Note

Host susceptibility to MERS-CoV infection, a retrospective cohort study of the 2015 Korean MERS outbreak

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ABSTRACT

To evaluate host susceptibility factors to Middle East respiratory syndrome coronavirus (MERS-CoV) infection, we conducted a retrospective cohort study from the single largest exposure event of the 2015 Korean MERS outbreak. A total of 175 patients were closely exposed to a super-spreader, 26 of which were infected (14.9%). In a multivariate analysis, history of autologous stem cell transplantation (HR, 31.151; 95% CI, 5.447—178.145; $P < 0.001$) and tachypnea at ED (HR, 4.392; 95% CI, 1.402—13.761; $P = 0.011$) were significantly associated with MERS-CoV infection.

Close exposure is a critical factor for human-to-human transmission of Middle East respiratory syndrome coronavirus (MERS-CoV), but clinical factors affecting host susceptibility to MERS-CoV have not been properly identified [1—3]. To identify host susceptibility factors to MERS-CoV infection, we performed a retrospective cohort study from the largest exposure event during the 2015 Korean MERS outbreak [3,4].

A retrospective cohort study was performed to identify risk factors for increased host susceptibility to MERS-CoV. This exposure event was previously described in detail [3]: While a severely-coughing MERS patient stayed at our emergency department (ED) for three days, 675 patients stayed at the ED and had chance to be exposed. After meticulous contact tracing, 175 closely exposed patients were identified and classified into two groups by exposure time and location: group A, patients who stayed in the same examination rooms at the same time with the index case (our ED is composed of zone I ~ IV for adult patients, and the index case used zone II ~ IV); and group B, patients who shared the same radiology room or registration area at the same time period (30 min before and 2 h after) with the index case. Exposure sites of group A were subdivided into the zone II, III, and IV, as attack rates of each zone were significantly different (23% (13/57), 32% (7/22), and 8% (3/38), respectively; $P = 0.047$) [3]. Included patients were followed for 14 days, which is a previously determined incubation period of MERS-CoV [1]. The Institutional Review Board of Samsung Medical Center approved this study. For simple comparison of clinical variables, Student's t-tests or Mann-Whitney U tests were used for continuous variables, and chi-square tests or Fisher's exact tests for categorical variables. The Cox proportional hazard model was used to examine the association of clinical variables with MERS-CoV infection. Variables with statistical significance in univariate analyses were included in the multivariate analysis. The effect of exposure intensity was adjusted by including exposure sites in the multivariate analysis. 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.

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During the study period, a total of 175 patients were closely exposed to the index case, 26 of whom (14.9%) were infected with MERS-CoV (3 patients at radiology rooms or registration area, 13 at zone II, 7 at zone III, and 3 at zone IV) [3]. Baseline characteristics and clinical presentation of the study population at the time of ED visit are presented in Table 1. There was no statistical difference in age, sex, body mass index, and immunosuppressive conditions. Patients exposed at zone II and III showed higher attack rates as previously described [3]. Among underlying diseases, hypertension and cardiovascular diseases were significantly different between infected and non-infected patients (all $P < 0.05$). Significantly higher proportion of MERS-infected patients presented with tachypnea (respiratory rate > 24/min) at ED visit, compared to non-infected patients (15.4% (4/26) and 2.7% (4/149), respectively; $P = 0.018$). The proportion of concomitant infections and laboratory test results were not statistically different between the two groups.

To identify possible risk factors for increased host susceptibility to MERS-CoV, all the obtained clinical variables and exposure sites were evaluated. History of autologous stem cell transplantation (SCT), underlying hypertension and cardiovascular disease, tachypnea at ED visit, and exposure sties of zone II and III were statistically significantly associated with MERS-CoV infection in univariate analyses (Supplementary Table 1). In the multivariate analysis, history of autologous SCT (HR, 31.151; 95% CI, 5.447–178.145; $P < 0.001$) and tachypnea at ED visit (HR, 4.392;

95% CI, 1.402–13.761; $P = 0.011$) were identified as risk factors for increased host susceptibility to MERS-CoV (Table 2). Significant association of exposure sties of zone II and III was relevant with the previous analysis [3].

Although many studies have reported poor prognosis factors of MERS-CoV infection since the discovery of MERS-CoV in 2012, little has been determined about host susceptibility to the virus [1]. Evaluating an exposure cohort for host susceptibility is often not feasible as enough number, medical records, contact tracing, and follow-up of the exposed patients is required. We experienced a unique situation in that discrete population of patients was exposed to the single index case in the defined space of ED, which made it possible to conduct the first cohort study to evaluate host susceptibility to MERS-CoV. Of note, previously reported poor prognostic factors, including old age, male sex, concomitant infection, low albumin concentrations, lymphopenia, diabetes, and multiple comorbidities [3,5,6], were not statistically significant in the multivariate analysis. These factors were evaluated in the present cohort with sufficient numbers, and the analysis indicated that they did not play critical roles in host susceptibility to MERS-CoV infection. This finding suggests that risk factors associated with poor prognosis and host susceptibility need to be separately considered. Meticulous surveillance of MERS-CoV exposed patients should be conducted regardless of presence of poor prognosis factors.

On the other hand, history of autologous SCT showed statistical significance in the multivariate analysis. Although susceptibility of autologous SCT recipients to viral infections after engraftment has not been well evaluated, two of three autologous SCT recipients (66.7%) in the present cohort were infected with MERS-CoV despite relatively low exposure intensity (at radiology room and zone IV). Because all the autologous SCT recipients in this cohort had underlying lymphoma and had multiple chemotherapy before SCT, whether autologous SCT per se or heavily-treated aggressive lymphoma would be a risk for increased host susceptibility for MERS-CoV infection is not conclusive. Also, immunocompromising conditions generally associated with viral infections including hematologic malignancies other than lymphoma, allogeneic SCT, and corticosteroid use were scarcely included in this cohort [7,8]. Therefore, it would be more relevant to interpret the present data that severely immunocompromised hosts could be more vulnerable to MERS-CoV infection and need special caution when exposed to the virus.

Interestingly, tachypnea at ED (HR, 4.392; 95% CI, 1.402–13.761; $P = 0.011$) was associated with MERS-CoV infection. Although association between respiratory rate and increased susceptibility to a certain respiratory virus has not been evaluated, theoretically patients with tachypnea may inhale more virus-containing droplets or aerosols. A recent study reported isolation of MERS-CoV from the air in MERS outbreak units, suggesting possibility of air-borne transmission [9]. Although this association needs to be further evaluated, patients with tachypnea at the time of exposure should to be monitored with caution, especially when the exposure occurs from severely-coughing MERS patients at a restricted space.

Our study has several limitations. Although we could not identify entire routes of exposed patients, we adjusted the exposure intensity by specific exposure sites. Sizes, structure, crowdedness, exposure time from the index case were different between each site, which resulted in significantly different attack rates by exposure site [3]. In addition, we only evaluated a single exposure cohort, which could be biased by some special situation.

In conclusion, in a cohort study from the single largest exposure event, history of autologous SCT and tachypnea at ED were identified as host susceptibility factors to MERS-CoV infection.

Table 1
Baseline characteristics and clinical presentation of the study population at ED visit.

Variables	Infected with MERS (n = 26)	Not infected with MERS (n = 149)	P value
Demographics			
Age, years (mean ± SD)	56.5 ± 16.8	52.2 ± 19.9	0.306
Male sex	13 (50%)	61 (40.9%)	0.388
BMI (kg/m^2, median, IQR)	22.0 (19.8–24.4)	22.1 (19.8–24.1)	0.992
Exposure sites			
Radiology or registration	3 (11.5%)	55 (36.9%)	0.011
Zone II	13 (50.0%)	44 (29.5%)	0.040
Zone III	7 (26.9%)	15 (10.1%)	0.026
Zone IV	3 (11.5%)	35 (23.5%)	0.173
Immunosuppressive therapies			
Chemotherapy	3 (11.5%)	36 (24.2%)	0.154
Radiotherapy	1 (3.8%)	9 (6.0%)	1.000
Steroid use	1 (3.8%)	2 (1.3%)	0.385
Underlying diseases			
Hypertension	12 (46.2%)	38 (25.5%)	0.031
Diabetes mellitus	4 (15.4%)	25 (16.8%)	1.000
Cardiovascular diseases	9 (34.6%)	21 (14.1%)	0.020
Pulmonary diseases	1 (3.8%)	4 (2.7%)	0.557
Liver diseases	1 (3.8%)	6 (4.0%)	1.000
Renal diseases	2 (7.7%)	3 (2.0%)	0.160
Solid cancers	9 (34.6%)	58 (38.9%)	0.676
Hematologic diseases	3 (11.5%)	9 (6.0%)	0.391
Autologous SCT	2 (7.7%)	1 (0.7%)	0.058
Solid organ transplantation	0 (0.0%)	3 (2.0%)	1.000
Charlson's WIC (median, IQR)	2 (1–6)	2 (0–6)	0.444
Vital signs (median, IQR)			
Fever (>38 °C)	6 (23.1%)	20 (13.4%)	0.231
Hypotension (MAP < 65)	0 (0.0%)	7 (4.7%)	0.596
Tachycardia (HR > 90)	11 (42.3%)	44 (29.5%)	0.195
Tachypnea (RR > 24)	4 (15.4%)	4 (2.7%)	0.018
SIRS	7 (26.9%)	36 (24.2%)	0.763
Concomitant infections	10 (38.5%)	45 (32.8%)	0.652
Bacterial	8 (30.8%)	53 (35.8%)	0.795
Tuberculosis	1 (3.8%)	1 (0.7%)	0.276
Viral	1 (3.8%)	7 (4.7%)	1.000

Data are expressed as the number (%) of patients, unless indicated otherwise.
Abbreviations: MERS, Middle East respiratory syndrome; SD, standard deviation; BMI, body mass index; IQR, interquartile range; SCT, stem cell transplantation; WIC, weighted index of comorbidity.

Table 2
Multivariate analysis for host susceptibility factors to MERS-CoV infection.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Exposure sites				
Radiology or registration area	1		1	
Zone II	4.711 (1.342–16.535)	0.016	5.990 (1.503–23.867)	0.011
Zone III	7.413 (1.916–28.686)	0.004	5.520 (1.199–25.411)	0.028
Zone IV	1.531 (0.309–7.587)	0.602	1.313 (0.263–6.550)	0.740
Autologous SCT	6.181 (1.458–26.200)	0.013	31.151 (5.447–178.145)	<0.001
Tachypnea	6.535 (2.243–19.037)	0.001	4.392 (1.402–13.761)	0.011
Hypertension	2.283 (1.056–4.937)	0.036	1.872 (0.746–4.698)	0.181
Cardiovascular diseases	2.788 (1.242–6.257)	0.013	2.004 (0.762–5.270)	0.159

Abbreviations: MERS-CoV, Middle East respiratory syndrome coronavirus; SCT, stem cell transplantation.

Previously reported poor prognostic factors did not show association with increased host susceptibility to the virus.

Conflicts of interest

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

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jiac.2017.09.008.

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