identify most important variables
Dias et al[25]						
Prospective cohort study	1042 Hospitalized patients	Laboratory-confirmed COVID-19	Telephone interview	≥3 mo Posthospital discharge	Female sex, higher BMI, ICU admission, longer length of stay were independent predictors of PCC	Multivariable logistic model with all characteristics as predictors and PCC as the outcome
Emecen et al[26]						
Cross-sectional study	5610 Hospitalized and nonhospitalized patients	Positive RT-PCR test	Telephone interview	3 mo and 6 mo after the first positive test	Older age, female sex, low economic status, current smoking, vaccination status, underlying comorbidities, and hospitalization were associated with PCC	Multivariate generalized estimating equation regression model used to further evaluate the factors associated with reporting symptoms 1, 3, and 6 mo after diagnosis
Estrada-Codecido et al[27]						
Retrospective cohort study	206 Hospitalized and nonhospitalized patients	Laboratory-confirmed COVID-19	Email survey, clinical assessment, EHS	90 d Postinfection	Persistent symptoms were more common in older patients, those diagnosed in hospital, and those with initial constitutional and rheumatologic symptoms	Multivariable logistic regression with prespecified predictor variables (age, sex, cardiorespiratory comorbidity—asthma, CVD, or chronic lung disease) presence/absence of each symptom at baseline assessment, location (outpatient vs in-hospital), and hospital admission during illness
Fernández-de-Las-Peñas et al[28a]						
Multicenter cohort study	1950 Hospitalized patients	Positive RT-PCR test	Prevalence data and associated risk factors of PCC cough	1 y Posthospital discharge (mean, 11.2 mo)	No association between PCC cough and other PCC symptoms. Regression analysis did not reveal any clinical variable associated with the presence of PCC cough	Multivariate Poisson regression prediction and risk models to identify variables independently associated with presence of cough as a PCC symptom
Fernández-de-Las-Peñas et al[29a]						
Multicenter case-control study (2:1)	145 Patients with diabetes and 290 controls hospitalized with COVID-19 (age- and sex- matched)	Positive RT-PCR test	List of PCC symptoms systematically evaluated. HADS and PSQI to assess anxiety and depressive symptoms and sleep quality	7.2 mo Posthospital discharge (mean)	Diabetes was not a risk factor for PCC. Most prevalent symptoms were fatigue, dyspnea on exertion, and pain. No between-group differences in any PCC symptom observed	Multivariable conditional logistic regression models to identify the variables associated with the presence of diabetes
Fernández-de-Las-Peñas et al[30a]						
Multicenter case-control study (2:1)	88 Patients with obesity and 176 controls hospitalized with COVID-19 (age- and sex-matched)	Positive RT-PCR test	List of PCC symptoms was systematically evaluated. HADS and PSQI to assess anxiety and depressive symptoms and sleep quality	7.2 mo Posthospital discharge (mean)	Obesity was independently associated with a greater number of PCC symptoms and poor sleep quality	Multivariable conditional logistic regression models were applied to identify those variables independently associated with obesity
Fernández-de-Las-Peñas et al[31a]						

(continued)

Table. Characteristics of Included Studies of Risk Factors Associated With Post–COVID-19 Condition (PCC), 2021 to 2022 (continued)

Source and study design	Population	COVID-19 test type	Aims/parameter	Follow-up	Main findings	Analysis methods
Multicenter observational study	1142 Hospitalized patients	Positive RT-PCR test	List of PCC symptoms was systematically evaluated	7.0 mo Posthospital discharge (mean)	Female sex, number of days at hospital, previous comorbidities, and number of symptoms at hospital admission were associated with higher number of PCC symptoms. Fatigue, hair loss, and dyspnea were most prevalent symptoms	Multivariate Poisson regression prediction and risk models to identify clinical and hospitalization variables associated with number of PCC symptoms
Fernández-de-Las-Peñas et al[32a]						
Multicenter cohort study	1969 Hospitalized patients	Positive RT-PCR test	Assessed differences between COVID-19 –related symptoms and PCC symptoms between male and female COVID-19 survivors	8.4 mo Posthospital discharge (mean)	Female sex was a risk factor for development of some PCC symptoms—mood disorders, fatigue, dyspnea, pain, hair loss, ocular problems, depressive levels, worse sleep quality	Multivariate logistic regression analysis for PCC symptoms adjusted by all variables collected at hospital admission (age, height, weight, preexisting medical comorbidities, COVID-19 onset symptoms at hospital admission, ICU admission, hospital stay)
Fernández-de-Las-Peñas et al[33a]						
Multicenter cohort study	1969 Hospitalized patients	Positive RT-PCR test	List of PCC symptoms systematically evaluated	8.4 mo Posthospital discharge (mean)	Female sex, a greater number of symptoms at hospital admission, a greater number of preexisting comorbidities, and longer hospital stay were risk factors for developing more long-term PCC	Multivariate logistic regressions to analyze associations between clinical and hospitalization variables with the number of symptoms after COVID (dependent variable) using Python library stats model 0.11.1
Fernández-de-Las-Peñas et al[11a]						
Multicenter cohort study	1593 Hospitalized patients	Positive RT-PCR test	Prevalence of musculoskeletal post-COVID pain	8 mo and 13 mo Postdischarge	Female sex, previous history of pain symptoms, pain symptoms at onset, and days of hospital stay were factors associated with musculoskeletal pain 1 y after hospitalization	Multivariate logistic regression analysis
Ioannou et al[34]						
Retrospective cohort study	198 610 Hospitalized and nonhospitalized patients	Positive RT-PCR test	EHR data	≥3 mo Postacute infection	Factors significantly associated with documented PCC were older age, Black or American Indian/Alaska Native race, Hispanic ethnicity, geographic region, high CCI score, documented symptoms at the time of acute infection, and requiring hospitalization or mechanical ventilation. Fully vaccinated patients less likely to receive PCC care	Multivariable logistic regression with adjustment for age, sex, self-reported race, self-reported ethnicity, urban vs rural residence, CCI score, VA Integrated Service Network, time period of infection (categorized by pandemic waves), and number of primary care, mental health, and specialty care encounters in the 2 y before infection
Jones et al[35]						
Observational study	310 Hospitalized and nonhospitalized patients	Self- or clinician-diagnosed or test-confirmed COVID-19	Patient-reported online questionnaire	4 mo (data for ≥12 y used in meta-analysis)	PCC risk predictors were age ≥40 y, female sex, frailty, visit to emergency department, hospital admission for COVID-19 symptoms	Multivariable regression analyses (adjusted for demographic variables, hospital visit for COVID-19, frailty, comorbidities, COVID-19 status) to compare characteristics and symptoms in patients with PCC vs symptoms of shorter duration
Kisiel et al[36]						
Prospective longitudinal cohort studies	366 Nonhospitalized patients	Positive RT-PCR test	Questionnaire/survey	1 y Postpositive test result (51-54 wk)	Predictors of persistent symptoms were being born abroad, lower physical fitness vs peers before COVID-19, BMI >25, co-occurring hypertension and chronic pain, and having >7 COVID-19 symptoms at onset	Predictors of symptoms after 12 mo calculated with RRs and 95% CIs
Kostev et al[37]						
Retrospective cohort study	51 630 Nonhospitalized patients	Positive RT-PCR test or clinician diagnosed	EHR data	3-12 mo Postdiagnosis	Age >30 y and female sex were significantly associated with PCC	Multivariable logistic regression model (covariates included age, sex, and comorbidities)

(*continued*)

Table. Characteristics of Included Studies of Risk Factors Associated With Post–COVID-19 Condition (PCC), 2021 to 2022 (continued)

Source and study design	Population	COVID-19 test type	Aims/parameter	Follow-up	Main findings	Analysis methods
Menezes et al[38]						
Prospective observational study	108 Hospitalized and nonhospitalized patients	Positive RT-PCR test (105 patients), IgG antibody test (2 patients), CT (1 patient)	Clinical evaluation and self-administered questionnaire	12 wk	Simultaneous presence of ≥15 COVID-19 symptoms, age >45 y, and obesity associated with higher probability of severe COVID-19	Binary logistic regression analysis with stepwise variable filtering
Munblit et al[39]						
Longitudinal cohort study	2649 Hospitalized patients	Positive RT-PCR test or clinical diagnosis (when laboratory test negative, inconclusive, or unavailable)	Telephone interview/questionnaire	218 d Postdischarge (median)	Half of adults admitted to hospital with COVID-19 reported persistent symptoms 6-8 mo after discharge. Fatigue and respiratory symptoms were most common. Female sex associated with PCC	Multivariable logistic regression to investigate associations of demographic characteristics, comorbidities, and severity of acute phase COVID-19 with physical symptoms at follow-up
Pazukhina et al[40]						
Prospective cohort study	1013 Hospitalized patients—only adult cohort data were used in meta-analysis	Positive RT-PCR test	Telephone interviews	6 mo and 12 mo Posthospital discharge	Female sex and preexisting hypertension were risk factors of PCC	Multivariable logistic regression analysis. Selection of variables was: COVID-19 severity as exposure; PCC as outcome; comorbidities as covariates; sex and age as effect modifiers
Peghin et al[41]						
Bidirectional cohort study	599 Hospitalized and nonhospitalized patients	Positive RT-PCR test and IgG antibody test	Telephone interview/questionnaire	6 mo Postdisease onset	Female sex, a proportional increase in the number of symptoms at the onset of COVID-19 and ICU admission were all independent risk factors for PCC	Multivariable logistic regression performed. All clinically/microbiologically relevant variables or those significant at $P < .10$ in univariable analysis were included
Peters et al[42]						
Cross-sectional survey of employees in health or social facilities	1930 Hospitalized and nonhospitalized patients	Positive RT-PCR test and/or clinical diagnosis	Questionnaire	≥3 mo Duration of symptoms	Risk factors for persistent symptoms were older age, female sex, previous illness, many/severe symptoms during the acute phase, outpatient medical care	Binary logistic regression model used to identify risk factors for persistent symptoms, and ORs with associated 95% CIs were calculated
Petersen et al[43]						
Prospective longitudinal study	170 Nonhospitalized patients	Positive RT-PCR test	Telephone interview, clinical examination, questionnaire	3 mo	PCC was more common in people reporting daily medication use. Age, smoking status, BMI were not risk factors for PCC	Multivariable logistic regression analyses (adjusted for sex, groups, BMI categories, smoking status, self-reported daily medication use)
Righi et al[44]						
Prospective cohort study	465 Hospitalized and nonhospitalized patients	Positive RT-PCR test and clinical symptoms	Telephone interview	9 mo +/− 2 Postdisease onset	Patients with older age, ICU stay, or multiple symptoms at onset were more likely to have long-term symptoms	Multivariable Cox proportional hazards model
Silverberg et al[45]						
Observational study	390 Nonhospitalized patients	Anti-SARS-CoV-2 IgG antibody testing	Electronic survey	11 mo (median)	Female sex, severity of acute phase, higher anti-SARS-CoV-2 IgG levels associated with highest risk of having PCC	Multivariable models included all variables tested in bivariable models (age, sex, household size, household sick contacts), state of residence as potential confounders per theoretical differences in exposures and mitigation strategies
Štěpánek et al[46]						
Observational cohort study	305 Patient-health care workers	Positive RT-PCR test	Clinical assessment	≥12 wk Postonset of symptoms	Statistically significant predictors of PCC were female sex and increasing age	Logistic regression analysis with PCC symptoms as a dependent (response) variable was applied to explore relationships between symptoms and other variables
Subramanian et al[47]						

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Table. Characteristics of Included Studies of Risk Factors Associated With Post–COVID-19 Condition (PCC), 2021 to 2022 (continued)

Source and study design	Population	COVID-19 test type	Aims/parameter	Follow-up	Main findings	Analysis methods
Retrospective matched cohort study	486 149 Nonhospitalized patients	Positive COVID-19 test	UK-based primary care database	≥12 wk Postinfection	PCC risk factors were female sex, ethnic minority, socioeconomic deprivation, smoking, obesity, comorbidities and increased with increasing age	Cox proportional hazards model, adjusting for age, sex, ethnic group, socioeconomic status, index year, vaccination status, symptoms before COVID-19, and comorbidities
Thompson et al[48]						
Analyses of 10 UK established population-based longitudinal studies[49-57] and EHRs (OpenSAFELY data set of primary care)[b]	6907 Nonhospitalized patients from LS and 4189 from EHR (only LS data meta-analyzed)	Self-reported COVID-19 infection	COVID-19 questionnaire and analysis EHR data	≥12 wk	Older age, female sex, White race, poor prepandemic general/mental health, overweight/obesity, asthma associated with prolonged symptoms in both LS and EHR data; findings for other factors, inconclusive	Logistic regression analysis to assess if PCC was associated with each sociodemographic or prepandemic health characteristic. Confounders analysis adjusted for age (as categorical variable), sex, ethnicity
Tleyjeh et al[58]						
Prospective cohort study	222 Hospitalized patients	Positive RT-PCR test	Telephone interviews	122 d Postdischarge; 4 mo postacute infection (median)	Female sex, preexisting hypertension, and length of hospital stay were associated with increased risk of new or persistent symptoms	Multivariate Cox proportional hazards model to identify factors associated with persistence of symptoms at follow-up with time-dependent days since discharge
Whitaker et al[59]						
Cross-sectional survey	55 730 Hospitalized and nonhospitalized patients	Self-reported symptomatic COVID-19 infection	Data from rounds 3-5 (main analysis) and round 6 (replication of the REACT-2)	12 wk Postdiagnosis	Female sex, older age, obesity, smoking, vaping, hospitalization with COVID-19, deprivation, being a health care worker associated with higher probability PCC	Multivariate logistic regression model
Wu et al[60]						
Cross-sectional survey	308 Hospitalized and nonhospitalized patients	Positive laboratory test or diagnosed by clinician	Online survey	12 wk Postdiagnosis	PCC more likely in patients with obesity, hair loss, headache, sore throat during infection. No association with age, sex, race/ethnicity, education, smoking, comorbidities	Multivariate logistic regression model was used to identify sociodemographic and health-related risk factors associated with PCC
Zhang et al[61]						
Retrospective cohort study	2433 Hospitalized patients	Laboratory-confirmed COVID-19	Telephone interviews (questionnaire and COPD assessment test)	12 mo Posthospital discharge	Older age, female sex, severe disease associated with higher risks of fatigue. Older age, severe disease associated with higher risk of ≥3 symptoms	Univariate logistic regression analysis to identify potential risk factors with $P < .10$. Then used in stepwise selection process in multivariate logistic regression model
Zisis et al[12]						
Retrospective study	25 225 Patients	Positive RT-PCR test	Data collection/analysis from EHS	3 mo Postdiagnosis	COVID-19 vaccine protective against PCC symptoms, new onset of health conditions, and mortality	Propensity score matching (1:1) using greedy nearest-neighbor method used to balance 2 cohorts on age, sex, race, comorbidities

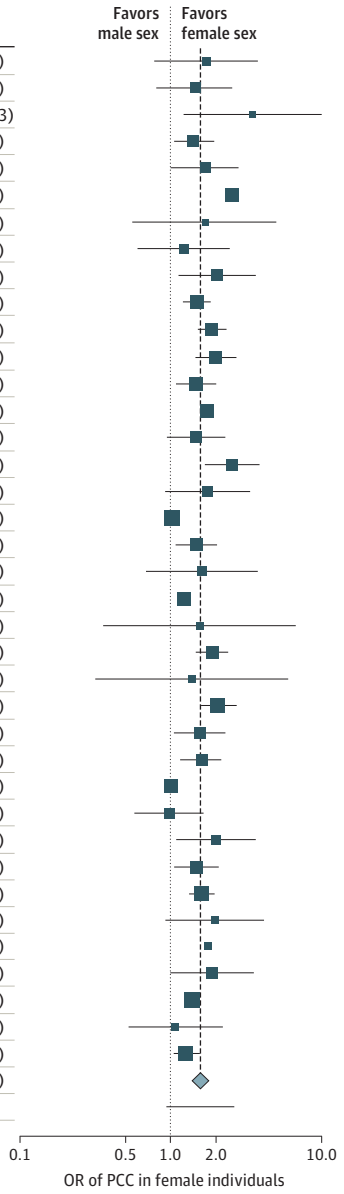
Abbreviations: BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; EHR, electronic health care records; HADS, Hospital Anxiety and Depression Scale; ICU, intensive care unit; LS, longitudinal studies; NHS, UK National Health Service; PSQI, Pittsburgh Sleep Quality Index; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Where more than 1 study by the same authors is mentioned, only 1 was included in the meta-analysis (each to the relevant subgroup meta-analysis).

[b] The data meta-analyzed was obtained solely from the study by Thompson et al,[48] which analyzed 10 longitudinal studies that included patients aged 18-96 years old: ALSPAC G0 (Avon Longitudinal Study of Parents and Children-Generation 0), ALSPAC G1 (Avon Longitudinal Study of Parents and Children-Generation 1), BCS70 (British Cohort Study 1970), GS (Generation Scotland: the Scottish Family Health Study), MCS (Millennium Cohort Study), NCDS (National Child Development Study), NS (Next Steps, formerly known as Longitudinal Study of Young People in England), USOC (Understanding Society: the UK Household Longitudinal Survey), TwinsUK (the UK Adult Twin Registry).

Figure 1. Association of Sex With Post–COVID-19 Condition (PCC), 2021 to 2022

Source	OR (95% CI)
Abdelrahman et al[10]	1.72 (0.78-3.79)
ALSPAC GO[50]	1.44 (0.80-2.60)
Aranda et al[15]	3.50 (1.21-10.13)
Asadi-Pooya et al[16]	1.42 (1.05-1.91)
Augustin et al[17]	1.69 (1.02-2.79)
Baruch et al[19]	2.50 (2.21-2.83)
BCS70[53]	1.67 (0.56-4.98)
Bellan et al[20]	1.22 (0.61-2.44)
Blomberg et al[21]	2.02 (1.12-3.66)
Chudzik et al[22]	1.48 (1.19-1.84)
Daitch et al[23]	1.87 (1.52-2.31)
Debski et al[24]	1.99 (1.47-2.70)
Dias et al[25]	1.49 (1.09-2.03)
Emecen et al[26]	1.74 (1.57-1.93)
Estrada-Codecido et al[27]	1.46 (0.94-2.27)
Fernandez-de-Las-Peñas et al[32]	2.54 (1.67-3.86)
GS[56]	1.73 (0.91-3.29)
Ioannou et al[34]	1.03 (0.99-1.08)
Jones et al[35]	1.47 (1.06-2.03)
Kisiel et al[36]	1.61 (0.70-3.73)
Kostev et al[37]	1.23 (1.15-1.32)
MCS[49]	1.55 (0.36-6.75)
Munblit et al[39]	1.88 (1.49-2.37)
NS[52]	1.37 (0.32-5.85)
Pazukhina et al[40]	2.04 (1.57-2.65)
Peghin et al[41]	1.55 (1.05-2.28)
Peters et al[42]	1.60 (1.18-2.17)
Petersen et al[43]	1.00 (0.98-1.02)
Righi et al[44]	0.97 (0.59-1.59)
Silverberg et al[45]	1.99 (1.09-3.63)
Štěpánek et al[46]	1.48 (1.06-2.07)
Subramanian et al[47]	1.61 (1.35-1.92)
Tleyjeh et al[58]	1.96 (0.92-4.17)
TwinsUK[57]	1.75 (0.73-4.20)
USOC[55]	1.89 (1.03-3.48)
Whitaker et al[59]	1.38 (1.32-1.45)
Wu et al[60]	1.08 (0.53-2.21)
Zhang et al[61]	1.27 (1.06-1.52)
Total (random effects)	1.56 (1.41-1.73)
Prediction interval	(0.94-2.61)
Heterogeneity: χ^2_{37} = 613.22 (P < .001); I^2 = 94%	



Female sex was shown to have a statistically significant association with high risk of developing PCC. The dotted line represents the point where there is no difference between the 2 groups; the dashed line represents the average effect of all studies when pooled together. Note that when >1 study by the same author(s) was identified, only 1 was included in the meta-analysis (in the relevant subgroup meta-analysis). Data for 10 longitudinal studies[49-57] of patients 18-96 years old were obtained solely from a single study by Thompson et al,[48] including ALSPAC GO, which refers to the Avon Longitudinal Study of Parents and Children-Generation O; GS, the Generation Scotland–the Scottish Family Health Study; MCS, Millennium Cohort Study; NS, Next Steps (formerly the Longitudinal Study of Young People in England); BCS70, the British Cohort Study 1970; NCDS, the National Child Development Study; TwinsUK, the UK Adult Twin Registry; and USOC, Understanding Society–the UK Household Longitudinal Survey. OR indicates odds ratio.

Subgroup analysis by study quality showed no significant differences (eFigure 12 in Supplement 1). Egger test suggested no significant publication bias (intercept = .08; 95% CI, 0.05 to 0.11; P = .07), and meta-regression analysis by study size also showed no significance (effect size = −0.0001; 95% CI, −0.0001 to 0.001; P = .14).

Comorbidities

Meta-analysis was performed for 34 studies that investigated the presence of comorbidities potentially associated with the risk of PCC syndrome. Specifics for each comorbidity follow.

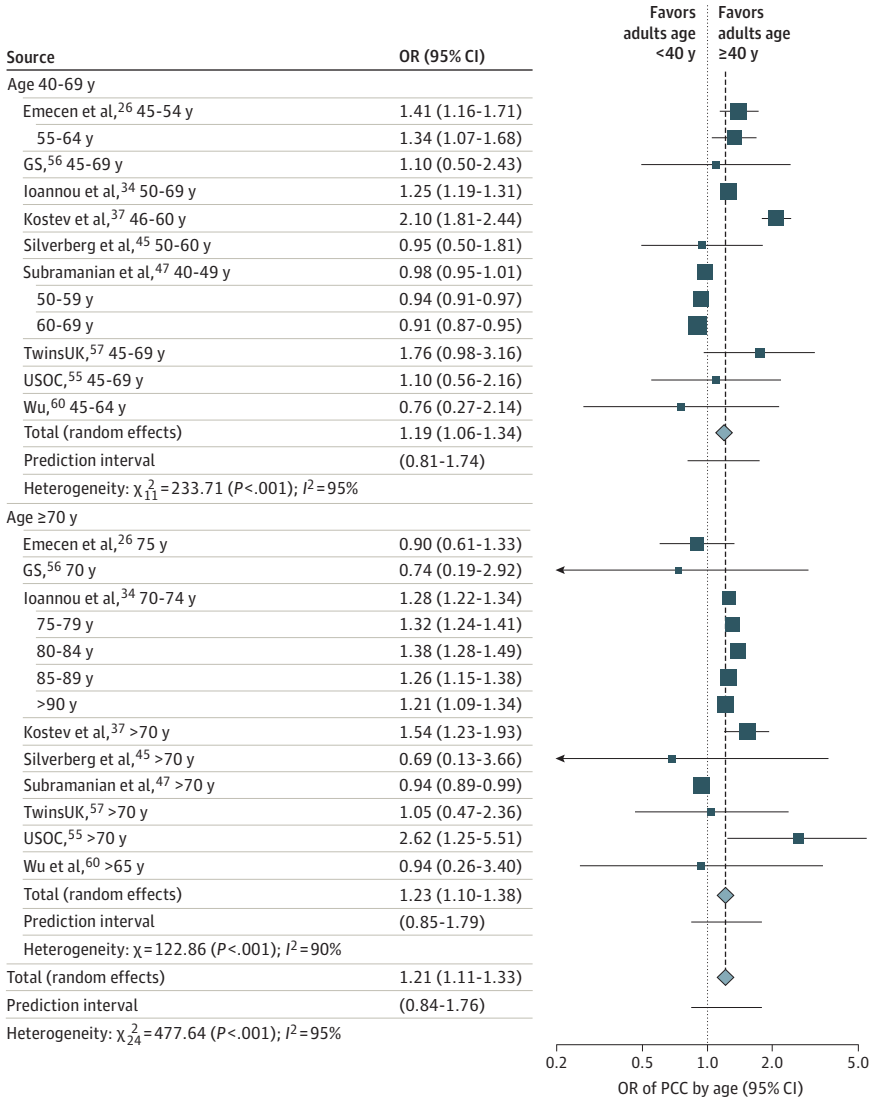
Anxiety and/or Depression

Four studies including 634 734 patients investigated the risk of PCC in patients with anxiety and/or depression. Pooled analysis of these studies showed a significant association with PCC (OR, 1.19; 95% CI, 1.02 to 1.40; I^2 = 96%; eFigure 24 in Supplement 1). Egger test for small study effects was not significant (intercept = 0.22; 95% CI, 0.03 to 0.41; P = .47). Meta-regression analysis for study size was not performed owing to the small number of studies in each group. Subgroup analysis by study quality is shown in eFigure 25 in Supplement 1.

Asthma

Meta-analysis of 13 studies including 639 397 patients showed that patients with asthma had significantly higher risk of developing PCC (OR, 1.24; 95% CI, 1.15 to 1.35; I^2 = 53%; eFigure 13 in Supplement 1). All of these studies were of high quality; therefore, subgroup analysis for this factor was not conducted. Meta-regression analysis for study size showed sig-

Figure 2. Association of Age With Post–COVID-19 Condition (PCC), 2021 to 2022



Older individuals (40-69 and ≥70 y) had a significantly higher risk of ongoing persistent PCC symptoms compared with adults <40 years old. The dotted line represents the point of no difference between the 2 groups, and the dashed line represents the average effect of all studies when pooled together. Data for 10 longitudinal studies[49-57] of patients 18-96 years old were obtained solely from a single study by Thompson et al,[48] including GS, which refers to the Generation Scotland–the Scottish Family Health Study; TwinsUK, the UK adult Twin Registry; and USOC, the Understanding Society–the UK Household Longitudinal Survey. OR indicates odds ratio.

nificance (effect size = −0.0001; 95% CI, −0.0003 to −0.0001; P < .001), which was confirmed by subgroup analysis of studies by their sample size (eFigure 14 in Supplement 1). In this analysis, larger studies demonstrated a significant association between asthma and PCC, whereas smaller studies (<1000 patients) failed to reach significance. Egger test showed no significant publication bias (intercept = 0.23; 95% CI, 0.13 to 0.34; P = .51).

Chronic Kidney Disease

A pooled analysis of 8 studies with a total of 255 791 patients showed that CKD was not a significant risk factor for PCC (OR, 1.12; 95% CI, 0.98 to 1.28; I^2 = 22%; eFigure 19 in Supplement 1). Subgroup analysis by study quality is shown in eFigure 20 in Supplement 1. Meta-regression analysis for study size showed no significance (effect size = 0.10; 95% CI, −0.05 to 0.25; P = .20), and Egger test showed no publication bias (intercept = 0.04; 95% CI, −0.21 to 0.29; P = .56).

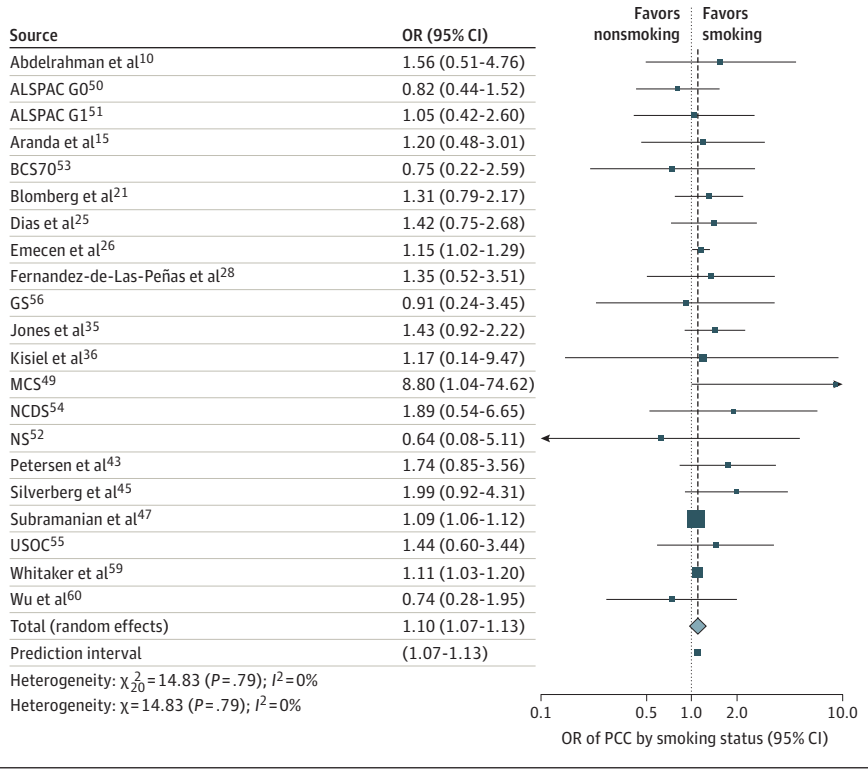
Chronic Obstructive Pulmonary Disease

Analysis of 10 studies including 257 340 patients showed that COPD was a risk factor associated with persistent symptoms after COVID-19 infection (OR, 1.38; 95% CI, 1.08 to 1.78; I^2 = 77%; eFigure 15 in Supplement 1). Nevertheless, this significance may not be shown in all future studies (95% PI, 0.70 to 2.74). Subgroup analyses by study quality is shown in eFigure 16 in Supplement 1. Meta-regression analysis for study size and Egger test were both nonsignificant (effect size = −0.0002; 95% CI, −0.0003 to 0.0001; P = .66; and intercept = 0.23; 95% CI, 0.14 to 0.33; P = .69, respectively).

Diabetes

Meta-analysis of 18 studies including 259 978 patients showed that patients with diabetes (OR, 1.06; 95% CI, 1.03 to 1.09; I^2 = 0%) had a significant risk of PCC (eFigure 17 in Supplement 1). Subgroup analysis by study quality is shown in eFigure 18 in Supplement 1. Meta-regression analysis showed that

Figure 3. Association of Smoking Status With Post–COVID-19 Condition (PCC), 2021 to 2022



Individuals who smoked had 1.10 times higher risk of developing PCC compared with individuals who did not smoke. The dotted line represents the point of no difference between the 2 groups, and the dashed line represents the average effect of all studies when pooled together. Data for 10 longitudinal studies[49-57] of patients 18-96 years old were obtained solely from a single study by Thompson et al,[48] including ALSPAC G0, which refers to the Avon Longitudinal Study of Parents and Children-Generation 0; ALSPAC G1, the Avon Longitudinal Study of Parents and Children-Generation 1; BCS70, British Cohort Study 1970; GS, Generation Scotland–the Scottish Family Health Study; MCS, the Millennium Cohort Study; NS, Next Steps (formerly the Longitudinal Study of Young People in England); NCDS, the National Child Development Study; and USOC, Understanding Society–the UK Household Longitudinal Survey. OR indicates odds ratio.

study size did not have a significant effect (effect size = 0.001; 95% CI, −0.0002 to 0.0002; *P* = .15), and Egger test showed no publication bias (intercept = −0.008; 95% CI, −0.14 to 0.12; *P* = .34).

Immunosuppression

Three studies with a total of 967 patients evaluated whether patients with immunosuppression exhibited higher risk of PCC. Meta-analysis of these studies showed a significant association of immunosuppression with PCC (OR, 1.50; 95% CI, 1.05-2.15; I^2 = 0%; eFigure 23 in Supplement 1). Egger test did not show significant publication bias. Owing to the small number of studies, subgroup analysis and meta-regression were not performed for these studies.

Ischemic Heart Disease

Five studies including 201 906 patients investigated the association of preexisting IHD. Meta-analysis of these studies showed that patients with IHD had 1.28 times higher risk of developing PCC (OR, 1.28; 95% CI, 1.19 to 1.38; I^2 = 0%; eFigure 21 in Supplement 1). Subgroup analysis by study quality is shown in eFigure 22 in Supplement 1. Meta-regression analysis for study size and Egger test for small study effects did not show significance (effect size = −0.0001; 95% CI, −0.0003 to 0.001; *P* = .49, and intercept = 0.23; 95% CI, 0.14 to 0.33; *P* = .69, respectively).

Hospitalization and ICU Admission

Meta-analysis of 8 studies with a total of 265 466 patients previously hospitalized for COVID-19 infection was performed. The findings showed that patients who required hospitalization during the acute phase of COVID-19 had significantly higher risk of developing PCC (OR, 2.48; 95% CI, 1.97 to 3.13; I^2 = 86%; eFigure 26 in Supplement 1). Subgroup analysis by study quality is shown in eFigure 27 in Supplement 1. Meta-regression analysis for study size and Egger test did not demonstrate statistical significance (effect size = 0.002; 95% CI, −0.001 to 0.0001; *P* = .73 and intercept = 0.96; 95% CI, 0.47 to 1.43; *P* = .78, respectively).

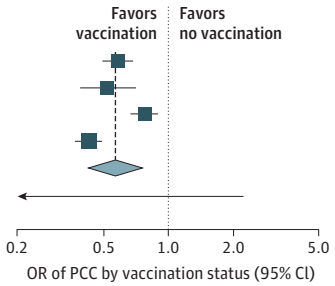
Similarly, a meta-analysis of 10 studies with a total of 213 441 patients showed that patients who required ICU admission during the acute phase were at higher risk for PCC (OR, 2.37; 95% CI, 2.18 to 2.56; I^2 = 0%; eFigure 28 in Supplement 1). Subgroup analysis by study quality is shown in eFigure 29 in Supplement 1. Meta-regression analysis for study size showed that there was an effect (effect size = 0.0001; 95% CI, 0.0001 to 0.002; *P* = .01); however, subgroup analysis of studies by sample size did not demonstrate significant between-group differences (eFigure 30 in Supplement 1). Egger test showed no significance (intercept = 0.92; 95% CI, 0.82 to 1.02; *P* = .06).

Vaccination Status

Four studies with a total of 249 788 patients evaluated the effect of vaccination status on the risk of developing PCC. Meta-analysis of these showed that individuals who had been vaccinated with 2 doses (in all included studies) had a 40% lower risk of developing PCC (OR, 0.57; 95% CI, 0.43 to 0.76; I^2 = 91%; **Figure 4**). This may not be demonstrated in all future studies (95% PI, 0.15 to 2.22). Subgroup analysis by study quality and

Figure 4. Association of Vaccination Status With Post–COVID-19 Condition (PCC), 2021 to 2022

Source	OR (95% CI)
Ayoubkhani et al[18]	0.59 (0.50-0.69)
Emecen et al[26]	0.53 (0.40-0.71)
Ioannou et al[34]	0.78 (0.68-0.90)
Zisis et al[12]	0.43 (0.37-0.49)
Total (random effects)	0.57 (0.43-0.76)
Prediction interval	(0.15-2.22)
Heterogeneity: $\chi^2_3 = 35.00$ ($P < .001$); $I^2 = 91\%$	



Individuals who were vaccinated against COVID-19 with 2 doses had a significantly lower risk of developing PCC than individuals who had not been vaccinated. The dotted line represents the point of no difference between the 2 groups, and the dashed line represents the average effect of all studies when pooled together. OR indicates odds ratio.

meta-regression for study size were not performed because all these studies were of high quality and included more than 1000 patients each. Egger test showed no significant publication bias (intercept = −0.44; 95% CI, −1.38 to 0.48; P = .80).

Sensitivity Analyses

One original publication[48] of 10 longitudinal studies[49-57] and another study[35] included patients that were self- or clinician-diagnosed with COVID-19 during the acute phase. For this reason, in addition to the aforementioned analyses, we performed sensitivity analyses for all the risk factors excluding these studies (eFigure 31 in Supplement 1). Overall, there were no differences in the outcomes of any risk factor investigated. Additional sensitivity analyses were performed based on the studies that investigated 5 or more risk factors (eFigure 32 in Supplement 1). There were no changes noted in the outcomes of each risk factor. Meta-regression analyses by geographic location were also performed for the risk factors (eTable 2 in Supplement 1); however, given the limited geographic diversity (30 studies from Europe; only 1 from Africa, 6 from the Americas [Brazil, Canada, US], and 5 from Asia), the interpretation of results should be guarded.

Discussion

This meta-analysis of 41 studies that included a total of 860 783 patients demonstrates that there were certain epidemiologic and clinical risk factors that are associated with a higher risk of developing PCC. In particular, female sex, older age, higher BMI, and smoking were significantly associated with increased risk of persistent symptoms of 3 months or more after the acute phase of COVID-19 infection, ie, PCC. In addition, preexisting comorbidities, including anxiety and/or depression, asthma, COPD, diabetes, IHD, and immunosuppression were also found to be significantly associated with higher risk of PCC. Furthermore, patients who needed hospitalization or ICU care during the acute phase of COVID-19 infection were found to have more than twice the risk of developing PCC compared with those who were not. On the other hand, vaccination (with 2 doses) for COVID-19 was noted to have a protective role against PCC—vaccinated patients had a significantly lower risk of developing the persistent symptoms of PCC.

The aforementioned findings confirm that PCC is a multifactorial and complex clinical syndrome.[62] These results strengthen the evidence available regarding the association of female sex with PCC.[8,63,64] A previous meta-analysis by Maglietta and colleagues[65] including 13 340 patients also highlighted that female sex was significantly associated with the persistent COVID-19 symptoms. A recent large analysis and meta-regression of more than 2 million patients[64] confirmed this finding. Many authors have hypothesized mechanistic processes to explain the association between certain risk factors, including female sex, and PCC.[1,66-69] For example, it has been suggested that hormones may play a role in perpetuating the hyperinflammatory status of the acute phase of COVID-19 even after recovery.[66,67] Also, stronger IgG antibodies production in female individuals in the acute phase has been reported[68] and could contribute to perpetuating disease manifestations.[68,69]

As previous research has suggested,[48,65] older age appears to be an independent risk factor for PCC. Subgroup analysis showed that individuals 40 to 69 years old and those 70 years or older are at equally high risk of PCC when compared with younger patients. However, it is important to consider that the prevalence of PCC consists of individuals who have survived the acute phase of COVID-19 infection. Older individuals, possibly with multiple underlying comorbidities, may not survive the acute phase of COVID-19 because they are at higher risk of severe illness.[70] As highlighted by Di Toro and colleagues,[71] PCC reflects the population of COVID-19 survivors, not the epidemiologic characteristics of COVID-19.

Additionally, the results of our meta-analysis revealed that obesity and smoking were significantly associated with higher risk of developing PCC. These findings concur with recent evidence identifying these characteristics as important risk factors for PCC.[48,72,73] Obesity and PCC share a metabolic proinflammatory state that promotes inflammatory processes and their associated signs and symptoms to linger for a prolonged period of time.[74] Smoking has been shown to be a significant risk factor for both PCC and severe acute COVID-19 infection.[75,76] However, it is unclear whether smoking per se or the associated severe illness predisposes this cohort of patients to higher risk of PCC.

Our meta-analysis revealed that patients who were hospitalized or admitted to the ICU had more than double risk of developing PCC. Severe illness has been found to be a significant risk factor for PCC in previous studies. In a multicenter

cohort study that included 246 patients, 74.3% had ongoing physical symptoms 1 year after ICU admission for COVID-19.[77] However, it should be noted that ICU survivors may experience postintensive care syndrome after an episode of critical care illness.[78,79] Postintensive care syndrome is well-recognized and entails a variety of symptoms that may persist for months or years; therefore, there may be an important overlap with PCC sequelae. Nevertheless, the results of our meta-analysis and those of other studies highlight that patients with previous critical illness represent a high-risk population and their follow-up should reflect intensive plans for prevention, rehabilitation, and treatment of the ongoing debilitating symptoms of PCC.

The results of our study showed that vaccination for COVID-19 has a protective role against PCC, with vaccinated individuals having a significantly lower risk compared with unvaccinated individuals. This finding concurs with those of other studies and the recent report from the UK Office of National Statistics that found a 42% lower risk of PCC after 2 doses of a COVID-19 vaccine.[80-82] Importantly, emerging evidence suggests that vaccination reduces the risk of PCC and its sequelae even in individuals with other risk factors, such as older age or high BMI,[81] expanding the benefits of vaccination beyond the morbidity and mortality benefits seen during the acute COVID-19 phase.

Individuals with PCC may experience long-lasting adverse effects requiring long-lasting support. It has been reported that 15% of individuals with PCC were absent from work owing to illness.[5] Follow-up outpatient services may be needed to manage this condition and to better understand the possible association between symptoms and residual organ impairment. Given that health care systems worldwide have been substantially burdened by the COVID-19 pandemic,[83] routine follow-up may not be possible to all those living with PCC.

Limitations

This review had some limitations. Some of the meta-analyses performed had considerable statistical heterogeneity, which may have affected results. Large meta-epidemiologic studies have shown that studies at high risk of bias tend to overestimate the strength of associations. In addition, all the included studies were observational. Consequently, the results of the performed meta-analyses were based on observational data. Although the observational studies were of moderate or high quality per the Newcastle-Ottawa scale, the scale itself is not without limitations.[84] Furthermore, by virtue of being observational, all the studies (even those with a high rating) have an unavoidable risk of bias. Despite this and considering that randomized studies (with the current COVID-19 strains) will not be undertaken, studies providing risk factors following multivariable regression allow us to draw important conclusions. Furthermore, as discussed previously, PCC is a clinically heterogenous condition with a range of manifestations and symptoms. In this analysis, we considered all the various manifestations as a single entity. For this meta-analysis, we relied on the diagnosis identified by the authors of the included studies, accepting that the definition of symptoms included among the different studies might not have been exactly the same. Lastly, the studies spanned across various COVID-19 variants, but were all pooled together independent of variant. It is possible that the various variants, including the effect of vaccination, could alter the absolute value of patients with PCC; however, it is unlikely that the risk factors associated with PCC would change.

Conclusions

The findings of this systematic review and meta-analysis demonstrated that certain demographic characteristics (eg, age and sex) and comorbidities were significantly associated with an increased risk of developing PCC, whereas vaccination had a protective role against developing PCC sequelae. Given these results, a holistic approach and integrated care pathways may enable suitable support for patients who develop PCC and may allow physicians to be better prepared to care for patients at high risk of developing PCC. Moreover, in addition to preventing and diminishing the acute phase of the infection, COVID-19 vaccination may protect against PCC, giving vaccination additional evidence of benefit.

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