Is SARS-CoV-2 Now More Like the Seasonal Coronaviruses Following Its Evolution?

Gülsüm İclal Bayhan, MD, Işıl Altan, MD,† Halise Mercan, MD,† Aslınur Özkaya Parlakay, MD,* Zehra Nihan Coşkun, MD,‡ Bedia Dinç, PhD,§ Belgin Gülhan, MD,‡ and Saliha Kanık-Yüksek, MD‡*

Background: SARS-CoV-2 has evolved significantly since the beginning of the COVID-19 pandemic. COVID-19 mortality has decreased due to increased population immunity and possibly the reduced intrinsic severity of the new variants. SARS-CoV-2 is now considered an endemic virus, but the extent to which its clinical findings resemble those of seasonal coronaviruses (sCoV) is not fully understood.

Methods: Pediatric patients under 18 years of age who were sent for SARS-CoV-2 polymerase chain reaction real-time reverse transcription polymerase chain reaction between January 1, 2022 and January 14, 2023 and whose results were positive were included in this study. To include only symptomatic COVID-19 patients in the study, asymptomatic patients who were positive in their screening tests were excluded. For the sCoV patients' group, patients who had a respiratory viral polymerase chain reaction assay between January 10, 2022 and January 11, 2023 and were positive for any type of sCoV were included in the study. The 2 groups were compared for clinical and laboratory characteristics.

Results: The study included 213 patients with COVID-19 and 194 patients with sCoV infection. Fever was a more common symptom in patients with COVID-19. sCoV was associated with lower respiratory involvement while increasing age was protective. The likelihood of hospitalization was decreased by increasing age but increased by the presence of comorbid conditions and lower respiratory tract involvement. The type of virus had no effect on the likelihood of hospitalization.

Conclusions: In conclusion, sCoV infections carry a higher risk for lower respiratory involvement than COVID-19, and COVID-19 has a milder course than sCoV infections in children.

Key Words: COVID-19, SARS-CoV-2, seasonal coronaviruses, lower respiratory infection

(*Pediatr Infect Dis J* 2024;XX:00–00)

SARS-CoV-2 has evolved significantly since the beginning of the COVID-19 pandemic. Variants such as Omicron have increased their transmissibility by evading immunity. COVID-19 mortality has decreased due to increased population immunity and possibly the reduced intrinsic severity of the new variants.[1,2] In May 2023, the World Health Organization highlighted the reduction in COVID-19 deaths, the decrease in COVID-19-related hospitalizations and intensive care unit admissions, the high level of immunity to SARS-CoV-2 and the benign course of the currently circulating variants, and stated that SARS-CoV-2 is now an established and ongoing health concern that no longer constitutes a public health emergency of international concern. No new wave of COVID-19 has been observed since early 2023.[3,4]

Human coronaviruses are endemic in humans and cause 10%–30% of respiratory infections. They usually cause upper respiratory tract infections with a mild course.[5] There are 4 subtypes that cause infection in humans: HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1. HCoV-OC43 is the most common coronavirus pathogen in children.[6] Typically, human coronaviruses in the northern hemisphere exhibit a seasonal pattern that peaks in the winter months.[7]

SARS-CoV-2 is now considered an endemic virus, but the extent to which its clinical findings resemble those of seasonal coronaviruses (sCoVs) is not fully understood. There are very few studies comparing the clinical features of SARS-CoV-2 with those of sCoVs in the same cohort.[8–10] In this study, we aimed to compare the clinical pictures of COVID-19 and sCoV infections in childhood.

MATERIALS AND METHODS

This study was conducted at the Children's Hospital of the Ankara City Hospital. Pediatric patients under 18 years of age who were sent for SARS-CoV-2 polymerase chain reaction (PCR) real-time reverse transcription PCR [Bio-Speedy COVID-19 RT-qPCR Detection Kit (Bioeksen, Istanbul, Turkey)] between January 1, 2022 and January 14, 2022 and whose result was positive were included in this single-center, observational study. This date was chosen to include the period when omicron was dominant.[11] To include only symptomatic COVID-19 patients in the study, asymptomatic patients who were positive in their screening tests (SARS-CoV-2 PCR test performed for school contact, for out-of-school contact, before traveling abroad, before social activities, before surgical or interventional procedures) and patients with missing medical information in the hospital database were excluded (Fig. 1).

For the sCoV patients' group, patients who had a respiratory viral PCR assay between January 10, 2022 and January 11, 2023 and were positive for any type of sCoV were included in the study.

Respiratory viral PCR was only performed in patients with fever or at least 1 respiratory symptom in the hospital where the study took place. The respiratory viral PCR assay [QIAstat-Dx Respiratory SARS-CoV-2 Panel (Qiagen, Hilden, Germany)] included hCoV-229E, hCoV-HKU1, hCoV-NL63, hCoV-OC43 and other respiratory pathogens (*Mycoplasma pneumoniae, Chlamydophila pneumoniae, Bordetella pertussis,* Influenza A, Influenza A subtype H1N1/2009, Influenza B, Parainfluenza Virus, Adenovirus, respiratory syncytial virus A/B, human metapneumovirus A/B, bocavirus, rhinovirus/enterovirus and SARS-CoV-2).

The study included swab (for SARS-CoV-2 or for sCoV) results from the pediatric emergency department, outpatient departments, inpatient departments and pediatric intensive care units (PICU). All PCR tests within the Ankara City Hospital use the same PCR laboratory.

Both SARS-CoV-2 PCR and respiratory viral PCR assay tests were studied in some patients. These patients were included

Accepted for publication February 20, 2024
*From the Department of Pediatric Infectious Disease, Faculty of Medicine, Ankara Yıldırım Beyazıt University; †Department of General Pediatrics; ‡Department of Pediatric Infectious Disease; and §Department of Microbiology, Ankara City Hospital, Ankara, Turkey.
The authors have no funding or conflicts of interest to disclose.
Address for correspondence: Gülsüm İclal Bayhan, MD, Department of Pediatric Infectious Disease, Ankara City Hospital, Üniversiteler Mahallesi, Bilkent Caddesi, Çankaya, Ankara, Turkey. E-mail: gibayhan@aybu.edu.tr.

ISSN: 0891-3668/24/XXXX-0000
DOI: 10.1097/INF.0000000000004327

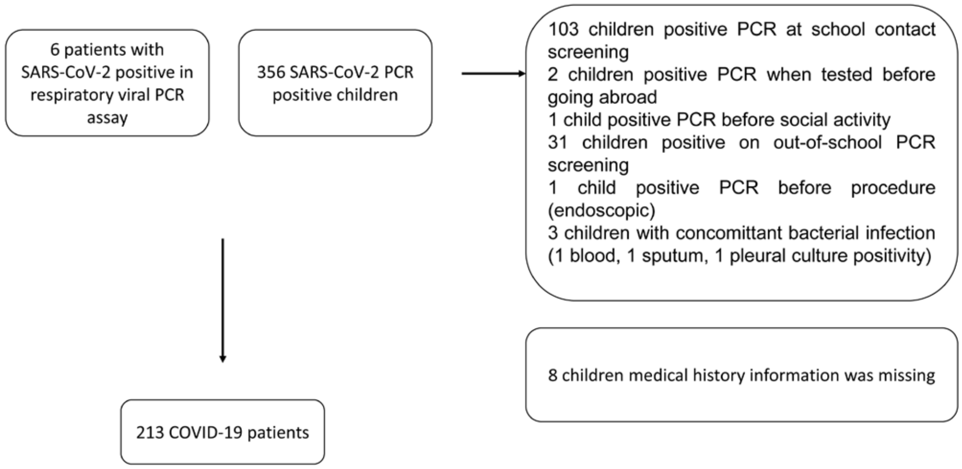

FIGURE 1. The flowchart of included and excluded COVID-19 patients.

in the COVID-19 group if the SARS-CoV-2 PCR test result was negative, but the respiratory viral PCR assay result was positive for SARS-CoV-2. Patients with concomitant bacterial infection in either group were excluded from the study to exclude patients with mixed bacterial and viral pneumonia. Concomitant bacterial infection was defined as the presence of bacteria in the blood, sputum, bronchoalveolar lavage, or pleural culture.

Demographic characteristics, underlying comorbidities, presenting symptoms, clinical diagnoses, laboratory evaluation results at admission, whether they were followed up as outpatients or inpatients, whether they had febrile seizures during their current infection, whether they required admission to the PICU, mechanical ventilation requirements, the outcomes and whether COVID-19 patients had multisystem inflammatory syndrome in children at follow-up were evaluated from the hospital database. Comorbid conditions were defined as cerebral palsy and other complex neurological disorders, metabolic disorders, chronic renal failure, diabetes mellitus, complex cardiac anomalies, immune deficiency, malignancy and asthma.

The clinical diagnosis was grouped into upper respiratory tract infection, bronchiolitis, pneumonia and acute gastroenteritis. The final diagnosis was assessed by the medical history and the physical examination findings in the medical records. Upper respiratory tract infection was defined as the presence of at least one of the following symptoms: cough, runny nose, hoarseness, sore throat, nasal congestion and normal respiratory examination. Acute gastroenteritis was defined as the presence of ≥3 loose/watery stools per day for less than 2 weeks. Bronchiolitis was defined as the first episode of wheezing in infants younger than 24 months. Pneumonia was diagnosed by the presence of cough with abnormal lung examination findings (at least one of the following findings was positive: tachypnea, retractions, rales, or rhonchi). Lower respiratory tract involvement was defined as the presence of bronchiolitis or pneumonia.

Some patients become positive for coronavirus during hospitalization for other reasons. Given the incubation period of the virus, positivity 4 days or more after admission has been defined as hospital-acquired coronavirus infection.[5]

Statistical Analysis

SPSS 22.0 was used for the statistical analysis of the data. Descriptive statistics were presented as numbers and percentages for qualitative data and medians and interquartile ratios for quantitative data. The Shapiro–Wilk test was used to analyze the conformity of the variables to the normal distribution. When comparing the characteristics of the COVID-19 patients and sCoV patients, Pearson's χ^2 test and Fisher exact test were used to compare the groups for categorical variables, and the Mann–Whitney *U* test was used to compare quantitative data. Laboratory findings were compared in the whole cohort, and then separately for patients aged ≤5 years and >5 years. Lower respiratory tract involvement and hospitalization due to coronavirus infection and related factors were analyzed by binary logistic regression.

RESULTS

The study included 213 patients with COVID-19 and 194 patients with sCoV infection. Of the 194 sCoV-infected patients, 133 (68.6%) were infected with the HCoV-OC43 subtype, 57 (29.3%) with HCoV-NL63 and 4 (2.1%) with HCoV-HKU1. Patients with sCoV infection were younger and were more likely to have underlying comorbidities. No patient acquired SARS-CoV-2 infection from the hospital, while 8.8% of sCoV infections were hospital-acquired.

Fever was a more common symptom in patients with COVID-19. While hospitalization due to infection was significantly more common in patients infected with sCoV, there was no difference in the duration of hospitalization between the groups. Lower respiratory tract involvement was significantly more common in the sCoV group (Table 1). Factors influencing lower airway involvement and hospitalization were evaluated with the binary logistic regression model. sCoV was associated with lower respiratory involvement while increasing age was protective. The presence of comorbid conditions and hospital-acquired infection were not associated with lower airway involvement (Table 2).

Age, sex, the presence of comorbidities and lower respiratory tract involvement were found to be associated with hospitalization. The likelihood of hospitalization was decreased by increasing age and female sex, but increased by the presence of comorbid conditions and lower respiratory tract involvement. The type of virus had no effect on the likelihood of hospitalization (Table 3).

The rates of PICU admission, high-flow nasal oxygen therapy requirement and mechanical ventilation requirement are shown in Table 1. A total of 5 patients were admitted to the PICU as follows: A 10-month-old patient, born at 28 weeks' gestation, with a history of necrotizing enterocolitis in the neonatal period and bronchopulmonary dysplasia, was admitted to the PICU for COVID-19 pneumonia and maintained on noninvasive ventilation. A 1-year-old patient with hemophagocytic lymphohistiocytosis was infected with

TABLE 1. Demographic Characteristics, Symptoms, Diagnoses, Hospitalization and Pediatric Intensive Care Unit and Mechanical Ventilation Needs of Patients With COVID-19 or Seasonal Coronaviruses Infection

	SARS-CoV-2 N = 213 (%)	sCoV N = 194 (%)	*P*
Age (years) (median + IQR)	12 (6.5–16)	3 (1–6)	0.000
Sex (female)	110 (51.6)	68 (35.1)	<0.001
Comorbidity	11 (5.2)	52 (26.8)	<0.001
Acquiring the virus during hospitalization	0 (0)	17 (8.8)	<0.001
Fever	122 (57.3)	80 (41.2)	0.024
Cough	116 (54.5)	102 (52.6)	0.441
Runny nose	35 (16.4)	38 (19.6)	0.183
Diarrhea	4 (1.9)	7 (3.6)	0.234
Diagnosis			
URI	204 (95.8)	154 (79.4)	
Gastroenteritis	3 (1.4)	2 (1)	
Lower respiratory tract involvement (pneumonia or bronchiolitis)	6 (2.8)	38 (19.6)	<0.001
Hospitalization due to coronavirus infection	11 (5.2)	40 (20.6)	<0.001*
Duration of hospitalization (days) (median + IQR)	3.5 (3–6.25)	5 (3–7)	0.242
PICU admission	1 (0.5)	4 (2.1)	
HFNO	0 (0)	7 (3.6)	
Mechanical ventilation	1 (0.5)	6 (3.1)	
Noninvasive ventilation	1 (0.5)	0 (0)	
Invasive ventilation	0	4 (2.1)	

*Analysis performed on 51 hospitalized patients.

HFNO indicates high-flow nasal oxygen; PICU, pediatric intensive care unit; URI, upper respiratory tract infection.

sCoV during inpatient care and was admitted to the PICU for pneumonia and intubated. A 30-day-old term infant was admitted to the PICU with sCoV pneumonia and intubated. A 3-month-old patient with transposition of the great arteries and ventricular septal defect was admitted to the PICU and intubated for sCoV pneumonia. A 4-month-old patient born at 25 weeks' gestation with a history of respiratory distress syndrome was admitted to the PICU and intubated for sCoV pneumonia. None of the patients in either group developed acute respiratory distress syndrome and none died due to coronavirus infection. One patient in the COVID-19 group and 3 patients in the sCoV group had febrile seizures. Multisystem inflammatory syndrome in children did not occur in any patient in the COVID-19 group.

A comparison of the laboratory findings between the groups is shown in Table 4. When laboratory findings were compared in the whole cohort, white blood cell count and absolute lymphocyte count were lower in the sCoV group. When ages ≤5 years and >5 years were analyzed separately, there was no difference between the groups.

DISCUSSION

This study comparing COVID-19 and sCoV infections in children shows that the clinical picture of COVID-19 and sCoV is very similar and cannot be easily distinguished. Lower respiratory tract involvement is more common in sCoV infection. There was no difference between SARS-CoV-2 and sCoV in terms of laboratory findings.

Another study comparing the clinical features of COVID-19 and sCoV infections in children has found cough and rhinorrhea to be more common in sCoV patients, whereas fever was more common in COVID-19 patients.[9] Among hospitalized adult patients

TABLE 2. Comparison of Patients With and Without Lower Respiratory Tract Involvement

	Lower Respiratory Involvement			
	No (N:345)	Yes (N:62)	OR (95% CI)	*P*
Age	8.9 ± 5.7	3.2 ± 3.4	0.8 (0.7–0.9)	*P* < 0.001
Acquiring the virus during hospitalization				
No	335 (97%)	55 (89%)	1.5 (0.4–5.2)	0.503
Yes	10 (3%)	7 (11%)		
Comorbidity				
No	300 (87%)	44 (71%)	1.3 (0.6–2.9)	0.509
Yes	45 (13%)	18 (29%)		
Virus type				
sCoV	143 (41%)	51 (82%)		0.049
SARS-CoV-2	202 (59%)	11 (18%)	0.5 (0.2–0.996)	

TABLE 3. Comparison of Patients With and Without Required Hospitalization

	Hospitalization			
	No (n:355)	Yes (n:51)	OR (95% CI)	*P*
Age	8.6 ± 5.7	3.7 ± 4.2	0.9 (0.8–0.99)	0.027
Gender				
Male	187 (53%)	41 (80%)	0.3 (0.2–0.8)	0.008
Female	168 (47%)	10 (20%)		
Comorbidity				
No	311 (88%)	32 (63%)	2.8 (1.3–6.1)	0.007
Yes	44 (12%)	19 (37%)		
Lower respiratory involvement				
No	321 (90%)	23 (45%)	6.4 (3.1–13.3)	<0.001
Yes	34 (10%)	28 (55%)		
Virus type				
sCoV	154 (43%)	40 (78%)	0.8 (0.4–2)	0.671
SARS-CoV-2	201 (57%)	11 (22%)		

TABLE 4. Laboratory Findings in All Patient Groups and in Groups Separated According to Age Groups (≤5 Years of Age or >5 Years of Age)

(Median + IQR)	SARS-CoV-2 N = 27	sCoV N = 124	*P*	≤5 Years of Age			>5 Years of Age		
				SARS-CoV-2 N = 18	sCoV N = 91	*P*	SARS-CoV-2 N = 9	sCoV N = 33	*P*
Hgb	11.9 (10.4–13.5)	11.4 (10.3–12.6)	0.173	11.7 (11.2–12.9)	11.3 (10.1–12.3)	0.266	12.5 (5.3–14.3)	12.4 (11.3–13.2)	0.578
WBC	7.620 (5.430–9.440)	9.305 (6.702–12.795)	0.027	8.780 (6.570–11.030)	9.870 (7.230–12.880)	0.326	5.500 (4.255–6.135)	8.125 (2.880–11.825)	0.118
ANC	4.170 (2.630–5.570)	4.135 (2.330–6.935)	0.646	4.360 (2.555–6.070)	4.030 (2.290–6.820)	0.963	3.690 (2.660–4.390)	3.985 (1.902–8.245)	0.470
ALC	1.880 (1.090–3.630)	3.060 (1.912–4.425)	0.035	3.210 (1.785–4.380)	3.460 (2.400–4.940)	0.286	1.080 (810–1.310)	1515 (512–2510)	0.720
AMC	680 (340–1090)	640 (372–900)	0.774	940 (620–1.175)	740 (440–980)	0.166	340 (315–400)	535 (210–787)	0.452
PLT	301.000 (235.000–362.000)	332.000 (254.500–418.500)	0.427	345.000 (284.000–441.000)	358.000 (284.000–474.000)	0.673	232.000 (214.500–322.000)	228.500 (137.000–318.750)	0.944
AST	40 (31–48)	38 (30–53)	0.728	42 (36–54)	40 (31–54)	0.405	35 (22–41)	33 (28–44)	0.813
ALT	22 (18–29)	22 (16–34)	0.745	23 (19–28)	21 (16–28)	0.509	20 (17–41)	27 (19–67)	0.686
CRP	10 (6–20)	7 (1–21)	0.509	14 (9–20)	6 (1–18)	0.197	5.5 (0.25–10)	7 (2.7–40)	0.531

ALC indicates absolute lymphocyte count; ALT, alanine transferase; AMC, absolute monocyte count; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CRP, C-reactive protein; Hgb, hemoglobin; PLT, platelet count; WBC, white blood cell count.

with COVID-19 or sCoV infection, cough, and chills were more common in the sCoV-infected patients while fever, anosmia and diarrhea were more common in the COVID-19 patients.[8] In the present study, fever was more common in those with COVID-19 but there was no difference regarding the other symptoms. With the available data, it can be said that fever is more common in COVID-19 than in sCoV infection. However, the presenting symptoms are similar in COVID-19 and sCoV infections, and it is not easy to distinguish the 2 conditions based on the symptoms. The various variants of COVID-19 including the wild type, delta, gamma and lambda variants have the same symptoms such as fever, rhinorrhea, cough, headache and sore throat.[9] Therefore, although SARS-CoV-2 continues to evolve, it is predicted that COVID-19 will continue to cause symptoms that are very similar to sCoV infections unless a new highly mutated variant emerges.

Pediatric patients with SARS-CoV-2 and sCoV predominantly present with the common cold. The incidence of acute lower respiratory tract infections was found to be 3% in patients with COVID-19 and 16% in those with sCoV infection, while the hospitalization rates were similar between the groups. These findings indicate that COVID-19 is like sCoV infection and even less severe.[9] In the present study, lower respiratory tract involvement was more common in the sCoV group. However, the age of the patients in this group was younger, and the frequency of comorbidity in addition to the frequency of healthcare-associated infections was higher. Therefore, the factors affecting lower airway involvement were analyzed separately. When the effect of age was held constant, sCoV continued to increase the likelihood of lower respiratory tract involvement. Although COVID-19 has been reported to be more severe than sCoV infection in adults, the opposite appears to be true in children.[8] The results of the current study not only confirm that COVID-19 is mild in children, but also that it is milder than sCoV infection.

Younger age, male sex, underlying comorbidity and lower respiratory tract involvement were the factors associated with hospitalization, but the hospitalization rates were similar in both groups. In addition to the mild course of COVID-19 in children, the fact that this study coincided with the last wave of the pandemic, a time when COVID-19 was well known, is also associated with the low hospitalization rate.

In a cohort that included the period before the emergence of the omicron variant, SARS-CoV-2 occurred more frequently than sCoV in older children.[9] Similarly, the mean age of patients with COVID-19 was higher in the present study. It is now known that COVID-19 can affect all age groups. At the time of this study, the pandemic was still ongoing and the omicron wave was rising sharply. The number of cases among school children had also increased sharply, resembling the country's pandemic curve.[12] The higher prevalence of COVID-19 among school children, who are more likely to be exposed, is an expected finding and explains the age difference between the study groups. Comparing COVID-19 cases with sCoV infections in the postpandemic period will provide more helpful information about the age groups involved.

It has been reported that the most common abnormal hemogram findings in COVID-19 patients are decreased lymphocytes with mild thrombocytopenia. Among biochemical parameters, elevated levels of lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase are the most common abnormal laboratory findings.[13] In this study, the laboratory findings were similar in both groups and within the normal range. However, the number of patients and the single-center nature of the study preclude generalization of the study results.

The retrospective nature of the study is an important limitation as it introduces the possibility of selection bias. At the time of the study, a time when pandemic restrictions had been significantly relaxed, the threshold for requesting a COVID-19 PCR test was still very low due to the ongoing pandemic. On the other hand, the respiratory PCR test may have been requested more frequently by physicians from those patients with a more severe clinical presentation, although this test is covered by health insurance. The fact that most of the sCoV-positive patients had an upper respiratory tract infection suggests that selection bias, if any, was small.

In conclusion, sCoV infections carry a higher risk for lower respiratory involvement than COVID-19, and COVID-19 has a milder course than sCoV infections in children. Otherwise, the clinical and laboratory findings of COVID-19 and sCoV infections are similar.

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