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ORIGINAL RESEARCH

Epidemiological characteristics and initial clinical presentation of patients with laboratory-confirmed MERS-CoV infection in an emergency department

Zohair Al Aseri[1,*], Jaffar A. Al-Tawfiq[2,3,4], Mohammed Alnakhli[5], Abdullah AlNooh[5], Abdulaziz Alnassar[5], Salah Alkhalid[5], Abdulaziz Al Dughayman[5], Tariq Wani[6], Abdulkarim Alhetheel[7], Mazin Barry[8]

[1]Departments of Emergency Medicine and Critical Care, College of Medicine, King Saud University, 11472 Riyadh, Saudi Arabia
[2]Specialty Internal Medicine and Quality Department, Johns Hopkins Aramco Healthcare, 31311 Dhahran, Saudi Arabia
[3]Infectious Disease Division, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA
[4]Infectious Disease Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[5]Clinical Sciences Department, College of Medicine, Dar Al Uloom University, 13314 Riyadh, Saudi Arabia
[6]Research Center, King Fahad Medical City, 11525 Riyadh, Saudi Arabia
[7]Department of Pathology and Laboratory Medicine, College of Medicine, King Saud University, 11472 Riyadh, Saudi Arabia
[8]Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, King Saud University, 11472 Riyadh, Saudi Arabia

***Correspondence**
zohairalaseri@yahoo.com;
zalaseri@ksu.edu.sa
(Zohair Al Aseri)

Abstract

Emergency departments have been implicated as a source of index cases of the Middle East Respiratory Syndrome (MERS) coronavirus infection. We describe the epidemiological characteristics and initial clinical presentation of patients with Middle East respiratory syndrome coronavirus infection in an emergency department at a hospital in Riyadh, in the Kingdom of Saudi Arabia. The records of all patients presenting to the emergency department who tested positive for Middle East respiratory syndrome coronavirus infection on real-time reverse transcriptase polymerase chain reaction testing from April 2014 to November 2019 were reviewed, and the outcomes were assessed. The clinical presentations and outcomes were compared according to sex. A total of 68 patients with Middle East respiratory syndrome coronavirus infection were identified, of whom 40 (58.8%) were female, and 28 (41.2%) were male. The mean age was 50.7 (standard deviation: 16.4) years, and female patients were younger (44.7 $\pm$ 13.1 years) than male patients (59.4 $\pm$ 16.9 years). Nineteen of the 68 patients (27.9%) were asymptomatic of whom the majority (16/19, 84%) were female (p = 0.012). The most common symptoms were fever (n = 29, 42.6%), cough (n = 25, 36.8%), upper respiratory tract infection (n = 23, 33.8%), and pneumonia (n = 15, 22.1%). Pneumonia, diarrhea, dyspnea, and vomiting/diarrhea were more common among male patients. Male patients were more likely than female patients to require hospital admission (78.6% vs. 30.0%), intensive care unit admission (64.3% vs. 15.0%), and invasive mechanical ventilation (32.1% vs. 10.0%). The most common presentation of Middle East respiratory syndrome coronavirus infection in this cohort was asymptomatic infection. A high proportion of asymptomatic infections has not been reported previously. The study did not identify typical clinical features of MERS patients. Male patients tended to develop more severe disease than female patients. A larger study is needed to confirm these findings.

Keywords

MERS-CoV; Emergency department; Clinical presentation; Outbreak

1. Introduction

The Middle East respiratory syndrome coronavirus (MERS-CoV) was first described in the Kingdom of Saudi Arabia (KSA) in 2012 in a man with severe pneumonia [1]. Subsequently, it spread to 27 countries. By the end of June 2021, 2574 laboratory-confirmed cases, and 886 deaths, have been reported, with a case fatality ratio (CFR) of 34.4%. Most cases (n = 2174) occurred in KSA, including 808 deaths (CFR: 37.2%) [2]. MERS-CoV infection has a wide spectrum of presentations, ranging from asymptomatic to acute respiratory distress syndrome [3, 4]. However, there are currently no specific treatments or vaccines for MERS-CoV infection, and the virus is included in the World Health Organization (WHO) Research and Development Blueprint priority list because it poses a high public health risk [5].

The main hallmark of Middle East respiratory syndrome (MERS) is healthcare-associated outbreaks, most of which have occurred in KSA and South Korea [6–27]. Emergency departments have been implicated as the initial source of the index cases in several such outbreaks [23]. Although various MERS outbreaks are well described, limited data on patients' initial presentation in the emergency department are available. This information is vital for the early detection of the disease and to help prevent future outbreaks.

This study aimed to describe the epidemiological characteristics and initial clinical presentation of patients

with laboratory-confirmed MERS-CoV infection admitted to an emergency department at a tertiary care university hospital in Riyadh, KSA over a 5-year period. We also compared presentations and outcomes according to sex.

2. Materials and methods

2.1 Study site and study population

This study was conducted at a university hospital in Riyadh, KSA after approval by the institutional review board and ethics committee. In this study, we included MERS-CoV infected patients who were seen in the emergency department between April 2014 and November 2019. All patients who met the clinical criteria for the definition of MERS, with MERS-CoV infection confirmed by polymerase chain reaction (PCR) testing of either a nasopharyngeal swab or lower respiratory tract specimen, were included in the study. Patient demographics and clinical data were obtained from electronic health records within the hospital system and manually from the medical records department.

2.2 Detection of MERS-CoV using reverse transcription polymerase chain reaction

MERS-CoV RNA was detected from nasopharyngeal swabs stored in a sample collection tube containing 3 mL of the viral transport medium (Copan, Brescia, Italy) as previously described [28]. The total RNA was extracted from 400 μL of sample using a MagNA Pure Compact nucleic acid isolation kit I (Roche Diagnostics, Indianapolis, IN) and tested using the MagNA Pure LC system (Roche Applied Science, Indianapolis, IN). The extracted RNA was then eluted in 50 μL of elution buffer. Next, RNA (10 μL) was reverse transcribed to cDNA using random primers. The cDNA was amplified and screened for the MERS-CoV upstream of the E gene (UpE) and the open-reading frame gene 1a (Orf1a) genes using the primers and probes of the RealStar MERS-CoV RT-PCR kit (Altona Diagnostics, Hamburg, Germany) and Rotor-Gene Q system (Qiagen, Santa Clarita, CA). A patient was considered positive if both the UpE and Orf1a genes were detected.

2.3 Statistical analyses

SPSS software (version 21.0; IBM Corp., Armonk, NY, USA) was used for data analysis. Categorical data were reported as frequencies and percentages, and continuous data were reported as the mean and standard deviation (mean $\pm$ SD). A 95% confidence interval (CI) was used to draw statistical inferences. The Kolmogorov–Smirnov test based on patient sex confirmed that age, oxygen saturation, systolic blood pressure, and respiratory rate showed a skewed distribution. Similarly, oxygen saturation, systolic blood pressure, and respiratory rate showed skewed distributions according to survival status. Inter-group comparisons of the variables with a skewed distribution were performed using the Mann–Whitney U test, whereas normally distributed data were compared using Student's *t*-test. The chi-square test was used to measure the associations between categorical variables and the underlying dependent variables. All significantly associated variables in the univariate analysis were included for backward stepwise multivariable logistic regression analysis. Results were presented as adjusted odds ratios with 95% CIs.

3. Results

A total of 68 patients were admitted to the emergency department with MERS-CoV-2 infection during the study period, of whom 40 (58.8%) were female and 28 (41.2%) were male (Table 1). Most of the male patients (64.3%) were Saudi nationals, whereas most of the female patients (67.5%) were non-Saudi nationals ($p < 0.001$). The mean age of the female patients was 44.7 $\pm$ 13.1 years; 57.5% were aged 31–50 years. The mean age of the male patients was 59.4 $\pm$ 16.9 years; 50.0% were aged >60 years ($p = 0.005$). A history of contact with another MERS case was more common in female patients (42.5%) than in male patients (17.9%). Flu-like symptoms were more common in female patients than in male patients ($p = 0.002$) (Table 1).

The clinical characteristics of the patients included fever ($n = 29$, 42.6%), cough ($n = 25$, 36.8%), upper respiratory tract symptoms ($n = 23$, 33.8%), dyspnea ($n = 14$, 50%), vomiting and diarrhea ($n = 8$, 28.6%), and pneumonia ($n = 11$, 39.3%) (Table 2). There were significantly more asymptomatic cases in female patients ($n = 16$, 40%) than in male patients ($n = 3$, 10.7%). The incidence of cough ($n = 25$, 36.8%) and upper respiratory infection ($n = 23$, 33.8%), which did not differ significantly according to sex.

More than 50% of patients had a medical history of chronic kidney disease (CKD), diabetes mellitus, hypertension, respiratory illness (asthma, pneumonia), or other chronic disease (Table 3). CKD was the only condition that differed significantly according to sex and was significantly more common in males ($n = 6$, 21.4% vs. $n = 0$, 0%; $p = 0.003$). Cardiac disease was observed in 14 (21.2%) patients and was significantly higher in male patients (37.0%) than in female patients (10.3%). The incidence of other chronic diseases was very low and, thereby, did not show any significant difference between both sexes.

Of all patients, 50% required admission, 35.3% needed ICU, and 19.1% needed assisted ventilation (Table 4). There was a difference between male patients and female patients in terms of the need for ventilation and hospital and ICU admission (Table 4).

The mean oxygen saturation in male patients (93.6 $\pm$ 7%) was significantly lower than in female patients (97.6 $\pm$ 3.7%). However, differences in heart rate, systolic blood pressure, diastolic blood pressure, and respiratory rate were not significantly different between the sexes (Table 5).

Compared with female patients, male patients were more likely to have unilateral (21.4%) and bilateral (28.6%) infiltrations (Table 6). Male patients were also significantly more likely to be admitted to hospital (78.6% vs. 30.0%), or the ICU (64.3% vs. 15.0%), and to need assisted ventilation (32.1% vs. 10.0%) (Table 6). The survival rate was higher in female patients ($n = 36$, 90%) than in male patients ($n = 21$, 75%); however, this difference was not statistically significant.

In the logistic regression analysis comparing male and female patients, male patients were significant less likely to

TABLE 1. Socio-demographic characteristics of patients with MERS-CoV–positive patients infection stratified by sex (*n* = 68).

Characteristics	Female	Male	Total	*p* value
	(*n* = 40, 58.8%)	(*n* = 28, 41.2%)	(*n* = 68)	
Nationality				<0.001
Saudi national	11 (27.5)	18 (64.3)	29 (42.6)	
Non-national	27 (67.5)	5 (17.9)	32 (47.1)	
Unknown	2 (5.0)	5 (17.9)	7 (10.3)	
Age, mean ± SD [range], (years)	44.7 ± 13.1 [25–75]	59.4 ± 16.9 [22–88]	50.7 ± 16.4 [22–88]	0.005
≤30	4 (10.0)	2 (7.1)	6 (8.8)	
31–40	15 (37.5)	2 (7.1)	17 (25.0)	
41–50	8 (20.0)	3 (10.7)	11 (16.2)	
51–60	7 (17.5)	7 (25.0)	14 (20.6)	
61–70	4 (10.0)	5 (17.9)	9 (13.2)	
>70	2 (5.0)	9 (32.1)	11 (16.2)	
Diagnosis				0.002
Exposure to other MERS cases	17 (42.5)	5 (17.9)	22 (32.4)	
Flu-like symptoms	8 (20.0)	2 (7.1)	10 (14.7)	
Pneumonia	1 (2.5)	7 (25.0)	8 (11.8)	
Testing	14 (35.0)	14 (50.0)	28 (41.1)	

Data are presented as n (%) unless otherwise specified.

TABLE 2. Clinical characteristics of patients with MERS-CoV infection stratified by sex (*n* = 68).

Characteristics	Female	Male	Total	*p* value
	(*n* = 40, 58.8%)	(*n* = 28, 41.2%)	(*n* = 68)	
Fever	10 (25.0)	19 (67.9)	29 (42.6)	0.001
Cough	14 (35.0)	11 (39.3)	25 (36.8)	0.801
Sputum	6 (15.0)	5 (17.9)	11 (16.2)	0.753
Hemoptysis	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Dyspnea	5 (12.5)	14 (50.0)	19 (27.9)	0.001
Fatigue	4 (10.0)	6 (21.4)	10 (14.7)	0.190
Myalgia/arthralgia	4 (10.0)	5 (17.9)	9 (13.2)	0.471
Abdominal pain	6 (15.0)	3 (10.7)	9 (13.2)	0.727
Vomiting/diarrhea	3 (7.5)	8 (28.6)	11 (16.2)	0.041
Headache	1 (2.5)	3 (10.7)	4 (5.9)	0.298
Confusion	1 (2.5)	3 (10.7)	4 (5.9)	0.298
Asymptomatic	16 (40.0)	3 (10.7)	19 (27.9)	0.012
Upper respiratory infection	12 (30.0)	11 (39.3)	23 (33.8)	0.462
Pneumonia	4 (10.0)	11 (39.3)	15 (22.1)	0.007

Data are presented as n (%).

have asymptomatic disease (odds ratio [OR]: 0.19, 95% CI: 0.04–0.96), and similarly low levels of oxygen saturation in patients were predicted (0.95, 95% CI: 0.93–0.98). However, male patients had a significantly greater risk of cardiac disease (OR: 5.89, 95% CI: 1.09–31.74), and the male patients were significantly older (OR: 1.09, 95% CI: 1.04–1.14).

4. Discussion

In this study, we evaluated the epidemiological characteristics and initial clinical presentations of patients with laboratory-confirmed MERS-CoV infection admitted to an emergency department of a tertiary hospital in KSA. In this study, 58.8% of the cases were among females and 41.2% were males. This finding is dissimilar from the initial studies. The initial cases

TABLE 3. Medical history of patients with MERS-CoV infection, stratified by sex (*n*= 68).

Characteristics	Female	Male	Total	*p* value
	(*n* = 40, 58.8%)	(*n* = 28, 41.2%)	(*n* = 68)	
Chronic kidney disease	0 (0.0)	6 (21.4)	6 (8.8)	0.003
Diabetes mellitus	6 (15.0)	6 (21.4)	12 (17.6)	0.532
Hypertension	7 (17.5)	4 (14.3)	11 (16.2)	>0.999
Respiratory tract infections (asthma, pneumonia)	6 (15.0)	4 (14.3)	10 (14.7)	>0.999
Other chronic medical conditions	6 (15.0)	1 (3.6)	7 (10.3)	0.226
Any chronic medical condition	18 (45.0)	16 (57.1)	34 (50.0)	0.460

Data are presented as n (%).

TABLE 4. In-hospital evaluation of patients with MERS-CoV infection, stratified by sex (*n* = 68).

Characteristic	Female	Male	Total	*p* value
	(*n* = 40, 58.8%)	(*n* = 28, 41.2%)	(*n* = 68)	
Radiology evaluation				
Done	11 (27.5)	16 (57.1)	27 (39.7)	0.014
Normal	6 (15.0)	2 (7.1)	8 (11.8)	0.003
Unilateral infiltration	1 (2.5)	6 (21.4)	7 (10.3)	0.013
Bilateral infiltration	4 (10.0)	8 (28.6)	12 (17.6)	0.048
Required hospital admission	12 (30.0)	22 (78.6)	34 (50.0)	<0.001
Required intensive unit care	6 (15.0)	18 (64.3)	24 (35.3)	<0.001
Required assisted ventilation	4 (10.0)	9 (32.1)	13 (19.1)	0.030
Acute lung injury/acute respiratory distress syndrome	2 (5.0)	4 (14.3)	6 (8.8)	0.220
Acute kidney injury	1 (2.5)	5 (17.9)	6 (8.8)	0.074
Liver dysfunction	1 (2.5)	2 (7.1)	3 (4.4)	0.564
Rhabdomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	>0.999
Pneumothorax	0 (0.0)	1 (3.6)	1 (1.5)	0.412
Arrhythmias	1 (2.5)	3 (10.7)	4 (5.9)	0.298
Disseminated intravascular coagulation	0 (0.0)	0 (0.0)	0 (0.0)	>0.999
Seizures	0 (0.0)	0 (0.0)	0 (0.0)	>0.999
Cardiac disease	4 (10.3)	10 (37.0)	14 (21.2)	0.014
Final outcome				0.179
Survived	36 (90.0)	21 (75.0)	57 (83.8)	
Died in hospital	4 (10.0)	7 (25.0)	11 (16.2)	

Data are presented as n (%).

TABLE 5. Vital signs of patients with MERS-CoV infection, stratified by sex (*n* = 68).

Characteristic	Female	Male	Total	*p* value
	(*n* = 40, 58.8%)	(*n* = 28, 41.2%)	(*n* = 68)	
Oxygen saturation (%)	97.6 ± 3.7 [83–100]	93.6 ± 7 [65–100]	95.9 ± 5.6 [65–100]	0.004
Heart rate (beats/min)	88.1 ± 15.2 [57–117]	87.5 ± 16 [60–120]	87.9 ± 15.4 [57–120]	0.876
Systolic blood pressure (mmHg)	129.7 ± 19.7 [100–177]	131.2 ± 25.1 [63–189]	130.3 ± 21.8 [63–189]	0.798
Diastolic blood pressure (mmHg)	71.5 ± 10.4 [45–95]	68.7 ± 12.4 [43–88]	70.4 ± 11.2 [43–95]	0.319
Respiratory rate (breaths/min)	20.2 ± 4 [16–40]	22 ± 6.9 [16–46]	20.9 ± 5.4 [16–46]	0.213

Data are presented as mean ± SD [range].

of MERS-CoV were thought to have male predominance, with a male-to-female ratio of 2.8–3.3 to 1 [28, 29]. The initial male predominance was related to the nature of the MERS-CoV outbreaks. However, a study describing the largest outbreak

TABLE 6. Multivariable logistic regression analysis of sex-dependent variables.

	Variables	Description	OR [95% CI]	*p* value
Step 1	Nationality	Saudi national	Reference	0.132
		Non-national	0.04 [0–3.51]	0.158
		Unknown	21.15 [0.57–784]	0.098
	Diagnosis	Exposure	Reference	0.435
		Flu-like symptoms	0.77 [0.03–17.26]	0.867
		Pneumonia	0.01 [0–39.55]	0.279
		Routine testing	0.34 [0.01–7.82]	0.999
		Unrelated	0 [0–2.97]	0.092
	Symptom	Fever	0.03 [0–3.43]	0.145
		Dyspnea	4.67 [0.22–97.39]	0.320
		Vomiting/diarrhea	8.21 [0.12–580]	0.332
		Asymptomatic	0.02 [0–2.92]	0.121
	Medical history	Chronic kidney disease	21.82 [1.16–409.25]	0.999
	Radiological evaluation		0.47 [0.02–8.84]	0.611
	Hospital admission		18.26 [0.09–3730]	0.284
	Need for intensive care unit care		76.63 [0.22–26500]	0.146
	Assisted ventilation		0.24 [0–12]	0.473
	Cardiac disease		2.31 [0.18–28.98]	0.515
	Outcome (died)		0.04 [0–2.13]	0.114
	Age (year)		1.1 [0.99–1.21]	0.075
	Oxygen saturation (%)		0.98 [0.92–1.04]	0.471
Step 12	Asymptomatic		0.19 [0.04–0.96]	0.045
	Cardiac disease		5.89 [1.09–31.74]	0.039
	Age (year)		1.09 [1.04–1.14]	0.001
	Oxygen saturation (%)		0.95 [0.93–0.98]	<0.001

OR, odds ratio; CI, confidence interval.

of MERS-CoV outside KSA, i.e., in the Republic of Korea, also showed a male predominance [30]. Multiple hypotheses were proposed, including differences in terms of sex, gender roles, social paradigms, culture, and behavioral attributes [31].

In this study, 19 (27%) of the included patients were asymptomatic. The occurrence of asymptomatic patients with MERS-CoV infection is well known. Initial outbreaks of MERS-CoV have been characterized by severe clinical cases [7, 32]. However, the occurrence of asymptomatic cases was also well established. In a study conducted from April 2013 to October 2013, 12.5% of 144 PCR laboratory-confirmed cases were asymptomatic, and this percentage increased to 25.1% among 255 confirmed cases in 2014 [33]. The average prevalence of asymptomatic MERS cases was 9.8% according to previous studies [33, 34]. There was also a variation in the prevalence of asymptomatic patients among different age groups, with higher rates, ranging from 41.9% to 81.8%, reported among children [33]. The contribution of asymptomatic patients to the transmission of MERS-CoV infection has been investigated [33, 35–39]. In addition, controlling asymptomatic transmission is challenging.

Interestingly, we found that asymptomatic cases were more common among female patients (40%) than among male patients (10.7%). This difference might be secondary to physiological differences or related to the sample size. The most prevalent symptoms of MERS-CoV infection on presentation include non-specific symptoms such as cough and dyspnea [25, 27, 28, 40]. In this study, the prevalence of dyspnea, pneumonia, and fever were more common among male patients than among female patients. To our knowledge, no study has yet described the differences between male and female patients with MERS-CoV infection. Previous studies have noted that 33% of patients with MERS experienced vomiting and diarrhea [7, 23, 27, 28, 40–42]. In this study, these symptoms were present in 16.2% of patients, with a sex-based difference (males: 28.6%, females: 7.5%). In another study, 62.5% of ICU patients were male, and 37.5% were female [43]. The need for ICU admission and mechanical ventilation was observed in 44.4% and approximately 25–100% of patients, depending on the study population [44]. The need for ICU admission was noted in 35.3% of all patients and was more common among male patients (64.3%) than among female patients (15%). Previous studies have reported that those with severe disease tend to have respiratory failure, acute kidney

disease, acute liver injury, and cardiac arrhythmias [7, 27, 41, 45]. The rate of death was associated with the presence of comorbidities (RR = 3), male sex (RR = 1.6), occupational camel exposure (RR = 1.6), and raw milk consumption (RR = 1.5) [46]. In this study, we revealed the differences in presentations and outcomes of MERS-CoV among male and female patients. Such disparities in outcomes and presentations have also been noted among COVID-19 patients, especially among those of different races and nationalities [47–49].

This study had a few limitations. First, we only analyzed a small sample size limited from a single center. However, the length of the study period was a strength of this study. Second, we did not further evaluate all risk factors pertinent to exposure and the exact source of infection. We also did not have data on the duration of symptoms prior to the presentation, and there was no further analysis of the virus to examine its phylogenetic evolution. In addition, since most of the females were non-Saudi nationals and males were Saudi nationals, the comparison between males and females might be influenced by the nationality. Despite these limitations, this study provided valuable information, especially sex-based differences among MERS patients.

5. Conclusions

The most common symptoms among the diagnosed patients were fever, cough, and dyspnea. The study did not identify typical clinical features of MERS patients. The need for ICU admission and mechanical ventilation were more common among male patients. This study also showed a high rate of asymptomatic cases. Further studies are needed to explore the differences in MERS-CoV presentations and outcomes among different sexes and elucidate the underlying reasons for these differences.

AUTHOR CONTRIBUTIONS

ZAA—designed the study, wrote original draft, reviewed, supervised, and edited; JAAT—wrote original draft, reviewed and edited and corrected English; MA, AAIN, AAln, SA, and AAD—designed the study and data collection and wrote original draft; TW—designed the study, reviewed and edited the result and statistical analysis; AAlh—design and wrote the method; MB—wrote original draft, reviewed and edited and corrected English.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the intuitional review board of college of medicine and King Khalid University Hospital (approval No. E-17-2369).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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