

TITLE PAGE

Evaluation of Pulmonary Functions After Discharge in Pediatric Patients with Covid-19

Sevcan İpek¹, Ufuk Utku Güllü², Betül Kızıldağ³, Mehmet Yaşar Özkars⁴, Sadık Yurttutan⁵, Meliha Kübra Kütükçü⁶

¹ Kahramanmaraş Sütçü İmam University Medical Faculty, Department of Pediatrics, Kahramanmaraş, Turkey. drsevcanipek@gmail.com, ORCID ID: 0000-0002-1406-4895

² Kahramanmaraş Sütçü İmam University Medical Faculty, Department of Pediatric Cardiology, Kahramanmaraş, Turkey. ufukutkugullu@gmail.com, ORCID ID: 0000-0002-5561-3598

³ Kahramanmaraş Sütçü İmam University Medical Faculty, Department of Radiology, Kahramanmaraş, Turkey. dr.betulkizildag@hotmail.com, ORCID ID: 0000-0002-2567-4330

⁴ Kahramanmaraş Sütçü İmam University Medical Faculty, Department of Pediatric Allergy and Immunology, Kahramanmaraş, Turkey. myozkars@hotmail.com, ORCID ID: 0000-0003-1290-8318

⁵ Kahramanmaraş Sütçü İmam University Medical Faculty, Department of Pediatrics, Department of Neonatal Intensive Care Unit, Kahramanmaraş, Turkey, dryurttutan@gmail.com, ORCID ID: 0000-0002-4994-9124

⁶ Kahramanmaraş Sütçü İmam University Medical Faculty, Department of Pediatrics, Kahramanmaraş, Turkey, meliha_kubra@hotmail.com, ORCID ID: 0000-0003-1203-8594

Statement of financial support: No financial assistance was received in support of the study.

The authors declare that this paper was not presented at any meeting.

Correspondence:

Sevcan İpek, MD;

Department of Pediatrics,

Kahramanmaraş Sütçü İmam University Medical Faculty,

Avşar Kampüsü, Kahramanmaraş, 46100, Turkey

Tel: +90-3443003349, Fax: +90-3443003409

E-mail: drsevcanipek@gmail.com

Key words: Covid-19, Pandemic, Pulmonary function test, Pediatrics, Spirometry

Running head: A Prospective Study

Abstract:

Objective: In some adult patients diagnosed with Covid-19, abnormal lung imaging and then pulmonary fibrosis were detected in these patients after discharge. Studies on pulmonary function tests have been carried out in these patients, but not yet in pediatric patients. In our study, we performed pulmonary function tests 1 month after discharge in pediatric patients diagnosed with Covid-19. Thus, we thought that when we encountered pulmonary dysfunction in our patients, we could reduce morbidity and mortality by enabled them get involved in pulmonary rehabilitation programs.

Material and Methods: In this prospective study, pediatric patients aged 5-18 years who were hospitalized and discharged with the diagnosis of Covid-19 were included. Pulmonary function tests were performed with spirometry in our patients.

Results: 76 patients were screened. 34 patients were able to perform pft. When the percentage values of the patients in pulmonary function tests were compared with the test value of 100, no significant decrease was found. When the actual values measured by spirometry were compared with the predictive values that should be at the same age, weight and height, no significant decrease was found. However, in the correlation analysis, a moderately negative correlation was found between the length of hospital stay and Fef 25-75.

Conclusion: The fact that the decreasing of Fef 25-75 as the hospitalization period increases due to Covid-19 may be meaningful in terms of showing us that having covid 19 worsens lung functions even in pediatric patients. More comprehensive studies are needed to understand the prognosis of these patients.

Introduction

Sars-CoV-2 was declared as a pandemic by WHO on March 11, 2020 ¹. It has been reported that it is transmitted from person to person by droplets or by contact with eyes, mouth and nasal mucosa after touching contaminated places ². It has been reported that the virus can remain on inanimate surfaces for 72 hours ³. It is stated that it generally affects adults, and that the disease is overcome with mild symptoms in children ⁴. As it is known, radiological imaging may not be correlated with lung functions. Pulmonary function test is the most objective test that evaluates pulmonary functions in the evaluation of lung diseases ⁵. Abnormalities were detected in lung imaging of patients diagnosed with Covid-19 while they were discharged, and pulmonary fibrosis was detected in some patients ⁶. Huang et al. performed respiratory function tests on adult patients diagnosed with Covid-19 after recovery and found that pulmonary functions were impaired ⁷. When we scanned the literature, we realized that pulmonary functions were evaluated after Covid-19 disease in adult patients, but such studies were not conducted in pediatric patients. We evaluated the pulmonary functions of our pediatric patients who were followed up with the diagnosis of Covid-19 1 month after discharge with a pulmonary function test. Thus, we thought that when we encountered pulmonary dysfunction in our patients, we would ensure their early diagnosis and treatment by taking them into pulmonary rehabilitation programs.

Materials and Methods

Patients

The study started after obtaining the approval of the ethics committee (No: 2020/15-08). In this prospective study, pediatric patients aged 5-18 years who were hospitalized and discharged with the diagnosis of Covid-19 were included in the study. Patients with chronic diseases such as neurological disease, heart disease, pulmonary hypertension, cystic fibrosis, immunodeficiency, incompatible children who cannot perform pulmonary function test (children who can't blow into the spirometer), children under 5 years old and mentally retarded patients were excluded from the study. Patients diagnosed and treated with Covid -19 according to WHO Diagnostic Criteria were called to the hospital at least 1 month after discharge with recovery. Written informed consent was obtained from the patients before the pulmonary function test, and pulmonary function test was performed with a spirometer. Predicted values for the same age, height and weight of the patients were taken as a control. It was compared with the actual values of the patients. In addition, congenital heart disease and pulmonary hypertension were

evaluated by the pediatric cardiologist, and as a result, patients with congenital heart disease and pulmonary hypertension were excluded from the study.

Spirometry

Pulmonary function tests were performed with the Zan 100 spirometer (Zan 100, nSpire, Health Inc., Germany) device. Each test was repeated at least 3 times and the highest values were recorded. In the pulmonary function test of the patients, FVC (forced vital capacity), FEV1 (forced expiratory volume in the first second) and FEF 25-75 (forced expiratory flow between 25% and 75% of FVC) were examined.

Statistical Analysis

In this study, using the program "G Power-3.1.9.4", the minimum number of patients was calculated as 34 with 5% type 1 error when the effect size was taken as 0.5 with 80% power at 95% confidence level. Patients were selected randomly. SPSS 25 (Statistical Package for Social Sciences) package program was used. The data were presented as statistics, as mean, standard deviation, frequency and percentage distributions. The suitability of the data to normal distribution was evaluated with the Kolmogorov-Smirnov Test. Single-sample T test was used for the analysis of numerical data meeting the parametric test assumptions, and the Chi-square test was used for the analysis of categorical data. Sign test was used to analyze non-normally distributed data. In comparison of predictive and actual data, independent sample T test (Student T test) was used for normally distributed data, and Mann Whitney-U test was used for non-normally distributed data. Spearman correlation test was used to detect the correlations among data. Retrospectively, patients' chest radiographs were evaluated by 2 observers (1 pediatricist and 1 radiologist). The kappa value was checked to measure the harmony between the 2 observer. For statistical significance, the probability of error (p value) was chosen as 0.05. Test results were considered significant if $p < 0.05$.

Results

A total of 76 patients were screened. Of these, 39 were eligible for the study. Others were excluded from the study because they had asthma, history of allergic disease, immunodeficiency, and other underlying diseases. 5 of the patients could not perform pft. All 34 patients were able to perform pft. The demographic and clinical characteristics of the patients participating in the study are given in table 1. There were 18 female and 16 male patients and the mean age was 12.7 ± 3.12 years old. Eleven of the patients were asymptomatic, 14 were mild, and 9 were moderate. Time remaining Covid-19 PCR positive

median was 6 days (IQR 5). Length of stay in hospital day 7 (9), time after discharge day 49 (36). Chest radiographs of 34 pediatric patients were retrospectively interpreted by 2 observers. Accordingly, chest radiography of 7 children was interpreted as atypical and 6 of them were in the form of major airway disease. The kappa value was measured to measure the agreement between the two observer who interpreted the chest radiographs retrospectively. The agreement between two observer was very good $k = 0.83$, Spearman correlation $r = 0.849$, $p = 0.000$. When the pft results of the patients were compared with the test value of 100, the results obtained were shown in table 2. The comparison of the actual values of the patients predicted to be at the same age, height and weight is shown in table 3, figure 1 and figure 2. A negative correlation was found between the length of hospital stay and FEF 25-75 ($r: -0.364$ $p: 0.035$). The all patients were evaluated by a pediatric cardiologist. Pulmonary hypertension and congenital heart disease were excluded.

Discussion

Worldwide, by WHO, 44,888,869 confirmed cases and 1,178,475 deaths were reported due to covid-19 until October 30, 2020 ⁸. There are still unclear points on many issues such as the pathogenesis of COVID-19, clinical findings, and the course of the disease in children and adults. Generally, it is stated that adult patients have more severe disease and pediatric patients experience milder and mostly asymptomatic ^{9; 10}. It is not known exactly how the lungs are affected in the short and long term after the illness. Related to this, studies have been conducted on respiratory function tests in adult patients. However, when we scanned the literature in pediatric patients, we found that no such study was performed. We conducted this study to understand how Covid-19 disease affects the functions of the lungs in pediatric patients. In our study, we evaluated the respiratory functions of pediatric patients who were discharged due to Covid-19 using spirometry.

In our study, when the percentage values of the patients in pulmonary function tests were compared with the test value of 100, no significant decrease was found. When the actual values measured by spirometry were compared with the predictive values that should be at the same age, weight and height, no significant decrease was found. However, in the correlation analysis, a moderately negative correlation was found between the length of hospital stay and Fef 25-75. This shows us that Fef 25-75 decreases as the duration of hospitalization increases. Fef 25-75 gives information about obstruction in medium and small diameter bronchi. As the degree of restrictive diseases increases, indirect decreases can be observed in the FEF25-75 value ¹¹. Lv et al. found restrictive ventilation disorder and increased small airway disease in

critically ill patients in the respiratory function test they performed in adults during Covid -19 disease ¹². In our study, it may be significant in terms of showing that it worsens lung functions in pediatric patients as the length of hospitalization due to Covid-19 increases.

Data on CT findings of COVID-19 pneumonia in children are very limited. The American Pediatric Radiology Association recommends that another imaging method should be preferred instead of tomography in children, and if there is an absolute necessity for use, applications should be made in line with the principle of "ALARA" (As Low as Reasonably Achievable) ¹³. We did not have our patients underwent computed tomography unless there was a medical necessity. Follow-up thoracic CT can be used to evaluate the development and / or occurrence of fibrotic lung disease in patients with persistent changes in pulmonary function tests after the disappearance of acute infection ¹⁴.

For COVID-19 pneumonia in children, a structured reporting style in 4 categories, typical, indeterminate, atypical and negative, was created for plain radiography ¹⁴. Chest radiographs of 34 pediatric patients were retrospectively interpreted by 2 observers. Accordingly, chest radiography of 7 pediatric patients was interpreted as atypical. 6 of them were in the form of major airway disease. We think that this may show us that covid-19 is passed on as an upper respiratory tract infection in children, does not affect alveoli, and therefore is more easily overcome in children.

Kara et al. evaluated the patients who were followed up with pneumonia from a cardiac perspective during active infection and suggested that even mild pneumonia may affect the cardiovascular system ¹⁵. In our study, we evaluated our patients in terms of cardiac conditions and we did not find any significant cardiac pathology in our patients. This may be because we evaluate after patients recover.

It is not recommended to perform pft because it is a high-risk situation for droplet formation during the disease ¹⁶. Therefore, pft could not be performed on our patients during infection. It is recommended to perform two negative real-time Polymerase Chain Reaction (RT-PCR) tests for SARS-CoV-2 at 24-hour intervals on nasopharynx and throat swabs after symptoms have improved, and 30 days after discharge ^{16; 17}. We performed pft after the specified conditions were met for our patients.

According to current data, COVID-19 is milder in children than in adults. While the rate of patients with a poor course of COVID-19 in adult patients is 18.5%, severe prognosis and need for intensive care have been reported in 5.9% of pediatric patients. COVID-19 is

classified as asymptomatic, mild, moderate, severe, and critical, according to clinical, laboratory and radiological findings ¹⁸. Patients with mild and moderate intensity were included in our study. Severe patients could not be studied because our pediatric patients with severe clinics usually had comorbid conditions that prevented them from performing pulmonary function tests.

It is alarming that the disease has a high mortality rate in adults and its severe course especially in children with underlying diseases. In our study, the fact that the Fef 25-75 flow was found to be low as the length of hospitalization increases in Covid-19 disease with a moderate and mild course is significant in terms of worsening lung functions. There is a need for larger studies in the short and long term to understand the prognosis of these patients.

Acknowledgments: No acknowledgments.

Conflict of interest: The author declares that there are no conflict of interests.

References:

1. Cucinotta D, Vanelli MJAb-mAP. 2020. Who declares covid-19 a pandemic. 91(1):157.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY et al. 2020. Early transmission dynamics in wuhan, china, of novel coronavirus-infected pneumonia. The New England journal of medicine. 382(13):1199-1207.
3. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI et al. 2020. Aerosol and surface stability of sars-cov-2 as compared with sars-cov-1. The New England journal of medicine. 382(16):1564-1567.
4. Chen Z, Tong L, Zhou Y, Hua C, Wang W, Fu J, Shu Q, Hong L, Xu H, Xu Z et al. 2020. Childhood covid-19: A multi-center retrospective study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.
5. Koopman M, Zanen P, Kruitwagen CL, van der Ent CK, Arets HG. 2011. Reference values for paediatric pulmonary function testing: The utrecht dataset. Respiratory medicine. 105(1):15-23.

6. Lechowicz K, Drożdżał S, Machaj F, Rosik J, Szostak B, Zegan-Barańska M, Biernawska J, Dabrowski W, Rotter I, Kotfis K. 2020. Covid-19: The potential treatment of pulmonary fibrosis associated with sars-cov-2 infection. *Journal of clinical medicine*. 9(6).
7. Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, Zhou X, Liu X, Huang X, Yuan S et al. 2020. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respiratory research*. 21(1):163.
8. Weekly operational update on covid-19 - 30 october 2020. 2020. World Health Organization: World Health Organization; [accessed 30 October 2020]. <https://www.who.int/publications/m/item/weekly-operational-update---30-october-2020>.
9. Molloy EJ, Bearer CF. 2020. Covid-19 in children and altered inflammatory responses. *Pediatric research*. 88(3):340-341.
10. Yurttutan S, İpek S, Güllü UU. 2020. Why the sars-cov-2 has prolonged spreading time in children? *Pediatric pulmonology*. 55(7):1544-1545.
11. Lee H, Chang B, Kim K, Song WJ, Chon HR, Kang HK, Kim JS, Jeong BH, Oh YM, Koh WJ et al. 2016. Clinical utility of additional measurement of total lung capacity in diagnosing obstructive lung disease in subjects with restrictive pattern of spirometry. *Respiratory care*. 61(4):475-482.
12. Lv D, Chen X, Wang X, Mao L, Sun J, Wu G, Lin Z, Lin R, Yu J, Wu X et al. 2020. Pulmonary function of patients with 2019 novel coronavirus induced-pneumonia: A retrospective cohort study. *Annals of palliative medicine*. 9(5):3447-3452.
13. Slovis TL. 2002. The alara concept in pediatric ct: Myth or reality? *Radiology*. 223(1):5-6.
14. Jin YH, Zhan QY, Peng ZY, Ren XQ, Yin XT, Cai L, Yuan YF, Yue JR, Zhang XC, Yang QW et al. 2020. Chemoprophylaxis, diagnosis, treatments, and discharge management of covid-19: An evidence-based clinical practice guideline (updated version). *Military Medical Research*. 7(1):41.
15. Kara SS, Gullu UU, Fettah AJCMJ. 2017. Cardiological findings of pediatric patients with the diagnosis of pneumonia. 42(4):702-708.

16. Bignamini E, Cazzato S, Cutrera R, Ferrante G, La Grutta S, Licari A, Lombardi E, Midulla F, Piacentini G, Pifferi M et al. 2020. Italian pediatric respiratory society recommendations on pediatric pulmonary function testing during covid-19 pandemic. Italian journal of pediatrics. 46(1):68.
17. Gemicioğlu B, Börekçi Ş, Dilektaşlı AG, Ulubay G, Azap Ö, Saryal S. 2020. Turkish thoracic society experts consensus report: Recommendations for pulmonary function tests during and after covid 19 pandemic. Turkish thoracic journal. 21(3):193-200.
18. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong SJP. 2020. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in china.