

Post-COVID-19 conditions in children and adolescents diagnosed with COVID-19

Running title: Post-COVID-19 in children / adolescents

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Impact

- The prevalence of post-COVID-19 condition was 2.0% in this population of children and adolescents.
- Older children and adolescents were more likely to be diagnosed with post-COVID-19 condition than their younger counterparts.
- Anxiety disorder, somatoform disorder, and allergic rhinitis were significantly associated with post-COVID-19 condition.
- More data from other settings and countries are warranted to corroborate or refute these findings.

Abstract

Background: This study aimed to investigate the prevalence of and the factors associated with post-COVID-2019 condition in COVID-19 children and adolescents in Germany.

Methods: The present retrospective cohort study used data from the Disease Analyzer database (IQVIA), and included patients aged <18 years who were diagnosed with COVID-19 in one of 524 general and 81 pediatric practices in Germany between October 2020 and August 2021 (index date: first COVID-19 diagnosis). Post-COVID-19 condition was assessed between index date and November 2021. Covariates included age, sex, type of practice, and chronic conditions documented in at least 1% of the population.

Results: There were 6568 children and adolescents included in this study (mean [SD] age 10.1 [4.9] years; 49.2% girls). The prevalence of post-COVID-19 condition was 2.0% in the population. Patients aged 13-17 years were more likely to be diagnosed with post-COVID-19 condition compared with those being aged ≤ 5 years (RR=3.14). Anxiety disorder (RR=2.53), somatoform disorder (RR=2.11), and allergic rhinitis (RR=2.02) were also significantly associated with post-COVID-19 condition.

Conclusion: Post-COVID-19 condition was rare in COVID-19 children and adolescents in Germany. Data from other settings are warranted to confirm these findings.

Introduction

Coronavirus disease 2019 (COVID-19) is a disorder caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ COVID-19 is a systemic disease with pulmonary manifestations such as cough, sputum production and shortness of breath, as well as extra-pulmonary manifestations such as diarrhea, erythematous rash and arrhythmia.² COVID-19 emerged in the city of Wuhan in China in December 2019,³ and in March 2020, the World Health Organization declared COVID-19 a global pandemic.⁴ As of 28 March 2022, more than 480 million people have contracted COVID-19, while the number of related deaths approximates 6.1 million.⁵

Less than 10% of all COVID-19 cases occur in children and young adolescents.⁶ In this age group, more than one out of two COVID-19 infections are symptomatic, and the two most frequent symptoms are fever and cough.⁷ Less frequent symptoms include, for example, rhinorrhoea, sore throat and headache. Although COVID-19 manifestations usually last only several days, some children and adolescents may display persistent symptoms and may experience post-COVID-19 condition. In the past months, at the time of writing, a substantial body of literature has investigated the prevalence of post-COVID-19 condition in young patients.^{8–17} For example, one study, including 129 patients aged ≤ 18 years from Italy and diagnosed with COVID-19 in March – November 2020, showed that 58.2% of the sample had persistent symptoms more than a month after the diagnosis, and the three most frequent symptoms were insomnia, nasal congestion/rhinorrhoea and fatigue.¹¹ Another study of 312 patients from Norway found that the prevalence of persistent symptoms was around 61% six months after being tested positive for COVID-19.⁹ Although these studies have advanced the field, they display several limitations that need to be acknowledged. First, the majority of these

studies had relatively small sample sizes (i.e., less than 1000 participants were included), thus limiting the generalizability of their findings. Second, persistent symptoms were assessed at different time points following COVID-19 diagnosis, and most of this research failed to use a standardized definition of post-COVID-19 condition. Third, little is known on how demographic and clinical factors are associated with this disorder. In this context, more data on post-COVID-19 condition in children and adolescents are urgently warranted.

Therefore, the aim of this retrospective study was to investigate the prevalence of and the factors associated with post-COVID-19 condition in patients aged <18 years who were diagnosed with COVID-19 in pediatric and general practices in Germany between October 2020 and August 2021.

Methods

Database

Data from the Disease Analyzer database (IQVIA) were used for this retrospective study. This database has already been described in the literature.¹⁸ Briefly, the Disease Analyzer database includes demographic, diagnosis and prescription data anonymously obtained in general and specialized practices in Germany. Diagnoses are coded using the International Classification of Diseases, 10th revision (ICD-10), while prescriptions are coded using the Anatomical Classification of Pharmaceutical Products of the European Pharmaceutical Marketing Research Association (EphMRA). Data are regularly transferred from the computers of practices to IQVIA, and the quality of these data is assessed based on several criteria, such as completeness of information and linkage between diagnoses and prescriptions. The database does not contain missing values on demographic and diagnosis variables. Laboratory values are often missing;

however these values were not used in the present study. Practices included in the Disease Analyzer database are selected using several variables (i.e., physician's age, specialty group, community size category, and German federal state), and approximately 3% of all practices from Germany are available in the database.

Ethic statement

The database used includes only anonymized data in compliance with the regulations of the applicable data protection laws. German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data.

Because patients were only queried as aggregates and no protected health information was available for queries, no Institutional Review Board approval was required for the use of this database or the completion of this study.

Study population

This retrospective cohort study included children and adolescents aged <18 years who were diagnosed with COVID-19 (ICD-10: U07.1 [COVID-19, virus identified] or U08.9 [personal history of COVID-19, unspecified]) in one of 524 general and 81 pediatric practices in Germany between October 2020 and August 2021. The median (interquartile range) number of children and adolescents with COVID-19 per practice was 3.0 (1.0-714.0) for general practices and 16.0 (1.0-276.0) for pediatric practices. Only general and pediatric practices having used the ICD-10 code U09.9 at least once during the study period were selected. Index date corresponded to the visit date on which COVID-19 was diagnosed for the first time. Data were collected until November 2021, and patients were followed after COVID-19 diagnosis for a minimum of three

months. Mean (standard deviation) duration of follow-up was 106 (87) days in patients with post-COVID-19 condition and 103 (85) days in those without post-COVID-19 condition. The flow diagram of study patients is displayed in **Figure 1**. Finally, this study adheres to STROBE guidelines for cohort studies (**Supplementary Table 1**).

Study variables

Post-COVID-19 condition was defined using the ICD-10 code U09.9 (post COVID-19 condition, unspecified), and was assessed between index date and November 2021. Covariates included age, sex, type of practice (general or pediatric), and chronic conditions diagnosed in at least 1% of patients in the year prior to the index date. Chronic conditions were the following: dermatitis and eczema (ICD-10: L20-L30), disorders of psychological development (ICD-10: F80-F89), chronic bronchitis (ICD-10: J42), asthma (ICD-10: J45 and J46), allergic rhinitis (ICD-10: J30), obesity (ICD-10: E66), urticaria (ICD-10: L50), sleep disorders (ICD-10: G47), somatoform disorder (ICD-10: F45), gastritis and duodenitis (ICD-10: K29), reaction to severe stress, and adjustment disorders (ICD-10: F43), chronic otitis media (ICD-10: H65.2, H65.3, H65.4, H66.1, H66.2, and H66.3), vitamin D deficiency (ICD-10: E55), and anxiety disorder (ICD-10: F41).

Statistical analyses

Demographic and clinical characteristics were compared between patients with and those without post-COVID-19 condition using chi-square tests for categorical variables and Wilcoxon tests for continuous variables. The prevalence of post-COVID-19 condition was further studied in the overall sample. Finally, associations between covariates and post-COVID-19 condition were analyzed with unadjusted and adjusted Poisson regression models. The adjusted Poisson regression model included all covariates. The results of these regression

analyses are displayed as risk ratios (RRs) and 95% confidence intervals (CIs). P-values lower than 0.050 were considered statistically significant. All analyses were conducted with SAS 9.4.

Results

This study included 6568 children and adolescents aged <18 years (mean [standard deviation] age 10.1 [4.9] years; 49.2% girls; **Table 1**). The majority of patients (64.5%) were followed in general practices. The three most frequent chronic conditions documented in the year prior to the diagnosis of COVID-19 were dermatitis and eczema (23.6%), disorders of psychological development (15.7%), and chronic bronchitis (8.0%). The prevalence of post-COVID-19 condition in the sample was 2.0%. The results of the unadjusted and adjusted Poisson regression models are displayed in **Table 2**. The adjusted regression model showed that patients aged 13-17 years were more likely to be diagnosed with post-COVID-19 condition compared with their counterparts being aged ≤ 5 years (RR=3.14, 95% CI: 1.71-5.78). Furthermore, anxiety disorder (RR=2.53, 95% CI: 1.05-6.11), somatoform disorder (RR=2.11, 95% CI: 1.02-4.39), and allergic rhinitis (RR=2.02, 95% CI: 1.10-3.82) were significantly associated with post-COVID-19 condition.

Discussion

Main findings

In this study of more than 6,500 children and adolescents with COVID-19 from Germany, the prevalence of post-COVID-19 condition was around 2%. In addition, older age, anxiety disorder, somatoform disorder, and allergic rhinitis were positively and significantly associated with post-COVID-19 condition compared with younger age and the absence of these chronic

conditions, respectively. To the best of the authors' knowledge, this is one of the largest studies to date to have investigated the prevalence of and the factors associated with post-COVID-19 condition in children and adolescents.

Interpretation of findings

Several studies have suggested that post-COVID-19 condition is relatively rare in children and adolescents. For example, a study, including 258,790 children aged 5-17 years who were tested for SARS-CoV-2 in the United Kingdom between March 2020 and February 2021, found that 1.8% of those who were initially symptomatic had symptoms persisting at least 56 days.¹² It was observed, in another cohort of 1355 COVID-19 children living in Switzerland, that the prevalence of symptoms lasting more than 12 weeks was 2.4%, and the most frequent symptoms were tiredness, concentration difficulties and increased need for sleep.¹⁴ There are several hypotheses to explain the persistence of symptoms in some COVID-19 patients. First, SARS-CoV-2 may cause injury to tissues and organs, and these lesions may favor the occurrence of post-COVID-19 condition.¹⁹ Second, data are suggesting that SARS-CoV-2 is not always cleared out from the organism after the acute phase of the infection, and that the virus may be found in some reservoirs in the body.²⁰ Third, post-COVID-19 condition may involve persistent immunological dysfunctions, such as activation of innate immune cells, lack of naive B and T cells, and overexpression of interferon molecules.²¹ The prevalence of post-COVID-19 condition may be higher in hospital settings, but these settings were not included in the present study. For example, previous research found persistent symptoms in approximately a quarter of children previously hospitalized for COVID-19.¹³ Similar findings were obtained in adults, suggesting that the severity of SARS-CoV-2 infection may predict post-COVID-19 condition.²²

This body of research further showed a positive and significant relationship of older age (versus younger age) and several chronic conditions (versus the absence of these conditions) with post-COVID-19 condition. One study, including 58 children and adolescents from Iran, found that older participants were more likely to be diagnosed with long COVID-19 than their younger counterparts.⁸ Similar results were obtained in a prospective cohort of 518 patients aged ≤ 18 years living in Russia, as persistent symptoms were significantly more frequent in those aged 6-11 and 12-18 years than in those aged < 2 years.¹³ The association between age and post-COVID-19 condition in youths may be explained by the fact that symptoms at the diagnosis of COVID-19 are more common in adolescents than in children,²³ and that the presence of multiple symptoms during the early phase of the disease predicts the occurrence of post-COVID-19 condition.²⁴ Interestingly, the present study identified three chronic diseases positively associated with post-COVID-19 condition, and these diseases were anxiety disorder, somatoform disorder, and allergic rhinitis. In terms of psychiatric disorders, similar results have been obtained in the adult population. It was observed in one study, including 128 COVID-19 adults from Ireland, that pre-existing anxiety and depression favored the persistence of fatigue in the weeks following the onset of the initial symptoms.²⁵ People with preexisting psychiatric comorbidities have been found to be at particular risk for severe COVID-19,^{26,27} and this could indirectly increase the incidence of post-COVID-19 condition in this population of patients.^{28,29} In terms of physical disorders, some literature has also found children with a history of allergic diseases (i.e., asthma, allergic rhinitis, eczema, or food allergy) to be at a significantly increased risk for post-COVID-19 condition compared with their counterparts without a history of allergic diseases (odds ratio=1.67, 95% CI: 1.04-2.67).¹³ It has been hypothesized that aberrant mast cell activation is involved in the physiopathology of both allergic diseases^{30,31} and post-COVID-19 condition,³² and this could explain the relationship between these conditions.

Clinical implications and directions for future research

Based on the results of this study, post-COVID-19 condition is relatively rare in children and adolescents. That being said, general practitioners and pediatricians should regularly follow young COVID-19 patients, particularly those with preexisting psychiatric and allergic conditions. Although post-COVID-19 condition at a young age is insufficiently understood, the management of children and adolescents with this disorder is of utmost importance. As in adults, this management should include physical rehabilitation, management of pre-existing physical and psychiatric disorders and social support. In terms of future research, more studies with large sample sizes are warranted on the prevalence of post-COVID-19 condition, while there is a need for more data on the risk factors for this chronic condition.

Strengths and limitations

Two strengths of this study are the number of participants and the use of data obtained in general and pediatric practices. Nonetheless, the study findings should be interpreted in light of several limitations. First, there was no information on the type of persistent symptoms (e.g., cough, fatigue and anosmia). Second, it is possible that post-COVID-19 condition was diagnosed at the hospital for some patients, and the prevalence of this disorder may have therefore been underestimated. Third, the ICD-10 code for post-COVID-19 condition may have been underused by general practitioners and pediatricians, and this may have biased the results of the study. Fourth, no data was available on the severity of the initial SARS-CoV-2 infection, although children and adolescents with severe COVID-19 may be more likely to be subsequently diagnosed with post-COVID-19 condition than those with mild or moderate COVID-19.

Conclusions

This study, including approximately 6600 children and adolescents with COVID-19 from Germany, revealed that the prevalence of post-COVID-19 condition was around 2%. Older age, psychiatric disorders and allergic rhinitis were significantly and positively associated with post-COVID-19 condition. More data collected in other countries and settings are warranted to corroborate or invalidate these results, while further studies should seek to identify predictors of post-COVID-19 condition better.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

Karel Kostev contributed to the design of the study, performed the statistical analyses, and corrected the manuscript. Lee Smith, Ai Koyanagi, and Marcel Konrad corrected the manuscript. Louis Jacob contributed to the design of the study, managed the literature searches, wrote the first draft of the manuscript, and corrected the manuscript. All authors contributed to and have approved the final manuscript.

Competing interests

The authors declare no competing financial interests.

Statement of ethics

German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data.

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Tables and Figures

Table 1. Demographic and clinical characteristics of the study sample (N=6568)

Variable	Total (n=6568)	Patients without post- COVID-19 condition (n=6454)	Patients with post-COVID- 19 condition (n=114)	P-value ¹
<i>Age (in years)</i>				
Mean (standard deviation)	10.1 (4.9)	10.0 (4.9)	12.1 (4.7)	<0.001
≤5	1511 (23.0)	1497 (23.2)	14 (12.3)	<0.001
6-9	1055 (16.1)	1043 (16.2)	12 (10.5)	
10-12	1481 (22.5)	1459 (22.6)	22 (19.3)	
13-17	2521 (38.4)	2455 (38.0)	66 (57.9)	
<i>Sex</i>				
Girls	3230 (49.2)	3168 (49.1)	62 (54.4)	0.262
Boys	3338 (50.8)	3286 (50.9)	52 (45.6)	
<i>Type of practices</i>				
General	4239 (64.5)	4172 (64.6)	67 (58.8)	0.194
Pediatric	2329 (35.5)	2282 (35.4)	47 (41.2)	
<i>Chronic conditions diagnosed in at least 1% of patients in the year prior to the index date</i>				
Dermatitis and eczema	1551 (23.6)	1465 (22.7)	35 (30.7)	0.044
Disorders of psychological development	1032 (15.7)	1016 (15.7)	16 (14.0)	0.620
Chronic bronchitis	527 (8.0)	519 (8.0)	8 (7.0)	0.690
Asthma	461 (7.0)	448 (6.9)	13 (11.4)	0.065
Allergic rhinitis	416 (6.3)	402 (6.2)	14 (12.3)	0.009
Obesity	300 (4.6)	294 (4.6)	6 (5.3)	0.720
Urticaria	225 (3.4)	220 (3.4)	5 (4.4)	0.570
Sleep disorders	190 (2.9)	187 (2.9)	3 (2.6)	0.867
Somatoform disorder	188 (2.9)	179 (2.8)	9 (7.9)	0.001
Gastritis and duodenitis	157 (2.4)	154 (2.4)	3 (2.6)	0.865
Reaction to severe stress, and adjustment disorders	125 (1.9)	122 (1.9)	3 (2.6)	0.566
Chronic otitis media	122 (1.9)	120 (1.9)	2 (1.8)	0.934
Vitamin D deficiency	94 (1.4)	92 (1.4)	2 (1.8)	0.769
Anxiety disorder	83 (1.3)	77 (1.2)	6 (5.3)	0.001

Data are N (%) unless otherwise specified.

¹ P-values were estimated using chi-square tests for categorical variables and Wilcoxon tests for continuous variables

Table 2. Association between demographic variables, chronic conditions and post-COVID-19 condition in children and adolescents diagnosed with COVID-19 in Germany (unadjusted and adjusted Poisson regression)

Variable	Unadjusted Poisson regression		Adjusted Poisson regression	
	RR (95% CI)	P-value	RR (95% CI)	P-value
<i>Age (in years)</i>				
≤5	Reference			
6-9	1.33 (0.61-2.90)	0.469	1.39 (0.64-3.06)	0.408
10-12	1.80 (0.91-3.55)	0.090	1.74 (0.87-3.49)	0.115
13-17	3.40 (1.88-6.18)	<0.001	3.14 (1.71-5.78)	<0.001
<i>Sex</i>				
Girls	Reference			
Boys	0.89 (0.55-1.16)	0.243	0.85 (0.59-1.24)	0.398
<i>Chronic conditions diagnosed in at least 1% of patients in the year prior to the index date</i>				
Dermatitis and eczema	1.35 (0.30-3.17)	0.574	1.47 (0.91-2.37)	0.117
Disorders of psychological development	0.84 (0.45-1.56)	0.582	0.83 (0.29-2.41)	0.729
Chronic bronchitis	0.87 (0.42-1.77)	0.693	0.67 (0.31-1.46)	0.309
Asthma	1.71 (0.96-3.04)	0.070	1.38 (0.72-2.63)	0.338
Allergic rhinitis	2.07 (1.18-3.62)	0.011	2.02 (1.10-3.82)	0.013
Obesity	1.16 (0.51-2.64)	0.722	0.80 (0.34-1.87)	0.609
Urticaria	1.29 (0.53-3.17)	0.574	0.89 (0.35-2.30)	0.815
Sleep disorders	0.91 (0.29-2.86)	0.868	0.72 (0.22-2.41)	0.601
Somatoform disorder	2.91 (1.47-5.74)	0.002	2.11 (1.02-4.39)	0.045
Gastritis and duodenitis	1.10 (0.35-3.47)	0.866	0.74 (0.23-2.39)	0.614
Reaction to severe stress, and adjustment disorder	1.40 (0.44-4.48)	0.571	0.82 (0.25-2.74)	0.752

Chronic otitis media	0.94 (0.23-3.81)	0.935	0.64 (0.15-2.68)	0.539
Vitamin D deficiency	1.23 (0.30-4.98)	0.772	0.86 (0.21-3.56)	0.834
Anxiety disorder	4.34 (1.90-9.88)	<0.001	2.53 (1.05-6.11)	0.038

Abbreviation: COVID-19 coronavirus disease 2019; RR risk ratio; CI confidence interval.

Significant associations are indicated in bold.

All variables listed in the table were included in the adjusted Poisson regression.

Figure

1

