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Clinical Features, Epidemiology, and Climatic Impact of Genotype-specific Human Metapneumovirus Infections: Long-term Surveillance of Hospitalized Patients in South Korea

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Background. Human metapneumovirus (hMPV) commonly causes upper and lower respiratory tract infections. Here, we performed long-term retrospective surveillance of hMPV infection among patients hospitalized in South Korea between 2007 and 2016 and investigated seasonal dynamics and clinical characteristics associated with each virus subtype/genotype.

Methods. Patient specimens were tested for hMPV and other respiratory viruses by commercial molecular assays. Medical records of hMPV-positive patients were reviewed, and hMPV subtype/genotype analysis was performed. We also collected meteorological data and analyzed relationships with hMPV activity.

Results. Of 23 694 specimens, 1275 (5.4%) were positive; among them, 94.0% were classified into 5 subtypes (A1, A2a, A2b, B1, and B2). Some clinical manifestations differed according to hMPV genotype; however, there was no correlation between hMPV subtype and clinical outcome. Viral activity peaked at 13–20 weeks (April and May) and was associated with climate-specific factors, including temperature, relative humidity, diurnal temperature variation, wind speed, and sunshine duration.

Conclusions. This large-scale, 10-year study provides valuable information about the clinical characteristics associated with hMPV subtypes and climate factors contributing to virus transmission.

Keywords. human metapneumovirus; genotype; acute respiratory tract infection; epidemiology; meteorological factors.

Human metapneumovirus (hMPV) is a pathogenic virus that causes respiratory tract infections especially among children, older adults, and immunosuppressed persons [1, 2]. hMPV is an antisense single-stranded RNA virus that belongs to the new virus family Pneumoviridae [3]. Phylogenetic analysis of the F and G genes has shown that hMPV can be classified into 2 main antigenic subtypes, A and B, with each subtype further separated into genetic sublineages (A1/A2a/A2b and B1/B2) [4]. It is known that the 2 main subgroups circulate in all parts of the world and concurrent annual circulation is common for all hMPV sublineages, with predominant hMPV subtype switching each year [5, 6].

The clinical manifestations of hMPV infections range from asymptomatic carriage to severe disease including fatal cases [2]. Because of its genetic diversity, previous studies have attempted to associate hMPV subtypes with clinical characteristics. Some studies found that the different clinical characteristics of hMPV infection might be associated with hMPV genotype and that disease severity could be increased with specific hMPV subgroup infections [7, 8]. However, it was also reported that there is no relationship between hMPV sublineages and the severity of illness or clinical manifestations [9, 10]. Therefore, whether there is an association between hMPV genotypes and clinical characteristics is debatable.

The association between climatic factors and hMPV infections is also unclear. Some researchers have assumed that most hMPV infections in humans would occur with strong seasonal predominance patterns [11, 12]. However, the seasonality of hMPV is not fully understood, and there is still very little information available regarding the association between meteorological parameters and hMPV activity.

Here, we conducted a long-term surveillance study of hMPV in South Korea from January 2007 to December 2016. The aim was to compare clinical characteristics including symptoms, diagnoses, laboratory findings, and concurrent pathogen infections and to evaluate the seasonal dynamics of hMPV infections according to hMPV subtypes. Additionally, we investigated the climatic factors that would explain the seasonal prevalence of hMPV infections in South Korea.

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MATERIALS AND METHODS

Clinical Samples

This retrospective study was approved by the Institutional Review Board (IRB) of the Chung-Ang University Hospital (IRB number 1807-009-16189). From January 2007 to December 2016, respiratory specimens from 23 694 hospitalized patients with acute respiratory illness were tested by molecular assays for respiratory viral pathogens at the Chung-Ang University Hospital. Among the patients, 21 184 were children (aged <18 years) and 2510 were adults. Respiratory samples were tested for hMPV and other respiratory viral pathogens using Seeplex RV6 or Anyplex II RV16 Detection kits (Seegene, Seoul, South Korea). Specimens were nasal swabs (n = 17 414 [73.5%]), throat swabs (n = 4340 [18.3%]), nasal aspirate (n = 1716 [7.3%]), sputum (n = 145 [0.6%]), and bronchial washing (n = 79 [0.3%]). Seeplex can detect 6 common respiratory viruses including adenovirus, influenza A and B, respiratory syncytial virus (RSV), parainfluenza virus (PIV), and hMPV. With Anyplex, 16 respiratory viruses can be detected and these include adenovirus, influenza A and B, PIV types 1, 2, 3, and 4, rhinovirus A/B/C, RSV A and B, bocavirus, hMPV, enterovirus, and coronavirus 229E, NL63, and OC43. Seeplex was used for routine molecular analysis until December 2012, and Anyplex was employed thereafter.

Clinical and Laboratory Findings

Among the hospitalized patients with acute respiratory illness, 1275 were diagnosed with hMPV infection. We reviewed the medical records for patients with hMPV infection, and the following clinical data were obtained: basic patient characteristics, past medical history, symptoms, and physical examination findings. In addition, we collected the results of routine laboratory testing upon admission. The following analytes were included in admission tests: sodium, potassium, chloride, calcium, phosphorous, glucose, total protein, albumin, total bilirubin, direct bilirubin, blood urea nitrogen, creatinine, uric acid, cholesterol, aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase, γ-glutamyl transferase, alkaline phosphatase, C-reactive protein, and complete blood cell results. The results of arterial blood gas analysis (n = 458) and procalcitonin (n = 123) were collected when available. To determine the presence of other bacterial and viral infections, we also reviewed various bacterial and tuberculosis culture test results for any specimen, antigen testing (*Streptococcus pneumoniae*, influenza A and B, RSV, rotavirus, norovirus), antibody testing (*Mycoplasma pneumoniae*, *Legionella pneumophila*, cytomegalovirus, Epstein-Barr virus), and molecular tests for respiratory bacterial pathogens (*S. pneumoniae*, *Haemophilus influenzae*, *Chlamydophila pneumoniae*, *L. pneumophila*, *Bordetella pertussis*, *M. pneumoniae*, tuberculosis, and nontuberculous mycobacteria), respiratory viral pathogens, and diarrhea viruses (rotavirus, norovirus, enteric adenovirus, and astrovirus).

Climatic Data

Meteorological data between January 2007 and December 2016 were collected from the database of the Korea Meteorological Administration (KMA; https://data.kma.go.kr/). The surface observation for the KMA was conducted by the Seoul automated synoptic observing system (ASOS station 108), and the 16 meteorological elements, including temperature, relative humidity, wind speed, and atmospheric pressure, among others, were measured every 3 hours [13].

hMPV Genotyping Assays and Sequencing Analysis

A total of 1275 hMPV-positive samples based on respiratory virus polymerase chain reaction (PCR) assays were analyzed by nested PCR–restriction fragment length polymorphism (RFLP) analysis, as described previously [14, 15]. The nested PCR was conducted with 2 primer–probe sets targeting the hMPV fusion (F) gene. Outer primers targeted 450 bp of the F gene, and inner primers were designed to detect 348 bp of the first PCR products. After amplification, PCR-amplified fragments were digested with 10 units of restriction enzyme (Tsp509I, Thermo Fisher Scientific, Pittsburgh, Pennsylvania) for 16 hours at 65°C and electrophoresed.

For the samples that showed negative results or unknown band patterns by RFLP analysis, PCR products were directly sequenced using the inner primer set employed for the nested PCR step. Target nucleotides were analyzed using an ABI PRISM 3730XL Genetic Analyzer (Applied Biosystems, Foster City, California), and the sequences were compared for similarity based on the GenBank database (https://www.ncbi.nlm.nih.gov/genbank/).

Statistical Analysis

Datasets were entered into Microsoft Excel (Microsoft, Washington) and analyzed using R version 3.5.1 (http://www.R-project.org/). For clinical characteristics and laboratory findings, the values were presented as median with interquartile range (continuous variables) or count with percentage (binomial or categorical variables). The Fisher exact test was used to compare differences between binomial variables. Continuous variables were compared by the Kruskal-Wallis test, and post hoc tests were performed using the Dunn multiple comparisons test. Associations between hMPV-positive rates and climate factors were explored by univariate regression analysis based on the Pearson correlation coefficient. Independent associations were analyzed by the multiple linear regression model using the stepwise selection method. A P value <.05 was considered a significant difference. We also utilized principal components analysis (PCA) to determine the contribution of climate variables to hMPV infections. Using PCA, we could reduce high-dimensional data spaces (1 axis per meteorological variable) to 2-dimensional planes for further analysis [16, 17]. Based on the results of PCA, we could select dominant climate factors that

affect hMPV infections, and 2-dimensional density plots were generated to evaluate the impact of climate factors in hMPV infections.

RESULTS

Epidemiological Distribution of hMPV Infections

During the study period, 23 694 patients were subjected to molecular testing for respiratory viruses, and 13 871 patients (58.5%) were positive for at least 1 respiratory virus including the following: 3631 cases of rhinovirus (15.3%), 3482 RSV (14.7%), 2652 adenovirus (11.2%), 1842 PIV (7.8%), 1275 hMPV (5.4%), 1223 influenza A (5.2%), 1017 enterovirus (4.3%), 719 influenza B (3.0%), 703 bocavirus (3.0%), and 539 coronavirus (2.3%).

The rate of positivity and weekly distribution of hMPV infections are shown in Figure 1A. These rates for hMPV infections varied from 0% to 21.1% across the weeks. Significant increases in isolation rates occurred between 10 and 25 weeks, and half of the hMPV infections occurred between 13 and 20 weeks (April and May). Of the hMPV-positive specimens, 1199 (94.0%) were subtyped as follows: 570 (44.7%) hMPV A2a, 304 (23.8%) hMPV B1, 279 (21.9%) hMPV B2, 21 (1.6%) hMPV A2b, and 24 (1.9%) mixed-genotype infections. Only 1 patient was infected with hMPV A1 (0.1%). Among mixed-genotype infections, 12 were hMPV A2a/B1 infections, 9 were hMPV A2a/B2, and 3 were hMPV A2a/B2. Specimens from 76 patients could not be genotyped (not determined).

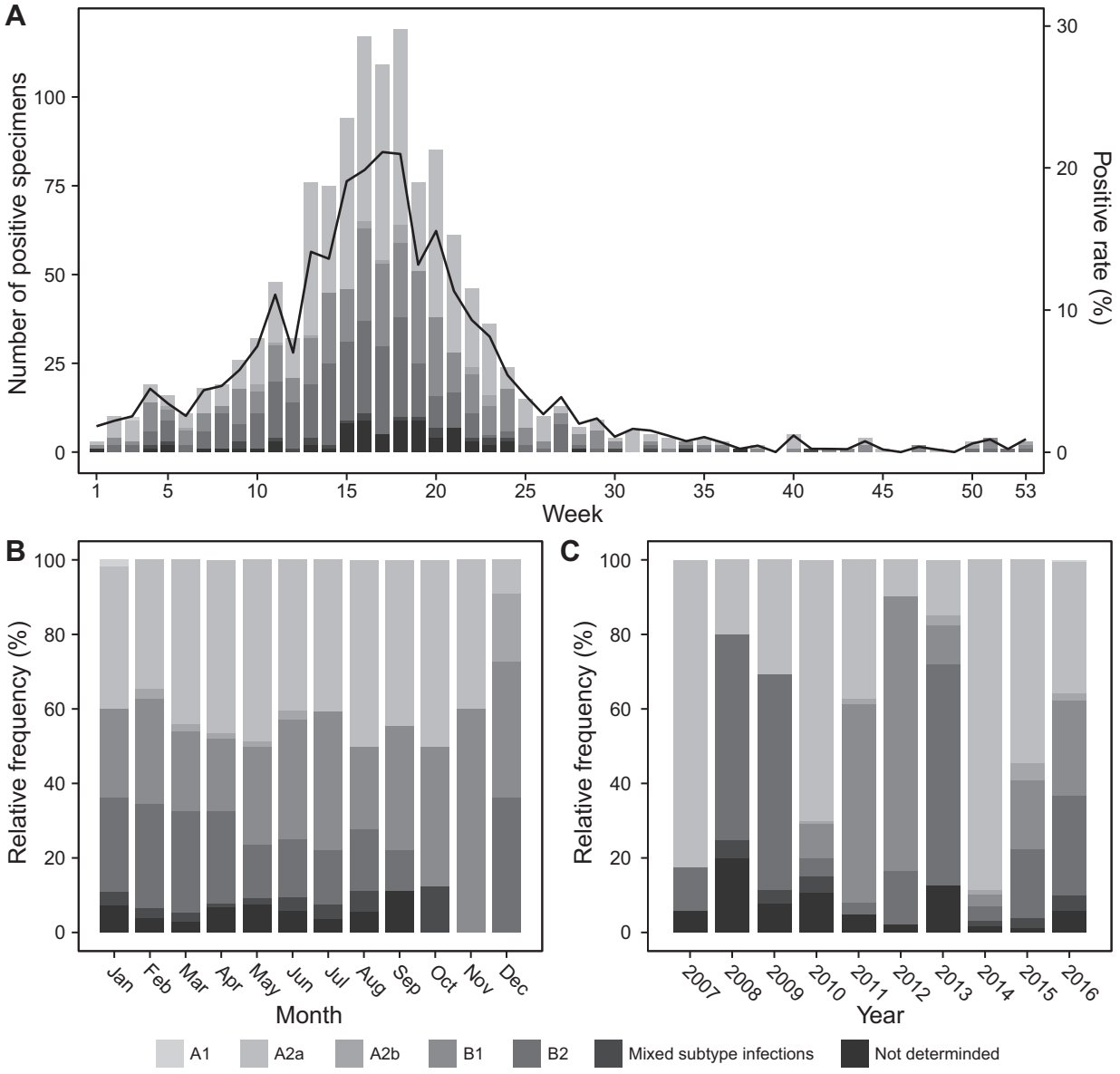

Figure 1. Number of human metapneumovirus (hMPV)–positive specimens (bars) and hMPV-positive rate (black lines) from 2007 to 2016 (*A*). Monthly (*B*) and annual (*C*) relative frequencies in the numbers of hMPV infections.

The dominant hMPV genotype in peak season was hMPV A2a, and the relative frequencies of hMPV B1 and B2 increased in the winter season (Figure 1B). However, the annual predominance patterns across the study period were complex and unpredictable (Figure 1C).

Clinical Characteristics of hMPV Infections

The clinical characteristics of hMPV infections in pediatric and adult patients are summarized in Tables 1 and 2. The majority of patients with hMPV were children (1200/1275 [94.1%]). Further, clinical manifestations were similar between the pediatric and adult patient groups. Most individuals infected with this virus exhibited upper respiratory symptoms such as cough, fever, sputum, and rhinorrhea, and the median onset of symptoms was 3 days. In both groups, pneumonia was the most common clinical diagnosis associated with hMPV infections. For the pediatric group, all hospitalized patients showed good prognosis and the median length of hospitalization was 5 days. However, a mortality rate of 9.3% was observed in the adult patient group. Most clinical characteristics were not significantly different between hMPV subtypes. In the pediatric group, however, there were significant differences among hMPV subtypes and clinical manifestations (cough, seizure, abdominal pain, and rhonchi) and concurrent infections (*M. pneumoniae*, adenovirus, and enterovirus). In terms of hMPV subtype infections, there was no significant difference in laboratory findings between children and adults (Supplementary Tables 1 and 2).

Meteorological Characteristics Associated With hMPV Infections

The meteorological characteristics associated with hMPV infections are shown in Table 3. Comparing 4 hMPV genotypes, the *P* values associated with the mean temperature, minimum temperature, maximum temperature, ground surface temperature, and relative humidity were all <.05. Specifically, the isolation of hMPV genotype A2a occurred more frequently with higher temperatures and wet weather, whereas hMPV B2 was frequently isolated with relatively low temperatures and dry environments.

Correlation Between Climatic Factors and hMPV Infections

Figure 2 shows annual variations in the rates of hMPV positivity and climatic variables. The intervals between 13 and 20 weeks are marked with orange boxes, and more than half of the infections occurred during these intervals. As shown in Table 4, diurnal temperature variation, wind speed, relative humidity, atmospheric pressure, and sunshine duration were directly correlated with rates of positivity based on univariate regression analyses. When the correlations were further analyzed by multivariate regression analysis, diurnal temperature variation, wind speed, and sunshine duration were found to be independent associative factors.

Results of PCA of hMPV infection cases indicated that the first principal component could explain 52.0%–55.8% of the total variances (Supplementary Table 3 and Supplementary Figure 1). The most important contributors to the first principal component were temperature variables including mean, minimum, maximum, and ground surface temperatures. The second principal component, which was dominated by diurnal temperature variation and relative humidity, could explain about 20% of the total variances. The third principal component was dominated by wind speed, which explained approximately 10% of the total variances. From the PCA results, we could assume that temperature, relative humidity, and diurnal temperature variation were the significant climatic factors associated with hMPV infections.

Density plots were created to visualize the relationships between climate factors and hMPV infections (Supplementary Figure 2). Mean temperature with diurnal temperature variation and relative humidity were selected to generate the density plots. Most hMPV infections occurred at a temperature interval of 8°C–22°C, a diurnal temperature difference between 6°C and 14 °C, and a relative humidity interval of 40%–60%.

DISCUSSION

In our study, hMPV was detected in 5.4% of respiratory specimens and was the fifth most commonly isolated respiratory virus. hMPV infections occurred more frequently in children, and a seasonal peak was found to be prominent in the spring season. These results were consistent with previous reports conducted in South Korea [6, 18, 19].

The hMPV subtypes A2a, A2b, B1, and B2 co-circulated throughout the study period, and the annual predominant genotypes were hMPV A2a in 2007, 2010, 2014, 2015, and 2016; B1 in 2011 and 2012; and B2 in 2008 and 2009. hMPV genotype predominance was thus observed both for 1 year and a maximum of 3 consecutive years, whereas the predominant genotype changed every 3–4 years. However, there were no regular cyclic patterns of predominant hMPV genotypes throughout our study period. This circulation complexity was also found in long-term studies from the United States and Germany [11, 20]. In addition, we could not find any similarities in annual predominance patterns between our study and other studies conducted in neighboring counties including China and Japan [21–23]. These results suggest that the varying annual predominance of hMPV subtypes/genotypes is a local phenomenon, and not synchronized across a wide geographic region [11].

The clinical features of hMPV infections in our study were consistent with those described in previous reports [9, 21]. Pediatric patients with hMPV infection showed mild respiratory symptoms before 2–5 days of hospitalization. Most inpatient children were diagnosed with pneumonia and stayed in the hospital for 4–6 days. hMPV infections seemed to cause more severe illness in adult patients; however, it was difficult to draw a conclusion with these results because the proportion of

Table 1. Clinical Characteristics of Human Metapneumovirus Infections in Children

Characteristic	All hMPV Infections (n = 1200)[a]		hMPV A2a (n = 547)		hMPV A2b (n = 16)		hMPV B1 (n = 290)		hMPV B2 (n = 259)		Mixed-subtype Infections (n = 23)		*P* Value[b]
Basic patient characteristics													
Age, mo, median (IQR)	25	(13–39)	25	(14–38)	32	(20–42)	24	(13–39)	25	(12–40)	30	(12–42)	.9128
Age, mo													
<6	116	(9.7)	49	(9.0)	2	(12.5)	30	(10.3)	25	(9.7)	3	(13.0)	.8456
6–12	163	(13.6)	68	(12.4)	2	(12.5)	36	(12.4)	42	(16.2)	4	(17.4)	
12–36	572	(47.7)	274	(50.1)	6	(37.5)	145	(50.0)	114	(44.0)	9	(39.1)	
>36	349	(29.1)	156	(28.5)	6	(37.5)	79	(27.2)	78	(30.1)	7	(30.4)	
Sex, male	644	(53.7)	296	(54.1)	8	(50.0)	156	(53.8)	141	(54.4)	12	(52.2)	.9962
Past medical history													
Asthma	26	(2.2)	12	(2.2)	1	(6.3)	6	(2.1)	6	(2.3)	0	(0)	.6601
Previous TB infection	4	(0.3)	2	(0.4)	0	(0)	0	(0)	1	(0.4)	1	(4.3)	.1214
Congestive heart failure	1	(0.1)	0	(0)	0	(0)	1	(0.3)	0	(0)	0	(0)	.5181
Symptoms													
Onset (day), median (IQR)	3	(2–5)	4	(2–5)	3	(2–4)	3	(2–5)	3	(2–5)	4	(2–5)	.1000
Cough	1164	(97.0)	536	(98.0)	14	(87.5)	278	(95.9)	256	(98.8)	22	(95.7)	.0193
Fever	1086	(90.5)	494	(90.3)	15	(93.8)	261	(90.0)	239	(92.3)	21	(91.3)	.9011
Sputum	966	(80.5)	449	(82.1)	11	(68.8)	223	(76.9)	215	(83.0)	19	(82.6)	.2039
Rhinorrhea	870	(72.5)	410	(75.0)	10	(62.5)	218	(75.2)	179	(69.1)	16	(69.6)	.2904
Dyspnea	52	(4.3)	24	(4.4)	0	(0)	10	(3.4)	14	(5.4)	1	(4.3)	.7717
Sore throat	40	(3.3)	23	(4.2)	0	(0)	7	(2.4)	4	(1.5)	1	(4.3)	.2341
Headache	8	(0.7)	3	(0.5)	0	(0)	3	(1.0)	1	(0.4)	0	(0)	.6956
Muscle pain	2	(0.2)	2	(0.4)	0	(0)	0	(0)	0	(0)	0	(0)	.7535
Seizure	40	(3.3)	26	(4.8)	0	(0)	4	(1.4)	4	(1.5)	1	(4.3)	.0310
Vomiting	102	(8.5)	44	(8.0)	2	(12.5)	25	(8.6)	21	(8.1)	3	(13.0)	.7500
Abdominal pain	24	(2.0)	10	(1.8)	1	(6.3)	2	(0.7)	9	(3.5)	1	(4.3)	.0474
Diarrhea	72	(6.0)	28	(5.1)	2	(12.5)	16	(5.5)	19	(7.3)	3	(13.0)	.1840
Physical examination findings													
Body temperature, °C, median (IQR)	38.3	(37.6–38.9)	38.2	(37.6–38.8)	38.7	(38.2–39.0)	38.4	(37.8–39.0)	38.3	(37.7–39.0)	38.0	(37.4–38.8)	.0511
Pulse rate, beats/min, median (IQR)	126	(120–132)	126	(120–132)	128	(112–131)	128	(119–132)	128	(120–132)	120	(120–133)	.8605
Systolic BP, mm Hg, median (IQR)	90	(90–100)	90	(90–93)	90	(80–93)	90	(90–100)	90	(80–90)	90	(90–90)	.9620
Diastolic BP, mm Hg, median (IQR)	60	(50–60)	60	(50–60)	60	(50–60)	60	(50–60)	60	(50–60)	60	(50–60)	.3808
Respiratory rate, breaths/min, median (IQR)	28	(26–32)	28	(26–32)	29	(26–32)	28	(26–32)	30	(26–32)	28	(26–32)	.6153
Rale	645	(53.8)	314	(57.4)	9	(56.3)	149	(51.4)	134	(51.7)	13	(56.5)	.4216
Wheezing	172	(14.3)	82	(15.0)	3	(18.8)	40	(13.8)	39	(15.1)	2	(8.7)	.8932
Rhonchi	88	(7.3)	49	(9.0)	0	(0)	20	(6.9)	10	(3.9)	4	(17.4)	.0199
Chest wall retraction	23	(1.9)	12	(2.2)	1	(6.3)	2	(0.7)	6	(2.3)	1	(4.3)	.1251
Cyanosis	4	(0.3)	2	(0.4)	0	(0)	1	(0.3)	0	(0)	0	(0)	1

Table 1. Continued

Characteristic	All hMPV Infections (n = 1200)[a]		hMPV A2a (n = 547)		hMPV A2b (n = 16)		hMPV B1 (n = 290)		hMPV B2 (n = 259)		Mixed-subtype Infections (n = 23)		*P* Value[b]
Pharyngeal injection	496	(41.3)	223	(40.8)	5	(31.3)	127	(43.8)	96	(37.1)	13	(56.5)	.2436
TM injection	54	(4.5)	27	(4.9)	0	(0)	12	(4.1)	10	(3.9)	1	(4.3)	.9475
Clinical diagnosis													
Pneumonia	768	(64.0)	353	(64.5)	12	(75.0)	192	(66.2)	159	(61.4)	16	(69.6)	.8191
Acute bronchiolitis	203	(16.9)	96	(17.6)	1	(6.3)	46	(15.9)	49	(18.9)	4	(17.4)	
Acute bronchitis	80	(6.7)	37	(6.8)	1	(6.3)	20	(6.9)	19	(7.3)	1	(4.3)	
Acute pharyngitis	76	(6.3)	30	(5.5)	0	(0)	16	(5.5)	18	(6.9)	0	(0)	
Croup	28	(2.3)	16	(2.9)	0	(0)	5	(1.7)	5	(1.9)	0	(0)	
Acute gastroenteritis	17	(1.4)	6	(1.1)	1	(6.3)	3	(1)	4	(1.5)	1	(4.3)	
Others	28	(2.3)	9	(1.6)	1	(6.3)	8	(2.8)	5	(1.9)	1	(4.3)	
Clinical outcome													
Length of hospital stay, d, median (IQR)	5	(4–6)	5	(4–6)	6	(4–7)	5	(4–7)	5	(4–6)	5	(4–6)	.8189
ICU admission	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	1.0000
Intubation	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	1.0000
Mortality rate	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	1.0000
Concurrent bacterial infection													
Mycoplasma pneumoniae	167	(13.9)	58	(10.6)	6	(37.5)	46	(15.9)	42	(16.2)	5	(21.7)	.0035
Streptococcus pneumoniae	132	(11.0)	64	(11.7)	1	(6.3)	30	(10.3)	25	(9.7)	3	(13.0)	.8749
Haemophilus influenzae	59	(4.9)	24	(4.4)	2	(12.5)	13	(4.5)	15	(5.8)	0	(0)	.3848
Chlamydophila pneumoniae	4	(0.3)	1	(0.2)	0	(0)	2	(0.7)	1	(0.4)	0	(0)	.5294
Other bacteria	5	(0.4)	2	(0.4)	0	(0)	2	(0.7)	1	(0.4)	0	(0)	.8690
Concurrent viral infection													
Rhinovirus	236	(19.7)	112	(20.5)	3	(18.8)	49	(16.9)	51	(19.7)	4	(17.4)	.8088
Adenovirus	107	(8.9)	54	(9.9)	3	(18.8)	11	(3.8)	30	(11.6)	2	(8.7)	.0019
Bocavirus	60	(5.0)	28	(5.1)	1	(6.3)	10	(3.4)	18	(6.9)	2	(8.7)	.2547
Parainfluenza viruses	35	(2.9)	12	(2.2)	0	(0)	10	(3.4)	9	(3.5)	0	(0)	.6795
Influenza A virus	21	(1.8)	5	(0.9)	1	(6.3)	3	(1.0)	8	(3.1)	0	(0)	.0697
Enterovirus	19	(1.6)	12	(2.2)	1	(6.3)	0	(0)	4	(1.5)	1	(4.3)	.0125
Influenza B virus	18	(1.5)	7	(1.3)	1	(6.3)	3	(1.0)	4	(1.5)	1	(4.3)	.0697
Respiratory syncytial virus	13	(1.1)	6	(1.1)	0	(0)	4	(1.4)	2	(0.8)	0	(0)	.9119
Coronaviruses	12	(1.0)	4	(0.7)	0	(0)	3	(1.0)	3	(1.2)	0	(0)	.8376
Rotavirus	8	(0.7)	3	(0.5)	0	(0)	2	(0.7)	3	(1.2)	0	(0)	.6866
Noroviruses	2	(0.2)	1	(0.2)	0	(0)	0	(0)	0	(0)	1	(4.3)	.0676
Enteric adenovirus	2	(0.2)	0	(0)	0	(0)	1	(0.3)	0	(0)	0	(0)	.5181
Other viruses	12	(1.0)	4	(0.7)	0	(0)	3	(1.0)	3	(1.2)	1	(4.3)	.3994

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: BP, blood pressure; hMPV, human metapneumovirus; ICU, intensive care unit; IQR, interquartile range; TB, tuberculosis; TM, tympanic membrane.

[a]One hMPV A1 infection and 64 hMPV infections of undetermined genotype were included.

[b]*P* values were calculated by Fisher exact test or Kruskal-Wallis test.

Table 2. Clinical Characteristics of Human Metapneumovirus Infections in Adults

Characteristic	All hMPV Infections (n = 75)[a]		hMPV A2a (n = 23)		hMPV A2b (n = 5)		hMPV B1 (n = 14)		hMPV B2 (n = 20)		*P* Value[b]
Basic patient characteristics											
Age, y, median (IQR)	73	(57–80)	71	(65–79)	56	(42–79)	70.5	(55–80)	74	(61–82)	.8109
Sex, male	31	(41.3)	9	(39.1)	2	(40.0)	5	(35.7)	8	(40.0)	1.0000
Past medical history											
Asthma	18	(24.0)	3	(13.0)	2	(40.0)	3	(21.4)	4	(20.0)	.5124
Hypertension	28	(37.3)	9	(39.1)	3	(60.0)	8	(57.1)	6	(30.0)	.3866
Renal disease	12	(16.0)	4	(17.4)	1	(20.0)	2	(14.3)	4	(20.0)	1.0000
Diabetes mellitus	14	(18.7)	7	(30.4)	1	(20.0)	2	(14.3)	2	(10.0)	.3788
Neoplastic disease	8	(10.7)	2	(8.7)	0	(0)	0	(0)	3	(15.0)	.4760
Previous TB infection	6	(8.0)	2	(8.7)	0	(0)	2	(14.3)	2	(10.0)	.9234
Liver disease	6	(8.0)	3	(13.0)	0	(0)	0	(0)	2	(10.0)	.5753
COPD	4	(5.3)	4	(17.4)	0	(0)	0	(0)	0	(0)	.1134
Bronchiectasis	4	(5.3)	1	(4.3)	0	(0)	1	(7.1)	1	(5.0)	1.0000
Congestive heart failure	4	(5.3)	2	(8.7)	0	(0)	0	(0)	2	(10.0)	.7633
Cerebrovascular disease	1	(1.3)	0	(0)	0	(0)	0	(0)	1	(5.0)	.6290
Symptoms											
Onset (day), median (IQR)	3	(1–6)	2	(1–7)	3	(1–7)	3	(1–4)	2	(1–7)	.9304
Cough	62	(82.7)	20	(87.0)	4	(80.0)	10	(71.4)	17	(85.0)	.6579
Sputum	61	(81.3)	20	(87.0)	4	(80.0)	10	(71.4)	16	(80.0)	.7043
Fever	36	(48.0)	9	(39.1)	3	(60.0)	9	(64.3)	7	(35.0)	.3032
Dyspnea	34	(45.3)	9	(39.1)	4	(80.0)	5	(35.7)	9	(45.0)	.3995
Rhinorrhea	5	(6.7)	0	(0)	1	(20.0)	1	(7.1)	1	(5.0)	.1627
Muscle pain	2	(2.7)	0	(0)	0	(0)	1	(7.1)	0	(0)	.3065
Abdominal pain	2	(2.7)	0	(0)	0	(0)	1	(7.1)	1	(5.0)	.5865
Sore throat	1	(1.3)	0	(0)	0	(0)	0	(0)	1	(5.0)	.6290
Vomiting	1	(1.3)	0	(0)	0	(0)	1	(7.1)	0	(0)	.3065
Physical examination findings											
Body temperature, °C, median (IQR)	37.4	(37.0–38.3)	37.1	(36.8–37.8)	39.1	(37.6–39.2)	37.3	(37.0–38.0)	37.4	(37.2–38.1)	.2394
Pulse rate, beats/min, median (IQR)	86	(78–96)	86	(75–92)	84	(83–92)	95.5	(84–102)	82	(74–93)	.0969
Systolic BP, mm Hg, median (IQR)	120	(110–130)	120	(105–134)	120	(110–130)	115	(110–120)	115	(108–132)	.7400
Diastolic BP, mm Hg, median (IQR)	70	(70–80)	70	(70–90)	70	(70–80)	70	(70–75)	70	(60–80)	.3205
Respiratory rate, breaths/min, median (IQR)	20	(20–22)	20	(20–23)	20	(20–20)	20	(20–20)	20	(20–20)	.8387
Rale	4	(5.3)	0	(0)	0	(0)	0	(0)	2	(10.0)	.3046
Wheezing	3	(4.0)	1	(4.3)	1	(20.0)	0	(0)	0	(0)	.2041
Pharyngeal injection	3	(4.0)	0	(0)	0	(0)	0	(0)	3	(15.0)	.0923
Clinical diagnosis											
Pneumonia	63	(84.0)	19	(82.6)	4	(80.0)	12	(85.7)	18	(90.0)	.7547
Acute bronchitis	6	(8.0)	2	(8.7)	0	(0)	1	(7.1)	2	(10.0)	

Table 2. Continued

Characteristic	All hMPV Infections (n = 75)[a]		hMPV A2a (n = 23)		hMPV A2b (n = 5)		hMPV B1 (n = 14)		hMPV B2 (n = 20)		*P* Value[b]
Acute pharyngitis	1	(1.3)	1	(4.3)	0	(0)	0	(0)	0	(0)	
Others	5	(6.7)	1	(4.3)	1	(20)	1	(7.1)	0	(0)	
Clinical outcome											
Length of hospital stay, d, median (IQR)	8	(6–16)	10	(7–17)	6	(6–11)	10	(7–14)	8	(6–20)	.6337
ICU admission	13	(17.3)	4	(17.4)	1	(20.0)	2	(14.3)	4	(20.0)	.6148
Intubation	11	(14.7)	3	(13.0)	0	(0)	1	(7.1)	4	(20.0)	.6965
Mortality rate	7	(9.3)	1	(4.3)	1	(20.0)	0	(0)	2	(10.0)	.3028
Concurrent bacterial infection											
Streptococcus pneumoniae	36	(48.0)	12	(52.2)	4	(80.0)	5	(35.7)	10	(50.0)	.4192
Mycoplasma pneumoniae	24	(32.0)	7	(30.4)	1	(20.0)	7	(50.0)	7	(35.0)	.6146
Haemophilus influenzae	8	(10.7)	4	(17.4)	0	(0)	1	(7.1)	3	(15.0)	.8551
Other bacteria	2	(2.7)	1	(4.3)	0	(0)	1	(7.1)	0	(0)	.7567
Concurrent viral infection											
Rhinovirus	5	(6.7)	1	(4.3)	1	(20.0)	1	(7.1)	1	(5.0)	.5386
Parainfluenza viruses	3	(4.0)	0	(0)	0	(0)	0	(0)	1	(5.0)	.6290
Enterovirus	2	(2.7)	0	(0)	0	(0)	0	(0)	1	(5.0)	.6290
Influenza A virus	1	(1.3)	0	(0)	0	(0)	1	(7.1)	0	(0)	.3065
Respiratory syncytial virus	1	(1.3)	0	(0)	1	(20.0)	0	(0)	0	(0)	.0806
Coronaviruses	1	(1.3)	0	(0)	0	(0)	1	(7.1)	0	(0)	.3065

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; hMPV, human metapneumovirus; ICU, intensive care unit; IQR, interquartile range; TB, tuberculosis.

[a]One hMPV mixed-genotype infection and 12 hMPV infections of undetermined genotype were included.

[b]*P* values were calculated by Fisher exact test or Kruskal-Wallis test.

Table 3. Meteorological Variables Related to the Isolation of Human Metapneumovirus

Meteorological Variables	All hMPV Isolations (n = 1275)[a]		hMPV A2a (n = 591)[b]		hMPV A2b (n = 21)[b]		hMPV B1 (n = 319)[b]		hMPV B2 (n = 291)[b]		*P* Value[c]	Difference Between Groups
Mean temperature (°C)	13.5	(8.0–17.9)	14.6	(9.8–18.1)	13.2	(7.3–17.3)	13.5	(7.2–18.7)	12.2	(5.3–16.0)	.0003	A2a > B2; B1 > B2
Minimum temperature (°C)	9.0	(3.3–13.3)	9.8	(5.1–13.8)	7.3	(3.7–14.1)	8.8	(2.7–14.5)	7.1	(1.8–12.0)	.0001	A2a > B2; B1 > B2
Maximum temperature (°C)	18.8	(12.7–23.7)	20.0	(14.5–24.0)	18.4	(11.0–23.8)	19.1	(12.4–24.6)	17.3	(10.4–21.8)	.0006	A2a > B2; B1 > B2
Diurnal temperature variation (°C)	9.9	(7.4–11.6)	10.1	(7.4–11.8)	10.4	(8.1–12.3)	9.7	(7.4–11.5)	9.7	(7.5–11.8)	.5742	
Ground surface temperature (°C)	15.7	(9.6–21.3)	16.8	(11.5–21.8)	13.6	(7.3–19)	15.9	(8.0–23.1)	13.9	(6.9–18.5)	<.0001	A2a > B2; B1 > B2
Rainfall (mm)	0	(0–0.4)	0	(0–0.2)	0	(0–1.0)	0	(0–0.5)	0	(0–0.5)	.7532	
Wind speed (m/s)	2.7	(2.2–3.3)	2.7	(2.3–3.2)	2.6	(2.4–3.4)	2.7	(2.2–3.3)	2.6	(2.2–3.3)	.9524	
Relative humidity (%)	55.0	(43.8–66.5)	56.9	(45.9–68.8)	49.5	(45.4–66.0)	53.8	(42.8–65.9)	51.3	(42.6–64.0)	.0015	A2a > B1; A2a > B2
Atmosphere pressure (mm Hg)	1005.0	(999.6–1009.2)	1005.0	(999.6–1008.7)	1004.0	(1000.3–1008.4)	1004.0	(998.1–1009.4)	1005.0	(1001.0–1009.8)	.1558	
Sunshine duration (hour)	13.3	(12.4–14)	13.4	(12.5–14.1)	13.4	(11.7–13.8)	13.3	(12.3–14.1)	13.2	(12.1–13.7)	.0790	

Data are shown as median with interquartile range.

Abbreviation: hMPV, human metapneumovirus.

[a]Seventy-six hMPV infections of undetermined genotype were included.

[b]Mixed-genotype hMPV infections were counted for each of the corresponding hMPV genotype isolations.

[c]*P* values were calculated by Kruskal-Wallis test, and post hoc analyses were performed by Dunn test to determine differences between groups.

adult patients was too small and more severe cases were more likely to be tested in the adult patient group.

Various studies have focused on the correlation between hMPV subtypes and clinical characteristics in infected patients. Vicente et al found that the clinical severity of hMPV A infections was higher than that of hMPV B infections [8]. Matsuzaki et al indicated that laryngitis was more associated with hMPV B1 infections, whereas wheezing was more prevalent with hMPV B1 and B2 infections [7]. However, there were also many reports suggesting that there are no differences in clinical characteristics caused by various hMPV subtypes [9, 10, 21]. In our study, according to hMPV subtypes, statistical significance was found in terms of symptoms, physical examination findings, and concurrent infections in pediatric patients. However, we found that there were no distinct differences in clinical diagnoses, clinical outcomes, and laboratory findings according to hMPV genotypes. These results support the contentions that certain clinical manifestations are different among hMPV genotypes but that there is no significant relationship between the hMPV subtype and disease severity.

We also attempted to assess the effects of meteorological factors on hMPV infections. hMPV activity was affected by temperature variables, relative humidity, diurnal temperature variation, wind speed, and sunshine duration. Among these factors, the rate of hMPV positivity was positively correlated with 3 variables including diurnal temperature variation, wind speed, and sunshine duration. Our results also showed peaks of hMPV activity at temperatures of approximately 13.5°C and relative humidity of 55.0%; furthermore, this activity tended to be associated with increasing diurnal temperature variation, wind speed, and sunshine duration. Previous studies conducted in other regions suggested that low temperature is the main driver of hMPV seasonality [11, 24–26]. However, based on the results of our study, we could not conclude that temperature variables are not linearly correlated with hMPV epidemics. Because the climate of Seoul is characterized by large seasonal temperature differences, which are not observed in previously studied countries, we hypothesized that hMPV would not be prevalent at low temperatures but would be prevalent at a certain temperature interval. In addition, the amount of rainfall was found to be correlated with the incidence of hMPV infections in subtropical and tropical regions [27–29], whereas hMPV activity was not affected by rainfall in our study. These findings suggest that hMPV infections were affected by climate factors, but that the meteorological drivers of virus activity vary by region and climate group [11, 24].

We also investigated differences in environmental factors that affect the transmission of each hMPV genotype. Our study showed that adaptation to climatic conditions, with respect to the occurrence of human cases of hMPV subgroups, was slightly different. For example, hMPV B2 infections appeared when the

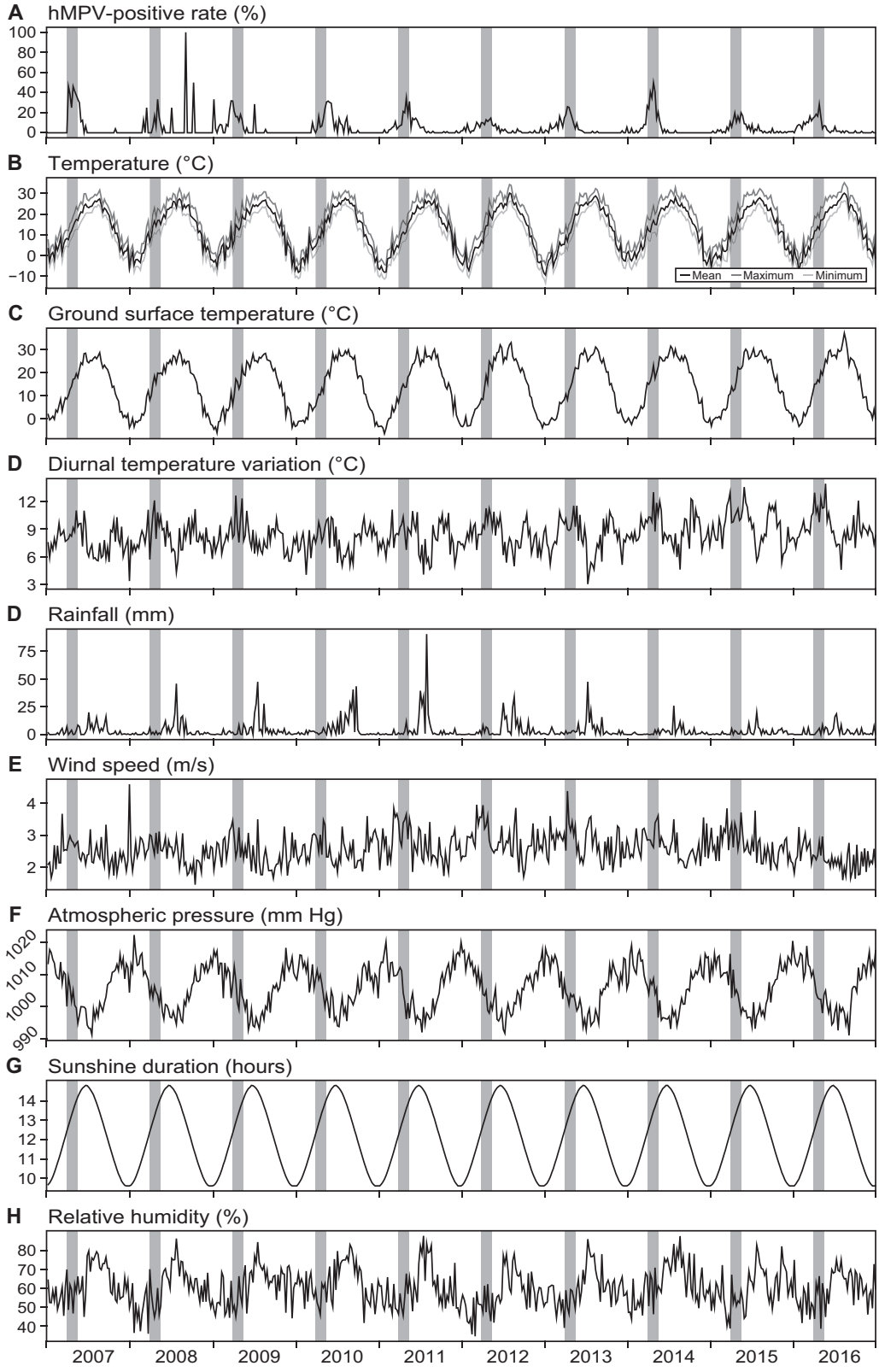

Figure 2. *A–H*, Human metapneumovirus (hMPV)–positive rate and climate variables. Gray bars represent the time interval between 13 and 20 weeks; more than half of all hMPV infections occurred within this interval.

Table 4. Correlation Between Weekly Rates of Human Metapneumovirus Positivity and Meteorological Variables

	Univariate Regression Analysis		Multivariate Regression Analysis	
Meteorological Variables	Coefficient	*P* Value	Coefficient	*P* Value
Mean temperature (°C)	−0.0644	.1436	−0.0015	.1790
Minimum temperature (°C)	0.0253	.5649	…	
Maximum temperature (°C)	0.0694	.1148	…	
Diurnal temperature variation (°C)	0.2675	<.0001	0.0130	<.0001
Ground surface temperature (°C)	0.0736	.0944	0.0009	.4390
Rainfall (mm)	0.0366	.4057	…	
Wind speed (m/s)	0.2024	<.0001	0.0195	.0308
Relative humidity (%)	−0.1440	.0010	…	
Atmosphere pressure (mm Hg)	−0.1262	.0040	0.0024	.0521
Sunshine duration (hour)	0.2656	<.0001	0.0457	<.0001

temperature was colder, whereas hMPV A2a infections were more prevalent in milder weather with a more humid environment. However, the origins of these differences in adaptation to meteorological conditions among hMPV subtypes were not clear, and further research should be performed to elucidate the link between the transmission abilities of hMPV subgroups and climatic factors.

Although we attempted to minimize errors, there were several limitations to this study. First, 6% of hMPV-positive specimens could not be genotyped due to sample problems such as deficiencies and RNA degradation after long-term storage. Although the proportion of "not determined" specimens was not relatively large, it could have affected the results of our study. Second, the clinical information of hMPV-positive patients was only tracked by medical records due to the nature of our retrospective study. We admit that some information could be misrepresented or omitted, and this possibility could also affect the results of this study. Third, because respiratory molecular testing was routinely used only for pediatric patients, and not for adult patients, the study population was biased for pediatric patients and the number of adult patients was relatively insufficient. Therefore, further long-term prospective surveillance should be performed to solve the present limitations and provide more informative results regarding hMPV infections.

In conclusion, our study provides long-term data on hMPV infections from a tertiary hospital serving a South Korean population. hMPV was the fifth most isolated respiratory virus and patients of various ages were infected, mainly between weeks 13 and 20 (April and May). Among the 5 subtypes of hMPV, hMPV A2a was most frequently isolated and each hMPV subtype showed annual predominance every 3–4 years. There were also significant differences between hMPV genotypes and clinical characteristics; however, disease severity was not altered according to hMPV subtype. Our study also showed that hMPV infections occurred with a seasonal rhythm and were associated with several climate factors including temperature, relative humidity, diurnal temperature variation, wind speed, and sunshine duration. In addition, each hMPV genotype had a different affinity for certain meteorological conditions. The results of our study contribute to the understanding of the clinical characteristics of infections caused by each hMPV subtype, as well as climate factors that contribute to the transmission of hMPV.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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