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The Coronavirus Disease 2019 Pandemic and Time to Diagnosis for Childhood Pulmonary Diseases: Outcomes of a Tertiary Care Center

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What is already known on this topic?

- *Studies investigating the impact of the coronavirus disease 2019 (COVID-19) pandemic on the diagnostic process of diseases other than COVID-19 infection have been widely evaluated in terms of oncological, obstetric, cardiovascular diseases, and mainly infectious respiratory diseases during pandemic are widely investigated. These studies mostly involve adult patients.*

What this study adds on this topic?

- *General health services are expected to be affected by the pandemic. However, the continuity of health services for chronic diseases can be ensured without this negative effect. We have shown that the duration and age of diagnosis of chronic lung diseases during the pandemic period are similar to previous periods.*

ABSTRACT

Objectives: Coronavirus disease 2019 pandemic caused many changes in the social behaviors of individuals and the provision of health systems. Many studies revealed reductions in the number of diagnoses and delays in diagnosis time during the pandemic. This study aimed to evaluate the effect of the pandemic on the time to diagnosis of major diseases of pediatric pulmonology.

Materials and Methods: Newly diagnosed patients with cystic fibrosis (CF), childhood interstitial lung disease (chILD), tuberculosis (TB), and primary ciliary dyskinesia (PCD) were grouped into pandemic (group 1) and 2 consecutive pre-pandemic periods divided into equal intervals (groups 2 and 3). For each disease group, the time to diagnosis was compared between the specified periods.

Results: A total number of patients were 171 in this study. In the CF group, there was no statistically difference in time to diagnosis between periods. In the chILD group, there was a statistically significant difference in time to diagnosis (P = .036) between groups (group 1: 2 months, group 2: 4 months and group 3: 10.5 months) that was not originated from pandemic period. In TB group there was no statistically significant difference between groups. In the PCD group, the impact of the pandemic on the time to diagnosis could not be clarified because the time interval to diagnosis (minimum: 2 years, maximum: 16 years) exceeded the studied periods (21 months).

Conclusion: In our study, no effect found between the pandemic and age at diagnosis or time to diagnosis in patients with PCD, chILD, CF, and TB at our center.

Keywords: COVID-19, primary ciliary dyskinesia, cystic fibrosis, tuberculosis, interstitial lung disease

INTRODUCTION

The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first detected in Wuhan, China, in December 2019, was named coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) later declared a pandemic.[1] In Turkey, the pandemic was declared on March 11, 2020.[2] With the escalation of the disease, many nations developed emergency health policies and took national actions to slow the spread of the virus. These changes led to a decline in access to health institutions due to mandatory restrictions and/or patients preferences. Many studies reported that the COVID-19 pandemic caused disruptions in most settings, especially access to preventive health services, pediatric emergency and oncology departments, and in the routine clinical follow-up of chronic diseases in both adults and children.[3-4] At the same time, the pandemic has led to changes in the epidemiology of diseases.[5] Besides the decline in the number

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of admissions to healthcare services during the pandemic, delays in the diagnosis time of many diseases have been reported.[6-8] A study reported that the duration of symptoms of pediatric acute appendicitis before presentation to the emergency department was significantly longer in patients treated in 2020 compared with the previous year.[9] The results of the studies conducted in Turkey also supporting the above mentioned results. A study evaluated the effect of the pandemic on prenatal diagnostic procedures showed a reduction in the number of prenatal diagnoses and screening tests during the COVID-19 pandemic.[3] An audit performed by Kutluk et al notified a negative trend in the diagnosis of new pediatric cancers but no change in presentation delays during the "COVID-19 period."[4]

As mentioned above, several studies have shown disruptions in admissions to health services and delays in diagnosis in most settings during the COVID-19 pandemic.[3-10] There is a lack of data about the impact of COVID-19 on time to diagnosis of pediatric pulmonary diseases in the literature. We aimed to investigate the effect of the COVID-19 pandemic on age of diagnosis and time to diagnosis in primary ciliary dyskinesia (PCD), cystic fibrosis (CF), tuberculosis (TB), and interstitial lung diseases of childhood (chILD) in our clinic.

MATERIALS AND METHODS

Study Design and Data Resources

This study conducted in Hacettepe University İhsan Doğramacı Children's Hospital, Pediatric Pulmonology Department between September 9, 2016, and December 31, 2021. Following the approval of the Ethics Committee of Hacettepe University (approval number: GO 22/269, date: March 15, 2022), demographic, and clinical data of patients diagnosed with PCD, CF, TB, and chILD were collected retrospectively through the hospital system. Informed consent was obtained from the patients who agreed to take part in the study.

Study Periods

Comparative analyses were performed between the "pandemic period" and 2 pre-pandemic periods. To assess the time effect on median age at diagnosis and time to diagnosis, pre-pandemic patients were analyzed in 2 separate groups with the same time period as the pandemic group. Group 1 is the pandemic period between March 11, 2020, and December 31, 2021, group 2 is the pre-pandemic period between June 10, 2018, and March 10, 2020, and group 3 is the pre-pandemic period between September 9, 2016, and June 9, 2018. Cases except PCDs were grouped according to the time of the onset of their complaints. Patients with PCD were evaluated according to the time to diagnosis because the interval between the onset of symptoms and diagnosis was longer than the specified time periods/groups.

Variables

The median value was used as our data showing skewed distribution feature. The median age at diagnosis and median time to diagnosis was calculated separately for each period. The median age was calculated in months or years. The time to diagnosis was determined as the time between the first presentation of the child with disease related symptoms and the diagnosis time of the disease.

Diagnostic Criteria of the Diseases

Primary Ciliary Dyskinesia

The diagnostic process for each patient was performed by same pediatric pulmonologist team with same diagnostic protocols. PCD diagnoses were based on the presentation of the characteristic clinical phenotype (chronic cough, persistent perennial rhinitis, chronic ear, and hearing complaints), "Primary Ciliary Dyskinesia Rule" (PICADAR) scores (suspected as positive if score >6), the presence of abnormal ciliary movements (as determined using high-speed video microscopy) and/or nasal nitric oxide (NO) results (<11.5 ppb with NIOXMINO® device), the presence of ciliary ultrastructural defects (visualized by electron microscopy), a genetic mutation recognized to cause PCD, if present.[10]

Cystic Fibrosis

Patients with positive sweat tests (macroduct chloride ≥60 mmol/L) were referred to our hospital due to elevated immunoreactive trypsinogen (IRT) (≥90 µg/L and ≥70 µg/L in the first and second measures) results in newborn screening and were included in the CF group.[11]

Childhood Interstitial Lung Disease

The diagnosis of chILD was made according to the guidelines of the "European Protocols for the Diagnosis of Intestitial Lung Disease in Childhood."[12] The genetic compatibility of the patients was also reviewed. chILD diagnoses were based on compatible diagnostic methods for each subgroup of child.[12]

Tuberculosis Disease

TB was diagnosed based on clinical signs, symptoms, chest x-ray, chest computed tomography studies, immunological tests (IFN-γ release assay and tuberculin skin test), and microbiologic analyses including acid-fast staining for acid-resistant bacilli (ARB), polymerase chain reaction (PCR), and culture methods.[13]

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY, USA). Distributions of data were examined with histograms and Kolmogorov–Smirnov test. The median value was used for our data showing skewed distribution feature. The Kruskal–Wallis *H*-test was used to compare more than 2 groups containing continuous variables. One-way analysis of variance (ANOVA, normally distributed data) with Tamhane t2 post hoc test was used to determine statistically significant differences between group of each diseases.

$P < .05$ was considered statistically significant.

RESULTS

A total of 171 patients were enrolled in the study (Table 1). The distribution of patients in each disease group is shown in Figure 1.

Primary Ciliary Dyskinesia

For the PCD group, total number of patients were 58. The median age at diagnosis was 9.5 (IQR: 7.5), 3 (IQR: 2.75), and 10 years (IQR: 5) and median time to diagnosis was 6 (IQR: 4.75), 2.5 (IQR: 2.5), and 7.5 years (IQR: 3) in group 1, 2, and

Table 1. Distribution of Patients in Groups for Each Disease

Disease	All, n	Group 1, n (%)	Group 2, n (%)	Group 3, n (%)
Primary ciliary dyskinesia	58	16 (27,5%)	8 (13.7%)	34 (58.6%)
Cystic fibrosis	35	22 (62.8%)	3 (8.5%)	10 (28.5%)
Interstitial lung disease	42	7 (16.6%)	9 (21.4%)	26 (61.9%)
Tuberculosis	36	13 (36.1%)	11 (30.6%)	12 (33.3%)

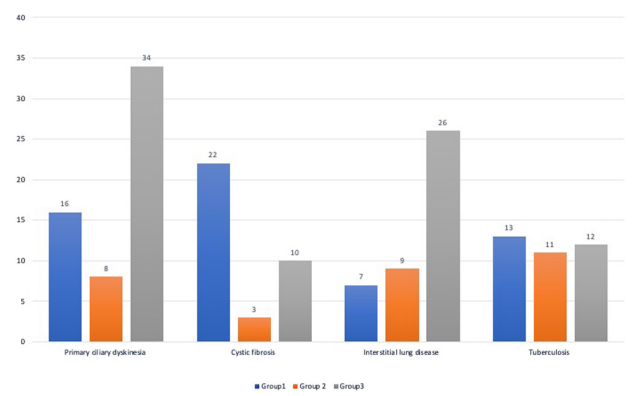

Figure 1. Distribution of the number of patients between groups.

3, respectively. When we grouped patients diagnosed with PCD according to the age of onset of their complaints, as in other diseases we mentioned above, we saw that the number of cases was not sufficient for analysis. For this reason, we grouped these patients according to their diagnosis time. There was a statistically significant difference in median ages ($P < .001$) and time to diagnosis ($P < .001$) between groups (Tables 2 and 3). These differences are due to group 2; both of the median ages and time to diagnosis are lower than the other groups.

Cystic Fibrosis

In the CF group, the number of new cases were 22, 3, and 10 for group 1, 2 and 3, respectively. All patients were diagnosed before age 1 year in both periods (Tables 2 and 3).

Table 2. Comparison of Age of Diagnosis in Each Period

Disease	Group 1 Median (IQR) Months Years[a]	Group 2 Median (IQR) Months Years[a]	Group 3 Median (IQR) Months Years[a]	*P*[b]
Primary ciliary dyskinesia	9.5[a] (7.5)	3[a] (2.75)	10[a] (5)	<.001
Cystic fibrosis	<1[a]	<1[a]	<1[a]	–
Interstitial lung disease	3 (10)	0 (1)	2 (5)	.009
Tuberculosis	12 (15)	13 (8)	11 (11)	.421

[a]Values in years for ages.
[b]$P < .05$ accepted as significant between groups on Kruskal–Wallis (for continuous variables).

Table 3. Comparison of Time to Diagnosis of the Diseases in Each Period

Disease	Group 1, Median (IQR) Months Years[a]	Group 2, Median (IQR) Months Years[a]	Group 3, Median (IQR) Months Years[a]	*P*[b]
Primary ciliary dyskinesia	6[a] (4.75)	2.5[a] (2.5)	7.5[a] (3)	<0.001
Cystic fibrosis	<1[a]	<1[a]	<1[a]	-
Interstitial lung disease	2 (7)	4 (3)	10.5 (15)	0.036
Tuberculosis	2 (1.5)	1.5 (3.75)	2 (3)	0.239

[a]Values in years used for time to diagnosis.
[b]$P < .05$ accepted as signfiicant between groups on Kruskal–Wallis (for continuous variables).

Interstitial Lung Disease of Childhood

For the chILD group, total number of patients were 42 (Table 4). The median age at diagnosis was 3 (IQR: 10), 0 (IQR: 1), and 2 years (IQR: 5) and median time to diagnosis was 2 (IQR: 7), 4 (IQR: 3), and 10.5 months (IQR: 15) in group 1, 2 and 3, respectively. There was a statistically significant difference in median ages ($P = .009$) and time to diagnosis ($P = .036$) between groups (Tables 2 and 3). Post hoc analysis for median age of diagnosis showed that this difference was between the pre-pandemic groups and no difference was observed between the pre-pandemic and pandemic groups. Difference for the median time to diagnosis was due to group 3, which had the longest time to diagnoses.

Tuberculosis Disease

For the TB group, total number of patients were 36. The median age at diagnosis was 12 (IQR: 15), 13 (IQR: 8), and 11 years (IQR: 11) and median time to diagnosis was 2 (IQR: 1.5), 1.5 (IQR: 3.75), and 2 months (IQR: 3) in group 1, 2 and 3, respectively. There was no statistically significant difference in term of median age of diagosis and median time to diagnosis between groups (Tables 2 and 3).

DISCUSSION

The COVID-19 pandemic has raised concerns about the delayed diagnosis of diseases other than COVID-19. This retrospective study aimed to determine the effect of the COVID-19 pandemic on the time to diagnosis of PCD, CF, chILD, and TB in children. We observed that the duration between the onset of symptoms and the time to diagnosis was not affected during the pandemic period when compared with the pre-pandemic periods in the CF, chILD, and TB groups. However, we cannot make such a statement for PCD groups because the time to diagnosis of PCD patients exceeds the time intervals of the pandemic and pre-pandemic groups. To assess the time effect on median age of diagnosis and time to diagnosis, we analyzed the pre-pandemic patients in 2 separate groups with the same time period as the pandemic group.

The median time to diagnosis of CF patients were not affected during the pandemic period. We also evaluated the median age of diagnosis to interpret delays in diagnosis, but there was no change in median age between the 3 periods. In Turkey, CF

Table 4. Patient Distribution of chILD

Subgroups of chILD	Number of Patients (n)
Surfactant dysfunction disorders (ABCA-3, usual interstitial pneumonia, pulmonary alveolar proteinosis)	10
Rheumatological diseases (systemic juvenile arthritis, juvenile dermatomyositis, scleroderma, mixed connective tissue disorders)	9
Bronchiolitis obliterans, disorders of the immune compromised host (GLILD)	7
Hypersensitivity pneumonia	4
Follicular bronchitis, lymphocytic interstitial pneumonia	2
Inflammatory bowel disease	2
FARS-B mutation	2
ILD related to inherited metabolic disorders	2
Neuroendocrine cell hyperplasia	2
Others (Langerhans cell histiocytosis, pulmonary hemosiderosis)	2

disease has been screened by IRT measurement as part of the newborn screening program since 2015.[14] Patients referred to our hospital with high IRT are diagnosed through sweat tests and then confirmed in genetic tests. A study conducted in Turkey reported that there was no pandemic-related change in the time between sample collection and hospital admission within the scope of the newborn screening program.[15] The absence of delay in diagnosis may be attributable to the success of the newborn screening program and easy access of the patients to our CF reference center. We observed that the number of the newly diagnosed CF patients increased in pandemic period compared with the pre-pandemic. Our clinic is one of the CF centers in Turkey and patients were referred to our clinic for diagnosis due to problems in access to sweat chloride test in other CF centers during the pandemic period. This may explain the increased number of patients seen during the pandemic period.

In the chILD group, the number of patients applying to our clinic was highest in group 3. There was no difference between group 1 and group 2. Therefore, we can say that the pandemic has not affected the number of admission of patients. Compared to the other groups, the time to diagnosis of chILD was longest in group 3. In addition, there is no difference in time to diagnosis between the pandemic group and group 2, which is one of the pre-pandemic groups, shows that the difference as mentioned above is not caused by the pandemic. We found that the time to diagnosis decreased over time in all groups (10.5, 4 and 2 months for groups 3, 2 and 1 respectively). Although this was not statistically significant between all groups, it may have been due to the small number of cases. When we analyzed the patients in these groups according to their diagnosis methods, we saw that the rate of patients diagnosed by genetic evaluation increased over time (%75, %11, and %11 for group 1, 2, and 3 respectively) (Supplementary Table 1). We wanted to share this data with you as a secondary outcome. The development of genetic diagnostic methods and easier access to genetic methods are important in diagnosing and/or confirming the diagnosis of chILD patients.[16-18]

There is no statistically significant difference between all TB groups regarding number of cases, median age of diagnosis and time to diagnosis. In a study from Turkey that evaluated adult patients who were diagnosed as having pulmonary TB, there was a significant decrease in the number of patients who presented for TB testing and pulmonary TB diagnoses compared with the 3 years before the pandemic (P = .001).[19] In World Health Organization's 2020 global tuberculosis report, it was reported that there was a significant decrease in the notification of newly diagnosed TB during the pandemic period.[20] It has also been reported that there is a decrease in the number of patients admitted to hospitals and tested for TB due to reasons such as the decrease in TB healthcare services, patients' fear of contracting COVID-19 infection.[19,21,22] Pulmonary tuberculosis and COVID-19 are both respiratory factors and the clinical picture can be confused with each other.[23,24] A study conducted in Ghana showed that 14.3% of cases with suspected COVID-19 infection were diagnosed with COVID-19 infection, while 0.8% of cases were diagnosed with pulmonary TB.[25] Since 90% to 92% of our patients in all groups had extrapulmonary TB, they are less likely to be misdiagnosed with COVID-19 infection, and therefore the number of patients diagnosed during the pandemic period may not have decreased compared with previous periods. (Supplementary Table 2) In addition, it is very important to have health workers who specialize in diagnosing TB,[24] and our clinic continued to provide services with all its staff throughout the pandemic period. In this case, it can be considered a positive effect on TB diagnosis. Since these data are from a single center, no definitive conclusion can be made and more studies are needed on this subject.

To the best of our knowledge, this is the first study to investigate the effect of the COVID-19 pandemic on the age of diagnosis and the time to diagnosis in the setting of pediatric pulmonology. Our study observed that the age of diagnosis and the time to diagnosis were not affected during the pandemic period compared with the pre-pandemic periods in all disease groups.

Our study has some limitations. Policies and actions taken by authorized institutions during COVID-19, such as restrictions to hospital admissions, social distancing rules, patients' concerns about transmission of the virus, economic deterioration during the pandemic period, patients residing outside of the city of the clinic, and protocols created against COVID-19 in clinics are possible factors that contribute to delays in diagnosis time. These factors were not evaluated in our study.

In our study, no effect found between the pandemic and age at diagnosis or time to diagnosis in patients with PCD, chILD, CF, and TB at our center. It is not possible to generalize our results to the whole population because the study consists of single-center data, our center is a reference center for paediatric chest diseases, and the technical equipment and personnel required for diagnosis continue in the pandemic period compared to the pre-pandemic period. Although the design of our study did not allow us to assess causality, our results suggest that services for chronic lung diseases, including pandemic conditions, can be provided similarly to previous periods. There is a need for multicenter research on causality and to identify

the factors that influence this situation. We hope this study will provide guidance in case of a possible pandemic in the future.

Ethics Committee Approval: The study was approved by the non-interventional ethics committee of the Medical Faculty of Hacettepe University (approval date: March 15, 2022; number: 2022/05-20).

Informed Consent: Informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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Supplementary Table 1. Ratio of Genetic Tests Used for chILD Diagnosis		
Groups	**Number of Genetical Diagnosis n (%)**	**Number of Other Diagnostic Methods (Out of Genetic Tests) n (%)**
1	3 (42%)	4 (57%)
2	1 (11%)	8 (89%)
3	3 (12%)	23 (88%)
chILD, childhood interstitial lung diseases.		

Supplementary Table 2. Numbers of Pulmonary and Extrapulmonary Tuberculosis Diagnosis		
Groups	**Number Pulmonary TB n (%)**	**Number of Extrapulmonary TB n (%)**
1	1 (8%)	12 (92%)
2	1 (9%)	10 (91%)
3	1 (8.3%)	11 (91.6%)
TB, tuberculosis.		