

## Coronavirus Pandemic

### Coinfection in SARS-CoV-2 Infected Children Patients

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#### Abstract

**Introduction:** The aim of this study is to determine the coinfections with other respiratory pathogens in SARS-CoV-2 infected children patients in a pediatric unit in Istanbul.

**Methodology:** This retrospective descriptive study was conducted in a 1000-bedded tertiary education and research hospital in Istanbul. All children hospitalized with the diagnosis of SARS-CoV-2 infection had been investigated for respiratory agents in nasopharyngeal secretions. Laboratory confirmation of SARS-CoV-2 and the other respiratory pathogens were performed using reverse transcriptase-polymerase chain reaction (RT-PCR).

**Results:** A total of 209 hospitalized children with suspected SARS-CoV-2 infection between March 2020-May 2020 were enrolled in this study. Among 209 children, 93 (44.5%) were RT-PCR positive for SARS-CoV-2 infection, and 116 (55.5%) were RT-PCR negative. The most common clinical symptoms in all children with SARS-CoV-2 infection were fever (68.8%) and cough (57.0%). The other clinical symptoms in decreasing rates were headache (10.8%), myalgia (5.4%), sore throat (3.2%), shortness of breath (3.2%), diarrhea (2.2%) and abdominal pain in one child. In 7 (7.5%) patients with SARS-CoV-2 infection, coinfection was detected. Two were with rhinovirus/enterovirus, two were with Coronavirus NL63, one was with adenovirus, and one was with *Mycoplasma pneumoniae*. In one patient, two additional respiratory agents (rhinovirus/enterovirus and adenovirus) were detected. There was a significantly longer hospital stay in patients with coinfection ( $p = 0.028$ ).

**Conclusions:** Although the coinfection rate was low in SARS-CoV-2 infected patients in our study, we found coinfection as a risk factor for length of hospital stay in the coinfecting patient group.

**Key words:** SARS CoV-2; coinfection; children; respiratory pathogen.

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#### Introduction

In December 2019, a novel Coronavirus was detected in Wuhan, China, which caused viral pneumoniae in a cluster of patients with a history of Huanan wholesale seafood market exposure [1,2]. Firstly, the World Health Organization (WHO) named this new coronavirus as “2019 novel coronavirus (2019-nCoV)”. On February 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) termed the virus as “Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)” and the WHO announced the disease caused by SARS-CoV-2 as COVID-19 (coronavirus disease-2019). In a short period of time, cases had been reported worldwide, and WHO declared SARS-CoV-2 infection as a pandemic on March 11, 2020, with more than 118,000 cases in 114 countries [3]. In Turkey, the first case was detected on 11 March 2020. On 5 May 2020, a total of 129,491 cases and 3,520 deaths had been reported [4].

SARS-CoV-2 is thought to be transmitted by respiratory droplets and direct contact. Viruses on the respiratory droplets released by the patients, while talking loudly, sneezing or coughing, infect the mucous membranes of the susceptible cases. If a susceptible person touches a surface that was contaminated with the virus and touches his/her mucous membranes such as eyes, noses or mouth, they may become infected [5]. Most respiratory viral pathogens are transmitted by the same route.

Respiratory viruses are the most common causes of respiratory tract infections (RTI) among children. The most common viral agents are; respiratory syncytial virus (RSV), influenza viruses, human rhinovirus (hRV), enteroviruses (EV), coronavirus (CoV), adenovirus (AV), parainfluenza viruses type 1 to 4 (PIV 1-4), human metapneumovirus (hMPV) and human bocavirus (hBoV) [6].

Current studies show that there are SARS-CoV-2 infected patients who have coinfections with other

respiratory agents like Influenza A, parainfluenza 4 and Human Metapneumovirus (HMV) [7-9]. However, there are not many studies investigating coinfection rates and how coinfection effects the clinical course of the disease in pediatric patient groups. This may help to the therapeutic approach. Therefore, we aimed to investigate the frequency and the effect of coinfections in children with SARS-CoV-2 infection.

## Methodology

This retrospective descriptive study was conducted in a tertiary education and research hospital in Istanbul, Turkey, from March 2020 to May 2020.

The participants were identified through the department's patient files archive (age, sex, RT-PCR for SARS-CoV-2 infection and other respiratory agents, laboratory findings, the hospital stay). A total of 209 patients were collected in this study, including 93 with PCR-positive for SARS-CoV-2 and 116 with PCR-negative for SARS-CoV-2. A nasopharyngeal swab was collected from the patient's single nostril according to our Health Ministry guideline for SARS-CoV-2 infection [10].

All the children hospitalized had also been investigated for other respiratory agents (Influenza A, Influenza B, Coronavirus NL63, 229E, OC43, HKU1, Parainfluenza virus type1, 2,3,4, Human metapneumovirus, Respiratory syncytial virus, adenovirus, rhinovirus/enterovirus, *Mycoplasma pneumoniae*, *Bordetella pertussis* and *Chlamydia*

*pneumoniae*) in nasopharyngeal secretions with polymerase chain reaction (PCR).

This study was approved by the Medical Research Ethics Committee of our institution.

## Statistical Analysis

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used when evaluating the study data. The suitability of quantitative data for normal distribution was tested by Kolmogorov-Smirnov, Shapiro-Wilk test and graphical evaluations. Mann-Whitney U test was used to compare two groups of non-normally distributed data. In the comparison of qualitative data, Fisher-Freeman-Halton Exact test and Fisher's Exact test were used. Statistical significance was set at  $p < 0.05$ .

## Results

Of the total 209 suspected SARS-CoV-2 infected hospitalized children in our pediatric unit, 93 (44.5%) patients were PCR-positive for SARS-CoV-2 infection and 116 (55.5%) were negative. There were 45 (48.4%) females and 48 (51.6%) males with a mean±standard deviation (SD) age of  $10.02 \pm 5.82$  years (range; 1 month-17.8 years). In confirmed SARS-CoV-2 infected patients, coinfection was detected in 7 of 93 (7.5%) patients. The detected respiratory agents were

**Table 1.** Comparative of findings between the patients only PCR positive for SARS-CoV-2 infection and the patients co-infected both with SARS-CoV-infection and another respiratory pathogen.

	The patients only PCR positive for SARS-CoV-2 infection (n = 86)	The patients co-infected both with SARS-CoV-infection and another respiratory pathogen (n = 7)	p-value
Age (Mean) (years)	9.94 ± 5.81	10.99 ± 6.44	0.570
Sex			
Female	43 (50.0)	2 (28.6)	0.437
Male	43 (50.0)	5 (71.4)	
<b>Clinical Findings</b>			
Fever	58 (67.4)	6 (85.7)	0.428
Cough	49 (57.0)	4 (57.1)	1.000
Headache	9 (10.5)	1 (14.3)	0.568
Diarrhea	2 (2.3)	0 (0)	1.000
Sore Throat	3 (3.5)	0 (0)	1.000
<b>WBC (Median) (mm<sup>3</sup>)</b>	6,150	9,000	0.130
<b>Lymphocyte (Median) (mm<sup>3</sup>)</b>	2,000	1,900	0.453
<b>Platelet (Median) (mm<sup>3</sup>)</b>	248,000	244,000	0.878
<b>CRP</b>			
Negative	53 (61.6)	2 (28.6)	0.117
Positive	33 (38.4)	5 (71.4)	
<b>CRP value in positive patients (Median) (mg/L)</b>	8.5	25.5	0.055
<b>Hospital Stay (Mean) (days)</b>	5.24 ± 2.67	7.14 ± 2.12	0.028

WBC: White Blood Cell; CRP: C-reactive protein.

rhinovirus/enterovirus in two patients, Coronavirus NL63 in two patients, adenovirus in one patient and *Mycoplasma pneumoniae* in one patient. In one patient, two additional respiratory agents (rhinovirus/enterovirus and adenovirus) were detected.

In patients with PCR negative for SARS-CoV-2 infection, one or more respiratory agents were detected in 47 of 116 (40.5%). The most detected respiratory agents in decreasing rates in PCR-negative group were; rhinovirus/enterovirus (40.4%), adenovirus (21.2%), Coronavirus NL63 (12.7%), Influenza-B (8.5%), *Mycoplasma pneumoniae* (6.3%), RSV (6.3%), Metapneumovirus (4.2%), *Chlamydia pneumoniae* (4.2%) and Parainfluenza type 3 (4.2%). Also, Parainfluenza type 4 was detected in one patient.

The most common clinical symptoms in children with SARS-CoV-2 infection were fever (68.8%) and cough (57.0%). The other clinical symptoms in decreasing rates were headache (10.8%), myalgia (5.4%), sore throat (3.2%), shortness of breath (3.2%), diarrhea (2.2%) and abdominal pain in one child.

We compared some of our findings between the patients only PCR positive for SARS-CoV-2 infection and patients coinfecting both with SARS-CoV-infection and another respiratory pathogen (Table 1). There were no statistical differences for age, sex, clinical findings (fever, cough, headache, diarrhea, sore throat), median WBC count, median lymphocyte count, median platelet count, C-reactive protein positivity between the groups. We also compared the C-reactive protein-positive groups for the median C-reactive protein value. We found a higher median C-reactive protein value in patients co-infected with SARS-CoV-infection and another respiratory pathogen. However, it was not statistically different ( $p = 0.055$ ). On the other hand, there was a significantly longer hospital stay in patients with coinfecting both with SARS-CoV-infection and another respiratory pathogen ( $p = 0.028$ ).

Thirty-five patients showed radiological findings concordant with pneumoniae on chest computed tomography (CT) scans. The typical findings of chest CT images were bilateral patchy shadows or lung consolidations. However, there was no statistical difference between the two groups ( $p = 0.231$ ). All patients received supportive care and the patients with the diagnosis of pneumoniae received azithromycin. None of the patients required respiratory support due to hypoxemia or intensive care unit hospitalization.

None of the patients died and a clinical cure was achieved in all patients in both groups.

## Discussion

Coinfections with respiratory viruses detected in up to 30% of children patients with acute respiratory tract infection show the seasonal distribution in temperate climates [11]. In a study that investigated the association between the meteorological parameters and acute respiratory tract infections, du Prel *et al.* showed that Human rhinovirus, enterovirus, and adenovirus were detected all around the year. On the other hand, RSV, influenza A virus and human metapneumovirus showed distinctive winter peaks [12]. In our study, in the non-SARS-CoV-2 group, we found a high coinfection rate of 40.5% and the most common pathogens were rhinovirus/enterovirus, adenovirus and coronavirus NL63. On the other hand, in the SARS-CoV-2 positive group, coinfection rate was low, 7.5% and the most commonly detected respiratory pathogens were rhinovirus/enterovirus, adenovirus and coronavirus NL63. Coinfection rates may change at different times of the year. We believe that if our study was conducted with a larger-scale patient group before March with the start of the influenza season, we might have found higher coinfection rates with influenza in the SARS-CoV-2 positive group as we know that outbreaks of influenza mostly occur during the winter months. On the other hand, in the non-SARS-CoV-2 infected group, we detected four children with influenza B. Also, in our study, in the SARS-CoV-2 infected patient group, we did not find any RSV coinfection. We think that this is because of the older age of our patients who needed hospitalization due to COVID-19.

A study that closely resembles our study which was conducted in Wuhan by Wang *et al.* examined the coinfection rates and reported that 6 of 104 (5.8%) confirmed COVID-19 patients were coinfecting with other respiratory agents such as coronavirus, influenza A virus, rhinovirus and influenza A H3N2. However, they found coinfection rates as high as 18.4% in the non-2019-nCoV-infected patient group [13]. Tagaro *et al.* reported 41 children with confirmed COVID-19 and 5% of patients were found coinfecting with influenza B [14]. 168 children were investigated in a multicenter study in Italy and findings showed that coinfection was documented in 10 (5.9%) children (three with rhinovirus, three with RSV, two with Epstein-Barr virus, one with non-SARS coronavirus and one with influenza A virus) [15]. Jiang *et al.* screened 161 hospitalized children patients for respiratory viruses and they found coinfection only in two patients with SARS-CoV-2; one patient with SARS-CoV-2, human respiratory syncytial virus and human metapneumovirus and one patient with SARS-CoV-2,

*Mycoplasma pneumoniae* and human metapneumovirus [16]. Oliva *et al.* described a series of seven adult patients coinfecting with *C. pneumoniae* (n = 5) or *M. pneumoniae* (n = 2) and SARS-CoV-2 and compared clinical outcomes (intensive care unit admission and intra-hospital mortality) of 175 patients without *M. pneumoniae* or *C. pneumoniae* coinfection and no differences were observed in the study [17]. In New York, Nowak *et al.* found the coinfection rate to be 3% and the mean age of the patients was 60.1 years [18]. In all these studies, coinfection rates are low, similarly with our study. Differently, Kim *et al.* reported high coinfection rates in SARS-CoV-2 infected patients. Of the 116 specimens positive for SARS-CoV-2, 24 (20.7%) were positive for one or more viral pathogens. In the same study, the most common viral pathogens associated with coinfection were rhinovirus/enterovirus, respiratory syncytial virus, and non-SARS-CoV-2 Coronaviridae [19].

Coinfections may reduce or increase the disease severity [20-22]. In viral coinfections, one virus generally impacts the replication of the other virus, described as viral interference, which can lead to continuity of one virus and the clearance of the other [23]. Host defense system also plays a significant role on the effects of coinfection [24]. Scotta *et al.* evaluated the relation between respiratory viral coinfection and illness severity in children; however, they found that viral coinfection did not impact risks of outcomes such as; the need for hospitalization, length of supplemental oxygen, need of intensive care, mechanical ventilation and death [20]. On the other hand, Cilla *et al.* reported in their study that children with coinfection required more hospital admission than children with a single viral infection [21]. Differently, Marguet *et al.* showed a protective effect of coinfection as; shorter hospital stays in children with coinfecting with RSV and rhinovirus than single RSV infection [22]. In our study, we did not compare so many parameters between the groups; however, we found coinfection as a risk factor for a longer hospital stay. Despite available data, we know little about the influence of the coinfection in SARS-CoV-2 coinfecting children patients. We believe that further studies are needed to assess if coinfection in SARS-CoV-2 infected patients has any impact upon disease outcome.

The limitations of this study were; firstly, the number of patients in this study was limited. We believe that large-scale studies are needed in consecutive seasons. Secondly, in our study, we detected coinfection at low rates, so it was challenging to

compare the coinfecting patient group to the non-coinfecting patient group.

In conclusion, we think coinfection in SARS-CoV-2 infected patients may be at risk for longer hospital stay and therefore these patients should be screened for coexisting respiratory pathogens, for both specific therapies and appropriate isolation precautions.

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All authors have participated in the drafting of the manuscript and/or critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

### Authors' Contributions

AK and CÇ analyzed the data and drafted the manuscript, AK and CÇ critically reviewed the analyses, AK, CÇ, YA, SDT, ES and RD reviewed and commented on the initial and final drafts of the manuscript, all authors read and approved the final manuscript. All authors have participated in the drafting of the manuscript and/or critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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