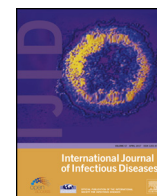




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# Diagnostic delays in 537 symptomatic cases of Middle East respiratory syndrome coronavirus infection in Saudi Arabia



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## ABSTRACT

**Background:** Although the literature indicates that patient delays in seeking medical support for Middle East respiratory syndrome coronavirus (MERS-CoV) infections are associated with poor clinical outcomes, delays in the diagnosis itself remain poorly understood in these patients. This study aimed to determine the median time interval from symptom onset to a confirmed diagnosis and to identify the potential predictors of this interval in Saudi Arabian MERS patients.

**Methods:** This was a retrospective study of patients with confirmed MERS who were publicly reported by the World Health Organization (WHO).

**Results:** Five hundred and thirty-seven symptomatic cases of MERS-CoV infection were included. The median time interval between symptom onset and confirmation of the MERS diagnosis was 4 days (interquartile range 2–7 days), ranging from 0 to 36 days. According to the negative binomial model, the unadjusted rate ratio (RR) of delays in the diagnosis was significantly higher in older patients (>65 years) (RR 1.42), non-healthcare workers (RR 1.74), patients with severe illness (RR 1.22), those with an unknown source of infection (RR 1.84), and those who had been in close contact with camels (RR 1.74). After accounting for confounders, the adjusted rate ratio (aRR) of delays in the diagnosis was independently associated with unknown source of infection (aRR 1.68) and close contact with camels (aRR 1.58).

**Conclusions:** The time interval from symptom onset to diagnosis was greater in older patients, non-healthcare workers, patients with severe illness, patients with an unknown source of infection, and patients who had been in close contact with camels. The findings warrant educational interventions to raise general public awareness of the importance of early symptom notification.

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## Introduction

The emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) (Zaki et al., 2012) has placed a large burden on the healthcare systems of several countries, in particular those where outbreaks have occurred (Drosten et al., 2015; Kim and Lee, 2015). According to the Saudi Ministry of Health, 1579 MERS-CoV cases had been reported across the Kingdom of Saudi Arabia up until April 25, 2017, with 660 deaths related to MERS-CoV (Saudi Ministry of Health, 2017). The mortality rate has been high (Das et al., 2015; Al-Dorzi et al., 2016; Al-Hameed et al., 2016;

Kim et al., 2016a; Sherbini et al., 2017), particularly in patients with symptoms (Sherbini et al., 2017).

Despite the fact that most cases experience early MERS-related signs and symptoms (Al-Dorzi et al., 2016; Sherbini et al., 2017; Assiri et al., 2013a), a considerable number of cases are diagnosed only when the illness becomes more severe (Al-Dorzi et al., 2016; Rivers et al., 2016; Banik et al., 2016). A Saudi Arabian study included MERS patients diagnosed between 2012 and July 2015, documenting that one-third of the cases reported their symptoms after 7 days (Al-Sahafi and Cheng, 2016). According to the authors, no association was found between the long time interval before reporting symptoms and patient outcomes. However, their findings were based on the time interval between symptom onset and hospital admission rather than diagnosis.

Park et al. investigated the diagnostic accuracy of serological assays in a sample of 17 patients with confirmed MERS-CoV infection at different time intervals after the onset of illness (Park et al., 2015). The study reported that the serological assays were

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highly sensitive at 21 days following the onset of illness (Park et al., 2015).

Kim et al. investigated the clinical progression and cytokine profiles after the first appearance of illness in a Korean population with MERS-CoV (Kim et al., 2016b). Their study reported that the time interval was associated with a poor outcome in patients with severe illness. The median time interval from symptom onset to transfer to the isolation unit was reported to be 5 days, with a range of 2–11 days (Kim et al., 2016b). More studies are warranted to investigate the time interval from symptom onset to diagnosis and the factors associated with this interval in other MERS populations, specifically in Saudi Arabia, where MERS-CoV was first reported and where the world's largest outbreaks occur.

Several studies have reported that people might not be able to identify MERS symptoms, the transmission cycle (Banik et al., 2015; Malik et al., 2016), and its etiology (Malik et al., 2016), due to the complexity of the disease. During the circulation of MERS-CoV in the past 5 years, the time interval between symptom onset and diagnosis has remained poorly understood in these patients. No research has addressed the factors associated with the time to a confirmed MERS diagnosis after symptom onset in Saudi Arabia.

The early identification of MERS-related signs and symptoms could result in early diagnosis and thus provide medical support to help mitigate the symptoms and improve the prognosis of patients. Early diagnosis may reduce the spread of the illness to people who are in close contact with the cases (Zumla et al., 2015).

The hypothesis of this study was that the time interval between symptom onset and the diagnosis of MERS may differ by age group, sex, region, severity of illness, source of infection, and other factors. The study aimed to estimate the median time interval to a confirmed diagnosis after symptom onset and to identify potential predictors of this time interval in Saudi Arabian MERS patients.

## Methods

The study utilized publicly available data recorded by the World Health Organization (WHO). Since the emergence of MERS in September 2012, the WHO has received notification of confirmed MERS-CoV cases from 27 countries (WHO, 2017). MERS-CoV continues to be reported to the WHO from countries of the Middle East. The data are publicly available at [http://www.who.int/csr/don/archive/disease/coronavirus\\_infections/en/](http://www.who.int/csr/don/archive/disease/coronavirus_infections/en/).

As at April 26, 2017, the WHO had recorded 1938 laboratory-confirmed cases of MERS globally (WHO, 2017). The data were extracted by a research assistant and reviewed for quality by the study author. The extracted data were compared to the data that are publicly reported by the Saudi Ministry of Health. The study included MERS patients from Saudi Arabia reported between January 5, 2015 and the most recent report on April 3, 2017. The author reviewed data from January 5, 2015, as this is the date that the WHO began using standardized case presentations and also started reporting cases by the country in which they were identified. The study included only symptomatic patients, patients who had an available date of symptom onset, and patients who had an available date of diagnosis. A total of 537 symptomatic cases of MERS-CoV infection with available date of symptom onset and diagnosis were identified.

The author retrieved patient data and clinical information including sex, age, and region in Saudi Arabia, along with comorbidities, whether the patient was a healthcare worker, the severity of the illness, whether the patient died, and the source of the infection. The date of final laboratory diagnosis and the date of symptom onset were also collected. The primary outcome was the time interval from symptom onset to a confirmed diagnosis, defined as the number of days after developing symptoms until diagnosis.

## Statistical analysis

The statistical analysis was performed using IBM SPSS 24.0 (IBM Corp., Armonk, NY, USA). The characteristics of the study population were summarized using the frequency and percentage (%) for categorical variables and the mean and standard deviation ( $\pm$ SD), or median and interquartile range (IQR) when necessary, for numerical variables. The study outcome modeled was the time interval from symptom onset to a confirmed diagnosis. The author investigated multivariate count models using Poisson regression and negative binomial models. Initially, over-dispersion was assessed and the adequacy of negative binomial and Poisson regression models was checked. The log likelihood and the deviance goodness-of-fit were calculated for each model and compared. It was found that the negative binomial model outperformed the Poisson regression model. The negative binomial model was used to estimate unadjusted and adjusted rate ratios (RR and aRR) and to identify predictors of the time interval to confirmed diagnosis after symptom onset. The RR was used to assess the strength of the association between the predictor and the time interval of confirmed diagnosis after symptom onset. If the RR was  $>1$  it was considered that the predictor increased the time interval to confirmed diagnosis after symptom onset; if the RR was  $<1$  it was considered that the predictor reduced the time interval to confirmed diagnosis after symptom onset. A  $p$ -value of  $<0.05$  was considered statistically significant.

## Results

A total of 537 MERS patient records were retrieved and included in the study. The mean age of these patients was  $55 \pm 17.9$  years (range 1–109 years), and 41.4% of patients were aged above 60 years. Two-thirds of patients were male, 73.9% had a comorbidity, 10.4% were healthcare workers, and 46.5% had severe illnesses. Other characteristics are reported in Table 1. The mean time from the onset of symptoms to MERS-CoV diagnosis was  $5.6 \pm 4.4$  days (range 0–36 days). The median time from onset of symptoms to MERS-CoV diagnosis was 4 days (IQR 2–7 days). Among the 537 symptomatic MERS patients, 39.5% were diagnosed within 3 days, 75.6% within 7 days, and 90% within 10 days after symptom onset.

**Table 1**

Characteristics of symptomatic laboratory-confirmed Middle East respiratory syndrome patients, January 2015 to March 2017 ( $N=537$ ).

Characteristics	Levels	<i>n</i>	%
Sex	Male	370	68.9
	Female	167	31.1
Age group, years	<30	58	10.8
	30–59	257	47.9
	60–65	61	11.4
	>65	161	30.0
Region	Center	327	60.9
	East	77	14.3
	West	69	12.8
	South	44	8.2
Comorbidity	North	20	3.7
	Yes	397	73.9
Healthcare worker	No	140	26.1
	Yes	56	10.4
Severe illness	No	481	89.6
	Yes	249	46.5
Died	No	286	53.5
	Yes	218	40.6
Source of infection	No	319	59.4
	Unknown	140	26.1
	Camels	136	25.3
	Hospital-acquired	208	38.7
	Household	53	9.9

**Table 2**

Bivariate negative binomial model: unadjusted rate ratio (RR) and the predictors of the time interval between symptom onset and a confirmed diagnosis.

Factor	Time interval	B	SE	Wald Chi-square	p-Value	RR	95% Wald CI for RR	
							Lower	Upper
Sex								
Male	5.90	0.19	0.10	3.58	0.059	1.21	0.993	1.480
Female	4.87					1.00		
Age group, years								
>65	6.04	0.35	0.17	4.27	0.039 <sup>*</sup>	1.42	1.018	1.974
60–65	5.64	0.28	0.20	1.94	0.163	1.32	0.892	1.965
30–59	5.58	0.27	0.16	2.82	0.093	1.31	0.956	1.796
<30	4.26					1.00		
Region								
Center	5.14	−0.21	0.25	0.73	0.394	0.81	0.498	1.316
East	6.52	0.03	0.27	0.01	0.922	1.03	0.605	1.743
West	5.87	−0.08	0.27	0.08	0.774	0.92	0.541	1.580
South	6.41	0.01	0.29	0.00	0.975	1.01	0.572	1.782
North	6.35					1.00		
Comorbidity								
Yes	5.86	0.20	0.11	3.62	0.057	1.23	0.994	1.515
No	4.78					1.00		
Healthcare worker								
No	5.84	0.55	0.16	11.97	0.001 <sup>*</sup>	1.74	1.271	2.380
Yes	3.36					1.00		
Severe illness								
Yes	6.19	0.20	0.09	4.65	0.031 <sup>*</sup>	1.22	1.019	1.473
No	5.06					1.00		
Died								
Yes	6.13	0.16	0.10	2.93	0.087	1.18	0.977	1.419
No	5.21					1.00		
Source of infection								
Unknown	6.96	0.61	0.18	11.54	0.001 <sup>*</sup>	1.84	1.293	2.608
Camels	6.60	0.55	0.18	9.48	0.002 <sup>*</sup>	1.74	1.223	2.474
Hospital-acquired	4.44	0.16	0.17	0.84	0.359	1.17	0.835	1.642
Household	3.79					1.00		

SE, standard error; RR, rate ratio; CI, confidence interval.

<sup>\*</sup> Significant at  $\alpha=0.05$ .

The unadjusted RRs for delays in the diagnosis are reported in Table 2. Older patients (RR 1.42,  $p=0.039$ ), non-healthcare workers (RR 1.74,  $p=0.001$ ), patients with a severe illness (RR 1.22,  $p=0.031$ ), patients with an unknown source of infection (RR 1.84,  $p=0.001$ ), and patients who had been in close contact with camels (RR 1.74,  $p=0.002$ ) were associated with a greater number of days from symptom onset to MERS-CoV diagnosis.

After accounting for confounders (Table 3), source of infection remained a significant predictor that increased the time interval to a confirmed diagnosis after symptom onset (Figure 1). Specifically, the adjusted RR of delays in the diagnosis was independently associated with an unknown source of infection (aRR 1.68,  $p=0.005$ ) and those in close contact with camels (aRR 1.58,  $p=0.018$ ). The adequacy of the final model was compared between the negative binomial and Poisson regression models. The log likelihood (negative binomial −1482.4; Poisson regression −1545.3) and the deviance (negative binomial 0.383; Poisson regression 2.514) indicated that the negative binomial model was superior to the Poisson model. All the adjusted and unadjusted RRs presented in this section were produced with the negative binomial regression model.

## Discussion

This study appears to be the first to estimate the time interval between symptom onset and a confirmed diagnosis and to identify

the potential predictors of this time interval in symptomatic cases of MERS-CoV infection in Saudi Arabia. The average time interval to a confirmed diagnosis after symptom onset was 5.6 days (median 4 days). Kim et al. reported a similar median estimate (5 days) in a sample of MERS patients in the Republic of Korea (Kim et al., 2016b).

The results of the present study are consistent with those of a Saudi Arabian study using Saudi Ministry of Health public data on MERS cases reported between September 2012 and September 2015, in which it was estimated that the mean time from symptom onset to confirmation was 6.60 days and the mean time from symptom onset to notification was 5.30 days (Alhamlan et al., 2017). The median time from symptom onset to confirmation was not reported in that study.

In this study, it was possible to estimate the unadjusted RR by the characteristics of the patients and the disease. It was found that older age ( $\geq 65$  years) was significantly associated with a prolonged time interval to reporting MERS-related symptoms. The RR of delayed diagnosis was 42% higher in patients over the age of 65 years compared to the youngest age group of patients ( $<30$  years). This might explain the high mortality rate observed in this age group (Rivers et al., 2016; Banik et al., 2015; Assiri et al., 2013b).

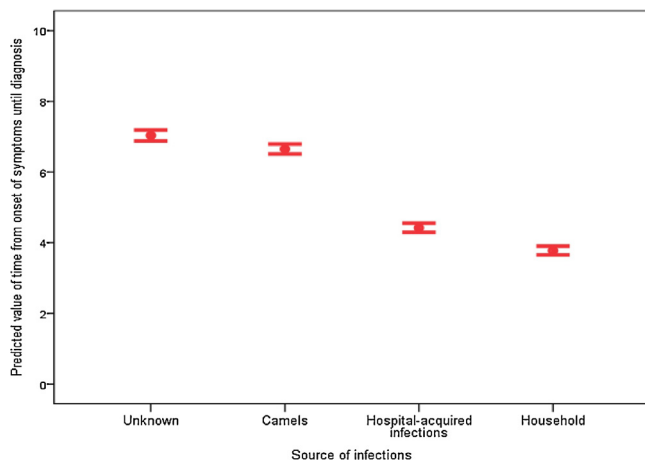
Non-healthcare workers had a higher rate of a prolonged time interval in reporting MERS-related symptoms than healthcare workers (RR 1.74, 95% confidence interval 1.271–2.380). This may be attributed to several factors: (1) access to healthcare facilities

**Table 3**

Multivariate negative binomial model: adjusted rate ratio (aRR) and the predictors of the time interval between symptom onset and a confirmed diagnosis.

Factor	B	SE	Wald Chi-square	p-Value	aRR	95% Wald CI for RR	
						Lower	Upper
Sex							
Male	0.08	0.11	0.55	0.457	1.08	0.877	1.340
Female					1.00		
Age group, years							
>65	0.12	0.20	0.33	0.567	1.12	0.753	1.679
60–65	0.04	0.23	0.02	0.878	1.04	0.661	1.624
30–59	0.06	0.18	0.11	0.735	1.06	0.751	1.499
<30					1.00		
Region							
Center	−0.04	0.25	0.02	0.880	0.96	0.584	1.585
East	0.21	0.28	0.60	0.437	1.24	0.721	2.128
West	−0.05	0.28	0.04	0.849	0.95	0.549	1.639
South	0.01	0.30	0.00	0.998	1.00	0.561	1.786
North					1.00		
Comorbidity							
Yes	0.04	0.14	0.08	0.777	1.04	0.790	1.372
No					1.00		
Healthcare worker							
No	0.28	0.20	2.04	0.154	1.33	0.900	1.955
Yes					1.00		
Severe illness							
Yes	0.12	0.10	1.27	0.259	1.13	0.917	1.381
No					1.00		
Died							
Yes	0.03	0.11	0.06	0.812	1.03	0.825	1.278
No					1.00		
Source of infection							
Unknown	0.52	0.19	7.74	0.005*	1.68	1.167	2.433
Camels	0.46	0.19	5.63	0.018*	1.58	1.083	2.298
Hospital-acquired	0.13	0.19	0.44	0.508	1.13	0.780	1.650
Household					1.00		

SE, standard error; RR, rate ratio; CI, confidence interval.

\* Significant at  $\alpha = 0.05$ .**Figure 1.** The impact of the source of infection on the time interval between symptom onset and a confirmed diagnosis.

could be an issue for non-healthcare workers, and thus warrants further investigation, (2) the symptoms of MERS may not be clearly obvious to non-healthcare workers, as there are gaps in knowledge about the virus and symptoms in this group (Assiri et al., 2013b; Alqahtani et al., 2017). An interventional study may target the level

of knowledge in the non-healthcare worker group to improve their understanding of the virus and symptoms, and the importance of the early notification of symptoms.

The finding of the current study that the severity of illness is associated with a prolonged time interval between onset and diagnosis is consistent with the study by Kim et al., (2016b). The estimated time interval between onset and diagnosis in patients with severe illness was 6.19 days, while it was 5.06 days in patients with a stable condition. This seems to be an important finding that could justify early symptom notification, which could be addressed through a public health education campaign to mitigate and control MERS-CoV in its early stages.

The uniqueness of this work lies in the investigation of the association between the time interval from onset to diagnosis and the source of infection in symptomatic cases of MERS-CoV infection in Saudi Arabia. It was found that the time interval from onset to diagnosis was independently associated with the source of infection. Those who had an unknown source of infection and those who had been in contact with camels had a 68% and 58%, respectively, higher risk of a delay in seeking diagnosis or medical support compared to those who had household-acquired infections. These findings have not previously been reported elsewhere. A lack of knowledge about the primary source of the virus and recognition of MERS-CoV symptoms could be barriers to early presentation and identification of the virus.



A Saudi Arabian study measured awareness of MERS-CoV in a sample of Twitter users in Saudi Arabia (Al-Mohrej et al., 2016). More than half (53%) of these Twitter users were unaware that camels and bats are the primary source of the virus (Al-Mohrej et al., 2016). The study recommended that individuals in close contact with camels should be targeted in future MERS-CoV education campaigns. These individuals need to be aware that they are at increased risk of MERS-CoV. This could help to screen for MERS-CoV early and limit the spread of the virus. Furthermore, detailed investigations should be performed in patients with an unknown source of infection; any exposure needs to be considered and documented as a possible source of infection. The decreased risk of a delay in seeking diagnosis in patients with household-acquired infections could be due to the case definition of MERS-CoV as per the Saudi Ministry of Health. The case definition of MERS-CoV includes whether there has been close contact with a confirmed or probable case of MERS-CoV infection. Al-Mohrej et al. reported that 74% of their sample knew that the MERS-CoV infection is transmitted via close contact (Al-Mohrej et al., 2016).

This study has some limitations. The study used public source data, in which details of the patients' clinical characteristics had not been reported. The results should be interpreted with caution, as the findings reflect association but not causation. Despite several limitations, the findings highlight valuable information on the predictors of a delay in seeking diagnosis or medical support in symptomatic cases of MERS-CoV infection in Saudi Arabia. The study highlights the importance of early notification of symptoms related to MERS-CoV, as a delay in diagnosis could contribute to a worse clinical outcome and to the MERS burden in Saudi Arabia and worldwide.

In conclusion, the time interval from symptom onset to diagnosis was greater in older patients, non-healthcare workers, patients with severe illness, patients with an unknown source of infection, and patients in close contact with camels. The delay in diagnosis could explain the worse clinical outcomes in symptomatic cases of MERS-CoV infection. The findings warrant educational interventions to raise general public awareness of the importance of early symptom notification.

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None

#### Conflict of interest

I declare that I have no competing interest.

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