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Coronavirus Pandemic

Predictors of post-COVID-19 syndrome: a meta-analysis

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Abstract

Introduction: Post Coronavirus Disease 2019 (COVID-19) Syndrome also known as long COVID-19 would affect survivors of various patients. At present, the evidence for predicting a poor prognosis of COVID-19 remains insufficient. This study aims to explore potential predictors of post-COVID-19 syndrome.

Methodology: A systematic review process and meta-analysis method are applied to identify the predictors. Systematic searches were conducted without language restrictions from December 1, 2019, to February 28, 2022, on PubMed, Embase, Google Scholar, Web of Science, and Cochrane Library using specific keywords relevant to our targets. The Newcastle Ottawa Scale observational research tool was used to assess study quality and the R (4.1.1) package *meta* was used for statistical analysis.

Results: Our meta-analysis of 14 studies showed that females (OR = 1.42, 95% CI: 1.19-1.70), the severity of patients (OR = 2.43, 95% CI: 1.26-4.68), comorbidity (OR = 2.08, 95% CI: 1.29-3.35), dyspnea (OR = 2.02, 95% CI: 1.34-3.04) associated with a higher risk of post-COVID-19 syndrome.

Conclusions: Our study showed that females, the severity of COVID-19, comorbidity, and dyspnea were associated with a higher risk of post-COVID-19 syndrome. More attention should be paid to these factors to prevent and treat post-COVID-19 syndrome.

Key words: Post COVID-19 syndrome; predictors; risk factor.

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Introduction

Post-COVID-19 Syndrome also known as long COVID-19 would affect survivors of patients, even including children, young adults, and those who have not been hospitalized [1]. Patients with this syndrome, have persistent symptoms and potential sequelae beyond 28 days from diagnosis, including laboratory abnormality, which would increase the mortality and the medical cost significantly [2-4]. The common symptoms of post-COVID-19 syndrome include fatigue, breathlessness, cognitive impairment, pain, anxiety, depression, gastroenterological symptoms, myalgia, bone aches, and anemia [5]. Patients with this syndrome had a higher risk of heart failure, arrhythmia, and myocardial infarction [6-8]. Patients with respiratory diseases and body mass index (BMI) > 25 kg/m^2 would increase the risk of developing long COVID, even causing multiple systems and organ dysfunction [9]. COVID-19 patients with severe diseases and acute respiratory distress syndrome (ARDS) would possibly develop into intensive care unit (ICU) syndrome, which would be more likely to take medications, such as painkillers, opioids, and non-opioids, antidepressants, anti-anxiety drugs, antihypertensive drugs, or increase oral hypoglycemic drugs, then leading to multi-organ function abnormalities [4]. Currently, predictors of post-COVID-19 syndrome vary across studies and lack comprehensive generalizations. Therefore, this study aims to explore potential risk factors for post-COVID-19 syndrome through a systematic review and meta-analysis, and then provide clues to predict its occurrence.

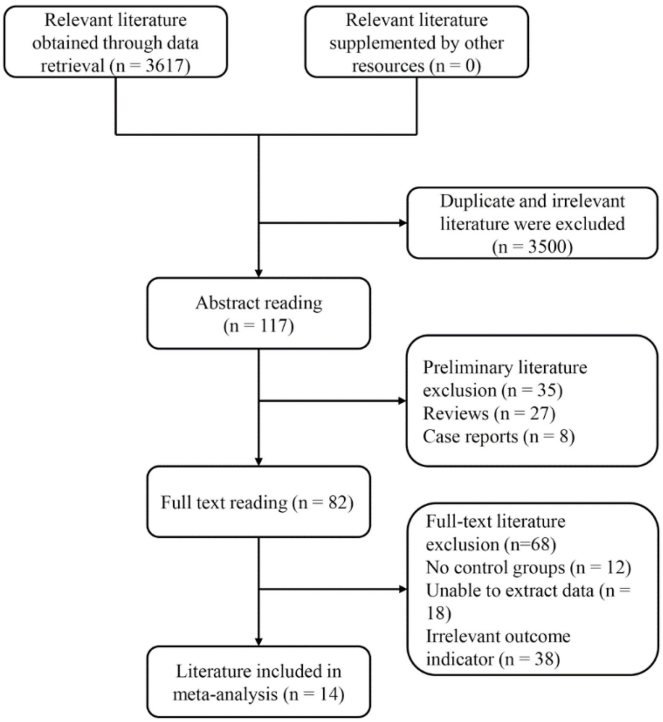
Methodology

Correlation search was conducted through PubMed, Embase, Google Scholar, Web of Science, and Cochrane Library. The retrieval period was from December 1, 2019, when COVID-19 occurred to February 28, 2022. Due to the lack of relevant Chinese studies on risk factors and clinical features of post-COVID-19 syndrome, the language was set as English.

Main search terms: post-acute COVID-19 syndrome, free term was long-COVID OR long-haul COVID OR post-acute COVID syndrome OR persistent COVID-19 OR post-acute OR COVID19 syndrome OR long hauler COVID OR long COVID OR post-acute sequelae of SARS-CoV-2 infection OR long haul COVID OR chronic COVID syndrome. Literature inclusion criteria: Subject aged ≥ 18 years old and confirmed COVID-19; full text on risk factors and clinical features of COVID-19 patients; longitudinal design was used. Exclusion criteria: article types are reviews, editorials, commentaries, case reports, treatment consensus, or guidelines. EndNote20 management software was used to eliminate all repeated documents. Literature was screened independently by two researchers at the same time, and discussion was conducted when there was disagreement on the inclusion and exclusion and the third researcher made the final decision. As shown in Figure 1, a total of 3,617 records were preliminarily obtained, and 14 literatures were finally included. The included literature was published between 2021 and 2022, all of which were cohort studies. The specific general information is shown in Table 1.

Quality evaluation and data extraction. Before data extraction, members of the research team jointly formulated Excel tables suitable for data extraction of different research types, which were extracted independently by two researchers at the same time.

Figure 1. The literature screening process of risk factors for post-COVID-19 syndrome.



Differences were resolved by the third researcher or through consensus. The following variables were extracted: first author, year of publication, duration of the study, method of study, source of patients, follow-up time, criteria for sequelae definition, diagnostic criteria, number/total number of symptomatic patients, site of observation, and risk factors. Newcastle-Ottawa scale (NOS) was used to evaluate the quality of the studies. Eight criteria across three overall categories of NOS related to research rigor were used to assess the risk of bias. NOS allocated one star for each criterion when the study met, more stars indicate better literature quality. The best was 9 stars, and it was generally believed that 5 stars or above would be medium to best research quality [9]. Quality assessment was carried out by two researchers simultaneously and independently. The results of the quality assessment are shown in Table 2.

Analysis Methods

R version 4.1.1 was used for the meta-analysis, and odds ratio (OR) and 95% confidence interval (95%CI) were used as effect indicators. I^2 statistics and Q statistics were used to evaluate the heterogeneity test. It could be considered that there was no heterogeneity between the studies when $I^2 \leq 25\%$ and $p > 0.05$, and the fixed effects model was adopted; otherwise, a random effects model was adopted. Funnel plot and Egger test were used for publication bias analysis, and sensitivity analysis was carried out by eliminating literature one by one to check the robustness of the results. A $p < 0.05$ was considered statistically significant.

Results

Sex

Ten papers reported the relationship between females and post-COVID-19 syndrome, a random-effects model was selected due to heterogeneity among studies ($I^2 = 86.5\%$, $p < 0.05$), and the results showed that females were a risk factor for post-COVID-19 syndrome (OR = 1.49, 95% CI: 1.19-1.86) (Figure 2A).

Severity

Five articles reported the relationship between patient severity and post-COVID-19 syndrome, random-effects model was selected due to heterogeneity among studies ($I^2 = 83.1\%$, $p < 0.05$), and the results showed that the severity of patients was a risk factor for post-COVID-19 syndrome (OR = 2.43, 95% CI: 1.26-4.68) (Figure 2B).

Table 1. Basic features of the included studies.

Author	Year	Method	Duration	Patient	Follow-up time	Definition of sequalae	Diagnostic criteria	Toll/Total (n)	Male toll n (%)	Country	Risk factor
Blidda [12]	2021	Prospective cohort	4 months	Non-hospitalized	1 month	Symptoms persist 4 to 12 weeks after an acute phase	SARS-CoV-2 PCR positive	72/185	17 (23.6)	Denmark	Female, high BMI
Kingery [13]	2022	Retrospective cohort	9 months	Hospitalized and ER	3 weeks	Not mentioned	RT-PCR positive	234/530	294 (55.5)	U.S.A.	Female, obesity, mechanical ventilation, AIDS, asthma
Asadi-Pooya1 [16]	2021	Retrospective cohort	9 months	Hospitalized	14 days	Symptoms persist for more than 12 weeks and cannot be explained by other diagnoses	RT-PCR positive	2915/4681	148 (50.9)	Iran	Female, respiratory symptoms and severity of COVID
Kayaaslan [17]	2021	Prospective cohort	3 months	Hospitalized and out patient	3 months	Persistent signs and symptoms for more than 12 weeks	SARS-CoV-2 PCR positive	478/1007	248 (51.9)	Turkey	Severity, comorbidities
Naik [18]	2021	Prospective cohort	4 months	Hospitalized	6 months	Signs and symptoms that persist or advance after acute COVID-19	SARS-CoV-2 PCR positive	272/1234	191 (70.2)	India	Hypothyroidism and hypoxia
Mahmud [21]	2021	Prospective cohort	2 months	Hospitalized	1 month	Signs and symptoms persisted after virus clearance, 14 days after the initial positive	RT-PCR test	162/355	84 (51.9)	Bangladesh	Female dyspnea, drowsiness, long duration and severity of disease
Peghin [22]	2021	Prospective cohort	6 months	Hospitalized and out patient	3 months	Symptoms lasted ≥12 weeks and were not resolved by alternative diagnosis	NAA positive	241/599	95 (39.4)	Italy	IgG antibody, female, severity, numbers of symptoms
Augustin [23]	2021	Prospective cohort	8 months	Outpatient	4 months	Not mentioned	SARS-CoV-2 PCR positive	123/795	39 (31.7)	Germany	Relatively low IgG level, loss of smell and diarrhea
Munblit [24]	2021	Retrospective cohort	4-8 months	Hospitalized	1 month	Symptoms that occur only after discharge from hospital	RT-PCR positive	1358/2649	683 (50.3)	Russia	Age, female, comorbidities, severity of COVID
Subramani-an [25]	2022	Retrospective cohort	2.5 months	Non-hospitalized	3 months	Symptoms appear 3 months after PCR positive, persist for at least 2 months and cannot be explained by other diagnoses	SARS-CoV-2 PCR positive	29,869/384,137	9,090 (5.3)	Britain	Female, deprivation of social economics, smoking, comorbidities
Kim [26]	2022	Prospective cohort	12 months	Hospitalized and non-hospitalized	6 months	Not mentioned	RT-PCR positive	127/247	29 (22.8)	South Korea	Senior age, female, severity of COVID
Fumagalli [27]	2022	Prospective cohort	9 months	Hospitalized	1 month	Symptoms persist for more than 12 weeks	SARS-CoV-2 PCR positive	103/254	53 (51.5)	Italy	Age, female, weakness, multiple symptoms and COPD
Sun [28]	2022	Prospective cohort	8 months	Hospitalized and outpatient	Not mentioned	A wide range of clinical manifestations, including psychiatric symptoms and organ dysfunction caused by SARS-CoV-2	SARS-CoV-2 PCR positive	319/1038	144 (45.6)	U.S.A.	Comorbidities
Sadat [30]	2022	Retrospective cohort	7 months	Hospitalized and non-hospitalized	Not mentioned	Symptoms appear after the disease presents for more than three weeks	SARS-CoV-2 PCR positive	201/316	41 (49.1)	Iran	Female, hypertension

Comorbidities

Seven papers reported the relationship between comorbidities and post-COVID-19 syndrome, due to heterogeneity among studies (I^2 = 94.9%, p < 0.05), a random-effects model was selected, and the results showed that comorbidity was a risk factor for post-COVID-19 syndrome (OR = 2.08, 95% CI: 1.29-3.35) (Figure 2C).

Dyspnea

As Figure 2D shows, three papers were included in the meta-analysis, due to heterogeneity among studies (I^2 = 75.1%, p < 0.05), a random-effects model was selected, and the results showed that dyspnea was a risk factor for the post-COVID-19 syndrome (OR = 2.02, 95% CI: 1.34-3.04).

Sensitivity analysis

The results of sensitivity analysis showed that after removing included papers one by one, there was no significant difference among the risk factors of post-COVID-19 syndromes, which were female gender, the severity of patients, the presence of complications, the presence of dyspnea and the presence of post-coronavirus syndrome. The combined results were stable (Supplementary Figure 1).

Publication bias

Publication bias was detected in women (p = 0.0006) and whether there were comorbidities (p = 0.0264) by the Egger test, and no publication bias was found in patients' severity (p = 0.2896) and dyspnea (p = 0.1410).

Figure 2. Evaluation of effect index. (**A**) Ten papers reported the relationship between female and post-COVID-19 syndrome; (**B**) Five articles reported the relationship between patient severity and post-coronavirus syndrome; (**C**) Seven literatures reported the relationship between comorbidities and post-COVID-19 syndrome; (**D**) Three researches reported the relationship between patients with dyspnea and post-coronavirus syndrome.

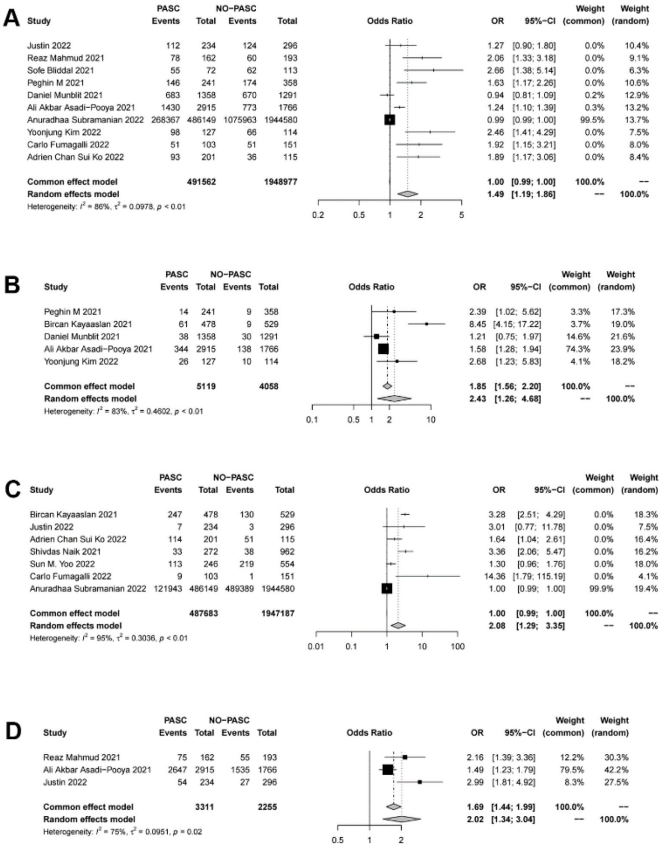


Table 2. Newcastle-Ottawa Scale (NOS) for cohort studies.

Author	Study population selection	Comparability between groups	Result measurement
Bliddal [12]	★★★★	★	★★★
Kingery [13]	★★★	★	★★★
Asadi-Pooya1 [16]	★★★★	★★	★★★
Kayaaslan1 [17]	★★★★	★	★★★
Naik [18]	★★★★	★	★★
Mahmud [21]	★★★★	★★	★★★
Peghin [22]	★★★★	★	★★★
Augustin [23]	★★★★	★	★★★
Munblit [24]	★★★★	★★	★★★
Subramanian [25]	★★★★	★★	★★★
Kim [26]	★★★★	★★	★★★
Fumagalli [27]	★★★★	★★	★★★
Sun [28]	★★★★	★★	★★★
Sadat [30]	★★★	★	★★★

Discussion

Post-COVID-19 syndrome is a major health problem affecting people diagnosed with COVID-19 worldwide. Its pathogenesis is unknown and may be attributed to the direct effects of the virus, immune response, and loneliness. Antibodies against beta-adrenergic and muscarinic receptors due to viral or autoimmune etiology may be responsible for the persistence of symptoms [11]. Post-COVID-19 syndrome can lead to absence from work and impaired daily functioning, thus affecting the quality of life and posing significant challenges not only to individuals but also to society and the social economy [11]. Therefore, it is very important to understand the risk factors of post-COVID-19 syndrome and prevent it as early as possible.

This study shows that female is an important risk factor and female cases were more even in mild cases. The risk of being diagnosed with post-COVID-19 syndrome was 3 times higher than that in men. More than 50% of female patients had symptoms lasting for more than 2 months, which was also common in patients recovering from mild illnesses [12]. The mechanism is divided into two categories, one is the direct influence of the virus, and the other is the indirect influence caused by the immune response to the virus [13]. The outbreak of viral suppression may suppress processes such as virus entry and/or replication during the acute phase of COVID-19, but this, in turn, may lead to prolonged and low levels of immune activation and subsequent post-COVID-19 syndrome in women [14]. During the acute phase of COVID-19, women produce stronger IgG antibodies, which may also play a role in perpetuating symptoms of the disease. It may also be related to women's greater attention to their bodies and associated pain [13].

Comorbidities are another important risk factor, including obesity, cardiovascular disease, hypertension, etc. The presence of complications increases the risk of post-COVID-19 syndrome by 12 times. Some patients with complications cannot go back to work, and the proportion of post-COVID-19 syndrome will increase with the increase in the number of complications [15].

Severity is associated with the occurrence of post-COVID-19 syndrome [4,5]. The mechanism is unclear but may be related to viral infection, corticosteroid therapy, immune response, and ICU admission [16]. The severity of the disease can lead to a stronger immune response and cytokine storm, causing damage to vital organs such as the lungs, heart, and brain. At the same time, due to the severity of the disease, more glucocorticoids and other drugs would be used for treatment, and iatrogenic damage such as tracheal intubation and intrahospital infection is also associated with it, resulting in long-lasting post-COVID-19 syndrome [17]. Post-COVID-19 syndrome is common in patients with moderate to severe disease, and these symptoms can seriously affect the exercise tolerance of patients in their daily lives [14].

Dyspnea is also a risk factor for post-COVID-19 syndrome. COVID-19 can cause more serious complications in the lungs, such as pulmonary fibrosis, coughing, and bronchiectasis. Long-term lung injury such as irreversible dyspnea is one of the characteristics of COVID-19, and it is also the second most common complaint [18]. Direct viral injury, cell and cytokine-mediated cell injury, activation of the compliant fibrosis pathway, and trauma caused by positive pressure ventilation can all cause permanent scarring of lung parenchyma. In up to 98% of patients, chest imaging findings such as ground glass and fibrosis zone still exist even after 28 days [19]. Patients with COVID-19 develop chronic shortness of breath sequelae and have a significantly higher mMRC score (which is associated with forced expiratory volume 1.0 and decreased diffusion capacity) than patients prior to hospitalization. Carbon monoxide (DL CO) is used in practical respiratory function tests. MMRCS can objectively assess the relationship between sequelae of dyspnea and acute phase treatment or severity, and determine whether the symptom has improved [20]. The fibrotic state in some patients with dyspnea may be caused by cytokines. Pulmonary blood vessel thrombosis in patients may have adverse consequences for long-term COVID-19 patients [21].

In addition to the above risk factors, studies have also shown that asthma, hypothyroidism, and aging are risk factors for post-COVID-19 syndrome [14,17-19,22-29]. During follow-up, asthma was associated with an increased risk of post-COVID-19 syndrome, specifically neuro system, emotion, and behavior. Recent studies have suggested that the post-COVID-19 syndrome may be related to mastocyte activation syndrome [15], and that a Th-2 biased immune response in asthmatic patients may account for the increased risk of long-term consequences of infection [25]. Thyroid disease increases the burden of cardiovascular and psychiatric complications due to the influence of viruses on the distribution of ACE2 receptors in tissues, which in turn affects metabolic stress and may adversely affect disease outcomes in a variety of ways. Hypothyroidism has a long-term negative impact on COVID-19 patients [30].

Strengths and limitations

This study searched strictly according to the inclusion and exclusion criteria and is currently the most comprehensive study on the risk factors of post-COVID-19 syndrome. However, there are certain limitations. The first is the high heterogeneity of the selected studies, particularly between the different assessments used. Additionally, the studies included in our review lacked uniform symptom terminology, standardized recording methods, and grouping multiple symptoms under umbrella terms. This limited our ability to compare the prevalence and frequency of these symptoms across studies.

Conclusions

Due to our rigorous literature screening and relatively few studies on risk factors for post-COVID-19 syndrome, by analyzing all the included literature, we only found that female gender, the severity of COVID-19, complications, and dyspnea were risk factors for post-COVID-19 syndrome. Further analysis could be carried out with the increase of research on risk factors of post-COVID-19 syndrome in the future. Patients with post-COVID-19 syndrome need to adopt multidisciplinary team consultation. More attention should be paid to this vulnerable group, effective treatment intervention should be conducted, and future follow-up rehabilitation plans should be laid according to relevant risk factors [31].

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Authors' contributions

R.W, Z.W, and X.X. planned, designed, and screened the literature and wrote the manuscript. R.W and S.Y analyzed the features, evaluated the quality of the literatures and were involved in manuscript preparation. Z.W and X.H were involved in the discussion and edited the manuscript. R.W and M.L supervised and wrote the manuscript. All authors have read and agreed to the current version of the manuscript.

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Conflict of interests

No conflict of interests is declared.

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Annex – Supplementary Items

Supplementary Figure 1. The sensitivity analysis by removing included papers one by one. (**A**) The relationship between female and post-COVID-19 syndrome; (**B**) The relationship between patient severity and post-coronavirus syndrome; (**C**) The relationship between comorbidities and post-COVID-19 syndrome; (**D**) The relationship between patients with dyspnea and post-coronavirus syndrome.