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Clinical and molecular characteristics of severe respiratory syncytial virus pneumonia in critically ill adults

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Revised abstract

- **Background**: Respiratory syncytial virus (RSV) has been increasingly recognized as a frustrating cause of morbidity and mortality in adults. However, its clinical impact and molecular characteristics of severe RSV-associated pneumonia in critically ill adult patients have rarely been addressed.
- **Methods**: This study, nested in a prospective cohort of severe pneumonia, was conducted at a 2,700-bed tertiary care hospital and comprised two parts. In part 1, we compared the clinical characteristics of severe RSV-associated pneumonia with severe influenza virus (IFV)-associated pneumonia between 2010 and 2019. In part 2, we performed phylogenetic and amino acid analyses of the G protein of RSV strains from three groups of different infection severity between 2015 and 2019 (Figure 1).
- **Results**: In part 1, 92 RSV- and 163 IFV-positive patients were identified. Structural lung diseases, diabetes mellitus, and malignancy were common underlying diseases. Immunocompromise (57.6% vs. 34.4%, p < 0.001) and hospital acquisition (47.8% vs. 23.9%, p < 0.001) were more common in the RSV group. Clinical manifestations at diagnosis between the groups were generally similar. Co-infection with *Streptococcus pneumoniae* (3.3% vs. 9.8%, p = 0.08) and methicillin-susceptible *Staphylococcus aureus* (1.1% vs. 6.8%, p = 0.06) tended to less frequent in the RSV group. The mortalities of patients in both groups were similarly high (Table 1). In part 2, 26 RSV strains from three groups (group 1: 11 strains, group 2: 8 strains, and group 3: 7 strains) were analyzed. All isolated RSV-A and -B strains belonged to the ON1 and the BA9 genotypes, respectively. The phylogenetic analysis revealed that the adult severe pneumonia strains (group 1) clustered by contemporary strains from other groups rather than severe pneumonia strains. There were no significantly different genetic variations among the three groups of different diseases severity, including the subtype clades, amino acid sequence substitutions, and changes in potential glycosylation sites.
- **Conclusions:** Severe RSV pneumonia was associated with substantial morbidity and mortality in critically ill adult patients, similar to IFV. The higher incidence of RSV in severe HAP suggests that the transmissibility of RSV can exceed that of IFV in a hospital setting. The molecular characteristics of RSV strains from the adults with severe pneumonia were not distinct from strains from non-pneumonic adults or children, underscoring that host factors, not viral factors, mainly determine the severity of RSV respiratory tract infection.

Background

- Respiratory syncytial virus (RSV) has been increasingly recognized as an important cause of morbidity and mortality in adults. However, even in recent studies regarding the burden and outcomes of RSV infection in adult hospitalized patients, no attention has been paid to the role of RSV in severe pneumonia.
- Thus, using 10-year prospective cohort data, we evaluated the epidemiology, clinical characteristics, and outcomes of severe RSV-associated pneumonia compared with severe influenza virus (IFV)-associated pneumonia. In addition, we explored the relationship between RSV strain variability and severity of RSV infection in adults hospitalized using whole-genome sequencing.

Methods

- This study, nested in a prospective cohort of patients with severe pneumonia, was conducted at a 28-bed medical ICU at the Asan Medical Center, a 2,700-bed tertiary hospital in Seoul, Republic of Korea.
- **Part 1 (clinical part)**: March 2010 – February 2019, aged ≥ 16 years admitted to the ICU with severe pneumonia were prospectively identified; patients with severe RSV- or IFV –associated pneumonia were included.
- **Part 2 (molecular part)**: Available RSV-positive respiratory specimens, obtained during the period between September 2015 and February 2019, underwent whole-genome sequencing (WGS). Additionally adult non-pneumonic RSV-positive samples for each epidemic season and pediatric RSV-positive clinical samples' complete genomes were sequenced to ascertain the whole genome of RSV-A and –B strains circulating in South Korea (Figure 1).

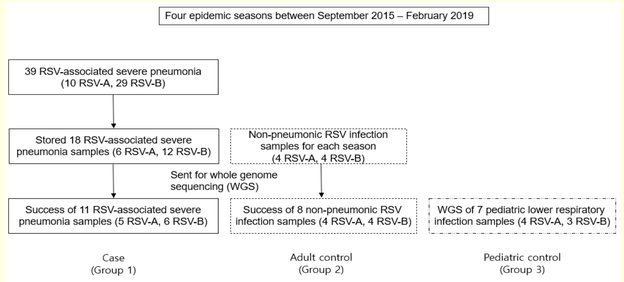

Figure 1. Flowchart of clinical sample selection process for the whole-genome sequencing

Results

(Part 1) 1. Epidemiology of severe viral pneumonia over nine years

- A total of 2,865 patients with severe pneumonia were identified.
- Bacterial and viral pathogens were identified in 46.5% (1331/2865) and 26.1% (747/2865).
- IFV (6.1%) > rhinovirus (5.7%) > parainfluenza virus (4.4%) > RSV (3.6%) > endemic human coronavirus including HCoV-OC43/HKU1 & HCoV-229E/NL63 (3.0%) > metapneumovirus (2.1%).
- RSV and IFV accounted for 3.4% and 8.1% of 1,589 cases of severe CAP, respectively, whereas 3.8% and 3.5% of 1,276 cases of severe HAP were caused by RSV and IFV, respectively.

2. Comparison of patients with severe RSV and IFV

- After excluding 9 patients with RSV and IFV co-infection, 92 (47 RSV-A and 45 RSV-B) patients with RSV and 163 (132 IFV-A and 31 IFV-B) with IFV were analyzed (Table 1).
- Immunocompromised (57.6% vs. 34.4%, p<0.001) and hospital acquisition (47.8% vs. 23.9%, p<0.001) were more common in the RSV group than in the IFV group.
- During the nine epidemic seasons, RSV-A and RSV-B predominated alternately (B-A-A-B-A-B-A-B-A).
- In the RSV group, 50 patients (54.3%) received oral ribavirin therapy, 6 (6.5%) received intravenous immune globulin (IVIG) only, and 25 (27.2%) received oral ribavirin with IVIG. Most patients (96.9%) with IFV received oseltamivir (73.6%) or peramivir (21.5%).
- The two groups' 90-day morality rates were similar (43.5% vs. 40.5%, p=0.69).
- In the RSV group, structural lung disease (adjusted odds ratio [aOR], 6.51; 95% confidence interval [CI], 1.78–23.8, p=0.005), a low platelet count (≤100,000/mm3) (aOR, 4.0; 95% CI, 1.38–11.56, p=0.01), and an APACHE II score ≥25 at ICU admission (aOR, 3.42; 95% CI, 1.19–9.86, p=0.02) were associated with 90-day mortality.

(Part 2) All isolated RSV-A and –B strains belonged to the ON1 and BA9 genotypes, respectively.

- Phylogenetic analysis: RSV-A and -B strains could be categorized into several distinct clades, clustering with Korean children's bronchiolitis strains and upper respiratory tract infection strains from other parts of the world.
- Among the three groups of different severity, there were no significantly different genetic variations, including amino acid substitutions and changes in potential glycosylation sites.

Table 1. Characteristics of 255 patients with severe virus-associated pneumonia

Characteristic	Respiratory syncytial virus (n = 92)	Influenza virus (n = 163)	p value
Demographics			
Male sex	51 (55.4)	99 (60.7)	0.43
Median age, year (IQR)	65.0 (57–73)	68.0 (58–77)	0.62
Underlying disease or condition*			
Structural lung disease	19 (20.7)	68 (29.5)	0.14
Chronic obstructive lung disease	8 (8.7)	22 (13.5)	0.31
Interstitial lung disease	10 (10.9)	15 (9.2)	0.67
Bronchiectasis	1 (1.1)	7 (4.3)	0.27
Destroyed lung due to tuberculosis	1 (1.1)	4 (2.5)	0.66
Bronchiolitis obliterans	0	1 (0.6)	0.45
Diabetes mellitus	32 (34.8)	44 (27.0)	0.20
Hematologic malignancy	30 (32.6)	23 (14.1)	0.01
Solid cancer	9 (9.8)	18 (11.0)	0.83
End-stage renal disease	4 (4.4)	12 (7.4)	0.43
Congestive heart failure	5 (5.4)	10 (6.1)	> 0.99
Liver cirrhosis	2 (2.2)	5 (3.1)	> 0.99
Chronic renal failure	4 (4.4)	12 (7.4)	0.43
Immunocompromised state†	53 (57.6)	56 (34.4)	**< 0.001**
Body mass index (mean, SD)	22.7, 3.4	22.0, 3.7	0.18
Underweight (BMI <18.5 kg/m^2)	9 (9.8)	30 (18.5)	0.06
Overweight (25≤ BMI < 30 kg/m^2)	18 (19.6)	31 (19.1)	0.93
Obesity (BMI >30 kg/m^2)	3 (3.3)	3 (1.9)	0.48
Category of pneumonia			
Community-acquired	48 (52.2)	124 (76.1)	**< 0.001**
Hospital-acquired	44 (47.8)	39 (23.9)	**< 0.001**
General ward	43/44 (97.7)	34/39 (87.2)	0.09
Intensive care unit	1/44 (2.3)	5/39 (12.8)	
Manifestations			
Dyspnea	82 (89.1)	143 (88.3)	> 0.99
Fever (≥ 38℃)	75 (81.5)	135 (82.8)	0.87
Cough	56 (60.9)	122 (75.3)	0.02
Sputum	59 (64.1)	118 (72.8)	0.16
Septic shock at ICU admission	51 (55.4)	106 (65.0)	0.14
Mechanical ventilation	89 (96.7)	159 (97.6)	0.71
APACHE II score (mean, SD)	27.3, 6.9	26.9, 7.3	0.67
Co-pathogen‡			
Any	38 (41.3)	80 (49.1)	0.24
Bacteria	26 (28.3)	60 (36.8)	0.17
Streptococcus pneumoniae	3 (3.3)	16 (9.8)	**0.08**
Staphylococcus aureus	7 (7.6)	18 (11.0)	0.51
Methicillin-susceptible *S. aureus*	1 (1.1)	11 (6.8)	**0.06**
Methicillin-resistant *S. aureus*	6 (6.5)	7 (4.3)	0.56
Other virus	12 (13.0)	17 (10.4)	0.54
Fungus	8 (8.7)	13 (8.0)	0.84
Mycobacteria	0	2 (1.2)	0.54

Data are presented as a number (%) unless otherwise stated.
APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

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

‡ Defined as one of the following conditions: (i) daily receipt of immunosuppressants, including corticosteroids; (ii) human immunodeficiency virus infection; (iii) solid organ or hematopoietic stem cell transplant recipients; (iv) receipt of chemotherapy for underlying malignancy during the previous six months; and (v) presence of underlying immune deficiency disorder.

† Within 24 hours before or after a diagnosis of viral infection.

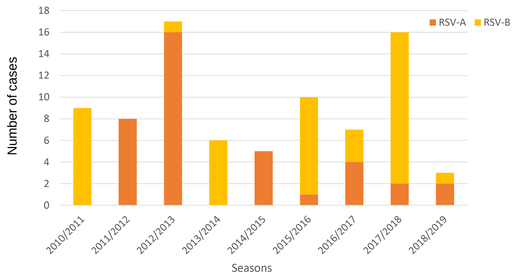

Figure 2. Prevalence data for RSV serotypes over nine epidemic seasons.

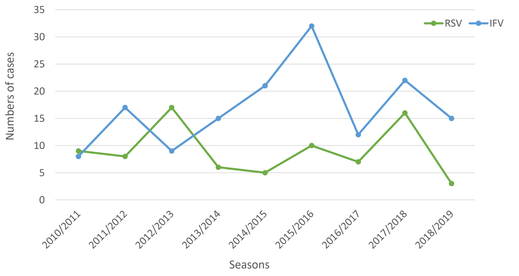

Figure 3. Yearly prevalence of severe RSV and IFV-associated pneumonia.

- Limitations: 1) the single-center analysis, limiting generalizability of the data; 2) we may have included coincidental upper respiratory viral infections or colonization cases, because fewer than half of the patients underwent BAL.

Conclusions

- RSV infection constitutes substantial morbidity and mortality in critically ill adult patients, similar to IFV.
- The higher incidence of RSV in severe HAP suggests that the transmissibility of RSV exceeds that of IFV in hospital settings.
- The sole genotypes were RSV-A ON1 and RSV-B BA9 over four epidemic seasons.
- Finding no significant association between severe diseases and RSV genetic variability indicates that the host factors might be essential to determine the disease severity.
- This study also highlighted the need for thorough infection control measures and novel therapeutic approaches to RSV infection, especially in hospitalized immuno-compromised hosts.