Correlation between Pneumonia Severity and Pulmonary Complications in Middle East Respiratory Syndrome

Wan Beom Park,1 Kang Il Jun,1 Gayeon Kim,2 Jae-Phil Choi,2 Ji-Young Rhee,4 Shinhyea Cheon,5 Chang Hyun Lee,6,7 Jun-Sun Park,8 Yeonjae Kim,2 Joon-Sung Joh,2 Bum Sik Chin,2 Pyeong Gyun Choe,1 Ji Hwan Bang,1 Sang-Won Park,2 Nam Joong Kim,1 Dong-Gyun Lim,2 Yeon-Sook Kim,3 Myoung-don Oh,1 and Hyoung-Shik Shin2

1Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
2Center for Infectious Diseases, National Medical Center, Seoul, Korea
3Department of Internal Medicine, Chungnam National University Hospital, Daejeon, Korea
4Division of Infectious Disease, Department of Medicine, Dankook University College of Medicine, Cheonan, Korea
5Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
6Institute of Radiation Medicine, Seoul National University Medical Research Center, Seoul, Korea
7Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, National Medical Center, Seoul, Korea

ABSTRACT

This nationwide, prospective cohort study evaluated pulmonary function and radiological sequelae according to infection severity in 73 survivors from the 2015 Middle East respiratory syndrome (MERS) outbreak in Korea. Patients with severe pneumonia in MERS-coronavirus infection had more impaired pulmonary function than those with no or mild pneumonia at the 1-year follow-up, which was compatible with the radiological sequelae. Severe pneumonia significantly impairs pulmonary function and makes long radiological sequelae in MERS.

Keywords: MERS; Complication; Coronavirus; Outbreak

The 2015 outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the Republic of Korea developed from a traveler returning from the Middle East,1 which is the largest outbreak outside of the Arabian Peninsula to date. This unprecedented nationwide outbreak resulted in 186 laboratory-confirmed cases with 38 fatalities and >16,000 individuals being quarantined.2-4 During the outbreak, a comprehensive screening test including MERS-CoV real-time reverse transcription polymerase chain reaction (rRT-PCR) was performed in all possible contacts to prevent further spread of the disease. Positive MERS-CoV rRT-PCR findings were observed in patients with no or mild symptoms, who were also subjected to epidemiological investigation and follow-up.1

There have been many reports of long-term sequelae of severe acute respiratory syndrome (SARS),5-10 but to the best of our knowledge no report has addressed long-term sequelae in...

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The severity of pneumonia was defined as the patient requiring oxygen therapy, mild pneumonia was defined as the patient presenting with infiltration on chest X-ray but not requiring oxygen therapy, and no pneumonia was defined as the patient without radiographic evidence of pneumonia.

Linear regression or linear by linear association was used to evaluate the association between the severity of pneumonia and continuous or categorical variables, as appropriate. The correlation between pneumonia severity and pulmonary function or radiological sequelae was evaluated using a multivariable linear regression model including age, sex, underlying lung disease, and smoking. All pulmonary function values were presented as predicted percentage considering age, sex, height, body weight, and race. Radiological sequelae were scored as the number of involved lung segments (total score = 19) on chest CT that were suspected to be post-inflammation sequelae, including sub-segmental atelectasis, ground glass opacity, and consolidation by a radiologist. Emphysema, sequelae of tuberculosis, and bronchiectasis were excluded. Severe pneumonia was defined as the patient requiring oxygen therapy, mild pneumonia was defined as the patient presenting with infiltration on chest X-ray but not requiring oxygen therapy, and no pneumonia was defined as the patient without radiographic evidence of pneumonia.

Among a total of 146 survivors in the outbreak, 49 (34%) refused to participate in the study and 24 (16%) could not be contacted by any method. Therefore, 73 patients were enrolled in the study: 18 (25%) patients without pneumonia, 35 (48%) patients with mild pneumonia, and 20 (27%) patients with severe pneumonia. The mean patient age was 51 ± 13 years, 30 (41%) were female, and the severe pneumonia group tended to have more male patients (Table 1). Fourteen patients (19%) had a history of smoking and the patients with pneumonia were more likely to have a history of smoking. None of the underlying diseases were associated with the severity of pneumonia.

The frequency of patients with lung function parameters < 80% of predicted values was as follows: FVC (6/73, 8%), FEV₁ (6/73, 8%), and DLCO (25/68, 37%). After adjusting for age, sex, underlying lung disease, and smoking, FVC and DLCO significantly correlated with the severity of pneumonia (P = 0.008 and P = 0.046; Table 2). The patients with severe pneumonia had lower FVC and DLCO than the patients with no or mild pneumonia (Fig. 1). TLC, FEV₁, FEV₁/FVC, and the walking distance in the 6-minute walk test were not significantly associated with the severity of pneumonia.
CT was performed 1 year after MERS-CoV infection in 65 (89%) patients. Radiological sequelae were revealed in 25% (4/16), 63% (19/30), and 95% (18/19) of patients in the no, mild, and severe pneumonia groups, respectively ($P < 0.001$). The median radiological sequelae score was 0, 1, and 3 in the no, mild, and severe pneumonia groups, respectively, and the radiological sequelae scores were significantly correlated with the severity of pneumonia ($P < 0.001$, Table 2).

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Table 1. Baseline characteristics of 73 patients with MERS-CoV infection

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 73)</th>
<th>No pneumonia (n = 18)</th>
<th>Mild pneumonia (n = 35)</th>
<th>Severe pneumonia (n = 20)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>51 (25–80)</td>
<td>47 (25–80)</td>
<td>56 (25–78)</td>
<td>54 (28–69)</td>
<td>0.872</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>30 (41)</td>
<td>9 (50)</td>
<td>17 (49)</td>
<td>4 (20)</td>
<td>0.056</td>
</tr>
<tr>
<td>Health care provider</td>
<td>20 (27)</td>
<td>8 (44)</td>
<td>7 (20)</td>
<td>5 (25)</td>
<td>0.200</td>
</tr>
<tr>
<td>Smoker</td>
<td>14 (19)</td>
<td>0 (0)</td>
<td>9 (26)</td>
<td>5 (25)</td>
<td>0.059</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (22)</td>
<td>5 (28)</td>
<td>4 (11)</td>
<td>7 (35)</td>
<td>0.543</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (12)</td>
<td>3 (17)</td>
<td>3 (9)</td>
<td>3 (15)</td>
<td>0.904</td>
</tr>
<tr>
<td>Lung disease</td>
<td>4 (6)</td>
<td>1 (6)</td>
<td>1 (3)</td>
<td>2 (10)</td>
<td>0.528</td>
</tr>
<tr>
<td>Liver disease</td>
<td>3 (4)</td>
<td>1 (6)</td>
<td>2 (6)</td>
<td>0</td>
<td>0.379</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>3 (4)</td>
<td>0</td>
<td>3 (9)</td>
<td>0</td>
<td>0.543</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2 (3)</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (5)</td>
<td>0.351</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>2 (3)</td>
<td>1 (6)</td>
<td>0</td>
<td>1 (5)</td>
<td>0.957</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>0.970</td>
</tr>
</tbody>
</table>

Data are presented as median (range) or No. (%).

MERS-CoV = Middle East respiratory syndrome coronavirus.

Table 2. Pulmonary function and radiological sequelae of 73 patients with MERS-CoV infection

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>No pneumonia</th>
<th>Mild pneumonia</th>
<th>Severe pneumonia</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC, %</td>
<td>97 (57–154)</td>
<td>112 (87–154)</td>
<td>95 (79–121)</td>
<td>97 (57–148)</td>
<td>0.843</td>
</tr>
<tr>
<td>FVC, %</td>
<td>93 (42–142)</td>
<td>94 (81–142)</td>
<td>94 (74–126)</td>
<td>88 (42–108)</td>
<td>0.008</td>
</tr>
<tr>
<td>FEV1, %</td>
<td>88 (40–154)</td>
<td>91 (74–154)</td>
<td>88 (64–143)</td>
<td>84 (40–120)</td>
<td>0.072</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>79 (53–94)</td>
<td>79 (67–94)</td>
<td>78 (53–87)</td>
<td>80 (74–85)</td>
<td>0.291</td>
</tr>
<tr>
<td>DLCO, %</td>
<td>77 (28–117)</td>
<td>75 (42–83)</td>
<td>83 (70–117)</td>
<td>68 (28–101)</td>
<td>0.046</td>
</tr>
<tr>
<td>6 min walking test, m</td>
<td>540 (50–738)</td>
<td>563 (50–738)</td>
<td>490 (317–600)</td>
<td>540 (315–721)</td>
<td>0.750</td>
</tr>
<tr>
<td>Score of radiological sequelae</td>
<td>1 (0–12)</td>
<td>0 (0–5)</td>
<td>1 (0–11)</td>
<td>3 (0–12)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as median (range) or No. (%).

MERS-CoV = Middle East respiratory syndrome coronavirus, TLC = total lung capacity, FVC = forced volume vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity, CT = computed tomography.

*Adjusted for age, sex, underlying lung disease, and smoking.

Fig. 1. Comparison of pulmonary function in patients with no or mild pneumonia and patients with severe pneumonia. (A) FVC. (B) FEV1. (C) DLCO. $P$ values were adjusted for age, sex, underlying lung disease, and smoking. Whiskers indicate minimum and maximum values.

FVC = forced volume vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity, MERS = Middle East respiratory syndrome.
This is the first cohort study showing long-term pulmonary complications of MERS-CoV infection. The findings suggest that more severe MERS pneumonia can result in more impaired lung function at least 1 year after MERS-CoV infection. These findings were compatible with radiological sequelae.

Several studies have examined the effect of SARS on pulmonary function 1 year after infection. A previous study showed that 24% of SARS survivors have impaired DLCO and 5% reduced lung volume at 12 months. Several studies on acute respiratory distress syndrome survivors showed that their pulmonary function usually returns to normal or near normal by 6–12 months, but a mild reduction of DLCO may persist in up to 80% of patients at 1 year after recovery. These findings were very similar to the results of the present study. We also showed that 37% of MERS survivors have impaired DLCO at 12 months, whereas only 8% of patients had a reduced FVC.

The previous study found that SARS survivors who required intensive care unit admission had lower predicted FVC and DLCO than those who did not, but there were no differences in the 6-minute walking test. These findings were also compatible with our results, which showed that severe pneumonia requiring oxygen therapy is associated with more impaired lung function, but there was no difference in exercise capacity.

The present study has several limitations. First, the patients with underlying lung diseases and impaired lung function may have more severe MERS pneumonia. The patients with severe pneumonia had more underlying lung diseases, though the difference was not significant. However, even after adjusting for underlying lung diseases and smoking, the correlation between the MERS pneumonia severity and lung function impairment was significant. Second, because we defined pneumonia as infiltration on chest X-ray, we may classify a patient with mild pneumonia in the group without pneumonia. In fact, radiological sequelae on chest CT was observed in approximately 25% of the patients without pneumonia. Third, only 50% of the eligible MERS-CoV infected survivors were enrolled, which may not represent all of the MERS-CoV survivors in Korea. Forth, no baseline pulmonary function or CT scans were not available. Lastly, our definition of severe pneumonia as requirement of oxygen therapy may be broad and subjective. Ventilator care or mortality may indicate the patients with more severe pneumonia, although small number of patients hampered further classification in this study.

In summary, patients with more severe MERS-CoV pneumonia may have more impaired pulmonary function at 1 year, which is compatible with the radiological sequelae.
REFERENCES


