Respiratory virus of severe pneumonia in South Korea: Prevalence and clinical implications

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Abstract

Background

Severe viral pneumonia is associated with a high mortality rate. However, due to the vulnerability of critically ill patients, invasive diagnostic methods should be performed with caution in the intensive care unit (ICU). It would be helpful if the prevalence, risk factors, and clinical impact of virus detection are elucidated.

Methods

We evaluated patients with severe pneumonia between January 1st 2008 and December 31st 2015. Reverse transcription-polymerase chain reaction (RT-PCR) analysis was performed for 8 respiratory viruses when viral pathogen could not be excluded as the origin of severe pneumonia. The baseline characteristics, laboratory results, microbiological findings, and clinical outcomes of the patients were analyzed.

Results

Of the 2,347 patients admitted to the medical ICU, 515 underwent RT-PCR for respiratory viruses, 69 of whom had positive results. The detection rate was higher during the winter, with a community onset, in patients with history of recent chemotherapy, and low platelet count. Additional bronchoscopic sampling along with upper respiratory specimen increased the yield of viral detection. Respiratory syncytial virus was the most common pathogen detected, while influenza A was the most common virus with bacterial coinfection. Respiratory virus detection led to changes in clinical management in one-third of the patients.

Conclusions

The detection of viral pathogens in patients with severe pneumonia is not rare, and can be more common in certain group of patients. Invasive sampling for RT-PCR can be helpful, and such detection can lead to positive changes in clinical management.
Introduction

Respiratory viruses are common pathogens in adults hospitalized with pneumonia and are more frequently detected than bacterial pathogens in certain groups of patients [1]. Influenza virus is the most well-known respiratory viral pathogen, but others, including respiratory syncytial virus (RSV) and parainfluenza virus, are also common [2, 3]. Such viral pathogens are not easily distinguishable based on clinical findings alone [4]. Therefore, it is suggested that reverse transcription-polymerase chain reaction (RT-PCR) assays should be performed in patients when a viral pathogen is suspected [5]. Such testing for respiratory viruses can decrease the inappropriate use of antibiotics and other medical resources [6].

Viral pneumonia is also a major cause of patient deterioration in the intensive care unit (ICU) [7]. Respiratory viruses are well-known for their high prevalence in patients with community-acquired pneumonia (CAP) who exhibit milder clinical presentations [8]. Furthermore, their role as nosocomial pathogens in the more severely ill group of patients is being highlighted [9]. However, only limited data exist regarding the prevalence of respiratory viruses among healthcare associated pneumonia (HCAP) and hospital-acquired pneumonia (HAP) patients. Additionally, considering the narrow range of antiviral agents against respiratory viruses and the potential harm of invasive respiratory sampling for RT-PCR in critically ill patients, it is crucial to reveal in which patients the sampling should be performed, and whether such detection leads to a change in the clinical management or outcome of patients.

In this study, we aimed to identify the presence of common respiratory viral pathogens in patients with severe pneumonia who were admitted to the ICU, including those with CAP, HCAP, and HAP. In addition, we aimed to analyze the risk factors and clinical impact of such detection.

Material and methods

Study design and patients

We conducted a retrospective cohort study of adult patients who were admitted to a 22-bed medical ICU for severe pneumonia between January 1, 2008 and December 31, 2015. Pneumonia was diagnosed by the attending physician with the combination of a new lung infiltrate and clinical evidence including new onset fever, purulent sputum, leukocytosis, and a decline in oxygenation [10]. Pneumonia was categorized as CAP, HCAP, or HAP according to the American Thoracic Society and Infectious Disease Society of America guidelines [10, 11]. Respiratory specimen sampling for RT-PCR was performed when the attending physician considered it necessary for routine care.

This study was conducted in accordance with the amended Declaration of Helsinki. It was reviewed by the institutional review board of Seoul National University Hospital (protocol number: H-1603-106-750). This institutional review board approved this study. The requirement for informed consent was waived because all data were de-identified before analysis.

Respiratory samples and multiplex PCR

RT-PCR analysis was performed when severe pneumonia did not respond to empirical antibacterial agents, when radiographic findings revealed ground glass opacities suggestive of atypical pathogens, or when patients were immune compromised. The decision regarding the type of specimen collected for RT-PCR analysis was made by the attending physician. Specimen collection included invasive (bronchoalveolar lavage [BAL]) and noninvasive (nasopharyngeal swab, sputum, or endotracheal aspirate) methods.
From 2008 to 2014, our institution utilized the Seeplex Respiratory Virus Detection assay (Seegene Inc., Seoul, Korea). This assay is based on the multiplex PCR method and uses a dual priming oligonucleotide system, which detects influenza virus types A and B, parainfluenza virus types 1, 2, and 3, RSV types A and B, adenovirus, metapneumovirus, coronavirus 229E, NL63 and OC43, and rhinovirus. After 2014, the Anyplex™ II RV16 with Tagging Oligonucleotide Cleavage and Extension technology (Seegene, Seoul, Korea) was used. The RV16 uses 16 primer sets for the simultaneous detection of 16 respiratory viruses: influenza virus types A and B, parainfluenza virus types 1, 2, 3, and 4, RSV types A and B, adenovirus, metapneumovirus, coronavirus 229E, NL63 and OC43, rhinovirus, bocavirus, and enterovirus. Both assays are known to have good sensitivity and specificity [12–14]. However, due to South Korea’s national insurance policy, results for only 8 pathogens (influenza virus types A and B, parainfluenza virus types 1, 2, and 3, RSV types A and B, and adenovirus) were reported to the attending physicians throughout the study period.

Variables and data collection

The baseline characteristics of patients, such as age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Charlson Comorbidity Index (CCI) score and underlying comorbidities, were reviewed. Patients with chronic obstructive pulmonary disease, asthma, bronchiectasis, pneumoconiosis, and tuberculosis destroyed lung were defined to have chronic lung disease [15–17]. The laboratory results analyzed included the white blood cell count, platelet count, C-reactive protein level, and clinical outcomes, including hospital length of stay (in days), ICU length of stay (in days), change of management, and in-hospital mortality. The causes of in-hospital mortality were also obtained from the medical records and death certificates of the patients.

Patients with and without virus detection were compared in terms of their baseline demographics, laboratory results, and clinical outcomes. Viral detection rates were described for each month and pneumonia category, and the pathogens of viral and bacterial coinfection were specified. Bacterial coinfection was considered to exist if both viruses and bacteria were detected, and bacteria were considered to be pathogens when blood cultures, respiratory tract specimen cultures, or urine pneumococcal antigens revealed positive results. Information about the impact on the clinical decision was obtained through a retrospective review of electronic medical records and orders from a communicating system.

Statistical analysis

Categorical variables are reported as numbers and percentages, and continuous variables are reported as medians and interquartile ranges (IQR) or as means and standard deviations (SD), depending on their patterns of distribution. All statistical analyses were performed using IBM SPSS software (version 22.0; IBM Corp., Armonk, NY), and graphs were created using Prism 5 software (GraphPad software, San Diego, CA). A two-tailed P-value of less than 0.05 was considered statistically significant.

Results

Characteristics of patients with and without virus detection

During the 8-year study period, 2,347 patients were admitted to the medical ICU for severe pneumonia. Of these patients, 515 underwent RT-PCR for respiratory virus pathogens, 69 (13.4%) of whom had positive results.
The patients with and without respiratory virus detection showed no significant differences in terms of age, sex, and disease severity, which was presented as the APACHE II score. However, patients with a community onset, history of recent (<2 weeks) chemotherapy, and lower platelet count (<200,000/μL) had higher rates of virus detection. Additionally, the rate of RT-PCR detection of respiratory viral pathogens showed seasonality: the rate was higher during February (35.6%) and January (26.7%) and was lower in September (2.5%) and May (2.7%). Seasonality was more prominent with CAP, compared to HCAP and HAP (Fig 1). Clinical outcomes, such as the length of hospital stay, length of ICU stay, and in-hospital mortality, did not differ between the two groups (Table 1).

The detection rate was the highest when both invasive and noninvasive samplings were performed (25 among 82 patients, 30.5%). Among the 25 patients who underwent both types of sampling, new information was acquired from additional invasive sampling in 7 patients. Additional information was not obtained in the other 18 patients: 10 patients had the same
results from invasive and noninvasive sampling, and 8 patients had negative results from the additional invasive sampling.

**Pathogens for severe pneumonia**

Among the 69 patients with positive RT-PCR results, RSV A was the most common pathogen detected (n = 21), followed by influenza A (n = 18), parainfluenza 3 (n = 12), RSV B (n = 9), adenovirus (n = 7), influenza B (n = 3), and parainfluenza 1 (n = 2). The detection rates showed similar distributions when they were divided into the 3 pneumonia categories, except for that of influenza A, which tended to be more prevalent in community settings (Table 2).
Bacterial coinfection was detected in 27 (39.1%) patients. The most common bacterial pathogens were *Staphylococcus aureus* (n = 8), followed by *Enterococcus faecium* (n = 4), *Klebsiella pneumoniae* (n = 4), *Acinetobacter baumannii* (n = 2), and *Pseudomonas aeruginosa* (n = 2). Bacteria were most commonly detected when influenza A was confirmed (n = 11), followed by RSV A (n = 7), parainfluenza 3 (n = 4), adenovirus (n = 3), RSV B (n = 2), and influenza B (n = 1) (Table 3). Patients with bacterial coinfection had a higher neutrophil count, lower lymphocyte count, and lower CD4/CD8 ratio from the BAL fluid than those without coinfection. Otherwise, the two groups did not show significant differences in their demographics and clinical outcomes (S1 Table).

### Clinical impact of virus detection

The detection of a viral pathogen led to changes in the management of the disease in 23 (33.3%) patients. Twelve patients received antiviral therapy such as oseltamivir and ribavirin, and empirical antiviral therapy was continued or extended in 4 patients. The use of immunosuppressive agents, including steroids, was decreased or stopped in 3 patients. In some

| Type of respiratory virus | Total n = 515 | CAP n = 126 | HCAP n = 202 | HAP n = 187 | P  |
|--------------------------|--------------|-------------|--------------|-------------|----|
| Respiratory syncytial virus A | 21 (4.1) | 8 (6.4) | 9 (4.5) | 4 (2.1) | 0.171 |
| Influenza A | 18 (3.5) | 8 (6.4) | 7 (3.5) | 3 (1.6) | 0.081 |
| Parainfluenza 3 | 12 (2.3) | 3 (2.4) | 5 (2.5) | 4 (2.1) | >0.999 |
| Respiratory syncytial virus B | 9 (1.8) | 3 (2.4) | 2 (1.0) | 4 (2.1) | 0.528 |
| Adenovirus | 7 (1.4) | 1 (0.8) | 3 (1.5) | 3 (1.6) | 0.899 |
| Influenza B | 3 (0.6) | 2 (1.6) | 1 (0.5) | 0 (0.0) | 0.257 |
| Parainfluenza 1 | 2 (0.4) | 0 (0.0) | 2 (1.0) | 0 (0.0) | 0.344 |

Values are presented as number (percentage). CAP, community acquired pneumonia; HCAP, healthcare associated pneumonia; HAP, hospital acquired pneumonia.

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| Bacteria of coinfection | Influenza A | RSV A | Parainfluenza 3 | Adenovirus | RSV B | Influenza B | Total |
|-------------------------|-------------|-------|-----------------|------------|-------|-------------|-------|
| **Gram positive** | | | | | | | |
| *Staphylococcus aureus* | 5 | - | 1 | 1 | 1 | 1 | 15 |
| *Enterococcus faecium* | 1 | 3 | - | - | - | - | 4 |
| *Staphylococcus epidermidis* | 1 | 1 | - | - | - | - | 1 |
| *Streptococcus viridans* | - | 1 | - | - | - | - | 1 |
| *Corynebacterium striatum* | - | - | - | - | 1 | - | 1 |
| **Gram negative** | | | | | | | |
| *Klebsiella pneumoniae* | 1 | 1 | - | - | 1 | - | 4 |
| *Acinetobacter baumannii* | 1 | - | - | 1 | - | - | 2 |
| *Pseudomonas aeruginosa* | - | 1 | 1 | - | - | - | 2 |
| *Klebsiella oxytoca* | 1 | - | - | - | - | - | 1 |
| *Escherichia coli* | 1 | - | - | - | - | - | 1 |
| *Moraxella catarrhalis* | - | 1 | - | - | - | - | 1 |
| *Stenotrophomonas maltophilia* | - | 1 | 1 | - | - | - | 1 |
| **Total** | 11 | 7 | 4 | 3 | 2 | 1 |  |

Values are presented as numbers.

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patients, antibiotics (n = 2) or antiviral agents (n = 1) were discontinued because bacterial pathogen was no longer suspected, or the detected virus had no effective antiviral agent (Table 4).

The clinical outcomes, such as the length of hospital stay, length of ICU stay, and in-hospital mortality, were compared according to changes in management. However, the differences were not statistically significant (S2 Table).

Discussion

Our study identified the risk factors, prevalence, and clinical impact of virus detection among patients with severe pneumonia who were admitted to the medical ICU. Respiratory viral infection should be suspected in patients from the community, during the winter season, in patients with recent chemotherapy, and in patients with a low serum platelet count. The overall virus detection rate was 13.3%, with RSV A being the most common pathogen and influenza A virus being the most common pathogen of bacterial coinfection. Such detection of respiratory viruses led to changes in management in one-third of the patients.

The virus detection rate was higher in February and January as well as in patients with a community onset. This finding supports the recommendation to use empirical therapy against influenza virus during the winter season for hospitalized CAP patients [18]. Patients with recent chemotherapy were at a higher risk for viral pneumonia, which is consistent with previous knowledge that immunosuppression is a risk factor for influenza viral pneumonia [19].

The virus detection rate was highest in patients who had undergone both invasive and noninvasive sampling (n = 25), and more information was obtained from further invasive sampling in approximately 28% of the patients (n = 7). Although the potential harm of BAL in critically ill patients must be thoroughly reviewed before the procedure, further invasive samplings should be considered in selected patients stated above (winter seasons, community onset, recent chemotherapy, low platelet count, and so on) for additional virus detection.

RSV, an important pathogen that can result in severe pneumonia, especially in the elderly, was the most common pathogen detected [20]. Previous studies have differed in the detailed distribution of pathogens, but many have reported that the most common viral pathogens include influenza, parainfluenza, and RSV [21–23]. Considering the limited strategies for treating and preventing respiratory viruses other than influenza, this distribution of various pathogens may further emphasize the need for the development of novel antiviral agents and vaccines.

This study is the first to specify the clinical impact of adult-onset severe viral pneumonia according to the detection of respiratory viruses. Previous studies have been conducted in

Table 4. Impact of respiratory virus detection on clinical decision among the patients in intensive care unit.

| Variables                                      | Values       |
|------------------------------------------------|--------------|
| Change of clinical management                  | 23 (33.3)    |
| Addition of antiviral therapy                  | 12 (17.4)    |
| Continue or extend empirical antiviral therapy | 4 (5.8)      |
| Reduction or cessation of immunosuppressant    | 3 (4.3)      |
| Stop antibiotics                               | 2 (2.9)      |
| Change antiviral agent                         | 1 (1.4)      |
| Stop antiviral agent                           | 1 (1.4)      |
| No change of clinical management               | 46 (66.7)    |

Values are presented as number (percentage).

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children or with milder forms of pneumonia [24]. However, children have much higher rates of respiratory viral illnesses than adults and should be discussed separately, and severe pneumonia is of most interest in the ICU setting [6, 25]. Among the 23 patients whose management was changed, the most common change was in antiviral agents (n = 18). Currently, anti-influenza agents are the only actively used antiviral agents, and ribavirin is the only antiviral treatment option for non-influenza respiratory viruses [26]. Our study results emphasize the need for the development of novel antiviral agents against respiratory viruses. Apart from antiviral agents, respiratory viral detection in critically ill patients led to a reduction or cessation of immunosuppressant treatment in 3 patients. The use of high-dose steroids is known to be associated with a higher mortality rate and longer viral shedding in influenza A patients [27]. Therefore, it can be helpful to reduce the use of immune-modulating agents, including steroids, to improve patient outcomes. Two other patients stopped using empirical antibiotics, and their treatment focused on the respiratory viruses as pathogens. The long-term use of antibacterial agents in patients with viral pneumonia is known to increase the risk for developing multidrug-resistant pathogens and *Clostridium difficile* infection rather than improving clinical outcomes [28, 29].

The bacterial coinfection rate of the present study was similar to that of previous reports [8, 30], which further supports the fact that patients with viral infection should be carefully examined for any additional bacterial infection. The most common bacterial pathogens of coinfection were common colonizers of the nasopharynx [31]. However, we failed to show a significant difference in mortality related to coinfection. This result is also consistent with previous reports, which showed comparable results for patients with and without bacterial coinfection [32]. The consequences of bacterial coinfection require further study.

Our study has several limitations. First, it was a retrospective study performed in a single center. Second, we considered all detected microorganisms as pathogens. However, a detected respiratory virus was unlikely to be neutral and was pathogenic in certain group of patients according to a previous report [33]. Although further studies are required, the possibility of invasiveness of detected respiratory virus should be taken into account. Third, although the RT-PCR kit of our institution is known to have good sensitivity and specificity [12–14], the risk of false-negativity cannot be perfectly ruled out. Fourth, the detection rate was lower than that of previous reports [21, 22]. The limited number of reported pathogens and inclusion of HAP may be responsible for this result. Of the 519 patients who underwent multiplex RT-PCR detection of respiratory viral pathogens, 188 (36.2%) were HAP patients. The detection rate increased to 18.8% when only CAP patients were considered, which is comparable to the results from a recent systematic review [34].

In conclusion, non-influenza respiratory viruses were commonly detected in severe pneumonia patients, and the detection of viral pathogens in patients with severe pneumonia can lead to changes in clinical management strategies. Therefore, RT-PCR analysis should be actively performed for severe pneumonia in the ICU, especially among those with risk factors for viral infection. Furthermore, future efforts are required to develop novel antiviral agents for non-influenza respiratory viruses.

**Supporting information**

S1 Table. Characteristics and clinical outcomes of viral pneumonia patients with and without bacterial coinfection.

(DOCX)

S2 Table. Clinical outcomes according to change in clinical management after detection of respiratory viruses.

(DOCX)
S1 File. Anonymized minimal dataset of the study.
(XLSX)

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