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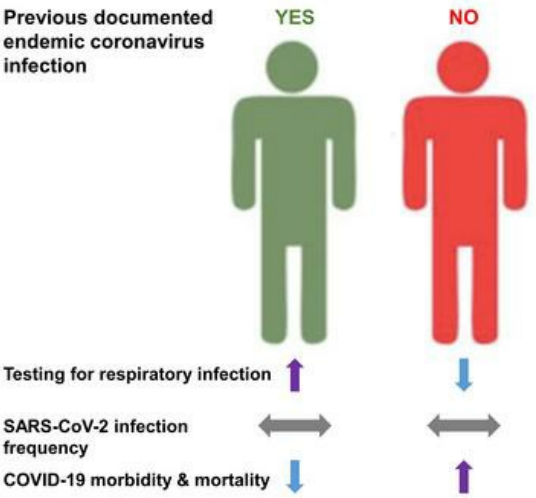
Graphical abstract



Recent endemic coronavirus infection is associated with less severe COVID-19

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Abstract

Four different endemic coronaviruses (eCoVs) are etiologic agents for the seasonal “common cold,” and these eCoVs share extensive sequence homology with human severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Here, we show that individuals with as compared to without a relatively recent documented eCoV were tested at greater frequency for respiratory infections but had similar rate of SARS-CoV-2 acquisition. Importantly, the patients with a previously detected eCoV had less severe coronavirus disease-2019 (COVID-19) illness. Our observations suggest that pre-existing immune responses against endemic human coronaviruses can mitigate disease manifestations from SARS-CoV-2 infection.

Introduction

While severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged recently, other coronaviruses are endemic in the human population. Four different human coronaviruses (HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E) are among the most common etiologic agents for the seasonal "common cold" and also cause pneumonia (1, 2). SARS-CoV-2 induced disease, termed coronavirus disease 2019 (COVID-19), can vary from asymptomatic to acute respiratory distress syndrome requiring mechanical ventilation and often leading to death (3, 4). The endemic coronaviruses (eCoVs) share extensive sequence homology with SARS-CoV-2, and immune responses to the eCoVs can cross-react with SARS-CoV-2 antigens (5-8). Whether prior infections with eCoV elicits immunologic memory that influences SARS-CoV-2 acquisition and COVID-19 outcomes remains uncertain.

Results and Discussion

We examined SARS-CoV-2 infections and COVID-19 outcomes among patients who had previously been assessed with a comprehensive respiratory panel polymerase chain-reaction (CRP-PCR, FilmArray Respiratory Panel, RP2, BioFire Diagnostics) test. The CRP-PCR detects nucleic acids for the 4 eCoVs along with 16 other pathogens, and thus, a positive test indicates ongoing rather than prior infections. We retrospectively collected data from patients with an available CRP-PCR result from May 18, 2015 to March 11, 2020 in the electronic medical record (EMR). March 11, 2020 was chosen as the end date because the first available SARS-CoV-2 test in the Boston Medical Center (BMC) EMR was on March 12, 2020. We also obtained all SARS-CoV-2 reverse transcription PCR (RT-PCR) results between March 12, 2020 and June 12, 2020 that were available in the EMR. Analysis was restricted to patients not recorded deceased prior to March 11, 2020, above 18 years of age, and with the first SARS-CoV-2 result at least 7 days after the CRP-PCR test.

A total of 15,928 different patients had at least one CRP-PCR test. An eCoV was previously detected in 875 of these patients (termed eCoV+), and the remaining 15,053 individuals (classified as eCoV-) never had a documented eCoV infection. Most but not all, of the demographic characteristics showed no significant difference between the eCoV+ and eCoV- group (Table 1), although there were some variation in race and human immunodeficiency virus (HIV) infection status. The proportion of patients with no, one, or two or more co-morbidities was not significantly different between the eCoV+ as compared to eCoV- group. The CRP-PCR test was more frequently ordered while patients were at a hospital (inpatient, observation unit, or emergency department) in the eCoV- as compared to eCoV+ patients. These observations imply that the patients in the two groups had relatively similar level of pre-existing morbidity, but the eCoV- as compared to the eCoV+ patients may have had more severe clinical presentation at the time of CRP-PCR testing.

A total of 1,812 (11.4%) of the patients under investigation had an available SARS-CoV-2 result (Table 2). A significantly higher proportion of eCoV+ (15.2%) individuals were tested for SARS-CoV-2 as compared to the eCoV- (11.2%) patients (odds ratio (OR) 1.4, 95% confidence interval (CI) 1.2 – 1.7). The odds of SARS-CoV-2 testing (OR 1.4, 95% CI 1.2 – 1.7) remained significantly higher in the eCoV+ as compared to eCoV- patients after adjusting for race/ethnicity, chronic obstructive pulmonary disease, HIV, number of co-morbidities, and level of clinical care. The last documented CRP-PCR result prior to the SARS-CoV-2 RT-PCR test occurred significantly more recently in the eCoV+ (median 121 days, interquartile range (IQR) 69 - 440

days) as compared to the eCoV- (median 359 days, IQR 117 - 799 days, $p < 0.0001$) patients (Fig. 1a). The eCoV+ (median 2, IQR 1 - 3) as compared to eCoV- (median 1, IQR 1 – 2, $p = 0.002$) patients also had significantly more frequent CRP-PCR testing (Fig. 1b). The more recent and frequent CRP-PCR testing in the eCoV+ individuals suggests a greater likelihood of having a clinical presentation prompting respiratory evaluation. The greater likelihood of illness prompting CRP-PCR evaluation may also account for the higher level of SARS-CoV-2 RT-PCR testing among the eCoV+ as compared to eCoV- group.

Among the patients evaluated for SARS-CoV-2, 470 (25.9%) had at least 1 positive SARS-CoV-2 RT-PCR at some point (Table 2). A total of 252 (53.6%) of the SARS-CoV-2 infected patients had a COVID-19 related hospitalization during the study period. The frequency of documented SARS-CoV-2 infection among those tested, and of hospitalization among those infected, did not differ between the eCoV+ and eCoV- groups (Table 2). Some risk factors associated with more severe COVID-19, such as older age, male gender, higher body mass index (BMI), and pre-existing diabetes mellitus (DM) (9, 10), were significantly different between the eCoV+ as compared to eCoV- patients that were eventually hospitalized after SARS-CoV-2 infection (Supplemental Table 1). The number of prior diagnoses, however, were not different among the hospitalized eCoV+ and eCoV- group, suggesting they had a similar level of pre-existing morbidity.

The eCoV+ as compared to eCoV- hospitalized patients had a significantly lower odds for intensive care unit (ICU) admission (OR 0.1, 95% CI 0.0 – 0.7) and a trend towards lower odds of mechanical ventilation (OR 0.0, 95% CI 0.0 – 1.0). The odds of ICU care (OR 0.1, 95% CI 0.1–0.9) remained significantly lower in the eCoV+ as compared to eCoV- patients after adjusting for age, gender, BMI, and DM. The percentage of hospitalized patients that eventually died over follow up was lower in the eCoV+ (4.8%) as compared to the eCoV- (17.7%) group. Survival probability was significantly higher in the hospitalized eCoV+ as compared to eCoV- COVID-19 hospitalized patients (hazard ratio (HR) 0.3, 95% CI 0.1 – 0.7, Fig. 2). After adjusting for age, gender, BMI, and DM, the HR remained 0.3, although the confidence interval became much wider and encompassed unity (0.0 – 2.0). Cumulatively, these observations suggest that recent documented eCoV infection is associated with less severe COVID-19.

Lower virus levels in the respiratory tract associate with less severe COVID-19 (11). The EMR provides scant information from which a patient's burden of infection may be inferred, but cycle threshold (C_t) values from SARS-CoV-2 tests may be used for extrapolation. Both, an Abbott commercial assay and an in-house

assay (12) were used to determine the presence of SARS-CoV-2 in our hospital during this study period due to testing and material limitations. Patients tested with the two assays did not show significantly different C_t values ($p = 0.13$, Supplemental Fig. 1a). In the patient's initial or only positive SARS-CoV-2 RT-PCR, the eCoV+ as compared to eCoV- patients had, if anything, more abundant virus in the nasopharynx as indicated by lower C_t values (Supplemental Fig. 1b). A multivariable linear regression model demonstrated that the eCoV+ as compared to the eCoV- patients had around a 4 unit lower C_t value ($\beta = 4.0$, 95% CI -0.6 – 8.7, $p = 0.09$), but this difference was not statistically significant. The in-house assay also trended to yield around 2 unit lower C_t values compared to the commercial Abbott assay ($\beta = 2.0$, 95% CI -0.3 – 4.4, $p = 0.09$). In both analyses, the data did not reach statistical significance, and the number of data points was extremely limited especially for the eCoV+ patients. Although limited by the upper airway site of sampling, single time of analysis, and small sample size, these data do not support the hypothesis that the better outcomes of eCoV+ patients were due to lower viral burdens. Combined with the SARS-CoV-2 acquisition frequency data (Table 2), these observations potentially imply that the eCoV+ patients do not possess immunological memory that constrains initial virus replication.

Less severe outcomes from similar viral loads may be due to decreased "cytokine storm" or inflammatory injury. Higher plasma inflammatory markers, such as C-reactive protein (CRP) and lactate dehydrogenase (LDH), correlate with more severe disease (13), supporting the concept that inflammatory responses contribute to pathophysiology. The eCoV+ as compared to the eCoV- patients trended towards lower CRP (eCoV+ median 24.0 ng/L, IQR 7.2 – 69.3 ng/L versus eCoV- median 55.1 ng/L, IQR 16.6 – 109.0 ng/L, $p = 0.06$) and LDH (eCoV+ median 284.0 units/L, IQR 191 – 344.5 units/L versus eCoV- median 306.0 units/L, IQR 241 – 385.5 units/L, $p = 0.09$) levels upon their initial presentation for their COVID-19 related hospitalization (Supplemental Fig. 2a and 2b). These observations possibly suggest that patients with a previously documented eCoV infection may have more subdued inflammatory responses soon after SARS-CoV-2 infection (14, 15).

As a whole, patients with previous CRP-PCR tests prior to SARS-CoV-2 acquisition are hospitalized at a higher frequency as compared to the general population at our and other medical centers (16, 17). This population may represent a sicker group with a higher propensity to acquire a respiratory infection and require hospitalization. We find that, within that population, those with a recent prior documented eCoV infection were

more likely to have a clinical presentation triggering SARS-CoV-2 testing, but their likelihood of being infected was relatively similar. The level of hospitalization after infection also did not differ between the two groups. We interpret these data to suggest that those with recent eCoV infection may not have neutralizing immunity that prevents acquisition. Indeed, a previous study suggests that neutralizing responses against eCoVs are relatively short lived, and previously infected patients are susceptible to re-infection albeit with less severe disease (18). Importantly, we observed that the eCoV+ as compared to the eCoV- group was less likely to have ICU admission and death after COVID-19 diagnosis. Even without neutralizing immunity, patients with prior eCoV infections may have lung-localized primed immune responses that prevent severe disease from a heterologous virus (19). Heterotypic lung-localized resident memory T and B cells prevent severe infections from respiratory pathogens (20). Future studies should determine whether lung-localized heterotypic immunity is elicited by prior eCoV infection and is capable of ameliorating COVID-19 manifestations. The durability and extent of the potential immune protection and distinct effects of different eCoVs will also need to be investigated.

This study had limitations. It was associative, and thus cannot determine causality. It involved small numbers from one hospital, so findings may not generalize. The observed morbidity and mortality may be linked to but not directly caused by SARS-CoV-2 infection. The absence of an eCoV+ result does not preclude coronavirus infections throughout the study period, so some individuals may have been classified inappropriately. The relatively low observed morbidity and mortality in the eCoV+ group, however, suggests that removing individuals with undocumented eCoV infection from the eCoV- group would further increase the effect size away from the null. Several different RT-PCR assays were used for SARS-CoV-2 testing at our institution during the study period; inherent differences in their targets and C_t values are acknowledged. With these limitations, results suggest prior eCoV infection was associated with less severe COVID-19. Larger studies and causal investigations are needed to identify the mechanisms and persistence of this inferred heterotypic immune protection.

Methods

Study approval. This retrospective study did not require patient consent and was approved by the Boston University institutional review board (H40391).

Patient data. All data was obtained from patient's EMR. All test results were based on clinical care, and no tests were done for research purposes. All tests and clinical care were at the discretion of the treating physicians. There are no limitations or perquisites for CRP-PCR testing at BMC. A patient with a documented eCoV on CRP-PCR was classified as eCoV+ regardless of whether they had other CRP-PCR results. All other patients were classified as eCoV-. The test date of interest was the day with documented eCoV for the eCoV+ group and the most recent CRP-PCR for the eCoV- group. For each patient, we also recorded the day of the most recent CRP-PCR result. The first positive SARS-CoV-2 RT - PCR result was deemed as the SARS-CoV-2 test day regardless of whether they had other results. For the patients with negative SARS-CoV-2 RT-PCR results, the first negative test was denoted as the SARS-CoV-2 test day. An individual patient was only counted once regardless of the number of CRP-PCR or SARS-CoV-2 test results. All data from pediatric patients under 18 years of age were excluded from the analysis.

Quantitative SARS-CoV-2 RT-PCR testing. The RT-PCR C_t values were obtained from a commercial Abbott assay and an in-house assay (12). The Abbott assay gene target is proprietary. The in-house assay targeted the SARS-CoV-2 nucleocapsid gene. The C_t values obtained from the different assays were examined using multivariable linear regression. In this model, eCoV+ versus eCoV- (group) and the Abbott versus the in-house assay (platform) were categorical independent variables, and C_t was the dependent variable. An interaction term between the group and platform variable did not improve the model, and thus it was omitted from the final analysis.

Statistical analyses. Analyses were conducted using GraphPad Prism (version 8.4.3) and SPSS Statistics (version 26.0). ßDescriptive statistics were used to summarize the data and report medians and interquartile ranges as appropriate. Outcomes of interest were proportion SARS-CoV-2 tested, SARS-CoV-2 positivity, hospitalization, ICU admission, mechanical ventilation, and death. Patient characteristics were assessed using Fisher's exact, Mann-Whitney U, and Chi-square tests. Unadjusted and adjusted OR were estimated using Fisher's exact tests and multivariate or penalized likelihood logistic regression respectively. Mortality rate differences were compared using log-rank HR, and multivariate Cox proportional hazard analysis. All patients

were right censored after July 14, 2020. Multivariate comparisons incorporated characteristics deemed important for COVID-19 and those that demonstrated a p-value < 0.2 in univariate analyses. Tests were two-sided with a p-value < 0.05 considered statistically significant.

Author contributions

JPM conceived the study. MS and JPM designed the study. KR, MR, MS collected data. NSM provided the quantitative PCR data. MS, PS, LFW conducted the statistical analyses. MS, PS, LFW, JPM analyzed and interpreted the data. MS and JPM wrote the manuscript.

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Table 1. Demographics of the patients with and without a documented endemic coronavirus[a]

	eCoV- (n = 15,053)	eCoV+ (n = 875)	p-value
Age, median (IQR)	55 (38 – 68)	55 (37 – 68)	0.34[b]
Male	6,938 (46.1)	421 (48.1)	0.25
Race / Ethnicity			0.05[c]
Black	6,757 (44.9)	365 (41.7)	
White	4,311 (28.6)	248 (28.3)	
Hispanic/Latin	3,282 (21.8)	219 (25.0)	
Body mass index, median (IQR)	27.9 (23.8 – 32.8)	27.8 (23.9 – 32.8)	0.59[b]
Diabetes mellitus	4,481 (29.8)	270 (30.9)	0.49
Hypertension	7,525 (50.0)	443 (50.6)	0.73
Coronary artery disease	1,515 (10.1)	87 (9.9)	0.95
Congestive heart failure	1,311 (8.7)	77 (8.8)	0.90
Chronic obstructive pulmonary disease	2,342 (15.6)	151 (17.3)	0.18
Asthma	3,583 (23.8)	216 (24.7)	0.54
Renal disease	1,681 (11.2)	103 (11.8)	0.58
Human immunodeficiency virus	659 (4.4)	53 (6.1)	0.02
Cancer	1,459 (9.7)	93 (10.6)	0.38
End stage renal disease	464 (3.1)	33 (3.8)	0.27
Number of co-morbidities			0.18[c]
0	4,298 (28.6)	244 (27.9)	
1	3,892 (25.9)	206 (23.5)	
≥2	6,863 (45.6)	425 (48.6)	
Level of clinical care[d]			<0.0001[c]
Inpatient	7,047 (46.8)	331 (37.8)	
Observation unit	2,681 (17.8)	134 (15.3)	
Emergency department	4,118 (27.4)	308 (35.2)	
Outpatient	1,174 (7.8)	99 (11.3)	
Missing data	33 (0.2)	3 (0.3)	

Abbreviations include eCoV: endemic coronavirus; IQR: interquartile range; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: coronavirus disease-2019.
Race and diagnoses are based on patient supplied information and the most current problem list in the medical record respectively.
[a] Data are expressed as number (%) and p-value was calculated using Fisher's exact test unless otherwise indicated.
[b] Mann Whitney U test
[c] Chi Square Test
[d] Level of clinical care at the time of the comprehensive respiratory panel – PCR test.

Table 2. SARS-CoV-2 infection and COVID-19 outcomes in the patients with and without a documented endemic coronavirus[a]

	eCoV- (n = 15,053)	eCoV+ (n = 875)	OR (95% CI) eCoV+/eCoV-	Adjusted OR (95% CI)
SARS-CoV-2 tested, no. (% of total)	1,679 (11.2)	133 (15.2)	1.4 (1.2 – 1.7)	1.4 (1.2 – 1.7)[b]
SARS-CoV-2+, no. (% of tested)	437 (26.0)	33 (24.8)	0.9 (0.6 – 1.4)	
Hospitalized, no. (% of SARS-CoV-2+)	231 (52.9)	21 (63.6)	1.6 (0.8 – 3.2)	
Intensive care unit, no. (% of hospitalized)	65 (28.1)	1 (4.8)	0.1 (0.0 – 0.7)	0.1 (0.1 – 0.9)[c]
Mechanical ventilation, no. (% of hospitalized)	38 (16.4)	0 (0)	0.0 (0.0 – 1.0)	

Abbreviations include eCoV: endemic coronavirus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: coronavirus disease-19; OR: odds ratio; CI: confidence interval

[a] Data are expressed as number (%) and odds ratio was calculated using Fisher's exact test.

[b] OR after adjusting for race/ethnicity, chronic obstructive pulmonary disease, HIV, number of co-morbidities, and level of clinical care using multivariate logistic regression.

[c] OR after adjusting for age, gender, body mass index, and diabetes mellitus using penalized logistic regression.

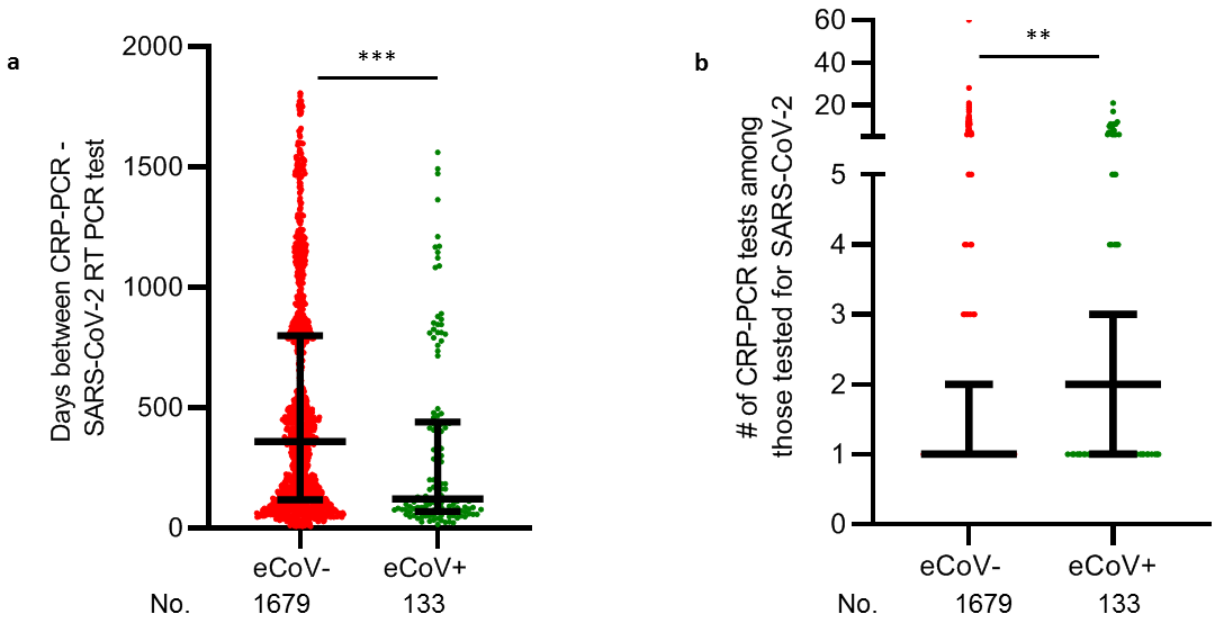

Figure 1. Testing among patients with and without a documented endemic coronavirus. Days between the last available CRP-PCR and first SARS-CoV-2 RT-PCR test (**a**) and the number of independent CRP-PCR tests from May 18, 2015 to March 11, 2020 (**b**) among the patients without (eCoV-) and with a (eCoV+) documented endemic coronavirus. The number of patients (No.) contributing to the data are denoted below the x-axis. The black lines in the dot plots represent the median and interquartile range. Asterisks denote p-value with the Mann Whitney test (** < 0.01 and *** < 0.001).

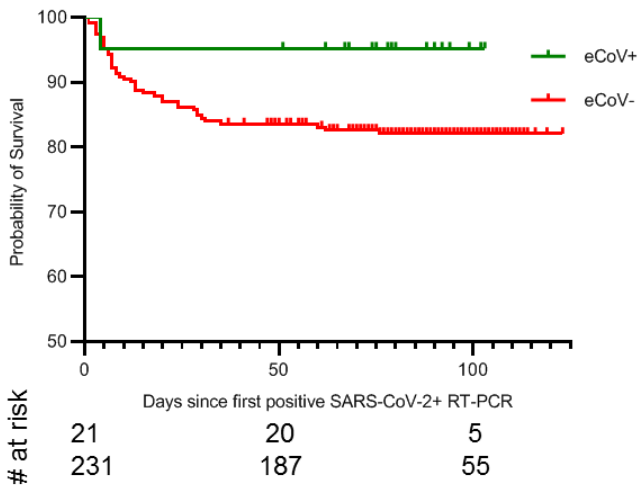

Figure 2. Mortality among patients with and without a documented endemic coronavirus. Unadjusted Kaplan-Meier survival curve for eCoV- (red) and eCoV+ (green) SARS-CoV-2 infected hospitalized patients. The y-axis shows the probability of survival and the x-axis shows days after first SARS-CoV-2 positive RT-PCR result. The tick marks denote right censoring after July 14, 2020. Number of patients at risk at different time points is displayed below the survival curve. The unadjusted (0.3, 95% CI 0.1 – 0.7) and adjusted (0.3, 95% CI 0.0 – 2.0) survival hazard ratios were calculated using the log-rank test and Cox proportional hazard model respectively.