

Characteristics and Outcomes of Patients with Pulmonary Acute Respiratory Distress Syndrome Infected with Influenza versus Other Respiratory Viruses

Jung-Wan Yoo, M.D.¹, Sunmi Ju, M.D.¹, Seung Jun Lee, M.D., Ph.D.¹, Min-Chul Cho, M.D., Ph.D.², Yu Ji Cho, M.D., Ph.D.¹, Yi Yeong Jeong, M.D., Ph.D.¹, Jong Deog Lee, M.D., Ph.D.¹ and Ho Cheol Kim, M.D., Ph.D.³

Departments of ¹Internal Medicine and ²Laboratory Medicine, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, ³Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Gyeongsang National University School of Medicine, Changwon, Korea

Background: Although the frequency of respiratory viral infection in patients with pulmonary acute respiratory distress syndrome (ARDS) is not uncommon, clinical significance of the condition remains to be further elucidated. The purpose of this study was to compare characteristics and outcomes of patients with pulmonary ARDS infected with influenza and other respiratory viruses.

Methods: Clinical data of patients with pulmonary ARDS infected with respiratory viruses January 2014–June 2018 were reviewed. Respiratory viral infection was identified by multiplex reverse transcription–polymerase chain reaction (RT-PCR).

Results: Among 126 patients who underwent multiplex RT-PCR, respiratory viral infection was identified in 46% (58/126): 28 patients with influenza and 30 patients with other respiratory viruses. There was no significant difference in baseline and clinical characteristics between patients with influenza and those with other respiratory viruses. The use of extracorporeal membrane oxygenation (ECMO) was more frequent in patients with influenza than in those with other respiratory viruses (32.1% vs 3.3%, $p=0.006$). Co-bacterial pathogens were more frequently isolated from respiratory samples of patients with pulmonary ARDS infected with influenza virus than those with other respiratory viruses. (53.6% vs 26.7%, $p=0.036$). There were no significant differences regarding clinical outcomes. In multivariate analysis, acute physiology and chronic health evaluation II was associated with 30-mortality (odds ratio, 1.158; 95% confidence interval, 1.022–1.312; $p=0.022$).

Conclusion: Respiratory viral infection was not uncommon in patients with pulmonary ARDS. Influenza virus was most commonly identified and was associated with more co-bacterial infection and ECMO therapy.

Keywords: Acute Respiratory Distress Syndrome; Respiratory Virus; Multiplex Reverse Transcription Polymerase Chain Reaction; Outcomes

Address for correspondence: Ho Cheol Kim, M.D., Ph.D.

Department of Internal Medicine, Gyeongsang National University Changwon Hospital, 91 Samjeongja-ro, Seongsan-gu, Changwon 51472, Korea

Phone: 82-55-214-3730, **Fax:** 82-55-214-8618, **E-mail:** hochkim@gnu.ac.kr

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Introduction

Acute respiratory distress syndrome (ARDS) is one of the chief conditions for which patients are admitted to the intensive care unit (ICU) and contributes to substantial mortality rates¹. Respiratory viral infection is not uncommon in critically ill patients who received invasive mechanical ventilation due to respiratory failure². Some studies have reported that the frequency of respiratory viral infection ranged from 13.4% to 49%³⁻⁵. Availability of multiplex reverse transcription–polymerase chain reaction (RT-PCR) has facilitated the identification of respiratory viral infection⁶. Among the diverse risk factors for ARDS, respiratory viral infection has been shown to contribute to development and progression of pulmonary ARDS^{7,8}. Although several studies have reported the clinical impact of respiratory viruses on critically ill patients^{3,9}, further studies are needed to clarify the significance on those with pulmonary ARDS. Influenza viral infection in pulmonary ARDS has gained attention to intensivists due to high morbidity and mortality^{10,11}, but little data comparing characteristics and outcomes of the different types of viruses in patients with pulmonary ARDS. Moreover, differences in clinical outcomes between patients infected with influenza and other respiratory viruses have not been clearly elucidated.

The aim of this study was to compare the characteristics and clinical outcomes of patients with pulmonary ARDS infected with influenza vs. other respiratory viruses.

Material and Methods

1. Patients

Patients diagnosed with pulmonary ARDS who were admitted to the medical ICU at a tertiary hospital and received invasive mechanical ventilation were searched from January 2014 to June 2018. ARDS was fulfilled for the Berlin diagnostic criteria¹². Among them, those who underwent RT-PCR for respiratory viral infection were reviewed. Respiratory specimens such as bronchial and endotracheal aspirate, nasopharyngeal swab or sputum were obtained for RT-PCR analysis. Advansure RV real-time RT-PCR (LG Chemistry, Seoul, Korea) assay based on the multiplex polymerase chain reaction method was used to identify respiratory viruses (influenza virus, parainfluenza virus, respiratory syncytial virus, adenovirus, metapneumovirus, rhinovirus, bocavirus, and coronavirus). Baseline (age, sex, body mass index, and comorbidities) and clinical characteristics (Acute Physiology and Chronic Health Evaluation [APACHE] II score, Sequential Organ Failure Assessment [SOFA] score, clinical complications [shock, acute kidney injury], management, etc.) were assessed. Additionally, data from laboratory (neutrophil count, lymphocyte count, hemoglobin, platelet, C-reactive protein [CRP] level, total

protein level, albumin level, etc.), microbiologic data (types of respiratory virus, co-respiratory bacterial or fungal pathogens) and clinical outcomes (length of stay in ICU and hospital, mortality) were analyzed. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital (No. 2018-05-015). Informed consent was waived due to retrospective nature of the study. The study was in accordance with the ethical standards of institutional and/or national research committees and with the Helsinki declaration and its later amendments or comparable ethical standards.

2. Statistical analysis

Continuous data were expressed as mean±standard deviation (SD) and compared using the Mann-Whitney U test. Non-continuous data were expressed as numbers and percentages and were analyzed using the chi-square or Fisher exact test. To evaluate factors associated with a 30-mortality, logistic regression analysis was used. Factors with p-value <0.1 in univariate analysis were entered into multivariate analysis. All data were analyzed using the SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

One hundred sixty-seven patients with pulmonary ARDS were admitted to the medical ICU. Figure 1 shows flow of patients with ARDS during the period. One hundred and twenty-six patients with pulmonary ARDS (75.4%) underwent multiplex RT-PCR to evaluate the presence of respiratory viral infection, which was identified in 46% (58/126) subjects. Community-acquired respiratory viral infection was identified

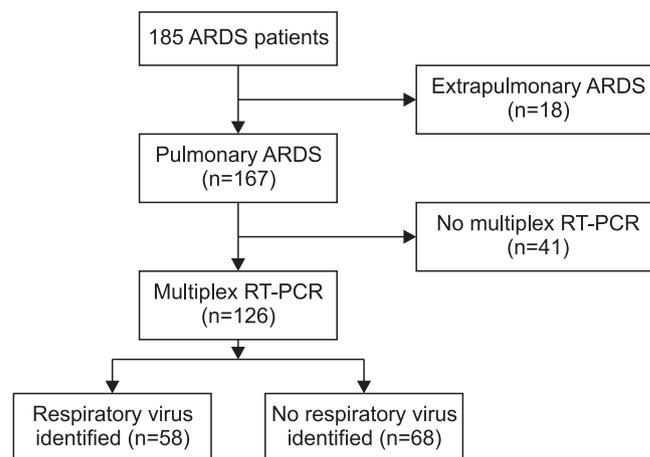


Figure 1. The number of patients with acute respiratory distress syndrome during the period. ARDS: acute respiratory distress syndrome; RT-PCR: reverse transcription–polymerase chain reaction.

Table 1. Comparison of characteristics between patients with influenza and those with other respiratory virus infection

Variable	Total (n=58)	Influenza virus (n=28)	Other respiratory virus (n=30)	p-value
Age, yr	67.6±13.4	65.7±16.2	69.3±10.1	0.714
Male sex	41 (70.7)	19 (67.9)	22 (73.3)	0.647
BMI, kg/m ²	23.1±4.3	23.9±3.8	22.3±4.6	0.286
DM	19 (32.8)	11 (39.3)	8 (26.7)	0.306
CHF	4 (6.9)	2 (7.1)	2 (6.7)	>0.999
CKD	6 (10.3)	1 (3.6)	5 (16.7)	0.195
CLD	7 (12.1)	6 (21.4)	1 (3.3)	0.048
CVD	11 (19)	5 (17.9)	6 (20.0)	0.835
Active malignancy	7 (12.1)	1 (3.6)	6 (20.0)	0.104
COPD	10 (17.2)	3 (10.7)	7 (23.3)	0.301
APACHE II	27.9±7.1	27.3±7.8	28.5±6.4	0.498
SOFA	12.3±2.7	11.9±2.7	12.6±2.8	0.339
Septic shock	37 (63.8)	18 (64.3)	19 (63.3)	0.940
AKI	41 (70.7)	21 (75)	20 (66.7)	0.486
RRT	20 (34.5)	10 (35.7)	10 (33.3)	0.849
HFNC before IMV	27 (46.6)	16 (57.1)	11 (36.7)	0.118
NM blocker	19 (32.8)	9 (32.1)	10 (33.3)	0.923
Steroid	14 (24.1)	6 (21.4)	8 (26.7)	0.641
Prone position	3 (5.2)	2 (7.1)	1 (3.3)	0.605
ECMO	10 (17.2)	9 (32.1)	1 (3.3)	0.005

BMI: body mass index; DM: diabetes mellitus; CHF: chronic heart failure; CKD: chronic kidney disease; CLD: chronic liver disease; CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; AKI: acute kidney injury; RRT: renal replacement therapy; HFNC: high flow nasal cannula; IMV: invasive mechanical ventilation; NM: neuromuscular; ECMO: extracorporeal membrane oxygenation.

Table 2. Comparison of laboratory results and radiologic score between patients with influenza and those with other viruses

Variable	Total (n=58)	Influenza virus (n=28)	Other viruses (n=30)	p-value
WBC, ×10 ³ /mm ³	11.9±13.6	10.1±8.9	13.7±16.9	0.479
Hb, g/dL	11.6±2.6	12.2±2.2	11.1±2.8	0.081
Platelet, 10 ³ /mm ³	197.9±122.5	178.0±112.4	216.4±130.3	0.176
Albumin, g/dL	2.7±0.6	2.7±0.5	2.7±0.6	0.668
CRP, mg/dL	21.8±11.1	24.9±11.8	18.9±9.7	0.076
NT-pro-BNP, pg/mL	6,374.8±9,421.8	6,154.4±9,358.3	6,587.1±9,655.9	0.270
Lactate, mmol/L	4±3.3	4.1±3.1	3.8±3.5	0.915
PaCO ₂ , mm Hg	40.8±10.1	40.1±9.1	41.4±11	0.938
P/F ratio	112.1±52.6	108.8±54.2	115.1±43.9	0.409

WBC: white cell count; Hb: hemoglobin; CRP: C-reactive protein; NT-proBNP: N terminal probrain natriuretic peptide; PaCO₂: partial pressure of carbon dioxide; P/F: partial pressure of oxygen/fractioned inspired oxygen.

in 37 of 85 patients (43.5%) with community-acquired ARDS whereas hospital-acquired respiratory infection was detected in 21 of 41 those with hospital-acquired ARDS (51.2%)

(p=0.417).

The mean age of patients was 67.6±13.3 years and the proportion of men was 70.7%. In all cases, the risk factor for pul-

monary ARDS was pneumonia. Twenty-eight patients (48.3%) were infected with influenza virus while other respiratory viruses were identified in 30 patients (51.7%). Table 1 shows the characteristics of patients with influenza and those with other respiratory virus infection. There was no significant difference regarding baseline characteristics, severity of illness and clinical complications between patients with influenza and those with other respiratory viruses. Extracorporeal membrane oxygenation (ECMO) was significantly more used in patients with influenza virus than those with other respiratory viruses as a rescue therapy (32.1% vs. 3.3%, $p=0.006$).

Table 2 compares laboratory results and radiologic scores of patients with influenza and those with other viruses. There was a trend toward higher hemoglobin and CRP levels in

patients with influenza than in those with other respiratory viruses. No significant difference was observed in other parameters between the two groups. Transthoracic echocardiography was done in 75.9% (44/58) patients on admission of medical intensive care unit to evaluate acute heart failure. The mean ejection fraction was $59.2\pm 7.76\%$. Stress induced cardiomyopathy and right ventricular dysfunction were featured in three (6.7%) and five (11.1%) patients, respectively.

Table 3 enlists the types of respiratory viruses and co-respiratory pathogens in patients with pulmonary ARDS. Influenza A was the most common virus (21 cases) and other respiratory virus infection (10 coronavirus, 5 RSV, 4 parainfluenza virus, 4 rhinovirus, 3 adenovirus, 3 metapneumovirus, and 1 bocavirus) were isolated. Overall 43.1% co-respiratory

Table 3. Types of respiratory viruses and co-infected pathogens

Variable	Total (n=58)	Influenza virus (n=28)	Other viruses (n=30)	p-value
Types of respiratory virus				
Influenza A	-	21 (75.0)	-	
Influenza B	-	7 (25.0)	-	
Human coronavirus	-	-	10 (33.3)	
RSV	-	-	5 (16.7)	
Parainfluenza virus	-	-	4 (13.3)	
Rhinovirus	-	-	4 (13.3)	
Metapneumovirus	-	-	3 (10)	
Adenovirus	-	-	3 (10)	
Bocavirus	-	-	1 (3.3)	
Co-respiratory pathogen	25 (43.1)	16 (57.1)	9 (30)	0.037
Bacteria	23 (39.7)	15 (53.6)	8 (26.7)	0.036
Gram (+) pathogen	14 (24.1)	11 (39.3)	3 (10.0)	
<i>Streptococcus pneumoniae</i>	3 (5.2)	3 (10.7)	0 (0)	
<i>Staphylococcus aureus</i>	10 (17.2)	8 (28.6)	2 (6.6)	
MSSA	5 (8.6)	4 (14.3)	1 (3.3)	
MRSA	5 (8.6)	4 (14.3)	1 (3.3)	
<i>Streptococcus pyogenes</i>	1 (1.7)	0 (0)	1 (3.3)	
Gram (-) pathogen	9 (15.5)	4 (14.3)	5 (16.7)	-
<i>Klebsiella pneumoniae</i>	4 (6.8)	1 (3.6)	3 (10.0)	
ESBL-negative	2 (3.4)	1 (3.6)	1 (3.3)	
ESBL-positive	2 (3.4)	0 (0)	2 (6.7)	
<i>Acinetobacter baumannii</i>	5 (8.6)	3 (10.7)	2 (6.7)	
Carbapenem				
Susceptible	1 (1.7)	1 (3.6)	0 (0)	
Resistant	4 (6.9)	2 (7.1)	2 (6.7)	
<i>Pneumocystis jirovecii</i>	2 (3.4)	1 (3.6)	1 (3.3)	>0.999

RSV: respiratory syncytial virus; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; ESBL: extended-spectrum β -lactamase.

pathogens were isolated simultaneously. Patients with influenza presented with significantly higher co-bacterial pathogens than those with other respiratory viruses. Gram-positive bacteria co-infection was common in patients with influenza virus than those with other respiratory viruses (39.3% vs. 10%).

Clinical outcomes are presented and compared in Table 4. Patients with influenza virus were treated with neuraminidase inhibitor such as oseltamivir or peramivir but those any antiviral agent was not administered in those with other respiratory viruses. Overall ICU mortality and hospital mortality rates were 51.7% and 55.2%, respectively. There were no significant differences in extubation success, duration of mechanical ventilation, mortality, and length of stay in the ICU and hospital.

Multivariate analysis associated with 30-day mortality was performed and has been shown in Table 5. APACHE II score at admission was associated with ICU mortality. Influenza virus and co-bacterial infection were not associated with ICU mortality.

Factors associated with 30-day mortality are shown in Table 5. In univariate analysis, APACHE II, SOFA and low partial

pressure of oxygen/fractionated inspired oxygen ratio were associated with 30-day mortality. APACHE II only was associated with a 30-day mortality in multivariate analysis. Fourteen patients were treated with steroid. The reasons of use of steroid were treatment of concomitant exacerbation of airway disease (n=4, 6.9%), refractory septic shock (n=4, 6.9%), and adjunct treatment of ARDS (n=6, 10.3%), which might not affect mortality in ARDS patients with respiratory viral infection.

Discussion

The present study showed that approximately 46% patients with pulmonary ARDS had a concomitant respiratory viral infection and influenza A virus was most commonly isolated. Co-respiratory infection was more frequent in patients with influenza infection than in those with other respiratory viral infection. Although patients with influenza virus received more invasive treatment such as ECMO, clinical outcomes did not differ between patients with influenza infection and those

Table 4. Comparison of clinical outcomes between patients infected with influenza virus and those with other viruses

Variable	Total (n=58)	Influenza virus (n=28)	Other viruses (n=30)	p-value
ICU mortality	30 (51.7)	14 (50)	16 (53.3)	0.800
In hospital mortality	32 (55.2)	16 (57.1)	16 (53.3)	0.771
14-Day mortality	24 (41.4)	10 (35.7)	14 (46.7)	0.397
30-Day mortality	31 (53.4)	15 (53.6)	16 (53.3)	0.986
MV duration, day	10.9±11	12.2±11.4	9.6±10.7	0.236
LOS, ICU, day	12.2±11.6	13.4±11.3	11.1±11.1	0.300
LOS, hospital, day	16.3±14.1	17.1±13.8	15.6±14.6	0.414

Values are presented as number (%) or mean±SD.

ICU: intensive care unit; MV: mechanical ventilation; LOS: length of stay; SD: standard deviation.

Table 5. Univariate and multivariate analyses for factors associated with 30-day mortality in patients with ARDS with respiratory viral infection

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.033	0.991–1.076	0.126	-	-	-
Male sex	0.519	0.162–1.671	0.272	-	-	-
APACHE II	1.181	1.066–1.309	0.001	1.158	1.022–1.312	0.022
SOFA	1.320	1.061–1.643	0.013	1.021	0.753–1.384	0.893
Steroid	1.800	0.519–6.237	0.354	-	-	-
PaO ₂ /FiO ₂ ratio	0.987	0.975–0.998	0.027	0.391	0.979–1.008	0.391
Influenza virus	1.010	0.360–2.835	0.986	-	-	-
Co-infected pathogen	2.133	0.735–6.195	0.164	-	-	-

ARDS: acute respiratory distress syndrome; OR: odds ratio; CI: confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; PaO₂: arterial partial pressure of oxygen; FiO₂: fraction of inspired oxygen.

with other viral infection. APACHE II was associated with ICU mortality in patients with pulmonary ARDS.

ARDS is a common reason of admission to the ICU in critically ill patients with one-quarter of the total number of patients receiving mechanical ventilation being diagnosed with the condition¹. ARDS also contributes to substantial mortality in the ICU¹. Various risk factors are associated with ARDS and pulmonary ARDS is frequently encountered in ICU. Pneumonia has been known as the most common etiology of pulmonary ARDS¹³. The co-infection of respiratory virus was found in patients with severe pneumonia admitted to ICU ranging from 13.4% to 49%³⁻⁵. The frequency of respiratory viral infection in pulmonary ARDS has not been established. The current study showed similar frequency of respiratory viral infection in pulmonary ARDS as those of severe pneumonia in patients admitted to the ICU. Respiratory viruses play a role in development and progression of ARDS⁸; therefore, it is important to elucidate the clinical significance of them in patients with pulmonary ARDS. Several studies have reported clinical outcomes in patients infected with respiratory viruses receiving mechanical ventilation¹⁴⁻¹⁷. In the present study, clinical outcomes did not differ between patients with infected with influenza virus and those with other respiratory viruses. Similar clinical outcomes were reported in patients with respiratory syncytial virus or rhinovirus compared to influenza virus^{17,18}. In the current study, comparison of clinical outcomes in each respiratory viruses was not performed due to a few cases except for influenza virus. APACHE II score was associated with a 30-day mortality in patients with ARDS infected with respiratory viruses, which suggests that severity of illness has an impact on overall clinical outcomes.

In the present study, ECMO was more frequently used in patients with influenza virus than those with other respiratory virus. Several studies have reported the use of ECMO in case of refractory hypoxemia in patients with influenza-related ARDS^{14,19,20}. However, the clinical implication of more frequent application of ECMO in patients with influenza virus should be interpreted cautiously in the present study. The use of ECMO is generally determined by multiple factors including the severity of illness, comorbidities of patients rather than types of respiratory viruses²¹.

In the current study, co-respiratory bacterial pathogens was in more than half of patients with influenza. The current study is consistent with previous studies that influenza virus infection was commonly complicated with co-infection by bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae*^{22,23}. This supports the use of empirical antibiotics in cases of ARDS infected with influenza virus.

The present study has several limitations. First, this study was conducted at a single center and analyzed data retrospectively, therefore selection bias cannot be excluded. Second, the site obtaining respiratory sample was not the same, therefore, whether respiratory viruses were pathogens cannot be ac-

curately distinguished. The miss to detect respiratory viruses by multiplex RT-PCR cannot be ruled out. Third, the change in clinical decision by identifying respiratory viruses was not evaluated as in a previous study⁵. Fourth, the prone position was performed in the low proportion of patients with ARDS compared to a recent study¹.

In conclusion, respiratory viral infection was frequently observed in patients with pulmonary ARDS as demonstrated by multiplex RT-PCR. Patients with influenza virus had more co-bacterial infection and received ECMO than those with other respiratory viruses without significant difference with respect to clinical outcomes.

Authors' Contributions

Conceptualization: Yoo JW. Methodology: Ju S, Lee SJ, Cho MC, Cho YJ, Jeong YY, Lee JD. Data curation: Ju S, Lee SJ, Cho MC, Cho YJ, Jeong YY, Lee JD. Writing - original draft preparation: Yoo JW. Writing - review and editing: Kim HC. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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