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Predictive factors for pneumonia development and progression to respiratory failure in MERS-CoV infected patients

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Summary  Background: After the 2015 Middle East respiratory syndrome (MERS) outbreak in Korea, prediction of pneumonia development and progression to respiratory failure was emphasized in control of MERS outbreak.
Methods: MERS-CoV infected patients who were managed in a tertiary care center during the 2015 Korean MERS outbreak were reviewed. To analyze predictive factors for pneumonia development and progression to respiratory failure, we evaluated clinical variables measured within three days from symptom onset.
Results: A total of 45 patients were included in the study: 13 patients (28.9%) did not develop pneumonia, 19 developed pneumonia without respiratory failure (42.2%), and 13 progressed to respiratory failures (28.9%). The identified predictive factors for pneumonia development...
Predictive factors for MERS progression

Introduction

Middle East respiratory syndrome (MERS) is an emerging lethal respiratory disease caused by a novel betacoronavirus (MERS-CoV). From May to July 2015, there was a hospital-associated MERS outbreak in the Republic of Korea reporting 186 laboratory-confirmed cases, which is the largest recorded outbreak outside the Arabian Peninsula. The outbreak featured several super-spreading events with unexpectedly high human-to-human transmission rate: 136 of 186 cases (73.1%) were transmitted from only three patients. As these large transmission clusters were exclusively originated from patients with pneumonia, prediction of pneumonia development has been emphasized in control of MERS outbreak. In addition, pneumonia progression to respiratory failure should be anticipated in advance to avoid urgent intubation or cardiopulmonary resuscitation which might break protection of healthcare workers. Although several studies analyzed prognostic factors for fatal outcome, predictive factors for pneumonia development and progression to respiratory failure have not been reported. To identify factors which can predict pneumonia development and progression to respiratory failure at the early course of the disease, we evaluated MERS-CoV infected patients managed in a tertiary care center during the 2015 MERS outbreak in Korea.

Methods

Study design and patient grouping

To identify factors which can predict pneumonia development and progression to respiratory failure at the early course of the disease, we reviewed the electronic medical records of who were diagnosed with MERS-CoV infection and admitted at Samsung Medical Center, a 1950 tertiary care university hospital which managed the largest number of MERS-CoV infected patients as a single center during the 2015 Korean MERS outbreak. As it is still unclear whether initially asymptomatic patients would develop pneumonia or not, we included all the MERS-CoV infected patients managed at our hospital during the outbreak regardless of symptoms presence. To avoid confusion with the case definition was used in the present analysis. Thrombocytopenia was defined as a platelet count lower than 150 × 10³ cells/mm³, lymphopenia as an absolute lymphocyte count lower than 1,000 cells/mm³, and hypoalbuminemia as albumin concentration lower than 3.5 g/dL. Lower respiratory tract specimens including sputum and endotracheal aspirates were used for MERS-CoV rRT-PCR. Cycle threshold (Ct) values of MERS-CoV rRT-PCR were used as a surrogate of viral load. Pneumonia development of MERS-CoV infected patient was defined as presence of parenchymal infiltration on chest X-ray with respiratory symptoms. Test days or events were counted from the day of symptom onset for each patient: day 1 was defined as the day of symptom onset. For asymptomatic patients, the day of diagnosis of MERS-CoV infection was considered as day 1.

Statistical analysis

To identify predictive factors for pneumonia development and progression to respiratory failure, clinical variables measured within three days from symptom onset were compared. For evaluation of pneumonia development, patients who developed pneumonia (group 1), patients who developed pneumonia without respiratory failure (group 2), and pneumonia patients who progressed to respiratory failure (group 3). For practical purposes, respiratory failure was defined as the need for mechanical ventilation (MV). The institutional review board of our hospital approved the present study.

Data collection and operational definitions

We retrospectively collected data from electronic medical records and epidemiologic investigation. To identify factors which can predict pneumonia development and progression to respiratory failure at the early course of the disease, we evaluated clinical variables measured within three days from symptom onset. During the 2015 Korean MERS outbreak, fever was defined as body temperature ≥37.5 °C to increase sensitivity of screening and the same definition was used in the present analysis. Thrombocytopenia was defined as a platelet count lower than 150 × 10³ cells/mm³, lymphopenia as an absolute lymphocyte count lower than 1,000 cells/mm³, and hypoalbuminemia as albumin concentration lower than 3.5 g/dL. Lower respiratory tract specimens including sputum and endotracheal aspirates were used for MERS-CoV rRT-PCR. Cycle threshold (Ct) values of MERS-CoV rRT-PCR were used as a surrogate of viral load. Pneumonia development of MERS-CoV infected patient was defined as presence of parenchymal infiltration on chest X-ray with respiratory symptoms. Test days or events were counted from the day of symptom onset for each patient: day 1 was defined as the day of symptom onset. For asymptomatic patients, the day of diagnosis of MERS-CoV infection was considered as day 1.
categorical variables. Statistically significant continuous variables were re-categorized into binary factors using threshold values between mean of each group, which showed lowest $P$ value. Statistically significant categorical variables and binary factors re-categorized from continuous variables were defined as predictive factors. For significant predictive factors, as a measure of association, odds ratio (OR) and 95% confidence interval (CI) for OR were calculated using the Woolf procedure.$^{20}$ Multivariate analysis was not performed due to the limited sample size. All $P$-values were two-tailed, and those $<0.05$ were considered to be statistically significant. IBM SPSS Statistics version 20.0 for Windows (IBM, Armonk, NY, USA) was used for all statistical analyses.

Results

Time course of pneumonia development and progression to respiratory failure

A total of 45 MERS-CoV infected patients were hospitalized during the outbreak with 13 patients in group 1 (including 3 asymptomatic patients), 19 patients in group 2, and 13 patients in group 3. The clinical course of symptomatic MERS patients progressed serially: patients developed initial symptoms after a median 5-day incubation period (IQR 3.5–7.0), pneumonia after a median of 6 days from symptom onset (IQR 5.0–7.0), and respiratory failure after a median of 12 days from symptom onset (IQR 10.0–13.0). In group 3 patients, it took a median of 2 days from desaturation to respiratory failure (IQR 1–3 days). The development and progression of pneumonia by time sequence is depicted in Fig. 1. No one developed pneumonia before day 4 of symptom onset.

Predictive factors for pneumonia development

To evaluate predictive factors for pneumonia development, demographics, underlying diseases, and clinical variables of patients in group 2 and 3 were compared to those of patients in group 1 (Tables 1 and 2). Identified predictive factors are summarized in Table 3 with odd ratios (OR). Increasing age was significantly associated with pneumonia development as a continuous variable ($P = 0.015$), and age older than 45 years was a predictive factor for the development of pneumonia (OR, 8.04; 95% CI, 1.52–42.43; $P = 0.007$). Although proportion of male also increased with progression of pneumonia (38.5%, 57.9%, and 84.6% for group 1, 2, and 3, respectively), statistically significant association between male sex and the pneumonia development was not identified ($P = 0.097$).

Fever over 37.5°C by day 3 were more frequently detected in patients with pneumonia (18.2%, 71.4%, and 77.8% in groups 1, 2, and 3, respectively), and was identified as a predictive factor for the development of pneumonia (OR, 12.75; 95% CI, 2.12–76.57; $P = 0.002$). Thrombocytopenia (OR, not applicable (NA); $P = 0.007$), lymphopenia (OR, 17.50; 95% CI, 1.88–163.02; $P = 0.003$), elevated C-reactive protein (CRP $\geq$ 2 mg/dL; OR, NA; $P = 0.018$), and high viral load (Ct value $< 28.5$ OR, 14.00; 95% CI, 1.14–172.65; $P = 0.024$) were distinctly observed in pneumonia patients from the initial presentation, and identified as predictive factors for pneumonia development.

Predictive factors for progression to respiratory failure

To evaluate predictive factors for progression to respiratory failure, patients in group 3 were compared to those in group 1 and 2 (Tables 1–3). Although the mean age of patients in each group tended to increase with progression of pneumonia (37.3, 47.7, and 55.2 years in groups 1, 2, and 3, respectively) and increasing age was significantly
associated with respiratory failure as a continuous variable ($P = 0.036$), there was no statistically significant cut-off value for prediction of respiratory failure. Proportion of male also increased with progression of pneumonia, and male sex was a predictive factor for respiratory failure (OR, 5.50; 95% CI, 1.05–28.88; $P = 0.045$). Among underlying diseases, hypertension was identified as a predictive factor for respiratory failure (OR, 6.04; 95% CI, 1.18–30.88; $P = 0.021$).

Initial symptoms including fever were not significantly different between patients who progressed to respiratory failure and those who did not. Among initial laboratory test results, thrombocytopenia (OR, 6.67; 95% CI, 1.18–37.78; $P = 0.023$), lymphopenia (OR, 14.88; 95% CI, 1.56–142.20; $P = 0.006$), hypoalbuminemia (OR, 14.17; 95% CI, 1.83–109.86; $P = 0.005$), and elevated CRP (CRP ≥ 4 mg/dl; OR, 23.00; 95% CI, 2.01–262.57; $P = 0.002$) were distinctly observed in group 3 patients, and identified as predictive factors for respiratory failure.

### Predictability of predictive factors for pneumonia development and respiratory failure

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) by number of predictive factors were presented in Table 4. When patients presented with ≥ two of the predictive factors for pneumonia development, 100% of these patients developed pneumonia (sensitivity 56.3%, specificity 100.0%, PPV 100%, and NPV 48.1%). Patients lacking the predictive factors for respiratory failure did not progress to respiratory failure. When patients presented with ≥ two of these predictive factors, 50.0% of these patients progressed to respiratory failure (sensitivity 69.2%, specificity 75.0%, PPV 52.9%, and NPV 85.7%).

### Discussion

Initial rapid propagation of MERS-CoV during the Korean MERS outbreak was caused by three super-spreading events responsible for 73.1% of all transmissions.\textsuperscript{5,7,8} In addition to these super-spreaders, transmission of MERS-CoV despite application of personal protective equipment (PPE) occurred from patients with progressed pneumonia at our hospital.\textsuperscript{9} In this regard, identifying the predictive factors for pneumonia development and progression is not only important in patient care, but also in infection control to prevent further in-hospital transmission.

The present analysis of predictive factors for pneumonia development and progression to respiratory failure using variables obtained by day 3 of symptom onset could be conducted owing to the observation of entire clinical course of the disease from the exposure to MERS-CoV. Compared to MERS outbreaks in the Arabian Peninsula where community-acquired infections might simultaneously occur from animals, identifying epidemiologic links, exposure date, and symptom onset were relatively clear for each case.\textsuperscript{5,19} In our observation, the clinical course of symptomatic MERS patients progressed serially and no one developed pneumonia before day 4 of symptom onset. This is the reason why we used clinical data obtained by day 3 of symptom onset. There is no other comparable data to which presented time interval from the symptom onset to the development of pneumonia. Although there were no ideal cut-off scores of predictive factors with good sensitivity and specificity, it should be noted that 100% of patients with ≥ two predictive factors for
Table 3  Predictive factors for development of pneumonia and respiratory failure in MERS-CoV infected patients.

| Predictive factors | Pneumonia OR (95% CI) | P value | Respiratory failure OR (95% CI) | P value |
|--------------------|-----------------------|---------|-------------------------------|---------|
| Age ≥45 years      | 8.04 (1.52–42.43)     | 0.007   | 6.67 (1.18–37.78)             | 0.023   |
| Ct value <28.5     | 14.00 (1.14–172.65)   | 0.024   | 14.88 (1.56–142.20)           | 0.006   |
| CRP ≥2 mg/dL       | NA a                  | 0.018   | 5.50 (1.05–28.88)             | 0.045   |
| Fever ≥37.5 °C by day 3 | 12.75 (2.12–76.57) | 0.002   | 14.17 (1.83–109.86)           | 0.005   |
| Thrombocytopenia   | NA a                  | 0.007   | 1.75 (1.88–163.02)            | 0.003   |
| Lymphopenia        | 17.50 (1.88–163.02)   | 0.003   | 14.23 (2.01–262.57)           | 0.002   |
| Male sex           | 5.50 (1.05–28.88)     | 0.045   | 6.04 (1.18–30.88)             | 0.021   |
| Hypoalbuminemia    | 14.17 (1.83–109.86)   | 0.005   | 23.00 (2.01–262.57)           | 0.002   |
| CRP ≥4 mg/dL       | 23.00 (2.01–262.57)   | 0.002   | 6.04 (1.18–30.88)             | 0.021   |

Abbreviations: OR, odds ratio; CI, confidence interval; Ct, threshold cycle; CRP, C-reactive protein; NA, not applicable.

a OR was not applicable as none of the group 1 patients reached thrombocytopenia or CRP values ≥2 mg/dL.
pneumonia actually progressed to pneumonia. Thus, careful and intensive management should be implemented for such patients including adequate isolation of patient in an airborne infection isolation room (AIIR), minimizing chance for exposure, application of PPE with hooded coverall, and consideration of experimental antiviral treatment.9,21–24 For patients with ≥2 two predictive factors for respiratory failure, AIIRs in intensive care units should be prepared for early elective intubation. Although the time interval from symptom onset to MV support was much longer than in previous reports (median 12 days versus 7 days),1 we also experienced rapid progression of pneumonia from the moment of desaturation: 73% of group 3 patients required MV within 2 days from desaturation (median 2, IQR 1–3 days). To avoid urgent situations which might break protection of healthcare workers, elective intubation should be considered when desaturation begins to progress. In addition, sensitivities of predictive values are relatively low with cut-off value of ≥2 factors, clinical course of patients with any predictive factors also should be carefully monitored.

Of note, thrombocytopenia, lymphopenia, and increased CRP level were shared predictive factor for the pneumonia development and respiratory failure. They were observed in the very early course of the illness, indicating that inflammation had already been enhanced. Lymphopenia and thrombocytopenia presenting from the initial presentation of severe MERS-CoV infected patients were also observed in the recent report by Min et al.25 Although time of measurements were not specifically described, these laboratory abnormalities were previously observed in severe MERS cases and other respiratory viral illnesses including severe acute respiratory syndrome (SARS) and influenza, which are caused by intense inflammatory response to the viruses.15,26–33 This is the first report that identified these laboratory findings as predictive factors for pneumonia development and progression to respiratory failure in MERS.

Although other predictive factors for pneumonia development and respiratory failure were different due to discordance of statistical significance, they shared the same spectrum of etiology. Age increased according to pneumonia progression and was associated with both pneumonia and respiratory failure as a continuous variable \( (P = 0.015 \text{ and } P = 0.036, \text{ respectively}) \). These findings correlate with previous data suggesting that old age is associated with poor prognosis.11,13–15,34,35 Similarly, the proportion of males increased according to disease severity, though male sex was only significant for predicting respiratory failure. Although the mean age of males was older than that of females (49.7 and 42.6 years, respectively), it was not statistically significant \( (P = 0.169) \). Previous data also reported that overall proportion of male was higher and was associated with severe infection.15,34 It could be meaningful observation that the same finding was observed in the Republic of Korea where the social activity of females is not restricted, especially among healthcare workers. On the other hand, hypoalbuminemia and hypertension were predictive factors only for respiratory failure, while high viral load was predictive factor for the development of pneumonia. These factors were related with severe disease and poor prognosis of MERS in previous reports.11,13–15,16,34,35

Our study has several strengths and limitations. Due to its retrospective nature, there may be a bias regarding collecting medical information in retrospective manner. However, as all electronic medical records were standardized to record symptoms and signs in the same way from the beginning of the outbreak, bias was minimized. Secondly, there were missing values when calculating the sensitivity and specificity of predictive factors, which is another limitation of retrospective study. Lastly, the present study did not perform multivariate analysis due to limited sample size and need to be validated. Prospective studies with sufficient number of patients are required for validation of the predictive factors identified in the present study. Despite these limitations, our data would be suitable for identifying predictive factors because we could observe entire course of the disease from exposure and apply homogenous management to patients.

In conclusion, based on 45 cases from a single tertiary care hospital during the largest MERS outbreak outside of the Arabian Peninsula, we identified six predictive factors for the development of pneumonia and progression to respiratory failure, respectively. Thrombocytopenia, lymphopenia, and high CRP level were shared predictive factors. MERS-CoV infected patients with ≥2 two predictive factors should be intensively managed from the initial presentation for successful control of MERS outbreak.

### Table 4  Sensitivity, specificity, PPV and NPV by number of predictive factors for pneumonia development and progression to respiratory failure.

| No. of factors | Pneumonia | | | | | | Respiratory failure | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sensitivity | Specificity | PPV | NPV | | Sensitivity | Specificity | PPV | NPV | |
| ≥0 | 100.0 | 0.0 | 71.1 | NA | 100 | 0.0 | 28.9 | NA | |
| ≥1 | 90.6 | 53.8 | 82.9 | 70.0 | 100 | 31.3 | 37.1 | 100 | |
| ≥2 | 56.3 | 100 | 100 | 48.1 | 69.2 | 75.0 | 52.9 | 85.7 | |
| ≥3 | 40.6 | 100 | 100 | 40.6 | 46.2 | 87.5 | 60.0 | 80.0 | |
| ≥4 | 28.1 | 100 | 100 | 36.1 | 38.5 | 96.9 | 83.3 | 79.5 | |
| ≥5 | 15.6 | 100 | 100 | 32.5 | 30.8 | 100 | 100 | 78.0 | |

Data are expressed as percentages.
Abbreviations: PPV, positive predictive value; NPV, negative predictive value; NA, not applicable.
Potential conflicts of interest

There are no potential conflicts of interest relevant to this article to report.

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