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Distribution of Viral Respiratory Pathogens During the COVID-19 Pandemic: A Single-Center Pediatric Study from Turkey

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What is already known on this topic?

- *Acute respiratory tract infections are important causes of morbidity and mortality for children globally.*
- *Viruses are reported to be responsible for 80% of acute respiratory tract infections.*
- *Prevention and control strategies for COVID-19 have provided an opportunity to observe the impact of non-pharmaceutical interventions on the spread of respiratory viruses.*

What this study adds on this topic?

- *There was a decrease in the positivity rate of viral respiratory pathogens and no detection of influenza virus or respiratory syncytial virus in our study.*
- *Circulating viruses may change due to multifactorial approaches applied during the pandemic period.*
- *Understanding the prevalence of co-infections may supply information for decision making for future epidemics.*

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ABSTRACT

Objective: To evaluate the distribution and characteristics of respiratory viral pathogens and to assess the epidemiological data, clinical features, and prognoses of infected children in a pediatric emergency department during the COVID-19 pandemic.

Materials and Methods: Between September 1, 2020, and April 30, 2021, patients aged between 0 and 18 years arrived at the pediatric emergency department and were tested by nasopharyngeal/tracheal specimen polymerase chain reaction for both SARS-CoV-2 and other viral respiratory pathogens. Demographics, symptoms, laboratory and radiologic investigations, respiratory viruses detected by PCR, presence of co-infection and co-infecting viruses, need for respiratory support, hospitalization, length of hospital stay, and prognosis were recorded.

Results: There were 327 patients for whom PCR tests were performed and 118 (36.0%) of them had positive results for SARS-CoV-2 and/or other respiratory viruses. Rhinovirus was the most commonly detected pathogen with 74 (62.7%) cases, followed by enterovirus with 38 (32.2%) and adenovirus with 20 (16.9%) cases. There was no detection of influenza virus or respiratory syncytial. SARS-CoV-2 PCR results were positive in 14 (11.9%) cases and there was only 1 co-infection of SARS-CoV-2 occurring together with rhinovirus. For 43 (36.4%) patients, there was co-infection, and among co-infections, the most common was that of rhinovirus and enterovirus, seen in 37 (86.0%) cases.

Conclusion: A decrease was observed in the positivity rate of respiratory viral pathogens, while no cases of influenza virus or respiratory syncytial virus were observed in our study. Circulating viruses may change due to multifactorial approaches during the COVID-19 pandemic.

Keywords: children, COVID-19, SARS-CoV-2, co-infection, respiratory virus, pandemic

INTRODUCTION

Acute respiratory tract infections (ARTIs) are important causes of morbidity and mortality for the pediatric population globally.[1,2] It was reported that 70% of children who were aged between 1 and 4 years and 90% of those aged <1 year require hospitalization in cases of ARTIs.[2] Viruses are reported to be responsible for 80% of ARTIs.[4] Differentiation according to clinical findings is usually impossible because there are no specific symptoms that could be pathogen-related.[1] Pharmaceutical treatment options for the majority of viral respiratory agents are still limited, which contributes significantly to public health measures in order to avert transmission, referred to as non-pharmaceutical interventions (NPIs).[5]

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The coronavirus-related disease-2019 (COVID-19) spread rapidly worldwide and caused an urgent concern for public health all over the world.[6,7] The first severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) reverse transcription-polymerase chain reaction (RT-PCR) positive patient was declared on March 10, 2020, in Turkey, and on April 2, 2020, the first pediatric patient was detected in our hospital. To contain or slow the transmission of the disease, several preventive NPIs were implemented according to the recommendations of World Health Organization (WHO) in Turkey as well as many other countries. These interventions have included the use of personal protection such as masks, hand hygiene, remote work, social distancing, restrictions of personal movement, and cancellation of large events. Similar NPIs have been key measures in reducing the circulation of other respiratory viruses.[8,9]

Prevention and control strategies for COVID-19 based on NPIs have provided an opportunity to observe the effect of NPIs on the spread of viral respiratory agents. At the same time, viruses can still cause co-infections together with SARS-CoV-2 during outbreaks of respiratory disease caused by this novel pathogen.[10] However, data on pediatric COVID-19 co-infections are limited.

The aim of the present study was to evaluate the distribution and characteristics of viral respiratory pathogens and to assess the epidemiological data, clinical findings, hospitalization admissions, and prognoses of infected children during the COVID-19 pandemic.

MATERIALS AND METHODS

Study Design

This single-center retrospective study was carried out in the pediatric emergency department (ED) of a tertiary hospital that has nearly 120 000 visits per year. The local ethics committee study approved the study protocol.

Respiratory tract samples were collected from patients who had fever and symptoms of ARTIs, such as runny nose, cough, or respiratory distress. Subjects who were aged between 0 and 18 years who arrived at the ED and were tested by nasopharyngeal/tracheal specimen PCR for SARS-CoV-2 based on the guidelines published by the Turkish Ministry of Health's Scientific Committee on COVID-19, which have been revised intermittently according to the recommendations of the Coronavirus Scientific Advisory,[11] and other viral respiratory agents together, were included. During the pandemic period, PCR testing for respiratory viruses other than SARS-CoV-2 was available from September 1, 2020, in our hospital. Therefore, the time period between September 1, 2020, and April 30, 2021, was chosen for the study. Among these patients, those who had positive PCR results for SARS-CoV-2 or other respiratory viruses were assessed. The International Classification of Diseases codes were used to detect cases. Information was taken from a computer database and electronic medical records. Demographics, presence of underlying conditions, symptoms, laboratory results, and radiologic tests were recorded for each case. Because the description of symptoms such as sore throat or loss of smell or taste cannot be possible for infants and preschool-aged children, the presence of sore throat was evaluated for children aged >3 years and loss of smell/taste for those aged >5 years. Patients were divided into 4 groups according to age: as those aged younger than 1 year, 1–6 years, 6–10 years, and older than 10 years. Finally, requirements for respiratory support, admission to hospital, admission to pediatric intensive care unit (PICU), length of hospital stay, and prognosis were recorded.

Respiratory Tract Sample Analysis

The respiratory virus detected by PCR, presence of co-infection, and co-infecting viruses were recorded. Samples were tested at the Dokuz Eylul University Hospital core laboratory. COVID-19 diagnosis was detected by quantitative RT-PCR positivity with identification of SARS-CoV-2 with double targets, the N-gene and ORF ab1 region, at a cycling threshold value of <35 cycles [SARS-CoV-2 (2019-nCoV) qPCR Detection Kit, Bio-Speedy®, Istanbul, Turkey]. For the identification of other viral respiratory agents, a Fast-Track Diagnosis/Respiratory Pathogens 21 kit (FTD 21; Fast-Track Diagnosis, Junglinster, Luxembourg) was used. The FTD 21 test detects 20 respiratory viruses in 5 reaction tubes by multiplex real-time PCR assay. These pathogens are influenza A virus and subtype H1N1 (pandemic H1N1); influenza B virus; respiratory syncytial virus (RSV); rhinovirus; human coronaviruses NL63 (HCoV-NL63), 229E (HCoV-229E), OC43 (HCoV-OC43), and HKU1 (HCoV-HKU1); parainfluenza virus-1, -2, -3, and -4; mycoplasma pneumonia; human bocavirus; human metapneumovirus A/B; adenovirus; enterovirus; and human parechovirus. Detection of a positive result for one or more respiratory viruses on PCR testing was recorded as a co-infection.

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences 22.0 (IBM SPSS Corp.; Armonk, NY, USA) package program. Categorical and continuous variables were reported as frequencies and percentiles and as means with standard deviations (SDs) or medians with interquartile ranges (IQRs). The Mann–Whitney *U*-test was used to compare nonparametric variables and Student's *t*-test was used for parametric data. A value of $P < .05$ was considered statistically significant.

RESULTS

Study Population

There were 327 patients for whom PCR tests were performed for both SARS-CoV-2 and other viral respiratory agents. Among them, 118 (36.0%) tests resulted positive for SARS-CoV-2 and/or other viral respiratory agents. There was a slight male predominance with 66 (55.9%) male patients among the positive cases. The median age of the subjects was 2.1 [interquartile range (IQR): 0.8–7.0] years and 42 (35.6%) patients were aged <1 year as the most common age group. A total of 51 (43.1%) patients had underlying diseases. The most common symptoms at presentation were fever (n: 72, 61.0%), cough (n: 57, 48.3%), and respiratory distress (n: 37, 31.4%) (Table 1).

There were 26 (22.0%) patients who required respiratory support. Of those, 5 underwent intubation, 1 underwent noninvasive ventilation (bi-level positive airway pressure), 10 underwent high-flow nasal cannula (HFNC) oxygen therapy, and 10 received oxygen by simple face mask.

Table 1. Demographics, Clinical Findings, and Prognoses of Patients with Positive PCR Results for SARS-CoV-2 and/or Other Respiratory Viruses

Variable	n: 118
Male gender, n (%)	66 (55.9)
Age in years, median (IQR)	2.1 (0.8–7.0)
Age group, n (%)	
0–1 year	42 (35.6%)
1–6 years	34 (28.8)
6–10 years	22 (8.6)
>10 years	20 (16.9)
Underlying disease, n (%)	51 (43.1)
Symptoms, n (%)	
Fever	72 (61.0)
Cough	57 (48.3)
Respiratory distress	37 (31.4)
Fatigue	6 (5.1)
Sore throat	3 (2.5)
Headache	1 (0.8)
Runny nose	34 (28.8)
Taste/smell loss	-
Myalgia	2 (1.7)
Diarrhea	8 (6.8)
Nausea/vomiting	14 (11.9)
Abdominal pain	-
Chest pain	2 (1.7)
Rash	4 (3.4)
Conjunctivitis	2 81.7)
Admission to the ward, n (%)	35 (29.7)
Admission to the PICU, n (%)	13 (11.0)
Total length of stay in hospital (days), median (IQR)	1.2 (0.5–8.4)
Mortality, n (%)	2 (1.7)

SD, standard deviation; IQR, interquartile range; PICU, pediatric intensive care unit; PCR, polymerase chain reaction.

Table 2. Distribution of Viral Respiratory Pathogens Identified in the Study

Viral Pathogens	n	% of Samples (n: 327)	% of Positive Samples (n: 118)
Rhinovirus	74	21.3	62.7
Enterovirus	38	10.9	32.2
Adenovirus	20	5.7	16.9
SARS-CoV-2	14	4.0	11.9
Human coronaviruses (HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1)	11	3.1	9.3
Parainfluenza virus-1, -2, -3, and -4	3	0.8	2.5
Human bocavirus	2	0.5	1.6
Influenza virus	-	-	-
Respiratory syncytial virus	-	-	-
Human metapneumovirus	-	-	-
Human parechovirus	-	-	-
Co-infection	43	12.3	36.4
Total negative PCR tests	229	64.0	

PCR, polymerase chain reaction.

Finally, 35 (29.7%) patients were admitted to the ward and 13 (11.0%) to the PICU. The median length of total hospital stay was 1.2 (IQR: 0.5–8.4) days. Two cases resulted in death (Table 1). These cases were 9-month-old and 5.5-year-old boys who had already been diagnosed with arthrogryposis, renal dysfunction, cholestasis syndrome, and Ewing sarcoma, admitted to the ED with septic shock and acute respiratory distress syndrome. The length of PICU stay was 8.4 and 22.0 days for these cases.

Respiratory Tract Sample Analysis

The most commonly detected viral pathogen was rhinovirus with 74 (62.7%) cases, followed by enterovirus with 38 (32.2%), and adenovirus with 20 (16.9%) cases. There was no detection of influenza virus or RSV in our study. The distribution of viral respiratory agents is shown in Table 2. There was also a slight shift in the positivity rate of respiratory pathogens toward spring; the full distribution according to months is shown in Figure 1.

For 14 (11.9%) cases, the SARS-CoV-2 PCR test was positive in this study. The median age of cases positive by SARS-CoV-2 PCR was 3.3 (IQR: 0.2–10.5) years and that of negative patients was 2.1 (IQR: 1.0–6.5) years. There was no difference in terms of age between SARS-CoV-2 PCR-positive and PCR-negative subjects (*P*: .647). There was only one co-infection of SARS-CoV-2, with the co-infecting pathogen identified as rhinovirus. This patient was a previously healthy boy who was aged 3 months and presented with respiratory distress. He underwent HFNC oxygen therapy for 4 days, and after 8 days of hospitalization, he was discharged without any complications. There were no cases of the multisystem inflammatory syndrome among the children in this study.

In 43 (36.4%) cases, there was a co-infection with more than one virus. All but one co-infection included 2 viral pathogens. For 1 (0.8%) patient, 3 co-infecting pathogens were detected—rhinovirus, enterovirus, and adenovirus. Among co-infections, the most common co-infection included rhinovirus and enterovirus in 37 (86.0%) cases (Table 3). There was no difference for hospital admission or PICU admission rates or length of hospital stay for patients with and without co-infection [patients with co-infection: hospital admission rate: 23.8%, PICU admission rate: 9.5%, length of hospital stay in days, median (IQR): 1.0 (0.4–5.9); patients without co-infection: hospital admission rate: 35.7%, PICU admission rate: 12.9%, length of hospital stay in days, median (IQR): 2.5 (0.5–8.9), *P*: .134, *P*: 0.418, *P*: .141]. In order to prevent confusion, cases were divided into 2 groups—patients having and not having underlying conditions. There was still no difference for hospital admission or PICU admission rates or length of hospital stay for those having an underlying disease or not in terms of the presence of co-infection [patients having underlying conditions: co-infection (+): hospital admission rate: 40.0%, PICU admission rate: 5.0%, length of hospital stay in days, median (IQR): 1.0 (0.4–10.2), co-infection (−): hospital admission rate: 48.1%, PICU admission rate: 18.5%, length of hospital stay in days, median (IQR): 1.0 (1.0–21.1), *P*: .399, *P*: .178, *P*: .078; patients not having underlying conditions:

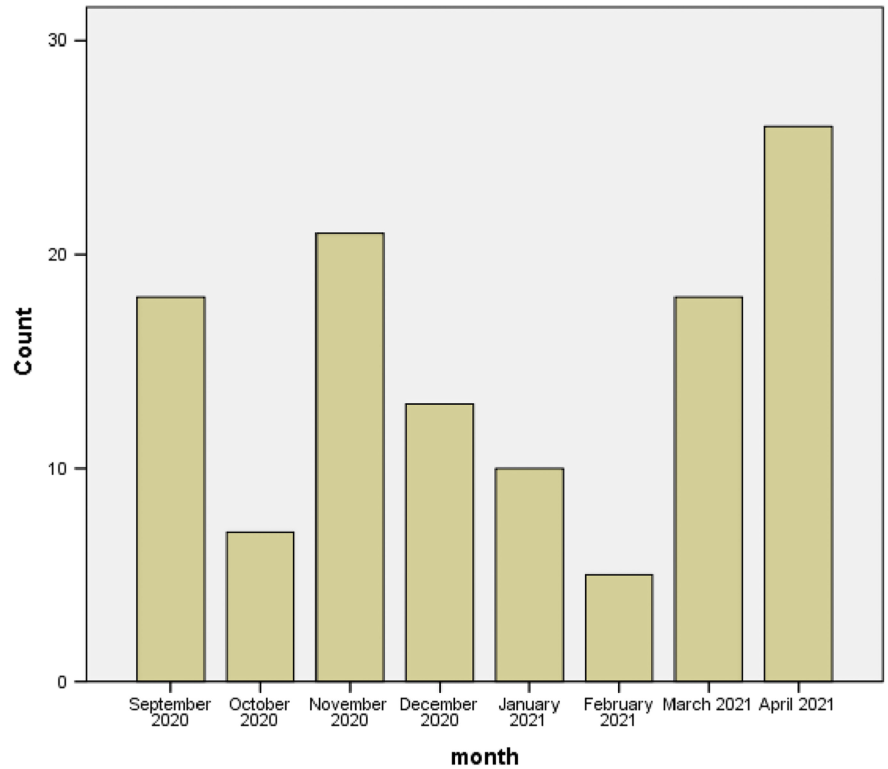

Figure 1. Distribution of positive tests for SARS-CoV-2 and/or other viral respiratory pathogens according to months.

Table 3. Distribution of Viral Respiratory Pathogens in Co-infections

Viral Pathogens in Co-Infection	n	% of Samples (n = 327)	% of Positive Samples (n = 118)
Rhinovirus/enterovirus	37	10.6	31.3
Rhinovirus/coronavirus	2	0.5	1.7
Rhinovirus/parainfluenza virus	1	0.2	0.8
Rhinovirus/SARS-CoV-2	1	0.2	0.8
Parainfluenza virus/coronavirus	1	0.2	0.8
Rhinovirus/enterovirus/adenovirus	1	0.2	0.8
Total	43	12.3	36.4

co-infection (+): hospital admission rate: 9.1%, PICU admission rate: 13.6%, length of hospital stay in days, median (IQR): 0.8 (0.4–2.6), co-infection (−): hospital admission rate: 27.9%, PICU admission rate: 9.3%, length of hospital stay in days, median (IQR): 1.2 (0.4–6.9), *P*: .079, *P*: .442, *P*: .408].

DISCUSSION

COVID-19 pandemic has rapidly evolved and caused healthcare concern worldwide. It was reported that there was a decline in the volume of pediatric ED visits and visits due to ARTIs during the pandemic period.[12] It was also declared that there was a significant decrease in the frequency of seasonal respiratory virus infections such as influenza and RSV in the pediatric population during lockdown periods compared to previous years.[13]

During the pandemic period, in COVID-19 suspected children, the positivity rate for respiratory viruses was calculated as 36% and the most commonly identified agents were rhinovirus, enterovirus, and adenovirus, followed by SARS-CoV-2; there was no detection of influenza virus or RSV in the present study. There seems to be a decrease in the positivity rate compared to previous years; according to a study conducted at the same center including cases between April 2011 and April 2018, the positivity rate was 58.7%, and the most commonly detected respiratory viral pathogens were rhinovirus/enterovirus (36.2%), RSV (19.0%), and influenza virus (14.7%).[1]

The ongoing annual influenza and RSV seasons were also reported to end more rapidly among children in 2020 compared to previous years.[12] The decline in the incidence of RTIs may be related to social isolation and to the fact that children did not attend school, daycare centers, or social activities. Schools and daycare centers were identified to be sources of viral infections in previous studies;[14,15] children attending daycare were reported to be at higher risk of having ARTIs than those who stayed at home.[16–18] Although the influenza season of the pandemic period had similarities to the season of 2018–2019, it was reported to end more suddenly. These data suggest that NPIs may have declined the spread of influenza. Previous data also reported that the timing of holidays and school closures reduced the spread of influenza epidemics.[19–21] Another pediatric study found that only 3 hospitalizations for influenza in 2020 and no PICU admissions compared to 796 hospitalizations and 91 PICU admissions in 2019.[22] For RSV cases, there was a similar reduction, respectively.[12] Daycare attendance was reduced remarkably during the pandemic, suggesting that social isolation and smaller daycare groups may decrease the disease burden and hospital admissions due to RSV.[12]

Rhinovirus was found as the most common viral pathogen of upper RTIs; surveillance studies reported that the positivity rate of rhinovirus was 16.4–35.1%.[23–25] In the current study, rhinovirus was the most commonly detected viral pathogen during the pandemic. Although there was a reduction in the frequency of most of viral respiratory agents, it was reported that the spread of rhinovirus did not change and that rhinovirus was still the most common viral agent.[26] In another study, surgical face masks were found to decrease the detection of coronavirus RNA in aerosols and influenza virus RNA in respiratory droplets.[27] However, no significant difference was observed in the viral load of individuals with and without face masks in cases of rhinovirus infection, both in aerosols and respiratory droplets.[27] Furthermore, rhinovirus and enteroviruses have very similar DNA sequence that causes the cross reactions during the PCR, so this similarity may cause confusion.

Lockdown measures taken to contain the spread of the SARS-CoV-2 outbreak may have altered the detection of other common respiratory viruses due to changes in characteristics of symptomatic individuals seeking health care or changes in propensity of physicians to test.[28] These changes were attributed to both changes related to decreases in routine healthcare visits for ARTIs and changes in respiratory virus circulation due to the widespread NPIs to mitigate the spread of SARS-CoV-2.[29] Decline in respiratory viral pathogens may also be related to the reduction in testing, because patients who had respiratory symptoms were primarily referred for assessment for SARS-CoV-2 testing.

Co-infections of SARS-CoV-2 and other respiratory viruses have been reported in some studies.[26,30,31] SARS-CoV-2 PCR (+) cases co-infected with other respiratory agents are increasingly reported to present with mycoplasma, legionella, cytomegalovirus, parainfluenza virus, RSV, Ebstein-Barr virus, human metapneumovirus, rhinovirus, and other coronaviruses.[32] In a review that evaluated co-infection with SARS-CoV-2, the co-infection rate was found to be low and rhinovirus/enterovirus, RSV, and influenza virus were the co-infecting pathogens identified most frequently.[33] Co-infection rates ranged between 0% and 3% in previous reports.[10,34,35] Although the results vary, recent data show that pediatric SARS-CoV-2 co-infection rates may be as high as 51%.[30,31] However, the present single-center study has revealed that the viral co-infection rate among SARS-CoV-2 PCR-positive children was low; there was only one co-infection of SARS-CoV-2 among 14 SARS-CoV-2 PCR-positive cases. Li et al evaluated children with COVID-19 with co-infections or single infections and found no difference in terms of clinical manifestations and hospital stays, suggesting that co-infection might not aggravate disease severity.[36] No increase was observed in morbidity and mortality associated with co-infections in cases of COVID-19 in another study.[10]

The limitations of the present study include lack of data for the period between the start of the pandemic in March 2020 and September 2020 because testing for respiratory viruses other than SARS-CoV-2 was not available at that time. Another limitation is the limited number of cases because this study aimed to portray a single-center's experience. Finally, we could not test for other viral respiratory agents for all patients for whom SARS-CoV-2 PCR tests were performed during the study period, so it was not possible to calculate the real rate of co-infections with SARS-CoV-2.

CONCLUSION

There was a decrease in the positivity rate of viral respiratory agents and no detection of influenza virus or RSV in our study. Circulating viruses may change due to multifactorial approaches applied during the COVID-19 pandemic. Strict public healthcare measures can significantly reduce respiratory virus transmission. Understanding the prevalence of co-infections with SARS-CoV-2 is crucial for delineating its true clinical impact and may supply evidence for decision making for future epidemics.

Ethics Committee Approval: This study was approved by the Ethics Committee of Dokuz Eylül University (Approval No: 2020/29-59).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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