Viral Infection in Patients with Severe Pneumonia Requiring Intensive Care Unit Admission

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Rationale: **The role of viruses in pneumonia in adults and the impact of viral infection on mortality have not been elucidated. Previous studies have significant limitations in that they relied predominantly on upper respiratory specimens.**

Objectives: **To investigate the role of viral infection in adult patients with pneumonia requiring intensive care unit (ICU) admission.**

Methods: **A retrospective analysis of a prospective cohort was conducted in a 28-bed medical ICU. Patients with severe community-acquired pneumonia (CAP) or healthcare-associated pneumonia (HCAP) were included in the study.**

Measurements and Main Results: **A total of 198 patients (64 with CAP, 134 with HCAP) were included for analysis. Of these, 115 patients (58.1%) underwent bronchoscopic bronchoalveolar lavage (BAL), 104 of whom were tested for respiratory viruses by BAL fluid reverse-transcription polymerase chain reaction (RT-PCR). Nasopharyngeal specimen RT-PCR was performed in 159 patients (84.1%). Seventy-one patients (35.9%) had a bacterial infection, and 72 patients (36.4%) had a viral infection. Rhinovirus was the most common identified virus (23.6%), followed by parainfluenza virus (20.8%), human metapneumovirus (18.1%), influenza virus (16.7%), and respiratory syncytial virus (13.9%). Respiratory syncytial virus was significantly more common in the CAP group (CAP, 10.9%; HCAP, 2.2%; $P = 0.01$). The mortalities of patients with bacterial infections, viral infections, and bacterial-viral coinfections were not significantly different (25.5, 26.5, and 33.3%, respectively; $P = 0.82$).**

Conclusions: **Viruses are frequently found in the airway of patients with pneumonia requiring ICU admission and may cause severe forms of pneumonia. Patients with viral infection and bacterial infection had comparable mortality rates.**

Keywords: pneumonia; viral pneumonia; bronchoalveolar lavage; intensive care units; rhinovirus

Severe pneumonia that requires intensive care unit (ICU) admission is associated with high morbidity and mortality. Viruses, except the influenza virus, have not traditionally been considered important causes of severe respiratory infections in adults. However, several recent reports of adult viral pneumonia in which polymerase chain reaction (PCR) was used to test for the presence of respiratory viruses reported that viruses accounted for approximately 13.5 to 56.2% of the cases of community-acquired pneumonia (CAP) (1–8). These studies have several significant limitations. First, they relied predominantly on upper respiratory specimens, such as nasopharyngeal aspirates or swabs, for virus identification, and the presence of a virus in the nasopharynx could be due to a coincidental upper respiratory tract infection (9). Second, previous studies included a limited number of patients with severe pneumonia with viral infection.

Moreover, the role of viral infections in patients with healthcare-associated pneumonia (HCAP), which is a recently proposed category that has specific risk factors based on the probability of a resistant pathogen (10, 11), has not yet been investigated. Considering the fact that respiratory viral infections are mostly of community origin and would not be directly influenced by previous healthcare exposure or antimicrobial agent usage, the viral etiologies of CAP and HCAP might not be different, as opposed to the findings for bacterial pneumonia. Consequently, the concept of HCAP might not be applicable to viral pneumonia.

The main objective of this prospective study was to investigate the role of viral infection in patients with severe CAP and HCAP who required admission to a medical ICU.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Several reports suggested that viruses accounted for a considerable proportion of community-acquired pneumonia (CAP). However, they relied predominantly on upper respiratory specimens, such as nasopharyngeal aspirates, for virus identification.

What This Study Adds to the Field

This report provides a direct basis for establishment of viral etiology in patients with severe pneumonia. About one-third of patients with severe CAP or healthcare-associated pneumonia had viral infections, and the mortality from viral infection and bacterial infection were comparable.

METHODS

Study Setting

This study was performed at a 28-bed medical ICU of the Asan Medical Center, a 2,700-bed tertiary referral hospital in Seoul, Republic

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of Korea. During the study period, fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) was the preferred procedure for patients with bilateral interstitial-pattern pneumonia or pneumonia not responding to empirical antimicrobial therapy for more than 48 to 72 hours. However, when the likely pathogen was strongly suggested or identified in the initial work-up (e.g., typical lobar pneumonia with gram-positive cocci on adequate sputum smear, pneumococcal/*Legionella* urinary antigen-positive, or positive blood culture after 1 d of incubation) or when the risk of bronchoscopy with BAL was high (e.g., patients with critical hypoxemia in a prone position, severe thrombocytopenia, or severe heart failure with ventricular arrhythmia), bronchoscopy was not performed for diagnostic purposes. That is, the study did not interfere with patient-management decisions, and no additional bronchoscopy with BAL was performed for the study. BAL was performed following a standardized protocol (*see* online supplement). Antimicrobial therapy for CAP and HCAP was administered according to the American Thoracic Society/Infectious Disease Society of America guidelines (11, 12).

Study Design and Patients

This study was based on data from a prospective cohort study conducted from March 1, 2010 to February 28, 2011. All patients admitted to our medical ICU with the diagnosis of pneumonia were prospectively identified and monitored until discharge. All patients 18 years of age or older with severe CAP and severe HCAP were included in the current study. Prospectively collected data were retrospectively analyzed. The study was approved by the hospital's Institutional Review Board and the requirement for informed consent was waived because of the observational nature of the study.

Definitions

Definitions of pneumonia (13), adequate antimicrobial treatment, and the responses to initial antimicrobial treatment are summarized in online data supplement. CAP and HCAP were defined according to American Thoracic Society/Infectious Disease Society of America guidelines (11). Severe pneumonia was diagnosed if there was a requirement for invasive mechanical ventilation or septic shock with the need for a vasopressor (12).

Microbiologic Evaluation

Microbiological studies included the following: three sets of blood cultures, sputum or endotracheal aspirates, or BAL fluid for Gram staining and culture; BinaxNOW urinary antigen test for *Streptococcus pneumoniae* (Binax Inc., Portland, ME) and *Legionella pneumophila* serogroup 1 (Binax Inc.); nasopharyngeal aspirates or BAL fluid multiplex reverse-transcription PCR (RT-PCR) for influenza virus A and B, respiratory syncytial virus A and B, adenovirus, human metapneumovirus, parainfluenza virus types 1 to 4, enterovirus, rhinovirus, human coronavirus 229E/NL63, human coronavirus OC43, human coronavirus HKU1, and bocavirus using Seeplex RV15 ACE Detection (Seegene Inc., Seoul, Republic of Korea); shell vial culture for influenza virus, respiratory syncytial virus, parainfluenza virus, adenovirus, and cytomegalovirus (Diagnostic Hybrids, Inc., Athens, OH); PCR for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *L. pneumophila* using BD ProbeTec ET Atypical Pneumonia Assay (Becton Dickinson, Sparks, MD); and direct fluorescence assay for *Pneumocystis jirovecii* (when indicated). The performance of the respiratory virus multiplex RT-PCR kit used in this study has been evaluated in published studies (14, 15) (*see* online supplement).

Statistical Analyses

The chi-square test or Fisher exact test was used to compare categorical variables and Student *t* test or the Mann-Whitney *U* test were used to compare continuous variables as appropriate. Multivariate logistic regression analysis was used to identify independent risk factors. Variables with a plausible relationship with mortality or with *P* values less than 0.2 in the univariate analysis were entered into the multivariate analyses. Results are summarized as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). A *P* value less than 0.05 was considered significant. Data were recorded and analyzed using SPSS (version 18.0; SPSS, Chicago, IL).

RESULTS

Patient Characteristics

During the 1-year study period, 970 patients were admitted to our medical ICU, and 257 of these patients had CAP or HCAP. Twenty-eight patients were excluded because they did not meet the criteria for severe pneumonia at ICU admission; the clinical characteristics and microbiological results of these patients are summarized in Table E1 in the online supplement. Of the 229 patients with severe pneumonia, those (n = 31) for whom multiplex RT-PCR for respiratory viruses was not performed were excluded. Finally, a total of 198 consecutive patients (64 patients with CAP, 134 patients with HCAP) were included in our analysis.

Table 1 shows the demographics, underlying diseases and conditions, and clinical characteristics of the 198 enrolled patients. The mean age was 65.4 years (range: 17–96 yr). Structural lung disease (31.3%, n = 62) and diabetes mellitus (27.3%, n = 54) were the most common underlying diseases. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score at ICU admission was 25.1 ± 6.3. A total of 101 patients (51.0%) presented with septic shock, and 182 patients (91.9%) were mechanically ventilated. The associations between the severity and etiology of severe pneumonia are shown in Table E2. Thirty-seven patients (18.7%) received antimicrobial agents more than 24 hours before ICU admission.

Distribution of Respiratory Pathogens and Specimens

A total of 133 patients (67.2%) had one or more respiratory pathogens that were identified, and 113 patients (57.0%) underwent bronchoscopic BAL for etiologic diagnosis. Seventy-one patients (71 of 198, 35.9%) had bacterial infections, 72 (72 of 198, 36.4%) had viral infections, and 18 (18 of 198, 9.1%) had bacterial-viral coinfections (Table 2). There were no significant differences in the proportions of bacterial infections, viral infections, and bacterial-viral coinfections in the CAP and HCAP groups.

Bacterial Pathogens and Empirical Antimicrobial Therapy

A total of 77 bacterial pathogens were identified in 71 patients. Two pathogens were identified in four patients, and three pathogens in one patient. Bacteria were identified from expectorated sputum cultures or endotracheal aspirate cultures of 51 patients (71.8%), from urinary antigens of 23 patients (32.4%, 20 with pneumococcal antigens, 3 with *Legionella* antigens), from blood cultures of 21 patients (29.6%), from BAL fluid cultures or PCRs of 15 patients (21.1%), and from pleural fluid cultures of 1 patient (1.4%). Twenty-eight patients (39.4%) had two or more positive tests. Among the 113 patients who underwent bronchoscopic BAL, there was no significant difference between the bacterial recovery rate in those exposed to antimicrobial treatment more than 24 hours before undergoing BAL and those without previous treatment (11.1% [6 of 54] vs. 15.3% [9 of 59], $P = 0.59$).

There were substantial differences in the bacterial pathogens in the CAP and HCAP groups. *S. pneumoniae* was more common in patients with CAP, whereas methicillin-resistant *Staphylococcus aureus* (MRSA) or nonfermenting gram-negative bacilli were more common in patients with HCAP. Empirical antimicrobial treatment regimens for documented bacterial infections are summarized in the online supplement. Inadequacy

TABLE 1. DEMOGRAPHICS, UNDERLYING DISEASE/CONDITION, AND CLINICAL CHARACTERISTICS OF PATIENTS WITH SEVERE COMMUNITY-ACQUIRED PNEUMONIA AND HEALTHCARE-ASSOCIATED PNEUMONIA

	Total (*n* = 198)	CAP (*n* = 64)	HCAP (*n* = 134)	*P* Value
Male sex	144 (72.7)	49 (76.6)	95 (70.9)	0.50
Age, yr (mean ± SD)	65.4 ± 12.7	65.8 ± 14.5	65.2 ± 11.7	0.78
Underlying diseases or conditions				
Structural lung disease	62 (31.3)	19 (29.7)	43 (32.1)	0.75
COPD	28 (14.1)	13 (20.3)	15 (11.2)	0.13
Interstitial lung disease	21 (10.6)	3 (4.7)	18 (13.4)	0.08
Bronchiectasis	12 (6.1)	3 (4.7)	9 (6.7)	0.76
Tuberculosis destroyed lung	4 (2.0)	0	4 (3.0)	0.31
Pneumoconiosis	1 (0.5)	0	1 (0.7)	1.00
Diabetes mellitus	54 (27.3)	18 (28.1)	36 (26.9)	0.87
Solid cancer	34 (17.2)	0	34 (25.4)	< 0.001
Hematologic malignancy	18 (9.1)	0	18 (13.4)	0.002
Heart failure	9 (4.5)	2 (3.1)	7 (5.2)	0.72
End-stage renal disease	8 (4.0)	0	8 (6.0)	0.056
Cerebrovascular attack	8 (4.0)	5 (7.8)	3 (2.2)	0.12
Alcoholism	6 (3.0)	5 (7.8)	1 (0.7)	0.01
Liver cirrhosis	6 (3.0)	4 (6.3)	2 (1.5)	0.09
Bone marrow transplantation	5 (2.5)	0	5 (3.7)	0.18
Chronic renal failure	4 (2.0)	2 (3.1)	2 (1.5)	0.60
Solid organ transplantation	3 (1.5)	0	3 (2.2)	0.55
Receipt of recent chemotherapy (within 1 mo)	34 (17.2)	0	34 (25.4)	< 0.001
Neutropenia (absolute neutrophil count < 500/mm^3)	12 (6.1)	0	12 (9.0)	0.01
Receipt of immunosuppressive therapy	10 (5.1)	0	10 (7.5)	0.03
Recent surgery (within 1 mo)	6 (3.0)	0	6 (4.5)	0.18
Active smoker	24 (12.1)	16 (25.0)	8 (6.0)	< 0.001
APACHE II score (mean ± SD)	25.1 ± 6.3	24.5 ± 6.3	25.4 ± 6.3	0.34
SOFA score (mean ± SD)	9.6 ± 3.3	9.5 ± 3.3	9.6 ± 3.3	0.79
Septic shock at admission	101 (51.0)	36 (56.3)	65 (48.5)	0.36
Mechanical ventilation	182 (91.9)	59 (92.2)	123 (91.8)	1.00

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CAP = community-acquired pneumonia; COPD = chronic obstructive pulmonary disease; HCAP = healthcare-associated pneumonia; SOFA = Sequential Organ Failure Assessment.

Data are presented as the number (percentage) of patients unless indicated otherwise.

of the initial antimicrobial therapy was more common in the HCAP group than in the CAP group (CAP, 4.5% [1 of 22]; HCAP, 30.6% [15 of 49]; $P = 0.02$). MRSA was most frequently associated with inadequate therapy (n = 7), followed by multidrug-resistant nonfermenting gram-negative bacilli (n = 4).

Viral Pathogens

Figure 1 shows the flow of virus identification testing and the obtained results in patients with severe pneumonia. A total of 81 viruses were identified in 72 patients. One virus was identified in 63 patients and two viruses in 9 patients (12.5%). Overall, rhinovirus was the most common identified virus (23.6%, 17 of 72), followed by parainfluenza virus (20.8%, 15 of 72), human metapneumovirus (18.1%, 13 of 72), influenza virus (16.7%, 12 of 72), respiratory syncytial virus (13.9%, 10 of 72), cytomegalovirus (11.1%, 8 of 72), human coronavirus OC43 (5.6%, 4 of 72), and adenovirus/enterovirus (1.4%, 1 of 72). Nineteen patients (26.4%) received antimicrobial agents more than 24 hours before virus identification test. Forty-nine patients (68.1%) underwent fiberoptic bronchoscopy BAL. Viruses were detected from BAL fluid specimens of 40 patients (55.6%) and from nasopharyngeal aspirates or swabs of 47 patients (65.3%). In 15 patients (20.8%), viruses were detected in BAL fluid and nasopharyngeal samples. Among the 23 patients who underwent simultaneous respiratory virus PCR testing of BAL and nasopharyngeal samples, 5 patients were BAL positive but nasopharyngeal negative and 3 patients were BAL negative but nasopharyngeal positive. The number of virus test–positive specimens for each viral pathogen is summarized in Table E3.

Comparison of the distributions of viral pathogens indicated that respiratory syncytial virus was the only pathogen that was significantly more common in patients with CAP (CAP, 10.9% [7 of 64]; HCAP, 2.2% [3 of 134]; $P = 0.01$).

The identity of viral pathogens in patients with and without coinfection is shown in Table E4. Among the 72 patients with identified viral pathogens, 43 patients (59.7%) were infected by a single virus and 9 (12.5%) had coinfection with another virus. We identified coinfection with bacteria in 18 patients (25.0%). Coinfection with bacteria was most common in patients with parainfluenza virus (46.7%, 7 of 15), and influenza virus (33.3%, 4 of 12). Rhinovirus (11.8%, 2 of 17) and human metapneumovirus (15.4%, 2 of 13) were less commonly associated with bacterial coinfection, and none of the respiratory syncytial viruses were associated with bacterial coinfection (0 of 10).

Demographics, Clinical Manifestations, Laboratory Findings, Radiologic Findings, Seasonality, and Antiviral Therapy of 72 Patients with Viral Infections

Table 3 shows the demographics, clinical manifestations, laboratory results, and radiologic findings of 72 patients with viral infections with and without coinfection. The median duration of clinical symptoms before hospital admission was 4 days (interquartile range: approximately 2–4 d). The median serum levels of C-reactive protein and procalcitonin were significantly higher in patients with bacterial coinfection ($P = 0.02$ and $P = 0.046$, respectively). Bilateral lung involvement was present in 65 patients (90.3%). The most commonly dominant chest X-ray patterns were interstitial (43.1%), peribronchial (37.5%), and alveolar (19.4%). Pleural effusion was present in 14 patients (19.4%).

Rhinovirus was present during all four seasons and was more common in spring and autumn. Respiratory syncytial virus

TABLE 2. IDENTITY OF PATHOGENS IN PATIENTS WITH SEVERE COMMUNITY-ACQUIRED PNEUMONIA AND HEALTHCARE-ASSOCIATED PNEUMONIA

Identified organism*	Total (*n* = 198)	CAP (*n* = 64)	HCAP (*n* = 134)	*P* Value
None	65 (32.8)	16 (25.0)	49 (36.6)	0.11
Bacteria	71(35.9)	22 (34.4)	49 (36.6)	0.87
Streptococcus pneumoniae	23 (11.6)	12 (18.8)	11 (8.2)	0.04
Staphylococcus aureus	12 (6.1)	1 (1.6)	11 (8.2)	0.11
Methicillin-susceptible	5 (2.5)	1 (1.6)	4 (3.0)	1.00
Methicillin-resistant	7 (3.5)	0	7 (5.2)	0.10
Haemophilus influenzae	1 (0.5)	1 (1.6)	0	0.32
Moraxella catarrhalis	2 (1.0)	0	2 (1.5)	1.00
Legionella species	4 (2.0)	0	4 (3.0)	0.31
Enteric gram-negative bacilli	18 (9.1)	7 (10.9)	11 (8.2)	0.60
Klebsiella pneumoniae	12 (6.1)	5 (7.8)	7 (5.2)	0.53
Escherichia coli	3 (1.5)	1 (1.6)	2 (1.5)	1.00
Enterobacter cloacae	2 (1.0)	0	2 (1.5)	1.00
Serratia marcescens	1 (0.5)	1 (1.6)	0	0.32
Citrobacter freundii	1 (0.5)	0	1 (0.7)	1.00
Nonfermenting gram-negative bacilli	15 (7.6)	2 (3.1)	13 (9.7)	0.15
Pseudomonas aeruginosa	10 (5.1)	1 (1.6)	9 (6.7)	0.17
Acinetobacter baumannii	4 (2.0)	1 (1.6)	3 (2.2)	1.00
Stenotrophomonas maltophilia	1 (0.5)	0	1 (0.7)	1.00
Mycoplasma pneumoniae	1 (0.5)	1 (1.6)	0	0.32
MRSA or nonfermenting gram-negative bacilli	22 (11.1)	2 (3.1)	20 (14.9)	0.01
Virus	72 (36.4)	26 (40.6)	46 (34.3)	0.43
Rhinovirus	17 (8.6)	4 (6.3)	13 (9.7)	0.59
Parainfluenza virus	15 (7.6)	3 (4.7)	12 (9.0)	0.39
Type 3	8 (4.0)	0	8 (6.0)	0.06
Type 1	5 (2.5)	2 (3.1)	3 (2.2)	0.66
Type 2	1 (0.5)	1 (1.6)	0	0.32
Type 4	1 (0.5)	0	1 (0.7)	1.00
Human metapneumovirus	13 (6.6)	5 (7.8)	8 (6.0)	0.76
Influenza virus	12 (6.1)	6 (9.4)	6 (4.5)	0.21
Influenza A	11 (5.6)	6 (9.4)	5 (3.7)	0.18
Influenza B	1 (0.5)	0	1 (0.7)	1.00
Respiratory syncytial virus	10 (5.1)	7 (10.9)	3 (2.2)	0.01
Respiratory syncytial virus A	4 (2.0)	4 (6.3)	0	0.01
Respiratory syncytial virus B	6 (3.0)	3 (4.7)	3 (2.2)	0.39
Cytomegalovirus	8 (4.0)	0	8 (6.0)	0.056
Human coronavirus OC43	4 (2.0)	3 (4.7)	1 (0.7)	0.10
Adenovirus	1 (0.5)	1 (1.6)	0	0.32
Enterovirus	1 (0.5)	0	1 (0.7)	1.00
Other				
Mycobacterium tuberculosis	7 (3.5)	4 (6.3)	3 (2.2)	0.22
Pneumocystis jirovecii	5 (2.5)	0	5 (3.7)	0.18
Aspergillus species	5 (2.5)	2 (3.1)	3 (2.2)	0.66

Definition of abbreviations: CAP = community-acquired pneumonia; HCAP = healthcare-associated pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*.

Data are presented as the number (percentage) of patients.

*More than one pathogen was detected in some patients.

predominated from November to February, parainfluenza virus was mainly present from June to September, influenza virus was present from December to April, human metapneumovirus peaked from April to June, and human coronavirus was present in February to May (Figure 2). Of the 12 patients with influenza pneumonia, the influenza vaccination history was available for 6 patients, 1 of whom had a history of influenza vaccination.

Forty-three patients (59.7%) received antiviral treatment. Antiviral treatment was started at a median of 2 days (interquartile range [IQR], 0–4.0) after admission, and the median duration of antiviral treatment was 11.0 d (IQR, 8.0–16.0). Antiviral treatment regimens for documented viral infections are shown in the online data supplement.

Response to Initial Antimicrobial Therapy, Outcomes, and Risk Factors for 28-Day Mortality

At 72 hours after ICU admission, 100 patients (50.5%) exhibited improvement, whereas treatment failure was observed for 98 patients (49.5%; 6 deaths before 72 h, 64 cases of persistent pneumonia, and 28 cases of progressive pneumonia). Table E5 summarizes the results of our analysis of 28-day mortality. The overall 28-day mortality was 34.8% (CAP, 32.8% [21 of 64]; HCAP, 35.8% [58 of 154]; $P = 0.75$) and the in-hospital mortality was 44.4% (CAP, 37.5% [24 of 64]; HCAP, 47.8% [64 of 134]; $P = 0.22$). The median ICU stay was 10 days (IQR, 6–22 d). The mortalities of patients with bacterial infections, viral infections, and bacterial-viral coinfections were 25.5% (13 of 51), 26.5% (13 of 49), and 33.3% (6 of 18) ($P = 0.82$), respectively.

Among the respiratory viruses, rhinovirus was associated with highest mortality (52.9%), followed by influenza virus (33.3%), human coronavirus (25.0%), parainfluenza virus (20.0%), respiratory syncytial virus (20.0%), and human metapneumovirus (15.4%). The mortality rates of patients for whom rhinovirus was identified in the upper respiratory tract specimen only and patients for whom virus was identified in BAL fluid were 75.% (3 of 4) and 46.2% (6 of 14), respectively ($P = 0.58$). Multivariate analysis indicated that the independent risk factors for 28-day mortality were underlying liver cirrhosis

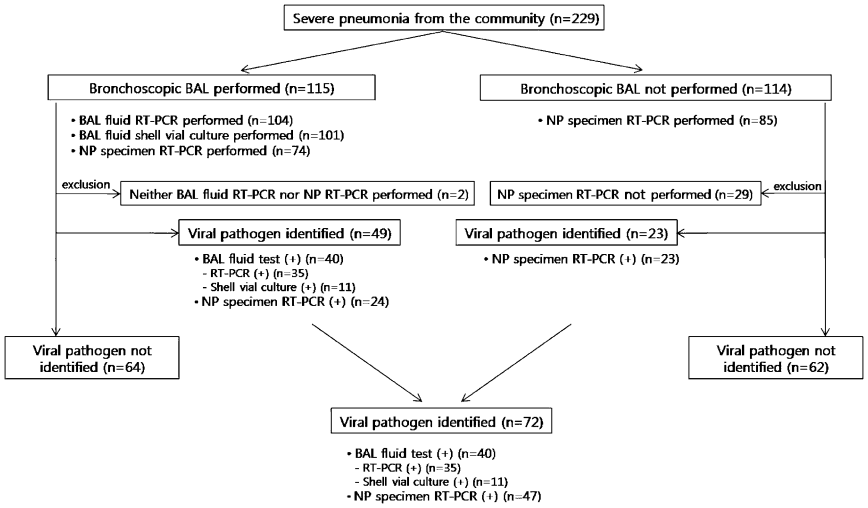

Figure 1. Flow of virus identification testing and the obtained results in 229 patients with severe pneumonia. After excluding 31 patients in whom respiratory multiplex reverse transcriptase–polymerase chain reaction (RT-PCR) was not performed, a total of 198 patients were finally included in the analysis. The bronchoalveolar lavage (BAL) fluid shell vial culture included influenza virus, respiratory syncytial virus, parainfluenza virus, adenovirus, and cytomegalovirus cultures. NP = nasopharynx.

(aOR = 13.6; 95% CI, 1.2–149.6; $P = 0.03$), failure of initial antimicrobial treatment (aOR = 3.4; 95% CI, 1.7–6.8; $P = 0.001$), and elevated APACHE II score (aOR = 1.1; 95% CI, 1.1–1.2; $P < 0.001$).

DISCUSSION

This study demonstrated that viral infection is common in adult patients with severe pneumonia. About one-third of patients with severe CAP or HCAP had viral infections, and the mortality from viral infection and bacterial infection were comparable. This is the first study to use lower respiratory tract specimens in more than half of the cases for the diagnosis of viral pneumonia. This provides a strong basis for our establishment of etiology, because these isolates were not merely spurious and clinically insignificant isolates that colonized upper airways.

In agreement with our results, two previous reports suggested that rhinovirus was the major cause of viral pneumonia, with infection rates of 17.1% (4) and 10.2% (1) of patients with CAP. In another study, which primarily included immunocompromised patients with or without pneumonic infiltration, rhinovirus was the second most common pathogen only to coronavirus identified from BAL fluid (16). Rhinovirus has long been considered simply the cause of the common cold. Increasing

TABLE 3. DEMOGRAPHICS, CLINICAL CHARACTERISTICS, IDENTITY OF PATHOGENS, AND OUTCOMES OF PATIENTS WITH SEVERE PNEUMONIA AND VIRAL INFECTION

	Total (*n* = 72)	No Coinfection (*n* = 43)	Coinfection with Other Virus (*n* = 9)	Coinfection with Bacteria (*n* = 18)
Male sex	50 (69.4)	30 (69.8)	3 (33.3)	15 (83.3)
Age, yr (mean ± SD)	65.1 ± 13.2	64.8 ± 15.0	65.4 ± 7.9	67.7 ± 9.4
Underlying disease				
Structural lung disease	21 (29.2)	9 (20.9)	4 (44.4)	7 (38.9)
Diabetes mellitus	20 (27.8)	13 (30.2)	3 (33.3)	4 (22.2)
Solid cancer	11 (15.3)	5 (11.6)	0	6 (33.3)
Hematologic malignancy	11 (15.3)	9 (20.9)	0	1 (11.1)
Clinical manifestation				
Fever > 38°C	59 (81.9)	34 (79.1)	8 (88.9)	16 (88.9)
Cough	62 (86.1)	35 (81.4)	9 (100)	16 (88.9)
Sputum	59 (81.9)	33 (76.7)	8 (88.9)	17 (94.4)
Dyspnea	66 (90.3)	41 (95.3)	9 (100)	13 (72.2)
Altered mentality	13 (18.1)	9 (20.9)	1 (11.1)	3 (16.7)
Laboratory findings, median (interquartile range)				
White blood cells/mm^3	8,000 (5,300–13,400)	8,100 (6,100–13,400)	10,100 (7,100–18,550)	4,500 (1,125–9,725)
Platelets, 10^3/mm^3	172 (96–244)	175 (94–258)	194 (144–251)	133 (50–192)
C-reactive protein, mg/dl	12.8 (5.8–22.1)	12.7 (5.4–20.4)	7.9 (5.9–19.8)	20.6 (10.3–34.2)
Procalcitonin, ng/ml	0.64 (0.15–16.5)	0.63 (0.15–18.1)	0.97 (0.12–3.65)	11.78 (1.17–22.4)
Radiologic findings				
Bilateral involvement	65 (90.3)	39 (90.7)	8 (88.9)	16 (88.9)
Diffuse involvement	42 (58.3)	25 (58.1)	5 (55.6)	9 (50.0)
Dominant pattern				
Interstitial pattern	31 (43.1)	17 (39.5)	6 (66.7)	5 (27.8)
Peribronchial pattern	27 (37.5)	18 (41.9)	1 (11.1)	9 (50.0)
Alveolar pattern	14 (19.4)	8 (18.6)	2 (22.2)	4 (22.2)
Pleural effusion	14 (19.4)	10 (23.3)	1 (11.1)	3 (16.7)
Atelectasis	5 (6.9)	5 (11.6)	0	0
Nodule	2 (2.8)	1 (2.3)	0	1 (5.6)

Data are presented as the number (percentage) of patients unless indicated otherwise. Categories of coinfection are not mutually exclusive. Some cases were associated with two or more pathogens. Cases of coinfection with organisms other than bacteria/other virus (three with *Pneumocystis jirovecii*, two with *Aspergillus* species, and one with *Mycobacterium tuberculosis*) are not presented.

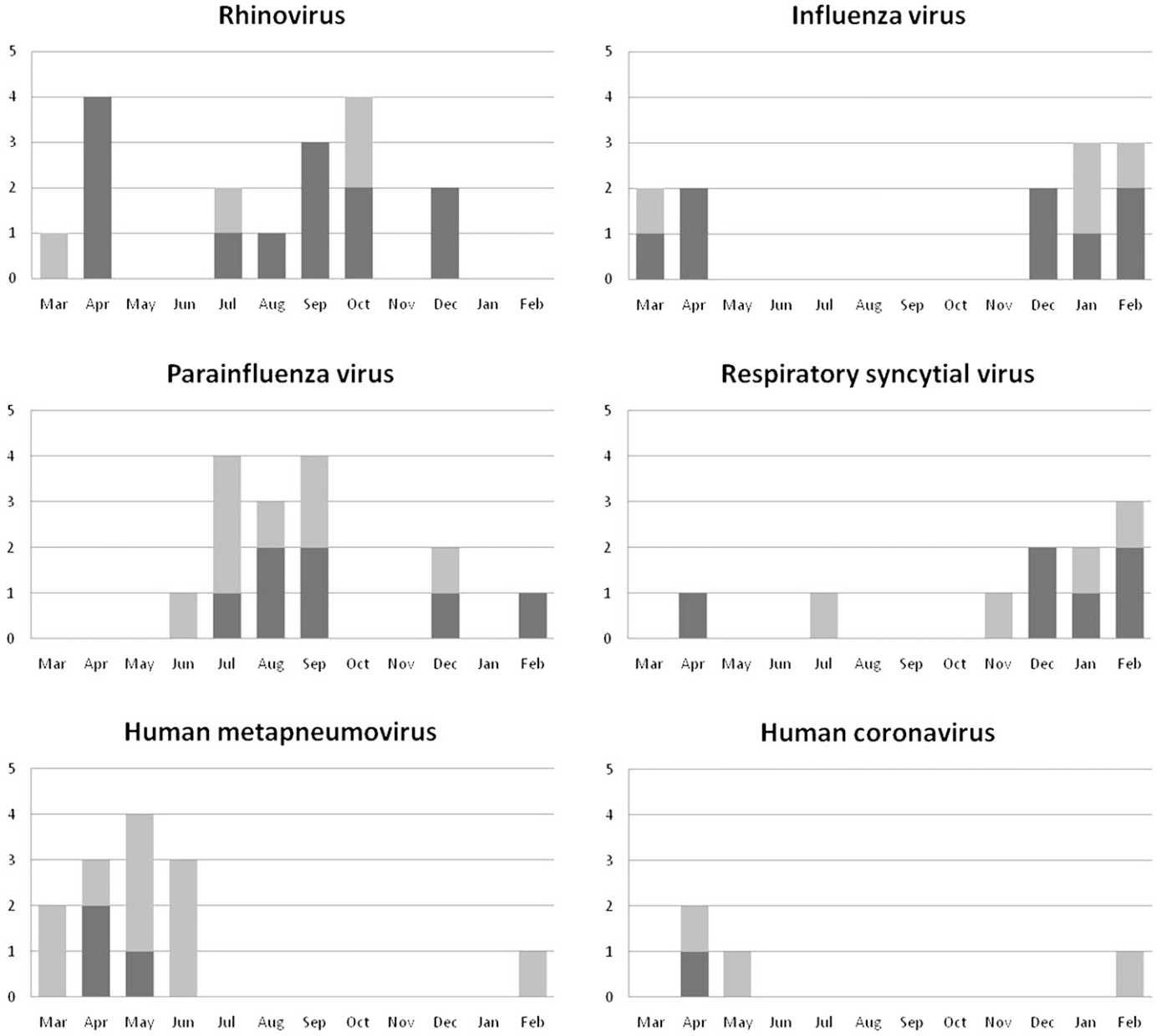

Figure 2. Monthly distribution of the respiratory viruses. *Solid bars* represent the cases of virus identification using bronchoalveolar lavage fluid and *shaded bars* represent the cases of virus identification using nasopharyngeal specimens only.

evidence indicates that rhinovirus may frequently be associated with lower respiratory tract diseases in adults (1, 4, 6, 17). Among our 17 patients with rhinovirus infection, 13 samples (76.5%) were isolated from bronchoscopic BAL fluid. Ten patients (58.8%) had rhinovirus as the only identified pathogen, five (29.4%) had coinfection with other viruses, and two (11.8%) had coinfection with bacteria. These results stand in contrast to those of previous studies, which reported that rhinovirus commonly occurred with bacterial coinfection (approximately 41.9–57.1%) (1, 18), and suggest that rhinovirus should be considered as an independent cause of severe pneumonia. Furthermore, among the respiratory viruses, rhinovirus infection was associated with the highest mortality (52.9%, 9 of 17). Of the 17 patients with rhinovirus infection, the majority of those patients had a severe underlying disease or condition (six malignancy, three chronic obstructive lung disease, three interstitial lung disease, two bone marrow transplant, and one solid organ transplant). The higher mortality of rhinovirus infection may be the result of a more serious underlying disease or condition rather than the consequence of rhinovirus strains with higher virulence. Notably, influenza virus was the fourth most common pathogen associated with severe pneumonia. The relatively high rate of influenza vaccine coverage in the elderly population in our country might explain the relatively low rate of influenza infection (19).

The rates and significance of polymicrobial etiology are important issues regarding pneumonia. Recently, Cillóniz and colleagues found that polymicrobial infection was present in 11% of ICU admitted patients with CAP, and respiratory viruses were identified in 39% of cases of polymicrobial etiology (8). Polymicrobial pneumonia was a risk factor for inadequate initial antimicrobial treatment and was an independent predictor of hospital mortality. It is increasingly clear that a respiratory viral infection increases the risk of bacterial infection (20) and that

bacterial-viral coinfection can lead to more severe disease (1, 5). Previous studies have examined the mechanism and impact of influenza-bacteria coinfection (21, 22), including that during the 2009 H1N1 influenza pandemic (23, 24). However, there are limited laboratory (25–27) and clinical data (1, 5) on coinfection with other respiratory viruses. Our study indicates that 9.1% (18 of 198) of patients with severe pneumonia had bacterial-viral coinfection, similar to the rates of approximately 4.1% to 29.5% reported in previous PCR studies of CAP (1–7). The rate of viral-bacterial coinfection in patients with a virus infection was 25.0% (18 of 72) in our study, lower than that of previous reports (approximately 27.6–70.0%) (1–7). This suggests that viruses alone can more readily invade the lower respiratory tract and cause primary viral pneumonia, especially in patients with severe pneumonia, than reported previously. The reported histopathological changes of severe viral pneumonia responsible for respiratory failure and acute respiratory distress syndrome include diffuse alveolar damage with alveolar hemorrhage in influenza A pneumonia (28, 29), thickening of the alveolar septum and hyperplasia of the alveolar lining cells in rhinovirus pneumonia (30), interstitial pneumonitis with cytoplasmic inclusions in parainfluenza virus pneumonia (31), inflammation of the bronchial and alveolar epithelium with resultant airway obstruction in respiratory syncytial virus pneumonia (32), and congestion of the alveolar septum and hemorrhage in the alveoli in human metapneumovirus pneumonia (33). It remains unclear whether a bacterial coinfection is associated with more severe disease. Some previous reports (1, 4, 34) have shown that viral-bacterial coinfections were associated with more severe clinical disease as measured by the Pneumonia Severity Index (35), and/or longer hospital stays, but other studies found no such associations (2, 3). Our study differs from previous studies in that we only studied patients with severe pneumonia. Previous studies could not meaningfully compare the mortalities of different groups because there were very few total deaths. Our comparison of 28-day mortalities indicated no significant differences in patients with sole bacterial infection (25.5%), sole viral infection (26.5%), and viral-bacterial coinfection (33.3%) ($P = 0.82$). However, the true impact of bacterial coinfection must be evaluated by overcoming heterogeneity of combinations of pathogens, comorbidities, and disease severities. Further studies with larger populations and more detailed subgroup analyses are necessary.

Another important aspect of our study is that we compared the etiologies of patients with CAP and HCAP who required ICU admission. To our knowledge, only one previous study examined patients with these characteristics (36), and that study was retrospective and only considered bacterial infections. In our population, bacterial etiology was different in patients with HCAP and CAP. In particular, MRSA and nonfermenting gram-negative bacilli (including *Pseudomonas aeruginosa*) were more common in the HCAP group, and *S. pneumoniae* was more common in the CAP group. This is in line with previous reports (36–39). On the other hand, our patients with CAP and HCAP had similar viral pathogens. In our population, only respiratory syncytial virus was more significantly common in one group (CAP, 10.9%; HCAP, 2.2%; $P = 0.01$). In contrast to bacterial infections, it is difficult to explain the association of healthcare exposure and viral etiology. We speculate that because the majority of our patients with HCAP were recently hospitalized (72.4%, 97 of 134) or resided in long-term care facilities (6.0%, 8 of 134), they might have less contact with other persons who carried respiratory syncytial viruses.

Our study has several limitations. First, we only included patients with severe pneumonia who were admitted to an ICU. Thus, we did not evaluate the role of viruses in patients with mild to moderate pneumonia. Second, this study was performed at a single center, thus limiting the generalization of our results. Third, as our study was a noninterventional observational study, some patients did not undergo bronchoscopic BAL. Fourth, approximately one-quarter of our patients received antimicrobial agents more than 24 hours before ICU admission. Therefore, some patients may have had false-negative findings regarding bacterial growth, and the proportion of patients infected by virus only might have been overestimated. Fifth, although we performed respiratory virus multiplex RT-PCR using BAL fluid for more than 90% of patients who underwent bronchoscopic BAL, respiratory virus multiplex PCR using nasopharyngeal samples was not uniformly performed. During the study period, respiratory virus multiplex PCR was not covered by the Korean National Medical Insurance System. Nasopharyngeal specimen testing was performed at the discretion of physician's judgment. For this reason, nasopharyngeal specimen PCR was performed for only 69.4% (159 of 229) of all patients with severe pneumonia. Sixth, we did not perform the virus testing for some of the viruses reported to cause CAP, including herpes simplex virus, hantavirus, and human herpesvirus 6 and 7 (9). Finally, among 72 patients with viral infection, nasopharyngeal specimens were the only specimens available for virus identification for 32 patients (44.4%) (Table E3). Therefore, we might have included cases of coincidental upper respiratory viral infection. Even in cases of virus identification from BAL, the virus could be a bystander or a false-positive artifact of the PCR/culture technique.

In conclusion, viruses are frequently identified in the airway of patients with pneumonia requiring ICU admission and may cause severe forms of pneumonia. Pneumonia has an enormous burden on public health resources; hence, further efforts should be devoted to the proper diagnosis and management of viral infection in adults.

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

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