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In the Name of Allah, the Most Gracious, the Most Merciful

Distribution Agreement

Predictors of Mortality Among Confirmed, Symptomatic MERS Cases in KSA 2012-2015

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A thesis submitted to the Faculty of the
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Abstract

Predictors of Mortality Among Confirmed, Symptomatic MERS Cases in KSA 2012-2015

By Abdulhameed Kashkary

BACKGROUND:
Since the 1960s when human coronaviruses (HCoVs) were first described, they were only associated with the common cold. Since 2003 scientists and health communities were giving more attention to coronaviruses after discovering the Severe Acute Respiratory Syndrome (SARS) Coronaviruse (CoV) and the Middle East Respiratory Syndrome (MERS-CoV) in 2012. SARS and MERS both have a relationship with the Acute Respiratory Distress Syndrome (ARDS), and both have high case fatality rates.

OBJECTIVE:
The objective of this study is to describe the survival experience of confirmed symptomatic MERS patients in the Kingdom of Saudi Arabia from July 2012 to December 2015 and looking for factors that are significantly related to their survival experience.

METHODS:
The dataset for this study was received from Saudi's Ministry of Health (SMoH), department of public health for the period of 2012 to the end of December 2015. Descriptive analysis and Cox Proportional Hazards Model were applied to address the relationship between the survival of the patients and the variables of interest.

RESULTS:
There were 1128 confirmed symptomatic MERS cases reported to SMoH from September 2012 to the end of December 2015 (48.67% mortality rate). Several factors were associated with mortality of confirmed symptomatic MERS. Being a health care personal (HCP) and infected inside the health care facility as a secondary case (HCP) means that their hazard of death is 18.5% of the hazard of death among cases who acquired their disease from the community as primary cases (HR_{adj} 0.185, CI 0.105-0.327, p-value <.0001). In contrast, the hazard of death of symptomatic MERS cases who acquired their infection in a health care facility are 41% more than the hazard of death of cases who are acquiring their disease from the community (HR_{adj} 1.409, CI 1.105-1.798, p-value 0.0057). Also, the hazard of death of symptomatic MERS cases who were 71 years and older was 152% more than the hazard of death of symptomatic MERS cases who were 40 year and less (HR_{adj} 2.520, CI 1.890-3.361, p-value <.0001). The history of camel contact has been investigated as the reservoir / or source of infection, but the data are not statistically significant associated with the MERS mortality.

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Chapter 1 – Introduction

Background

Respiratory illnesses have always been a major worldwide concern given how easily and quickly they can spread. Meticulous safety and precautionary measures should be taken when dealing with respiratory illnesses due to the imminent danger they pose if not contained in a timely manner. In 2012, one such illness called Middle East Respiratory Syndrome (MERS) disease started spreading, in Jeddah City, Saudi Arabia due to infection by Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [1]. MERS-CoV is an acute viral respiratory illness that originated from a new strain of a single-stranded RNA betacoronavirus. Coronaviruses, members of Coronaviridae family and the Coronavirinae subfamily, circulate in selected mammalian and such as humans, bats, pigs, cats, dogs, rodents, birds [2] and camels [3]. Four Coronaviruses species circulate exclusively in humans and all lead to generally mild respiratory illness: HCoV-229E, HCoV-NL63, HCoV-OC43 and HKU1. Over the last decade, two zoonotic Coronaviruses were introduced into the human population: Severe Acute Respiratory Syndrome CoV (SARS-CoV) and MERS-CoV. Both are both associated with Acute Respiratory Distress Syndrome (ARDS) and high case fatality rates [2, 4].

MERS is placed under the same group of SARS because they both initially lead to symptoms of upper respiratory infection, with fever being the most common presenting symptom along with cough and shortness of breath, which eventually results in severe lung damage, in most cases necessitating mechanical ventilation [5]. The person to person transmission route was recorded in healthcare settings, dialysis units and intensive care units [6]. MERS has also been hypothesized to spread from infected camels to humans [7] based on some reported cases that have shown epidemiological and genomic link [8-10]. Until now the methods of transmission, natural reservoir, and/or possible hosts not yet fully determined.

As of April 11, 2016, 1371 laboratory confirmed cases of MERS disease have been reported in Saudi Arabia alone, out of which 587 patients died [11]. In May 2015, a largest outbreak outside the Middle East occurred in South Korea. It consisted of 186 confirmed cases with 36 deaths [5]. The outbreak started from a 68 year old South Korean man who returned from a business trip to different Arabian Peninsula countries (Saudi Arabia, Qatar, United Arab Emiratis and Bahrain) [12, 13]. He started to have fever and myalgia on May 11 and he diagnosed with MERS disease on May 20 [12].

All cases identified so far have had a direct or indirect association (through residence or travel) to nine countries in or near Arabian Peninsula (Saudi Arabia, United Arab Emirates, Qatar, Oman, Jordan, Kuwait, Iran, Lebanon and Yemen). The travel-related cases have been documented in 23 countries [14, 15]; Algeria, Austria, Egypt, France, Germany, Greece, Italy, Jordan, Kuwait, Malaysia, Netherlands, Philippines, Oman, Qatar, Tunisia, Turkey, United Arab Emirates, United Kingdom, United States of America[14],China, Republic of Korea and Thailand [15].

Problem

Why do some patients with MERS experience a complete recovery while others die? Which patients with MERS are more likely to develop ARDS and can we predict this? Are there any risk factors that put certain populations at greater risk of severe complications and death? What measures and precautions can be taken to prevent MERS mortality? In order to best answer these questions, we need to continue to investigate the relationships between variables in the data that have been collected thus far. The Centers for Disease Control and Prevention (CDC) along with international partners are already conducting studies to try to identify the risk factors and transmission route of MERS in community and hospital settings [14]. Most of those diagnosed with MERS were previously diagnosed with other concurrent illnesses such as diabetes, hypertension, obesity, cancer and chronic kidney, heart and lung disease and neurological diseases. These pre-existing medical conditions have been listed as risk factors for MERS high mortality rates [2, 6, 16-18].

Though these comorbidities likely influence disease progression and outcome, the strong correlation between MERS and chronic illnesses could be misleading considering the high prevalence of these risk factors (for instance, in the Kingdom of Saudi Arabia, the prevalence of type-II diabetes mellitus across all ages is 31.6%, the prevalence of obesity is 31.1% and one quarter of adult males smoke [2, 19]).

Study Purpose

In this study, I will discern the major risk factors and predictors for MERS mortality. We will examine the Saudi Ministry of Health (MOH) dataset going back to the first reported positive MERS case in 2012. Our main purpose is to look at the predictors that affect mortality rate. In addition to taking into consideration basic information such as age, gender and nationality, we will also analyze the probable source of infection, and the duration between the date of onset and the date of outcome.

Significance

This study will make new contributions to the literature on MERS by scrutinizing relationships between key variables and trying to discern patterns that could eventually help lower the MERS mortality rate. First, we are going to take every person variation of their duration from the date of onset to the date of outcome in our concern by analyzing the data with survival methods. Second, we will utilize data collected by the Saudi Ministry of Health, the official source. In addition, this study will encompass the largest breadth of patient data, from the onset of the initial cases in 2012 to the end of 2015.

Chapter 2 – Literature Review

MERS-CoV Group

Coronaviruses belong to Coronavirinae subfamily, in the family Coronaviridae, in the order Nidovirales. Initially, human coronaviruses were only associated with the common cold. In humans, four coronaviruses circulate, usually leading to a mild respiratory illness: HCoV-229E, HCoV-NL63, HCoV-OC43 and HKU1 [2]. However, in 2003, a zoonotic coronavirus was identified in the human population, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and identified as the primary cause of Severe Acute Respiratory Syndrome (SARS) [20]. In 2012, another zoonotic coronavirus was identified in the human population, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), previously called HCoV-EMS and linked to Middle East Respiratory Syndrome (MERS) [1]. SARS and MERS both have a relationship with Acute Respiratory Distress Syndrome (ARDS), and both have high case fatality rates [2]. One of the interesting features of coronaviruses is their potential environmental resistance, despite the fragility of enveloped viruses. Indeed, several studies have described the ability of HCoVs (i.e., HCoV 229E, HCoV OC43, NL63, HKU1 or SARS) to survive in different environmental conditions (e.g., in a range of temperatures and humidity levels), on different hospital materials (such as aluminum, sterile sponges or latex surgical gloves), or in biological fluids [21].

Animal Source

Since the recognition of MERS-CoV in 2012, many studies have been conducted revealing the presence of closely-related MERS-CoV sequences in numerous bats species in the Chiroptera order [2]. Studies conducted in various countries such as Ghana, Europe [22], Mexico [23], Italy [24, 25], South Africa [26], Thailand [27] and Saudi Arabia [28] suggests that bats could be the possible origin of MERS-CoV. These studies and many others report that MERS-CoV is widely distributed among bats. The first reported MERS case was reported from Jeddah, Saudi Arabia, but the case's onset of symptoms started in Bisha, Saudi Arabia. A link was found between this human index MERS case and a *Taphozous perforates* bat that was captured in Bisha near the home and workplace of the MERS case. In other study, the feces of the same kind of bat had been tested in Egypt and was found to have a 190 nucleotide RNA fragment that perfectly matched the RdRp of MERS-CoV [2, 28]. In a recent experimental study [29], ten bats (*Artibeus jamaicensis*) were given the MERS disease in vitro to investigate their role as a potential reservoir. The results show that MERS-CoV can replicate in bats with no clinical signs of the disease. Their result supports the hypothesis that bats are the initial reservoir of MERS-CoV. However, until now, MERS-CoV has never been isolated from bats [30].

In Saudi Arabia and countries like it, urbanization is growing rapidly, which could limit the direct contact between humans and bats and prompt the consideration of intermediate hosts who may play a role in the circulation of MERS-CoV, as they do for many other zoonotic viruses [31, 32]. One of the earliest MERS studies demonstrated the potential role of an intermediate host or reservoir; in this study, the MERS antibody was detected in 100% (50 out of 50) of the dromedary camels tested in Oman and 15% (14 of 105) of the camels tested in Spain [33]. In the United Arab Emirates, a similar study was done on 651 serum samples of dromedary camels: 151 samples from 2003 and 500 samples from 2013. A total of 97% of the samples (151/151 in 2003 and 481/500 in 2013) had the MERS antibody, even in the sample taken before the discovery of MERS-CoV [34]. Evidence from archived sera revealed that the MERS antibody was found in dromedary camels in 1992 in Saudi Arabia [35].

In addition to detecting MERS antibodies in dromedary camels, the MERS infection was also reported [29]. The detection of the MERS infection among dromedary camels was done by qRT-PCR and virus isolation in several countries including Oman [36], Qatar [10], United Arab Emirates [37] and Saudi Arabia [8, 38]. Egypt also detected the MERS infection among dromedary camels. All of the camels in this study had been imported from Sudan or Ethiopia for slaughter [39]. Some studies reported the presence of clinical signs in some camels infected with MERS [7, 8].

MERS Transmission

- **Animal-human transmission**

Many studies have shown an epidemiological link between camels infected with MERS and humans who have MERS, but with direction of the infection has been ambiguous [2]. An animal-human transmission pattern has been involved in sporadic cases, which could be the start of MERS outbreaks in hospital settings [8, 40]. These sporadic cases call attention to the necessity of obtaining date concerning transmission.

In Qatar in 2013, two cases were confirmed with MERS. One was a farm owner who was reported to have visited the farm many times. The other was a farm employee who also had contact with the farm animals. Of the 14 samples taken from the farm, five of them had MERS, which was detected by RT-PCR [41].

In Jeddah in 2013, a confirmed MERS case died. He owned a farm of nine camels located 75km south of Jeddah. Four of his camels were ill and had nasal discharge before the onset of the patient's symptoms. After taking different samples (nasal, milk, urine, and fecal) from the nine camels, one camel had a nasal sample that was positive for MERS-CoV detected by PCR and culture [8, 9]. There was a 100% match between the full genome sequence of the virus from the human case and the camel (obtained from culturing) [8].

A recent study reported that MERS infection transmission from camel to camel, human to human, and camel to human are the documented directions of transmission. In contrast, MERS transmission from bats to camels, bats to humans, and humans to camels are still hypothesized directions of transmission [7].

- **Human-human transmission and hospital outbreaks.**

MERS transmission between humans is confirmed epidemiologically and through genome sequence studies. Inter-human transmission for MERS has been observed in hospital outbreaks and household settings [6, 42, 43]. The first MERS outbreak in Saudi Arabia occurred in the Eastern province between April 1 and May 23, 2013. In all, 23 MERS cases were identified and 16 of them died. Out of the 23 cases, 21 acquired the infection by inter-human transmission in different departments (intensive care unit, in-patient unit, or hemodialysis unit) in the three different hospitals. The positive MERS cases had 417 contacts: 217 household contacts and 200 HCP contacts. Two HCP and 5 household contacts developed MERS and all have contact with confirmed MERS cases except two of the household contacts [6]. Several other outbreaks due to human to human transmission have been reported from different cities in Saudi Arabia such as Jeddah and Riyadh [43, 44].

An outbreak occurred in Taif, Saudi Arabia, from September 2014 to January 2015 [16]. The Saudi Ministry of Health (SMOH) and US Centers for Disease Control and Prevention (CDC) conducted a study to determine any epidemiological and genome sequence links between the patients. This outbreak of 38 MERS cases was reported from four different hospitals. Deaths occurred in 21 of the 38 cases, and 13 of 38 cases involved HCP. The four hospitals were (1) a tertiary hospital with 368 beds that serves military personnel and their families; (2) an MOH tertiary hospital with 500 beds associated with a separate outpatient renal dialysis unit; (3) an MOH hospital with 250 beds designated as a referral hospital for MERS; and (4) a private hospital. Of the 38 MERS cases reported, 33 were associated with these four facilities; the researchers were unable to link the remaining 5 cases to other patients epidemiologically [16].

The most recent MERS outbreak in Saudi Arabia occurred between June and August of 2015 and involved 130 MERS cases (81 MERS confirmed, 49 MERS probable*). Forty-three of 130 MERS cases were HCP. Fifty-one of 130 MERS case died, and none of them was a HCP. Most of the confirmed MERS cases were linked to the emergency department. In this tertiary health care facility, the capacity of the emergency medicine department is one hundred fifty beds. The department registers a quarter million visits annually [40].

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* See page 17 for the definition.

A large MERS outbreak occurred outside the Middle East also occurred in a hospital setting. In May 2015, South Korea faced an unprecedented MERS outbreak [5]. A total of 98 health care facilities saw and/or admitted MERS patients [45]. This MERS outbreak involved 186 confirmed MERS cases, of which 39 were HCP. Of the total cases, 36 died. It was estimated that more than 16,000 people were exposed to MERS patients [45]. In the South Korea outbreak, the index case and two other secondary cases consider as superspreaders who are largely associated with the spread of MERS out [46].

Earliest outbreak to our knowledge

In addition to the abovementioned MERS outbreaks, other outbreaks have been documented that could have been MERS before it was identified as such. The first reported MERS case in the world was reported in July 2012 in Jeddah, Saudi Arabia [1]. Before that, in April 2012 in Jordan, a hospital outbreak of acute respiratory illness was reported in Zarqa city. In all, 13 people were identified in this outbreak, 10 of them HCP; 2 out of the 13 died. One of those who died was a 40-year-old nurse and another was a 25-year-old student [47]. In November 2012, after the identification of MERS, the stored samples of these two cases were tested and were confirmed with the MERS infection, which made them the first two detected MERS cases [48]. An intensive investigation into this outbreak was conducted in May 2013 by the Jordan Ministry of Health (JMoH) and CDC. The study included 124 subjects from the available members of the initial outbreak group and their households. HCP were also included from the different health care facilities that admitted the initial outbreak patients. The subjects were interviewed and serological samples were obtained from them. Seven out of 124 subjects were found to have the MERS antibody; one of the seven was a close family member but not identified in the original outbreak [42, 49]. Five of the seven who tested positive for the MERS antibody were HCP working in the same hospital where the original outbreak occurred. None were from the other hospitals that cared for these MERS patients. Thus, the first known MERS outbreak that occurred in Jordan involved 9 people; two who were detected by rRT-PCR in November 2012, and seven who were detected by convalescent antibody tests [42].

MERS Mortality Rate

The high mortality rate is of major concern. As of April 11, 2016, there have been 1,698 laboratory confirmed cases of MERS from 26 different countries reported to the WHO. Out of these, 609 patients have died (mortality rate ≈ 36%) [50].

From March 2012 to June 2015, there has been a total of 1288 confirmed MERS cases and 498 deaths (mortality rate ≈ 39%) [51]. The countries reporting the highest mortality rates during this period were Saudi Arabia at 43.87% (n=1028, died=479), United Arab Emirate at 12.99% (n=77, died=10), Jordan at 31.58% (n=19, died=6) and Qatar at 38.46 (n=13, died=5) [51].

A comparison of mortality rates between countries showed that comorbid conditions like diabetes and renal failure did affect mortality and outcome of MERS positive cases [16]. Several studies have identified the risk factors for mortality in patients with MERS: the presence of respiratory disease, age over 60 years, concomitant infections, and hypoalbuminaemia all increase the mortality risk. In one study, about 60% of the individuals with 'at risk' conditions died [17].

MERS Case definition

More experience has been obtained regarding MERS disease and thus lead to update in the MERS case definition. For example, The initial WHO case definition of MERS in September 2012 was a hospitalized person with acute respiratory illness with suspicious of lower respiratory involvement based on clinically or radiology evidence that is not explained by any other infection or disease [52]. The next update in February 2013 case definition removed the requirement of hospitalization [53, 54]. Reported cases from community or hospital outbreaks that did not identify by zoonotic or human source lead to the possibility that the MERS virus was transmitted from a mild or even asymptomatic cloud be the source. The WHO took this into consideration by updating the case definition in July 2013 to include patients with acute respiratory illness of any severity and recommended testing asymptomatic close contacts of confirmed MERS-CoV cases [53].

The WHO MERS case definition was most recently updated on July 14, 2015, and the SMoH's MERS case definition was last updated in June 2015 [55, 56]. The SMoH MERS case definition has the same concept as the WHO MERS case definition, with a few differences. The SMoH case definition includes 3 types of cases: suspected, probable, and confirmed, while the WHO case definition includes only two types of cases: probable (which is the combined suspected and probable cases based on the SMoH case definition) and confirmed cases. The other difference is the existence of an age classification in the SMoH's case definition: suspected cases are divided into adult and pediatric categories. There is no age classification in the WHO case definition [55, 56].

The interpretation of the term suspected, probable and confirmed in the SMoH MERS case definition is as follow; the suspected cases need to be tested for MERS and are categorized by age into adult (older than 14 years) and pediatric (14 years or younger) groups.

Suspected cases among adults include those with (I) acute respiratory illness with clinical and/or radiological, evidence of pulmonary parenchymal disease (pneumonia or Acute Respiratory Distress Syndrome); (II) healthcare associated pneumonia based on clinical and radiological evidence who are hospitalized; (III) upper or lower respiratory illness occurring within 2 weeks of exposure to a confirmed or probable case of MERS-CoV infection; (IV) unexplained acute febrile (≥38°C) illness, and body aches, headache, diarrhea, or nausea/vomiting, with or without respiratory symptoms, and leucopenia (WBC<3.5x109/L) and thrombocytopenia (platelets<150x109/L) [56].

Suspected cases among the pediatric group include those who meet one of the above case definitions and have either a history of exposure to a confirmed or suspected MERS-CoV in the 14 days prior to onset of symptoms and/or a history of contact with camels or camel products in the 14 days prior to onset of symptoms. In addition, children are suspected cases when they have unexplained severe pneumonia [56].

Probable cases meet the criteria of suspected cases and have inconclusive laboratory results for MERS-CoV and other possible pathogens, are close contacts of a laboratory-confirmed MERS-CoV case, or work in a hospital where MERS-CoV cases are cared for or have had recent contact with camels or camel's products [56].

Confirmed cases meet the criteria for suspected cases and have a confirmed lab result for MERS infection (1).

All suspected cases must be reported to the SMoH and the established protocol should be followed. Recently, the SMoH has been using the Health Electronic Surveillance Network (HESN) to report all suspected MERS cases directly to the SMoH.

Chapter 3 – Self-Contained Manuscript

Abstract

BACKGROUND:
Since the 1960s when human coronaviruses (HCoVs) were first described, they were only associated with the common cold. Since 2003 scientists and health communities were giving more attention to coronaviruses after discovering the Severe Acute Respiratory Syndrome (SARS) Coronaviruse (CoV) and the Middle East Respiratory Syndrome (MERS-CoV) in 2012. SARS and MERS both have a relationship with the Acute Respiratory Distress Syndrome (ARDS), and both have high case fatality rates.

OBJECTIVE:
The objective of this study is to describe the survival experience of confirmed symptomatic MERS patients in the Kingdom of Saudi Arabia from July 2012 to December 2015 and looking for factors that are significantly related to their survival experience.

METHODS:
The dataset for this study was received from Saudi's Ministry of Health (SMoH), department of public health for the period of 2012 to the end of December 2015. Descriptive analysis and Cox Proportional Hazards Model were applied to address the relationship between the survival of the patients and the variables of interest.

RESULTS:
There were 1128 confirmed symptomatic MERS cases reported to SMoH from September 2012 to the end of December 2015 (48.67% mortality rate). Several factors were associated with mortality of confirmed symptomatic MERS. Being a health care personal (HCP) and infected inside the health care facility as a secondary case (HCP) means that their hazard of death is 18.5% of the hazard of death among cases who acquired their disease from the community as primary cases (HR_{adj} 0.185, CI 0.105-0.327, p-value <.0001). In contrast, the hazard of death of symptomatic MERS cases who acquired their infection in a health care facility are 41% more than the hazard of death of cases who are acquiring their disease from the community (HR_{adj} 1.409, CI 1.105-1.798, p-value 0.0057). Also, the hazard of death of symptomatic MERS cases who were 71 years and older was 152% more than the hazard of death of symptomatic MERS cases who were 40 year and less (HR_{adj} 2.520, CI 1.890-3.361, p-value <.0001). The history of camel contact has been investigated as the reservoir / or source of infection, but the data are not statistically significant associated with the MERS mortality.

Introduction

From the 1960s until 2003, human coronaviruses (HCoVs) were only associated with the common cold [2, 57]. Science and health communities have paid more attention to coronaviruses since discovering the Severe Acute Respiratory Syndrome (SARS) Coronavirus (CoV) in 2003 [20] and Middle East Respiratory Syndrome (MERS-CoV) in 2012 [1]. SARS and MERS both have a relationship with Acute Respiratory Distress Syndrome (ARDS), and both have high case fatality rates [2].

As of April 11, 2016, 1,698 confirmed MERS cases have been reported globally from 26 different countries. Out of these, 609 patients have died (mortality rate ≈ 36%) [50]. Travel-related cases have been documented in at least 23 countries: Algeria, Austria, Egypt, France, Germany, Greece, Italy, Jordan, Kuwait, Malaysia, Netherlands, Philippines, Oman, Qatar, Tunisia, Turkey, the United Arab Emirates, the United Kingdom, the United States, China, the Republic of Korea, and Thailand [14, 15].

One of these countries is South Korea. In May 2015, the largest MERS outbreak outside of the Middle East occurred there, consisting of 186 confirmed cases and resulting in 36 deaths (mortality rate = 19.4%) [5]. The outbreak began with a 68-year-old South Korean man who returned from a business trip to different countries in the Arabian Peninsula (Saudi Arabia, Qatar, United Arab Emirates, and Bahrain) [12, 13]. In this outbreak, the index case and two other secondary cases were considered superspreaders largely responsible for the spread of MERS in South Korea [46].

In Saudi Arabia alone (as of April 11, 2016), a total of 1,371 confirmed MERS cases were reported, of which 587 died (mortality rate ≈ 43%) [11]. MERS cases have occurred in sporadic and clustering patterns [8, 16]. Some sporadic cases were linked to contact with bats and camels [9, 28]. Bats could be the possible origin of MERS-CoV according to studies conducted in various countries such as Ghana, Europe [22], Mexico [23], Italy [24, 25], South Africa [26], Thailand [27] and Saudi Arabia [28]. These studies and many others report that MERS-CoV is widely distributed among bats. However, until now, MERS-CoV has never been isolated from bats [30].

In addition to studies on bats, many studies have been conducted on camels to address their role in the spread of the MERS infection. In 2013, the MERS antibody was detected in 100% (50/50) of dromedary camels tested in Oman and 15% (14/105) of camels tested in Spain [33]. In the United Arab Emirates, 97% (632/651) of dromedary camels sample which collected in 2003 and 2013 were tested and had the MERS antibody [34]. In Saudi Arabia in 2013, the MERS antibody was found in 74% (150/203) of a countrywide sample of camels [35].

MERS infection in camels has also been detected by qRT-PCR and virus isolation in countries such as Oman [36], United Arab Emirates [37] and Egypt [39]. In Saudi Arabia in 2013, a confirmed MERS case died; he had owned a farm of nine camels located 75km south of Jeddah. Four of his camels were ill and had nasal discharge before the onset of the patient's symptoms. Of the different samples taken from the camels (nasal, milk, urine, and fecal), one nasal sample was found positive for MERS-CoV, detected by PCR and culture [8, 9]. There was a 100% match between the full genome sequence of the virus from the human and the camel (obtained from virus culture) [8].

A clustering pattern of MERS cases occurred in a hospital setting where human to human transmission was observed [16, 42, 46]. The most recent MERS outbreak in Saudi Arabia occurred between June and August of 2015 and involved 130 MERS cases (81 confirmed, 49 probable). Forty-three of 130 MERS cases were HCP. Of the 51 cases who died, none were HCP. Most of the confirmed MERS cases were linked to the emergency department. In this tertiary health care facility, the capacity of the emergency medicine department is one hundred and fifty beds, and the department registers a quarter million visits annually [40].

Globally, from March 2012 to June 2015, there were a total of 1,288 confirmed MERS cases and 498 deaths (mortality rate ≈ 39%) [51]. The countries reporting the highest mortality rates during this period were Saudi Arabia at 43.87% (n=1028, died=479), United Arab Emirates at 12.99% (n=77, died=10), Jordan at 31.58% (n=19, died=6) and Qatar at 38.46 (n=13, died=5) [51].

The objective of this study is to describe the survival experience of confirmed symptomatic MERS patients in the Kingdom of Saudi Arabia over the four-year period from September 2012 to December 2015 and look for factors that are significantly related to their survival experience.

Methods

Data Source

The dataset for this study was acquired from the SMoH for the period of September 2012 to December 2015. The data were compiled from the MERS surveillance system and includes all confirmed MERS cases in Saudi Arabia.

Case Definition

The last update for WHO MERS case definition was in July 14, 2015 and the last MERS case definition update for SMoH was in June 2015 [55, 56]. The SMoH MERS case definition is the same as the WHO MERS case definition concept for a few changes. The SMoH case definition of MERS includes 3 types of cases: suspected, probable, and confirmed cases while the WHO MERS case definition include only two types of cases: probable (which is the combined suspected and probable of the SMoH MERS case definition) and confirmed cases. Other difference is age the classification of suspected cases in SMoH MERS case definition which there is no age classification in WHO MERS case definition [55, 56].

The SMoH MERS suspected cases need to be tested for MERS and are categorized by age into adult (older than 14 years) and pediatric (14 years or younger) groups.

Suspected cases among adults include those with (I) acute respiratory illness with clinical and/or radiological, evidence of pulmonary parenchymal disease (pneumonia or Acute Respiratory Distress Syndrome); (II) healthcare associated pneumonia based on clinical and radiological evidence who are hospitalized; (III) upper or lower respiratory illness occurring within 2 weeks of exposure to a confirmed or probable case of MERS-CoV infection; (IV) unexplained acute febrile (≥38°C) illness, and body aches, headache, diarrhea, or nausea/vomiting, with or without respiratory symptoms, and leucopenia (WBC<3.5x109/L) and thrombocytopenia (platelets<150x109/L) [56].

Suspected cases among the pediatric group include those who meet one of the above case definitions and have either a history of exposure to a confirmed or suspected MERS-CoV in the 14 days prior to onset of symptoms and/or a history of contact with camels or camel products in the 14 days prior to onset of symptoms. In addition, children are suspected cases when they have unexplained severe pneumonia [56].

Probable cases meet the criteria of suspected cases and have inconclusive laboratory results for MERS-CoV and other possible pathogens, are close contacts of a laboratory-confirmed MERS-CoV case, or work in a hospital where MERS-CoV cases are cared for or have had recent contact with camels or camel's products [56].

Confirmed cases meet the criteria for suspected cases and have a confirmed lab result for MERS infection [56].

Lab Confirmation

The SMoH strongly recommends that the sample for MERS should be a lower respiratory specimen, but if this is not possible, then a nasopharyngeal and oropharyngeal specimen should be taken and combined in a single collection container and tested together [16].

A confirmed laboratory MERS case requires either a positive PCR on at least two specific gene targets: the region upstream of the E gene (upE) and the open reading frame 1a (ORF1a) or positive (upE) with sequencing of second target (RdRpSeq or NSeq) [16].

Study Variables

The dataset includes demographic data (age, gender, nationality, province, and year) for the 1,283 confirmed MERS cases. It also contains information about whether the confirmed MERS cases were hospitalized, had a history of camel contact, and what their probable source of infection was. The dataset specifies whether confirmed MERS cases were health care personnel (HCP) or not. In addition, the case outcomes (deceased or recovered) are included, as well as the time (in days) between the date of onset and the date of outcome or last update.

The age variable is continuous and represents the age (in years) of confirmed MERS cases at time of reporting. Binary variables coded as 0 or 1 included gender, nationality, hospitalization, HCP, history of camel contact, and outcome variables. The probable source of infection variable is categorical and classified as primary case, secondary case acquired from the health care facility, secondary case HCP, secondary case household, and unclassified.

Primary cases are defined as confirmed MERS patients who were diagnosed after seeking medical care and had no known link or contact with an active MERS case [58]. Secondary cases are confirmed MERS patients who had contact with another active MERS case. The provenance variable is categorical and classified into the 13 administrative provinces of Saudi Arabia. The survival time variable is a continuous variable representing duration from date of onset to date of death (for deceased patients) or date of last update (for cured or surviving patients).

Statistical Analysis

Data cleaning was performed in Microsoft Excel 2013, descriptive statistics were generated using SAS 9.4, and data analysis was conducted using SAS 9.4. An exploratory analysis was conducted among all variables of interest mentioned, and descriptive statistics were used to summarize the results. To address the relationship between the survival of the patient and the variable of interest, Cox Proportional Hazards Model was used. In preparing the data for the Cox model analysis, the Kaplan–Meier method was used and an assessment for proportional hazards (PH) assumption was applied using a log-log plot and goodness-of-fit test approaches. By the end of the statistical analysis, an estimate of the hazard of death for confirmed MERS cases given their variable of interest was interpreted.

For statistical analysis purposes, age is classified into 3 different groups: 40 years and younger, 41 to 70 years, and 71 years and older. Cases in 2012 and 2013 are combined together under the year variable. The region variable classifies provenance into the following areas: Central region (Riyadh and Al-Qasim provinces), East region (Eastern province), North region (Northern Borders, Tabouk, Al-Jowf, and Hael provinces), West region (Makkah and Madinah provinces), and South region (Najran, Al-Baaha, Aseer and Jazan provinces). Finally, the hospitalization variable was not included in the statistical model due to the absence of knowledge of deaths among non-hospitalized, confirmed MERS patients.

Results

There were 1,128 confirmed symptomatic MERS cases reported to the SMoH from September 2012 through December 2015 *(Table 1)*. Of those affected, Saudi citizens comprised the majority of cases (801, 71.01%), and non-Saudis a sizable minority (327, 28.99%). Men comprised 67.55% (762) of confirmed symptomatic MERS cases, and 16.93% (191) were HCP. The vast majority (1,086, 96.62%) of confirmed symptomatic MERS cases were hospitalized; only 3.38% (38) were not hospitalized. Only 6.03% (68) of cases were identified as having a history of camel contact. The largest proportion of confirmed symptomatic MERS cases were primary (373, 33.07%), followed by unclassified (311, 27.57%), secondary cases acquired from the hospital (159, 14.10%), secondary cases HCP (158, 14.01%), and the smallest proportion, secondary cases household contact (127, 11.26%). By year, 2014 had the highest number of confirmed symptomatic MERS cases (539, 47.78%) compared to all other year.

All 13 provinces of Saudi Arabia have been affected by the disease, but MERS rates vary widely among them. Riyadh province reported nearly half (531, 47.07%) of all confirmed symptomatic MERS cases, and Makkah province reported the second largest proportion (301, 27.48%). Seven of the 13 provinces reported fewer than 20 confirmed symptomatic MERS cases. The mean age of the 1,128 confirmed symptomatic MERS cases was 53.03 years (std $\pm$ 18.00), and the median survival time from date of onset to date of outcome was 16.00 days.

Table 1: The demographic characteristics of confirmed symptomatic MERS cases, KSA, 2012-2015 (n=1128)

Variable	*Level of variable*	*n(%)*	*Mean + SD*	*Missing*
Saudi / Non-Saudi	Saudi	801 (71.01%)		0
	Non-Saudi	327 (28.99%)		
Gender	Male	762 (67.55%)		0
	Female	366 (32.45%)		
Health care Personal (HCP)	HCP	191 (16.93%)		0
	Non-HCP	937 (83.07%)		
Hospitalization	Yes	1086 (96.62%)		4
	No	38 (3.38%)		
History of camel contact	Yes	68 (6.03%)		0
	No	1060 (93.97%)		
Probable source of infection	Primary	373 (33.07%)		0
	Secondary case inpatient	159 (14.10%)		
	Secondary case HCP	158 (14.01%)		
	Secondary case household contact	127 (11.26%)		
	Unclassified	311 (27.57%)		
Year	2012	4 (0.35%)		0
	2013	131 (11.61%)		
	2014	539 (47.78%)		
	2015	454 (40.25%)		
Provenance	Al-Baaha	1 (0.09%)		0
	Al-Jowf	14 (1.24%)		
	Al-Qasim	19 (1.68%)		
	Aseer	16 (1.42%)		
	Eastern Province	140 (12.41%)		
	Hael	4 (0.35%)		
	Jazan	3 (0.27%)		
	Makkah	310 (27.48%)		
	Madinah	54 (4.79%)		
	Najran	24 (2.13%)		
	Northern Borders	3 (0.27%)		
	Riyadh	531 (47.07%)		
	Tabouk	9 (0.80%)		
Age		1128	53.03 $\pm$ 18.00	0
Survival time from the date of onset to the date of outcome		1115	16.00 (median)	13

Mortality rate

As of December 31, 2015, 549 (48.67%) of the 1,128 confirmed symptomatic MERS cases reported to the SMoH had died *(Table 2)*. Among those who died, 82.88% were Saudi and 71.04% were

Table 2: Mortality rate of confirmed symptomatic MERS cases, KSA, 2012-2015 (n=1128)

Variable	Level of variable	n (%)	Died n (%)	Mortality Rate
Died or Not	Yes	549 (48.67%)	NA	NA
	No	579 (51.33%)	NA	NA
Saudi / Non-Saudi	Saudi	801 (71.01%)	455 (82.88%)	56.80%
	Non-Saudi	327 (28.99%)	94 (17.12%)	28.75%
Gender	Male	762 (67.55%)	390 (71.04%)	51.18%
	Female	366 (32.45%)	159 (28.96%)	43.44%
Health care Personal (HCP)	HCP	191 (16.93%)	18 (3.28%)	9.42%
	Non-HCP	937 (83.07%)	531 (96.73%)	56.67%
Hospitalization	Yes	1086 (96.62%)	548 (100%)	50.46%
	No	38 (3.38%)	0	0%
History of camel contact	Yes	68 (6.03%)	40 (7.29%)	58.82%
	No	1060 (93.97%)	509 (92.71%)	48.02%
Probable source of infection	Primary	373 (33.07%)	206 (37.52%)	55.22%
	Secondary case inpatient	159 (14.10%)	114 (20.77%)	71.70%
	Secondary case HCP	158 (14.01%)	15 (2.73%)	9.49%
	Secondary case household	127 (11.26%)	40 (7.29%)	31.50%
	Unclassified	311 (27.57%)	174 (31.69%)	55.95%
Year	2012+2013	135 (11.97%)	86 (15.66%)	63.70%
	2014	539 (47.78%)	270 (49.18%)	50.09%
	2015	454 (40.25%)	193 (35.15%)	42.51%
Region	Central	550 (48.76%)	255 (46.45%)	46.36%
	Eastern	140 (12.41%)	79 (14.39%)	56.43%
	Southern	44 (3.90%)	20 (3.64%)	45.45%
	Western	364 (32.27%)	178 (32.42%)	48.90%
	Northern	30 (2.66%)	17 (3.10%)	56.67%
Age (year)	40 and less	303 (26.86%)	76 (13.84%)	25.08%
	41 - 70	615 (54.52%)	305 (55.56%)	49.59%
	71 and more	210 (18.62%)	168 (30.60%)	80.00%

male. All of the deceased cases had been hospitalized. By age group, 13.84% of deceased cases were 40 years old and younger, 55.56% were between 41 and 70 years old, and 30.60% were older than 70. A small percentage (3%) of those who died were HCP, and 7.29% had a history of camel contact. As to the MERS source among those who died, 37.52% were primary cases, 31.69% were unclassified, 20.77% were secondary cases acquired from hospitals, 7.29% were secondary case household, and 2.73% were secondary cases HCP. Nearly half the deaths from confirmed symptomatic MERS occurred in 2014. The bulk of deceased cases (78.87%) occurred in the Central and Western regions. The mortality rate among Saudi citizens was 56.80% compared to 28.75% among non-Saudis. The mortality rate among HCP was

9.42% compared to 56.67% among non-HCP. Half of the hospitalized cases died. The mortality rate among cases with a history of camel contact was 58.82% compared to 48.02% among cases with no history of camel contact. For the probable source of infection, secondary cases acquired from the hospitals had the highest mortality rate (71.70%) compared to others. By age group, cases aged 71 years and older had an 80% mortality rate, dropping to 50% in the 41-70 year age group, and falling further, to 25%, in the group aged 40 years and under. By region, the mortality rate varied from 45% to 56%.

Exposures and Mortality Rate Association

Several factors were associated with mortality of confirmed symptomatic MERS, as revealed by unadjusted and adjusted Cox proportional hazards modeling *(Table 3)*. Nationality had a significant association with MERS mortality among confirmed symptomatic cases in the unadjusted model, and this association remained significant in the adjusted model after removing the age variable from the model (HR 2.001, CI 1.601-2.502, p-value <.0001 vs HR_{adj} 1.300, CI 1.028-1.644, p-value <0.0285).

Regarding the probable source of infection, the hazard of death among secondary cases inpatient was 40.9% greater than the hazard of death among primary cases (HR_{adj} 1.409, CI 1.105-1.798, p-value <.0057) controlling for other demographic characteristics among patients diagnosed in the same year. The adjusted hazard ratio for the probable source of infection among secondary cases HCP do have a statistically significant protective relationship in comparison to that of primary cases. Their hazard of death is 18.5% of the hazard of death of primary cases (HR_{adj} 0.185, CI 0.105-0.327, p-value <.0001) controlling for other demographic characteristics among patients diagnosed in the same year. Also, among secondary cases household, the hazard of death was 63% of the hazard of death among primary cases (HR_{adj} 0.631, CI 0.445-0.895, p-value <.0099) controlling for other demographic characteristics among patients diagnosed in the same year.

Table 3: Hazard ratios of MERS mortality factors among confirmed symptomatic MERS cases, KSA, 2012-2015

			Unadjusted				Adjusted			
Variable	Level	Reference Group	HR	95% Lower CI	95% Upper CI	p-value	HR	95% Lower CI	95% Upper CI	p-value
Saudi / Non-Saudi		Non-Saudi	2.001	1.601	2.502	<.0001	1.300+	1.028	1.644	0.0285
Gender		Female	1.180	0.981	1.420	0.0786	0.881	0.727	1.067	0.1936
History of camel contact		Cases with no history of camel contact	1.204	0.869	1.668	0.2643	1.103	0.785	1.550	0.5716
Probable source of infection	2ndry case inpatient	Primary	1.481	1.177	1.862	0.0008*	1.409	1.105	1.798	0.0057*
	2ndry case HCP**		0.157	0.093	0.265	<.0001*	0.185	0.105	0.327	<.0001*
	2ndry case household		0.603	0.430	0.846	0.0034*	0.631	0.445	0.895	0.0099*
	Unclassified		1.073	0.876	1.314	0.4965	1.110	0.900	1.370	0.3281
Region	Eastern	Central	1.366	1.061	1.759	0.0156*	1.480	1.130	1.940	0.0045*
	Northern		1.592	0.973	2.602	0.0640	1.896	1.149	3.129	0.0123*
	Southern		1.022	0.648	1.612	0.9243	1.072	0.675	1.703	0.7690
	Western		1.232	1.016	1.493	0.0339*	1.346	1.087	1.667	0.0065*
Age (year)	41-70	40 and less	2.015	1.567	2.592	<.0001*	1.525	1.175	1.980	0.0015*
	71 and more		3.717	2.834	4.876	<.0001*	2.520	1.890	3.361	<.0001*
Year***	2012+2013	2015	1.234	0.953	1.596	0.1102	-	-	-	-
	2014		1.299	1.079	1.563	0.0057*	-	-	-	-

* Statistical significance
** HCP: Health Care Personal
*** Year was stratified in the adjusted model
+ The adjusted model does not include age, due to the strong association between age and nationality. In particular, 24% of Saudi are 71 and older, compared to 6% of non-Saudi are 71 and older

Our study showed that some region had an increased MERS mortality rate. The hazard of death in each of the East, North and West regions are 48%, 89.6%, 34.6% more than the hazard of death in the Central region (East: HR_{adj} 1.480, CI 1.130-1.940, p-value 0.0045) (North: HR_{adj} 1.896, CI 1.149-3.129, p-value 0.0123) (West: HR_{adj} 1.346, CI 1.087-1.667, p-value 0.0065) controlling for other demographic characteristics among patients diagnosed in the same year.

The hazard of death for those aged 41-70 years was 52.2% greater than the hazard of death among those aged 40 years and under (HR_{adj} 1.525, CI 1.175-1.980, p-value 0.0015) controlling for other demographic characteristics among patients diagnosed in the same year. For MERS cases aged 71 years and older, their hazard of death is 152% more than the hazard of death MERS cases who are 40 years and younger (HR_{adj} 2.520, CI 1.890-3.361, p-value <0.0001) controlling for other demographic characteristics among patients diagnosed in the same year.

Discussion

As of December 31, 2015, data on 1,128 confirmed symptomatic cases of MERS were reported to the SMoH. This study does not include asymptomatic cases because their date of onset was unknown, which is essential for survival analysis. In this study, the association between gender and outcome was not found to be statistically significant, as reported in previous research [59-61].

There were about 30 different nationalities in Saudi Arabia that acquired MERS. Although nationality and mortality are significantly associated in the unadjusted model (HR 2.001, Cl 1.601-2.502, p-value <.0001) as reported in Table 3, the association remained significant when all other demographic characteristics, except age, were taken into account (see Table 3). The reason for this is the strong association between age and nationality. 24% of Saudi are 71 and older, compared to 6% of non-Saudi are 71 and older.

Despite the greater mortality rate of individuals who had camel contact (40/68=58.82%), compared to those who did not have camel contact (509/1060=48.02%), no significant association was observed between camel contact and mortality due to MERS. Underreporting may be an explanation for the lack of association; it is possible that MERS-infected individuals were concerned about possible government intervention. Another explanation is that the camel contact was self-reported and when physicians asked the question about camel contact, there was no conscientious effort to understand the actual details.

Our study has found that older age is associated with MERS mortality, which is in agreement with other studies in Saudi Arabia and North Korea have found [6, 60, 61]. Among individuals 71 years old or older, the hazard of death was 236 % more than the hazard of death among individuals 40 years old and less (HR_{adj} 2.520, CI 1.890-3.361, p-value <0.0001), controlling for other demographic characteristics among patients diagnosed in the same year. We know that the old age comes with comorbidities.

Because all HCP secondary cases of infection were health care personnel themselves, there was no point of adding the HCP variable when source of infection was in the model. Two secondary case categories who acquired the MERS from the health care facilities are HCP and inpatient. It is interesting to note that the hazard ratios are in opposite directions. In particular, the hazard of death among inpatients is 40.9% more than the hazard of death among primary cases (HR_{adj} 1.409, CI 1.105-1.798, p-value 0.0057) controlling for other demographic characteristics of patients diagnosed in the same year. In contrast, the hazard of death among secondary case HCO is 18.5% of the hazard of death among primary cases (HR_{adj} 0.185, CI 0.105-0.327, p-value <.0001) controlling for all other predictors. A possible explanation is that patients confined in hospitals have a greater number of comorbidities than health care workers. Another explanation is that health care workers are in better health than the inpatients.

MERS mortality rate is also linked in our study to different geographical distribution. This finding may be explained by the variability of the health care provided among regions, by the difference in comorbidities and viral load among regions.

Study Limitations

Our study was subject to a few limitations. The first limitation was the absence of information on preexisting concurrent health conditions among the confirmed symptomatic MERS cases, which could have helped in the understanding and interpretation of the findings. Second, information regarding the health status of hospitalized confirmed symptomatic MERS cases was not documented at the time of diagnosis (e.g., whether patients were in the ward, intensive care unit, or other department). Third, the probable source of infection of about 27% of the cases were unclassified. Fourth, the number of those with a history of camel contact could be higher than what was reported, as people may have been fearful of reporting contact, not wanting to draw the attention of health authorities to their animals. Fifth, interactions among the demographic characteristics were not considered in this analysis. Sixth, this survival analysis did not take in into account the clustering effect of patients within hospitals and hospitals within regions.

Chapter 4 – Conclusion and Recommendations

It has been three and a half years since MERS was identified in the world, and given the absence of a clear and specific source of infection and method of transmission, investigations are still urgently needed to determine risk factors for MERS morbidity and mortality.

The prevalence of hospital outbreaks is notable. Nearly 70% of the confirmed symptomatic MERS cases in Saudi Arabia acquired the infection within health care facilities. Their hazard of death is more than 40% higher than that of those who acquire the infection within the community (primary cases). This should alert us to the necessity of improving infection control protocol and compliance and applying these improvements to the effort to prevent cases within health care facilities. Admitted patients are there for treatment and do not expect to acquire MERS and possibly die from it on account of the health care facility.

More investigation and better documentation of each MERS case is needed to better understand the pattern of disease and what other variables are associated with MERS mortality, such as the status of patient at time of diagnosis and the period of virus shedding.

The precise reporting of animal contact is one of most challenging points. Does animal contact constitute only direct contact with camels or also contact with others who have had direct contact with camels? Defining camel contact is necessary to better understand its role in the spread of MERS and MERS-associated mortality.

In conclusion, this study has shown some evidence of factors that are associated with MERS mortality and also has shown some factors that do not have any evidence of an association with MERS mortality. These associations or lack of association all can be helpful in building knowledge in the scientific community.

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