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Diagnostic delays in Middle East respiratory syndrome coronavirus patients and health systems

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ABSTRACT

Background: Although Middle East respiratory syndrome coronavirus (MERS-CoV) diagnostic delays remain a major challenge in health systems, the source of delays has not been recognized in the literature. The aim of this study is to quantify patient and health-system delays and to identify their associated factors.

Methods: The study of 266 patients was based on public source data from the World Health Organization (WHO) (January 2, 2017–May 16, 2018). The diagnostic delays, patient delays, and health-system delays were calculated and modelled using a Poisson regression analysis.

Results: In 266 MERS-CoV patients reported during the study period, the median diagnostic delays, patient delays, and health-system delays were 5 days (interquartile [IQR] range: 3–8 days), 4 days (IQR range: 2–7 days), and 2 days (IQR range: 1–2 days), respectively. Both patient delay ($r = 0.894$, $P = 0.001$) and health-system delay ($r = 0.163$, $P = 0.025$) were positively correlated with diagnostic delay. Older age was associated with longer health-system delay (adjusted relative ratios (aRR), 1.011; 95% confidence intervals (CI), 1.004–1.017). Diagnostic delay (aRR, 1.137; 95% CI, 1.006–1.285) and health-system delays (aRR, 1.217; 95% CI, 1.003–1.476) were significantly longer in patients who died.

Conclusion: Delays in MERS-CoV diagnosis exist and may be attributable to patient delay and health-system delay as both were significantly correlated with longer diagnosis delay. Early MERS-CoV diagnosis may require more sensitive risk assessment tools to reduce avoidable delays, specifically those related to patients and health system.

Introduction

Delays in Middle East respiratory syndrome coronavirus (MERS-CoV) diagnosis are a serious challenge to health systems worldwide due to the potential transmission clusters in communities and in healthcare facilities [1,2]. Despite the presence of clinical suspicion in a majority of the MERS-CoV cases [3,4], delays in diagnosis and seeking prompt medical care remain common among MERS-CoV patients [5]. A South Korean study reported substantial lag duration between suspected clinical symptom onset and MERS-CoV laboratory confirmation, with a median of 6.5 days on 37 MERS-CoV infection cases [6].

Delayed diagnosis of MERS-CoV infection contributes positively to recovery delay [4] and poor prognosis [7,8]. In MERS-CoV patients, diagnostic delay may be attributed to the patient and/or to the health system which remain unaddressed in this population. Understanding the various sources of delays in diagnosis and in seeking medical care for MERS-CoV infection may be among the most essential efforts to improve the diagnostic process, as it is necessary to control transmission and optimize medical care.

Although MERS-CoV infection has been highlighted as a priority research area to address diagnosis-related challenges in Saudi Arabia, there have been no research topics addressing patient and health-system delays in terms of MERS-CoV diagnosis. The aim of this study was to quantify delay time intervals of MERS-CoV diagnosis and to determine factors that contributed to

Abbreviations: MERS-CoV, Middle East respiratory syndrome coronavirus; WHO, World Health Organization; IQR, interquartile; RR, relative ratios; aRR, adjusted relative ratios; CI, confidence intervals.

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Table 1
Characteristics of MERS-CoV patients (N = 266).

Factors	Levels	n	%
Gender	Male	191	71.8
	Female	75	28.2
Reporting country	Saudi Arabia	250	94.0
	Non-Saudi Arabia	16	6.0
Health care worker	Yes	43	16.2
	No	223	83.8
Comorbidities	Yes	164	61.7
	No	102	38.3
Exposure to camels	Yes	81	30.5
	No	185	69.5
Camel milk consumption	Yes	63	23.7
	No	203	76.3
Exposure to MERS-CoV cases	Yes	93	35.0
	No	173	65.0
Died	Yes	78	29.3
	No	188	70.7
		Median	IQR (25th–75th) percentile
Age (10–90 years)		54	38–65
Diagnostic delays (1–20 days)		5	3–8
Patient-related delays (0–14 days)		4	2–7
Health system-related delays (0–19 days)		2	1–2

diagnostic delay, patient delay in seeking medical care, and health-system delay.

Methods

The author utilized public MERS-CoV records that are available through the World Health Organization (WHO) webpage (http://www.who.int/csr/don/archive/disease/coronavirus_infections/en/). In 2018, and as of 31 May 2018, the WHO received notification of laboratory-confirmed MERS-CoV cases from various countries including Saudi Arabia, United Arab Emirates, Oman, and Malaysia. Since first identified in the Kingdom of Saudi Arabia in 2012 and until 31 May 2018, 2220 laboratory-confirmed MERS-CoV cases have been reported globally (with a fatality rate of 35.6%), in which 1844 laboratory-confirmed MERS-CoV cases were reported from Saudi Arabia (WHO, 2018). The study author extracted and included all MERS-CoV cases reported between January 2, 2017 and the latest report on May 16, 2018. The study covers this period because the WHO uses standardized case presentations to report the date of MERS-CoV symptom onset, date of first hospitalization, and date of MERS-CoV laboratory confirmation. This is organized by the reporting country in which each case was identified.

A total of 266 MERS-CoV laboratory-confirmed cases were identified during this period. Patient, clinical, and source of the MERS-CoV infection data were retrieved including age, gender, reporting country in which case was identified (Saudi Arabia or non-Saudi Arabia), comorbidities (yes/no), health-care workers (yes/no), exposure to camels (yes/no), camel milk consumption (yes/no), exposure to another MERS-CoV case, and whether the patient had died (yes/no).

Study outcomes

Three outcomes were measured: (1) Diagnostic delay, defined as the time interval (in days) between the onset of MERS-CoV symptoms and the MERS-CoV laboratory confirmed diagnosis, (2) Patient delay in seeking medical care defined as the time interval (in days) between the onset of MERS-CoV symptoms and the first hospitalization, and (3) Health-system delay in the MERS-CoV diagnosis, defined as the time interval (in days) between the first hospitalization and the MERS-CoV laboratory confirmed diagnosis. The author used the date of first hospitalization because the date of each patient's first visit to seek medical care at a healthcare center was not available.

Statistical analysis

The analysis was performed using IBM SPSS 25.0 (IBM Corp., Armonk, NY, USA). Counts and percentages were used to report categorical data (Table 1). The median value and interquartile range (IQR) were used to report quantitative data such as the time intervals (in days) of diagnostic delay, patient delay, and health-system delay (Table 1). Bivariate and multivariate Poisson model were used to model diagnostic delay, patient delay, and health-system delay as well as to identify factors associated with shorter or longer delays. The strength of the association was presented as crude relative ratios (RR), adjusted relative ratios (aRR), and the 95% confidence intervals (CI). A value of RR /aRR >1 indicates that the factor is associated with a longer delay; otherwise the factor is associated with a shorter delay. Significance level was set at $P \leq 0.05$.

Results

Of 266 MERS-CoV patients analyzed, 71.8% were male, 94% were reported from Saudi Arabia, and 30.5% were directly exposed to camels. The median diagnostic delay was 5 days (interquartile [IQR] range: 3–8 days), median patient delay was 4 days (IQR range: 2–7 days), and median health-system delay was 2 days (IQR range: 1–2 days).

The crude RR for various delays of MERS-CoV diagnosis is reported in Table 2. Saudi Arabia as a reporting country was a significant predictor of shorter diagnostic delay, patient delay, and health-system delay. Patients who had exposure to MERS-CoV cases were associated with shorter diagnostic delay, patient delay, and health-system delay. Health-care workers were associated with shorter diagnostic delay and patient delay.

Patients who had exposure to camels and those who consumed camel milk were associated with longer diagnostic delay and shorter health system delay. Older patients, males, those who had comorbidities, and those who had died were associated with longer health-system delay.

The adjusted relative ratio (aRR) for various delays of MERS-CoV diagnosis is reported in Table 3. Saudi Arabia as a reporting country was a significant predictor of shorter diagnostic delay (aRR, 0.549; 95% CI, 0.430–0.701), shorter patient delay (aRR, 0.688; 95% CI,

Table 2
Bivariate analysis of factors associated with delays in MERS-CoV diagnosis, patient, and health system-related delays (N = 266).

	Diagnostic delays				Patient-related delays				Health system-related delays			
			95% CI for RR				95% CI for RR				95% CI for RR	
Factors	P	RR	Lower	Upper	P	RR	Lower	Upper	P	RR	Lower	Upper
Age	0.079	1.003	1.000	1.007	0.378	1.002	0.998	1.006	0.047*	1.006	1.000	1.011
Gender												
Male	0.055	1.156	0.997	1.341	0.250	1.110	0.929	1.327	0.005*	1.437	1.114	1.854
Female												
Reporting country												
Saudi Arabia	0.001*	0.569	0.470	0.689	0.013*	0.712	0.544	0.932	0.001*	0.579	0.422	0.794
Non-Saudi Arabia												
Health care worker												
Yes	0.013*	0.572	0.368	0.890	0.002*	0.213	0.080	0.570	0.113	0.490	0.203	1.183
No												
Comorbidities												
Yes	0.469	0.951	0.829	1.090	0.488	0.943	0.800	1.112	0.001*	1.534	1.189	1.979
No												
Exposure to camels												
Yes	0.003*	1.190	1.059	1.338	0.395	1.062	0.925	1.219	0.001*	0.531	0.434	0.650
No												
Camel milk consumption												
Yes	0.014*	1.164	1.031	1.315	0.270	1.083	0.940	1.249	0.001*	0.527	0.422	0.657
No												
Exposure to MERS-CoV cases												
Yes	0.001*	0.356	0.279	0.455	0.001*	0.420	0.270	0.655	0.001*	4.643	3.876	5.563
No												
Died												
Yes	0.414	1.050	0.934	1.182	0.060	1.144	0.994	1.317	0.001*	1.597	1.337	1.908
No												

* Significant at $\alpha = 0.05$.

Table 3
Independent factors associated with delays in MERS-CoV diagnosis, patient,and health system-related delays (N = 266).

	Diagnostic delays				Patient- related delays				Health system- related delays			
			95% CI for aRR				95% CI for aRR				95% CI for aRR	
Factors	P	aRR	Lower	Upper	P	aRR	Lower	Upper	P	aRR	Lower	Upper
Intercept	0.001	9.912	6.974	14.086	0.001	6.296	4.044	9.801	0.042	1.844	1.021	3.331
Age	0.490	1.001	0.997	1.006	0.485	1.002	0.997	1.007	0.002*	1.011	1.004	1.017
Gender												
Male	0.787	0.978	0.829	1.152	0.801	1.026	0.842	1.249	0.065	1.291	0.985	1.693
Female		1.000				1.000				1.000		
Reporting country												
Saudi Arabia	0.001*	0.549	0.430	0.701	0.021*	0.688	0.501	0.946	0.001*	0.324	0.217	0.483
Non-Saudi Arabia		1.000				1.000				1.000		
Health care worker												
Yes	0.837	0.951	0.590	1.533	0.083	0.376	0.124	1.137	0.001*	0.193	0.077	0.483
No		1.000				1.000				1.000		
Comorbidities												
Yes	0.921	0.991	0.828	1.186	0.227	0.881	0.717	1.082	0.524	1.109	0.807	1.525
No		1.000				1.000				1.000		
Exposure to camels												
Yes	0.103	0.837	0.675	1.036	0.175	0.837	0.647	1.082	0.316	0.812	0.540	1.220
No		1.000				1.000				1.000		
Camel milk consumption												
Yes	0.083	1.231	0.973	1.557	0.169	1.216	0.921	1.606	0.663	1.104	0.707	1.724
No		1.000				1.000				1.000		
Exposure to MERS-CoV cases												
Yes	0.001*	0.374	0.287	0.486	0.033*	0.576	0.347	0.956	0.001*	5.616	4.461	7.071
No		1.000				1.000				1.000		
Died												
Yes	0.039*	1.137	1.006	1.285	0.057	1.150	0.996	1.327	0.046*	1.217	1.003	1.476
No		1.000				1.000				1.000		

* Significant at $\alpha = 0.05$.

0.501–0.946), and shorter health-system delay (aRR, 0.324; 95% CI, 0.217–0.483). Health-care workers were associated with shorter health-system delay (aRR, 0.193; 95% CI, 0.077–0.483).

Patients who had exposure to MERS-CoV cases were associated with shorter diagnostic delay (aRR, 0.374; 95% CI, 0.287–0.486), shorter patient delay (aRR, 0.576; 95% CI, 0.347–0.956), and longer health-system delay (aRR, 5.616; 95% CI, 4.461–7.071). Older patients and those who had died were associated with longer health-system delay (aRR, 1.011; 95% CI, 1.004–1.017), (aRR, 1.217; 95% CI, 1.003–1.476), respectively.

Discussion

Since the MERS-CoV infection first emerged in Saudi Arabia in 2012, there has been no literature reporting patient and health-system delays in the MERS-CoV diagnosis process and potential factors that may contribute to these delays. The median duration from the MERS-CoV onset of symptoms until making a diagnosis (diagnosis delay) was 5 days (interquartile [IQR] range: 3–8 days) which is in line with the author's previous report of 4 days (IQR range: 2–7 days) from cases reported between January 5, 2015 and April 3, 2017 [5]. The diagnosis delay in this study also compares similarly to a study in South Korea which reported frequent long delays in MERS-CoV diagnosis with a median duration of 6.5 days [6].

The study shows that median duration from the onset of MERS-CoV symptoms until first hospitalization (patient delay) was 4 days (IQR range: 2–7 days) with a range between 0 and 14 days. According to the study, patient delay significantly correlates with MERS-CoV diagnostic delay ($r = 0.894$, $P = 0.001$). The frequent long patient delay in seeking medical care after experiencing MERS-CoV symptoms may reflect limited patients' awareness of, and knowledge of MERS-CoV symptoms [9–11] and the need for health education programs for the public [9,10], and healthcare practitioners [10,11]

The median health-system delay was 2 days (IQR range: 1–2 days) with 86% of patients being diagnosed with MERS-CoV within two days after first hospitalization. This study shows that health-system delay significantly correlates with the MERS-CoV diagnostic delay ($r = 0.163$, $P = 0.025$). The health-system delay in identifying a MERS-CoV case may be attributed to the delay in the virus recognition in medical institutions [6] and to the limited awareness among healthcare-workers [11], as a survey conducted on 1216 healthcare-workers revealed that only 47.6% of the physicians and 30.4% of the nurses were aware that some infected patients had no symptoms [11]. Also diagnosis of MERS-CoV [3] and medical care for patients with MERS-CoV [12] remain major challenges in healthcare facilities. Further understanding on the causes of patient and health-system delay is needed, as it can be used as a modifiable factor to reduce diagnostic delay and to improve the diagnostic process.

The author identified factors associated with various delays (diagnostic, patient, and health system). Adjusting for other characteristics, longer diagnostic delay and health-system delay were noted among MERS-CoV cases of those who had died. An effective surveillance system and prompt screening are necessary to improve diagnostic strategies and prevent deaths [5].

As age increases by one year, the health-system delay in diagnosis tends to increase by 1.1%. A large proportion of the MERS-CoV patients are older [5], which indicates the necessity of prompt investigation to reduce health-system delay in this vulnerable group. Saudi Arabia as a reporting country was a significant predictor of shorter diagnostic, patient, and health-system delays. Unlike the other countries, Saudi Arabia has experienced multiple MERS-CoV outbreaks, and the majority (83%) of cases reported were from Saudi Arabia (WHO, 2018). The lessons learned from these outbreaks may help the health system in Saudi Arabia to improve clinical experience in detection, diagnosis, and management of new MERS-CoV cases [13].

Shorter patient delays and diagnostic delays were found in patients who reported exposure to MERS-CoV cases. This could be due to the immediate contact tracing after confirming a MERS-CoV case, which may lead to prompt and proper examination of individuals who were in close contact. Furthermore, exposure to MERS-CoV cases was heightened in standard risk assessment and screening guidelines released and disseminated by the Saudi Ministry of Health [14] and WHO [15].

Limitations in this study were noted. The author used WHO public source data with limited clinical characteristics. Significant findings in this study must be interpreted carefully, as it indicates correlation rather than causation. Patient and health-system delays were calculated using the date of first hospitalization rather than the date of first consultation in a health facility or a first doctor's visit. Despite these limitations, this is the first study to assess the source of MERS-CoV diagnostic delays (patient and health-system). Early diagnosis of MERS-CoV [3] and its delay [5] continues to be a major challenge, since neither has been sufficiently discussed in previous literature. Furthermore, the study identified several potential interventions related to the decision-making process at patient, doctor, and health-system levels to shorten avoidable delays in the MERS-CoV diagnosis process following symptoms and first doctor visit.

Conclusion

Delays in MERS-CoV diagnosis exist and may be attributable to patient- and health-system delays, as both were correlated with longer diagnosis delay. Further understanding on the causes of patient and health-system delay is needed, as it can be used as a modifiable factor to reduce diagnostic delay and to improve the diagnostic process. Early MERS-CoV diagnosis remains a major challenge and may require more sensitive risk assessment tools to reduce avoidable delays, specifically those related to patients and health system.

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Competing interests

None declared.

Ethical approval

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