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**Original Article**

# Seasonal coronaviruses infections in children: do they always cause mild illness?

Ayşegül Elvan Tüz[1], Selin Taşar[1], Eda Karadağ Öncel[1], Yıldız Ekemen Keleş[1], Aslıhan Şahin[1], Gülnihan Üstündağ[1], Yavuz Demirçelik[2], Nisel Özkalay Yılmaz[3], Ahu Kara Aksay[1], Dilek Yılmaz Çiftdoğan[1,4]

*Departments of [1]Pediatric Infectious Diseases, [2]Pediatrics and [3]Microbiology, University of Health Sciences, Tepecik Training and Research Hospital, İzmir; [4]Department of Pediatric Infectious Diseases, İzmir Katip Çelebi University, İzmir, Turkey.*

**ABSTRACT**

**Background.** Human coronaviruses (HCoVs) cause a comprehensive clinic ranging from asymptomatic course to pneumonia. We aimed to describe the HCoV infections in children to determine the clinical status and coinfection effects in a five-year retrospective surveillance study. The primary outcome was admission to the intensive care unit (ICU) and the secondary outcome was the need of high oxygen support.

**Methods.** Between September 2015 and November 2020, all patients whose reverse transcription polymerase chain reaction (RT-PCR) tests were positive were determined and patients with HCoVs were included in the study. Demographical characteristics, underlying chronic diseases, clinical diagnosis, laboratory data, subtypes of HCoVs, radiological findings, treatments, hospitalization, and ICU admission were analyzed.

**Results.** Of the 2606 children, the overall respiratory tract virus detection rate was 82.4%. Among these, 98 cases were HCoVs positive and of these 80 (81.6%) were under five years of age and most of the patients were admitted to the hospital in spring and 70% were a mixed infection with other respiratory viruses. Since lower respiratory tract infections are more common in HCoV coinfections, a significant difference was found in clinical diagnosis ($p<0.001$). The presence of hypoxia ($p=0.003$) and underlying disease ($p=0.004$) were found to be significantly more common in patients admitted to the ICU. The presence of hypoxia, infiltration on chest X-ray, and elevated C-reactive protein levels were more frequently determined in patients who received high oxygen support ($p=0.001$, $p=0.036$, $p=0.004$, respectively).

**Conclusions.** Clinical findings may be more severe if HCoVs, which generally cause mild respiratory disease, are coinfected with another viral agent.

**Key words:** HCoV, children, respiratory tract infections, coinfection, lower respiratory tract infection.

Human coronaviruses (HCoVs) have been known to infect humans and animals since the late 1960s.[1] There are seven subtypes, including OC43, NL63, 229E, HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2. HCoV-OC43 is the most common subtype and is commonly observed in children <5 years of age.[2] Although the infection can be asymptomatic, it can present with upper respiratory tract infections, croup, bronchiolitis, and pneumonia. HCoVs are thought to be responsible for approximately 10% of all upper and lower respiratory tract diseases.[3] For seasonal HCoVs, several including OC43, 229E, NL63, and HKU-1 have generally been associated with mild respiratory illnesses and have been assessed mainly in epidemiological studies.[4] Still, severe diseases, accompanied by lower respiratory tract infection, might also occur, especially in the elderly, neonates, and patients with underlying

✉ Ayşegül Elvan Tüz
aysegulelvan@hotmail.com

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conditions and risk factors.[5] HCoVs are often detected in coinfections with other respiratory viruses. Although the impact of infection has not been clearly demonstrated in HCoV coinfections, some studies have found that patients with coinfections experience worse morbidity.[6,7]

Although HCoV is widespread globally, the frequency of detection of its four major subtypes varies significantly both by geography and over time. Despite these epidemiology features, there is no study focusing on the frequency of HCoVs strains and their clinical manifestations from Turkey. In general, coronaviruses are thought to cause mild respiratory illnesses, but severe respiratory diseases or even intensive care admission may be seen in some patients. This study aimed to determine the frequency of HCoVs in a series of hospitalized infants and young children with symptoms of respiratory tract diseases. The present study's main focus was to detect clinical pictures and factors that affect the disease severity of the HCoVs in hospitalized children.

## Material and Methods

### *Study Design and Definitions*

This retrospective cohort study was conducted by the Division of Pediatric Infectious Diseases, Health Sciences University Izmir Tepecik Research and Training Hospital in Turkey between September 2015 and November 2020. The medical records of patients diagnosed with HCoVs infections were analyzed. Relevant information including demographical characteristics, clinical symptoms, prematurity, underlying diseases, clinical diagnosis, laboratory data, subtypes of HCoVs, radiological findings, treatments, hospitalization, and ICU admission were recorded.

Common cold and croup were regarded as upper respiratory tract infections. Symptoms of a common cold are nasal discharge, nasal obstruction, sneezing, sore throat, and cough. Croup is often seen with sudden onset of a bark like cough, hoarse voice, and nocturnal respiratory stridor.[7] The clinical diagnoses of acute bronchiolitis, asthma, and pneumonia defined the lower respiratory tract infections. Acute bronchiolitis is characterized by wheezing in children less than two years old.[8] Patients with infiltration on chest radiographs and without wheezing were classified as pneumonia.[9] In the diagnosis of asthma, the National Asthma Education and Prevention Program guidelines were followed.[10]

In this study, the term viral coinfection indicates the simultaneous detection of two or more respiratory viruses in the same sample taken from a respiratory infection patient.

The study protocol was approved by the Institutional Ethics Committee of Izmir Tepecik Training and Research Hospital (Protocol number: 2020/13-15)

### *Viral Assays*

Nasopharyngeal swab samples were examined for the *Respiratory syncytial virus A/B, Rhinovirus, Influenza virus A and B, Parainfluenza virus 1, 2, 3 and 4, Human metapneumovirus, Adenovirus, Human coronavirus OC43, 229E* and *NL63*, *Bocavirus*, and *Enterovirus* with multiplex reverse transcription-polymerase chain reaction (RT-PCR) method (Anyplex II RV 16 Detection; Seegene, Seoul, South Korea was used until December 2018; after January Bosphore, Respiratory pathogens panel kitv4, Anatolia, Turkey was used). One nasopharyngeal swab was collected from each enrolled child. A specimen was defined as being HCoVs positive when the RT-PCR assay was positive for HCoVs 229E, NL63, and OC43.

### *Primary and secondary outcome*

The primary outcome was considered as admission to ICU. Participants were divided into two main groups according to oxygen treatment to determine the secondary outcome. In the first group, patients did not receive any oxygen treatment or need oxygen with a mask. The second group consisted of patients who

received high flow nasal cannula (HFNC), noninvasive mechanical ventilator (MV), and invasive MV treatment.

### *Statistical Analysis*

Statistical data were analyzed with IBM SPSS for Windows version 25.0 (Chicago, IL). Values for numerical variables were given as median (interquartile range) (IQR) or mean ± standard deviation, depending on the normality distribution. Categorical variables were presented as numbers and percentages. Continuous variables following normal distribution were compared using one-way analysis of variance or t-tests. When distribution was not expected, the Kruskal-Wallis test was used. Categorical variables were compared using the Chi-Square test. A p-value of $<0.05$ was considered statistically significant for all predictions.

## Results

A total of 2606 pediatric cases were diagnosed with respiratory tract infections and a nasopharyngeal swab was obtained from these cases. Overall, in 82.4% (n=2147) of samples, one or more viruses were confirmed with the RT–PCR. Of whom 98 (4.6%) were infected with HCoVs. Single HCoVs infection was detected in only 29 (29.6%) cases; in 69 (70.4%) of the patients, at least one other viral agent was detected in addition to HCoVs.

### *Characteristics of HCoVs Infection*

A total of 98 children infected with HCoVs were enrolled in this retrospective study, 80 (81.6%) were under five years, and 62 (63.3%) were male. Considering the seasonality of HCoVs, 48 cases (49%) presented in spring. With regard to the distribution of cases in proportion to months, the highest admission was determined in March with 25 cases (25.5%). Half of the patients (50%) had an underlying disease, while 19 patients (19.4%) had a history of prematurity. The most common symptoms on the first presentation were fever (56/98, 57.1%), and cough (53/98, 54.1%). Physical and clinical findings on presentation were consistent with acute pneumoniae in 46 patients (46.9%). Infiltration was detected in the chest radiography of 51 cases (52%). It was observed that 77 cases (78.6%) received antibiotic treatment. Although 90 patients (91.8%) were hospitalized during follow-up, only 22 (22.4%) of them required the ICU.

### *Clinical Comparison Between HCoV Single Infections and HCoV Coinfections*

When patients with single and coviral infections were compared in terms of age, gender, prematurity history, underlying diseases, and laboratory findings, all variables were similar between groups. Although lower respiratory tract infections and infiltration in the chest X-ray were more common in HCoV coinfections, the differences were statistically significant ($p<0.001$ and $p=0.007$, respectively). While 26 (89.6%) patients were hospitalized with a single HCoV infection, 64 (92.7%) patients with coinfection had a hospitalization history. However; the difference was not statistically different between groups ($p=0.609$). The clinical comparisons in both groups are summarized in Table I.

### *Clinical Comparison Between HCoV Subtypes*

In terms of subtypes of HCoVs observed in the virally positive group OC43 was found in 53 cases (54%), NL63 was found in 32 (32.7%), and 229E was found in 13 (13.3%) cases. According to seasonal distribution, 15 cases (45.4%) with NL63, 26 cases (50%) with OC43, and seven cases (53.8%) with 229E were admitted in spring. There was a significant difference between the seasonal distribution of the three subtypes of HCoVs ($p=0.001$). When the clinical findings were evaluated, it was seen that the groups were similar in terms of fever, cough, rhinorrhea, and nasal obstruction. Wheezing was detected more frequently in nine patients (69.2%) infected with 229E, and the difference was statistically significant compared to the other groups ($p=0.042$). There was no difference

**Table I.** Clinical comparison between single HCoV infections and HCoV coinfections.

| | Single HCoV Infections (n=29) | HCoV Coinfections (n=69) | *P* Value |
|---|---|---|---|
| Gender* | | | 0.223 |
| Male | 21 (72.4) | 41 (59.4) | |
| Female | 8 (27.6) | 28 (40.6) | |
| Age (mo)** | 14 (6-71) | 11 (3-30) | 0.320 |
| Season* | | | 0.741 |
| Autumn | 2 (6.9) | 5 (7.2) | |
| Winter | 6 (20.7) | 21 (30.4) | |
| Spring | 15 (51.7) | 33 (47.8) | |
| Summer | 6 (20.7) | 10 (14.5) | |
| Clinical findings* | | | |
| Fever | 13 (44.8) | 43 (62.3) | 0.267 |
| Cough | 12 (41.4) | 41 (59.4) | 0.249 |
| Wheezing | 9 (31) | 36 (52.2) | 0.151 |
| Rhinorrhea | 3 (10.3) | 11 (15.9) | 0.594 |
| Nasal congestion | 1 (3.4) | 3 (4.3) | 0.718 |
| Hypoxia* | 9 (31) | 24 (34.8) | 0.292 |
| Prematurity* | 8 (27.6) | 11 (15.9) | 0.183 |
| Underlying disease* | 17 (58.6) | 32 (46.4) | 0.269 |
| Clinical condition* | | | **<0.001** |
| Upper RTI | 18 (62.1) | 16 (23.2) | |
| Lower RTI | 11 (37.9) | 53 (76.8) | |
| Laboratory findings | | | |
| Total WBC (10^3/uL)*** | 10.526±4.394 | 11.309±6.715 | 0.577 |
| Platelet counts (10^3/uL)*** | 344.444±178.900 | 354.042±169.931 | 0.807 |
| C-reactive protein (mg/L)** | 6.5 (0.8-28.7) | 11.3 (3.1-24.6) | 0.845 |
| Procalcitonin (μg/L)** | 0.06 (0.03-0.27) | 0.14 (0.05-1.8) | 0.243 |
| Infiltration in chest graphy* | 9 (31) | 42 (60.9) | **0.007** |
| Antibiotic treatment* | 22 (75.9) | 55 (79.7) | 0.672 |
| Hospitalization* | 26 (89.6) | 64 (92.7) | 0.609 |
| Days of hospital stay** | 12 (8-31) | 9 (7-16) | 0.309 |
| ICU admission* | 9 (31) | 13 (18.8) | 0.187 |
| Days of ICU stay** | 4 (3-10) | 5 (3-13) | 0.545 |

HCoV: human coronavirus, IQR: interquartile range, RTI: respiratory tract infection, WBC: white blood cell, ICU: intensive care unit, SD: standart deviation.
*n, % **median (IQR) ***mean±SD

between the clinical diagnoses of the cases, hospitalizations, and treatments. Clinical characteristics of cases infected with HCoVs subtypes are shown in Table II.

### *Clinical Comparison According to Primary Outcome*

A total of 22 patients required ICU admission, of whom 14 (63.6%) had hypoxia on ICU admission. The presence of hypoxia and underlying diseases were more common in patients who required ICU admission (p=0.003, p=0.004, respectively). In terms of respiratory support, while 21 patients (95.4%) received HFNC/noninvasive MV/invasive MV therapy only one patient had no need for any support, and the difference was statistically significant (p <0.001). When clinical diagnosis, laboratory findings, and the presence of coinfection were compared according to ICU admission, all variables were similar between groups (Table III).

**Table II.** Clinical comparison between HCoV subtypes.

| | NL63 (n=33) | OC43 (n=52) | 229E (n=13) | *P* Value |
|---|---|---|---|---|
| Sex* | | | | 0.618 |
| Male | 20 (60.6) | 35 (67.3) | 7 (53.8) | |
| Female | 13 (39.4) | 17 (32.7) | 6 (46.1) | |
| Age* | | | | 0.552 |
| <5 y | 26 (78.8) | 45 (86.5) | 10 (76.9) | |
| >5 y | 7 (21.2) | 7 (13.5) | 3 (23.1) | |
| Season* | | | | **0.001** |
| Autumn | 0 (0) | 6 (11.5) | 1 (7.7) | |
| Winter | 17 (51.5) | 6 (11.5) | 4 (30.8) | |
| Spring | 15 (45.4) | 26 (50) | 7 (53.8) | |
| Summer | 1 (3) | 14 (26.9) | 1 (7.7) | |
| Clinical findings* | | | | |
| Fever | 20 (60.6) | 31 (59.6) | 5 (38.5) | 0.434 |
| Cough | 21 (63.6) | 26 (50) | 6 (46.1) | 0.295 |
| Wheezing | 17 (51.5) | 19 (36.5) | 9 (69.2) | **0.042** |
| Rhinorrhea | 4 (12.1) | 8 (15.4) | 2 (15.4) | 0.637 |
| Nasal congestion | 1 (3) | 3 (5.8) | 0 (0) | 0.520 |
| Hypoxia* | 8 (24.2) | 21 (40.4) | 4 (30.8) | 0.474 |
| Prematurity* | 4 (12.1) | 14 (26.9) | 1 (7.7) | 0.126 |
| Underlying disease* | 18 (54.5) | 26 (50) | 5 (38.5) | 0.617 |
| Clinical condition* | | | | 0.420 |
| Upper RTI | 14 (42.4) | 17 (32.7) | 3 (23.1) | |
| Lower RTI | 19 (57.6) | 35 (67.3) | 10 (76.9) | |
| Hospitalization* | 30 (90.9) | 48 (92.3) | 12 (92.3) | 0.972 |
| ICU admission* | 6 (18.2) | 15 (48.1) | 1 (7.7) | 0.203 |
| Treatment* | | | | 0.878 |
| No/$O_2$ need | 20 (60.6) | 29 (55.8) | 7 (53.8) | |
| HFNC/noninvasive MV/invasive MV | 13 (39.4) | 23 (44.2) | 6 (46.1) | |

HCoV: human coronavirus, ICU: intensive care unit, RTI: respiratory tract infection, HFNC: high flow nasal cannula, MV: mechanical ventilator.
*n, %

### *Clinical Comparison According to Secondary Outcome*

Twenty-eight patients (28.6%) did not require any oxygen treatment or respiratory support. Of the patients treated with oxygen, 28 (28.6%) received oxygen with a mask, 22 (22.4%) HFNC, 12 (12.2%) continuous positive airway pressure (CPAP), eight (8.2%) MV support. Cough and nasal obstruction were more frequently seen in the group that did not need oxygen or only received oxygen with a mask (p=0.02, p=0.04, respectively). Fever, wheezing, and nasal discharge were more frequently seen in the group that received high oxygen support (p=0.038, p=0.002, p=0.039, respectively). The presence of hypoxia, infiltration on chest X-ray, and elevated C-reactive protein levels were more frequently detected in patients who received HFNC/noninvasive MV/invasive MV therapy (p=0.001, p=0.036, p=0.004, respectively). The clinical data of the cases according to the oxygen treatment are shown in Table IV.

**Table III.** Clinical comparison between ICU admission.

| | ICU Admission (n=22) | Non-ICU Admission (n=76) | P Value |
|---|---|---|---|
| Sex* | | | 0.122 |
| Male | 17 (77.3) | 45 (59.2) | |
| Female | 5 (22.7) | 31 (40.8) | |
| Age* | | | 0.907 |
| 0-5 y | 18 (81.8) | 63 (82.9) | |
| >5 y | 4 (18.2) | 13 (17.1) | |
| Season* | | | 0.272 |
| Autumn | 3 (13.6) | 4 (5.3) | |
| Winter | 3 (13.6) | 24 (31.6) | |
| Spring | 12 (54.5) | 36 (47.4) | |
| Summer | 4 (18.2) | 12 (15.8) | |
| Clinical findings* | | | |
| Fever | 16 (72.7) | 40 (52.6) | 0.150 |
| Cough | 9 (40.9) | 44 (57.9) | 0.051 |
| Wheezing | 9 (40.9) | 36 (47.4) | 0.215 |
| Rhinorrhea | 4 (18.2) | 10 (13.1) | 0.306 |
| Nasal congestion | 0 (0) | 4 (5.3) | 0.166 |
| Hypoxia* | 14 (63.6) | 19 (25) | **0.003** |
| Prematurity* | 3 (13.6) | 16 (21) | 0.438 |
| Underlying disease* | 17 (77.3) | 32 (42.1) | **0.004** |
| Clinical condition* | | | 0.406 |
| Upper RTI | 6 (27.3) | 28 (36.8) | |
| Lower RTI | 16 (72.7) | 48 (63.1) | |
| Laboratory findings | | | |
| Total WBC (10^3/uL)** | 11.595 ±5.715 | 10.937±6.288 | 0.661 |
| Platelet counts (10^3/uL)** | 357.590±134.204 | 349.485±182.005 | 0.847 |
| C-reactive protein (mg/L)*** | 22.2 (5.1-67.6) | 7.4 (2.4-20) | |
| Procalcitonin (μg/L)*** | 0.16 (0.03-3.6) | 0.13 (0.04-1.23) | |
| Respiratory viruses* | | | 0.187 |
| Single HCoV detection | 9 (40.9) | 20 (26.3) | |
| HCoV + ≥1 detection | 13 (59.1) | 56 (73.7) | |
| Infiltration in chest graphy* | 13 (59.1) | 38 (50) | 0.452 |
| Treatment* | | | **<0.001** |
| No/$O_2$ need | 1 (4.5) | 55 (72.4) | |
| HFNC/noninvasive MV/invasive MV | 21 (95.4) | 21 (27.6) | |

HCoV: human coronavirus, ICU: intensive care unit, RTI: respiratory tract infection, WBC: white blood cell, IQR: interquartile range, HFNC: high flow nasal cannula, MV: mechanical ventilator, SD: standart deviation.
*n, % **mean±SD *** median (IQR)

## Discussion

This study aimed to determine the rate of HCoVs and epidemiological characteristics during a five year period in Turkey. The overall detection rate of HCoVs in our study population was 4.6%, a value that is slightly lower than previously reported rates of 6.7% and 6%, but similar to studies from Turkey and Spain.[2,11,12] However,

**Table IV.** Clinical comparison between treatment.

| | No/$O_2$ Need (n=56) | HFNC/Noninvasive MV/Invasive MV (n=42) | *p* Value |
|---|---|---|---|
| Sex* | | | 0.147 |
| Male | 32 (57.1) | 30 (71.4) | |
| Female | 24 (42.8) | 12 (28.6) | |
| Age* | | | 0.218 |
| 0-5 y | 44 (78.6) | 37 (88.1) | |
| >5 y | 12 (21.4) | 5 (11.9) | |
| Season* | | | **0.045** |
| Autumn | 2 (3.6) | 5 (11.9) | |
| Winter | 20 (35.7) | 7 (16.7) | |
| Spring | 23 (41.1) | 25 (59.5) | |
| Summer | 11 (19.6) | 5 (11.9) | |
| Clinical findings* | | | |
| Fever | 28 (50) | 28 (66.7) | **0.038** |
| Cough | 32 (57.1) | 21 (50) | **0.020** |
| Wheezing | 18 (32.1) | 27 (64.3) | **0.002** |
| Rhinorrhea | 6 (10.7) | 8 (19) | **0.039** |
| Nasal congestion | 3 (5.3) | 1 (2.4) | **0.040** |
| Hypoxia* | 10 (17.8) | 23 (54.8) | **0.001** |
| Prematurity* | 8 (14.3) | 11 (26.2) | 0.140 |
| Underlying disease* | 24 (42.8) | 25 (59.5) | 0.102 |
| Clinical condition* | | | 0.050 |
| Upper RTI | 24 (42.8) | 10 (23.8) | |
| Lower RTI | 32 (57.1) | 32 (76.2) | |
| Laboratory findings | | | |
| Total WBC (10^3/uL)** | 10.319±5709 | 12.079±6587 | 0.246 |
| Platelet counts (10^3/uL)** | 345.278±178.479 | 359.140±164.145 | 0.458 |
| C-reactive protein (mg/L)*** | 5.9 (1.5-18.4) | 19.3 (6.2-47.4) | **0.004** |
| Procalcitonin (μg/L)*** | 0.14 (0.02-1.8) | 0.13 (0.05-0.52) | 1.000 |
| Infiltration in chest graphy* | 24 (42.8) | 27 (64.3) | **0.036** |

HCoV: human coronavirus, RTI: respiratory tract infection, WBC: white blood cell, IQR: interquartile range, HFNC: high flow nasal cannula, MV: mechanical ventilator, SD: standart deviation.
*n, % **mean±SD *** median (IQR)

in 70% of cases, these respiratory infections were coinfections with other viral agents. It was noticed that the cases were frequently young, and coinfection was associated with increased clinical severity. In a cohort study from Norway, it was found that coinfections were observed at a rate of 68%. HCoVs infection included a significant part of respiratory tract infections requiring hospitalization and was associated with lower respiratory tract infections.[13] Similarly, in a study involving hospitalized children with acute respiratory infections in Guangzhou, China, a significant difference was found between HCoV subtypes in terms of pneumonia.[14] In a Jordan centered study in which hospitalized children under two years of age were examined, the coinfection rate was 75.7%. However, there was no significant difference in clinical diagnosis in this study.[11] According to our results, lower respiratory tract

infections were more common in patients with coinfections.

It has long been established through several observational studies that weather conditions influence the seasonal incidence of many respiratory viruses. Regional and annual variations in the circulation of HCoVs have been described.[15] Epidemiologic studies of HCoVs infections suggest that they exhibit a seasonal pattern. In a temperate climate, HCoVs infections are primarily detected in winter and spring, with low-level circulation throughout the year.[5] The seasonal spread has been compatible with studies conducted in Europe and the USA.[15-20] According to studies from Asian countries, HCoVs can peak in all seasons.[15,21] During the 5-year follow-up period in this study, HCoV-OC43 was mostly seen in patients, similar to studies from Norway and China.[13,14] A survey conducted in Belgium showed that HCoV-OC43 and HCoV-229E were detected in all seasons.[22] On the other hand, HCoV-NL63 was caught mostly in winter and spring, with the number of new cases peaking in January and March.

In our population, one-fourth of children with HCoVs infection were admitted to the ICU. The presence of an underlying disease was associated as a significant risk factor. In a study conducted in New York, 11% of patients hospitalized with HCoV infection were admitted to the ICU. Moreover, the presence of chronic complex underlying conditions, including cardiovascular, genetic, and respiratory diseases, has been associated with increased disease severity.[23] Although the underlying disease was significant in ICU admission in both studies, there is a substantial difference in ICU admission rates. When the subtypes were examined, we could not find a difference in terms of ICU admission.

In our study, the rate of children who received respiratory support was 42%. In the study involving hospitalized children under the age of five, the need for respiratory support was around 14%.[24] In a study examining children under 18 who were hospitalized with HCoVs between January 2013 and December 2014, this rate was 18%. In the same study, children younger than two years old and those with underlying diseases were more likely to receive respiratory support.[20] According to our data, it is not possible to make this implication from our study. Remarkably, that our patients received a high rate of respiratory support compared to other studies. There is a point to consider that some of the reviews consisted of only inpatients and there was a specified age range.[18,25,26]

Antibiotics were administered to 78.6% of our population. This high frequency of antibiotic use is similar to that reported in the Southeast Brazil study.[23] Secondary bacterial infections and long-term respiratory viral panel results were among the factors causing unnecessary antibiotic use. Although viruses are the most common cause of acute respiratory infections, excessive or inappropriate antibiotics have been used in more than 50% of acute respiratory infections worldwide, leading to severe consequences such as drug side effects, high rates of resistance, and multidrug resistance in children with viral infections.[26]

Multiple pathogens detected in nasopharyngeal aspirates of patients with respiratory disease are increasingly recognized. Our study found that the respiratory tract viral panels have been frequently sent from hospitalized cases. Outpatient and asymptomatic cases can also be included in the study to demonstrate the reflections of HCoV on the clinic. However, there are some limitations to this method as well. It is difficult to determine whether these are true coinfections or indicate the continued transmission of pathogens from a previous infection. It has been shown that in 0.4% of patients without symptoms of respiratory tract infection, HCoV can be detected by PCR (polymerase chain reaction), and HCoV RNA is detected in real-time PCR up to 14 days after illness.[23]

This research had some limitations. One of the main limitations was that it was of retrospective

nature, and therefore, we could not access all clinical information of the patients. Due to our hospital's limited facilities, we were able to perform viral tests mainly on inpatients.

In conclusion, our five-year population-based study shows that the HCoV subtypes OC43, NL63, and 229E appear with characteristic outbreak patterns, primarily in the spring and winter. The cases were frequently under the age of five. It was seen that our population presented with wide clinical pictures such as upper respiratory tract infection, croup, bronchiolitis, asthma, and pneumonia. It should be kept in mind that clinical findings may be more severe if HCoVs, which generally cause mild respiratory diseases, are coinfected with another viral agent. Future multicenter studies with large populations involving all age groups are needed to provide additional information on the epidemiology and clinical features of HCoVs.

### Ethical approval

Ethics committee approval was obtained for non-interventional clinical research with the 2020/13-15 protocol number.

### Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AET, EKÖ; data collection: ST, YEK, AŞ; analysis and interpretation of results: GÜ, YD; draft manuscript preparation: NÖY, AKA, DYÇ: All authors reviewed the results and approved the final version of the manuscript.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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