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Severity of coronavirus respiratory tract infections in adults admitted to acute care in Toronto, Ontario

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ABSTRACT

Background: The World Health Organization has highlighted the need for improved surveillance and understanding of the health burden imposed by non-influenza RNA respiratory viruses. Human coronaviruses (CoVs) are a major cause of respiratory and gastrointestinal tract infections with associated morbidity and mortality.
Objectives: The objective of our study was to characterize the epidemiology of CoVs in our tertiary care centre, and identify clinical correlates of disease severity.
Study design: A cross-sectional study was performed of 226 patients admitted with confirmed CoV respiratory tract infection between 2010 and 2016. Variables consistent with a severe disease burden were evaluated including symptoms, length of stay, intensive care unit (ICU) admission and mortality.
Results: CoVs represented 11.3% of all positive respiratory virus samples and OC43 was the most commonly identified CoV. The majority of infections were community-associated while 21.6% were considered nosocomial. The average length of stay was 11.8 days with 17.3% of patients requiring ICU admission and an all-cause mortality of 7%. In a multivariate model, female gender and smoking were associated with increased likelihood of admission to ICU or death.
Conclusion: This study highlights the significant burden of CoVs and justifies the need for surveillance in the acute care setting.

1. Background

Human coronaviruses (CoVs) are a significant cause of community-acquired respiratory tract infections. The symptoms associated with CoV infection were first described over four decades ago [1], and can range from relatively mild upper- to more severe lower- respiratory tract infections with increased severity in certain patient populations [1,2]. It has been reported that immunocompromised patients, particularly hematopoietic cell transplant recipients, are at increased risk of lower respiratory tract infections, prolonged viral shedding and mortality, often comparable to what is seen with influenza virus [3,4]. Similar to other non-influenza respiratory viruses, CoVs are still relatively understudied despite being a common cause of hospital- and community-acquired respiratory infection [5,6].

There is currently a paucity of Canadian data on the burden of disease imparted by endemic CoVs, and their contribution to nosocomial respiratory virus outbreaks. This is likely due to the fact that laboratories may not routinely identify CoVs, and they are not generally reportable to public health agencies. Thus, the World Health Organization (WHO) has highlighted the need for improved epidemiological surveillance and a better understanding of the health burden imposed by CoVs, as well as other non-influenza RNA respiratory viruses [7].

Four types of endemic CoVs are in current circulation, OC43, 229E, HKU1, and NL63. Recent findings demonstrate a seasonality for CoV infections, with peak numbers being observed in the winter months [2]. However, this data is based on nationally-reported findings from the United States, and may not reflect local or national epidemiology in Canada. Moreover, the receptor-binding domain of the glycoprotein of 229E has undergone adaptation over the last 50 years [8], suggesting

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that ongoing viral evolution may influence which strains predominate from year to year. This is further supported by phylogenetic data examining OC43 isolates, which showed that the circulating genotypes in southeast Asia changed over time [9]. A recent study in the midwestern USA reported frequent identification of HKU1, whereas a separate study from China reported OC43 to be more prevalent [10,11]. Therefore, determining the regional prevalence is important to understand the burden of these infections.

2. Objectives

In acute care hospitals, much of the focus in diagnostics has been placed on influenza and respiratory syncytial virus (RSV) because of the severe infection and poor outcomes of hospitalized patients, yet the burden of CoV in acute care is not well studied. Most hospitals do not routinely test for CoV resulting in gaps in our clinical and epidemiologic understanding of this virus. The predictors of severe infection are well known for CoV associated with acute respiratory syndromes (eg. Middle East Respiratory Syndrome CoV, Severe Acute Respiratory Syndrome CoV), yet few studies have identified these predictors for the more common four circulating CoV strains such as OC43, 229E, HKU1 and NL63 [12,13]. The primary objective of this study was to describe the burden of CoV among patients admitted to an acute care hospital in Toronto, Canada over a six-year period, and identify the predictors of severe disease.

3. Study design

3.1. Design and setting

This cross-sectional study was performed at Sunnybrook Health Sciences Centre, a tertiary-care hospital with over 1300 total beds serving acutely ill and rehabilitating patients as well as long-term care residents. Institutional ethics approval was obtained (REB#066-2017).

3.2. Study participants and viral identification

The study participants included admitted patients ≥17 years of age who tested positive for a CoV infection between January 1st 2010 and December 31st 2016. Outpatients and residents of the affiliated long-term care facility were excluded. Viral test results were obtained from nasopharyngeal (NP), mid-turbinate (MT) swabs, and bronchoalveolar lavages (BALs) tested as part of routine care for respiratory viruses using multiplex PCR (xTAG RVP, xTAG RVP FAST v2 or RPP, Luminex). Viral targets in this assay included: influenza viruses A & B, RSV, adenovirus, rhinovirus/enterovirus, human metapneumovirus, parainfluenza viruses type 1–4 and coronavirus species OC43, 229E, NL63 and HKU1. Demographic and clinical data were obtained for all patients meeting inclusion criteria. Cases were considered to be community-acquired if they were diagnosed within 72 h of admission and nosocomial if they were diagnosed ≥72 h after admission [14]. Lower respiratory tract involvement was defined as radiographic evidence of acute disease, determined on review of radiology reports.

3.3. Statistical analysis

Dependent (outcome) variables were those associated with severity and burden of disease. These included: number of symptoms, presence or absence of fever, need for oxygen therapy or intubation, chest radiography changes, isolation of bacteria by conventional culture, admission to an intensive care unit (ICU), number of days spent in the ICU, antimicrobial and antiviral use, length of stay in hospital and death. Independent variables included coronavirus strain (OC43 vs. non-OC43), gender, smoking status (not a smoker, previously a smoker, current smoker), and age. The age variable was converted into a categorical variable with three categories including: less than 60 years of age, patients between 61 and 80 years of age, and patients over 80 years of age. The Chi-squared/Fisher's exact test, Kruskal Wallis, Mann-Whitney and unpaired T-tests were used to assess the presence of statistically significant correlations between dependent and independent variables. Statistically significant correlations were included in univariable logistic or non-parametric regression analyses to evaluate the predictive ability of the independent variable. A bivariate and a multivariate logistic regression analysis were also performed including the following variables: age, smoking status (current or previous smoker vs. non-smoker), viral strain (OC43 vs. non-OC43), nosocomial vs. community acquired infection, gender, and number of comorbidities (3 or more vs. less than 3). Statistical analysis was performed using SAS University Edition (SAS Institute, Cary, NC, USA).

4. Results

4.1. Coronavirus infections

During the study period, 5038 samples were positive for a respiratory virus of which 11.3 % (n = 569) were positive for CoV representing the third most frequently identified pathogen after influenza viruses and rhinoviruses/enteroviruses (Fig. 1a). It was noted that infections were identified year-round, but the peak number of cases occurred between November and February each year (data not shown). The number of CoV infections increased between 2010 and 2016 (Fig. 1c). From these samples, 226 patients met study inclusion criteria. Amongst the CoVs, the most frequently identified strain was OC43, representing 50 % (n = 285) of CoVs, followed by 229E (22.3 %, n = 127), HKU1 (13.9 %, n = 79) and NL63 (13.7 %, n = 78) (Fig. 1b).

4.2. Study participant demographics

The age of patients spanned from 18 to 99 years old and the median age was 77 (Table 1). Additionally, the distribution of cases was similar between males and females (44.7 % vs. 55.3 %).

As shown in Table 1, comorbidities were common amongst our cohort, with vascular, cardiac and pulmonary comorbidities being the most frequently reported. Only 3.1 % of patients were current smokers, and 12.8 % were former smokers.

4.3. Clinical data

Community-acquired infections accounted for 78.3 % (n = 177) of cases, and nosocomial infections accounted for 21.6 % (n = 49). Symptoms included cough (48.6 %, n = 110), shortness of breath (SOB) (37.1 %, n = 84), and fever (29.6 %, n = 67). Furthermore, 81 % of patients had a chest X-ray performed within 24 h of presentation, and the majority of individuals (57.3 %, n = 130) demonstrated acute radiographic changes. Hematology and biochemistry laboratory investigations indicated 30.9 % (n = 70) had elevated white blood cell counts. Additionally, 38.9 % (n = 88) of patients had decreased lymphocytes counts (Table 1). Bacterial co-infections were noted in 7.1 % of patients, and viral co-infections were detected in 3.9 % of patients, and in both groups no clear pathogen predominated (Tables 1 & 2). The average length of stay in hospital was 13 days (range 1 − 354 days), and 17.3 % required admission to the ICU with a mean duration of 11.8 days (range 1–240 days). All-cause mortality was 7%.

4.4. Predictors of severe infection

The predictor variables associated with severe disease outcomes are presented in Table 3. Patients with OC43 had 2-fold odds of requiring O2 or intubation compared to non-OC43 strains, while no difference in mortality or ICU admission was found based on CoV strain. Increased age was associated with increased numbers of symptoms, comorbidities, and radiographic changes. A bivariate analysis identified both

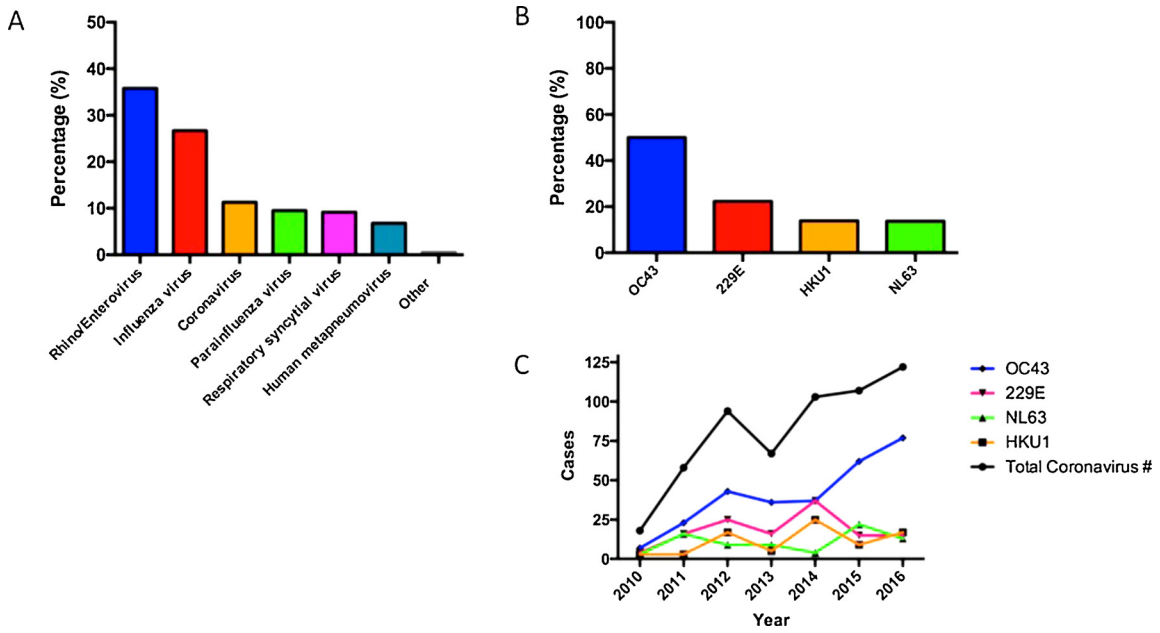

Fig. 1. Respiratory viruses identified during the study period (A) Viruses identified during the study period as a percentage of the total number of respiratory viruses. (B) Percentages of each coronavirus species identified during the study period. (C) Total number of isolates for each coronavirus species identified by year.

Table 1
Cohort characteristics.

Patient Description	
Median age (yrs)in years (Interquartile Range, N)	77 (58 – 86, 225)
Female, n (%)	124 (55, 225)
Symptoms & Signs	
Fever, n (%)	67 (29.6)
Cough, n (%)	110 (48.6)
Sore throat, n (%)	14 (6.2)
Congestion/rhinorrhea, n (%)	29 (12.8)
Difficulty breathing/SOB, n (%)	84 (37.1)
Chest Pain, n (%)	19 (8.4)
Diarrhea, n (%)	13 (5.7)
Nausea/vomiting, n (%)	14 (6.1)
Altered level of consciousness, n (%)	20 (8.7)
CXR changes, n (%)	13 (57.3)
Comorbidities	
Pulmonary, n (%)	67 (29.6)
Cardiac, n (%)	101 (44.7)
Vascular	115 (50.9)
Current or former smoker	36 (15.9)
Bacterial co-infection	16 (7.1)
Viral co-infection	9 (3.9)
Biochemistry	
White blood cells (x10E9/L), median, IQR, N	8.7 (6.7 – 11.5, 209)
Lymphocytes (x10E9/L), median, IQR, N	1.05 (0.7 – 1.5, 198)
Platelets (x10E9/L), median, IQR, N	199 (152 – 261.5, 208)
Creatinine (umol/L), median, IQR, N	77.5 (58 – 96, 188)
White blood cells > 10 (x10E9/L)	70 (30.9)
White blood cells < 4 (x10E9/L)	18 (7.9)
Lymphocytes > 4 (x10E9/L)	2 (0.8)
Lymphocytes < 1 (x10E9/L)	88 (38.9)
Outcomes	
Length of stay in hospital – days, median (IQR)	4 (2 – 10.5)
Patients requiring intubation, n (%)	11 (7)
Patients requiring non-invasive positive pressure ventilation, n (%)	13 (8.84)
ICU admissions, n (%, N)	39 (17.3 %)
Average length of stay in ICU in days (Interquartile Range)	11.8 (range 1 – 354)
All-cause mortality, n (%)	16 (7%)

Data are median where indicated and N = total number of patients where values were available.

nosocomial acquisition (OR 2.25; CI 1.089–4.655; p-value 0.02) and female gender (OR 0.485; CI 0.248 – 0.948, p-value 0.03) as being associated with ICU admission and/or mortality. The multivariate model passed the test for co-linearity, and indicated that female gender was significantly associated with ICU admission and/or mortality (OR 0.45; 95 % CI, 0.23 – 0.90; p = 0.02) as was smoking status (OR 0.30; 95 % CI, 0.084–1.06; p = 0.06, while strain type, co-morbidities, age and nosocomial-acquisition were not associated with ICU admission or mortality.

5. Discussion

This cross-sectional study spanning 6-years suggests that CoV accounts for an important burden of respiratory infection, representing 1 out of 9 viral respiratory infections, with a propensity to cause lower-respiratory tract infection and severe outcomes. Notably, all-cause mortality and risk of ICU admission were similar to rates reported for influenza and RSV [15,16].

Our findings indicate that CoV is not a benign infection among those who are hospitalized, and is similar to available data elsewhere. Garbino and colleagues found that 31 % of patients in their cohort were admitted to the ICU, and noted an all-cause mortality of 10 %. Lower-respiratory tract infections (LRTIs) are the fourth leading cause of mortality globally, and characterizing the epidemiology of respiratory viruses is a necessary first step to reducing the burden of disease [7].

Predictors of severe outcome including need for ICU admission or mechanical ventilation have been described for MERS-CoV, but there is a paucity of data on other CoVs [12,17]. In our cohort smoking predicted ICU admission and/or mortality, which is similar to what was reported in a prior study on patients infected with HKU1 CoV [18] The impact of gender on outcomes of CoV, as determined by our multivariate analysis is in contrast with what is reported for MERS CoV. With other coronaviruses including MERS-CoV, there is often a predominance of male cases [19,20]. However, females represented the majority of CoV infections in our cohort, and our analysis indicated that female gender was associated with more severe outcome. This finding differs from what has been reported for SARS-CoV patients in Singapore [21], and MERS-CoV 17] where male gender was predictive of poor outcomes. Interestingly, our bivariate analysis indicated that nosocomial acquisition was associated with poor prognosis. Similar findings

Table 2
Co-infections identified among 226 adult patients hospitalized with coronavirus respiratory tract infection.

Co-infection type	Pathogen Identified
Viral	Cytomegalovirus (n = 1), Entero/Rhinovirus (n = 3), human metapneumovirus (n = 2), parainfluenza virus 4 (n = 1), respiratory syncytial virus (n = 2)
Bacterial	*Capnocytophage* spp. (n = 1), Coagulase-negative Staphyloccocci (n = 4), *Escherchia coli* (n = 2), *Haemophilus influenzae* (n = 2), *Moraxella* spp. (n = 3), *Streptococcus pneumoniae* (n = 3), *Klebsiella pneumoniae* (n = 1), *Pseudomonas aeruginosa* (n = 1)

Table 3
Association between severity of coronavirus infection and clinical factors based on univariate logistic regression analysis. Independent variables included coronavirus strain (OC43 vs. non-OC43), gender, smoking status (not a smoker, previously a smoker, current smoker), and age.

Independent variable	Dependent variable	p-value	OR	p-value
OC43 vs non-OC43	Fever	0.004	0.41 (0.22 − 0.76)	0.004
	Need for O2 or intubation	0.04	2.05 (1.03 − 4.07)	0.04
Gender	Death as outcome	0.03	3.605 (1.111 − 11.694)	0.03
	ICU admission	0.02	2.372 (1.149 − 4.895)	0.02
	Bacteria isolated	0.02	4.491 (1.213 − 16.626)	0.02
	Death and/or ICU admission	0.02	2.182 (1.107 − 4.302)	0.02
Smoking status	ICU admission	0.04	0.320 (0.107 − 0.956)	0.04
Age (< 60 vs. 61 − 80 vs. > 80)	Number of symptoms	0.005	n/a	0.07
	CXR changes	0.03	1.674 (1.125 − 2.490)	0.01

have been noted for infections with MERS CoV, where acquisition of the virus in the hospital was predictor of 72 h mortality in a multivariate analysis of cases in Saudi Arabia [13].

Our findings indicate that there is heterogeneity in circulating strains, as OC43 and 229E were more prevalent than NL63 or HKU1. Previous studies have similarly shown OC43 and 229E account for up to approximately 30 % of common colds [22], and our data indicate that approximately 70 % of coronavirus infections in our cohort were due to these two strains. More recent four-year prevalence data from military personnel in the USA revealed season-to-season variability where OC43 and 229E alternated as the most common strain identified [23]. Other studies have highlighted prevalence of a particular strain, often showing variation between locations and patient populations (eg. transplant vs. non-transplant; inpatient vs. ICU etc) [3,10,11,23]. Sequencing analysis by Lau and colleagues of clinical isolates of OC43 suggested recombination may play a role in the generation of novel CoV genotypes [24]. This highlights the importance of determining the local epidemiology, and suggests that genomic sequencing of isolates may be a necessary next step to investigate genetic changes over time. Interestingly, there is increasing reports of both co-infections with multiple respiratory viruses and viral and bacterial pathogens, and data suggesting this may be associated with more severe disease [25–28]. In our cohort bacterial co-infections were only identified in 7.9 % of individuals, and viral co-infections in 3.1 %; both of which are lower than what has been reported by other groups [28,29], and we did not have sufficient numbers to investigate any correlations with disease severity. However, this is an area where additional studies are needed.

Our study has several important limitations. We only included patients who presented to the hospital for acute care, thus representing a subset of the most ill patients with CoV infection in the community. Furthermore, it cannot be discounted that higher number of positives were seen during influenza season due to heightened testing of respiratory viruses during this time of year. Importantly, our study did not include asymptomatic or subclinical cases or non-CoV controls, which makes it challenging to identify determinants of severity relative to these other populations. Moreover, as data emerges on the association of CoVs with central nervous system sequalae, future studies should investigate the incidence of strokes, and seizures in cases of CoV infection [30]. The number of patients receiving extracorporeal membrane oxygenation should also be considered in subsequent studies. Since our assay was not quantitative we are unable to determine the role of viral load in influencing disease severity, although it has been noted by others that viral load did not correlate with outcome [31]. Furthermore, we did not include biomarkers associated with liver function. It has been reported that elevated ALT was associated with adverse outcomes in patients infected with SARS [32], and further investigation is necessary to determine the prognostic value in other CoV infections. Finally, the relatively small numbers of cases of each strain (e.g. OC43, 229E, HKU1, NL63) prevented separate analysis of any potential effects of individual strains on patient outcome.

Our study describes burden and risk factors associated with disease severity in patients infected with CoV at a single urban healthcare centre. At present there is likely an under-reporting of CoV infections in Canadian hospitals, as many laboratories do not routinely test for these pathogens. Collectively, this study highlights the significant burden of CoVs and justifies the need for surveillance in the acute care setting.

Credit author statement

R.K. and S.M. were involved in the conceptualization and design of the study. R.K., K.P., L.Y., V.W., J.A.L. were involved in data collection and analysis. K.P. and J.A.L. performed statistical analysis and interpretation. Manuscript writing was performed by R.K., J.A.L. and S.M. and all authors participated in editing.

Declaration of Competing Interest

All authors declare no conflicts of interest

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