Prevalence and risk factors associated with long COVID in children and adolescents: A systematic review and meta-analysis

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Abstract. Background: The COVID-19 pandemic has led to a significant number of individuals experiencing persistent symptoms post-recovery, also known as "long COVID." While children generally present milder COVID-19 symptoms than adults, concerns about the prevalence of long COVID in this demographic are rising. This systematic review and meta-analysis aimed to assess the prevalence of long COVID in children and adolescents and identify associated risk factors. Methods: A comprehensive search was conducted on PubMed and Web of Science up to July 23rd, 2023. We assessed the pooled prevalence of long COVID in children. Subgroup analysis and meta-regression were performed by stratification with follow-up duration, mean age, and sex ratio. Results: Out of 5903 identified studies, 24 met the inclusion criteria, comprising 37,410 participants. The pooled prevalence of long COVID symptoms in children post-acute COVID-19 was 23.7% (CI: 16.1% to 34.8%). Age-stratified analysis revealed prevalence rates of 9.5% (0-6 years), 24.1% (6-12 years), and 52.0% (>12 years). Children with a history of COVID-19 were nearly twice as likely to develop long COVID symptoms compared to controls. Risk factors identified included older age, hospitalization status, COVID severity, and specific acute-phase symptoms. Conclusion: This meta-analysis highlights a concerning prevalence of long COVID in children, especially in those aged above 12 years. The findings underscore the need for standardized reporting methods, global research collaboration, and targeted interventions to address the potential long-term consequences of COVID-19 in the younger population.

Keywords: Long COVID, children, meta-analysis.

1. Introduction

The COVID-19 pandemic continues to escalate, resulting in more than 771 million cases and 6,978,175 deaths as of 5 November 2023 (1). While most of the infected individuals recover from COVID, a significant portion of the population experience persistent symptoms long after recovery from acute COVID infection (4). There is no consensus on the definition of long COVID: CDC identify the start of long COVID as four weeks after infection (2), and WHO defines as 3 months after infection and lasting for 2 months with no other explanation (3). The two definitions are used extensively in studies; thus, for the purpose of this meta-analysis, we define long COVID as symptoms that develop during or after acute COVID infection, lasting for more than four weeks and cannot be explained by alternative diagnosis.

Although COVID-19 is generally less severe in children compared to adults—usually asymptomatic or mild infection with low hospitalization and death rates (5)—the prevalence of long COVID in children is a growing concern. Children are less likely to get vaccinated compared to adults, and vaccine uptake appears to have slowed recently (7). With many remain unvaccinated, children are more prone to infecting covid and potentially developing long covid. There was a reported surge of covid cases in school-aged children after school reopened and restrictions eased (8). Long covid may pose implications in children as they move into adulthood. Contemporary data on long COVID in the younger population, however, is limited and heterogenous (6). Therefore, investigating the presentation of long COVID in children is essential to allow healthcare systems to allocation their resources accordingly.

The objective of this paper is first to assess the pooled prevalence of long COVID in children under the age of 18. Which methods to use/Which sample to choose, in brief Additionally, we determined risk factors associated with a higher prevalence of long COVID.

2. Methods

This meta-analysis was conducted following the PRISMA guidelines.

2.1. Search strategy

We conducted a systematic search on PubMed, and Web of Science databases for studies published from inception to July 23rd, 2023. The following keywords were used to identify literatures: ("COVID-19 Syndrome, Post-Acute" OR "Post-Acute COVID-19 Syndromes" OR "Long Haul COVID-19" OR "COVID-19, Long Haul" OR "Long Haul COVID 19" OR "Long Haul COVID-19s" OR "Post Acute COVID-19 Syndrome" OR "Post Acute COVID 19 Syndrome" OR "Long COVID" OR "Post-Acute Sequelae of SARS-CoV-2 Infection" OR "Post Acute Sequelae of SARS CoV 2 Infection" OR "Post-COVID Conditions" OR "Post COVID Conditions" OR "Post-COVID Condition" OR "Long-Haul COVID" OR "COVID, Long-Haul" OR "Long Haul COVID" OR "Long-Haul COVIDs") AND ("Children" OR "Child"). Reference lists of relevant articles were searched for additional studies that met the inclusion criteria.

Retrieved records were imported to Zotero and checked for duplicates. Titles and abstracts of all studies were examined by one author and verified by a second author.

2.2. Selection Criteria

Studies were included if they satisfy the following criteria: (1) age less than 18 years old, (2) exposure group has a history of confirmed COVID-19 infection using Reverse transcription polymerase chain reaction (RT-PCR), lateral flow antigen test (LFT), or serology, (3) all study designs were included except case studies and reviews, (4) mean follow up duration of more than four weeks, (5) contain the type and prevalence or risk factors of Long COVID symptoms.

2.3. Data extraction

Each author independently extracted data from included studies. The following data were extracted: COVID-19 diagnostic criteria, country, sample size, study design, participant demography, follow up duration, COVID-19 severity, vaccination status, outcomes, and definitions for Long COVID.

2.4. Risk of bias

The quality of included studies was independently assessed by Guo A. using the MINORS for cohort studies and AHRQ for cross-sectional studies.

2.5. Statistical Analysis

Meta-analysis was performed to estimate the pooled prevalence of long COVID in children recovered from acute COVID-19. A secondary analysis was performed to examine the odds ratio between the control group (participants without a history of COVID-19 infection but present long COVID symptoms) and experimental group. The I2 index was calculated to assess the heterogeneity; an I2 value of > 50 % was considered substantial heterogeneity. Random effects model was used to determine pooled prevalence with 95 % confidence intervals. Subgroup analyses and meta-regressions on the estimated prevalence of all symptoms were performed by stratifying with follow-up duration (>3 months vs. <3 months), median age of study participants (<6 years, 6-12 years, >12 years), the sex ratio (female proportion>50 % vs.<50 %). All analyses were performed with R and RevMan software.

3. Results

We identified 5903 studies initially through database search, and 1931 duplicates were removed. 3795 studies were excluded after screening title and abstract. Full texts of the remaining 177 studies were reviewed, and 153 did not meet selection criteria. A total of 24 studies were included in the analysis.

3.1. Baseline characteristic

The baseline characteristics of included studies are summarized in Table 1. All included studies were published in 2021 to 2023, including 6 cross-sectional studies and 18 cohort studies. A total of 37,410 participants were included. Follow up times was between 1 to 12 months. 5 studies were conducted in Asia, 1 study in North America, 15 studies in Europe, 1 study in Oceania, and 2 studies were conducted in multiple countries. Female proportion ranged from 39.1% to 63.7%, and age ranged between 1-18 years old.

Table 1. The baseline characteristics of included studies

Author	Site	Study Design	Follow Up Duration	Sample Size	Age	Female %	COVID severity	Asthma/chronic lung condition	Vaccination status	definition of Long COVID
Jarupan et al., 2023	Thailand	prospective cohort study	3, 6, 9 months	154	9(7, 13)	61	N-pneumonia: 134 (87) Pneumonia: 20 (13)	3 (2)	BNT162b2 No vaccine (87, 16) 1 dose (38, 24) 2 dose (19, 13)	4 weeks
Morello et al., 2023	Italy	prospective cohort study	3, 6, 12, 18 months	1234	3 months (recovered; long covid); 6.33 (3.50–9.42), 9.83 (7.40–12.85)	46.2	Asymptomatic: 109 mild: 1102 Moderate: 23	10 (0.8%)	NA	3 months
Alsaghaeir et al., 2023	Saudi Arabia	Cross sectional	> 4 weeks	1245	Median (Mean+-SD) 11 (1-17)	51.7	Critical 6(0.5), severe (hospitalization): 15(1.2), mild: 1224(98.3)	NA	No vaccine 619(49.7), 1 dose 35(2.8), 2 dose 525(42.2), 3 dose 66(5.3), 4 dose 1(0.1)	4 weeks
Adler et al., 2023	Israel	Cross sectional	4.39±1.5, 1–12 months	1148	(Mean +- SD) 10.8±0.08, 9.5±0.09	63.7	symptomatic 720 (62.7)	41	At least one dose: 172 (15), 1424 (68)	4 weeks
Buonsenso et al., 2021	Italy	Cross sectional	162.5 ± 113.7 days	129	11 ± 4.4 years	48.1	asymptomatic 33(25.6%), symptomatic 96(74.4%)	NA	NA	4 weeks
Lokanuwatsatien et al., 2023	Tailand	prospective cohort study	3, 6 months	802	0-3: 179 (22.3), 3-18: 623 (77.7)	43.9	Asymptomatic 131 (16.5), Mild 608 (76.5), Moderate 48 (6.0), Severe 6 (0.8), Critical 2 (0.3)	14 (1.7)	No vaccination 662 (82.5), One dose 40 (5.0), Two doses 84 (10.5), Three doses 15 (1.9), Four doses 1 (0.1)	3 months
Berg et al., 2022	Denmark	Cross sectional	> 4 weeks	10997	0-3: 2·4 (1·7–3·2), 4-11: 9·1 (6·9–10·7), 12-14: 13·6 (12·9–14·4)	47.9	Asymptomatic 5959, mild 4808, severe 230	570	NA	2 months
Pazukhina et al., 2022	Russia	prospective cohort study	6, 12 month	360	9.5 (2.4–14.8)	52	severe: 12/360 (3%)	5/360 (1%)	NA	6-12 months

Osmanov et al., 2022	Russia	prospective cohort study	256 (223–271) days	518	10.4 (3–15.2)	52.1	NA	12/514 (2.3)	NA	5 months
Zavala et al., 2021	England	cohort	> 4 weeks	472	10 (6,13), 9 (6.5,12)	50.2	NA	NA	NA	4 weeks
Asadi-Pooya et al., 2021	Iran	Cross sectional	3 months	58	range: 6-17, Mean SD 12.3+-3.3	52	NA	NA	NA	3 months
Roge et al., 2021	Latvia	ambidirectional cohort study	73.5 (110.0–43.0) days	236	10.0 (14.0–5.0)	44.5	NA	17 (7.2)	NA	4 weeks
Smane et al., 2021	Riga	Retrospective cohort study	55 (30–104)	92	12 (8–15)	39	NA	7 (8%)	complete: 85 (92%), incomplete: 12 (13%)	1-3 month
Stephenson 2022	England	cohort	3, 6, 12, 24 months	3065	11-14: 1244 (40·6%), 15-17: 1821 (59·4%)	63.5	NA	323	NA	3 months
Buonsenso et al., 2022	UK and US	cohort	3-6 months	510	10.3 ± 3.8	56.3	asymptomatic 62 (12.2%),	NA	NA	3months
Funk et al., 2022	8 countries	prospective cohort study	3 months	1884	3 (0-10)	47.2	NA	260 (13.8)	NA	3 months
Kostev et al., 2022	Germany	Retrospective cohort study	3 months	6568	10.1 (4.9)	49.2	NA	461 (7.0)	NA	3 months
Berg et al., 2022	Denmark	Cross sectional	2 months	6630	17·6 (16·5–18·6)	58.4	asymptomatic: 2241 (33·8%), mild: 3795 (57·2%), severe: 594 (9·0%)	507 (7·7%)	NA	2 months
Messiah et al., 2022	US	Retrospective cohort study	3 months	312	6.65 (5.91)	47.1	NA	NA	NA	4 weeks
Say et al., 2021	australia	cohort	3-6 months	171	Median IQR 3 (1–8)	47	Asymptomatic 61 [36%], mild100 [58%], moderate 9 (5%), severe 1(1%)	8 (5%)	NA	4 weeks
Blomberg et al., 2021	Norway	prospective cohort study	6 months	16	8 (6–12)	56	NA	NA	NA	NA
Sterky et al., 2021	Swedan	cohort	219 (123–324) days	55	0-1: 21 (38%), 1-5: 14 (25%), 6-12: 14 (25%), 13-18: 6 (11%)	41.8	NA	NA	NA	NA

Buonsenso 2022	Italy	prospective cohort study	1-5 months, 6-9, > 12	679	10.0 (6.0, 13.0)	51	NA	21	NA	4 weeks
Gennaro 2022	Italy	prospective cohort study	3 months	75	10.2 (4.9)	49.3	Asymptomatic: 4 (5.3%), mild: 60 (80%), severe: 11 (14.7%)	2 (2.7%)	NA	2 months

3.2. Pooled prevalence of Long COVID

In Figure 1, A high heterogeneity was observed with an I^2 value of 99.5%. The pooled prevalence of long COVID symptoms among the participants was 23.7% with a confidence interval [CI] of 16.1% to 34.8%. The overall effect size, was 4731.90 with a significance level of p = 0, suggesting that the pooled prevalence rate was highly significant.

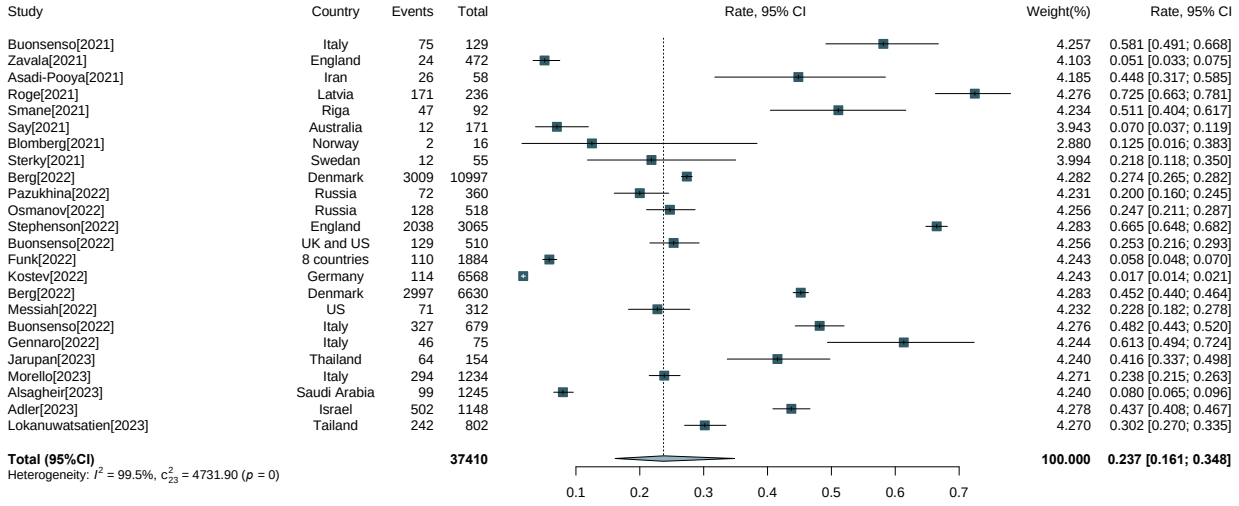

Figure 1. The pooled prevalence of long COVID symptoms

3.3. Pooled prevalence of Long COVID in different age groups

The forest plot was further stratified by age groups to investigate the prevalence in different age groups in Figure 2:

For children aged 0-6: The pooled prevalence rate was 9.5% with a CI of 4.2% to 21.2%.

For children aged 6-12: The pooled prevalence rate was 24.1% with a CI of 15.4% to 37.7%.

For children aged >12: The pooled prevalence rate was 52.0% with a CI of 39.7% to 68.1%.

The test for subgroup differences yielded a chi-squared value of 20.69 with 2 degrees of freedom, and the significance level was $p < 0.01$, indicating the differences in the prevalence rates among the age groups were statistically significant.

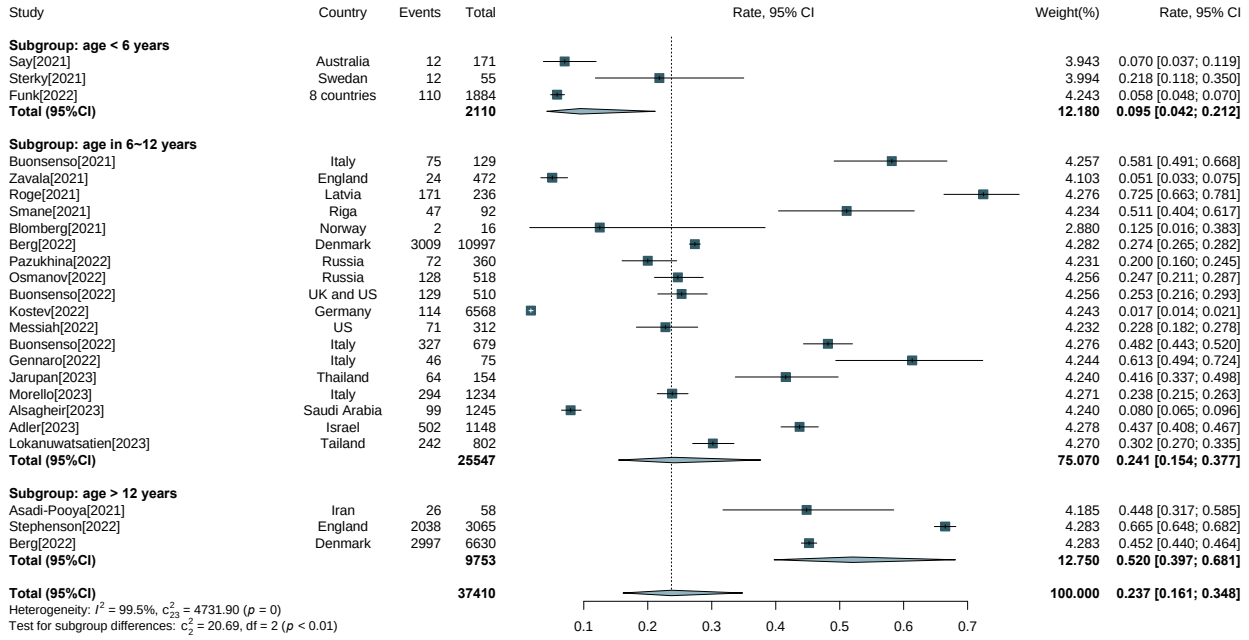

Figure 2. The prevalence in sub age groups

3.4. Controlled studies

In the controlled studies examined in Figure 3, the odds ratio was found to be 1.93, indicating that children who had a history of COVID-19 had almost twice the likelihood of developing long COVID symptoms compared to the control group. The confidence interval was between 1.05 and 3.53.

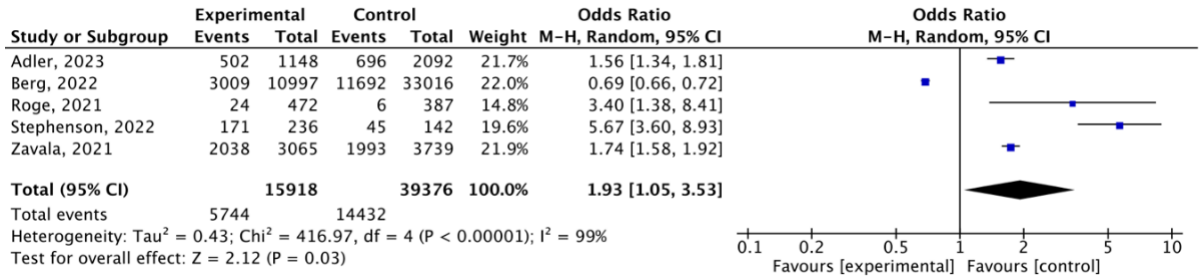

Figure 3. The prevalence in control group

3.5. Meta-regression

No significant difference was found in the meta-regression results for follow-up time, country of study, experiment type, and gender (as shown in Table 2).

Table 2. meta-regression

variable	beta	Z	Pvalue	ci.lower	ci.upper
Age < 6 years	1[Ref]				
Age 6~12 years	1.28	1.98	0.05	0.01	2.55
Age > 12 years	2.31	2.50	0.01	0.50	4.12
Follow up time	0.10	0.97	0.33	-0.10	0.30
female	-0.40	-0.91	0.36	-1.27	0.47

3.6. Publication bias

As shown in Figure 4, linear regression test of funnel plot asymmetry. Test result: t = -2.29, df = 22, p-value = 0.0317. multiplicative residual heterogeneity variance (tau^2 = 173.5553)

Table 3. The number of studies about different risks

Risk factor	Number of studies reported this risk factor 17 (70.8%)
Older Age	10 (41.7%)
sex	2 (8.3%)
Hospitalization status/length of hospital stay	3 (12.5)
COVID severity	5 (20.8%)
Comorbidity/pre-existing conditions	4 (16.7%)
Body weight	2 (8.3%)
Vaccination status	1 (4.2%)
COVID variant (Omicron associated with less long covid symptoms)	2 (8.3%)
Number of covid symptoms	1 (4.2%)
Specific covid symptom	2 (8.3%) (muscle pain and joint pain at acute phase)

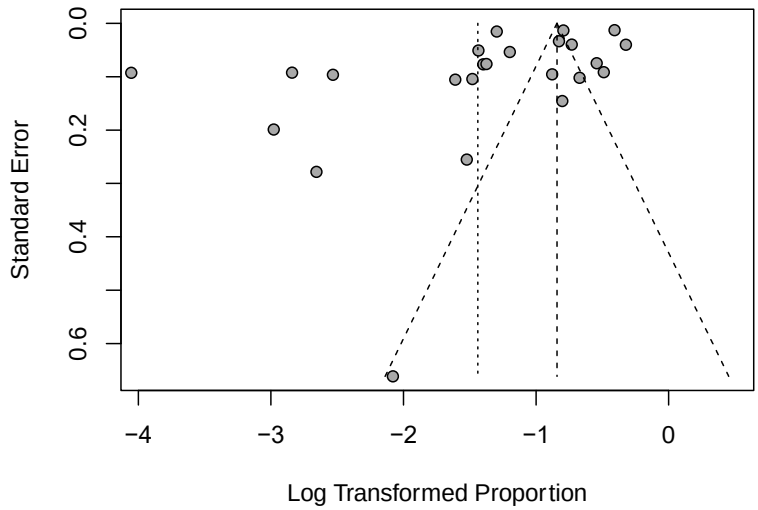

Figure 4. Funnel plot

As shown in Figure 5, among the studies that reported COVID severity, 9028 (38.5%) participants were asymptomatic, and 14420 (61.5%) participants were symptomatic including 897 reported severe cases of COVID-19.

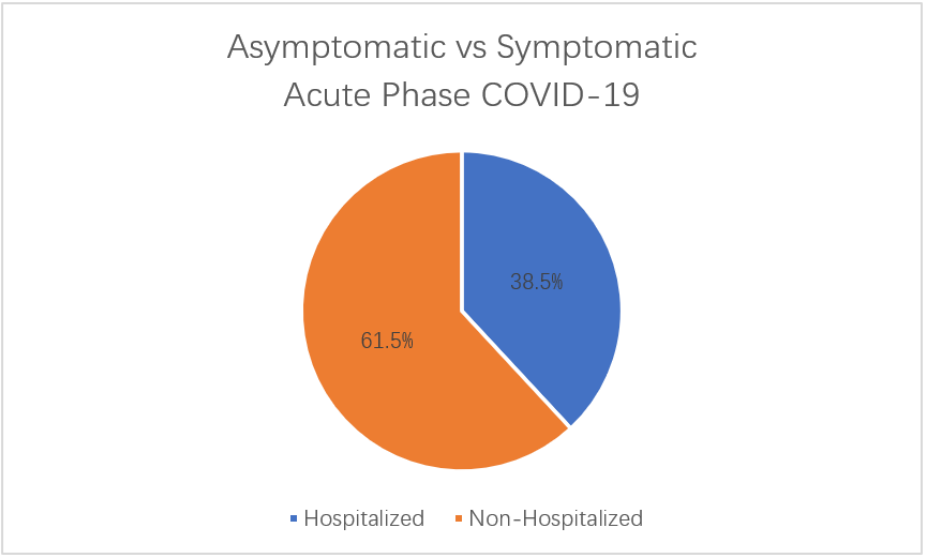

Figure 5. Acute phase Covid severity

In Figure 6, Among the 24 studies that reported hospitalization rate due to acute-phase COVID-19, 1846 (38.1%) participants were hospitalized and 2994 (61.9%) were not hospitalized. A total of three studies only included hospitalized participants.

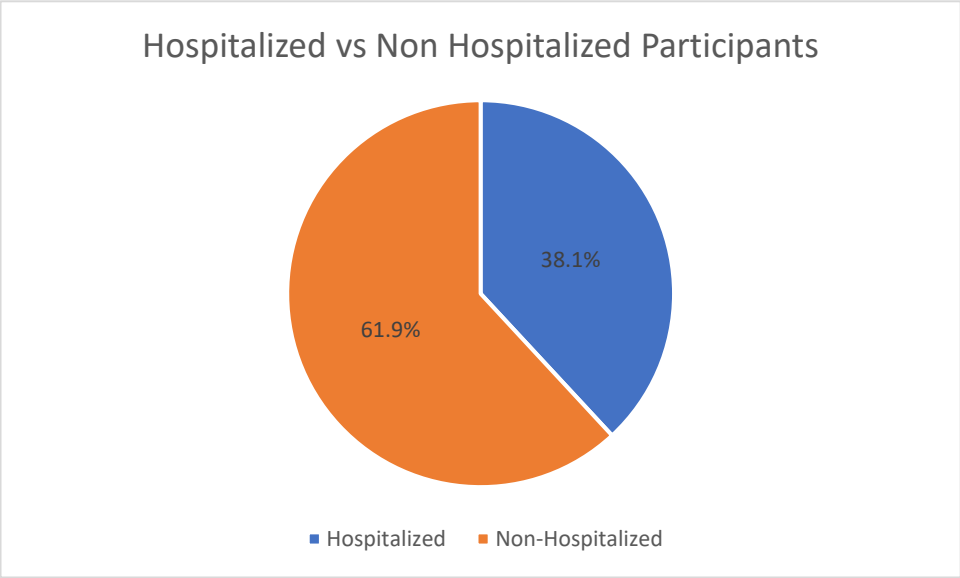

Figure 6. Hospitalization

4. Discussion

The aim of this study was to look for key factors that influence long-term discomfort in children infected with COVID-19. Through the analysis of relevant papers from 2021 to 2023, we found that the situation is far more complicated than we think, and there are many research blind spots. The findings of this meta-analysis shed light on the prevalence of long COVID in children and adolescents, one of the forefront concerns regarding COVID-19 implications. The data presents a notable heterogeneity in the prevalence of persistent post-COVID symptoms across different age groups. One of the key findings to be emphasized is the high prevalence rate of 52.0% for children aged > 12 (18, 21, 25), which is substantially higher than the younger cohort aged < 12 (8-17, 19-20, 22-24, 26-31).

A bias that could affect the interpretation of the results stems from the method of data collection in the included studies. For many of the younger age groups, it is common for parents or guardians to fill out questionnaires on behalf of their children. This could potentially introduce a bias, especially when compared to the older age group where self-reporting is more common. Parental perceptions and their inherent anxiety about their child's health, might lead to an inadvertent overreporting or underreporting of symptoms. This underscores the need for standardized, age-appropriate methodologies in reporting methods in future research on the topic. In addition, regional disparities in data were evident. While there was a significant amount of data from Europe and some parts of Asia, there is a noticeable shortage of studies from regions such as Africa and South America. This gap underscores the need for a more globally encompassing research approach to obtain a more holistic view of long COVID's prevalence and characteristics among children worldwide.

As the discussion around the long-term consequences of COVID-19 in children gains awareness, the scientific community should refine the definitions and diagnostic criteria surrounding long COVID. The variability in definitions—spanning from the CDC's benchmark of symptoms persisting four weeks post-infection to WHO's criteria of symptoms lasting two months after a three-month post-infection onset—can complicate the diagnosis and management of long COVID. Moreover, the lack of control groups in many studies can make it challenging to discern the true impact and causality of COVID-19 in the reported long-term symptoms. Finally, the preventive aspect of long COVID, particularly the efficacy of vaccinations in reducing its prevalence, remains a critical area for further exploration. As newer strains emerge and the global populace navigates subsequent waves of

infections, understanding the nuances of long COVID in children and adolescents becomes not only a medical imperative but also a social and educational one. The potential implications of this syndrome—ranging from physical health to cognitive development and educational attainment—underscore the urgency for continued, rigorous research and targeted interventions.

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