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Journal of Infection and Public Health 13 (2020) 1342–1346

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Original Article

Demographic, clinical, and outcomes of confirmed cases of Middle East Respiratory Syndrome coronavirus (MERS-CoV) in Najran, Kingdom of Saudi Arabia (KSA); A retrospective record based study

Hadi J. Al Sulayyim [a,*], Sherif M Khorshid [b], Satam H. Al Moummar [c]

[a] Department of Infection Prevention and Control, Khubash General Hospital, Najran Health Affiars, Najran, Saudi Arabia
[b] Departement of Infection Prevention and Control, King Khaled Hospital, Ministry of Health, Najran, Saudi Arabia
[c] Department of Clinical Pharmacy Services, Maternity and Children's Hospital, Ministry of Health, Najran, Saudi Arabia

ARTICLE INFO

Article history:
Received 12 January 2020
Received in revised form 29 March 2020
Accepted 15 April 2020

Keywords:
Demographic
Clinical
Outcome
MERS-CoV
Najran

ABSTRACT

Introduction: MERS is caused by a viral infection, which was first identified in KSA, 2012. MERS-CoV infection consequences with either hospitalization or death.
Methods: All positive MERS-CoV cases that diagnosed in and reported to a referral hospital in Najran, KSA from March/2014 to December/2018 were revised retrospectively. We identified patients from infection control department and medical records. Demographic, clinical, and outcome data were collected.
Results: Of the 54 positive MERS-CoV cases, 3 cases were excluded because no available data. Therefore, the final number of the included cases in the study was 51 cases (94.4). Most of the patients were Saudi 36 (70.6%), and majority of cases were reported in the winter 18 (35.3) season. Fever 47 (92.2%), cough 44 (86.3%), and shortness of breath 37 (72.5%) were reported as most common symptoms. Most patients had diabetes mellitus and hypertension. Overall mortality rate was 37.3%, and interestingly the mortality rate dropped sharply over 5 years. In logistic regression analysis, Season and Chronic Kidney disease patients were the only two variables statistically significantly associated with death. The odds of death the patients infected by MERS-CoV during Autumn and Winter season were 4.09 times higher than those patients who infected during Spring and Summer season (OR = 4.09, CI 1.18-14.15, P < 0.026). Compared with MERS-CoV patients who had Non-Chronic kidney diseases, the odds of death the MERS-CoV patients who had chronic kidney diseases were 18.08 times higher (OR = 18.08, CI -2.01-162.99, P < 0.01).
Conclusion: The case fatality rate of MERS-CoV infection was high. Further studies with large sample sizes are needed to explore the reasons behind the decrease in the mortality rate over the time period.

Background

Middle East Respiratory Syndrome (MERS) is caused by a viral infection, the virus belongs to a large family of viruses called genus Beta coronavirus (CoV) [1]. Middle East Respiratory Syndrome coronavirus (MERS-COV) is a zoonotic illness, infecting both humans and animals (camels and bats). Only two strains of coronaviruses were found to infect humans: MERS-CoV and Severe Acute Respiratory Syndrome whereas different species of animals are infected by several strains of corona viruses [2]. The MERS-CoV causes upper respiratory disease in human being, which ranges from mild to moderate [3]. In September 2012, the MERS-CoV was identified in Jeddah, Kingdom of Saudi Arabia (KSA) as a first public case [4]. The first nosocomial outbreak of MERS-CoV was reported in Al Zarqa, Jordan (eight healthcare workers) [5]. Subsequently, 2189 cases (782 deaths) of MERS-COV around the world were reported to World Health Organization from September 2012 to March 2018. Of 2189 cases worldwide, KSA reported 1814 cases (708 deaths) to WHO. Approximately 27 countries around the world have reported cases of MERS-CoV. Such countries included KSA, Qatar, Oman, Kuwait, Jordan, United Arab Emirates, Yemen, Bahrain, Lebanon, Egypt, Turkey, United Kingdom, United States, France, Germany, Austria, Algeria, Greece, Islamic Republic of Iran, China, Republic of Korea, Tunisia, Thailand, Malaysia, Italy, the Netherlands, and Philippines [6]. According to published studies, Arabian Peninsula

Abbreviations: MERS-CoV, Middle East Respiratory Syndrome coronavirus; KSA, Kingdom of Saudi Arabia; RT PCR, Real-time polymerase chain reaction; CKD, Chronic Kidney Disease.

* Corresponding author.
E-mail address: hadialsleem@hotmail.com (H.J. Al Sulayyim).

https://doi.org/10.1016/j.jiph.2020.04.007

has mainly represented the geographic distribution of the MERS-CoV cases, however, KSA was reported the highest percentage of cases [7–10]. In some countries that located in Asia, Africa, Europe, and North America, they reported that the MERS-COV was detected in people coming from endemic countries [10–16].

Studies have shown a direct and indirect contact with infected camels leads to human infection. Indirect contact includes ingesting camel's unpasteurized milk and non-well cooked meats [17–19]. The main reservoir of the MERS-CoV is the dromedary camels which infect humans. However, the mode of transmission from camels to human is not completely known. In term of transmission from humans to humans, the virus does not simply transmit between humans except if there is close contact, for example, touching the patient hands. It can be transmitted among people by exposure to infected person's respiratory secretion such as sneezing and cough [6,20,21].

The symptoms of MERS-CoV involve shortness of breath, cough, and fever. In addition, diarrhea and other gastrointestinal tract symptoms have been reported by many patients [6,22–23]. Real-time polymerase chain reaction (RT PCR) is found to be the best available confirmatory test of the MERS-CoV. It's also accurate for assessment of respiratory swabs and serum [24,25].

Regarding the treatment, it relies on a clinical situation of the patient and is considered supportive. Therefore, there is no current specific medication or vaccine [6]. There are preventive recommendations by Centers for Disease Control and Prevention (CDC) to prevent spreading of MERS-CoV among humans in communities, homes, and healthcare facilities. In term of communities and homes, the guidelines for people confirmed with the infection of the MERS-CoV; A) They should stay at home without going school, public places, or work, B) They have to be separated from other house members in a different room, C) They have to wear a face-mask, D) They should inform healthcare providers when there is a medical appointment, E) They should cover their nose and mouth by tissue when sneezing and coughing, F) They should wash their hand by soap and water thoroughly, G) They have to avoid sharing items at home, such as dishes, cups, towels, etc. In term of healthcare facilities; A) Exposure chance should be minimized, B) Ensure compliance with Standard, Contact and Airborne Precautions, C) Restrict and manage visitor's movement, D) Education and training healthcare providers, E) Implementation of the environmental infection control, F) Ensure reports to public health authorities and inside healthcare facilities [26].

Indeed, there is no study conducted in Najran region, KSA with respects to MERS-CoV. Hence, the current study aims to identify the demographic, clinical, and outcomes of confirmed cases of MERS-CoV in Najran, KSA.

Objectives

1 To identify demographic and clinical characteristics of confirmed MERS-CoV cases in Najran region.
2 To identify the case fatality rate and the associated factors with it.
3 To identify the association between the used medication and complication. As well as the outcome.

Methodology

Patients and methods

A retrospective study was carried out for all positive confirmed cases of MERS-CoV diagnosed and reported to a referral hospital in Najran, KSA from March/2014 to December/2018.

We identified patients from infection control department and medical records. Demographic, clinical, infection onset, laboratory, comorbidity, follow up until discharge or death, and outcome data were collected. This study was approved by Ethics Committee at King Fahad Medical City; protocol number 18-297E.

Complete blood count (CBC), blood chemistry, and chest X-ray were done at our center. Nasopharyngeal and throat swabs, and serum were routinely taken from patients by trained personnel and submitted to Ministry of health laboratory at Jeddah or Riyadh in order to perform RT-PCR tests. In addition to that, bronchoalveolar lavage and tracheal aspirates also are taken as samples of deep respiratory. Another sample is taken for the patient in case of week positive or suspicious results and sent again to Riyadh or Jeddah. A MERS-CoV case infection was confirmed if RT-PCR was positive.

In terms of the primary identification of viral infection, Cases are suspected according to MOH guidelines: Adults (> 14 years);

I. Acute respiratory illness with clinical and/or radiological, evidence of pulmonary parenchymal disease (pneumonia or Acute Respiratory Distress Syndrome).

II. A hospitalized patient with healthcare associated pneumonia based on clinical and radiological evidence.

III. Upper or lower respiratory illness within 2 weeks after exposure to a confirmed or probable case of MERS-CoV infection. IV. Unexplained acute febrile ($\geq$38 °C) illness, AND body aches, headache, diarrhea, or nausea/vomiting, with or without respiratory symptoms, AND leucopenia (WBC < 3.5 × 109/L) and thrombocytopenia (platelets<150 × 109/L).

Pediatrics ($\leq$ 14 years);

I. Meets the above case definitions and has at least one of the following

a. History of exposure to a confirmed or suspected MERS CoV in the 14 days prior to onset of symptoms b. History of contact with camels or camel products in the 14 days prior to onset of symptoms

II. Unexplained severe pneumonia

Regarding the management, the protocol of management of suspected case starting with ceftriaxone IV, azithromycin or clarithromycin and oseltamivir. Sputum and blood cultures are collected at time of admission. If patient deteriorates, doctors will escalate the antimicrobial spectrum in saving patient life. The wide spectrum may include vancomycin versus linezolid for gram positive coverage and beta lactams for gram negative coverage. If culture and sensitivity show growth of a definitive microorganism, treatment is rechecked for coverage. Some patients desaturates and gets hospital acquired infections, who are treated accordingly with sensitive antimicrobials including colistin.

Statistical analysis

Data were presented as proportions (%) or median (Q1 and Q3) and the χ^2 - test was used to compare them. Logistic regression analysis was used to identify factors associated with mortality. We entered all independent factors in univariate model (each factor was independent) and factors that were independently statistically significant were entered in the multivariate model. P- Value < 0.05 was considered significant. The statistical packages IBMSPSS (version 20) was used to analyze the data.

Results

Of the 54 positive MERS-CoV cases, 3 cases were excluded because their data were not available in the records. Therefore, the final number of the included cases in the study was 51 cases (94.4).

Demographic, historical, and clinical characteristics of 51 positive MERS-CoV cases are demonstrated in the Table 1. Median of age was 54 years (45-67) and majority of the patients were males 78.4. Most of the patients were Saudi 36 (70.6%) and only one was Lebanese (2%). Most of cases were reported in the winter

Table 1
Demographic, historical, and clinical characteristics of 51 positive MERS-CoV cases in Najran, KSA.

Characteristic		N	
Age, Median (Q1-Q3)		54	(45-67)
Sex	Female	11	21.6
	Male	40	78.4
Nationality	Bangladesh	2	3.9
	Egyptian	2	3.9
	Lebanese	1	2.0
	Saudi	36	70.6
	Unknown	1	2.0
	Yemeni	9	17.6
Season			
	Winter	18	35.3
	Spring	10	19.6
	Autumn	9	17.6
	Sumer	14	27.5
Symptoms			
Fever		47	92.2
Cough		44	86.3
Shortness of breath		37	72.5
Sore throat		7	13.7
Chest pain		2	3.9
Runny nose		0	0
Hemoptysis		2	3.9
Headache		4	7.8
Vomiting		5	9.8
Nausea		2	3.9
Diarrhea		7	13.7
Abdominal pain		4	7.8
Myalgia		9	17.6
History of chronic diseases			
Diabetes mellitus		29	56.9
Hypertension		23	45.1
Chronic kidney disease		8	15.7
Chronic respiratory disease (CKD)		4	7.8
Malignancy		0	0
Chronic heart disease		15	29.4
Hepatitis		2	3.9
Smoking Habit			
Smoker		5	9.8
Non-smoker		46	90.2
Obesity		3	5.9
Signs			
Pulse, Median (Q1-Q3)		90	(85-103)
Temperature (°C), Median (Q1-Q3)		37.5	(37.1-38)
Systolic blood pressure (mmHg), Median (Q1-Q3)		124	(113-136)
Diastolic blood pressure (mmHg), Median (Q1-Q3)		76	(64-81)
Respiration rate (rate of breathing), Median (Q1-Q3)		20	(20-23)

18 (35.3) season whereas the least were reported in the autumn 9 (17.6%). The most common symptoms were fever 47 (92.2%), cough 44 (86.3%), and shortness of breath 37 (72.5%). In addition, the most common chronic diseases were diabetes mellitus 29 (56.9%), Hypertension 23 (45.1%), and Chronic heart disease 15 (29.4%). Regarding the history of the patients, only 5 (9.8%) of the patients were smokers and 3 (5.9%) were obese. In term of signs which reported at emergency room, the median of temperature was 37.5 (37.1-38) and the median of respiration rate was 20 breath per minute (20-23).

The vast majority 46 (90.2%) of the patients had pneumonia. Hematological findings on admission were normal; WBC 5 (3-7.38), Hb 13 mg/dl (11-15.1), and platelet 174 (134-263). The median and IQR of neutrophil and lymphocyte were 72.4 (59.5-83.4) and 22.4 (12.5-31.6), respectively. Of 51 positive MERS-CoV cases, 2 (3.9%) septic shock, 4 (7.8%) respiratory failure, and 1 (2%) multi-organic failure were reported as complications of the MERS-CoV infection. The median of time from illness onset to diagnosis was 8 days (5-10) while the time from illness onset to death due to MERS-CoV infection was 15 days (13-17.5). Therefore, the overall mortality rate was 37.3. Table 2

Table 2
Radiology and laboratory results, Time course, Complication, and Outcome of 51 positive MERS-CoV cases in Najran, KSA.

Characteristic		N	%
Pneumonia Evidence			
Clinical and radiology Findings		46	90.2
Laboratory Findings			
WBC, Median (Q1-Q3)		5	(3-7.38)
Neutrophil, Median (Q1-Q3)		72.4	(59.5-83.4)
Lymphocyte, Median (Q1-Q3)		22.4	(12.5-31.6)
Hb, Median (Q1-Q3)		13	(11-15.1)
Platelet, Median (Q1-Q3)		174	(134-263)
Time course			
Time from illness onset to hospital admission, days, Median (Q1-Q3)		7	(4-7)
Time from illness onset to diagnosis, days, Median (Q1-Q3)		8	(6-10)
Time from illness onset to death, days, Median (Q1-Q3)		15	(13-17.5)
Time from illness onset to discharge from hospital, days, Median (Q1-Q3)		12	(7-14)
Complications Related to MERS-CoV infection			
Septic shock		2	3.9
Respiratory failure		4	7.8
Multiorganic failure		1	2.0
Outcome			
	Death	19	37.3
	Survive	32	62.7

Q1-Q3: first and third quartiles

Table 3
Medications were used during hospitalization of 51 positive MERS-CoV cases in Najran.

Medication	N	%
Ceftriaxone	14	27.5%
Oseltamivir	34	66.7%
Piperacillin / Tazobactam (Tazocin)	19	37.3%
Meropenem	9	17.6%
Vancomycin	14	27.5%
Azithromycin	34	66.7%
Moxifloxacin	5	9.8%
Linezolid	5	9.8%

Management of 51 positive MERS-CoV is demonstrated in the Table 3. The most common medications were used include Oseltamivir and Azithromycin which prescribed to 34 (66.7%) patients. Approximately19 (37.3%) patients received Piperacillin / Tazobactam (Tazocin). In contrast, the least common medications were used involve Moxifloxacin and Linezolid which accounted only for 5 (9.8%) patients.

Logistic regression analysis for factors associated with death is shown in Table 4. In univariate analysis, Season and CKD patients were the only two variables statistically significantly associated with death. In the final multivariate analysis model, the only variable that was independently significantly associated with death was chronic kidney disease ($P = 0.024$). The odds of death the patients infected by MERS-CoV during Autumn and Winter season were 4.09 times higher than those patients who infected during Spring and Summer season ($\beta = 4.09$, CI 1.18-14.15, $P < 0.026$). Compared with MERS-CoV patients who had Non-Chronic kidney diseases, the odds of death the MERS-CoV patients who had chronic kidney diseases were 18.08 times higher ($\beta = 18.08$, CI -2.01-162.99, $P < 0.01$).

Case fatality rates over five years is presented in Fig. 1. There was a gradual decline in the Case fatality rates over the given period. 50% of died cases that acquired MERS-CoV infection were in 2014. Since 2014, the case fatality rates were remarkably decreased especially in 2018, and it was obvious that it decreased to 15%. In 2017 it was

Table 4
Logistic regression analysis for factors associated with death.

Factor	N (%)	Univariate analysis OR (95% CI)	p	Multivariate analysis OR (95% CI)	p
Season					
Autumn & Winter	27 (52.9)	4.09 (1.18-14.15)	0.026	2.79 (0.733-10.622)	0.132
Spring & Summer	24 (47.1)	1		1	
Chronic Disease					
Chronic Kidney disease	8 (15.7)	18.08 (2.01-162.99)	0.01	13.18 (1.40-124.04)	0.024
Non-Chronic Kidney disease	43 (84.3)	1		1	

CI, confidence interval; OR, Odds Ratio *Significant at $\alpha = 0.05$.

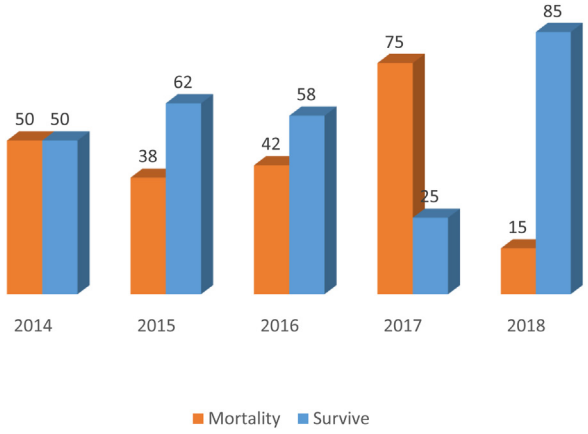

Fig. 1. Mortality rate of 51 positive MERS-CoV cases in Najran by years.

high in our study because some other cases were excluded from this study due to improper documentations.

Discussion

Emerging MERS-CoV is one of the significant public health issues which consequences with a large number of morbidity and mortality. Fifty one positive MERS-CoV cases were confirmed in Najran, KSA and there are various important findings have been highlighted in this study. As Najran region lacks epidemiological studies that concern the MERS-CoV, we conducted this retrospective study to identify the current public health issue.

Since 2012 to March 2018, roughly 2189 positive MERS-CoV cases were reported to MOH from different countries worldwide, however, over 80% of these cases were reported from KSA [6]. Our study found that approximately 78 % of positive cases were Saudi and majority of them males. The study conducted by Mustafa Saad et al. reported similar results [27]. Another study stated that the higher cases were men [28]. A local study in KSA reported 59% of the cases that infected by MERS-CoV were finally died [29]. Another study conducted by Abdulrahman et al. revealed that the mortality rate was 22.9% [30]. International study has been done in Republic of Korea accounted for around 21 % of died cases [31]. our study revealed the mortality rate was 37%.

In terms of symptoms, a large number of patients in our study admitted to the hospital with fever (92.2%), cough (86.3%), and shortness of breath (72.5%). Several national and international studies reported similar percentages of symptoms [29,27,32,31]. In contrast, a study conducted in KSA discovered that only 45% of the patients had fever as a symptoms.

The most common chronic diseases among the patients in this study were diabetes (56.9%) and hypertension (45.1%), which are consistent with the findings of the study in Braided, KSA; hypertension (55.6%) and diabetes (47.6%) [30]. As well as other studies [33,34].

Saad M etc. reported the time (days) from illness onset to hospital admission, diagnosis, death, and discharge from hospital was median (IQR) 5 (3-8.8), 7 (3-13.8), 20 (11.8-28), 27 (2-31) respectively [27]. Unfortunately, the data related to the time course in our study was found only for 18 patients. The reason behind this problem was that the electronic system was not functioning at time of emerging the MERS-CoV infection and the data was entering in the Archive system and some of them were missing. Additionally, after we searched the patient's records and communicated with public health in the region, we couldn't find the data that support identifying the incubation period in our study. Therefore, we cannot compare our findings of the time course to the previous study.

Regarding the medication and outcomes, in our study, no specific drug appears to be independently effective or superior. Similarly, In Guidelines of Yong Pil Chong etc. that is related to Antiviral Treatment for MERS-CoV, the author concluded that effect of antiviral agents were not obvious in the previous observational studies of MERS-CoV treatment [35].

A significant number of patients died as consequences of MERS-CoV infection. Although the risk factors of the complication still ambiguous, previous published studies reported from cohort MERS-CoV patients that elderly people, renal failure, and diabetes were significantly associated with mortality [27,33,34] our study shows one similar risk factor which is chronic kidney diseases. Season was another significant risk factor found in our study, however it was not highlighted by previous studies. Other risk factors might be presented in our study but because of a small number of cases, they were not appeared.

In 2014, Hussain etc. has reported a case fatality rate of 40% in Saudi Arabia [36]. In our study, case fatality rate in 2014, 2015, 2106, 2107, and 2018 was 50%, 33.3%, 42.8%, 75% and finally 15% respectively. In the year 2018 the case fatality rate has remarkably decreased. Donnelly et al, 2019 stated 'although 739 cases were reported in 2014 and 768 cases in 2015, only 244 cases were reported in 2016, another 244 in 2017, and 113 through September 2018. They assessed potential components of this reduction (i.e., reduction of community-acquired cases, human-to-human transmission cases, or both). The incidence of community-acquired cases was 177 in 2016, 151 in 2017, and 86 through September 2018. This means community prevalence is decreasing as well as survival rates are increasing. The author believe that affected countries are reducing the global threat of MERS through addressing knowledge gaps with regard to transmission, enhancing surveillance, and strengthening the ability to detect cases early and contain hospital outbreaks. The authors suggest that the reduction in cases has been achieved through improved infection prevention and control measures that are reducing human-to-human transmission. In addition, restriction of camel movement, stronger and more comprehensive investigations of cases and clusters at the time outbreaks are detected, and increased communication nationally and internationally have been critical in preventing international spread and sustained transmission [37].

Our study has the following limitations. First, the study design is a retrospective and was relied on chart review with some inher-

ited issues; these involve missing data with respect the time course (from illness onset to hospital admission, diagnosis, death, and discharge from hospital). Second, some positive MERS-CoV cases might be sent from non-referral or private hospitals in our region to referral hospitals out Najran such as King Abdullah Medical Complex in Jeddah or Prince Muhammad bin Abdul Aziz Hospital in Riyadh; or mild cases may not come to our referral hospital, for these reasons, our study might have a selection bias. Although these limitations, we were able to identify the demographic, clinical outcomes of confirmed cases of MERS-CoV, and associated factors with mortality in Najran region, KSA.

Conclusion

MERS-CoV infection is one of the public health issues in the KSA and more than 26 countries worldwide. The findings of this study reveal that the mortality rate was high (37.3%). CKD and acquiring MERS-CoV infection in winter and autumn are associated with increased case fatality rates. The case fatality rate dropped over five years to reach 15 % in 2018, and therefore, other studies are recommended to study MERS-CoV antibodies in different community classes to assess herd immunity whether it is the reason behind increasing the survival rate.

Funding

None.

Acknowledgment

We would like to thank Melani M. Lopez for extracting some data from patient records. We are also thankful for Dr Hassan Kasim Haridi for his comments and suggestions on our results.

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