

Title of the article: Respiratory sequelae after COVID-19 infection in Thai healthy children

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Abstract

Background and Aims: The long-term respiratory sequelae of COVID-19 infection in children remain poorly understood and may differ across countries. This study aims to investigate the respiratory sequelae, including residual respiratory symptoms and pulmonary function in Thai children. The secondary aim is to identify factors associated with the respiratory sequelae. **Materials and Methods:** This is an observational study involving 56 healthy children, aged between 7-18 years, who were diagnosed with COVID-19 infection from July 2021 to February 2023. Clinical data relating to COVID-19 infection and persistent symptoms after the infection were assessed after the infection up to six months. Spirometry was performed to assess pulmonary function. **Results:** Post COVID-19 symptoms were identified in 14 patients (25%), with fatigue, cough, and dyspnea being common symptoms (28-35%). A significant correlation was found between post COVID-19 symptoms and pneumonia (OR = 6.00, 95%CI [1.54,23.33], p=0.01). Abnormal pulmonary function was identified in 10 patients (17.8%) with obstructive impairment being the most common. However, there were no significant association between clinical factors and pulmonary function impairment. **Conclusion:** Prolonged respiratory symptoms and abnormal pulmonary function following COVID-19 infection are not uncommon in children. The post COVID-19 symptoms are possibly associated with COVID-19 pneumonia.

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Conclusion: Prolonged respiratory symptoms and abnormal pulmonary function following COVID-19 infection are not uncommon in children. The post COVID-19 symptoms are possibly associated with COVID-19 pneumonia.

Key-words: post COVID-19, pulmonary function test, pediatric

Key Messages: After COVID-19 infection, healthy children may exhibit persistent symptoms and abnormal pulmonary function. Although those who developed COVID-19 pneumonia are at a greater risk for the prolong symptoms, some children with less severe diseases also had the respiratory sequelae.

Introduction:

The pandemic coronavirus disease 2019 (COVID-19) has affected millions worldwide since March 2020. Among pediatric patients infected with the virus, only 15% remain asymptomatic, while 90% experience mild symptoms¹. However, some symptoms persist after the infection, known as post COVID and long COVID², and can significantly impact the patient's quality of life. The common symptoms include fatigue, insomnia, and difficulty breathing^{3,4}. Also, COVID-19 infection can result in pulmonary function impairment. In adults, a restrictive ventilatory defect was found in 64% of the patients after three months of recuperation from COVID-19 infection as a result of post-infection pulmonary fibrosis⁵.

In children, there is limited evidence on the long-term respiratory problems of COVID-19, including abnormal pulmonary function. Previous studies demonstrated various results that one study in children reported no abnormal spirometry⁶, while another study in adolescents identified abnormal spirometry in 24% of cases and obstructive impairment was the most common⁷. In addition, treatment guidelines for COVID-19 infection in developing countries are usually modified due to limitations in healthcare resources. For instance, in Thailand, many patients could not access to the service and patients with COVID-19 pneumonia were primarily treated with favipiravir. Variations in the management possibly lead to different respiratory outcomes after the infection, but the outcomes in such situations have been rarely examined.

Given that more specific data for developing countries are necessary, this study was undertaken to investigate prevalence of respiratory sequelae after COVID-19 infection, including residual respiratory symptoms and pulmonary function, in Thai pediatric patients. The secondary objective is to identify 1) the relationship between post COVID-19 symptoms and pulmonary function impairment, 2) factors associated with any respiratory sequelae and 3) factors associated with quantitative changes in spirometry parameters. The novel findings from this study may aid in comprehending the long-term effects of COVID-19 infection in Thai children and in monitoring patients at risk.

Subjects and Methods:

Design and setting

This is a cross-sectional study of pediatric patients who have experienced COVID-19 infection in the past 1-6 months. The study was undertaken from July 2021 to February 2023. This research was approved by the ethic committee (IRB No. 851/64). Informed consent was obtained from the parents of patients before proceeding the study.

Participants

Inclusion criteria is a child aged 7-18 years old, previously diagnosed with COVID-19 infection by an evidence of viral antigen detection between 1-6 months prior to the study, and the child must be able to perform acceptable spirometry in accordance with the American Thoracic Society (ATS) / European Respiratory

Society (ERS) criteria⁸. Exclusion criteria is any of the followings; 1) a history of smoking, 2) respiratory infection within four weeks prior to the assessment, 3) using corticosteroids within four weeks prior to the assessment, and 4) presence of other medical conditions that may affect pulmonary function, including asthma, restrictive lung diseases and neuromuscular weakness. Children who met the criteria were invited to participate in this study via telephone.

Data Collection

Relevant clinical data, including age, sex, anthropometry, past medical history, and COVID-19 infection, were collected from the parents and electronic medical records. Overweight and obesity were defined by body mass index (BMI) > 23.5 and > 25 kg/m² respectively⁹. The characteristics of COVID-19 infection included symptoms and severity classified based on National Institutes of Health (NIH) COVID-19 treatment guidelines⁹. Mild severity was defined by symptoms of upper respiratory tract infection (URI) (such as fever, cough, sore throat, headache or myalgia) and normal chest X-ray. Moderate severity was defined by symptoms of lower respiratory tract infection (such as increased respiratory rate, chest withdrawing or desaturation) or abnormal chest X-ray. All the chest X-rays were reviewed by radiologists outside the study at the time of diagnosis.

The definition of respiratory sequelae in this study refers to post COVID-19 symptoms or abnormal spirometry beyond four weeks after acute COVID-19 infection. Residual respiratory symptoms suggestive of post COVID conditions were assessed on interview with the parent one day before spirometry testing.

Pulmonary function was evaluated using spirometry. The testing was carried out by an experienced pediatric respiratory technician, adhering to the standardized procedures outlined by the ATS and ERS^{8,11}. Forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and FEV₁/FVC ratio are interpreted regarding the ATS/ERS spirometry impairments classification¹⁰. Abnormal pulmonary function is identified when FVC, FEV₁ or FEV₁/FVC ratio is less than lower limit of normal or z-score -1.64 . Abnormal FEV₁ and FEV₁/FVC ratio are classified as obstructive impairment and abnormal FVC is classified as possible restrictive impairment. If spirometry shows obstructive impairment, a bronchial responsiveness test is performed by inhaling 400 micrograms of salbutamol, followed by repeating spirometry 15 minutes later.

Statistical Analysis

Descriptive statistics were used to present patient's demographics, COVID-19 infection and respiratory sequelae. Then, the patients were categorized into two groups: those with any respiratory sequelae and those without. Continuous variables between the two groups were compared using Student's t-test and categorical variables were compared using Chi-square or Fisher Exact test.

The association between the presence of any post COVID-19 symptoms and the presence of pulmonary function impairments was examined using Fisher Exact test. Logistic regression was used to determine risk factors associated with the symptoms or the pulmonary function impairments. If there are more than one variable with p -value < 0.20 from univariate regression analysis, the variables will be subjected to multivariate regression analysis. Additionally, we evaluated pulmonary function as continuous data through linear regression analysis to evaluate its associated risk factors. Three measures of pulmonary function were assessed including FEV₁ z-score, FVC z-score, and FEV₁/FVC z-score.

P-value < 0.05 were considered statistical significance. The analysis was performed by using STATA version 17.1 (College Station, Texas 77845 USA).

Results:

Primary outcomes

Of 672 children who met the inclusion criteria, 392 were disqualified based on the exclusion criteria. All the eligible children were approached but only 56 were consent to participate in the study. The average time of assessment after COVID-19 infection was 98.6 ± 26.6 days. Twenty-one patients (37.5%) had respiratory sequelae with 11 patients (19.6%) having only prolonged respiratory symptoms, seven patients (12.5%) having

only abnormal pulmonary function and three patients (5.4%) having both. The respiratory sequelae were present in 66.7% of patients who had non-severe disease and 33.3% with pneumonia. There was no significant relationship between the presence of any post COVID-19 symptoms and the presence of pulmonary function impairments (p -value = 0.69).

Table 1 presents the characteristics of patients and the two groups categorized by the presence of respiratory sequelae (post COVID-19 symptoms and/or pulmonary function impairment defined by abnormal spirometry). The average age of patients was 10.7 ± 2.5 years. No significant difference was found in the baseline characteristics between the two groups, except FEV₁ z-score that was significantly higher in patients without respiratory sequelae (0.88 ± 1.11 vs -0.06 ± 1.18 , p -value = 0.003).

Regarding the history of acute COVID-19 infection, the most common symptoms were cough (62.5%), fever (62.5%), and rhinitis (50%). Forty-three patients (76.8%) had only upper respiratory symptoms, (mild COVID-19 infection) and 13 patients (23.2%) had pneumonia (moderate COVID-19 infection). After COVID-19 infection, 14 patients (25%) continued to experience post COVID symptoms. Among those with post COVID-19, fatigue was the most common (35%), followed by dyspnea and cough (28% each). Rhinorrhea was the least common symptom (14%).

Abnormal spirometry was observed in 10 patients (19.6%), accounting for approximately half of the patients with respiratory sequelae. Regarding the classification of pulmonary function impairment, seven patients (70%) had either low FEV₁ or FEV₁/FVC, i.e. obstructive impairment, and three of them responded to bronchodilator. Three patients (30%) had low FVC, i.e. possible restrictive impairment.

The proportion of history of COVID-19 pneumonia was higher in patients with respiratory sequelae than those without, but there was no statistical significance (33.3% vs 17.1%, p -value = 0.20). Seven of the patients with COVID-19 pneumonia (53.8%) had at least one post COVID symptoms, compared with seven of the patients with mild COVID-19 (16.2%). Two of the patients with COVID-19 pneumonia (15.3%) had pulmonary function impairment, compared with nine of the patients with mild COVID-19 infection (20.9%).

Table 1: The characteristics of children previously infected with COVID-19, grouped by the presence of respiratory sequelae (post COVID-19 symptoms and/or pulmonary function impairment on spirometry)

	All (N=56)	Without respiratory sequelae (N=35)	With respiratory sequelae (N=21)	p -value
Age (years), mean ± SD	10.7±2.5	10.4±2.3	11.3±2.7	0.19
Symptoms during COVID-19 infection, n(%)	35 (62.5) 35 (62.5) 28 (50) 14 (25) 3 (5.4) 2	20 (57.1) 20 (57.1) 16 (45.7) 10 (28.6) 1 (2.9) 0	15 (71.4) 15 (71.4) 12 (57.1) 4 (19.1) 2 (9.5) 2	0.29 0.29 0.58 0.53 0.55 0.14
Cough	(3.6)	(0)	(9.5)	
Fever				
Rhinitis				
Sore throat				
Dyspnea				
Fatigue				
Overweight or obesity, n (%)	15 (26.8)	10 (28.6)	5 (23.8)	0.70
History of atopy	1 (1.8)	0 (0)	1 (4.8)	0.38
Diagnosis COVID-19 infection, n (%)				0.20
Mild/URI				
Moderate/Pneumonia				

	All (N=56)	Without respiratory sequalae (N=35)	With respiratory sequalae (N=21)	p-value
	43 (76.8) 13 (23.2)	29 (82.9) 6 (17.1)	14 (66.7) 7 (33.3)	
SpO ₂ (%), mean ± SD	98.6±1	98.5 ±1	98.9±1	0.11
Pulmonary function, mean ± SD	0.53±1.18	0.88±1.11	-0.06±1.18	0.003
FEV ₁ z-score	0.61±1.21	0.85±1.12	0.20±1.48	0.052
FVC z-score	-0.08±1.09	0.05±0.87	-0.30±1.38	0.25
FEV ₁ /FVC (%) z-score				
Time since the last COVID-19 infection (days), mean ± SD	98.4±26.6	96.2±26.7	102±26.9	0.45
Pulmonary function impairment on spirometry, n (%)	10 (17.9) 6 (10.7) 1 (1.8) 3 (5.4)	- - - -	10 (41.6) 6 (28.6) 1 (4.8) 3 (14.3)	N/A
Low FEV ₁ /FVC				
Isolated Low FEV ₁				
Isolated Low FVC				

FEV₁ = forced expiratory volume in 1 second; FVC = Forced vital capacity; FEV₁/FVC = FEV₁over FVC ratio; SD = standard deviation; SpO₂ = oxygen saturation at room air

Secondary outcomes

Table 2 presents the risk factors for post COVID-19 symptoms and pulmonary function impairment shown in spirometry. The history of COVID-19 pneumonia significantly associated with the presence of post COVID-19 symptoms (OR = 6.00, 95% CI [1.54,23.33], $p = 0.01$). However, there was no statistically significant association between the pneumonia and subsequent pulmonary function impairment (OR = 0.79, 95% CI [0.15-4.32], $p = 0.79$). Other factors, including increasing age, being overweight or obese, and the interval between acute COVID-19 infection and assessment timepoint, did not show any significant association with post COVID-19 symptoms and pulmonary function impairment. FEV₁ z-score was added to the analysis due to the significant difference between patients with and without respiratory sequalae. However, it did not significantly increase the presence of post COVID-19 symptoms.

Table 2: Associated factors of the presence of post COVID-19 symptoms and pulmonary function impairment after COVID-19 infection

	Univariate regression analysis	Univariate regression analysis
	The presence of post COVID symptoms	The presence of post COVID symptoms
	OR (95% CI)	p-value
Increasing age	1.05 (0.82-1.35)	0.68
History of COVID-19 pneumonia	6.00 (1.54-23.33)	0.01
Overweight/obesity	1.13 (0.29-4.34)	0.86
Time interval between the infection and the assessment	0.99 (0.97-1.02)	0.84
FEV ₁ z-score	1.06 (0.63-1.78)	0.804

OR = odd ratio; CI = confidence interval; N/A = not applicable

* The association between the presence of pulmonary function impairment and FEV₁ z-score was not assessed because FEV₁ z-score is one of the determinant factors of pulmonary function impairment.

Table 3 presents factors that may impact on changes in pulmonary function measures in spirometry. Although there was a trend between increasing age and decreasing FEV₁ z-score, the trend did not show a statistically significant correlation. Moreover, there was no significant correlation between the pulmonary function measures with other factors, including the history of COVID-19 pneumonia, being overweight or obesity, the presence of post COVID-19 symptoms, and the interval between acute COVID-19 infection and assessment timepoint.

Table 3: Associated factors of changes in spirometry parameters after COVID-19 infection

	FEV ₁ z-score	FEV ₁ z-score	FVC z-score	FVC z-score	FEV ₁ /FVC z-score	FEV ₁ /FVC z-score
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Increasing age	-0.12 (-0.25, 0.01)	0.06	-0.08 (-0.21, 0.05)	0.24	-0.09 (0.21,0.03)	0.13
History of COVID-19 pneumonia	0.01 (-0.75, 0.77)	0.98	0.26 (-0.51, 1.03)	0.50	-0.29 (-0.99, 0.39)	0.39
Overweight or obesity	0.20 (-0.52, 0.93)	0.58	0.18 (-0.55, 0.92)	0.62	0.002 (-0.66, 0.66)	0.99
Presence of post COVID symptoms	0.09 (-0.65, 0.83)	0.81	0.26 (-0.48, 1.02)	0.48	-0.09 (-0.77, 0.59)	0.79
Time interval between the infection and the assessment	-0.002 (-0.01, 0.01)	0.70	-0.01 (-0.02, 0.005)	0.24	0.007 (-0.004, 0.02)	0.20

Discussion:

This is an observational study evaluating the respiratory sequelae following COVID-19 infection in Thai healthy children aged 7-18 years. The main findings of our study revealed that a quarter of the patients had at least one post COVID symptom which significantly associated with the history of COVID-19 pneumonia. Pulmonary function impairment was found in almost one-fifth of the patients and the obstructive impairment was the most common. However, no clinical characteristics were identified as a significant factor associated with the presence of pulmonary function impairment and changes in pulmonary function measures.

The prevalence of post COVID-19 symptoms in our study is consistent with previous literatures which ranged between 23-27%^{12,13,14}. In addition, fatigue, dyspnea and cough are common symptoms in our study and consistent with findings in other studies^{14,15}. These outcomes are likely to indicate that post COVID-19 symptoms are comparable across countries despite variations in management; and after recovering from COVID-19 infection ongoing follow-up for the patients is necessary despite their lack of remarkable medical backgrounds.

Pneumonia which represents the moderate severity of acute COVID-19 infection, was the only factor associated with respiratory sequelae. Approximately, half of our patients with COVID-19 pneumonia had at least one post COVID-19 symptom. This finding consolidates previous evidence that patients suffering more severe infections or requiring intensive care, are more susceptible to post COVID-19 symptoms, ranging

from 30-70%^{13,15,16,17}. This could be straightforwardly explained by infection-related and cytokine-induced airway and lung damage^{15,16}. Therefore, children who have been diagnosed with COVID-19 pneumonia are at a higher risk and in needs of careful follow-up evaluation. The additional evaluation should include both clinical review and pulmonary function tests.

Among the participants, almost one-fifth exhibited impaired pulmonary function, with obstructive impairment being the most prevalent, followed by possible restrictive impairment. Our findings aligned with existing studies which reported impaired pulmonary function in the patients from 0-24%^{7,14,16,18,19,20}. The wide range of the prevalence of impaired pulmonary function after COVID-19 infection could be explained by multiple reasons, for example children's medical backgrounds and the timepoint of pulmonary function assessment. In the previous study Palacios et al study, it was found that children who had pre-existing conditions such as asthma and obesity exhibited a higher incidence of pulmonary abnormalities⁷. They also reported that the rate of abnormal pulmonary function declined from 24% to 10% over a nine-month follow-up period, which could be a result of either natural healing process or the use of inhaled corticosteroids to treat bronchial hyperresponsiveness⁷.

Our research revealed no significant correlation between post COVID symptoms or COVID-19 pneumonia and impaired pulmonary function, corresponding with earlier research¹⁶. Nevertheless, around 15% of the participants who were diagnosed with COVID-19 URI and did not exhibit persistent symptoms after the infection showed abnormal spirometry results, mainly compatible with obstructive impairments. Probably, this is a consequence of chronic subclinical inflammation of peripheral airways caused by COVID-19, regardless of infection severity^{21,22}. These findings highlight the importance of undertaking pulmonary function tests in patients with COVID-19 infection to evaluate their post-infection progression.

Although this study provides additional data and highlights the importance of monitoring pediatric patients after COVID-19 infection, there are some limitations. First and foremost, the sample size was small as this study was undertaken in a single center. For assessing the respiratory sequelae, we relied on clinical review and spirometry and did not include computed tomography chest imaging, so we were unable to address lung parenchymal changes such as pulmonary fibrosis. Moreover, lung volume and diffusion capacity of the lungs were not routinely measured, so we could not provide additional data on other functional consequences of COVID-19 infection. Finally, this is a cross-sectional study without ongoing evaluations for both post COVID-19 symptoms and pulmonary function. We cannot ascertain whether the respiratory sequelae persist over time or resolve spontaneously. Henceforth, further studies are warranted to fill the gaps and improve the understanding of post COVID conditions in children.

Conclusion

Our study found that some children who had recovered from COVID-19 infection exhibited post COVID conditions and reduced pulmonary function, even in cases with mild diseases. COVID-19 pneumonia was a predictive factor of chronic symptoms in children but there was no remarkable factor associated with pulmonary function impairment. After COVID-19 infection, it is necessary to be aware of the long-term consequences and evaluate the children appropriately. References:

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