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Original article

CHARACTERISTICS OF ENDEMIC HUMAN CORONAVIRUS INFECTIONS DURING TIMES OF COVID-19 PANDEMIC

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Abstract

Introduction: After the implementation of mitigation strategies during the COVID-19 pandemic, the incidence of respiratory viruses, including human coronaviruses (HCoV), experienced a significant decrease. The aim of this study is to characterize the epidemiology and clinical aspects of HCoV infections in ambulatory adults during COVID-19 pandemic times.

Methods: descriptive, prospective, longitudinal study performed in a private hospital in La Plata, Buenos Aires, Argentina between November 2020 and October 2022; 458 outpatient adults with upper respiratory tract infections (URTI) were studied undergoing clinical and microbiological follow-up.

Results: 44 (9.6%) subjects were positive by multiplex PCR for HCoV. 14 of them for 229E (31.8%), 13 for OC43 (29.5%), 11 for HKU-1 (25.1%) and 6 for NL63 (13.6%). A repeated PCR was positive for the same HCoV in 19 (57%) of 33 patients on day 3-5. No hospitalizations or deaths were reported.

Discussion: Endemic HCoV caused a significant proportion of URTI among outpatient adults during COVID-19-related restrictions times. An alternating pattern of circulation between alfa-HCoV and beta-HCoV was observed.

Key words: human coronaviruses, respiratory tract infections, COVID-19 pandemic *Alphacoronavirus, Betacoronavirus*

Resumen

Características de las infecciones causadas por Coronavirus humanos endémicos durante la pandemia COVID-19

Introducción: Tras la implementación de estrategias de mitigación durante la pandemia de COVID-19, la incidencia de virus respiratorios, incluyendo los coronavirus humanos (HCoV), disminuyó significativamente. El objetivo de este estudio es caracterizar la epidemiología y los aspectos clínicos de las infecciones por HCoV en adultos ambulatorios durante la pandemia de COVID-19.

Métodos: estudio descriptivo, prospectivo, longitudinal, realizado en un hospital privado de La Plata, Buenos Aires, Argentina, entre noviembre de 2020 y octubre de 2022. Se estudiaron 458 pacientes adultos ambulatorios con infecciones del tracto respiratorio superior (ITRS) bajo seguimiento clínico y microbiológico.

Resultados: 44 (9.6%) sujetos fueron positivos por PCR multiplex para HCoV. Se detectaron 14 229E (31.8%), 13 OC43 (29.5%), 11 HKU-1 (25.1%) y 6 NL63 (13.6%). Una segunda PCR fue positiva para el mismo HCoV en 19 (57 %) de 33 pacientes en los días 3-5. No se reportaron hospitalizaciones ni muertes.

Discusión: los HCoV endémicos causaron una proporción significativa de ITRS entre pacientes adultos ambulatorios durante los tiempos de restricciones rela-

cionados con COVID-19. Se observó un patrón alternante de circulación entre alfa-HCoV y beta-HCoV.

Palabras clave: coronavirus humanos, infecciones de vía aérea superior, pandemia COVID-19, *Alphacoronavirus, Betacoronavirus*

KEY POINTS
Current knowledge

- Human coronaviruses frequently cause asymptomatic to mild or moderate upper respiratory tract infections although at a lower rate, severe cases can occur mainly in children, elderly, and immunocompromised adults, usually during cold seasons. Currently, there is scarce information on the epidemiology of HCoVs in adults in Argentina.

Contribution of this article to current knowledge

- Human coronaviruses cause about 10% of upper respiratory tract infections cases in ambulatory adult patients attending to a clinic in Buenos Aires, Argentina, even beyond the winter months, showing also an alternating circulation pattern between *alphacoronavirus* and *betacoronavirus*.

Seven species of coronaviruses can cause human infections: endemic human coronavirus (HCoV)-NL63, HCoV-229E, HCoV-HKU1, HCoV-OC43, SARS-CoV-1, MERS-CoV and SARS-CoV-2; the first two are *alpha coronavirus* and the remaining 5 are *betacoronavirus*1. The four HCoV (229E, NL63, OC43 and HKU1) have been associated with upper respiratory tract infections (URTI) during non-pandemic times. The incubation period is, on average, 2 days, and the peak of symptoms and virus shedding is 3 or 4 days after inoculation[2]. These HCoV cause from asymptomatic to mild, moderate and, at a lower rate, severe illness occurring mainly in children, elderly, and immunocompromised adults. Reinfections are common since infections usually do not provide solid immunity[2, 3]. During the COVID-19 pandemic the incidence of respiratory viruses, including HCoV, experienced a significant decrease due to mitigation strategies implemented to contain SARS-CoV-2[4,5]. In this sense, the decreased prevalence of HCoV infections, which predominates in pediatric populations, might be related to the periods of school attendance restriction. In addition, since most of the epidemiological studies on HCoV are performed in pediatric and hospitalized patients and, as these viruses are usually not included in the routine diagnostic testing, knowledge about HCoV epidemiology in adults is scarce, in Argentina and worldwide. Therefore, we decided to perform this study aiming to characterize the epidemiology and clinical aspects of HCoV in ambulatory adults during COVID-19 pandemic times.

Materials and methods

This is a descriptive, prospective, longitudinal study performed in a private hospital in La Plata, Buenos Aires, Argentina between November 2020 and October 2022. All consecutive patients attending to the clinic that were non-hospitalized adults suffering from an URTI episode with a confirmed viral diagnosis of OC43, NL63, HKU1 or 229E through nasal swabs were included in the study. The viral diagnosis was made using the Biomerieux BioFire FilmArray® Respiratory EZ Panel 2.1 that performs a real time nested multiplex polymerase chain reaction (PCR) designed to detect 15 virus including the four endemic HCoV, SARS-CoV-2, Adenovirus, Human Metapneumovirus, Rhinovirus/Enterovirus, Influenza A y B, Parainfluenza Virus 1-4, Respiratory Syncytial Virus (RSV), and 4 bacterial respiratory pathogens (*Bordetella parapertussis*, *Bordetella pertussis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*). A subgroup of patients underwent clinical evaluation between days 3 and 5 and on day 30 after the viral diagnosis; a repeated nasal multiplex PCR was carried out on the day 3-5 visit.

Statistical analysis was performed with IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. Categorical variables were analyzed through frequencies and percentage. Continuous variables were analyzed with Kolmogorov-Smirnov test in order to evaluate normality in which case, mean and standard deviation were used. On the other hand, median and interquartile range (IQR) was

performed for those which did not meet that criterion.

This study was performed with the approval of the Institutional Review Board and followed its ethics procedures. Informed consent was obtained from all study participants.

Results

During the study period 458 ambulatory patients of at least 18 years-old were evaluated successively for an acute episode of URTI. From this cohort of patients, 153 (33.4%) were positive for SARS-CoV-2, 56 (12.2%) for Rhinovirus/Enterovirus, 44 (9.6%) for HCoV, 15 (3.2%) for RSV, and 10 (2.1%) for Influenza A. The 44 patients (9.6%) positive for endemic HCoV included the following types: 14 (31.8%) 229E, 13 (29.5 %) OC43, 11 (25.1%) HKU-1, and 6 (13.6%) NL63. Co-detections with other viruses were found in 5 (11.4%) cases at baseline: three with Rhinovirus/Enterovirus, one each with Adenovirus and Parainfluenza 4. These 44 patients had a mean age of 41.5 years (range: 20 to 72 years) and 25 (56.8%) were women. The most common comorbidities were obesity (BMI above 30 kg/m^2) and hypertension in 7 (15.9%) and 5 (11.4%) subjects, respectively (Table 1).

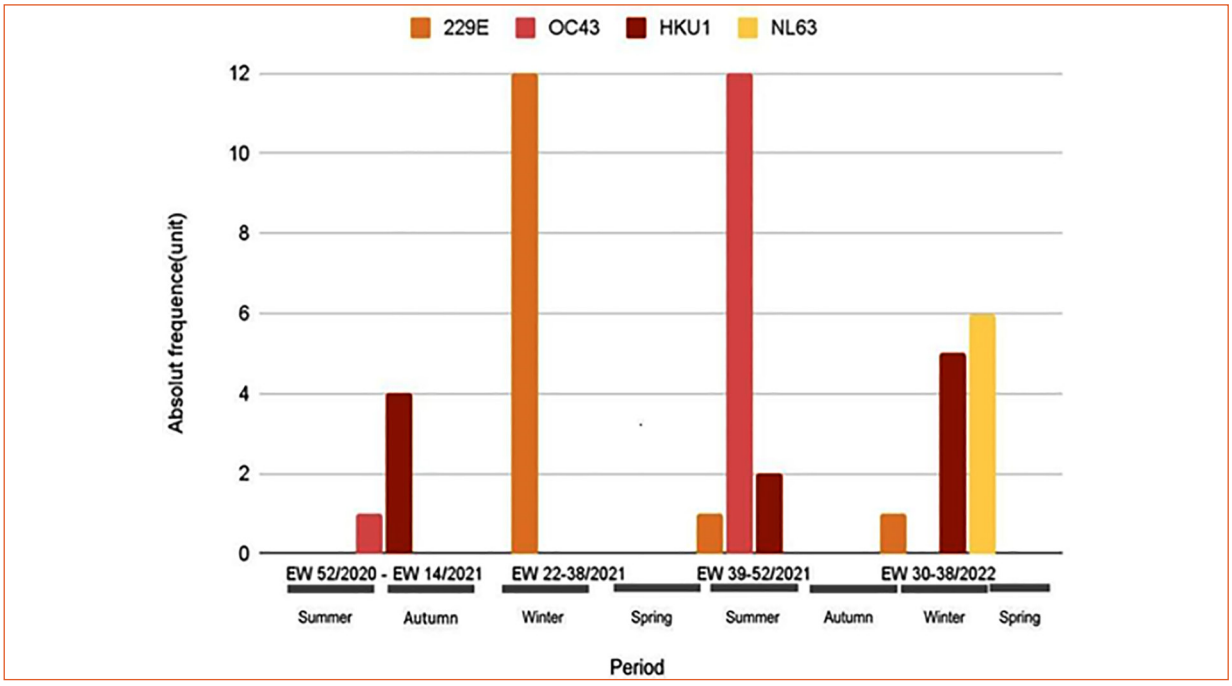
The distribution of the different HCoV according to epidemiological weeks and seasons is shown in Figure 1. During spring-summer and autumn-winter seasons, we documented 16 (36.4%) and 28 (63.6%) HCoV cases, respectively. *Alphacoronavirus* 229E and NL63 were identified mainly in the winter of 2021 and 2022, respectively. HKU-1 infections occurred both, in summer and winter, while OC43 was detected only in spring 2021.

The most common presenting symptoms were nasal congestion (77.3%), rhinorrhea (63.6%), cough (59.1%), headache (50%), sore throat (50%), malaise (45.5%), sneezing (40.9%), joint or muscle pain (34.1%), fever (13.6%), nausea (9.1%), dyspnea (9.1%) and diarrhea (6.8%). Most of the patients (86.3%) had at least 3 of these symptoms. Diarrhea was only seen in patients with OC43 infection. The median duration of symptoms was 4 days (IQR: 3-5 days). No hospitalizations or deaths were observed during the 30-days of follow-up and only one patient required treatment with oral antibiotics.

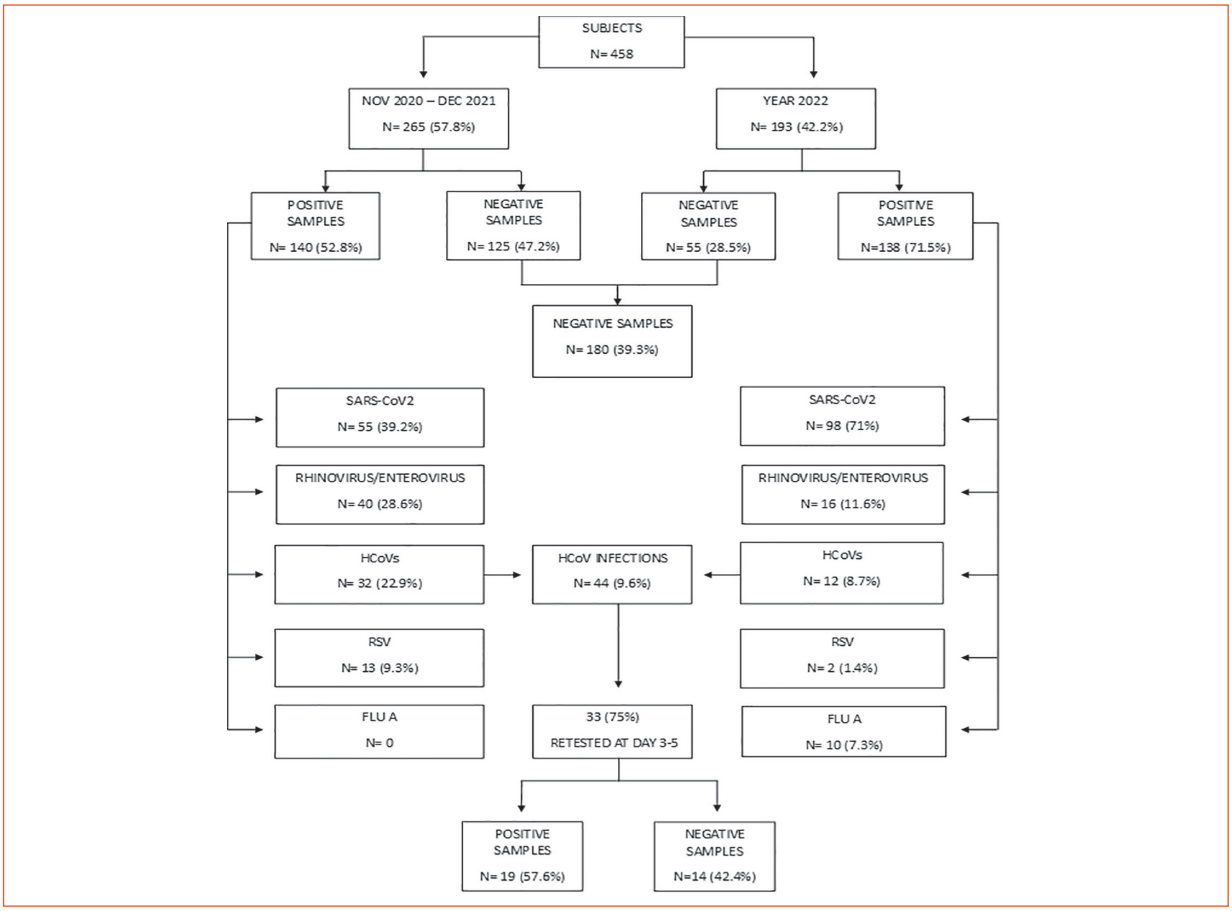
Tabla 1 | Epidemiological and clinical characteristics of 44 patients with human coronaviruses infection

Age (mean +/- DS)	41.5 +/- 15.4
Sex No. (%)	
Female 25 (56.8)	
Comorbidities No. (%)	
Obesity 7 (15.9)	
Hypertension 5 (11.4)	
Cardiovascular disease 3 (6.8)	
Diabetes mellitus 3 (6.8)	
Asthma 4 (9.1)	
Symptoms No. (%)	
Nasal congestion 34 (77.3)	
Rhinorrhea 28 (63.6)	
Headache 22 (50)	
Malaise 20 (45.5)	
Cough 26 (59.1)	
Sore throat 22 (50)	
Sneezing 18 (40.9)	
Muscle or joint pain 15 (34.1)	
Fever 6 (13.6)	
Nausea 4 (9.1)	
Dyspnea 4 (9.1)	
Diarrhea 3 (6.8)	
Days of symptoms: median (IQR) 4 (3-5)	

Figure 1 | Human coronaviruses distribution according to epidemiological weeks. (n=44)



Flowchart 1 | Samples analyzed between November 2020 and October 2022



Between days 3 and 5 of follow-up, 33 (75%) patients underwent clinical assessment and a repeated multiplex PCR assay and 19 (57%) had positive PCR for the same HCoV found initially, with codetection of two other viruses (Adenovirus and Rhinovirus). The rate of persistence was 71%, 58%, and 46% for HKU1, OC43 and 229E, respectively, and among the 6 patients with NL63, only one had a follow-up test which resulted positive.

Forty-one subjects (93%) reported receiving at least one dose of SARS-CoV-2 vaccine although in 19 (43%) of them more than 6 months had elapsed since the last administration. Seven subjects (15.9%) informed a prior diagnosis of COVID-19 disease, 3 of which occurred in the last 6 months.

Discussion

This prospective observational study evaluated ambulatory adults with symptomatic infection caused by HCoV in Argentina during two consecutive seasons at the time of ongoing COVID-19-related transmission mitigation measures. These results are relevant as there is a significant scarcity of epidemiological and clinical data of HCoV infection in ambulatory adults. We found that almost 10% of the patients presenting with URTI were positive for endemic HCoV; this prevalence is higher than that reported in Scotland between 2005 and 2017, where 5.3% of more than 12 000 outpatients with URTI were positive for HCoV[6].

We found that type 229E was the most prevalent HCoV detected, as it has been previously shown by the Center for Disease Control and Prevention in the United States when considering only the adult population[7]. Similarly, a prospective study in Michigan found that 229E was the most prevalent HCoV in adults between 18-49 years of age[8]. Of note, in the same study, 229E and NL63 types were both associated with higher odds of severe and mild illness, respectively, compared with the other 3 HCoV[8]. In the current report, we could not detect any difference in disease severity between the four HCoV infections, having all patients good clinical outcome with no hospitalizations.

We observed a peak of HCoV cases in spring/summer 2021/2022 (36.4%) after lifting mitigation measures applied to contain COVID-19 pandemic. This peak has been reported for almost all non-SARS-CoV-2 respiratory viruses except Rhinovirus / Enterovirus[5]. Interestingly, these HCoV appear to follow a pattern of circulation, where one type of alfa-HCoV predominates in one season and one beta-HCoV in the following; it was speculated that the 1-year lasting cross-immunity between alfa-HCoV (229E and NL63) and beta-HCoV (HKU1 and OC-43) might determine this alternating pattern[6,7]. Along with this, we observed that 229E (alfa-HCoV) predominated in the 2021 winter, OC43 (beta-HCoV) in the 2021 spring / 2022 summer, and NL63 (alfa-HCoV) and HKU1 (beta-HCoV) in the 2022 winter season. Even though the typical prevalence of HCoV infections in the community follows the influenza pattern with peaks in each winter, circulation of any of these HCoV out of the cold seasons has been described[3], particularly in recent studies looking at the prevalence of respiratory viruses after removing the COVID-19-related restrictions[4,5]. Of note, we found a rate of HCoV persistence by PCR test of almost 60% at days 3 to 5 of illness, which correlates with the mean viral shedding of HCoV in children of 6.4 days[9].

The majority of the subjects had at least one dose of a SARS-CoV-2 vaccine and only few (15.9%) reported prior diagnosis of COVID-19 disease. Even though previous HCoV infection may diminish the severity of COVID-19 disease[10,11], there is no data on how vaccination against SARS-CoV-2 might impact on HCoV infections. Nevertheless, prospective epidemiological studies including serological evaluation are required to better define the potential cross-immunity among the different HCoVs and SARS-CoV-2.

The presenting symptoms and the benign evolution of this cohort do not differ from those described by others[3]. Diarrhea was present only in patients with OC43 infection, which has been closely related to human enteric coronavirus[12]. Only one subject received a course of antibiotics in this cohort of patients; the rapid multiplex PCR assay is a useful diagnostic tool for decreasing inadequate antibiotic prescriptions in this setting[13].

The main findings of this report include: a) endemic HCoV caused a significant propor-

tion of URTI among adult outpatients during COVID-19-related restrictions times in a city in Argentina, b) 229E was the prevalent HCoV type, and c) an alternating pattern of circulation between alfa-HCoV and beta-HCoV was described. However, the enrollment of a relatively small number of patients from one medical center and the lack of comparison with patients suffering from other respiratory viruses are among the main limitations of the study. More prospective local evidence is required to better characterize the evolution, the patterns of prevalence, and the burden of the disease of HCoV among adults in the outpatient setting.

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Conflict of interest: None to declare

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