EC EMERGENCY MEDICINE AND CRITICAL CARE
Research Article

Risk Factors for Acquiring Middle East Respiratory Syndrome at an Emergency Room in a Large Tertiary Hospital in Riyadh, Saudi Arabia, 2015: Case-Control Study

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Received: March 18, 2019; **Published:** April 25, 2019

Abstract

Background: An outbreak of Middle East respiratory syndrome (MERS) caused by coronavirus occurred at a major hospital in Saudi Arabia in 2015 and provided an opportunity to assess the risk factors (chronic comorbidities) associated with MERS-CoV infection.

Methods: A case-control study was done in which we reviewed paper and electronic medical records of all laboratory-confirmed non-healthcare worker MERS cases (N = 87). Controls were 165 individuals selected from 22,320 visitors to the hospital using systematic random sampling. Risk factors assessed were 17 comorbidities. Bivariate and multivariable analyses were used to determine the odds ratios (OR) and 95% confidence intervals (95% CI).

Results: In the bivariate analysis, the following comorbidities were significantly associated with MERS-CoV infection: cancer, chronic kidney disease, hypothyroidism, hypertension, asthma, heart disease, benign prostatic hypertrophy, mental disease/disorder, cerebrovascular accident/disease, diabetes mellitus and lung disease. Chronic obstructive pulmonary disease, being bed-bound, Dyslipidaemia, anaemia, rheumatoid disease, obesity and liver diseases were not statistically significant risk factors for MERS CoV infection. Multivariable analysis identified four risk factors: Cancer (OR = 41.4, 95% CI: 8.0 - 213.4), chronic kidney disease (OR = 5.7, 95% CI: 1.8 - 18.2), hypothyroidism OR = 5.6, 95% CI: 1.2 - 25.3), and hypertension (OR = 2.96, 95% CI: 1.19 - 7.41). The likelihood of having MERS increased as the number of comorbidities increased.

Conclusion: This is the first study to report hypothyroidism as a risk for MERS. Knowing that patients with chronic comorbidities are vulnerable to MERS-CoV infection can help in triage, and early protect, suspect and isolate MERS cases, especially in emergency rooms.

Keywords: *Middle East Respiratory Syndrome; Coronavirus Infections; Comorbidity; Case-Control Study; Saudi Arabia*

Introduction

Middle East respiratory syndrome (MERS) is a zoonotic viral respiratory disease caused by a novel coronavirus (MERS-CoV) and has a high case fatality ratio [1,2]. Sporadic primary community-acquired infections with MERS-CoV have been found to be associated with exposure to young dromedary camels infected with the virus [3,4]. In addition, clusters of MERS infection have been acquired in healthcare facilities in the emergency room and were associated with inadequate adherence to proper infection prevention and control measures [5-7]. Factors associated with susceptibility and severity of MERS infections are not clearly understood. Although some MERS-CoV infections could be asymptomatic or mild, severe and fatal infections have occurred, especially in the elderly, immunocompromised people, and patients with chronic comorbidities [8-10]. A case-control study has been conducted to identify the risk factors for primary community-acquired MERS and emergency room-acquired MERS [11]. However, difficulties in recruiting a sufficient number of cases of MERS has limited the usefulness of these studies.

An outbreak of MERS occurred in a large non-Ministry of Health government tertiary care hospital in Riyadh City, Saudi Arabia. The emergency room of the hospital consists of seven adjacent units and has a total of 150 beds [12]. Patients can be moved frequently from one bed to another within and between different emergency room units according to their general condition, stability and bed availability. More than 1000 healthcare workers work in the emergency room. Details of the emergency room units are given elsewhere [13].

On 6 August 2015, the hospital notified the Ministry of Health of an unusual increase in the number of cases of MERS at its emergency room. On 11 August 2015, the Ministry of Health's rapid response team was allowed to join the hospital activities for infection prevention and control. The hospital management decided to close the emergency room, suspend elective surgeries, and postpone all outpatient appointments and visits for three weeks from 18 August 2015; complete evacuation of the emergency department was achieved on 22 August 2015. Upon a request of the Ministry of Health, the Saudi Field Epidemiology Training Program conducted an outbreak investigation to assess the risk factors associated with acquiring MERS, including 17 comorbidities and the outcome of this investigation which is reported here.

Materials and Methods

The Saudi Arabian Ministry of Health defines an adult case of MERS as an acute respiratory illness with clinical and/or radiological evidence of pulmonary parenchymal disease (pneumonia or acute respiratory distress syndrome); or a hospitalized patient with healthcare-associated pneumonia based on clinical and radiological evidence; or an upper or lower respiratory illness within 2 weeks of exposure to a confirmed or probable case of MERS infection; or unexplained acute febrile (≥ 38°C) illness, and body aches, headache, diarrhoea, or nausea/vomiting, with or without respiratory symptoms, and leukopenia (white blood cell count $<3.5 \times 10^9$/L) [14]. A case of MERS among children is defined as a child presenting with acute febrile illness (T ≥ 38°C) with/without respiratory symptoms OR gastrointestinal symptoms (diarrhea or vomiting), AND leukopenia (WBC $\leq 3.5 \times 10^9$/L) or thrombocytopenia (platelets $< 150 \times 10^9$/L) and reported at least one if the following three epidemiological within 14 days before symptom onset: (1) exposure to a confirmed case of MERS-CoV infection OR (2) visit to a healthcare facility where MERS-CoV patients(s) has recently (within 2 weeks) been identified/treated OR (3) contact with dromedary camels5 or consumption of camel products (e.g. raw meat, unpasteurized milk, urine).

A primary case of MERS was defined as a patient who came to the emergency room of the tertiary care hospital with a clinical presentation suggestive of MERS that started prior to his/her visit to the emergency room and with no history of visits or admissions to the hospital within one month of his/her presentation, and subsequent laboratory investigation confirmed the diagnosis of MERS. A secondary case of MERS was defined as a confirmed case that developed symptoms suggestive of MERS at least 48 hours after admission to the emergency room or hospital. An infected healthcare worker was any worker in the hospital who was symptomatic and tested positive for MERS or was asymptomatic and detected through MERS screening.

We included only laboratory-confirmed cases of MERS in this study. For all laboratory-confirmed cases diagnosed at the hospital during the outbreak period and the controls, we extracted their demographic details, clinical presentation (dates of onset of symptoms suggestive of MERS), comorbidities, weight and height and a detailed history of visits to the emergency room and clinics, and admissions, including movements within the emergency room units. We tracked the e-medical records of all primary cases for at least one month prior to their admission with MERS diagnosis to find out whether or not they were exposed to a known MERS case at the hospital. All laboratory tests used to confirm MERS diagnosis using real-time polymerase chain reaction from nasopharyngeal, endotracheal or sputum samples were obtained and reviewed. Medical records were carefully reviewed to ensure that primary community-acquired infections and emergency room-acquired infections were accurately classified.

A list of all emergency room visitors at the hospital between 30 June and 18 August 2015 (the date of closure of the emergency room) was obtained (N = 22,320). The emergency room visits were sorted by date and time to have an even distribution and complete representation of the outbreak period. Using systematic random sampling (k = 100, and a random start for selection of the first control), 200 patients were selected. Thirty-five controls were excluded as the medical records of 10 patients could not be accessed and other 25 controls were also removed as two healthcare workers and 23 females had visited a specialized gynecological emergency room which is in a separate building from the main adult emergency room where the outbreak occurred. We ended up therefore with 165 controls included in the analysis.

Patients with a psychiatric illness or disorder who were seen regularly at the referred clinics of the psychiatric department were classified as patients with mental illness or disorder. Adult body mass index (BMI), defined as weight in kilograms divided by the square of height in metres, was calculated for both cases and controls. BMI < 18.5 kg/m^2 was categorized as underweight, 18.5 - 24.9 kg/m^2 as normal, 25 - 29.9 kg/m^2 as overweight, 30 - 34.9 kg/m^2 as obese, and BMI > 35 kg/m^2 as morbidly obesity [15]. We excluded all healthcare workers with asymptomatic infections as they were mostly young and healthy expatriate nurses with no comorbidities and their inclusion could weaken the estimated significance of the studied risk factors. Cases with primary community-acquired infections and those with emergency room-acquired infections were pooled together and the estimated odds ratios (OR) for the primary community-acquired infections and those with emergency room-acquired infections were not stratified.

We used Excel 2013 and Epi Info 7 for data entry and analysis of data. We used the t-test to test the difference between two means with equal variance. P ≤ 0.05 was considered statistically significant. We calculated the OR and the related 95% confidence intervals (95% CI) using bivariate and multivariable analyses (unconditional binary logistic regression). Only statistically significant covariates in the bivariate analyses were included in the multivariable model.

Results

The outbreak started on 17 June and ended on 8 September 2015 and resulted in a total of 130 cases (Figure 1). About one third of the cases (43 cases, 33.1%) were healthcare workers with asymptomatic or mild infections. Of the remaining 87 (66.9%) laboratory-confirmed cases of MERS, 20 (23.0%) were primary community-acquired infections and 67 (77.0%) were secondary emergency room-acquired infections.

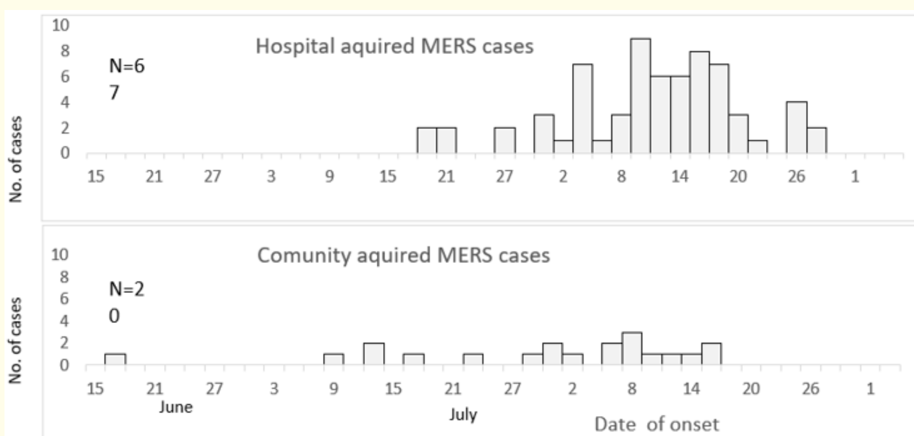

Figure 1: *Epidemiological curve of community- and hospital-acquired confirmed Middle East respiratory syndrome (MERS) cases in a large tertiary care hospital Riyadh, Saudi Arabia, June-August 2015.*

The mean age of cases with primary community-acquired infections was 63.5 (SD 18.3) years (IQR = 51.5-78.0), and mean age of cases with emergency room-acquired infections was 64.5 (SD 18.7) years (IQR = 26.0 - 55.0); the difference was not statistically significant (P > 0.05). More MERS cases were found among the elderly (60 years of age or older) in emergency room-acquired infections than in primary community-acquired infections; about half of the cases with emergency room-acquired infections were 70 years or older. There was no significant difference in gender or BMI distribution between primary community-acquired infections and emergency room-acquired infections or in the frequencies of the studied comorbidities. The risk of MERS infection increased with age (chi square for linear trend = 59.4, P < 0.001) (Table 1).

Variable	PCAI (N = 20)	ERAI (N = 67)	Total MERS cases (N = 87)	Controls (N = 165)	OR (95% CI)* Bivariate analysis	OR (95% CI)** Multivariable analysis	Statistical test
	No. (%)	No. (%)	No. (%)	No. (%)			
Age (years)							
11 - 19 (Reference group)	0 ( )	2 (3.0)	2 (2.3)	11 (6.7)	1	8.4 (4.3 - 16.2)	χ^2 for linear trend = 59.4, P < 0001
20 - 29	0 ( )	1 (1.5)	1 (1.1)	52 (31.5)			
30 - 39	2 (10.0)	4 (6.0)	6 (6.9)	22 (13.3)	5.7 (1.3 - 24.9)		
40 - 49	2 (10.0)	5 (7.5)	7 (8.0)	20 (12.1)	7.4 (1.7 - 31.1)		
50 - 59	5 (25.0)	11 (16.4)	16 (18.4)	31 (18.8)	10.8 (2.9 - 40.0)		
≥ 60	0 (25.0)	12 (17.9)	55 (63.2)	29 (17.6)	8.7 (2.3 - 33.2)		
Body mass index[a]							
18.5 - 24.9 (Reference group)	5 (25.0)	19 (28.4)	24 (27.6)	30 (22.6)	1	0.8 (0.5 - 1.2)	χ^2 for linear trend = 3.4, P = 0.072
< 18.9	0 (0)	4 (6.0)	4 (4.6)	4 (3.0)	1.3 (0.3 - 5.5)		
25 - 29.9	9 (45.0)	19 (28.4)	28 (32.2)	32 (24.1)	1.1 (0.5 - 2.3)		
30 - 34.9	2 (10.0)	15 (22.4)	17 (19.5)	34 (25.6)	0.6 (0.3 - 1.4)		
≥ 35	4 (20.0)	10 (14.9)	14 (16.1)	33 (24.8)	0.5 (0.2 - 1.2)		

Table 1: *Age and body mass index of cases with Middle East respiratory syndrome (MERS) and controls at an emergency room in a large tertiary care hospital in Riyadh, Saudi Arabia, 2015.*

PCAI: primary community-acquired infection, ERAI: emergency room-acquired infection, OR: odds ratio, CI: confidence interval.

a: We could not obtain the weight of 32 controls.

The mean age of all MERS cases was 64.3 (SD 18.2) years (median: 66 years) and of controls was 41.7 (SD 18.7) years (median age: 38 years; IQR: 55 - 78, (P < 0.01).

Only 7 (8.0%) cases had no comorbidities or chronic illnesses compared with 102 (61.8%) controls. About two thirds of all MERS cases (59 out of 87, 67.8%) were overweight/obese with just over a quarter of within the normal BMI (24 out of 87, 27.6%). In contrast, 99 controls (60.0%) were overweight/obese. There were 14 (16.1%) cases with morbid obesity compared with 33 (24.8%) controls but the difference was not statistically significant (P > 0.05) (Table 1).

Table 2 shows the bivariate and multivariable analyses of risk factors (comorbidities) for MERS infection. In the bivariate analysis, the following comorbidities were significantly associated with MERS-CoV infection: cancer, chronic kidney disease, hypothyroidism, hypertension, asthma, heart disease, benign prostatic hypertrophy, mental disease/disorder, cerebrovascular accident/disease, diabetes mellitus and lung disease. Being bed-bound, suffering from chronic obstructive pulmonary disease, dyslipidaemia, anaemia, rheumatoid disease, obesity and liver diseases were not statistically significant risk factors for MERS CoV infection. Multivariable analysis identified four risk factors: Cancer (OR = 41.4, 95% CI: 8.0 - 213.4), chronic kidney disease (OR = 5.7, 95% CI: 1.8 - 18.2), hypothyroidism OR = 5.6, 95% CI: 1.2 - 25.3), and hypertension (OR = 2.96, 95% CI: 1.19 - 7.41). On stratifying age of cases and controls into two categories: Equal or less than 40 years of age (coded as 0) and above 40 years of age (coded as 1); and including age in the logistic model; the following variables continued to emerge as significant risk factors: Having cancer (OR = 42.3; 95% CI: 7.8 - 228.9; having a chronic kidney disease (OR = 5.1; 95% CI: 1.6 - 16.1) and hypothyroidism (OR = 4.9; 95% CI: 1.1 - 21.7). The likelihood of having MERS increased as the number of comorbidities increased. The likelihood of acquiring MERS increased with the number of comorbidities a patient suffered from (Table 3).

Comorbidity	PCAI (N = 20)	ERAI (N = 67)	Total MERS cases (N = 87)	Controls (N = 165)	Bivariate analysis*	Multivariable analysis**	P-value
	No. (%)	No. (%)	No. (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Significant in bivariate and multivariate analyses							
Cancer	2 (10|)	14 (20.9)	16 (18.4)	2 (1.2)	18.4 (4.1 - 81.9)	41.4 (8.0 - 213.4)	< 0.0001
Chronic kidney disease	5 (25.0)	25 (37.3)	30 (34.5)	9 (5.5)	9.1 (4.1 - 20.4)	5.7 (1.8 - 18.2)	0.0320
Hypothyroidism	4 (20.0)	6 (9.0)	10 (11.5)	4 (2.4)	5.2 (1.6 - 17.2)	5.6 (1.2 - 25.3)	0.0252
Hypertension**	15 (75.0)	49 (73.1)	64 (73.6)	44 (26.7)	7.7 (4.2 - 13.8)	2.96 (1.19 - 7.41)	0.0201
Significant in the bivariate but not multivariable analysis							
Bronchial asthma	1 (5.0)	6 (9.0)	7 (8.0)	1 (0.6)	14.3 (1.7 - 119)	0.63 (0.14 - 2.8)	0.3456
Heart disease	9 (45.0)	30 (44.8)	39 (44.8)	18 (10.9)	6.6 (3.5 - 12.7)	0.70 (0.12 - 3.98)	0.6888
Benign prostate hypertrophy	1 (5.0)	5 (7.5)	6 (0.6)	1 (0.6)	12.1 (1.4 - 1`02.6)	4.59 (0.45 - 47.0)	0.1988
Mental disease/ disorder	3 (15.0)	3 (4.5)	6 (6.9)	2 (1.2)	6.0 (1.2 - 30.6)	6.14 (0.85 - 44.03)	0.0712
Cerebrovascular accident/disease	4 (20.0)	10 (14.9)	14 (16.1)	8 (4.8)	3.8 (1.5 - 9.4)	2.03 (0.63 - 6.53)	0.1883
Diabetes mellitus	17 (85.0)	43 (64.2)	60 (69.0)	48 (29.1)	5.4 (3.1 - 9.5)	2.13 (0.87 - 5.20)	0.0968
Lung disease	6 (30.0)	13 (19.4)	19 (21.8)	15 (9.1)	2.8 (1.3 - 5.8)	2.92 (0.96 - 8.91)	0.0590
Not significant in the bivariate analysis and not included in the multivariable analysis							
Tuberculosis	1 (5.0)	3 (4.5)	4 (4.5)	8 (4.8)	0.3 (0.9 - 3.2)	ND	ND
Bed - bound	2 (10.0)	5 (7.5)	7 (8.0)	2 (1.2)	7.1 (14 - 35.1)	ND	ND
Liver disease	0 (0.0)	6 (9.0)	6 (6.9)	3 (1.8)	4.0 (0.97 - 16.4)	ND	ND
Rheumatoid disease	0 (0.0)	2 (3.0)	2 (2.3)	2 (1.2)	1.9 (0.3 - 13.9)	ND	ND
Chronic obstructive pulmonary disease	2 (10.0)	0 (0.0)	2 (2.3)	8 (4.8)	0.5 (0.1 - 2.2)	ND	ND
Dyslipidaemia	1 (5.0)	8 (11.9)	9 (10.3)	18 (10.9)	0.94 (0.4 - 2.1)	ND	ND

Table 2: *Summary of the risk factors (comorbidities) for Middle East respiratory syndrome (MERS) at an emergency room in a large tertiary care hospital in Riyadh, Saudi Arabia, 2015.*

PCAI: Primary Community-Acquired Infection; ERAI: Emergency Room-Acquired Infection; OR: Odds Ratio; CI: Confidence Interval.

: Hypertension was not a significant risk factor when age was added to the multivariate analysis.

ND: Not Done.

Number of comorbidities[a]	Cases	Controls	Total MERS cases	OR (95% CI)	Mean age (SD) in years	IQR in years
	No. (%)‡	No. (%)	No. (%)			
No comorbidity (Reference group)	7 (8.0)	102 (61.8)	109 (43.3)	1.0	32.7 (13.4)	23 - 41
One comorbidity	15 (17.2)	26 (15.8	41 (16.3)	8.4 (3.1 - 22.7)	48.4 (19.0)	37 - 64
Two comorbidities	17 (19.5)	19 (11.5)	36 (14.3)	13.0 (4.8 - 37.0)	58.8 (14.0)	48 - 68
Three comorbidities	31 (35.6)	16 (9.7)	47 (18.7)	28.2 (10.6 - 74.8)	63.6 (12.0)	57 - 71
Four comorbidities	17 (19.5)	2 (1.2)	19 (7.5)	123.9 (23.7 - 647)	72.5 (13.4)	63 - 82

Table 3: *Distribution of multiple significant risk factors among cases and controls and the likelihood of acquiring Middle East respiratory syndrome (MERS), Riyadh, 2015.*

OR: Odds Ratio; CI: Confidence Intervals; SD: Standard Deviation; IQR: Interquartile Range.

[a]: Sum of the number of significant risk factors in the multivariable analysis: hypothyroidism, cancer, chronic kidney diseases and heart disease.

[b]: Adjusted odds ratio.

Discussion

This case-control study provides epidemiological evidence that the elderly and people with chronic illnesses are more likely to acquire MERS as compared with patients aged 30 years or less with no comorbidities. Old age (60 years or older) is a known risk factor for severe viral respiratory diseases, including MERS [10,16,17]. It is plausible that an old person would have one or more comorbidities compared with a younger person, and the immune system would be less competent with ageing. Our study showed that patients suffering from more than one comorbidity or chronic illnesses were at higher risk of acquiring MERS than those with no or fewer comorbidities. The results of this study are consistent with the findings of previous studies which found that the immunocompromised people and those suffering from comorbidities were more susceptible to acquiring primary MERS infection in the community [8,12,17-21]. The predominant comorbidities cited in the literature included hypertension, diabetes mellitus, respiratory and chronic renal disease, chronic cardiac disease and cancer. Some descriptive studies have reported that about 47-96% of MERS patients had at least one comorbidity; and in another study, only two of the 47 cases were previously healthy [8,19]. Some studies have concluded that pre-existing concurrent comorbidities or underlying medical conditions were associated with MERS infection and probably increased the risk of a fatal outcome, i.e. they were clinical predictors of death [10,12,19].

Hypothyroidism emerged as a risk factor for MERS and continued as one of four comorbidities associated with MERS in the multivariable analysis. A case report described the case of a 33-year-old pregnant, critical care nurse with a prior history of hypothyroidism and primary infertility who contracted MERS although she was using standard contact and droplet precautions while caring for her MERS patient [22]. The severity of viral pneumonia in pregnancy is evidently related to physiological and immunological changes that result in a shift from cell-mediated to humoral-mediated immunity [23].

Morbid obesity was not as a statistically significant risk factor for MERS. This might be explained by the relatively high prevalence of obesity and/or morbid obesity in both cases and controls which may have obscured the effect of a known risk factor for influenza and severe acute respiratory syndrome [24]. In addition, very heavy weight could have limited such patient's movements in the emergency and probably they were bed-bound most of the time and thus were less exposed to infection.

The descriptive analysis indicated that there was no important difference in risk factors between cases with primary community-acquired infection and those with emergency room-acquired infection.

Diabetes mellitus was not a significant risk factor for MERS infection as it could be presented by having chronic kidney disease. Likewise, chronic lung diseases and asthma were not significant risk factors. Susceptibility of an individual to MERS could be due to modifiable and non-modifiable risk factors. Comorbidities are mostly non-modifiable; therefore more effort should be made to modify the surrounding environment. Outbreaks of MERS have been predominantly associated with healthcare facilities, especially emergency rooms and renal dialysis units. Person-to-person transmission of MERS-CoV can occur, especially in the case of superspreading events [25,26]. Thus, it is necessary to establish and implement respiratory triage policies and procedures with appropriate infection prevention and control measures in emergency rooms to ensure early detection and isolation of suspected MERS cases [25,27]. Patients with comorbidities visiting emergency rooms should be encouraged to use masks and avoid being in close contact with other patients with respiratory tract infections (coughing or sneezing). In the respiratory triage area, there should be a negative pressure room for taking nasopharyngeal swabs or any other aerosol-generating procedures. The implementation of this procedure is especially critical during outbreaks or in case of mass gatherings, e.g. umra (minor pilgrimage for Muslims) and Hajj (pilgrimage to Mecca for Muslims) when the hospitals around the holy places become very crowded and congested. Healthcare workers with comorbidities should not be allowed to work in respiratory triaging areas for MERS. Emergency room hallways and rooms should have displays that educate visiting patients about the mode of transmission of and protection from MERS. As regards primary community-acquired infection, people-especially elderly people with multiple comorbidities-should avoid getting close to young camels, the reservoir for MERS-CoV.

The occurrence of a prolonged outbreak of MERS with an unusually large number of primary and secondary cases, and access to the medical records for ascertainment of comorbidities offered a unique opportunity to conduct this case-control study. There are nonetheless some limitations to the study. Comorbidities were classified into broad non-specific groups. More in-depth studies would be useful in order to refine its conclusion, including the determinants of severity of MERS-CoV infections. The infectivity, pathogenicity and virulence of MERS-CoV warrants further in-depth studies. It is not clear whether or not MERS-CoV is a highly infectious, opportunistic virus that tends to infect immunocompromised people or patients with specific predisposing comorbidities.

Conclusion

This is the first study to report hypothyroidism as a risk factor for MERS. Knowing that patients with chronic comorbidities are vulnerable to MERS-CoV infection help triage, early protect, suspect and isolate MERS cases, especially in emergency rooms.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests

None declared.

Ethical Approval

Not required because this was an outbreak investigation.

Author Contributions

HA, ZM, HEB and MM did the fieldwork, active surveillance data collection, abstraction of medical records, and data cleaning and management. AAB, HEB, HA, MM and AMA were involved in interpreting the results. HEB and HA did the statistical analysis. HEB and HA and MM prepared the manuscript. All authors reviewed, discussed and approved the final manuscript.

Acknowledgements

We thank the Command and Control Center, Ministry of Health, Saudi Arabia for facilitation of the fieldwork and guidance.

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Volume 3 Issue 5 May 2019