ORIGINAL RESEARCH

Endemic Human Coronaviruses in Hospitalized Adults with Community-Acquired Pneumonia in the City of Louisville, Kentucky

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Abstract

Introduction: There are four endemic serotypes of human coronavirus (HCoV) that may cause community-acquired pneumonia (CAP) in humans. The clinical syndrome of CAP due to HCoVs is not well characterized. The objectives of this study were to evaluate incidence, epidemiology, and outcomes of CAP in adults due to HCoV and to compare them to CAP due to influenza.

Methods: The Louisville Pneumonia Study (LPS) is a prospective observational study of hospitalized adult patients with CAP in the city of Louisville. Patients enrolled in the LPS in whom a respiratory viral panel polymerase chain reaction (PCR) was obtained were evaluated. Incidence, epidemiology, and outcomes were compared for patients with a positive PCR for HCoV versus patients with a positive PCR for influenza.

Results: From 1,974 CAP patients with a PCR performed, HCoV was identified in 65 patients (3.3%), corresponding to the following serotypes: HCoV-229E in 12 patients, HCoV-OC43 in 38 patients, HCoV-NL63 in 6 patients and HCoV-HKU1 in 9 patients. No differences were observed for clinical presentation and early outcomes for patients with CAP due to HCoV when compared to 244 patients with CAP due to influenza. One-year mortality after hospitalization was 32% for patients with CAP due to HCoV versus 13% for patients with CAP due to influenza.

Conclusions: When compared to patients with CAP due to influenza, the clinical presentation of patients with CAP due to HCoV is similar, but these patients have significantly worse outcomes one year after hospitalization.

Introduction

Community-acquired pneumonia (CAP) causes significant morbidity and causes more deaths in the US than any other infectious disease.[1] Approximately 23% percent of CAP is attributed to viruses.[2] That figure is made up of multiple viruses including: human rhinovirus, influenza A and B viruses, respiratory syncytial virus, parainfluenza virus types 1, 2, and 3, and coronaviruses 229E, OC43, NL63, and HKU1 among others. Presently, there is an interest in CAP due to the *Coronoviridae* family. Clinical aspects of the disease are well described in children, but not adults, especially with CAP. The Middle East Respiratory Syndrome (MERS-CoV), severe acute respiratory syndrome (SARS-CoV), and now the novel 2019 coronavirus (SARS-CoV-2) are well known, and fortunately not endemic like the others.

Coronaviruses are enveloped, single-stranded RNA viruses characterized by club-like spikes that project from their surface. Genera that can cause human disease include alphacoronaviridae and betacoronaviridae. Endemic strains of human coronavirus

(HCoV) include -229E, -OC43, -NL63 and -HKU1. These strains are associated mainly with illnesses of the upper respiratory and gastrointestinal tracts consistent with a common cold. Approximately 90% of epidemiological data is from samples obtained from children; it exhibits winter seasonality, a prevalent strain that varies year to year, and at least one strain, HCoV-OC43, that has a higher correlation with infections of the lower respiratory tract.[3,4] There is minimal existing data of adults with CAP due to HCoV. On the other hand, the clinical course of influenza with CAP and its outcomes have been well described, so it serves as a familiar infection to which HCoV with CAP may be compared.

In Louisville, KY, nasopharyngeal specimens were collected as standard of care for viral testing over three years in adult patients admitted with CAP.[5] Among those specimens were patients with viral infections, including influenza virus and HCoV. From those data, we sought to evaluate incidence, epidemiology, and outcomes of hospitalized adults with CAP due to endemic HCoV and compare them to CAP due to influenza virus.

Methods

This was a secondary analysis of adult patients from the Louisville Pneumonia Study; a large prospective population-based cohort study of hospitalized adults with CAP aged ≥18 years in Louisville, Kentucky. The primary study was performed in all nine adult acute-care hospitals in Louisville over three years, from June 1, 2014 to May 31, 2016 and from October 1, 2016 to March 31, 2017. It included 7,449 patients and defined incidence, epidemiology, and mortality of adult patients hospitalized with CAP in an entire city.[5] The study was exempt from informed consent. Both studies were approved by the research offices at each participating hospital, and by the Institutional Review Board (IRB number 11.0615).

Patients meeting screening requirements were further screened using the following inclusion criteria: positive lung imaging for CAP by chest radiograph or chest computed tomography plus one clinical criterion addressing cough, temperature or white blood cell count.[5] Patients with HCoV or influenza presented once in the study period. Multiple co-infections were acceptable for inclusion, with the exception of HCoV and influenza viruses together. Exclusion criteria were as follows: non-Louisville residency, incarceration, a diagnosis of pneumonia more than 72 hours after admission, a lack of a social security number and laboratory tests positive for both HCoV and influenza virus in the same patient.

Variables evaluated in the medical record at the time of enrollment are in **Table 1**. Pneumonia severity was measured using the pneumonia severity index. The four endemic strains HCoV-229E, -OC43, -NL63 and -HKU1, as well as influenza A and B, were detected by routine standard of care from a nasopharyngeal swab. Time to clinical stability was followed up to seven days as defined previously.[6] It required attaining four clinical criteria. Length of hospital stay was calculated by subtracting the date of admission from the date of discharge up to 14 days; after that time-period, length of stay was censored in an effort to capture length of stay only related to CAP. All-cause mortality was measured as in-hospital, 30-day, 6-month and 1-year.

Continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as frequencies and percentages. Mann-Whitney U tests and Chi-Squared tests were used to compare baseline characteristics between groups where appropriate. A Kaplan-Meier curve for time to mortality was produced. Survival times were compared using log-rank tests.

Results

Patients that had PCR viral tests performed in the study totaled 1,974. Among the excluded patients, one tested positive for both HCoV and influenza. Sixty-five patients had HCoV, and 244 had influenza virus. There were 23 HCoV patients with a co-infection and 45 influenza patients with a co-infection.(**Figure 1**) Serotypes identified in the 65 patients included: 229E in 12 patients, OC43 in 38 patients, NL63 in 6 patients, and HKU1 in 9 patients.

Epidemiology
The median age for patients with HCoV was 69 years, and with influenza was 68 years.(**Table 1**) The distribution of patients by age was highest for ages ≥65 years.(**Figure 2**) Female patients comprised 53% of patients with HCoV, and 57% of patients with influenza. Comorbidities were similar in both groups with four exceptions that were small, but statistically significant: body mass index (BMI), temperature, platelet count and white blood cell count.(**Table 1**) The proportion with two or greater comorbidities was 57% in both groups. More viral tests were performed during winter months, November to March, and the incidences for HCoV and influenza were higher during that time.(**Figure 3**)

Table 1. Characteristics of hospitalized adults admitted with community-acquired pneumonia with a positive test for either endemic human coronavirus or influenza virus. Frequency with percent or median with the interquartile range is used as marked accordingly.

Variable	Coronavirus	Influenza	*P*
Total no.	65	244	
Demographics			
Age, median [IQR]	69 [52, 79]	68 [56, 79]	0.607
Sex: Male, Frequency (%)	28 (43)	115 (47)	0.658
Race, Frequency (%)			0.078
Black	7 (11)	51 (21)	
White	58 (89)	188 (77)	
Other	0 (0)	5 (2)	
Current Smoker	16 (25)	72 (30)	0.534
Nursing Home Resident (%)	5 (8)	21 (9)	>0.999
Comorbidities	**Frequency (%)**		
HIV	0 (0)	5 (2)	0.542
Neoplastic disease	11 (17)	23 (9)	0.135
Congestive Heart Failure	12 (18)	56 (23)	0.543
Cerebrovascular Disease	10 (15)	23 (9)	0.248
Cirrhosis	1 (2)	5 (2)	>0.999
Liver Disease	4 (6)	14 (6)	>0.999
Renal Disease	14 (22)	65 (27)	0.498
Diabetes	19 (29)	82 (34)	0.603
COPD	25 (38)	108 (44)	0.485
BMI, median [IQR]	25 [22, 29]	28 [23, 33]	**0.035**
Obesity (BMI > 30)	15 (23)	89 (36)	0.060
Laboratory and Physical Findings	**Median [IQR]**		
Temperature (°C)	37 [37, 39]	38 [37, 39]	**0.010**
Diastolic blood pressure (mm Hg)	58 [49, 69]	57 [48, 66]	0.767
Systolic Blood Pressure (mm Hg)	115 [103, 131]	118 [100, 132]	0.844
Respiratory Rate (breaths/minute)	23 [20, 28]	22 [20, 27]	0.599
Heart Rate (beats/minute)	108 [94, 122]	104 [91, 118]	0.268
Serum Glucose (mg/dL)	144 [117, 197]	139 [113, 187]	0.393
Platelets per 1000/µL	231 [173, 282]	184 [152, 238]	**0.002**
Serum creatinine (mg/dL)	1 [1, 1]	1 [1, 1]	0.166
Serum Potassium (mEq/L)	4 [4, 4]	4 [4, 4]	0.304
Serum sodium (mEq/L)	136 [134, 140]	136 [134, 140]	0.897
Blood Urea Nitrogen (mg/dL)	17 [13, 23]	18 [13, 26]	0.929
WBC per 1000/µL	12 [10, 17]	9 [6, 13]	**<0.001**
Hemoglobin (g/dL)	12 [11, 13]	12 [11, 13]	0.691
Hematocrit (%)	36 [32, 39]	37 [33, 41]	0.356
Severity of Disease (on admission)	**Frequency (%)**		
Ventilatory Support	4 (6)	23 (9)	0.560
Vasopressors	2 (3)	5 (2)	0.979
PSI Risk Class IV/V	40 (62)	133 (55)	0.382
Altered Mental Status	11 (17)	37 (15)	0.877
Direct Admission to the ICU	12 (18)	30 (12)	0.278

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; PSI, pneumonia severity index; WBC white blood cell count
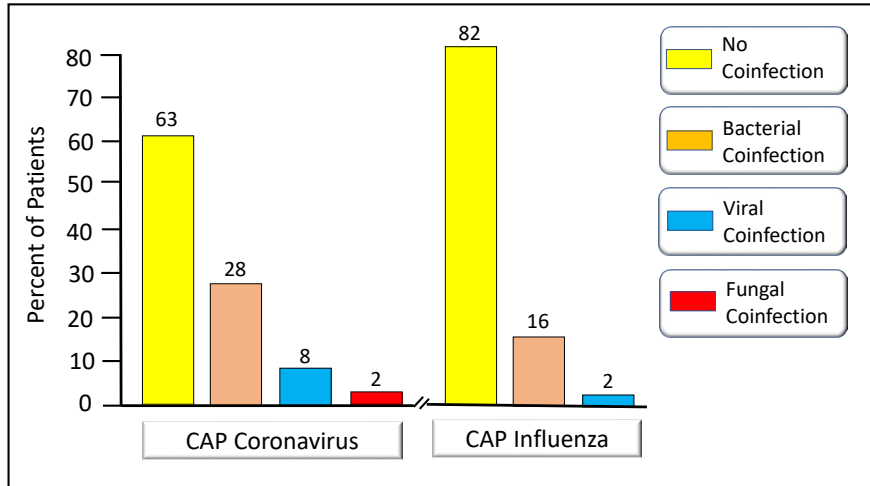
Figure 1. The proportion of each type of co-infection among hospitalized adults admitted with community-acquired pneumonia with either endemic coronavirus or influenza.
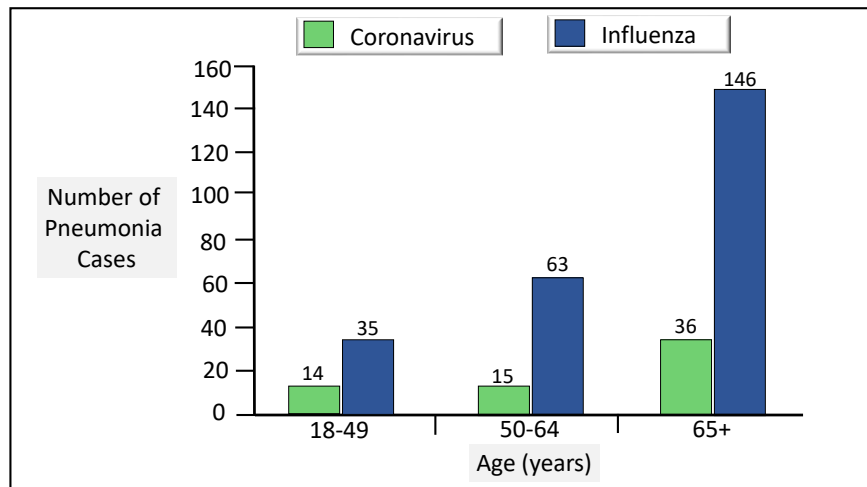

Figure 2. Characteristics of hospitalized adults admitted with community-acquired pneumonia with a positive test for either endemic human coronavirus or influenza virus.

Imaging
A representative chest radiograph of a patient with CAP due to HCoV showed a lobar infiltrate.(**Figure 4**) Older adults with comorbidities, such as chronic obstructive pulmonary disease, and a co-infection had infiltrates concomitant with chronic lung disease.(**Figure 4**)

Outcomes
No differences in early outcomes were found.(**Table 2**) For the entire population, the median time to clinical stability was 2 days with an interquartile range (IQR) of 1-4 days, and the length of stay was 4 days with an interquartile range of 3-7 days. Mortality was higher in those with influenza for in-hospital and 30-day mortality (*P*>0.05), while it was higher in those with HCoV for 6-month (*P*>0.05) and 1-year mortality (*P*=0.041).(**Table 2**) One-year survival is shown in **Figure 5**, with significant differences in survival found between the two groups (*P*=0.048).

Discussion

Our data showed that outcomes, including time to clinical stability, length of stay and mortality up to six months were similar to influenza, but the 1-year mortality was statistically different with 32% among HCoV patients and 17% among influenza patients. The reason for this difference in mortality is unknown; however, it is clear that the *Coronaviridae* family, including MERS-CoV, SARS-CoV and SARS-CoV-2, has the potential to cause significant morbidity and mor-
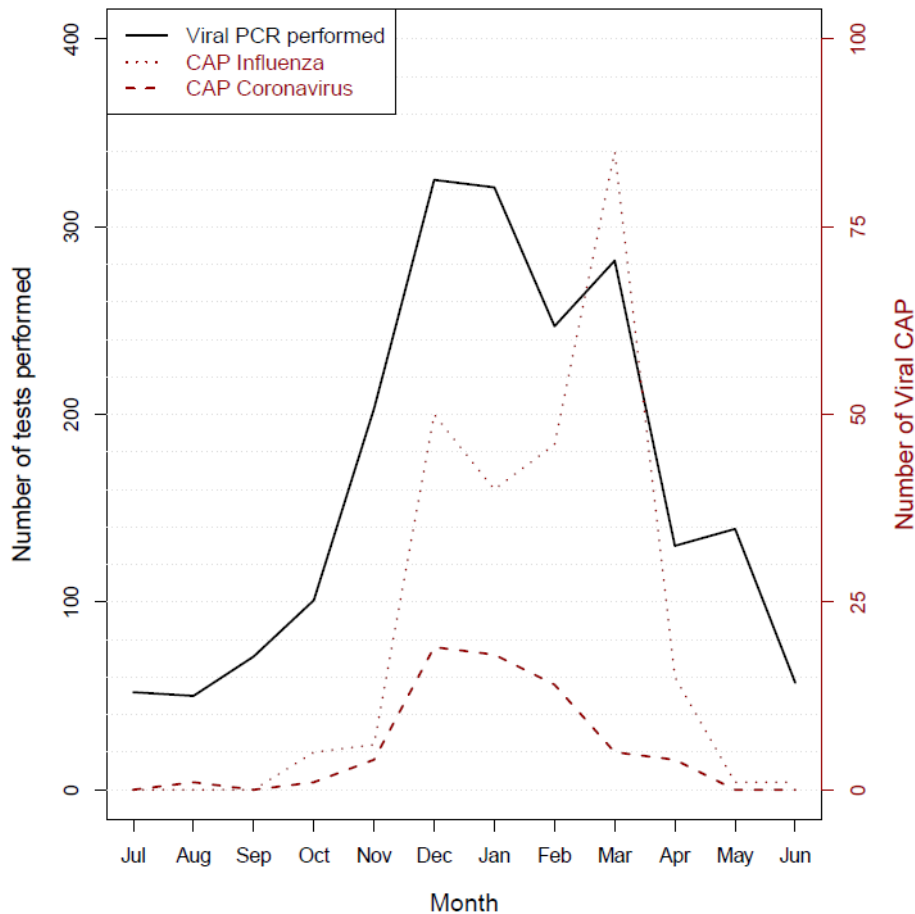
Figure 3. The incidences of endemic human coronavirus and influenza during each month of the three-year study for hospitalized adults admitted with community-acquired pneumonia.

tality. The incidence of HCoV CAP in our study was 3.6%. This figure is similar to what has been reported in the literature.[2,7]

Demographics were similar overall as well with most cases occurring in patients >65 years and in 57% having at least two comorbidities. There were a few statistically significant differences, including temperature, platelet count, white blood count, and body mass index, but the difference in platelet count between each group was not clinically significant.

For patients admitted with CAP, there did not appear to be any clinically discernable difference when considering a patient's hospital course, but this data reveals that a difference was found compared to influenza among patients after a year had passed. Physicians and other primary care professionals should be aware of the long-term consequences that a seemingly innocuous HCoV may have later for patients, especially if they are older or have comorbidities.

Most publications regarding adults with CAP due to HCoV are case reports or a series of ten or fewer patients. Although studies exist with larger sample sizes tested, all reported similarly small numbers of positive patients.[8-20] (**Table 3**) In one study of patients with CAP, 254 viral PCR tests were performed and only seven patients were positive for HCoV.[17] In another study of patients with lower respiratory tract infections, 3,104 viral PCR tests were performed and only six patients were positive for HCoV.[21] Two studies included other potentially relevant patients, but children and adults were reported together in one study and rhinovirus and HCoV were reported together in another study. [22,23] Overall, 52 cases have been reported until this study; six of whom died.

Patient characteristics for adults with CAP due to viral etiologies in general have been described. In a study of 78 patients with suspected CAP and a positive viral PCR test, the most common viruses were influenza (35%), rhinovirus (26%), RSV (9%), and coronavirus (9%).[17] The median patient age was 60 and the predominant clinical features were

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(**a**)

(**b**)

Figure 4. A representative chest radiograph of a 64-year-old female hospitalized with community-acquired pneumonia with a test positive for endemic human coronavirus (no co-infection) (**a**) and a similar patient, but who had chronic obstructive pulmonary disease (**b**).

Table 2. Outcomes of hospitalized adults admitted with community-acquired pneumonia with a positive test for either endemic human coronavirus or influenza. Frequency with percent or median with the interquartile range is used as marked accordingly.

Variable	Coronavirus	Influenza	*P*
Total no.	65	244	
Time to clinical stability (median [IQR])	3 [1, 5]	2 [1, 4]	0.152
Hospitalized length of stay (median [IQR])	5 [3, 8]	4 [3, 8]	0.621
In-hospital mortality (%)	1 (2)	10 (4)	0.540
30-day mortality (%)	3 (5)	21 (9)	0.418
6-month mortality (%)	14 (22)	31 (13)	0.134
1-year mortality (%)	19 (32)	39 (17)	**0.041**

IQR, interquartile range

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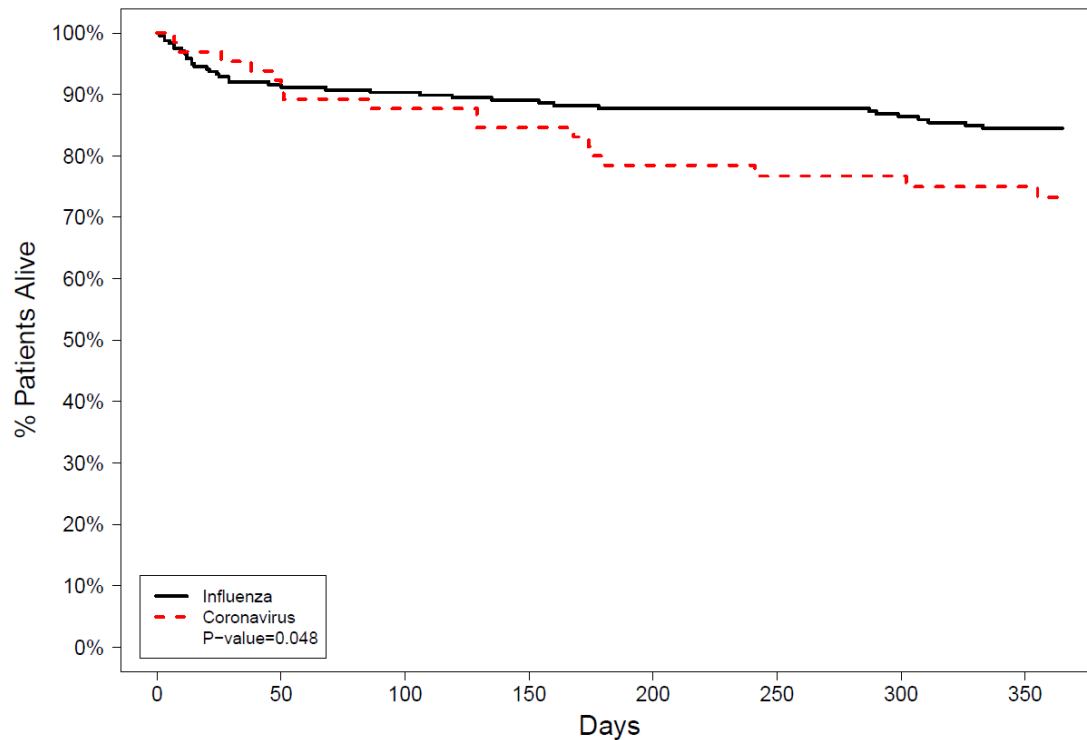

Figure 5. In patients with community-acquired pneumonia, Kaplan-Meier curves for time to mortality over one year were compared between those with endemic human coronavirus and influenza.

Table 3. Manuscripts identifying cases of adult patients hospitalized for community-acquired pneumonia with endemic human coronavirus.

Study	Year	Country	no. cases	HCoV strain	Deaths
Folz et al. [7]	1999	Durham, NC	1	-	0
Falsey et al. [8]	2002	Rochester, NY	2	-	-
van Elden et al. [9]	2002	Netherlands	1	-	0
van Elden et al. [10]	2004	Netherlands	2	-	-
Woo et al. [11]	2005	China	9	HKU1	2
Johnstone et al. [12]	2008	Canada	4	OC43	-
Oosterhof et al. [13]	2010	Denmark	1	NL63	1
van Gageldonk et al. [14]	2013	Netherlands	6	-	-
Zhan et al. [15]	2014	China	2	OC43	0
Das et al. [16]	2015	France	6 (**a**)	not HKU1	-
Mayer et al. [17]	2016	Germany	1	NL63	1
Galante O et al. [18]	2016	Israel	1	NL63	1
Pianana et al. [19]	2017	Spain	7 (**b**)	OC43, NL63	1
Ieven et al. [20]	2018	11 European countries	6	-	-
Arnold et al. (Present study)	2020	Louisville, KY	65	229E, OC43, NL63, HKU1	3 (**c**)

a.   Five definite cases, one probable and one possible.
b.   Three confirmed cases due to NL63, and four possible due to OC43.
c.   30-day mortality.

cough (92%), dyspnea (74%), sputum production (62%), and fever (36%). The most common underlying comorbidity was chronic lung disease, with 27% of the patients affected. Comparatively, in the nine adults with CAP due to HCoV-HKU1 described by Woo et al, the mean age was slightly older at 71 and the predominating symptoms were again fever (80%), cough (70%), sputum production (60%), and dyspnea (60%).[12] Seven of the nine patients had underlying comorbidities with three patients having underlying lung disease. Notably, two of the nine patients did die, and both had severe underlying comorbidities including malignancy. Overall, the patient characteristics were essentially clinically indistinguishable from other CAP illnesses.

One limitation of the present study was that viral PCR panels were obtained primarily during the winter seasons as standard of practice. Another limitation of the study was that co-infections might bias the comparisons between groups. One strength of the present study was that it nearly doubled the number of cases of HCoV CAP reported in the literature, providing a significant contribution to the epidemiology of the disease.

In conclusion, HCoV is found in 3% of patients hospitalized for CAP. The clinical presentation is similar to CAP caused by influenza. It is unclear, however, why patients with HCoV CAP have twice the one-year mortality compared to those with influenza CAP.

Acknowledgements

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Appendix: Center of Excellence for Research in Infectious Diseases (CERID) Coronavirus Study Group

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