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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

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included age ≥45 years, fever ≥37.5 °C, thrombocytopenia, lymphopenia, CRP ≥ 2 mg/dL, and a threshold cycle value of PCR less than 28.5. For respiratory failure, the indicators included male, hypertension, low albumin concentration, thrombocytopenia, lymphopenia, and CRP ≥ 4 mg/dL (all $P < 0.05$). With ≥ two predictive factors for pneumonia development, 100% of patients developed pneumonia. Patients lacking the predictive factors did not progress to respiratory failure.

Conclusion: For successful control of MERS outbreak, MERS-CoV infected patients with ≥ two predictive factors should be intensively managed from the initial presentation.

Introduction

Middle East respiratory syndrome (MERS) is an emerging lethal respiratory disease caused by a novel betacoronavirus (MERS-CoV).[1] 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.[2–6] 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.[5,7–10] As these large transmission clusters were exclusively originated from patients with pneumonia, prediction of pneumonia development has been emphasized in control of MERS outbreak.[9] 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,[11–16] 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,[17] 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 of MERS which did not included asymptomatic cases,[18] we used the term of 'MERS-CoV infected patient' rather than 'MERS patients' throughout the present paper. MERS-CoV infections were confirmed on the basis of rRT-PCR assays targeting upstream of the E gene and the open-reading frame gene 1a.[18,19] Disease status of included patients was assessed at six weeks from their symptom onset and patients were divided into three groups depending on pneumonia development and progression to respiratory failure: patients without the development of 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.[9] Thrombocytopenia was defined as a platelet count lower than 150×10^3 cells/mm^3, lymphopenia as an absolute lymphocyte count lower than 1,000 cells/mm^3, 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 2 and 3) were compared to those who did not (group 1). For factors for respiratory failure, patients who progressed to respiratory failure (group 3) were compared to those who did not (group 1 and 2). Student's t-tests or Mann–Whitney U tests were used to compare continuous variables, and chi-square tests or Fisher's exact tests were used to compare

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.

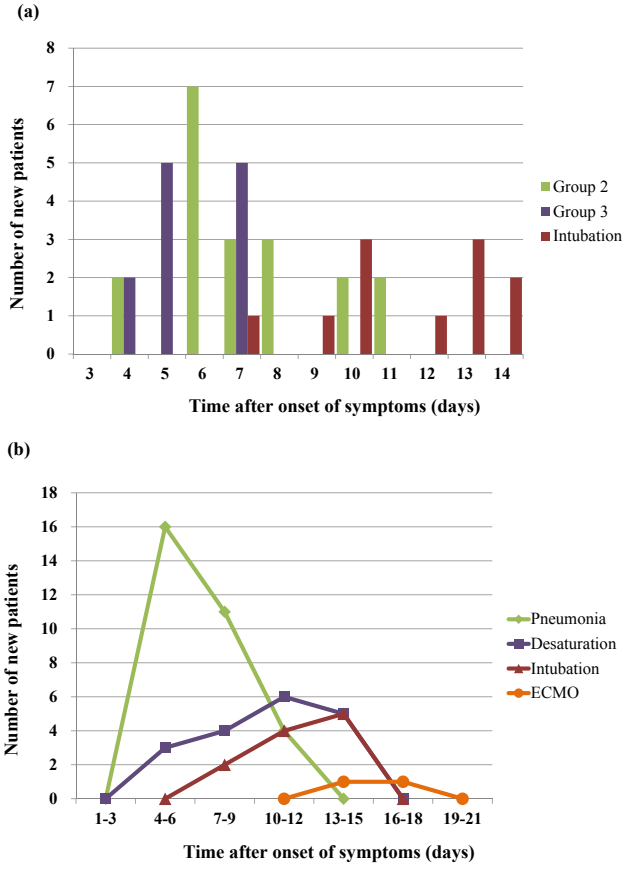

Figure 1 The development and progression of pneumonia in patients with MERS-CoV infection depicted by time sequence MERS-CoV infected patients were divided into three groups: patients without the development of pneumonia (group 1), patients who developed pneumonia without respiratory failure (group 2), and pneumonia patients who progressed to respiratory failure (group 3). (**a**) **Number of patients who developed pneumonia and who received endotracheal intubation due to respiratory failure by the days after symptom onset**. Patients in group 3 developed pneumonia earlier than those in group 2, and progressed to respiratory failure sequentially. (**b**) **Overall presentation of pneumonia development and progression**. The development of pneumonia, desaturation, endotracheal intubation, and application of ECMO occurred step by step. Abbreviations: ECMO, extracorporeal membrane oxygenation.

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

Table 1 Demographics and underling diseases of MERS-CoV infected patients compared depending on pneumonia development and progression to respiratory failure.

Variables	Group 1 *Without pneumonia* (n = 13)	Group 2 *Pneumonia* (n = 19)	Group 3 *Respiratory failure* (n = 13)	*P* value	
				Pneumonia (*Group 1 vs 2 & 3*)	Resp. failure (*Group 1 & 2 vs 3*)
Demographics					
Age, years	37.3 ± 17.1	47.7 ± 14.0	55.2 ± 17.4	0.015	0.036
Age ≥45 years	2 (15.4%)	10 (52.6%)	9 (69.2%)	0.007	0.098
Male sex	5 (38.5%)	11 (57.9%)	11 (84.6%)	0.094	0.045
BMI (kg/m^2)	22.1 ± 8.6	23.4 ± 2.4	24.8 ± 4.0	0.524	0.275
Underlying disease	5 (38.5%)	9 (47.4%)	8 (61.5%)	0.514	0.337
Diabetes mellitus	1 (7.7%)	2 (10.5%)	2 (15.4%)	1.000	0.617
Hypertension	2 (15.4%)	1 (5.3%)	5 (38.5%)	1.000	0.021
Chronic heart disease	1 (7.7%)	2 (10.5%)	4 (30.8%)	0.654	0.168
Chronic lung disease	0 (0.0%)	0 (0.0%)	1 (7.7%)	1.000	0.289
Liver disease	0 (0.0%)	0 (0.0%)	1 (7.7%)	1.000	0.289
Renal disease	0 (0.0%)	1 (5.3%)	2 (15.4%)	0.546	0.196
Neurologic disease	0 (0.0%)	2 (10.5%)	1 (7.7%)	0.546	1.000
Solid cancer	2 (15.4%)	4 (21.1%)	2 (15.4%)	1.000	1.000
Hematologic disease	0 (0.0%)	2 (10.5%)	1 (7.7%)	0.546	1.000
Charlson's WIC	0 (0.0–1.0)	0 (0.0–2.0)	0 (0.0–2.0)	0.333	0.363

Data are expressed as the number (%) of patients or mean ± SD. Continuous variables with statistical significance were re-categorized into binary factors which are presented in italics.
Abbreviations: Res., respiratory; BMI, body mass index; WIC, weighted index of comorbidity.

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.[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.[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.[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 2 Clinical presentation and initial laboratory findings of MERS-CoV infected patients compared depending on pneumonia development and progression to respiratory failure.

Variables	Group 1 *Without pneumonia* (n = 13)	Group 2 *Pneumonia* (n = 19)	Group 3 *Respiratory failure* (n = 13)	*P* value	
				Pneumonia *(Group 1 vs 2 & 3)*	Resp. failure *(Group 1 & 2 vs 3)*
Initial symptoms					
Fever ≥ 37.5 °C	2/11 (18.2%)	10/14 (71.4%)	7/9 (77.8%)	0.002	0.240
Myalgia	5 (38.5%)	10 (52.6%)	2 (15.4%)	1.000	0.088
Cough	4 (30.8%)	6 (31.6%)	5 (38.5%)	1.000	0.732
Sputum	4 (30.8%)	3 (15.8%)	3 (23.1%)	0.441	1.000
Diarrhea	0 (0.0%)	1 (5.3%)	2 (15.4%)	0.546	0.196
Initial laboratory tests[a]					
WBC (/mm^3)	5329 ± 1208	4230 ± 1588	4799 ± 3037	0.216	0.915
Hemoglobin (g/dL)	13.6 ± 1.6	13.0 ± 2.9	11.8 ± 4.2	0.255	0.352
Platelet (×10^3/mm$^{3)}$	223 ± 47	156 ± 52	104 ± 69	<0.001	0.003
Thrombocytopenia	0/11 (0.0%)	5/14 (35.7%)	5/8 (62.5%)	0.007	0.023
ALC (/mm$^{3)}$	1487 ± 424	1006 ± 446	733 ± 577	0.003	0.026
Lymphopenia	1/11 (9.1%)	7/14 (50.0%)	7/8 (87.5%)	0.003	0.006
Albumin (g/dL)	4.2 ± 0.5	4.2 ± 0.6	3.3 ± 0.8	0.184	0.003
Hypoalbuminemia	1/8 (12.5%)	1/11 (9.1%)	5/8 (62.5%)	0.633	0.005
Total bilirubin (mg/dL)	0.3 ± 0.1	0.7 ± 0.7	0.6 ± 0.4	0.190	0.981
AST (IU/L)	28 ± 13	33 ± 18	32 ± 11	0.438	0.863
ALT (IU/L)	34 ± 19	28 ± 19	29 ±23	0.463	0.808
BUN (mg/dL)	10 ± 2	15 ± 5	20 ± 18	0.064	0.285
Creatinine (mg/dL)	0.8 ± 0.2	1.0 ± 0.5	1.2 ± 0.4	0.089	0.066
CRP (mg/dL)	0.7 ± 0.6	1.3 ± 1.5	6.8 ± 7.5	0.031	0.063
≥ 2 mg/dL	0/11 (0.0%)	3/13 (23.1%)	5/8 (62.5%)	0.018	0.005
≥ 4 mg/dL	0/11 (0.0%)	1/13 (7.7%)	4/8(50.0%)	0.078	0.002
LD (IU/L)	388 ± 86	412 ± 131	441 ± 168	0.554	0.545
Ct value of rRT-PCR	31.3 ± 3.2	26.2 ± 5.7	26.5 ± 3.5	0.025	0.405
Ct value <28.5	1/8 (12.5%)	4/6 (66.7%)	2/3 (66.7%)	0.024	0.537

Data are expressed as the number (%) of patients or mean ± SD. As missing values were also removed from the population parameter, variables with missing values are expressed with modified population parameters. Continuous variables with statistical significance were re-categorized into binary factors which are presented in italics.

Abbreviations: Res., respiratory; WBC, white blood cell; ALC, absolute lymphocyte count; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; LD, lactate dehydrogenase; Ct, threshold cycle; rRT-PCR, real-time reverse transcriptase polymerase chain reaction.

[a] Data are presented as mean value of day 1−3 ± SD.

Table 3 Predictive factors for development of pneumonia and respiratory failure in MERS-CoV infected patients.

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

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.

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 ≥ 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 ≥ two 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 ($P = 0.015$ and $P = 0.036$, 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.[1,12,13,15,16,34,35]

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 ≥ two predictive factors should be intensively managed from the initial presentation for successful control of MERS outbreak.

Potential conflicts of interest

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

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References

1. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet* 2015;**386**:995—1007.
2. *Summary of current situation, Literature Update and Risk Assessment*. World Health Organization; 2015 July 7. http://www.who.int/csr/disease/coronavirus_infections/risk-assessment-7july2015/en.
3. *Middle east respiratory syndrome coronavirus (MERS-CoV) — Republic of Korea*. World Health Organization; 2015 July 10. http://www.who.int/csr/don/10-july-2015-mers-korea/en.
4. An unexpected outbreak of Middle East respiratory syndrome coronavirus infection in the Republic of Korea, 2015. *Infect Chemother* 2015;**47**:120—2.
5. Kim Y, Lee S, Chu C, Choe S, Hong S, Shin Y. The characteristics of middle eastern respiratory syndrome coronavirus transmission dynamics in South Korea. *Osong Public Health Res Perspect* 2016;**7**:49—55.
6. Cowling BJ, Park M, Fang VJ, Wu P, Leung GM, Wu JT. Preliminary epidemiological assessment of MERS-CoV outbreak in South Korea, May to June 2015. *Euro Surveill* 2015;**20**.
7. Nishiura H, Endo A, Saitoh M, Kinoshita R, Ueno R, Nakaoka S, et al. Identifying determinants of heterogeneous transmission dynamics of the Middle East respiratory syndrome (MERS) outbreak in the Republic of Korea, 2015: a retrospective epidemiological analysis. *BMJ Open* 2016;**6**:e009936.
8. Chowell G, Abdirizak F, Lee S, Lee J, Jung E, Nishiura H, et al. Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study. *BMC Med* 2015;**13**:210.
9. Park GE, Ko JH, Peck KR, Lee JY, Lee JY, Cho SY, et al. Control of an outbreak of Middle East respiratory syndrome in a tertiary hospital in Korea. *Ann Intern Med* 2016;**165**:87—93.
10. Cho SY, Kang JM, Ha YE, Park GE, Lee JY, Ko JH, et al. MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. *Lancet* 2016 Jul 8. http://dx.doi.org/10.1016/S0140- 6736(16)30623-7. pii: S0140-6736(16)30623-7. [Epub ahead of print].
11. Mizumoto K, Endo A, Chowell G, Miyamatsu Y, Saitoh M, Nishiura H. Real-time characterization of risks of death associated with the Middle East respiratory syndrome (MERS) in the Republic of Korea, 2015. *BMC Med* 2015;**13**:228.
12. Corman VM, Albarrak AM, Omrani AS, Albarrak MM, Farah ME, Almasri M, et al. Viral shedding and antibody response in 37 patients with Middle East respiratory syndrome coronavirus infection. *Clin Infect Dis* 2016;**62**:477—83.
13. Feikin DR, Alraddadi B, Qutub M, Shabouni O, Curns A, Oboho IK, et al. Association of higher MERS-CoV virus load with severe disease and death, Saudi Arabia, 2014. *Emerg Infect Dis* 2015;**21**:2029—35.
14. Majumder MS, Kluberg SA, Mekaru SR, Brownstein JS. Mortality risk factors for Middle East respiratory syndrome outbreak, South Korea, 2015. *Emerg Infect Dis* 2015;**21**:2088—90.
15. Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis* 2014;**29**:301—6.
16. Banik GR, Alqahtani AS, Booy R, Rashid H. Risk factors for severity and mortality in patients with MERS-CoV: analysis of publicly available data from Saudi Arabia. *Virol Sin* 2016;**31**:81—4.
17. *Management of asymptomatic persons who are RTPCR positive for Middle East respiratory syndrome coronavirus (MERS-CoV), Interim Guidance*. World Health Organization; July 27, 2015. http://www.who.int/csr/disease/coronavirus_infections/management_of_asymptomatic_patients/en/ [Accessed 27.05.16].
18. Madani TA. Case definition and management of patients with MERS coronavirus in Saudi Arabia. *Lancet Infect Dis* 2014;**14**:911—3.
19. Oboho IK, Tomczyk SM, Al-Asmari AM, Banjar AA, Al-Mugti H, Aloraini MS, et al. 2014 MERS-CoV outbreak in Jeddah — a link to health care facilities. *N Engl J Med* 2015;**372**:846—54.
20. Woolf B. On estimating the relation between blood group and disease. *Ann Hum Genet* 1955;**19**:251—3.
21. Al Ghamdi M, Alghamdi KM, Ghandoora Y, Alzahrani A, Salah F, Alsulami A, et al. Treatment outcomes for patients with Middle Eastern respiratory syndrome coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. *BMC Infect Dis* 2016;**16**:174.
22. Modjarrad K. Treatment strategies for Middle East respiratory syndrome coronavirus. *J Virus Erad* 2016;**2**:1—4.
23. Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, et al. Treatment with lopinavir/ritonavir or interferon-beta1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis* 2015;**212**:1904—13.
24. *Interim infection prevention and control recommendations for hospitalized patients with Middle East respiratory syndrome coronavirus (MERS-CoV), US CDC*. June 2015. http://www.cdc.gov/coronavirus/mers/infection-prevention-control.html [Accessed 27.05.16].
25. Min CK, Cheon S, Ha NY, Sohn KM, Kim Y, Aigerim A, et al. Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. *Sci Rep* 2016;**6**:25359.
26. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014;**160**:389—97.
27. Guery B, Poissy J, el Mansouf L, Sejourne C, Ettahar N, Lemaire X, et al. Clinical features and viral diagnosis of two cases of infection with Middle East respiratory syndrome coronavirus: a report of nosocomial transmission. *Lancet* 2013;**381**:2265—72.
28. Choi KW, Chau TN, Tsang O, Tso E, Chiu MC, Tong WL, et al. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. *Ann Intern Med* 2003;**139**:715—23.
29. Lupovitch A. White cell differential count and influenza A. *Am J Med* 2005;**118**:1306—7. author reply 7—9.
30. Yang M, Ng MH, Li CK. Thrombocytopenia in patients with severe acute respiratory syndrome (review). *Hematology* 2005;**10**:101—5.

31. Le VB, Schneider JG, Boergeling Y, Berri F, Ducatez M, Guerin JL, et al. Platelet activation and aggregation promote lung inflammation and influenza virus pathogenesis. *Am J Respir Crit Care Med* 2015;**191**:804—19.
32. Ying T, Li W, Dimitrov DS. Discovery of T cell infection and apoptosis by MERS Coronavirus. *J Infect Dis* 2016;**213**:877—9.
33. Chu H, Zhou J, Wong BH, Li C, Chan JF, Cheng ZS, et al. Middle East Respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates both the extrinsic and intrinsic apoptosis pathways. *J Infect Dis* 2016;**213**:904—14.
34. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infect Dis* 2013;**13**:752—61.
35. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *Clin Microbiol Rev* 2015;**28**:465—522.