

# An evaluation of patients with a previous endemic coronavirus infection during the COVID-19 pandemic

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## Abstract

Few studies exist on the clinical manifestation of coronavirus disease 2019 (COVID-19) in patients who previously had a common cold due to an endemic coronavirus (eCoV). In a retrospective scan of the data obtained in our microbiology laboratory, 64 patients who were diagnosed with an eCoV infection between 2016 and 2020 were identified. National COVID-19 surveillance data showed that four (6.2%) of 64 patients were infected with severe acute respiratory syndrome coronavirus 2 by the end of 2020, while, simultaneously, the COVID-19 prevalence in the city of Malatya ranged from 7.8% (polymerase chain reaction-based diagnosis) to 9.2% (total diagnosis). The differences were found statistically significant (6.2% vs. 7.8%,  $p < .01$ ; 6.2% vs. 9.2%,  $p < .001$ ). Patient interviews and evaluation of medical records revealed that these four patients did not manifest any severe COVID-19 symptoms despite their substantial comorbidities, and they did not require hospitalization. Consequently, despite a low number of samples, we determined a lower frequency of COVID-19 among the patients who had a prior eCoV infection, and the results of this study support the previous findings that people with a prior eCoV infection develop a milder case of COVID-19. Our results may provide some insights for future studies aiming at vaccine development, but detailed investigations are still required.

## KEYWORDS

coronavirus, pandemics, respiratory tract, SARS coronavirus

## 1 | INTRODUCTION

Coronaviruses were known to cause mild and self-limiting respiratory tract infections until the 2000s; however, from 2002 to 2020, they posed the third deadliest global health threat. Additionally, the most recent coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has the potential to be one of the most devastating pandemics in the history of humans. Thus, intense efforts have been made to produce a vaccine that can protect against the virus. Predictions have indicated that SARS-CoV-2 will be effective in the years to come and additional similar virulent strains may emerge in the future.<sup>1</sup> Therefore, an improved understanding of the interaction

between the human immune system and species of coronavirus is of utmost importance.

In a recent study from Boston Medical School, Sagar et al. reported that patients with a previous common cold infection due to an endemic coronavirus (eCoV) manifested less severe coronavirus disease 2019 (COVID-19). The authors concluded that pre-existing immune responses against endemic coronaviruses (eCoVs) were likely to play a role in the outcomes because eCoVs and SARS-CoV-2 share an extensive genome homology.<sup>2</sup> The results of the study (which, to our knowledge, is the sole publication on this topic to date) may provide substantial insight and potential advancements in the battle against SARS-CoV-2. However, these promising findings

required to be confirmed via further investigation. Therefore, the present study was conducted in our region to determine the outcome of patients who were documented during the COVID-19 pandemic to previously have had an eCoV infection.

## 2 | MATERIALS AND METHODS

This study was conducted in the molecular microbiology laboratory at the Turgut Ozal Medical Center, which provides a tertiary level healthcare service in Malatya, a medium-sized city in Turkey with approximately 625,000 inhabitants. The study was approved by the Health Ministry of Turkey (2021-01-11T13\_41\_22). From January 01, 2016 to February 28, 2020, 79 patients were determined to have an infection due to an eCoV species via a retrospective screening of the electronic records of the laboratory (which was the sole test facility in the city for the diagnosis of such pathogens). As 15 of the patients died before the emergence of COVID-19 in Turkey (March 2020), 64 of the 79 patients were included in this study. Endemic coronaviruses were detected in respiratory samples using the following polymerase chain reaction (PCR) kits: the BIOFIRE Respiratory 2.1 plus panel (from 2016 to 2018) (Bio Mérieux) and the QIAstat-Dx Respiratory Panel V2 (from 2019 to present) (Qiagen). Demographic and clinical data of the patients who were documented to have an eCoV infection were collected from the electronic records of the Turgut Ozal Medical Center information system.

Each of the 64 patients was queried in the electronic database to assess whether any of them had a diagnosis of COVID-19 between March 01, 2020 and January 01, 2021 (the end date of this study). First, the SARS-CoV-2 real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR) test results were screened in the Laboratory Information System of the Health Ministry. This was a national database that was updated daily according to the RT-PCR test results. The SARS-CoV-2 Rt-qPCR tests were performed with a Bio-Speedy SARS-CoV-2 RT-qPCR kit (Bioeksen R&D Technologies), which was the most widely used kit in Turkey throughout the pandemic and targeted the nucleocapsid (N) and ORF1ab regions of the SARS-CoV-2 genome. This kit was also listed by the World Health Organization among the molecular assays for COVID-19 diagnosis<sup>3</sup> and had a reported sensitivity of 97.3% and a specificity of 100%.<sup>4</sup> Secondly, each of the patients was queried further in the Public Health Data Management System to assess whether any of them had a diagnosis of COVID-19 even though his or her PCR test result was negative or was not performed. Additionally, clinical findings and progress of the patients diagnosed as COVID-19 were collected from this system. The COVID-19 prevalence in the city was calculated using the data obtained from the two above-mentioned electronic databases, according to PCR-based and clinical diagnoses. COVID-19 frequencies of eCoV patients and of the city population were statistically compared with the One-Sample Proportion Test. A *p* value lower than .05 was accepted as statistically significant.

An interview was conducted with each of the patients to identify the following issues: the duration of their COVID-19 symptoms (for

COVID-19-positive patients); whether they had a COVID-19 diagnosis that was not officially recorded; whether they experienced COVID-19 symptoms but did not see a doctor; their history of contact (close contact or low exposure contact) with any person having an active COVID-19 infection; and their adherence to the measures for protecting against the spread of the pandemic spread, such as using a mask and social distancing. Finally, 51 of 64 patients were queried either directly (*n* = 9) or via a telephone call (*n* = 42).

## 3 | RESULTS

The median age of the patients who had a previous eCoV infection was 32 years (*n* = 64, min-max: 0-69, IQR: 36). Thirty-eight of the patients (59.3%) were male and NL63 (35.9%) was the most frequent eCoV type determined. Almost one-third of these patients had a chronic disease such as diabetes mellitus (DM), cancer, renal failure, or a nervous system disorder.

A screening of the national surveillance system indicated that RT-PCR assays for SARS-CoV-2 were conducted for 21 of the 64 eCoV patients (32.8%) and by the end of this study (January 01, 2021), a total of four patients (6.25%) were determined to be positive. The ages of the positive patients ranged from 31 to 52 years and all of them had a chronic medical condition. The data obtained from the electronic COVID-19 surveillance system also showed that 33.9% of the city's inhabitants (non-repetitive) were tested for SARS-CoV-2 via RT-PCR. The overall PCR positivity of the city was 7.8%, and 9.2% of the inhabitants were diagnosed with COVID-19 (sum of the PCR-confirmed and clinically diagnosed cases) by the end of the present study.

Statistical analysis showed a significantly lower frequency of COVID-19 among the patients with prior eCoV than the city population (6.2% vs. 7.8%, *p* < .01; 6.2% vs. 9.2%, *p* < .001). Patient interviews and medical records did not indicate that any additional patients should be evaluated as a possible COVID-19 case. Furthermore, it was determined that 50.9% of the total 51 eCoV-positive patients queried had at least one contact with a family member or close friend who was diagnosed with COVID-19. Moreover, 84.3% of them adhered to the pandemic protection measures (such as using a mask and maintaining social distancing) as much as other people did and mostly continued their social and occupational lives.

The characteristics of the 64 patients who were analyzed are summarized in Table 1 and the demographic and clinical data for the four patients who tested positive for both eCoV and SARS-CoV-2 are presented in Table 2.

## 4 | DISCUSSION

In this study, we determined that the patients who had a previous eCoV infection had a significantly lower frequency of COVID-19 compared with the inhabitants of a city that had >9% prevalence of

**TABLE 1** Characteristics of 64 patients with prior eCoV infection

Patient characteristics	eCoV (+) (n = 64)
Age (year)	
Median, min-max, IQR	32, 0-69, 36
Female/male (n/%)	26 (40.6)/38 (59.3)
Types of eCoV (n/%)	
HKU1	16 (25)
NL63	23 (35.9)
OC43	15 (23.4)
229E	10 (15.6)
Year of eCoV test	
2016	12
2017	10
2018	9
2019-2020 <sup>a</sup>	38
Hospitalization due to eCoV	22 (34.3%)
Comorbidities	
DM	10
Cancer	7
Renal failure	6
Nervous system	4
Others <sup>b</sup>	7
Adherence to COVID-19 measures (n = 51)	
Using mask	47 (92.1)
Social distancing	47 (92.1)
Further measures <sup>c</sup>	8 (15.6)
COVID-19 contact <sup>d</sup> (n = 51)	
High-risk exposure	11 (21.5)
Low-risk exposure	15 (29.4)

Abbreviations: COVID-19, coronavirus disease 2019; DM, diabetes mellitus; eCoV, endemic coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup>2020: included January and February months.

<sup>b</sup>Others: lung diseases (n = 2), renal transplantation (n = 2), malnutrition (n = 1), immune deficiency disease (n = 1), and cardiac disease (n = 1).

<sup>c</sup>Further measures: strict curfew (n = 5), moving to rural areas to reduce SARS-CoV-2 exposure (n = 2), and indoor use of mask (n = 1).

<sup>d</sup>COVID-19 contact: contact history (close contact or low-risk exposure) with a person who had an active COVID-19.

COVID-19 simultaneously. Sagar et al. also reported a lower frequency of COVID-19 in eCoV positive patients compared with eCoV negative patients (according to PCR results only); however, the data was statistically insignificant. Previous studies have reported that 15%–31% of patients who have a SARS-CoV-2 infection may go unnoticed in a population.<sup>5,6</sup> However, we did not detect any additional patient who potentially had a COVID-19 infection. As

**TABLE 2** Characteristics of four patients double-positive for eCoV and SARS-CoV-2

No.	Sex/age	Date of eCoV+	eCoV type	Comorbidity	Date of SARS-CoV-2+	COVID-19 symptoms and duration	Contact characteristics	Lung involvement
1	F/31	Jan'17	NL63	Asthma	Nov'20	Mild fever, arthralgia (2 days)	Close contact; husband and kids	NR <sup>a</sup>
2	F/50	Feb'19	OC43	Breast cancer (5 years)	Aug'20	Loss of smell and taste, fatigue (2-3 days)	Close contact; husband	NR <sup>a</sup>
3	M/45	Apr'19	OC43	Renal transplant (2 years), DM	Sep'20	Muscle and joint pain, fatigue, mild cough (4 days)	Close contact; mother and brother	NR <sup>a</sup>
4	F/52	Dec'19	HKU1	Breast cancer (2 years)	Nov'20	Headache, arthralgia (3 days), cough (2 weeks)	Close contact; husband and kids	Minimal infiltrations

Abbreviations: COVID-19, coronavirus disease 2019; DM, diabetes mellitus; eCoV, endemic coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.  
<sup>a</sup>NR, not required.

SARS-CoV-2 can also present silent clinical manifestation in certain individuals,<sup>5,6</sup> an antibody test might have been indicative to exactly identify the persons caught by that virus. Although we recommended an antibody test to all the eCoV-positive patients we interviewed, only 11 of them did, which did not result in additional data that were useful for this study (data not shown). Consequently, it is possible that a higher number of eCoV-positive patients developed COVID-19. Nevertheless, the proportion of eCoV-positive persons in this study who manifested clinically diagnosed COVID-19 was much lower (approximately 32%) than that of the inhabitants of the same community.

In addition to a lower frequency, we also discovered that the eCoV-positive patients who also had a SARS-CoV-2 infection showed milder symptoms of COVID-19 despite having significant comorbidities for severe disease.<sup>7</sup> It was determined that their symptoms lasted for only a few days except for one patient (who had a cough for 2 weeks), and none of them required hospitalization (Table 2). These results were also consistent with the findings of Sagar et al.,<sup>2</sup> which demonstrated approximately sixfold less intensive care unit hospitalizations in eCoV-positive patients than in eCoV-negative patients. Although there is still no detailed study on the subject, we also hypothesized that the genomic homologies and structural similarities shared by the coronaviruses may have affected the positive outcomes of the patients. Furthermore, prior stimulation of almost the same response and memory mechanisms of the human's innate and acquired immune systems by the eCoVs could provide a somewhat ready state-to-answer in these pathways against SARS-CoV-2 invasion. However, a large number of unknowns have yet to be elucidated.

In an earlier study that included 79 cases of respiratory tract infection due to seasonal coronaviruses among otherwise healthy children, seven (8.8%) of the patients required hospitalization and the infection caused a median of 4 days of school absence.<sup>8</sup> In the present study, we determined that 22 of the patients (34.3%) were hospitalized due to a current eCoV infection (Table 1). The hospitalization rate of the patients with a comorbidity was higher than those without a comorbidity (42.4% vs. 25.8%, respectively [data not shown]). Therefore, the emergence of the clinically recognizable COVID-19 in a small proportion of such a vulnerable group was another interesting finding of this study.

The lower frequency of COVID-19 observed among the patients in this study prompted a query of their attitudes on the use of preventive measures. A large proportion of eCoV-positive patients reported that they were attentive to social distancing and using a mask, and eight patients reported further and strict measures (Table 1). Although there are some studies that reported the adaptation level of the people to such measures from different countries, we could not compare the adherence rate of our patients because there was no data on this issue from our country yet. Compliance with such measures is closely related to the socioeconomic and cultural levels of societies, and to how successfully communities can be convinced. Therefore, it was unclear whether less of the patients in our study contracted SARS-CoV-2 because of high adherence to these

measures. Nevertheless, most of the patients stated that they viewed themselves as normal in society on this issue. Additionally, we queried the patients according to their background of exposure to SARS-CoV-2. We discovered that approximately 40% of them reported either low- or high-risk contact; however, the remaining patients did not have any information on this. Therefore, we could not determine exactly whether fewer of our patients contracted SARS-CoV-2 because of a low frequency of exposure to the virus. Nevertheless, we determined that 4 of 11 patients (36.3%) with high-risk contact developed COVID-19 (Table 2), which is close to data reported in a separate study in which approximately 42% of patients with high-risk contact developed COVID-19.<sup>9</sup>

We determined that NL63 was the most frequently observed type of eCoV in the patients. However, two members of the *Betacoronavirus* genus, OC43 and HKU1, were detected in approximately half of the eCoV-positive patients (Table 1), and in three of four double-positive patients (Table 2). Additionally, an increase in the incidence of eCoV infections was observed in the last term (2019 and the first 2 months of 2020) compared with the previous years. However, this was most likely due to increasing awareness among clinicians concerning viral respiratory pathogens because of the emergence of SARS-CoV-2 in late December of 2019.

Broad range screening multiplex PCR panels are not frequently used diagnostic tools in our country and have been limited to certain laboratories due to cost, staff, and organizational issues. Therefore, our sample size was limited to 64 patients, which can be regarded as a low size for an improved evaluation. Additionally, a large number of personal factors can be associated with severe or mild disease (and even asymptomatic disease), and it may be expected of us to compare the patient groups all together with such variables to clarify whether a previous eCoV infection was an independent predictor for a better COVID-19 clinical course. However, in this study, the patient groups could not be balanced for correct analysis as one group included tens of thousands of positive patients (PCR-confirmed) and the other group included four positives from a total of 64 patients. Despite such limitations, our results support the promising knowledge that is currently available. Moreover, our results provide insights for further investigations such as studies aimed at developing a potential vaccine against COVID-19 via the utilization of eCoV strains. However, advanced data evaluations are required through the utilization of information collected via multicenter, national, or international surveys.

The world's population is getting more sensitive to pandemic spread due to globalization and crowding, and immunization is the most effective way of protection for such health threats. As was experienced in the current pandemic, millions of mortalities can occur before an effective vaccine is produced to target a specific pathogen. There is, therefore, a requirement for an improved understanding of the human immune system's response and memory dynamics, not only for certain pathogens but also for their low virulence family members.

#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Baris Otlu, Yusuf Yakupogullari, and Yasar Bayindir.  
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## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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