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Risk factors contributing to the Mortality in Middle East Respiratory Coronavirus Patients

Mohamd Shoukri[1]*, Sarah Al-Gahtani[2], Suhair Abozaid[3], Mohammed Al-Ahdal[3] and Futwan Al-Mohanna[1]

[1]*Department of Cell Biology, King Faisal Specialist Hospital and Research Center, Riyadh, 11211 Saudi Arabia*
[2]*College of Medicine, Al-Maarefa University of Science and Technology, 11211 Saudi Arabia*
[3]*Department of Infection and Immunity, King Faisal Specialist Hospital and Research Center, Riyadh, 11211 Saudi Arabia*

***Corresponding author:** Shoukri M, King Faisal Specialist Hospital, and Research Center P.O. Box 3354, Riyadh, Saudi Arabia, Tel: +966509491454; **E-mail:** shoukri@kfshrc.edu.sa

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Abstract

Purpose: To investigate the prevalence of risk factors associated with the Middle East respiratory Syndrome (MERS) coronavirus and quantify the relative hazard of death attributed to some selected risk factors among the confirmed patients reported by the World Health Organization (WHO). On reviewing the literature we identified four risk factors (consumption of unpasteurized camel milk, visiting camel farm, working at health care facility, and or having the co-morbid condition). These risk factors are associated with mortality among the MERS-coronavirus cases. The main objective is to quantify the relationship between the risk of death and these risk factors using survival analytic models.

Methods: We collected data available on the WHO web-site for reported cases who have complete information on date of admission to health care facility, data last seen, status on this date (dead or alive), gender, age, country of reporting, together with complete information on whether a reported case consumed unpasteurized dairy product, visited camel farm, working at a health care facility and potentially contacted an infected person, and or having comorbid condition. Complete data was available for 841 coronavirus patients and 274 associated deaths. Chi-square test for trend, independent samples t-test and survival analyses using Cox regression models are used to identify the relative hazard of death attributed to these suspected risk factors, after adjusting for the potentially confounding effect of age and gender.

Results: From June 2012 to July 2016,841 MERS coronavirus patients we included cases with complete information on age (54.36 ± 0.697), sex (male to female ratio 2.58:1), admission date to a health care facility, date last seen, giving median survival time 5 days (range from 0 to 63 days).The presence of comorbidity (0.26 ± 0.017), visiting camel farm (0.32 ± 0.018) consuming camel farm unpasteurized dairy product (0.32 ± 0.018), and working in a health care facility (0.11 ± 0.012) were analyzed. Only age, the presence of co-morbid condition and being a health care facility worker were significantly correlated with death. It is interesting to see that working in health care facility was significantly correlated with the hazard of death but it had a sparing effect because most of the health care workers were young. The mean age of health care workers who were infected with the coronavirus was 40.17 ± 13, and the mean age of those who were infected but did not work in a health care facility was 56.22 ± 18.

Conclusion: We show that being old (age above 66 years of age), the presence of co-morbid conditions, and visiting camel farms and consumption of unpasteurized dairy product contributed significantly to the hazard of death among the MERS-CoV patients. Apart from age, all the risk factors that contribute to mortality are modifiable and their impact on mortality may significantly be reduced when individual patients adhere to infection control measures.

Keywords: MERS-CoV; Epidemiology; Risk factors; Cochran-Armitage trend test; Kaplan-Meier survival curves; Cox regression.

Introduction

The Middle East Respiratory Syndrome coronavirus (MERS-CoV) is considered an emerging global public health threat. The disease was first detected in Saudi Arabia in 2012, [1]. As of 16 July 2016, the WHO has been notified of 1638 laboratory-confirmed human including 587 fatalities (http://www.who.int/csr/don/archive/disease/coronavirus_infections/en/). MERS-CoV has also been isolated from dromedary camels in several countries in the Near East and East Africa and antibodies to MERS-CoV have also been identified in very high proportions of camels in a number of countries across the Horn of Africa, North Africa and in the Near East. Evidence suggests that primary human cases might have been exposed to the virus through contact with an animal host, and several studies have shown dromedary camels to be a source of human infection [2]. A number of risk factors have been implicated in transmission to humans, although the exact mode of transmission is unknown. Although most cases of MERS have occurred in the Kingdom of Saudi Arabia (KSA) and the United Arab Emirates (UAE), cases have been reported in other countries. Although this virus appears to have originated in bats, several studies have been found over the last century that coronavirus can affect many different species such as mice, rats, dogs, cats, turkeys, horses, pigs, and cattle [2]. The virus has spread from camels to humans in the early 2010's. In human, it can cause pneumonia either direct viral pneumonia or a secondary bacterial pneumonia. In addition, it can also cause bronchitis, either as a direct viral bronchitis or a secondary bacterial bronchitis. Reports indicated that there are three areas of transmission which should be focused on for active surveillance and screening [3]. The first pattern is the occurrence of sporadic cases in communities. The true incidence of the disease in the community is not well known. The asymptomatic cases, in the community, or those with minimal symptoms are difficult to identify and are usually missed. The low infectivity of asymptomatic and mildly symptomatic cases is the finding of a low transmission rate within family contacts [4]. However, studies showed that family contacts had a higher positive rate of infectivity (3.6%) than healthcare worker contacts (1.12%) [5]. The second pattern of transmission is transmission within families. The rate of intra-familial transmission is not known. The third one is nosocomial transmission to health care workers. Handling of human biologic material such as sputum, respiratory secretion, faces, urine, and blood samples of MERS-CoV patients by healthcare workers make the risk of the transmission of viral infection quite significant. The transmission of MERS-CoV within healthcare facilities was noted in the Al-Hasa outbreak [5,6]. It was observed that almost all patients who died or who had been hospitalized had severe disease or other co-morbidities, and they were elder people. The majority of the MERS cases continue to be reported from the Middle East [7].

Given the continuous occurrence of MERS cases in the Middle East and the substantial number of people traveling between the region and EU, North American and Asian countries, sporadic importation of MERS cases can be expected [3]. The last reported MERS case in Europe was in Germany in March 2015. The majority of the reported cases have an exposure history involving a hospital with an admitted confirmed MERS cases. The recent outbreak in Jordan is centered on hospitals in Amman. In our study, we investigated the impact of some of the risk factors believed to be potentially correlated with mortality of coronavirus patients.

Methods

Study design

This is a cross-sectional study that focuses on the distribution of four risk factors, and two possible confounders; sex and age among coronavirus patients, and their potential for the hazard of death. All the data reported in this study are MERS-CoV reported cases on the WHO web-site: http://www.who.int/csr/don/archive/disease/coronavirus_infections/en/

Event History and Risk Factors Associated with Death

Event History: Since April 2012, cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have been identified in the following countries in the Middle East: Jordan [8], Saudi Arabia (KSA), Qatar, [9] the United Arab Emirates, Oman, Kuwait, Yemen, Lebanon, Iran, and Bahrain. The majority of all cases reported have been from KSA

http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV.

Several other countries have also reported cases in individuals who have travelled to the Middle East: Algeria, Austria, China, Egypt [10], France, Germany, Greece, Hong Kong, Italy, Malaysia, the Netherlands, the Philippines, South Korea, Thailand, Turkey, Tunisia, United Kingdom and United States.

Risk factors: The role of an animal reservoir in the transmission of MERS-CoV to humans has been actively considered since the first reported cases in 2012. Animals have been suspected as a source of primary infection since early in the emergence of MERS-CoV, particularly given the similarities to Severe Acute Respiratory Syndrome (SARS) coronavirus. Persons with early cases of MERS-CoV infection were observed to have had exposure to dromedary camels (henceforth dromedaries), and subsequent serologic studies from the Arabian Peninsula confirmed high seroprevalence of MERS-CoV neutralizing antibodies in dromedaries [11,12].

Additionally, living in the same household with persons who reported working on or visiting a farm where dromedaries were kept was a risk factor for illness; although the numbers were small, the highest risks were associated with other relatives and domestic helpers [6,13 and 14].

There is a large body of evidence that the main risk factors that control the spread of the disease are (I) spread from person to person through respiratory droplet secretions; (II) MERS has also infected people caring for a sick MERS-CoV infected individuals, (III) contact with infected body fluids, consumption of raw or undercooked camel meat, and unpasteurized dairy products of camels may be other sources of transmission to humans [1]. (VI) Health-care workers or contacts of an MERS-infected individual are at risk [15]. Hospital associated MERS-CoV outbreaks have occurred repeatedly in Saudi Arabia.

http://www.moh.gov.sa/en/CoronaNew/Regulations/MoHCaseDefinitionMERSCoVVersion

Since our main interest in the assessment of the hazard of death, which is estimated using time-to-event models, the inclusion criteria in the study was the availability of time from diagnosis to time of death for reported MERS-CoV cases. The difference between these two points provides the time length of follow-up. Therefore, our end point is the time-to-event, where event here is defined as death among coronavirus patients. Moreover, we recorded information regarding gender, age, country in which the patient was diagnosed with MERS-CoV. We focused our investigation on the following risk The first risk factor (RF1) is whether the patient consumed dairy camel farm product. The second risk factor (RF2) is whether the patient visited any camel farm. The third risk factor (RF3) is whether the patient was employed in a health care setting. The fourth risk factor (RF4) is the presence of co-morbidities. The collected information was entered into an Excel sheet and analyzed using the computer program IBM-SPSSv.20.

Results

The data base included complete information on n=841 MERS-CoV patients, who satisfied the inclusion criteria, with 274 confirmed deaths giving an over-all death rate of 32.6%. Table 1 gives the distribution of the number of MERS-CoV cases in each quarter of the years 2013-2016. The last two-quarters of 2016 do not have data since they fell outside the study period (Table 1).

The WHO web-site provided information about the distribution of the MERS-CoV cases worldwide, but for some countries, the incidences were quite sporadic, and we decided to aggregate these countries into one category under the code "other" countries (Netherland, UK, Germany and the USA). The distribution of cases and the death rates by country, for the study period, are shown in table 2. As can be seen, the largest cluster of coronavirus cases is in KSA (86.1%) with a death rate of (31.1%). Although the percentage of cases in Jordan is the second lowest, the country reported the highest mortality (55.6%). The most recent Middle East respiratory syndrome, an outbreak in Jordan is not unexpected. It is clear that the disease is of continuous occurrence worldwide with the largest cluster of cases reported in the Middle East. Although the KSA has the largest number of reported cases, it has the lowest death rate among the listed countries (Table-2).

To detect whether there is higher clustering of mortality in some countries relative to the others, we proceeded to analyze the data to explore if the between countries variations are higher than the within-country variations. Therefore we used the one-way random effects analysis of variance (ANOVA) for a binary response as was given in

Year	Quarter				
	Jan-March	April-June	July-Sept	Oct.-Dec	Total count
2013	5	32	33	29	99
2014	30	50	30	54	164
2015	151	33	218	30	432
2016	100	46	-		146

Table 1: Distribution of the number of coronavirus cases during the study period by year/quarter.

Country countries	Jordan	KSA	Oman	UAE	Other	Total count
% CV cases	2.1	86.1	1.2	6.1	4.5	841
% Deaths	55.6	31.2	50	37.3	38.8	274

Table 2: Distribution of cases and mortality by country.

Parameter	Mean ± SE
Age	54.36 ± 0.697
Gender(% females)	28% ± 1.5%
Male to female ratio is 2.58:1	
RF1 (consumed farm animal products)	0.26 ± 0.017
RF2 (visited camel farm):	0.32 ± .018
RF3 (Travelled to high risk area)	0.96 ± 0.008
RF4 (health care facility worker)	0.11 ± 0.012
RF5 (co-morbidity)	0.60 ± 0.017

Table 3: Summary statistics for the risk factors.

[16]. There was no significant difference in the death rate among the countries. However, to construct a more accurate confidence interval on the overall death rate we corrected for the intra-cluster correlation effect, as computed from the ANOVA for binary responses [17-19] which are about 1.4%. We, therefore, corrected for this moderate effect of clustering and constructed the 95% confidence interval on the overall percentage of death to be (27.3%-35.5%). The distribution of the risk factors, including age and gender, are summarized in table 3. The summary statistics are given as means, percentage and standard deviations.

We note that RF4 (presence of co-morbidity among the coronavirus cases) is the most prevalent risk factor, and RF3 (working in a health care facility) has the lowest prevalence. To build a predictive model that links the risk factors to the risk of death, the first step is to code these categorical variables. For epidemiological and clinical reasons it is desired to categorize a continuous variable such as age, to identify the optimal cut-off point that discriminates between these who died and those who are still alive at the end of the follow-up period. We used the "Receiver Operating Characteristic" (ROC) curve to achieve this purpose (Figure 1). We found that the optimal age that distinguishes between the dead and alive patients at the end of the follow-up period is 66 years. This is an agreement with other studies that claimed 60 years as a cut-off point [7].

We furthermore investigated the trend in mortality with age. As can be seen from Figure 2, the death counts increased with age, and therefore we decided to test the hypothesis of a linear relationship between age and the number of deaths using the one degree of freedom Cochran-Armitage test for trend [16]. The test gave a chi-square value=89.5, with p-value=0.00001 showing a significant increase in death rate with age.

Cox regression

To evaluate the effect of the measured covariates on the hazard of death, we first assessed the effect of each covariate separately using univariate Cox regression. Table 4,5 shows the estimated hazard ratio (HR), their significances summarized by the p-values and the 95% confidence intervals on the population HR parameters.

The interpretation of the hazard ratios is as follows: if the estimated HR is above 1 means that the exposure to the risk factor increases the risk of death. Accordingly, patients above 66 have approximately twice the risk of death as compared to those who are younger. Similarly, the presence of co-morbidity increases the risk of death by 10% when compared to someone who does not have co-morbid conditions. It is interesting to note that, being a health care worker with possible contact with an infected person has a sparing effect on the hazard since HR=0.70 is less than one.

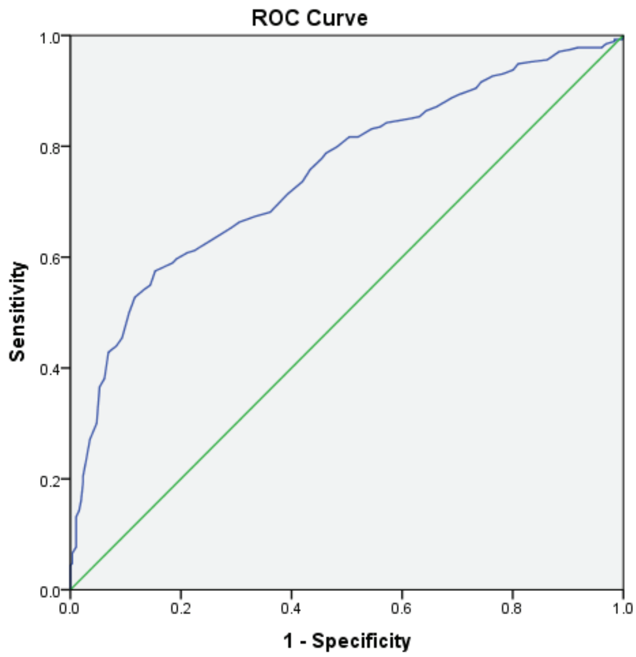

Figure 1: ROC curve for age. The (accuracy) sum of sensitivity and specificity is maximized at age =66 years.

Parameter	HR	p-value	95% CI	
			Lower limit	Upper limit
Age: age over 66	2.23	0.000001	1.75	2.84
RF1: contact with animals on camel farm	1.03	0.756	0.77	1.42
RF2: Contact with infected person	0.60	0.001	0.44	0.80
RF3: travelled to high risk region	0.78	0.364	0.45	1.3
RF4: health care worker	0.69			
RF5: presence of comorbidity	1.60	0.001	1.18	2.1

Table4: Cox Regression: univariate analysis cox

Parameter	HR	p-value	95% CI	
			Lower limit	Lower limit
Age: age over 66	2.42	0.000001	1.76	3.05
RF2: Contact with infected person	0.59	0.001	0.44	0.81
RF5:presence of comorbidity	1.01	0.966	0 .72	1.40

Table 5: Cox Regression: multivariate analysis.

The explanation that we can offer is that health care workers are in general young. The mean age for health care worker is 40.17 ± 13, and the mean age for non-health care worker is 56.22 ± 18 (p-value<0.0001).In figures 3 and 4we show the Kaplan-Meier survival curves, with the corresponding p-values of the log-rank test on the difference between the survivals probabilities of the exposed versus the non-exposed.

While the presence of co-morbidities is significant in the Cox regression univariate analysis, it is no longer significant in the multivariate model. This is because this risk factor is highly correlated with age. As a matter of fact, when we calculated the odds ratio as a measure the correlation

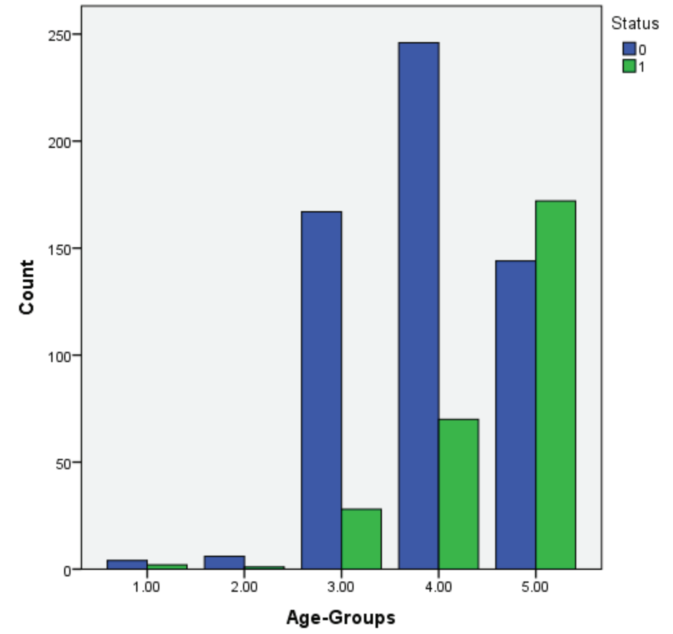

Figure 2: Age Groups: 1 = less than 10 years, 2= 10-20, 3= 20-40, 4= 40-60, and 5=above 60.
Note also that the green bars represent the number of deaths in the respective age group, and the blue bars correspond to the number surviving.

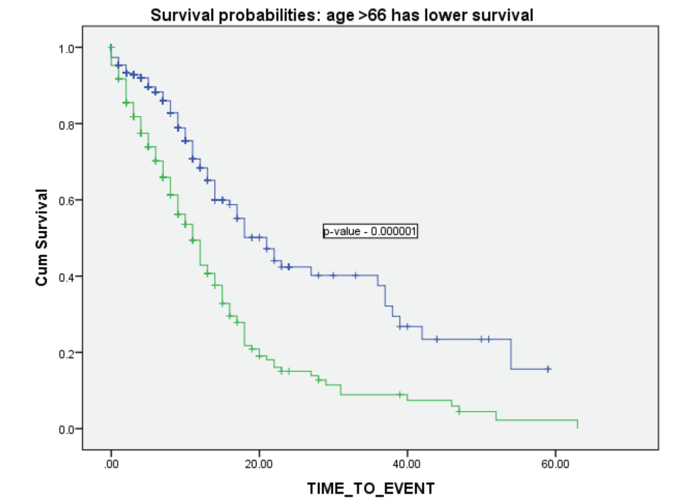

Figure 3: Kaplan Meier survival curve showing lower survival probabilities (green curve) for those who are older than 66 years.

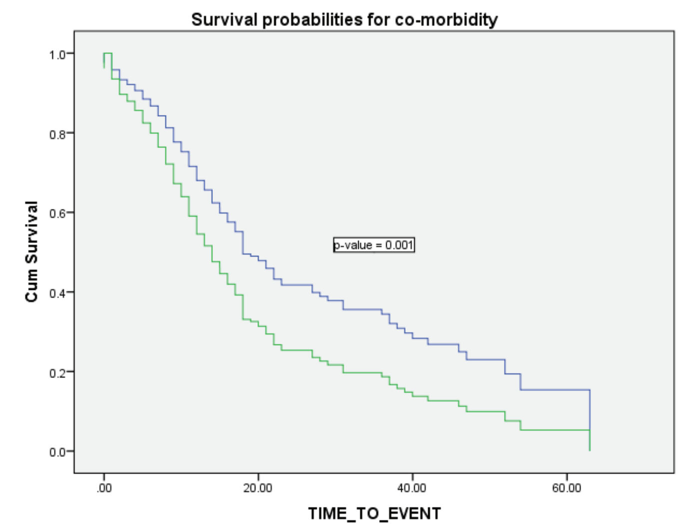

Figure 4: Kaplan Meier survival curve for co-morbidities. The green curve is for the people with co-morbidities. It shows lower survival probabilities for cases with co-morbidities.

between co-morbidity and age it turned out to be OR=15 (95% CI: 9.11-27-22). This means that the odds of having co-morbidity for an older person (age 66) are increased by 15 folds as compared to a younger person (age 66). The presence of this collinearity disqualifies this risk factor as a candidate covariate in the multivariate analysis (Figure3,4).

Discussion

In light of the data analyses of our study and the growing evidence of an MERS-CoV link between camels and humans, the WHO recommends avoiding contact with camels; not drinking raw camel milk or camel urine, and not eating meat that has not been thoroughly cooked.

There is a growing body of research from the Arabian Peninsula and Africa linking MERS-CoV transmission between dromedary camels and humans. Although it is evident that MERS-CoV is a zoonotic disease, the route of the camel to human transmission is not fully understood. The discovery of the route of transmission between camels and humans remains critical to preventing the introduction of MERS-CoV into the human population [1]. There continues to be a need for well planned, structured investigations carried out in conjunction with exposure investigations in humans [3].

FAO [20] is embarking on a field program to investigate MERS- CoV along the animal value chains in the Horn of Africa, North Africa, and the Near East to better understand the disease dynamics at the animal-human inter-face. In this regard, FAO convened a technical meeting to determine the extent of current scientific knowledge, identify the major study gaps, and develop practical and realistic approaches to minimize the risk of transmission to humans and reduce the adverse impacts of this virus.

Based on the current situation and available information, The WHO encourages all Member States to continue their surveillance for acute respiratory infections. Nearly 4 years since the discovery of MERS-CoV, several important questions about its epidemiology and routes of transmission, pathogenesis, and treatment remain unanswered. The sporadic nature of many cases of MERS has hindered in-depth case-control studies and investigation of rates of secondary transmission and hence the factors that affect mortality.

In conclusion, our findings represent an important initial step in understanding the risk factors for MERS-CoV infection, including zoonotic transmission and their potential effect on increased risk of death among infected persons.

Declaration

The authors declare no conflict of interest.

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