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Case Fatality Factors in Middle East Respiratory Syndrome-Coronavirus Outbreaks in 2015, the Republic of Korea

Tae-Jun Lee, Achangwa Chiara, Moo-Sik Lee
Department of Preventive Medicine and Public Health,
College of Medicine, Konyang University, Daejeon, Korea

2015년 한국의 중동호흡기증후군 유행에서 치명률

이태준, 아창과 키아라, 이무식
건양대학교 의과대학 예방의학교실

= Abstract =

배경: 2015년 한국의 중동호흡기증후군 유행에서 지역간 치명률의 차이는 극명하였다. 이 연구는 대전 클러스터와 다른 지역 간의 치명률의 관련된 일반적 특성 및 역학적 요인을 밝히고저 하였다.

방법: 입원병원 소재지를 기준으로 대전과 타 지역으로 구분하여 관련변수에 따른 카이제곱검정 및 피셔정확검정 등으로 분석하였다. 대전과 다른 지역의 치명률(CFR)의 차이와 관련된 요인을 분석하기 위하여 단변량 및 다변량 로지스틱 회귀분석를 실시하였다.

결과: 모형 I에서는 65세 이상 연령군일수록 7.12배(95% CI 2.33-21.8)(p=0.001), 동반질환이 있는 경우 10.29배(95% CI 2.94-36.06)(p<0.001), 잠복기가 7일 이하인 경우가 8.55배(95% CI 2.54-26.7), 입원기간이 17일 이하인 경우 10.08배(95% CI 2.99-31.9)(p<0.001) 등이었으며, 모형 II에서는 65세 이상 연령군일수록 5.34배(95% CI 1.65-17.2)(p=0.005), 잠복기가 7일 이하인 경우가 6.70배(95% CI 1.96-22.89), 입원기간이 17일 이하인 경우 8.90배(95% CI 2.59-30.6)(p=0.001), 동반질환에서 암의 경우에서 7.15배(95% CI 1.64-31.14)(p=0.009) 등이었다.

결론: 2015년 한국 중동호흡기증후군 유행에서 대전 클러스터의 높은 치명율은 연령(≥65세), 동반질환(특히 암), 잠복기(≤7일), 입원기간(≤17일) 등이 유의한 변수로 도출되었다.

주요단어: 메르스, 발병, 치명률, 대전

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* Corresponding author: 이무식, 대전광역시 서구 관저동로 158(우. 35365) 건양대학교 의과대학 예방의학교실
Moo-Sik Lee, Department of Preventive Medicine, College of Medicine, Konyang University, 158 Kwanjeodongro, Seogu, Daejeon, 35365, Korea
Tel: +82-42-600-8670, Fax: +82-42-600-6401, E-mail: mslee@konyang.ac.kr

INTRODUCTION

There is increasing continued interest in the epidemiology of Coronavirus infections starting from the epidemic of SARS in 2003 and MERS in 2012 in the Middle East and Korea[1]. Epidemiological and clinical interests in the factors related to the differences in CFR of MERS-CoV outbreak among hospitals, local communities and countries, are also on the rise[1][2][3].

In April 24, 2015, a 68-year-old Korean man returned from the Middle East and on May 4th, he reportedly started experiencing symptoms such as chills and fever, and visited the hospital on May 11th. He was confirmed to have contracted the Middle East respiratory syndrome and that marked the beginning of MERS in Korea in 2015.

A total of 186 patients developed MERS-CoV over a 56 day period. The disease spread across 17 hospitals mainly through hospital-to-hospital transmission. A 73-year-old male patient who was admitted in a different hospital died on September 13, 2017 due to organ damage by renal failure while being treated with the MERS-CoV sequelae of pulmonary fibrosis and heart failure. A total of 39 people died. The case fatality rate of Middle East respiratory syndrome epidemic was reported to be 21.0% in Korea, 2015.

However, due to the difference in the CFR among several clusters in several hospitals, the identification of the cause of death is vital for understanding the epidemiology of MERS-CoV in Korea.

In particular, 12 of the 29 confirmed patients in the Daejeon metropolitan city cluster(Daejeon cluster) died, and the CFR of Daejeon cluster was 41.4%, which was much higher than the national CFR 21.0% in Korea and compared to the CFR of 17.2% in other regions with the exception of Daejeon metropolitan city.

Several studies outside Korea have studied MERS-CoV CFR. However, there was a difference between the CFRs and related factors in each country and for each community studies[1][2][3]. Furthermore, there exista lack of research on the factors related to the CFR of Middle East respiratory syndrome outbreak in Korea in 2015.

The purpose of this study was to identify the general and epidemiological factors related to the fatalities of the MERS epidemic in the Daejeon cluster and other regions.

MATERIALS AND METHODS

A retrospective cohort study was carried out using 2015 data on MERS-CoV collected by Korean Centers for Disease Prevention and Control(KCDC). This study analyzed the MERS-CoV outbreak data of the Daejeon metropolitan city from the KCDC, which was in charge of nationwide confirmation of the disease. Detail information that were found missing duringthe information processing process or not included at the time of the survey were collected from official press releases of Korea government, press releases and statistics of World Health Organization, and media reports. The collected data included basic personal information such as age and gender, medical records such as symptoms, diagnosis, and admission records.

In this study, final confirmed diagnosis of MERS followed MERS response guidelines at each point in time from the revision and distribution of the MERS response guideline by the Korea Ministry of Health and Welfare, and Korea Center for Disease Prevention and Control[4].

The serial number of a confirmed patient was the number sequentially given in the order of confirmation. Those who were infected from the first patient were classified as the first generation, those infected from the first-generation patients were classified as the second generation, and those who were infected from the second-generation patients were classified as the third generation respectively. Specifically, this study included the first-generation patients who had contact with the first confirmed patient(index case) and who had symptoms within a maximum of 14 days. If a person had been contacted by multiple generations of confirmed patients, the most likely contact route of infection was selected. In cases where it could not be proven by images or concrete testimonies, the path with the highest probability of infection was selected for the estimated contact path.

In order to compare the fatality rate of Daejeon city with that of other regions, the fatality rate was calculated in percentage by dividing the number of MERS death cases by the total number of confirmed MERS patients in Daejeon and then together for the other regions.

Patients were classified as inpatients or others. Inpatients were the patients in the same room and floor of the hospital with the first case(index case). Others categories were care-givers, such as the patient's family, medical staff, health care workers, other patients and visitors who visited the outpatient and emergency rooms. In addition to medical doctors and nurses, medical staff and health care workers included safety personnel, emergency vehicle drivers, information technology managers, and emergency medical workers.

The comorbidities presented simultaneously in patients were hypertension, diabetes, cardiovascular disease, lung disease, kidney disease, neoplasm, and other chronic diseases.

Symptoms explored included fever and cold, cough, sputum, diarrhea, abdominal pain, dyspnea, nausea and vomiting, muscle pain, runny nose, sore throat, anorexia, weakness, headache and other symptoms. Digestive system symptoms were nausea, vomiting, diarrhea, and abdominal pain. Respiratory symptoms were runny nose, shortness of breath and sore throat. General symptoms were general weakness, fatigue, headache and dizziness and muscle ache.

The incubation period was the interval between contact time from the infection source(infection acquired) to the time of onset of the first clinical signs and symptoms. On the other hand, asymptomatic cases were confirmed using the time of diagnosis.

The confirmation period was defined as the period between contact time(infection acquired) and time of diagnosis confirmation. The admission period was the period between confirmation time of diagnosis and discharge or death time at admitted hospital(resolution or death). Cut-off point of the incubation period and length of hospital stay were determined by receiver operating characteristic (ROC) curve analysis.

1. Study subjects

This study involved 186 patients who were confirmed positive for MERS during the period between the first diagnosed MERS case on May 20, 2015 and December 23, 2015 when Korea government declared termination of MERS epidemic. Amongst them, 39 MERS patients died. The date of the last confirmed death among the confirmed patients was September 13, 2017. The regional classification of the confirmed patients was classified either into Daejeon or other regions based on the location of the hospital where MERS patients were hospitalized from May 20, 2015 to December 23, 2015.

A total of 28 MERS patients were included in the Daejeon cluster. These included 14 patients who were infected at Daechung Hospital, 11 patients who wereinfected at Konyang University Hospital and 3 patients who were infected at Samsung Medical Center(2 patients at Eulji University Hospital, 1 patent at Daejeon Saint Mary's hospital), respectively.

In other cases, they were classified as other local confirmation. According to the criteria, 28 patients(15.6%) of Daejeon cluster and 157 patients(84.4%) of the other regions were included among the 186 confirmed patients.

2. Laboratory test for confirmation

Laboratory tests for the confirmation of MERS were conducted in the department of respiratory viruses of the KCDC until June 3, 2015. However, on March 3, 2015, the MERS response guideline was revised, and laboratory tests were carried out together by KCDC and the Metropolitan city and Provincial Institute of Public Health and Environment[5].

Specimens for the diagnosis of MERS were collected in three kinds: the upper respiratory tract specimen, lower respiratory tract specimen, and blood.

Specimens were obtained from the lower respiratory tract essentially sputum from lower respiratory tract, bronchial aspirate, and bronchoalveolar lavage fluid. However, if the doctor judged that the sample could not be taken, upper respiratory tract samples (non-pharyngeal swab, oropharyngeal swab) and blood sample could be collected and used[5].

Genetic tests were performed by using specimens. Genetic testing was used to diagnose the onset of MERS-CoV infection by real-time reverse-transcription polymerase chain reaction(rRT-PCR) assay. The test was positive when two MERS-CoV specific genes were positive for rRT-PCR or one for MERS-CoV specific for conventional RT-PCR, and confirmed by sequencing of PCR product[5].

Diagnosis was positive when at least one of the three specimens was positive. However, in the case that lower respiratory tract specimen was not sampled, even if upper respiratory tract specimen and the blood test result were negative, the positive result could not be excluded, and the epidemiological and clinical aspects of the disease were considered[5].

3. Data analysis

Univariate analysis was performed by descriptive analysis, chi-square test, and Fisher's exact test that compared the distribution of general and epidemiological characteristics(gender, age, contact path), comorbidity, and symptoms between Daejeon cluster and other regions.

Univariate and multivariate logistic regression analysis were conducted to analyze the factors associated with the difference in CFR, the odds ratio(OR) and 95% confidence intervals of each factors for CFR were calculated.

This study was approved by Konyang University Institutional Review Board(No. 2017-109).

RESULTS

The first MERS case of Daejeon cluster was the 16th patient who was admitted for colonoscopic polypectomy in the same ward at Pyeongtaek St. Mary's Hospital where the first case of the Korean MERS epidemic, 2015(May 15-18) was also admitted. Thereafter, he was discharged from hospital and admitted forfever at Daechung Hospital in Daejeon, on May 22, 2015. He was then transferred to Konyang University Hospital on May 28, and was diagnosed with MERS on May 31, 2015.

While the index case of the Daejeon cluster currently in the fifth ward of Daecheong Hospital(May 22-28), 14 people(who included 9 patients and 5 health workers) were infected, and four of them died.

He was further transferred to Konyang University Hospital and there he infected a total of 11 people of the 101 inpatients in the wards(May 28-30). Of the 11 cases, 6 were inpatients, 2 were health care workers (including 1 nurse), and 3 patient caregivers. And amongst them 7 died(including 5 admitted patients and 2 family caregivers).

Three of the infected patients(2 patients at Eulji University Hospital and 1 patient at Daejeon St. Mary's Hospital) were confirmed at Samsung Medical Center in early June. The 90th patient who wasinfected from Samsung Medical Center died at Eulji University Hospital.

Confirmed patients of the MERS in Daejon city were diagnosed including the 16th patient on May 30th and 1 or 2 confirmed patients were reported daily. Six Confirmed MERS cases were diagnosed and the incidence reached its peak on June 7 concomitantly with the nationwide epidemic peak(28 cases of third generation and 1 case of 4th generation infection).

1. Comparison on the general, epidemiological characteristics, comorbidity, and symptoms of MERS cases between Daejeon cluster and other regions.

We analyzed the distribution of general, epidemiological characteristics(gender, age, contact path, generation of infection), comorbidity, and symptoms between Daejeon cluster and other regions. There was a statistically significant difference between the two groups in age-groups($p<0.001$), contact and infection path($p<0.001$), comorbidity($p=0.044$), generation of infection($p=0.032$). The number of patients aged 65 years or older weresignificantly higher in Daejeon cluster(17 patients, 58.6%) than that of other regions(38 patients, 24.2%). In the contact and infection pathway, the number of inpatients was significantly higher in Daejeon cluster(15 patients, 51.7%) than in the other regions(31 patients, 19.9%).

With respect to the comorbidity, 19 patients(65.5%) of Daejeon cluster were more likely to have comorbidities than others. There was a significant difference in hypertension($p<0.001$) and pulmonary disease ($p=0.007$) between the two groups. The generation of infection in Daejeon cluster was mostly by third generation. Death was 2.4 times more in Daejeon cluster(12 patients, 41.4%) compared to the other regions(27 patients, 17.2%)(Table 1).

Table 1. General, epidemiological characteristics, comorbidity, and symptoms distribution of MERS cases in Daejeon cluster and other regions of Republic of Korea, 2015.

Variables	Total (n=186, 100.0%)	Daejeon cluster (n=29, 15.6%)	Other regions (n=157, 84.4%)	p-value
Gender				
Male	111 (59.7)	15 (51.7)	96 (61.1)	0.227
Female	75 (40.3)	14 (48.3)	61 (38.9)	
Age(years)				
≥= 65	55 (29.6)	17 (58.6)	38 (24.2)	0.000
<= 64	131 (70.4)	12 (41.4)	119 (75.8)	
Contact routes				
Inpatients*	46 (24.9)	15 (51.7)	31 (19.9)	0.001
Other†	139 (74.7)	14 (48.3)	125 (79.6)	
Comorbidity‡				
No	97 (52.2)	10 (34.5)	87 (55.4)	0.044
Yes	89 (47.8)	19 (65.5)	70 (44.6)	
Generation time for transmission				
3rd & 4th	152 (81.7)	28 (96.6)	124 (79.0)	0.032
2nd	32 (17.4)	1 (3.4)	31 (20.0)	
Symptoms§				
No	6 (3.2)	-	6 (3.8)	0.592
Yes	180 (96.8)	29 (100.0)	151 (96.2)	
End results				
Death	39 (21.0)	12 (41.4)	27 (17.2)	0.006
Alive	147 (79.0)	17 (58.6)	130 (82.8)	
Incubation periods‖				
<= 7 days	101 (56.7)	14 (51.9)	87 (57.6)	0.674
≥= 8 days	77 (43.3)	13 (48.1)	64 (42.4)	
Confirmation periods¶				
<= 8 days	129 (70.5)	20 (71.4)	109 (70.3)	1.000
≥= 9 days	54 (29.5)	8 (28.6)	46 (29.7)	
Admission periods**				
<= 17 days	63 (34.6)	9 (32.1)	54 (35.1)	0.832
≥= 18 days	119 (65.4)	19 (67.9)	100 (64.9)	
Comorbidity				
Hypertension				
Yes	37 (19.9)	14 (48.3)	23 (14.6)	0.000
No	149 (80.1)	15 (51.7)	134 (85.4)	
Diabetes				
Yes	25 (13.4)	6 (20.7)	19 (12.1)	0.236
No	161 (86.6)	23 (79.3)	138 (87.9)	
Cardiovascular diseases				
Yes	15 (8.1)	2 (6.9)	13 (8.3)	1.000
No	171 (91.9)	27 (93.1)	144 (91.7)	

Lung diseases				
Yes	21 (11.3)	8 (27.6)	13 (8.3)	0.007
No	165 (88.7)	21 (72.4)	144 (91.7)	
Renal diseases				
Yes	5 (2.7)	1 (3.4)	4 (2.5)	0.576
No	181 (97.3)	28 (96.6)	153 (97.5)	
Neoplasm				
Yes	21 (11.3)	4 (13.8)	17 (10.8)	0.748
No	165 (88.7)	25 (86.2)	140 (89.2)	
Other chronic diseases or conditions				
Yes	32 (17.2)	5 (17.2)	27 (17.2)	1.000
No	154 (82.8)	24 (82.8)	130 (82.8)	
Symptoms				
Fever/chillness				
Yes	173 (93.0)	27 (93.1)	146 (93.0)	1.000
No	13 (7.0)	2 (6.9)	11 (7.0)	
Cough				
Yes	64 (34.4)	9 (31.0)	55 (35.0)	0.832
No	122 (65.6)	20 (69.0)	102 (65.0)	
Sputum				
Yes	37 (19.9)	3 (10.3)	34 (21.7)	0.209
No	149 (80.1)	26 (89.7)	123 (78.3)	
GI symptoms††				
Yes	26 (14.0)	5 (17.2)	21 (13.4)	0.565
No	160 (86.0)	24 (82.8)	136 (86.6)	
Respiratory symptoms‡‡				
Yes	28 (15.1)	4 (13.8)	24 (15.3)	1.000
No	158 (84.9)	25 (86.2)	133 (84.7)	
General symptoms§§				
Yes	81 (43.5)	8 (27.6)	73 (46.5)	0.068
No	105 (56.5)	21 (72.4)	84 (53.5)	

∗ Inpatients admitted in the same room or floor of hospitals with index cases(infected)

† Care-givers included patient's family member in hospitals, others included medical staffs or healthcare workers, and visitors. Medical staffs or healthcare workers included safety personnel, drivers, information technologist, emergency care personnel etc. Visitors in outpatient department or emergency room of the hospital as patient or family.

‡ Comobidity included hypertension, diabetes, cardiovascular diseases, lung diseases, renal diseases, neoplasm, etc.

§ Symptoms included fever/chill, cough, sputum, diarrhea, abdominal pain, shortness of breath, nausea/vomiting, myalgia, nasal discharge, anorexia, sore throat, general weakness/fatigue, headache/dizziness, etc.

∥ Periods from contact time(infection acquired) to first onset time of clinical symptoms orsigns(asymptomatic cases were used with diagnostic time)

¶ Periods from contact time(infection acquired) to confirmation time of diagnosis

** Periods from confirmation time of diagnosis to discharge time from admitted hospitals(resolution or death)

†† Nausea/vomiting, diarrhea, abdominal pain

‡‡ Nasal discharge, shortness of breath, sore throat

§§ General weakness/fatigue, headache/dizziness, anorexia, myalgia, etc.

2. Factors associated with fatality among the MERS case.

Odd ratios were calculated by applying univariate logistic regression analysis to identify the factors related to the difference of CFR. In the univariate analysis, CFR was statistically significantly associated with cluster, age, contact or infection route, comorbidity, incubation period, admission period, hypertension, diabetes, cardiovascular diseases, and cancer disease as comorbidity, respiratory symptoms, and general symptoms.

The CFR was 2.41 times(95% CI 1.38-4.18, $p=0.002$) higher in Daejeon cluster than that of the other regions, 4.76 times(95% CI 2.65-8.56, $p<0.001$) higher in those aged 65 and over, 1.89 times(95% CI 1.09-3.28, $p=0.024$) higher in hospitalized patients for contact and infection route, 7.41 times(95% CI 3.63-18.11, $p<0.001$) higher in comorbidity cases, 2.14 times(95% CI 1.11-4.12, $p=0.024$) higher in cases of the incubation period was less than 7 days, 2.60 times(95% CI 1.47-4.58, $p<0.001$) higher in case of 17 days for admission day or less.

With respect to the comorbidity, CFR was 2.80 times(95% CI 1.05-4.74, $p<0.001$) higher in hypertension, 2.07 times(95% CI 1.04-4.14, $p=0.038$) higher in cardiovascular diseases, 3.93 times(95% CI 2.41-6.39, $p<0.001$) higher in lung diseases, 3.09 times(95% CI 1.82-5.24, $p<0.001$) higher in cancer.

With respect to the symptoms, CFR was 1.95 times(95% CI 1.07-3.53, $p=0.029$) higher in cases with respiratory symptoms, 0.509 times(95% CI 0.27-0.96, $p=0.037$) higher in cases with general symptoms(Table 2).

Table 2. Factors associated with fatality by general, epidemiological variables, comorbidity, and symptom variables among MERS cases of Republic of Korea, 2015.

Variables	Total	Death(CFR*, %)	OR(95% CI)	p-value
Total	186	39 (21.0)		
Clusters				
Daejeon	29	12 (41.4)	2.41 (1.38 - 4.18)	0.002
Other regions	157	27 (17.2)	Reference	
Gender				
Male	111	27 (24.3)	1.52 (0.82 - 2.81)	0.181
Female	75	12 (16.0)	Reference	
Age(years)				
≥= 65	55	26 (47.3)	4.76 (2.65 - 8.56)	<0.000
<= 64	131	13 (9.9)	Reference	
Contact routes				
Inpatients*	46	15 (32.6)	1.89 (1.09 - 3.28)	0.024
Other†	139	24 (17.3)	Reference	
Comorbidity‡				
Yes	89	34 (38.2)	7.41 (3.63 - 18.11)	<0.000
No	97	5 (5.2)	Reference	

Generation time for transmission				
3rd & 4th	152	34 (22.4)	1.43 (0.61 - 3.38)	0.412
2nd	32	5 (15.6)	Reference	
Symptoms[§]				
Yes	180	38 (21.1)	1.28 (0.21 - 7.75)	0.798
No	6	1 (16.7)	Reference	
Incubation periods[‖]				
<= 7 days	101	28 (27.7)	2.14 (1.11 - 4.12)	0.024
≥= 8 days	77	10 (13.0)	Reference	
Confirmation periods[¶]				
<= 8 days	129	24 (18.6)	0.72 (0.40 - 1.28)	0.260
≥= 9 days	54	14 (25.9)	Reference	
Admission periods[**]				
<= 17 days	63	22 (34.9)	2.60 (1.47 - 4.58)	0.001
≥= 18 days	119	16 (13.4)	Reference	
Comorbidity				
Hypertension				
Yes	37	16 (43.2)	2.80 (1.65 - 4.74)	0.000
No	149	23 (15.4)	Reference	
Diabetes				
Yes	25	9 (36.0)	1.93 (1.05 - 3.57)	0.036
No	161	30 (18.6)	Reference	
Cardiovascular diseases				
Yes	15	6 (40.0)	2.07 (1.04 - 4.14)	0.038
No	171	33 (19.3)	Reference	
Lung diseases				
Yes	21	13 (61.9)	3.93 (2.41 - 6.39)	<0.000
No	165	26 (15.8)	Reference	
Renal diseases				
Yes	5	2 (40.0)	1.96 (0.64 - 5.95)	0.237
No	181	37 (20.4)	Reference	
Neoplasm				
Yes	21	11 (52.4)	3.09 (1.82 - 5.24)	<0.000
No	165	28 (17.0)	Reference	
Symptoms				
Fever/chillness				
Yes	173	37 (21.4)	1.39 (0.38 - 5.13)	0.621
No	13	2 (15.4)	Reference	
Cough				
Yes	64	14 (21.9)	1.07 (0.60 - 1.91)	0.825
No	122	25 (20.5)	Reference	
Sputum				
Yes	37	10 (27.0)	1.39 (0.75 - 2.58)	0.301
No	149	29 (19.5)	Reference	

GI symptoms††				
Yes	26	6 (23.1)	1.12 (0.52 - 2.40)	0.773
No	160	33 (20.6)	Reference	
Respiratory symptoms‡‡				
Yes	28	10 (35.7)	1.95 (1.07 - 3.53)	0.029
No	158	29 (18.4)	Reference	
General symptoms§§				
Yes	81	11 (13.6)	0.509 (0.27 - 0.96)	0.037
No	105	28 (26.7)	Reference	

* CFR, case fatality rate
∗ Inpatients admitted in the same room or floor of hospitals with index cases(infected)
† Care-givers included patient's family member in hospitals, others included medical staffs or healthcare workers, and visitors. Medical staffs or healthcare workers included safety personnel, drivers, information technologist, emergency care personnel etc. Visitors in outpatient department or emergency room of the hospital as patient or family.
‡ Comobidity included hypertension, diabetes, cardiovascular diseases, lung diseases, renal diseases, neoplasm, etc.
§ Symptoms included fever/chill, cough, sputum, diarrhea, abdominal pain, shortness of breath, nausea/vomiting, myalgia, nasal discharge, anorexia, sore throat, general weakness/fatigue, headache/dizziness, etc.
‖ Periods from contact time(infection acquired) to first onset time of clinical symptoms orsigns(asymptomatic cases were used with diagnostic time)
¶ Periods from contact time(infection acquired) to confirmation time of diagnosis
** Periods from confirmation time of diagnosis to discharge time from admitted hospitals(resolution or death)
†† Nausea/vomiting, diarrhea, abdominal pain
‡‡ Nasal discharge, shortness of breath, sore throat
§§ General weakness/fatigue, headache/dizziness, anorexia, myalgia, etc.

3. Multivariate logistic regression on the fatality by general, epidemiological, comorbidity, and symptoms amongst the MERS cases.

Significant variables in univariate logistic regression analysis were applied to multivariate logistic regression analysis, and a final model was derived by controlling for gender and age. Model I was the model including only the comorbidity conditions while Model II was the model including individual comorbid diseases.

In Model I, age, comorbidity, incubation period and admission period were found to be statistically significant variables. CFR was 7.12 times(95% CI 2.33-21.8, $p<0.001$) higher in those aged 65 years or more, 10.29 times(95% CI 2.94-36.06, $p<0.001$) higher in comorbidity, 8.55 times(95% CI 2.54-26.7, $p<0.001$) higher in cases where the incubation period was less than 7 days, 10.08 times(95% CI 2.99-31.9, $p<0.001$) higher in cases where hospital admission length was 17 days or less.

Age, incubation period, admission period, cases with cancer disease as comorbidity were found to be statistically significant in Model II. CFR was 5.34 times(95% CI 1.65-17.2, $p=0.005$) higher in those aged 65 or more, 6.70 times(95% CI 1.96-22.89, $p<0.001$) higher in cases in which the incubation period was less than 7 days, 8.90 times(95% CI 2.59-30.6, $p<0.001$) higher in cases that had days of hospital admission 17 day or less, 7.15 times(95% CI 1.64-31.14, $p<0.009$) higher in cases with cancer disease as the comorbidity(Table 3).

Table 3. Multivariable logistic regression on the fatality by general, epidemiological, comorbidity, and symptoms variables among MERS cases, Republic of Korea, 2015.

Variables	Model I		Model II	
	OR(95% CI)	p-value	OR(95% CI)	p-value
Clusters				
Daejeon	3.27 (0.73 - 14.6)	0.122	2.54 (0.51 - 12.6)	0.256
Other regions	Reference		Reference	
Gender				
Male	1.69 (0.57 - 5.02)	0.349	1.45 (0.48 - 4.34)	0.506
Female	Reference		Reference	
Age(years)				
≥= 65	7.12 (2.33 - 21.8)	0.001	5.34 (1.65 - 17.2)	0.005
<= 64	Reference		Reference	
Contact routes				
Inpatients*	0.49 (0.40 - 1.69)	0.257	0.46 (0.12 - 1.77)	0.260
Others†	Reference		Reference	
Comorbidity‡				
Yes	10.29 (2.94 - 36.06)	0.000		
No	Reference			
Incubation periods§				
<= 7 days	8.55 (2.54 - 26.7)	0.001	6.70 (1.96 - 22.89)	0.002
≥= 8 days	Reference		Reference	
Admission periods¶				
<= 17 days	10.08 (2.99 - 31.9)	0.000	8.90 (2.59 - 30.6)	0.001
≥= 18 days	Reference		Reference	
Comorbidity				
Hypertension				
Yes			2.29 (0.66 - 7.96)	0.193
No			Reference	
Diabetes				
Yes			1.09 (0.25 - 4.70)	0.907
No			Reference	
Cardiovascular diseases				
Yes			0.69 (0.30 - 9.58)	0.556
No			Reference	
Lung diseases				
Yes			4.29 (0.91 - 20.23)	0.070
No			Reference	
Neoplasm				
Yes			7.15 (1.64 - 31.14)	0.009
No			Reference	
Symptoms				
Respiratory symptoms**				
Yes	2.57 (0.60 - 11.08)	0.205	3.14 (0.74 - 13.2)	0.119
No	Reference		Reference	

General symptoms††				
Yes	0.51 (0.17 - 1.53)	0.230	0.53 (0.17 - 1.70)	0.284
No	Reference		Reference	

* CFR, case fatality rate
* Inpatients admitted in the same room or floor of hospitals with index cases(infected)
† Care-givers included patient's family member in hospitals, others included medical staffs or healthcare workers, and visitors. Medical staffs or healthcare workers included safety personnel, drivers, information technologist, emergency care personnel etc. Visitors in outpatient department or emergency room of the hospital as patient or family.
‡ Comobidity included hypertension, diabetes, cardiovascular diseases, lung diseases, renal diseases, neoplasm, etc.
§ Symptoms included fever/chill, cough, sputum, diarrhea, abdominal pain, shortness of breath, nausea/vomiting, myalgia, nasal discharge, anorexia, sore throat, general weakness/fatigue, headache/dizziness, etc.
‖ Periods from contact time(infection acquired) to first onset time of clinical symptoms orsigns(asymptomatic cases were used with diagnostic time)
¶ Periods from contact time(infection acquired) to confirmation time of diagnosis
** Periods from confirmation time of diagnosis to discharge time from admitted hospitals(resolution or death)
†† Nausea/vomiting, diarrhea, abdominal pain
‡‡ Nasal discharge, shortness of breath, sore throat
§§ General weakness/fatigue, headache/dizziness, anorexia, myalgia, etc.

DISCUSSION

This study was conducted on a total of 186 patients affected by the Middle East respiratory syndrome epidemic of Korea in 2015 including the 39 deaths among them. We reviewed the major related factors of fatalities by using domestic and international public data.

The 2015 epidemic of MERS in Korea showed a unimodal distribution with a human-to-human transmission following a hospital-to-hospital transmission centered on one Middle Eastern traveler[6][7].

The MERS, reported for the first time in Saudi Arabia in 2012, is a zoonotic disease that has not only a high probability for human transmission, but also has a high case fatality rate[1]. Nevertheless, the results of previous studies have shown that the mortality rate was different for each country, hospital, and community[8].

The fatality rate of MERS was reported to be highand the related factors were among the major issues reported in previous studies[8], and being higher than the reported 10% fatality rate of the similar coronavirus SARS. This also was one of major issues in the controversy over the different nature of the comorbidities[2].

Globally, the crude fatality rate was 32.1% until October 2016, and Korea's fatality rate was comparatively low at 21%[9]. However, there was a huge difference in the CFR for the Daejeon cluster(41.4%) and that of the other regions(17.2%). Other studies have reported epidemiological and clinical related factors to the MERS epidemic in hospital settings and in Daejeon region. But, the findings of theseauthors were in the middle of the epidemic during which death also occurred in non-cases, when two hospitals in Daejeon city were compared, and there was no multivariate analysis that could adjust for age and its related variables[9].

In this study, 59.7% of infected persons were men, which seemed to be consistent with the sociocultural characteristics of the disease among men of the Middle East region[10][11].

Several studies also suggested that men's high infection rates were associated with high smoking rates[12], but this study didn't test for smoking because data could not be reliably obtained.

The maincharacteristics of the Daejon cluster were a significant high number of the elderly patients(≥=65 years) with comorbidities(especially hypertension and lung diseases), third and fourth generations of infection, and a high fatality rate.

In the univariate analysis, CFR was significantly negatively associated with Daejeon cluster, elderly patients(≥=65 years), an admitted patient as contact or infection route, comorbidity, cases with short incubation periods, cases with short admission periods, cases with hypertension, diabetes, cardiovascular diseases, and cancer, and cases with respiratory and general symptoms. In multivariate analysis, the fatality rate was found to be significantly associated with the patients older than 65 years of age, cases of comorbidity(especially cancer), cases of short incubation period, and cases with short admission periods.

We found the factors related to fatality like old age, male gender, presence of comorbidity, short incubation periods similar to the reports by Zulma *et al.,* in 2015[2].

We noted in our series that the relationship between short incubation period and high fatality rates was due to a high dose of infection, which causes the viral replication to increase and an infection reaction to be severe and aggressive.

Thus, the results of this study that high fatality was associated with short admission periods suggested same features as mentioned above. Reports from global data suggests that mortality was highest during the 1st week following the infection, which was consistent with high fatality ratesat the beginning of the infection[8][12].

Comorbidity is important clinically because it determines the prognosis of the disease. Our analysis shows that comorbidity increases mortality, which is in accordance with other studies reported from global data that showed a 4-time higher mortality rate[3],[8]. This result was also consistent with the cases of SARS[13]. These comorbidities had different characteristics depending on the type of infectious diseases. For example, influenza associated with cardiovascular diseases, SARS associated with immunological, neurological, metabolic, and dermatologic diseases such as diabetes and end-stage renal diseases[2][14].

Results of univariate analysis were consistent with the findings that cases with lung disease as comorbidity had high fatality rates because of easy viral invasion. Also, these findings are consistent with reports that respiratory comorbidities are associated with a high MERS fatality.

In addition, cases with hypertension, diabetes, cardiovascular diseases, and cancer also showed high fatality. In particular,cases with cancer showed high fatality in multivariate analysis.

This study was limited by the following: firstly, this study didn't consider hospital-related factors including medical services related behaviors and hospital environments. Secondly, there was lack of patient behavior information including smoking. Thirdly, this study didn't include clinical information such as medical use and related information, clinical interventions and services, severity of diseases and symptoms. In addition, this study could not access hematologic, genetic, biochemical, and diagnostic information on the patients. This study couldn't rule out the effect of recall bias due to our self-reported questionnaire design. Finally, this study did not consider epidemiologic surveillance for communicable diseases in monitoring like, contact tracing, patient identification, time of medical intervention.

CONCLUSION

Model I was the model included comorbidity condition only, and Model II was the model included individual comorbid diseases. In model I, CFR was 7.12 times(95% CI 2.33-21.8, p<0.001) for the age group of 65 years or older, 10.29 times(95% CI 2.94-36.06, p<0.001) in patients with comorbidity, 8.55 times(95% CI 2.54-26.7) with an incubation period of 7 days or less, 10.08 times(95% CI 2.99-31.9, p<0.001) with length of hospital stay of 17 days or less than other regions. In model II, it was 5.34 times(95% CI 1.65-17.2, p=0.005) for the age group of 65 years or older, 6.70 times(95% CI 1.96-22.89) with an incubation period of 7 days or less, 8.90 times(95% CI 2.59-30.6, p<0.001) with length of hospital stay of 17 days or less, 7.15 times(95% CI 1.64-31.14, p=0.009) in cancer patients than other regions.

We recommend further studies on a variety of well-designed surveillance data and high-quality epidemiological investigation.

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