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The risk factors associated with MERS-CoV patient fatality: a global survey

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Running title: The risk factors associated with MERS-CoV.

ABSTRACT

Risk factors associated with Middle East respiratory syndrome coronavirus (MERS-CoV) infection outcome were established by analyses of WHO data from September 23, 2012 to 18 June 2018. Of the 2220 reported cases, 1408 cases, including 451 MERS-CoV deaths, were analyzed. The case fatality rate was 32% (95% CI: 29.4–34.5). Compared to MERS patients ≤ 30 years old, those with >30 years had the adjusted odds ratio estimate for death of 2.38 [95% CI: 1.75-3.22]. This index was 1.43 [95% CI: 1.06-1.92] for Saudi patients in comparison to non-Saudi; 1.76 [95% CI: 1.39-2.22] for patient with comorbidity in comparison to those without comorbidity; 0.58 [95% CI: 0.44-0.75] for those who had close contact to a camel in the past 14 days and 0.42 [95% CI: 0.31-0.57] for patients with >14 days with onset of signs and hospital admission compared to patients with ≤14 days.

Keywords: Middle East respiratory syndrome coronavirus; Epidemiology; Emerging infectious disease; Case fatality rate.

1. Introduction

The Middle East respiratory syndrome (MERS) is a relatively new viral respiratory infection caused by a novel coronavirus, the Middle East respiratory syndrome coronavirus, or MERS-CoV (Alshahrani et al., 2018). Coronaviruses are single-stranded positive-sense RNA viruses (Zumla et al., 2015), with human pathogenic strains resulting in a common cold to a severe acute respiratory syndrome (Castaño-Rodriguez et al., 2018). MERS-CoV, an emerging zoonotic virus (Alamoudi et al., 2018, Cong et al., 2018) is pathogenic in human, resulting in shortness of breath, cough, fever, diarrhea, and frequently pneumonia (Cong et al., 2018, Sherbini et al., 2017). The exact animal origin of MERS-CoV is not fully understood, but the transmission pattern and the evidence from virologic studies suggest that it may have originated in bats and was transmitted to camels sometime in the distant past (Hu et al., 2015, Wang et al., 2014, World Health Organization).

Several published studies have assessed the epidemiological status of MERS-CoV infection. Most of these epidemiological studies were derived from specific cohorts with a small sample size, or carried out in a single medical center (Alraddadi et al., 2016, Assiri et al., 2013, Harriman et al., 2013, Memish et al., 2013, Mobaraki et al., 2019, Park et al., 2017). However, numerous questions about the epidemiological status and associated risk factors of MERS-CoV at the global level remain unanswered.

For this study, we used the publicly available World Health Organization (WHO) MERS global epidemiologic data (World Health Organization, 2019) to assess characteristics, clinical information, global distribution status, and probable risk factors associated with MERS-CoV patient mortality.

2. Materials and methods

In this worldwide comprehensive survey, were analyzed publicly available data from the WHO website:(http://www.who.int/csr/don/archive/disease/coronavirus_infections/en/) related to laboratory-confirmed MERS-CoV cases from September 23, 2012 until June 18, 2018. Data for the analyses was downloaded on June 20, 2018. This WHO database is periodically updated by the WHO. Epidemiological characteristics of each patient was retrieved including: Age, gender, travel history to endemic countries, nationality, country/city of origin. Also retrieved was clinical data on the symptomatic MERS patients including day/month of the onset of symptom, day/month of the admission to the hospital, and comorbidities (diabetes mellitus, hypertension, and ischemic heart disease). Exposure to hazardous contacts was also collected, including healthcare workers (who worked in the hospital), camels, consumption of raw camel products, and exposure to MERS-CoV morbid patients at home or hospital within 14 days prior to the onset of symptomology.

All the collected information was checked for missing or invalid data. Of a total input of 2220 MERS patient cases, 1408 with a complete data set were included in the analysis. In order to avoid measurement bias and miscategorization of cases, 812 of the 2220 patients with incomplete data were not included.

2.1. Statistical analysis

Statistical analysis was conducted using the SPSS, version 21 (IBM Inc., Armonk, NY, USA). Quantitative measurement is expressed by the mean and standard deviation. Qualitative variables are presented as absolute frequency and percentage. Logistic regression was used to calculate the adjusted odds ratio (AOR) and unadjusted odds ratio (UOR) with a 95% confidence interval to assess the probable relationship between the risk factors and the final outcome (dead/survived) of laboratory-confirmed MERS-CoV cases. Any P-value given was two-sided and was considered statistically significant at 0.05.

3. Results

For this study, a total of 1408 sporadic/clusters patients with confirmed MERS-CoV infection and complete data were used in the analysis. The characteristics and the number of MERS cases per year can be found in Table 1. Among the global MERS cases, males (71.6% [1008/1408]) seem to be more affected than females (28.4% [400/1408]), with a male to female ratio of 2.52. The mean age of all cases reported worldwide was 50.21±18.73 years, and ranged from 2 to 109 years of age.

Most of the MERS cases were reported from Saudi Arabia (82.5% [1162/1408]). Also, 54.4% [771/1408] MERS cases had one or more comorbidity (the highest ranking comorbidities were diabetes mellitus, hypertension, and ischemic heart disease). The overall percentage of case fatality rate (%CFR) in MERS patients was 32% [451/1408].

Between September 23, 2012 to June 18, 2018, 27 countries have been affected by MERS-CoV infection. From our analyses of 1408 laboratory-confirmed cases of MERS-CoV infection, there were 451 confirmed deaths. Based on the collected data during the course of study, the overall %CFR of the pandemics with MERS-CoV was 32.0 % [451/1408]. Also this indicator for countries in the Middle East (Saudi Arabia, Iran, Jordan, Oman, Kuwait, Egypt, Qatar, United Arab Emirates, Yemen, Bahrain and Lebanon) was 32.7 % [431/1316], 83.3 % [5/6] for the countries in Africa (Egypt, Tunisia) 14.2 % [2/14] for Europe (Germany, Italy, Austria, Greece, the Netherlands, France, United Kingdom and Spain) 18.3 % [13/71] for countries in the Asia (Turkey, Thailand, Malaysia, Philippines, China and

South Korea) and 0% [0/3] for North America (United States and Canada). Most of the MERS cases were male and male-specific %CFR was approximately 33% (332/1008). The male vs. female ratio in the fatal and nonfatal cases was 2.9 (332/119) vs. 2.4 (676/281), respectively (see Table 2).

Table 3 illustrates unadjusted and adjusted OR for mortality in the laboratory-confirmed MERS-CoV cases in the survey period. The adjusted analysis showed that the age groups >30 years (2.38; 95% CI: 1.75-3.22), Saudi nationality (1.43; 95% CI: 1.06-1.92), and comorbidity (1.76; 95% CI: 1.39-2.22) were independently associated with higher chances of mortality. Additionally, in comparison to MERS patients who had ≤14 days from onset of clinical signs to hospital admission, adjusted OR estimates of the mortality was 0.42; 95% CI: 0.31-0.57 for those who had >14 days from the onset of clinical signs to hospital admission. The adjusted OR estimates of mortality was 0.58; 95% CI: 0.44- 0.75 for MERS patients who were exposed to a camel in the last 14 days compared to those who were not exposed. Other probable risk factors such as gender, exposure to a morbid case of MERS in the last 14 days, healthcare worker, and admission in negative pressure isolate room or ICU had no significant association with higher mortality (p>0.05 for all).

4. Discussion

MERS-CoV is a relatively new virus capable of creating an epidemic with fatalities (Kazhal Mobaraki and Ahmadzadeh, 2019, Memish et al., 2014). MERS-CoV started in Saudi Arabia by sporadic infections in mid-2012 and later its outbreak progressed to other countries (Alamoudi et al., 2018). Due to the occurrence of a large number of MERS-CoV cases and its high worldwide mortality rate, this infection must be considered a public health threat (Lessler et al., 2016). The current study focuses on the epidemiological trend of MERS-CoV infection and mortality rate analysis of its worldwide cases in the aforementioned dates. The findings of this study may have important implications for the infection control practice and also help to ensure global health security.

Based on the analysis, the overall global %CFR of MERS was 32.0% [451/1408], which is substantially lower than the %CFR in the MERS-CoV endemic region (Table 2). For example, Hunter et al. found an overall CFR of 67% in the Abu Dhabi (Hunter et al., 2016) and Petersen at al. found an overall CFR of 40% in the Kingdom of Saudi Arabia (Petersen et al., 2014) However, our estimates were higher than the largest MERS outbreak in South Korea (CFR of 21%) (Cowling et al., 2015). Our analyses of the WHO data was approximately similar to the CFR of 34% reported by Memish et al (Memish et al., 2014), and also CFR of 30.5% declared by Mobaraki et al. (Mobaraki and Ahmadzadeh, 2019). The regional variation of CFR from previously conducted studies may be skewed due to severity of disease and smaller sample sizes than have been investigated previously. On the whole, the CFR of 32% related to the MERS-CoV infection in the present study should be considered as a major health concern at the global scale. Thus, the characteristics of this disease and the potential risk factors associated with patient fatality should be studied comprehensively. Our findings confirm that the mortality pattern of the MERS in Saudi Arabia is different from the observed countries in the Middle East and affected countries beyond. By far, the greatest burden of this disease in terms of mortality and morbidity rates is located in four countries including Saudi Arabia, South Korea, United Arab Emirates, and Jordan. In this regards, differences in the virus and the genetic background of the population affected can play a role. Other reasons can include a difference in the availability or ability to implement patient isolation procedures as well as differences in overall medical technology among involved countries.

Consistent with the previous reports, age range >30 years is associated with death in cases of MERS-CoV infection (Alzeer, 2009, Gautret et al., 2013, Memish et al., 2014). This finding is in line with a

Saudi Arabian case report series. It showed that the age range of the individuals (>30 years) had a greater association with mortality and per every 1-year increase in age, the odds of mortality increased by 12% (Majumder et al., 2015). The reason for the higher fatality rates in this age range is unclear, but they may have underlying diseases and impaired immune functions that exacerbate the symptom of MERS-CoV infection and increase the chances of death. Also, calculating the OR (Table 3) suggested that having Saudi nationality, comorbidity, the interval time of onset sign and admission to the hospital >14 days are other potential risk factors for the disease progression and mortality related to MERS-CoV infection. Although camels are a suspected reservoir, this study could not find a risk relationship in the mortality of patients who had contact with camels in the 14 days prior to clinical signs. Meanwhile, global concern rests on the ability of MERS-CoV to cause major illnesses in direct and indirect contact with camels and its products, namely drinking unpasteurized camel milk (Conzade et al., 2018, Harrath and Abu Duhier, 2018, Kamau et al., 2018). Details as to the specific mechanism of zoonotic transmission from dromedaries to humans remain unclear, and further epidemiological studies are required in this regard. In line with the findings of Alghamdi et al. (Alghamdi et al., 2014), we observed a higher rate of MERS-CoV incidence in males than females (Table 1). However, based on our findings (Table 3) this gender difference in mortality rates related to MERS-CoV was not statistically significant (AOR=1.24; 95% CI: 0.96-1.60), p=0/098.

The current study suffered from some limitations. Of the total worldwide cases (2220 laboratory-confirmed cases of MERS-CoV), only 1408 cases with complete data were investigated in the current study. It should be noted that from 186 MERS-CoV cases in South Korea, only details related to 57 cases were published in the disease outbreak news on the WHO website. The lack of complete data for all MERS cases potentially increases the occurrence of selection and measurement biases in the result. Therefore, it might be more appropriate to conduct further large-scale epidemiological studies with complete data related to all morbid cases of MERS to obtain a better understanding of MERS-CoV emergence in humans and also associated risk factors related of this infection. In the future, we may closely monitor the MERS-CoV infections globally to better understand the risks of this new infection for public health and to provide helpful recommendations for controlling and preventing it. Recommendations might change and be updated as additional data becomes available. Indeed, despite the above limitations, such studies might be useful to implement educational programs, and access health care for early diagnosis and prevention of modifiable factors to reduce high mortality rates associated with MERS-CoV.

5. Conclusions

Based on our analyses of the WHO data, seven years after the emergence of the MERS-CoV incidence; Saudi Arabia still has the highest rate of infection. This study estimated a global 32% CFR (95% CI: 29.4–34.5) for MERS patients. The results demonstrated a link between mortality and some risk factors such as age >30 years-old, Saudi nationality, comorbidities, the interval time of onset sign and the admission to the hospital >14 days.

Ethical approval and consent to participate

Unlinked data.

Consent for publication

All authors express their satisfaction with the publication of this paper.

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Availability of supporting data

The data used for the analysis can be obtained from the study authors.

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Competing interests

The authors declare that they have no competing interests.

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Table1. Summary of demographic characteristics of laboratory-confirmed MERS-CoV cases in the world as of September 23, 2012, until June 18, 2018.

Year	**2012 (n=9)**	**2013 (n=118)**	**2014 (n=191)**	**2015 (n=590)**	**2016 (n=195)**	**2017 (n=229)**	**2018 (n=76)**	**Total (n=1408)**	**P-value**
Variables					**Number (%)**				
Age group									
0-14years	0(0.0)	6(42.9)	1(7.1)	6(42.9)	0(0.0)	0(0.0)	1(7.1)	14	
15-29years	0(0.0)	9(3.0)	31(10.4)	54(18.2)	20(6.7)	175(58.9)	8(2.7)	297	
30-44years	0(0.0)	21(8.6)	53(21.7)	124(50.8)	31(12.7)	0(0.0)	15(6.1)	244	0.001
45-59years	2(0.6)	32(9.1)	47(13.4)	177(50.3)	70(19.9)	0(0.0)	24(6.8)	352	
≥60years	7(1.4)	50(10.0)	59(11.8)	229(45.7)	74(14.8)	54(10.8)	28(5.6)	501	
Gender									
Female	4(1.0)	43(10.8)	46(11.5)	199(49.8)	34(8.5)	58(14.5)	16(4.0)	400	0.001
Male	5(0.5)	75(7.4)	145(14.4)	391(38.8)	161(16.0)	171(17.0)	60(6.0)	1008	
Nationality									
Non-Saudi	4(1.6)	31(12.6)	82(33.3)	102(41.5)	11(4.5)	13(5.3)	3(1.2)	246	0.001
Saudi	5(0.4)	87(7.5)	109(9.4)	488(42.0)	184(15.8)	216(18.6)	73(6.3)	1162	
[a]**Comorbidities**									
Yes	7(0.9)	25(3.2)	47(6.1)	335(43.5)	89(11.5)	204(26.5)	64(8.3)	771	0.001
No	2(0.3)	93(14.6)	144(22.6)	255(40.0)	106(16.6)	25(3.9)	12(1.9)	637	
Exposure with a morbid case in the previous 14 days									0.001
No	9(1.0)	64(7.0)	141(15.3)	374(40.7)	109(11.8)	177(19.2)	46(5.0)	920	
Yes	0(0.0)	54(11.1)	50(10.2)	216(44.3)	86(17.6)	52(10.7)	30(6.1)	488	
Exposure to a Camel in 14 days ago									0.001
No	9(1.0)	105(11.7)	156(17.4)	517(57.6)	61(6.8)	0(0.0)	49(5.5)	897	
Yes	0(0.0)	13(2.5)	35(6.8)	73(14.3)	134(26.2)	229(44.8)	27(5.3)	511	
Health care worker									
No	9(0.7)	114(8.6)	173(13.0)	542(40.8)	193(14.5)	223(16.8)	73(5.5)	1327	0.001
Yes	0(0.0)	4(4.9)	18(22.2)	48(59.3)	2(2.5)	6(7.4)	3(3.7)	81	
Travel history									
No	6(0.5)	99(9.0)	138(12.5)	465(42.1)	160(14.5)	181(16.4)	56(5.1)	1105	0.135
Yes	3(1.0)	19(6.3)	53(17.5)	125(41.3)	35(11.6)	48(15.8)	20(6.6)	303	
Outcome									
Dead	5(1.1)	71(15.1)	93(20.6)	186(41.2)	71(15.7)	2(0.4)	23(5.1)	451	0.001
Survived	4(4.0)	47(4.9)	98(10.2)	404(42.2)	124(13.0)	227(23.7)	53(5.5)	957	

Our mean for comorbidities are patients at the same time has other illnesses such as diabetes mellitus, hypertension, ischemic heart disease.

Table 2. Percentage of case fatality rate (%CFR)* related to MERS-CoV infection from reporting countries between September 23, 2012, until June 18, 2018.

Country	Number of cases (%)			Number of deaths (%)			Case fatality rate	
	Female	Male	Total	Female	Male	Total	Number of deaths/total number of cases	%
Saudi Arabia	330(28.4)	832(71.6)	1162	89(74.8)	263(79.2)	352	352/1162	30
South Korea	23(40.4)	34(59.6)	57	4(3.3)	4(1.2)	8	8/57	14
Qatar	3(13.0)	20(87.0)	23	2(1.7)	6(1.8)	8	8/23	34
Oman	0(0.0)	11(100.0)	11	0(0.0)	4(1.2)	4	4/11	36
United Arab Emirates	21(26.2)	59(73.8)	80	10(8.4)	26(7.8)	36	36/80	45
Iran	5(83.3)	1(16.7)	6	4(3.3)	1(0.3)	5	5/6	83
Jordan	8(30.8)	18(69.2)	26	7(5.8)	15(4.5)	22	22/26	84
Philippines	2(33.3)	4(66.7)	6	1(0.9)	2(0.6)	3	3/6	50
Tunisia	2(40.0)	3(60.0)	5	1(0.9)	3(0.9)	4	4/5	80
Kuwait	0(0.0)	3(100)	3	0(0.0)	1(0.3)	1	1/3	33
United Kingdom	2(66.7)	1(33.3)	3	0(0.0)	0(0.0)	0	0/3	0
United States of America	0(0.0)	3(100.0)	3	0(0.0)	0(0.0)	0	0/3	0
Malaysia	0(0.0)	3(100.0)	3	0(0.0)	2(0.6)	2	2/3	66
Italy	2(66.7)	1(33.3)	3	0(0.0)	1(0.3)	1	1/3	33
Thailand	0(0.0)	2(100.0)	2	0(0.0)	0(0.0)	0	0/3	0
France	0(0.0)	2(100.0)	2	0(0.0)	0(0.0)	0	0//2	0
Netherland	1(50.0)	1(50.0)	2	0(0.0)	0(0.0)	0	0/2	0
Lebanon	0(0.0)	2(100.0)	2	0(0.0)	0(0.0)	0	0/2	0
Germany	0(0.0)	1(100.0)	1	0(0.0)	0(0.0)	0	0/1	0
Turkey	0(0.0)	1(100.0)	1	0(0.0)	1(0.3)	1	1/1	100
Austria	0(0.0)	1(100.0)	1	0(0.0)	0(0.0)	0	0/1	0
China	0(0.0)	1(100.0)	1	0(0.0)	0(0.0)	0	0/1	0

Yemen	0(0.0)	1(100.0)	1	0(0.0)	1(0.3)	1	1/1	100
Egypt	0(0.0)	1(100.0)	1	0(0.0)	1(0.3)	1	1/1	100
Greece	0(0.0)	1(100.0)	1	0(0.0)	0(0.0)	0	0/1	0
Spain	1(100.0)	0(0.0)	1	1(0.9)	0(0.0)	0	0/1	0
Bahrain	0(0.0)	1(100.0)	1	0(0.0)	1(0.3)	1	1/1	100
Total	400(28.4)	1008(71.6)	1408	119(26.4)	332(73.6)	451	451/1408	32

* (%CFR) = case fatality rate (%) = (n/ N) × 100

Table 3. Epidemical and clinical comparison of potential risk factors on the final outcome (Dead/Survived) laboratory-confirmed MERS-CoV cases in the worlds from September 23, 2012, until June 18, 2018.

Variables	2012 until 2018		Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
	Dead N (%)	Survived N (%)				
Age group						
≤ 30 years	63(14.0)	269(28.1)	1.00		1.00	
>30 years	388(86.0)	688(71.9)	2.40 [1.78-3.25]	0.001	2.38 [1.75-3.22][a]	0.001
Gender						
Female	119(26.4)	281(29.4)	1.00		1.00	
Male	332(73.6)	676(70.6)	1.16 [0.90-1.49]	0.248	1.24 [0.96-1.60][b]	0.098
Nationality						
Non-Saudi	99(22.0)	147(15.4)	1.00		1.00	
Saudi	352(78.0)	810(84.6)	1.55 [1.16-2.05]	0.002	1.43 [1.06-1.92][c]	0.017
Comorbidities						
No	247(54.8)	390(40.8)	1.00		1.00	
Yes	204(45.2)	567(59.2)	1.76 [1.40-2.20]	0.001	1.76 [1.39-2.22][d]	0.001
Exposure with morbid in 14 days ago						
No	284(63.0)	636(66.5)	1.00		1.00	
Yes	167(37.0)	321(33.5)	1.16 [0.92-1.47]	0.200	1.14 [0.90-1.46][e]	0.266
Camel exposure in the previous 14 days						
No	338(74.9)	559(58.4)	1.00		1.00	
Yes	113(25.1)	398(41.6)	0.47 [0.36-0.60]	0.001	0.58 [0.44-0.75][e]	0.001
Health care worker						
No	427(94.7)	900(94.0)				
Yes	24(5.3)	57(6.0)	1.12 [0.69-1.84]	0.633	1.09 [0.66-1.80][e]	0.728
Travel history						
No	353(78.3)	752(78.6)	1.00		1.00	
Yes	98(21.7)	205(21.4)	1.01 [0.77-1.33]	0.895	1.07 [0.80-1.42][e]	0.634
Admission in negative pressure isolate room or ICU						
No	176(39.0)	384(40.1)	1.00		1.00	
Yes	275(61.0)	573(59.9)	1.04 [0.83-1.31]	0.694	1.12 [0.88-1.42][e]	0.336
Interval time of onset sign and admission in the hospital (day)						
≤14	362(80.3)	799(83.5)	1.00		1.00	
>14	89(19.7)	158(16.5)	0.41 [0.30-0.56]	0.001	0.42 [0.31-0.57][a]	0.001

Abbreviations: AOR, adjusted odds ratio; UOR, unadjusted odds ratio.

[a] Adjusted for gender, comorbidity, and nationality; **[b]** adjusted for age, comorbidity, and nationality;

[c] adjusted for age, gender, Comorbidity. [d] Adjusted for age, gender, and nationality; [e] adjusted for age, gender, nationality, and Comorbidity.