Clinical Features and Outcomes of Severe Pneumonia Caused by Endemic Human Coronavirus in Adults

To the Editor:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has the potential to become the fifth endemic human coronavirus (eHCoV), which would lead to severe SARS-CoV-2–associated pneumonia occurring seasonally (1). A better understanding of eHCoV-associated pneumonia would help prepare for the postpandemic era. Using 10-year prospective cohort data, we evaluated the clinical characteristics and outcomes of severe eHCoV-associated pneumonia compared with those of severe influenza virus (IFV)–associated pneumonia.

Methods

This study, nested in a prospective cohort of severe pneumonia, was conducted at a 2,700-bed tertiary hospital in Seoul, South Korea (2). We included patients admitted to the ICU because of severe eHCoV- or IFV-associated pneumonia between March 2010 and February 2020. Hospital-acquired pneumonia and community-acquired pneumonia (CAP) in adults were defined at the time of pneumonia suspicion as described previously (2). Microbiological evaluation was performed as described previously (2). Respiratory viruses were identified from nasopharyngeal swabs, nasopharyngeal aspirates, and BAL fluids, using the Allplex Respiratory Panel 1, 2, 3 (Seegene Inc.). Chi-square, Fisher exact, Student's *t*, and Mann-Whitney *U* tests were used as appropriate. Survival analysis was performed using the Kaplan-Meier method with the log-rank test. Variables with *P* values of less than 0.10 in the univariate analysis were included in the multivariate logistic regression analysis to identify independent risk factors for severe pneumonia.

Results

After excluding nine patients who had coinfection with eHCoV and IFV, 85 patients with eHCoV and 177 patients with IFV were analyzed (Table 1). In the eHCoV group, 43 and 41 patients were infected with human coronavirus (HCoV)–OC43/HKU1 and HCoV-229E/NL63, respectively, and 1 patient was coinfected with HCoV-OC43/HKU1 and HCoV-229E/NL63. There were no significant differences in the age or sex distribution between the eHCoV and IFV groups. CAP accounted for the majority of patients in both groups (76.5% vs. 74.0%; $P = 0.67$). The most common underlying diseases were structural lung disease and malignancy in both groups. Underlying immunocompromised state (63.5% vs. 37.3%; $P < 0.001$) and liver cirrhosis (5.9% vs. 1.1%; $P = 0.04$) were significantly more common in the eHCoV group. The eHCoV group had significantly higher rates of viral (18.8% vs. 8.5%; $P = 0.02$) and fungal (15.3% vs. 6.2%; $P = 0.02$) coinfection and a lower rate of *Staphylococcus aureus* coinfection (1.2% vs. 9.0%; $P = 0.02$). The dominant radiologic pattern was bronchopneumonia in both groups; however, although bronchopneumonia was more common in the IFV group (58.2% vs. 42.4%; $P = 0.02$), interstitial pneumonia was more common in the eHCoV group (32.9% vs. 21.5%; $P = 0.045$).

In the eHCoV group, steroids were given to 69 (81.2%) patients, whereas oral ribavirin and intravenous immunoglobulin were administered to 11 (12.9%) and 19 (22.4%) patients, respectively. The 90-day mortality rate was significantly higher in the eHCoV group than in the IFV group (67.1% vs. 44.6%; $P = 0.001$; Figure 1). A sensitivity analysis comparing patients infected with HCoV-OC43/NL63 and those in the IFV group yielded similar 90-day mortality results to the main analysis. In subgroup analysis, patients with nonimmunocompromised status (58.1% vs. 31.5%; $P = 0.01$), CAP (67.7% vs. 38.2%; $P < 0.001$; Figure 1), and bacterial coinfection (68.2% vs. 38.1%; $P = 0.02$) and those without coinfection (71.4% vs. 44.8%; $P = 0.03$) in the eHCoV group had a significantly higher 90-day mortality rate than those in the IFV group. In the eHCoV group, multivariate analysis, which included age, shock, structural lung disease, body mass index (BMI) < 18.5 kg/m^2, and use of oral ribavirin, indicated that age (for each increase of 1 yr: adjusted odds ratio [aOR], 1.05; 95% confidence interval [CI], 1.01–1.09) and BMI < 18.5 kg/m^2 (aOR, 14.36; 95% CI, 1.53–134.53) were independent risk factors of 90-day mortality. In patients with severe CAP, age (aOR, 1.05; 95% CI, 1.02–1.07; $P = 0.001$), interstitial lung disease (aOR, 3.20; 95% CI, 1.01–10.08; $P = 0.047$), immunocompromised status (aOR, 4.54; 95% CI, 2.27–9.09; $P < 0.001$), and eHCoV infection (aOR, 2.60; 95% CI, 1.29–5.24; $P = 0.01$) were independent risk factors of 90-day mortality in the multivariate analysis, which included age, ribavirin, steroid, solid cancer, interstitial lung disease, immunocompromised status, Acute Physiology and Chronic Health Evaluation II score, and eHCoV infection.

Discussion

We found that coinfection with *S. aureus* was less common in the eHCoV group than in the IFV group. The investigators of a previous study speculated that IFV-induced type 1 IFN promotes post-IFV *S. aureus* pneumonia by inhibiting T-helper cell type 17 immunity, which results in insufficient *S. aureus* clearance (3). Also, it was shown that HCoV-OC43 infection did not induce IFN-β expression (4). Strong type 1 IFN response was documented in severe coronavirus disease (COVID-19) caused by SARS-CoV-2, but not in mild COVID-19 (5). In a French study, *S. aureus* was the most common copathogen of severe COVID-19 (6). The types of viruses, disease severity, and host immune response could be responsible for this different pattern of coinfection.

The 90-day mortality of severe pneumonia in the eHCoV group (67.1%) was significantly higher than that in the IFV group in our study and was comparable to that of COVID-19 (31–50%) (7, 8). However, our mortality data should be interpreted with caution because only 12.9% of patients in the eHCoV group had received oral ribavirin, and there is no effective antiviral treatment for eHCoV to date. It is notable that BMI < 18.5 kg/m^2 was a risk factor of 90-day

Author Contributions: H.C. and S.-B.H. drafted the manuscript. J.W.H. helped conduct the study and collect the data. H.S. and K.-H.D. interpreted the data. S.-O.L., Y.K., and S.-H.C. critically reviewed the manuscript. C.-M.L. and S.-H.C. contributed to the conception and design of the study. All authors read and approved the final version of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202112-2797LE on February 4, 2022

Table 1. Characteristics of Patients with Severe Human Coronavirus–associated and Influenza Virus–associated Pneumonia

	Total (*N* = 262)	Coronavirus (*n* = 85)	Influenza Virus (*n* = 177)	*P* Value
Demographics				
Male sex	171 (65.3)	59 (69.4)	112 (63.3)	0.33
Age, yr, median (IQR)	68.0 (57.0–76.0)	68.0 (57.0–75.0)	68.0 (57.5–77.0)	0.46
Underlying disease or condition*				
Structural lung disease	70 (26.7)	21 (24.7)	49 (27.7)	0.61
Chronic obstructive lung disease	31 (11.8)	8 (9.4)	23 (13.0)	0.40
Interstitial lung disease	26 (9.9)	12 (14.1)	14 (7.9)	0.12
Bronchiectasis	8 (3.1)	0	8 (4.5)	0.06
Destroyed lung due to tuberculosis	3 (1.1)	1 (1.2)	2 (1.1)	1.00
Pneumoconiosis	2 (0.8)	0	2 (1.1)	1.00
Diabetes mellitus	59 (22.5)	16 (18.8)	43 (24.3)	0.32
Solid cancer	43 (16.4)	19 (22.4)	24 (13.6)	0.07
Hematologic malignancy	38 (14.5)	15 (17.6)	23 (13.0)	0.32
End-stage renal disease	16 (6.1)	3 (3.5)	13 (7.3)	0.23
Hematopoietic stem cell transplantation	11 (4.2)	4 (4.7)	7 (4.0)	0.75
Solid organ transplantation	8 (3.1)	4 (4.7)	4 (2.3)	0.28
Liver cirrhosis	7 (2.7)	5 (5.9)	2 (1.1)	0.04
Immunocompromised state†	120 (45.8)	54 (63.5)	66 (37.3)	<0.001
Body mass index, kg/m^2				
<18.5 (underweight)	47 (17.9)	17 (20.0)	30 (16.9)	0.55
18.5–24.9 (normal weight)	157 (59.9)	52 (61.2)	105 (59.3)	0.77
⩾25.0 (overweight)	52 (19.8)	13 (15.3)	39 (22.0)	0.20
⩾30.0 (obese)	6 (2.3)	3 (3.5)	3 (1.7)	0.39
Category of pneumonia				
Community-acquired pneumonia	196 (74.8)	65 (76.5)	131 (74.0)	0.67
Hospital-acquired pneumonia	66 (25.2)	20 (23.5)	46 (26.0)	0.67
Manifestation				
Dyspnea	224 (85.5)	72 (84.7)	152 (85.9)	0.80
Fever > 38°C	219 (83.6)	68 (80.0)	151 (85.3)	0.28
Cough	206 (78.6)	64 (75.3)	142 (80.2)	0.36
Sputum	195 (74.4)	61 (71.8)	134 (75.7)	0.49
Septic shock at ICU admission	158 (60.3)	46 (54.1)	112 (63.3)	0.16
Mechanical ventilation	257 (98.1)	84 (98.8)	173 (97.7)	1.00
APACHE II score, median (IQR)	26.0 (20.0–30.0)	27.0 (22.0–32.0)	25.0 (20.0–29.0)	0.04
SOFA score, median (IQR)	10.0 (7.0–12.0)	10.0 (7.5–12.0)	9.0 (7.0–12.0)	0.25
Coinfection				
Any coinfection	124 (47.3)	43 (50.6)	81 (45.8)	0.46
Bacterial coinfection	85 (32.4)	22 (25.9)	63 (35.6)	0.12
Viral coinfection	31 (11.8)	16 (18.8)	15 (8.5)	0.02
Fungal coinfection	24 (9.2)	13 (15.3)	11 (6.2)	0.02
Mycobacterial coinfection	5 (1.9)	2 (2.4)	3 (1.7)	0.66
Dominant radiologic pattern				
Bronchopneumonia	139 (53.1)	36 (42.4)	103 (58.2)	0.02
Interstitial pneumonia	66 (25.2)	28 (32.9)	38 (21.5)	0.045
Lobar pneumonia	51 (19.5)	21 (24.7)	30 (16.9)	0.14
Other	6 (2.3)	0	6 (3.4)	0.18

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range; SOFA = sequential organ failure assessment.

Data are presented as *n* (%) unless otherwise stated.

*Some patients had one or more underlying diseases or conditions.

†Defined as one of the following conditions: *1*) daily receipt of immunosuppressants, including corticosteroids; *2*) HIV infection; *3*) solid organ or hematopoietic stem cell transplantation; *4*) receipt of chemotherapy for underlying malignancy during the previous 6 months; and *5*) underlying immune deficiency disorder.

mortality in severe eHCoV-associated pneumonia. The association between BMI and infectious disease–related mortality has been controversial, with some studies reporting that obesity was associated with lower mortality in hospitalized patients with pneumonia (i.e., obesity paradox) and that being underweight was a risk factor of mortality (9). The prevalence of obese individuals is lower in South Korea than in Western countries (10); accordingly, only six (2.3%) patients in this study were categorized as obese, which limited the proper evaluation of the impact of obesity.

This study has several limitations. First, our findings are based on a single-center cohort and may not be generalizable to other populations. Second, fewer than half of the patients (48.2% of the eHCoV group and 27.1% of the IFV group) were tested using BAL samples. We may have included coincidental upper respiratory viral

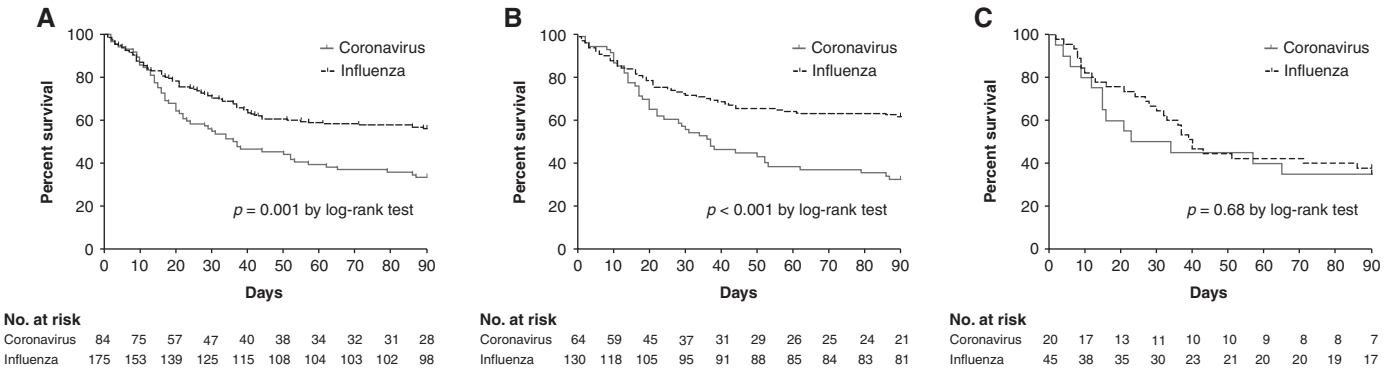

Figure 1. Kaplan-Meier survival curves for patients with severe endemic human coronavirus–associated and influenza virus–associated pneumonia during 90 days after ICU admission. (*A*) Overall patients. (*B*) Patients with community-acquired pneumonia. (*C*) Patients with hospital-acquired pneumonia.

infection or colonization in cases in which viruses were isolated only from upper respiratory tract specimens. There may be bias in detecting superinfection pneumonia. Third, we could not differentiate the strain types of eHCoVs and grouped them into HCoV-OC43/HKU1 and HCoV-229E/NL63.

In conclusion, severe eHCoV-associated pneumonia had a significantly higher mortality rate than severe IFV-associated pneumonia. Adult patients with eHCoV were more likely to be immunocompromised and less likely to have *S. aureus* coinfection. Special attention should be given to elderly and underweight patients with severe eHCoV-associated pneumonia. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Hyemin Chung, M.D.*
Sang-Bum Hong, M.D., Ph.D.*
Jin Won Huh, M.D., Ph.D.
Heungsup Sung, M.D., Ph.D.
Kyung-Hyun Do, M.D., Ph.D.
Sang-Oh Lee, M.D., Ph.D.
Chae-Man Lim, M.D., Ph.D.
Younsuck Koh, M.D., Ph.D.
Sang-Ho Choi, M.D., Ph.D.‡
University of Ulsan College of Medicine
Seoul, Republic of Korea

ORCID IDs: 0000-0002-4447-975X (H.C.); 0000-0003-2737-7695 (S.-B.H.); 0000-0002-3449-0461 (J.W.H.); 0000-0002-6062-4451 (H.S.); 0000-0003-1922-4680 (K.-H.D.); 0000-0003-1381-8787 (S.-O.L.); 0000-0001-5400-6588 (C.-M.L.); 0000-0001-5066-2027 (Y.K.); 0000-0002-4972-4531 (S.-H.C.).

*These authors contributed equally to this letter.
‡Corresponding author (e-mail: sangho@amc.seoul.kr).

References

1. Veldhoen M, Simas JP. Endemic SARS-CoV-2 will maintain post-pandemic immunity. *Nat Rev Immunol* 2021;21:131–132.
2. Choi SH, Huh JW, Hong SB, Jung J, Kim MJ, Chong YP, *et al.* Severe human bocavirus–associated pneumonia in adults at a referral hospital, Seoul, South Korea. *Emerg Infect Dis* 2021;27:226–228.
3. Kudva A, Scheller EV, Robinson KM, Crowe CR, Choi SM, Slight SR, *et al.* Influenza A inhibits Th17-mediated host defense against bacterial pneumonia in mice. *J Immunol* 2011;186:1666–1674.
4. Loo SL, Wark PAB, Esneau C, Nichol KS, Hsu AC, Bartlett NW. Human coronaviruses 229E and OC43 replicate and induce distinct antiviral responses in differentiated primary human bronchial epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2020;319:L926–L931.
5. Lee JS, Park S, Jeong HW, Ahn JY, Choi SJ, Lee H, *et al.* Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. *Sci Immunol* 2020;5:eabd1554.
6. Contou D, Claudinon A, Pajot O, Micaëlo M, Longuet Flandre P, Dubert M, *et al.* Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. *Ann Intensive Care* 2020; 10:119.
7. COVID-ICU Group on Behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med* 2021;47:60–73.
8. Li Y, Meng Q, Rao X, Wang B, Zhang X, Dong F, *et al.* Corticosteroid therapy in critically ill patients with COVID-19: a multicenter, retrospective study. *Crit Care* 2020;24:698.
9. King P, Mortensen EM, Bollinger M, Restrepo MI, Copeland LA, Pugh MJ, *et al.* Impact of obesity on outcomes for patients hospitalised with pneumonia. *Eur Respir J* 2013;41:929–934.
10. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; 384:766–781.