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Outcomes of severe human metapneumovirus-associated community-acquired pneumonia in adults

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ABSTRACT

Background: The outcomes of severe human metapneumovirus (HMPV)-associated pneumonia have not been adequately evaluated.
Objectives: We aimed to investigate the incidence and outcomes of severe HMPV-associated CAP and to compare them with those of severe IFV associated CAP.
Study design: From March 2010 to August 2017, all consecutive adult patients with severe HMPV-associated CAP and severe influenza virus (IFV)-associated CAP who required intensive care unit admission were prospectively identified and followed in a 2,700-bed tertiary care hospital. The characteristics and outcomes of severe HMPV-associated CAP patients were compared with those of severe IFV-associated CAP patients.
Results: HMPV and IFV were identified in 3.2% (50) and 7.0% (109) of the 1559 patients with severe CAP, respectively. The mortality rates were not significantly different between the HMPV and IFV groups (30-day mortality: 24.0% vs. 32.1%, p = 0.30; 60-day mortality: 32.0% vs. 38.5%, p = 0.43). Oral ribavirin therapy was not associated with improved outcome (60-day mortality: ribavirin therapy group 35.0% [7/20] vs. no ribavirin therapy group 30.0% [9/30], p = 0.71). Subgroup analyses showed no significant differences in mortality among non-immunocompromised (60-day mortality: HMPV 25.6% vs. IFV 31.1%, p = 0.55) and immunocompromised patients (60-day mortality; HMPV 54.5% vs. 54.3%, p = 0.99). The length of ICU and hospital stay did not differ between groups.
Conclusions: The incidence of HMPV infection was approximately half that of IFV infection in a cohort of patients with severe CAP. The mortality rate of severe HMPV-associated CAP was similar to that of severe IFV associated CAP.

1. Background

Since the first discovery of human metapneumovirus (HMPV) from young children in 2001 [1], HMPV has been recognized as an important agent of upper and lower respiratory tract disease worldwide. Although HMPV infection is regarded as generally mild and self-limiting in adults, it is gaining increased attention as the cause of severe pneumonia [2–4]. However, few investigators have addressed the outcomes of adults with severe HMPV-associated community-acquired pneumonia (CAP) requiring intensive care unit (ICU) admission [5,6]. Outcome analyses of prior ICU studies have been limited by its retrospective design, relatively small number of patients, lack of adequate control groups, and heterogeneous study populations.

Abbreviations: HMPV, human metapneumovirus; CAP, community-acquired pneumonia; ICU, intensive care unit; IFV, influenza virus; IVIG, intravenous immunoglobulin; APACHE, acute physiological and chronic health evaluation; SOFA, sequential organ failure assessment

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2. Objective

We aimed to investigate the incidence and outcomes of adult patients with severe HMPV-associated CAP and to compare them with those of patients with severe IFV-associated CAP.

3. Study design

This study is a part of an ongoing prospective observational cohort study in the 28-bed medical ICU of Asan Medical Center, a 2,700-bed university-affiliated tertiary care hospital in Seoul, Korea [7,8]. All patients aged ≥16 years admitted to the medical ICU with severe CAP from March 2010 to August 2017 were included. This study was approved by the Institutional Review Board of Asan Medical Center. Using a standardized protocol, investigators prospectively collected detailed data on demographics, comorbidities, medications, clinical and laboratory findings, the severity of illness score, management, and outcome information. The microbiological evaluation was performed as described previously [7,8]: respiratory viruses were identified from nasopharyngeal swabs, nasopharyngeal aspirates, and bronchoscopic lavage (BAL) fluids, and the microorganisms identified from specimens collected ≤ 72 h after hospital admission were considered CAP pathogens. The main outcome was all-cause 60-day mortality. The characteristics and outcomes of severe HMPV-associated CAP patients were compared with those of severe IFV-associated CAP patients. Subgroup analyses were performed according to the presence or absence of immunocompromised condition [9]. Categorical variables were compared using the chi-square test or Fisher's exact test, and continuous variables were compared using the Mann-Whitney *U* test. p values of < 0.05 were considered significant. All analyses were performed using SPSS for Windows version 23.0 (IBM SPSS, Armonk, New York).

4. Results

4.1. Distribution of respiratory virus pathogens and patient characteristics

In total, 1559 patients with severe CAP were admitted to the medical ICU. One or more pathogens were identified in 65.9% (1,027/1559) of patients. Overall, rhinovirus was the most commonly identified virus (7.7%, n = 120), followed by influenza virus (7.0%, n = 109), parainfluenza virus (4.6%, n = 71), human coronavirus (3.6%, n = 56), respiratory syncytial virus (3.3%, n = 52), and HMPV (3.2%), n = 50).

Table 1 lists the characteristics of the enrolled patients. The median ages of the HMPV group and the IFV group were 70.0 years and 68.0 years, respectively. Diabetes mellitus, structural lung disease, malignancy, and end-stage renal disease were the most common underlying diseases in both groups. Of these, diabetes mellitus was significantly more common in the HMPV group (38.0% vs. 21.1%, $p = 0.03$). Eleven patients (22.0%) in the HMPV group and 35 (32.1%) in the IFV group were categorized as immunocompromised, respectively ($p = 0.19$). Fever (> 38°C) tended to be more common in the IFV group ($p = 0.07$). Otherwise, the initial manifestations were similar between the groups. Co-pathogens were less commonly found in the HMPV group (30.0% vs. 48.6%, $p = 0.03$). The detailed composition of co-infections is summarized in Supplementary Table 1. The most common dominant radiology pattern was bronchopneumonia in both groups (66.0% vs. 57.8%, $p = 0.33$). Supplementary Figure 1 shows the monthly distribution of HMPV and IFV cases during the study period. Severe HMPV and IFV-associated CAP occurred predominantly from January to June and December to April, respectively. This finding was consistent with the observed pattern of HMPV and IFV incidence in the community. Of 50 HMPV patients, 20 (40.0%) were administered oral ribavirin therapy for more than 48 h, and 5 were administered intravenous immunoglobulin (IVIG) therapy. Six patients were administered IVIG therapy alone.

Table 1
Characteristics of 50 severe human metapneumovirus-associated community-acquired pneumonia and 109 severe influenza virus-associated community-acquired pneumonia patients.

Characteristic	Human metapneumovirus (n = 50)	Influenza virus (n = 109)	p value
Demographics			
Male sex	32 (64.0)	64 (58.7)	0.53
Median age, yr (interquartile range)	70.0 (55.0–75.3)[a]	68.0 (57.5–76.5)[b]	0.97
Underlying diseases or conditions			
Diabetes mellitus	19 (38.0)	23 (21.1)	0.03
Structural lung disease	15 (30.0)	33 (30.3)	0.97
Chronic obstructive pulmonary disease	8 (16.0)	14 (12.8)	0.59
Interstitial lung disease	6 (12.0)	9 (8.3)	0.56
Tuberculosis destroyed lung	1 (2.0)	3 (2.8)	1.0
Bronchiectasis	0	5 (4.6)	0.33
Pneumoconiosis	0	1 (0.9)	1.0
Bronchiolitis obliterans	0	1 (0.9)	1.0
End-stage renal disease	8 (16.0)	8 (7.3)	0.09
Heart failure	7 (14.0)	8 (7.3)	0.24
Chronic renal failure	5 (10.0)	5 (4.6)	0.29
Solid cancer	4 (8.0)	12 (11.0)	0.56
Hematologic malignancy	3 (6.0)	13 (11.9)	0.25
Immunocompromised state[c]	11 (22.0)	35 (32.1)	0.19
Manifestation			
Fever (> 38 °C)	35 (70.0)	90 (82.6)	0.07
Cough	42 (84.0)	97 (89.0)	0.38
Sputum	39 (78.0)	88 (80.7)	0.69
Dyspnea	43 (86.0)	97 (89.0)	0.59
Septic shock at admission	25 (50.0)	69 (63.3)	0.11
Mechanical ventilation	45 (90.0)	101 (92.7)	0.55
APACHE II score (mean ± SD)	25.5 ± 7.5	24.7 ± 7.5	0.54
SOFA score (mean ± SD)	8.8 ± 3.4	9.1 ± 3.7	0.69
Coinfection[d]	15 (30.0)[e]	53 (48.6)	0.03
Bacterial coinfection	12 (24.0)	39 (35.8)	0.14
Viral coinfection	1 (2.0)	12 (11.0)	0.07
Fungal coinfection	3 (6.0)	4 (3.7)	0.68
Nontuberculous mycobacteria	0	1 (0.9)	1.0
Dominant radiology pattern			
Bronchopneumonia	33 (66.0)	63 (57.8)	0.33
Interstitial pneumonia	11 (22.0)	26 (23.9)	0.80
Lobar pneumonia	6 (12.0)	19 (17.4)	0.38
Septic pneumonia	0	1 (0.9)	1.0

Data are presented as the number (percentage) of patients, unless otherwise indicated.
APACHE, Acute Physiology and Chronic Health Evaluation; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.
[a] Range, 20–92 years.
[b] Range, 17–90 years; one patient was < 18 years old.
[c] Defined as one of the following conditions: (i) daily receipt of immunosuppressants, including corticosteroids; (ii) human immunodeficiency virus infection; (iii) receipt of solid organ or hematopoietic stem cell transplantation; (iv) receipt of chemotherapy for underlying malignancy during the previous 6 months; and (v) presence of underlying immune deficiency disorder.
[d] Detailed lists of co-pathogens are summarized in Supplementary Table 1.
[e] One patient had simultaneous bacterial and fungal coinfection.

4.2. Outcomes

Outcomes of enrolled patients are summarized in Table 2. Supplementary Table 2 includes the outcomes of infection with other respiratory viruses, including human rhinovirus, parainfluenza virus, respiratory syncytial virus, and human coronavirus. The mortality rate was not significantly different between the HMPV group and IFV group (30-day mortality: 24.0% vs. 32.1%, $p = 0.30$; 60-day mortality: 32.0% vs. 38.5%, $p = 0.43$; in-hospital mortality: 38.0% vs. 35.8%, $p = 0.79$). Neither oral ribavirin therapy (60-day mortality: ribavirin therapy group 35.0% [7/20] vs. no ribavirin therapy group 30.0% [9/

Table 2
Outcomes in patients with severe human metapneumovirus-associated pneumonia and influenza virus-associated community-acquired pneumonia.

Outcome	Human metapneumovirus (n = 50)	Influenza virus total (n = 109)	Influenza virus A (n = 93)	Influenza virus B (n = 16)	p value[a]
ICU stay, day (median, IQR)	9.5 (5.0–14.5)	10.0 (6.0–21.0)	11.0 (6.0–21.0)	9.5 (3.5–26.8)	0.28
Hospital-stay (median, IQR)	16.5 (10.0–33.3)	23.0 (13.0–52.5)	25.0 (13.0–57.5)	19.0 (13.3–36.3)	0.11
Complicated by ventilator-associated pneumonia	2 (4.0)	13 (11.9)	11 (11.8)	2 (12.5)	0.15
Mortality					
Non-immunocompromised patients	*n* = 39	*n* = 74	*n* = 64	*n* = 10	
30-day mortality	8 (20.5)	18 (24.3)	15 (23.4)	3 (30.0)	0.65
60-day mortality	10 (25.6)	23 (31.1)	19 (29.7)	4 (40.0)	0.55
90-day mortality	12 (30.8)	25 (33.8)	21 (32.8)	4 (40.0)	0.75
In-hospital mortality	11 (28.2)	20 (27.0)	16 (25.0)	4 (40.0)	0.89
Immunocompromised patients	*n* = 11	*n* = 35	n = 29	*n* = 6	
30-day mortality	4 (36.4)	17 (48.6)	14 (48.3)	3 (50.0)	0.48
60-day mortality	6 (54.5)	19 (54.3)	16 (55.2)	3 (50.0)	0.99
90-day mortality	8 (72.7)	21 (60.0)	18 (62.1)	3 (50.0)	0.50
In-hospital mortality	8 (72.7)	19 (54.3)	16 (55.2)	3 (50.0)	0.32
Total	*n* = 50	*n* = 109	*n* = 93	*n* = 16	
30-day mortality	12 (24.0)	35 (32.1)	29 (31.2)	6 (37.5)	0.30
60-day mortality	16 (32.0)	42 (38.5)	35 (37.6)	7 (43.8)	0.43
90-day mortality	20 (40.0)	46 (42.2)	39 (41.9)	7 (43.8)	0.79
In-hospital mortality	19 (38.0)	39 (35.8)	32 (34.4)	7 (43.8)	0.79

Data are presented as the number (percentage) of patients, unless otherwise indicated.
ICU, intensive care unit; IQR, interquartile range.
[a] Comparison between the human metapneumovirus and total influenza virus groups.

30], $p = 0.71$) nor IVIG therapy (60-day mortality: IVIG therapy group 36.4% [4/11] vs. no IVIG therapy group 30.8% [12/39], $p = 0.73$) was associated with improved outcome. In a subgroup of non-immunocompromised patients, the 60-day mortality rates of HMPV and IFV group were 25.6% and 31.1%, respectively ($p = 0.55$). In immunocompromised patients, the 60-day mortality rates of the hMPV and IFV groups were 54.5% and 54.3%, respectively ($p = 0.99$). The median lengths of ICU stay (HMPV 9.5 days vs. IFV 10.0 days, $p = 0.28$) and hospital stay (HMPV 16.5 days vs. IFV 23.0 days, $p = 0.11$) were not significantly different between the two groups.

5. Discussion

We determined that HMPV and IFV accounted for 3.2% and 7.0% of ICU admissions for severe CAP, respectively. The mortality rate of severe HMPV-associated CAP was similar to that of severe IFV-associated CAP. Our findings show that HMPV infections are associated with a considerable incidence and mortality in patients with severe CAP.

The mortality data in our cohort should be interpreted with caution. Almost all patients with severe IFV-associated CAP received antiviral therapy, either oseltamivir or peramivir, whereas only 40.0% (20/50) of HMPV patients received antiviral therapy. The presence of end-stage renal disease (n = 8) or chronic renal failure (n = 5) may prohibit the use of ribavirin [10]. Furthermore, there has been no proven effective therapy for HMPV pneumonia. Oral ribavirin alone or in combination with IVIG was not beneficial for HMPV patients in our study. The similar mortality rates between the two groups, despite a lack of effective antiviral therapy in HMPV patients, indicate that the virulence potential of HMPV might be lower than that of IFV. Larger controlled studies are needed to clarify the effectiveness of antiviral therapy and virulence potentials of HMPV infection.

Limited information is available on the outcomes of severe HMPV-associated CAP patients. Recently, Hwang et al. retrospectively analyzed the risks of acute respiratory distress syndrome (ARDS) and mortality following HMPV infection in hospitalized adults [6]. The in-hospital mortality rate among 22 ARDS patients was 36.4%, which is similar to that noted in our study. They included some immunocompromised patients and cases of hospital-acquired infection. Because the mortality rates of those patients were not analyzed separately, it was difficult to directly compare these mortality rates with our results. Another study included 40 HMPV-positive patients admitted to the ICU [5]. The overall mortality was 18.0%. The proportion of patients who required mechanical ventilation (55.0%) was lower than that in our study (90.0%). None of these prior studies included control groups for comparison. Because the characteristics and outcomes of IFV-associated pneumonia have been well-documented, we compared the outcomes between severe HMPV-associated CAP and IFV-associated CAP patients. We combined the IFV-A and IFV-B subgroups and used it as control group in our analysis. The outcomes of the IFV-A and IFV-B subgroups may be different. We provided outcome data for each group in Table 2. When we compared the outcomes between the IFV-A and IFV-B groups, the differences were not significant (data not shown). However, considering the small number of IFV-B cases, this issue should be investigated in further studies.

Our study has several limitations. First, it was performed at a single center, which limits generalization. Second, we did not have an adequate number of fatal outcomes for multivariable analyses in HMPV patients. Third, we included co-infection cases in both groups, and these cases were more common in the influenza group. Co-infections may have affected the outcomes and bias comparisons between the groups [11]. Fourth, our cases may have included cases of incidental upper respiratory tract infection or colonization [12]. Finally, HMPV genotypic information and viral load, which may affect the disease outcome, were not available in our study.

In conclusion, the incidence of HMPV infection was approximately half that of IFV infection in patients with severe CAP. The mortality rate of severe HMPV-associated CAP was substantial and comparable to that of severe IFV-associated CAP.

Credit author statement

S.H. Choi, S.B. Hong, and Y. Koh conceived the presented idea and wrote the manuscript. J.W. Hur, J. Jung, M.J. Kim, and Y.P. Chong collected and analyzed the clinical data. H. Sung collected laboratory data and described the laboratory findings of the manuscript. H.J. Koo and K.H. Do collected radiological data and described the radiological findings of the manuscript, S.H. Kim, S.O. Lee, C.M. Lim, Y.S. Kim, and J.H. Woo analyzed the clinical data and described the clinical findings of the manuscript. All authors discussed the results and contributed to the final manuscript.

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Competing interests

The authors declare that there are no conflicts of interest to disclose.

Ethical approval

The study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Republic of Korea (2010-0079).

Acknowledgment

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2019.05.007.

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