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A Systematic Review on the Risk Factors of Developing Long COVID in Asia Pacific

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ABSTRACT

Recently, healthcare workers and patients noticed that COVID-19 survivors experienced persistent symptoms after recovering from the acute infection. Due to insufficient research on Long COVID especially in Asia Pacific, this study aims to determine the prevalence of Long COVID and its associations with selected socio-demographic factors (age, gender, BMI, and severity of acute COVID-19) among COVID-19 patients in this region. Articles were searched from several journal databases reporting at least one-month of persistent COVID symptoms. The selection of the studies was based on the PRISMA flow diagram. Newcastle-Ottawa Scale (NOS) was adopted for quality assessment of the articles and sixteen papers were included in this study. The prevalence of Long COVID reported in the studies ranged from 8.2% to 68%. Existing evidence suggested that female gender, older age, severe acute COVID-19 stage, and higher BMI were more likely to develop Long COVID. This study demonstrated a significant portion of the population may be affected with Long COVID, particularly those with a higher risk. Hence, more emphasis on Long COVID should be given to maintain the quality of life among COVID-19 patients.

Keywords: long covid, persistent COVID-19 symptoms, post-COVID syndrome, long-term sequelae, risk factors of long covid

INTRODUCTION

As Malaysia moves into the endemic phase of COVID-19, it is crucial to prioritize the care of Long COVID to ensure the well-being of COVID-19 patients. Preliminary data from the COVID-19 Rehabilitation Outpatient Specialized Services (CROSS) at Hospital Sungai Buloh indicated that 2,712 Long COVID patients were referred to the hospital between November 2020 and September 2021. [1] A follow-up after 12 weeks showed that 39.4% (914 patients) had fully recovered from Long COVID symptoms, while 60.6% (1,410 patients) still experienced multiple symptoms. [1] A study in Wuhan, China, revealed that among discharged COVID-19 patients, tiredness or myasthenia was the most common symptom (63%, 1,038 out of 1,655), followed by insomnia (26%, 437 out of 1,655). Additionally, 23% (367 out of 1,617) of the patients reported suffering from anxiousness or a depressive state. [2]

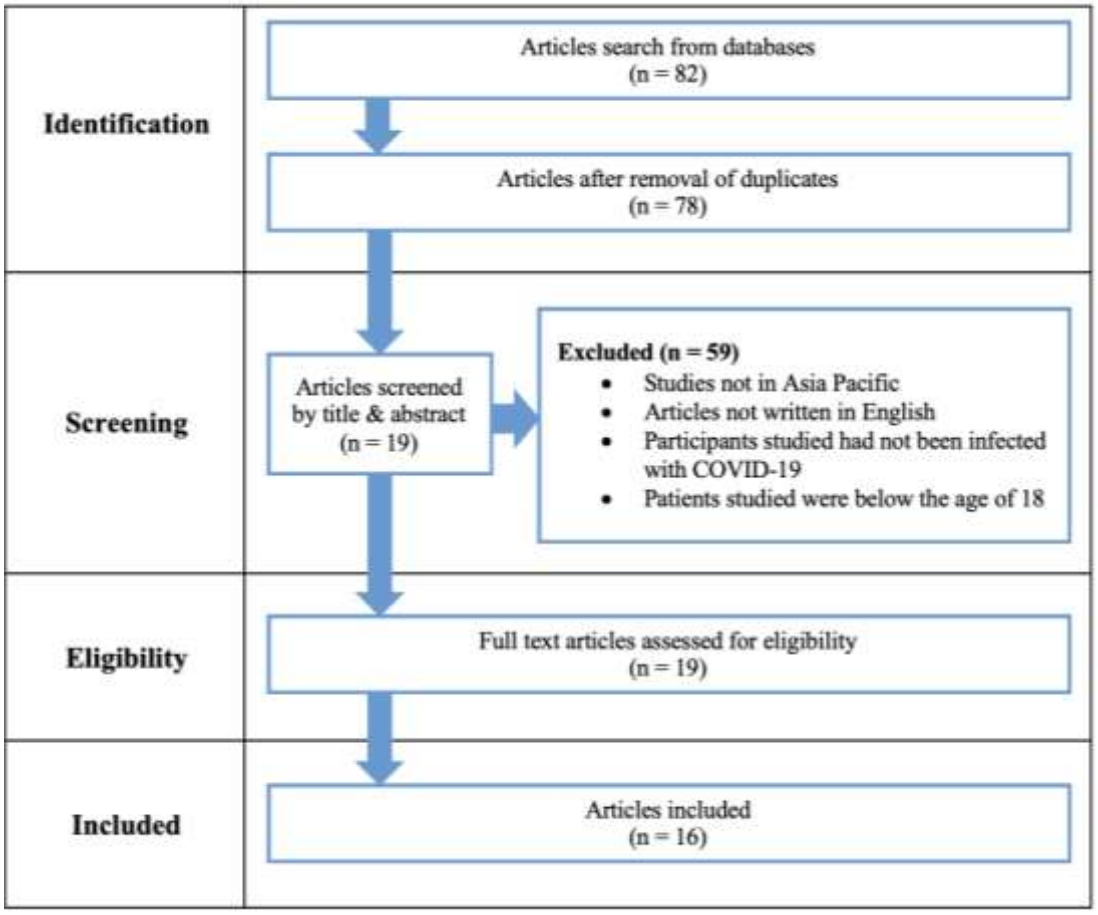
We have chosen to conduct a systematic review that focuses on the risk factors associated with the development of Long COVID. The reason behind this decision is the insufficient of systematic reviews on the prevalence of Long COVID and its associated risk factors. Moreover, we have decided to only include studies from the Asia Pacific region due to the current systematic reviews on Long COVID are mostly conducted in high income countries only. [3] We believe that this review will significantly contribute to the understanding of Long COVID risk factors in the Asia Pacific region and prove beneficial to other researchers and

healthcare systems in addressing Long COVID risk within their own countries.

MATERIALS & METHODS

The selection of studies for this study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram as represented in Figure 1. A sum of 82 articles were collected from various databases (BMJ Journal, Elsevier, Science Direct, Google Scholar), but only 16 articles were included after the quality assessment using Newcastle-Ottawa Scale (NOS) following the inclusion criteria: English-language papers, studies with patients who had COVID-19 and above 18-years-old in Asia Pacific. NOS consisted of 8 items with 3 categories (selection, comparability, outcome) and the total maximum score is 9. The articles included were the ones that scored 7 or above since that was considered a high-quality article according to a previous systematic review. [4] Data extraction was done by at least two researchers, so each pairing would review the articles independently. Any disagreements would involve a third researcher's opinion. The following information was extracted from the selected articles: study design, study objective, study population, prevalence of Long COVID symptoms and risk factors (age, gender, BMI and COVID-19 severity). Then, it will be tabulated using the dummy tables and analysed qualitatively. $P<0.05$ and odds ratio (OR) of 95% confidence interval (CI) that does not include 1.0 are considered as statistically significant.

Fig. 1: Adapted PRISMA Flow Diagram for Studies' Selection



RESULT

Out of 16 articles included in this study, fourteen were cohort studies (n=14) and two were cross-sectional studies (n=2). Table 1 shows that the prevalence of Long COVID in Asia Pacific ranged from 8.2% to 68%.

Table 1: Prevalence of developing Long COVID in Asia Pacific (n=16)

Study	Objective (s)	Study Design	Country of Study	Prevalence of Long COVID
Hossain *et al* [5]	To identify the prevalence of long COVID symptoms in a large cohort of people living with and affected by long COVID and identify any potential associated risk factors.	Cohort	**Bangladesh**	Among 2198 participants, the prevalence of long COVID symptoms at 12 weeks was 16.1%.
Mahmud *et al* [6]	To determine the incidence, association, and risk factors associated with development of the post-COVID-19 syndrome.	Cohort	**Bangladesh**	Among 355 patients, 46% of patients developed post-COVID-19 symptoms at least a month.
Huang *et al* [2]	To compare consequences between 6 months and 12 months after symptom onset among hospital survivors with COVID-19.	Cohort	**China**	The proportion of patients with at least one sequelae symptom decreased from 68% (831/1227) at 6 months to 49% (620/1272) at 12 months ($p<0.0001$).
Zhang *et al* [7]	To evaluate health outcomes of COVID-19 survivors 1 year after hospital discharge and to identify associated risk factors.	Cohort	**China**	1095 patients (45.0%) out of 2433 patients reported at least 1 symptom of long-term COVID-19 sequelae at 1 year follow up.
Munblit *et al* [8]	To assess the persistent symptoms in previously hospitalized patients with COVID- 19 and potential risk factors.	Cohort	**Russia**	1247 (47.1%) out of 2649 participants reported persistent symptoms 6 to 8 months after discharge.
Xiong *et al* [9]	To describe the prevalence, nature and risk factors for the main clinical sequelae in coronavirus disease 2019 (COVID-19) survivors who have been discharged from the hospital for more than 3 months.	Cohort	**China**	Based on follow-up results, 267 (49.6%) of 538 COVID-19 survivors had one or more general symptoms 3 months after discharge from hospital.
Wu *et al* [10]	To describe the temporal trends in respiratory outcomes over 12 months in patients hospitalised for severe COVID-19 and to investigate the associated risk factors.	Cohort	**China**	Out of 83 participants, radiological changes persisted in 20 (24%) patients at 12 months after discharge.
Zhao *et al* [11]	To evaluate the long-term consequences of COVID-19 survivors one year after recovery, and to identify the risk factors associated with abnormal patterns in chest imaging manifestations or impaired lung function.	Cohort	**China**	58 (61.70%) out of 94 patients reported at least one symptom that did not exist before COVID-19 infection at 1-year follow-up.
Solehan *et al* [12]	To identify the long-term clinical symptoms of COVID-19 and the associated risk factors among Malaysian populations.	Cross-sectional	**Malaysia**	More than half (56%) of the 215 patients still had symptoms at one-month after diagnosis, with 39% and 18% still having symptoms at the second and third months respectively.
Senjam *et al* [13]	To comprehensively assess self-reported post Covid-19 symptoms and its associated risk factors among beneficiaries of Hospital Employee Scheme of a tertiary healthcare institution in Delhi.	Cross-sectional	**India**	257 (33.2%) out of 773 participants had at least one or more ST-PCS (4 weeks or more) reported. But this number was reduced to 99 (12.8%) at 12 weeks or more and to 15 (0.90%) at 16 weeks or more since SARS-CoV-2 test positivity.
Shang *et al* [14]	To understand the sequelae of COVID-19.	Cohort	**China**	441 participants (55.4%) had some kind of sequelae.
Arjun *et al* [15]	To estimate the incidence, characteristics of symptoms, and predictors of long COVID among COVID-19 patients diagnosed during the Omicron wave in Eastern India.	Cohort	**India**	In the total sample, 43 participants self-reported having long COVID symptoms. Thus, the percentage of participants who self-reported long COVID symptoms was 8.2% (95% CI 6%–10.9%).
Naik *et al* [16]	To describe the clinical features and risk factors of post COVID-19 sequelae in the North Indian population.	Cohort	**India**	495 (40.1%) had persistent symptoms post-discharge or recovery. In 223 (18.1%) patients, the symptoms resolved within four weeks; 150 (12.1%) patients had symptoms till 12 weeks, and 122 (9.9%) patients had symptoms beyond 12 weeks of diagnosis/symptom-onset of COVID-19.
Arjun *et al* [17]	To measure the burden, the characteristics, and the predictors of Long COVID in India to bring much needed insight into this condition.	Cohort	**India**	Long COVID was reported by 29.2% (95% CI: 25.3%,33.4%) participants.
Liang *et al* [18]	To characterize 3-month outcomes including the symptoms, pulmonary function, dynamic changes of SARS-CoV-2 antibody and high-resolution computed tomography of patients who survived COVID 19 in the three months after discharged.	Cohort	**China**	During follow-up in the 3 months after hospital discharge, 15 (20%) patients had fever, 45 (60%) patients complained of cough, 33 (43%) had increased sputum production, 47 (62%) had activity chest tightness and palpitations, 45 (60%) complained of fatigue and 20 (26%) patients had diarrhea.

Asadi-Pooya *et al* [19]	To investigate the full spectrum of symptoms of patients suffering from LCS, the chronicity of symptoms and potential risk factors associated with the development of LCS.	Cohort	**Iran**	In total, 4,681 patients were studied, 2915 of whom (62.3%) reported symptoms of long covid.

Table 2 reveals that there is a significant association between the selected socio-demographic factors and Long COVID. Among the fifteen articles, only four articles [7,9,13,16] showed older age is significantly associated with Long COVID. Whereas, female gender was studied in all sixteen articles and eleven [5-6,2,7-10,12-14,19] of them were significantly related to Long COVID. In terms of BMI, only one [15] from four articles found a strong association between higher BMI and Long COVID. With regard to the severity of acute COVID-19, seven [6,7,13-14,16-17,19] out of twelve articles reported severe stage had a significant relation to Long COVID.

Table 2: Association of developing Long COVID by selected sociodemographic factors (n=16)

Study	Objective (s)	Study Design	Country of Study	Prevalence of Long COVID			
				Age	Gender	BMI	COVID-19 Severity
Hossain *et al* [5]	To identify the prevalence of long COVID symptoms in a large cohort of people living with and affected by long COVID and identify any potential associated risk factors.	Cohort	**Bangladesh**	There is no significant association between participants aged 30 years and below (p=0.079), as well as 50 years and below (p=0.194) with long COVID symptoms.	Male gender had a reverse relationship with long COVID symptoms (p<0.01).	-	There is no significant association between having mild COVID symptoms (p=0.397) to develop long COVID symptoms.
Mahmud *et al* [6]	To determine the incidence, association, and risk factors associated with development of the post-COVID-19 syndrome.	Cohort	**Bangladesh**	There is no significant association between age and post-COVID-19 symptoms (p=0.65).	Post-COVID-19 features were significantly higher among women (RR: 1.2, 95% CI: 1.02–1.48, p=0.03).	-	Patients with severe forms of the disease at presentation had a higher tendency to develop post-COVID-19 symptoms (p=0.02).
Huang *et al* [2]	To compare consequences between 6 months and 12 months after symptom onset among hospital survivors with COVID-19.	Cohort	**China**	There is no significant association between age with fatigue and muscle weakness (p=0.21) at 1-year follow-up.	Women has an OR 1.43 (95% CI 1.04 - 1.96) p=0.027 for fatigue or muscle weakness at 1-year follow up.	-	There is no significant association between disease severity with fatigue and muscle weakness (p=0.80) at 1-year follow-up.
Zhang *et al* [7]	To evaluate health outcomes of COVID-19 survivors 1 year after hospital discharge and to identify associated risk factors.	Cohort	**China**	Older age (OR 1.02; 95% CI, 1.01-1.02; P<.001) was associated with higher risks of fatigue.	Female sex (OR 1.27; 95% CI 1.06-1.52; P=0.008) was associated with higher risks of fatigue.	-	Severe disease during the hospital stay (OR 1.43; 95% Cl 1.18-1.74; P<0.001) was associated with higher risks of fatigue.
Munblit *et al* [8]	To assess the persistent symptoms in previously hospitalized patients with COVID- 19 and potential risk factors.	Cohort	**Russia**	-	Females sex was associated with any persistent symptoms category OR 1.83 (95% CI 1.55-2.17).	-	-
Xiong *et al* [9]	To describe the prevalence, nature and risk factors for the main clinical sequelae in coronavirus disease 2019 (COVID-19) survivors who have been discharged from the hospital for more than 3 months.	Cohort	**China**	There was significant association between age and physical decline or fatigue (p<0.01).	Female (p<0.01) was associated with physical decline or fatigue.	-	There was no significant association between the disease severity status and physical decline or fatigue (p=0.12).
Wu *et al* [10]	To describe the temporal trends in respiratory outcomes over 12 months in patients hospitalised for severe	Cohort	**China**	Univariate logistic regression showed no significant association between impaired DLCO	Univariate logistic regression showed increasing odds of impaired DLCO	Univariate regression showed no significant association between impaired DLCO and	-

	COVID-19 and to investigate the associated risk factors.			and age (OR 1.03 [95% CI 0.99-1.08; p=0.14).	associated with female sex (OR 7.14 [95% CI 2.53-20.16]; p=0.0002).	BMI (OR 0.94; [95% CI 0.80-1.10]; p=0.429).	
Zhao *et al* [11]	To evaluate the long-term consequences of COVID-19 survivors one year after recovery, and to identify the risk factors associated with abnormal patterns in chest imaging manifestations or impaired lung function.	Cohort	**China**	Univariate logistic regression showed no significant association between abnormal DLCO and age (p=0.722).	Univariate logistic regression showed no significant association between abnormal DLCO and female sex (p=0.461).	-	-
Solehan *et al* [12]	To identify the long-term clinical symptoms of COVID-19 and the associated risk factors among Malaysian populations.	Cross-sectional	**Malaysia**	There is no significant association between age and post-COVID-19 symptoms (p=0.511).	Post-COVID-19 symptoms were significantly higher among females (p=0.03).	-	-
Senjam *et al* [13]	To comprehensively assess self-reported post Covid-19 symptoms and its associated risk factors among beneficiaries of Hospital Employee Scheme of a tertiary healthcare institution in Delhi.	Cross-sectional	**India**	There is a significant association between age and post COVID-symptoms (p=0.0001).	Post-COVID-19 symptoms were significantly higher among females (p=0.0007)	There is no significant association between BMI and post-COVID-symptoms (p=0.21)	There is significant association between severity of COVID-19 disease and post COVID-symptoms (p=0.0001).
Shang *et al* [14]	To understand the sequelae of COVID-19.	Cohort	**China**	No difference was found between age groups (p=258).	Univariate logistic regression analyses revealed that women are more likely to have multiple symptoms (p=0.002), fatigue (p=0.009) and sleep disorder (p=0.008).	-	Critical cases were more likely to have cough (20.5% vs 11.6%, p=0.023) and hypomnesis (15.1% vs 8.0%, p = 0.041) than severe cases.
Arjun *et al* [15]	To estimate the incidence, characteristics of symptoms, and predictors of long. COVID among COVID-19 patients diagnosed during the Omicron wave in Eastern India.	Cohort	**India**	In univariable logistic regression, age was not statistically significant predictors OR of 0.63 (95% CI 0.27-1.44).	In univariable logistic regression, sex was not statistically significant predictors OR of 1.78 (95% CI 0.95-3.32).	Participants having a BMI greater than or equal to 25 had an OR of 1.92 (95% CI 1.03-3.60) compared with BMI less than 25.	In univariate logistic regression, severity was not statistically significant with OR of 1.33 (95% CI 0.30-5.96).
Naik *et al* [16]	To describe the clinical features and risk factors of post COVID-19 sequelae in the North Indian population.	Cohort	**India**	Univariate analysis shows that age is a statistically significant risk factor with p<0.001.	In univariate analysis, gender is not statistically significant (p=0.8).	-	Univariate analysis shows that disease severity is a statistically significant risk factor with p=0.01.

Arjun *et al* [17]	To measure the burden, the characteristics, and the predictors of Long COVID in India to bring much needed insight into this condition.	Cohort	**India**	Univariable analysis shows that older age is not statistically significant with long covid symptoms (p=0.22).	Univariable analysis shows that female is not statistically significant with long covid symptoms (p=0.16).	Univariable analysis shows that BMI is not statistically significant with long covid symptoms (p=0.95).	Univariable analysis shows that severe COVID-19 is significantly associated with long covid symptoms (p<0.001).
Liang *et al* [18]	To characterize 3-month outcomes including the symptoms, pulmonary function, dynamic changes of SARS-CoV-2 antibody and high-resolution computed tomography of patients who survived COVID 19 in the three months after discharged.	Cohort	**China**	There is no significant association between age and impaired PFT at 3-months after discharge (p=0.196).	There is no significant association between gender and impaired PFT at 3-months after discharge (p=0.667).	-	There is no significant association between disease severity status and impaired PFT at 3-months after discharge (p=0.404).
Asadi-Pooya *et al* [19]	To investigate the full spectrum of symptoms of patients suffering from LCS, the chronicity of symptoms and potential risk factors associated with the development of LCS.	Cohort	**Iran**	There is no significant association between age and long-term COVID syndrome (p=0.47).	Women were more likely to experience long-term COVID syndrome than men (OR: 1.268; 95% CI 1.122-1.432; p=0.0001) which was significant.		A shorter length of hospital stay was inversely correlated with having LCS (OR: 0.953; 95% CI: 0.941-0.965; P=0.0001).

DISCUSSION

Generally, this systematic review found that the prevalence of Long COVID among COVID-19 patients in Asia Pacific where the lowest was 8.2% [16] and the highest was 68% [2]. Variations in prevalence could be caused by factors such as the COVID-19 variations or vaccination. This is supported by previous studies whereby children infected during Omicron wave reported to have a lower risk of Long COVID [20] and there is a reduction of risk following vaccination [21]. Therefore, this highlights the need of a continuous study particularly with the new variants of COVID-19, as well as encouraging preventive measures against the virus.

Additionally, easy fatigability was identified as the most common symptom for Long COVID in twelve out of the sixteen articles. It was the highest at 25.3% compared to the other symptoms: sleep disorder (23.2%), dyspnea (20.4%), muscle joint pain (13.8%), cough (12.4%), digestive symptoms (10.9%), chest pain (9.9%) and hypomnesis (8.7%). [14] Studies also have shown that there is impairment in gaseous exchange measured by diffusing capacity of the lungs for carbon monoxide (DLCO) in 1-year discharged patients following COVID-19 hospital admission, although there was no relation to the severity of the infection. [11] This is a relevant finding since DLCO was incorporated in four out of the sixteen articles from our study. Furthermore, a study revealed that low DLCO could be the result of abnormal pulmonary interstitial and vascular changes caused by COVID-19. [22]

We found that the articles in our study which focuses only in Asia Pacific expressed similar significant risk factors for Long COVID as majority of the articles worldwide. This is evidenced by a systematic review with a global distribution that included articles from Europe (62%), Asia (23%), North America (8%) and Middle East (8%), which reported Long COVID association with females, increasing age and severity of the acute phase. [3] Moreover, they included non-English language papers in their study. [3] Female gender being the most significant risk factor might be due to their stronger immune response which causes not only excessive inflammatory cytokines production, but also an autoimmune reaction unmasked by the virus itself, possibly due to molecular mimicry leading to COVID-19 persistent symptoms. [23] Also, they seek medical attention more frequently compared to male as they were found to be more attentive to their body and related distress. [24] Meanwhile for age factor, older age is significantly associated with Long COVID which may be contributed by the weakening of the immune system as production of pro-inflammatory cytokines increases with age. [25] Following this, age above 40 were noted to have significantly lower frequency of ciliary beating, leading to longer time for Nasal Mucociliary Clearance (NMCC) ($P<0.05$). [26] Therefore, increasing the risk for them to develop chronic infection. Nevertheless, this does not represent the entire population since a study found that there was no association between functional decline and 6 months following COVID-19 hospitalisation when comparing the younger and older age group. [27] Furthermore, there were underrepresentation of the older age group especially for those above 70 years old, despite coming from cohort or cross-sectional studies.

Higher BMI demonstrate a significant relation to Long COVID. This connection may be attributed to the multisystemic changes associated with obesity, which can enhance prolonged systemic inflammation and consequently leads to a higher risk of severe Long COVID. [28] However, it is unclear whether obesity directly causes Long COVID or it is the result from underlying comorbidities in obese patients. Obese COVID-19 patients had worse disease prognosis, as well as being the only risk factor significantly increasing morbidity and mortality of COVID-19 ($P<0.001$). [29] Hence, obesity might independently cause Long COVID, but additional research is required to evaluate this association.

Other than that, severity of acute COVID-19 infection has been shown to be significantly

associated with the development of Long COVID. This may be due to structural and functional damage to vital organs and elevated proinflammatory cytokines levels. [30] However, patients admitted to intensive-care unit (ICU) may develop post-intensive care syndrome which may mimic Long COVID presentations. [31] Differences in method of classifying disease severity may also contribute to variations in the findings.

There are several limitations of this systematic review such as different variants of COVID-19 which may affect the development of Long COVID. Moreover, most studies used in this review are cohort studies has a few disadvantages such as selection bias, loss to follow-up and confounding variables. Also, studies included in this review focuses primarily on hospitalized patients. Hence, the generalizability to non-hospitalized patients may be limited.

CONCLUSION

This study deduces that the prevalence of Long COVID among COVID-19 patients in Asia Pacific ranges from 8.2% to 68% with age, gender, BMI and COVID-19 severity as the risk factors contributing to the development. By synthesizing data from various studies, this review has clarified the association of these risk variables in the rise of Long COVID, which may help in developing preventative measures as well as specific interventions for susceptible populations. The possibility for variability between datasets and the limitations of the currently available studies must be acknowledged. Therefore, more research and longitudinal studies need to be conducted to improve our comprehension of Long COVID and its risk factors, especially in Asia Pacific to open the door for more effective management and support for those affected by this persistent condition.

Declaration by Authors

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