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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.

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 (Alsahafi 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/.

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 (±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 ± 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 ± 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	*n*	%
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
	North	20	3.7
Comorbidity	Yes	397	73.9
	No	140	26.1
Healthcare worker	Yes	56	10.4
	No	481	89.6
Severe illness	Yes	249	46.5
	No	286	53.5
Died	Yes	218	40.6
	No	319	59.4
Source of infection	Unknown	140	26.1
	Camels	136	25.3
	Hospital-acquired	208	38.7
	Household	53	9.9