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ORIGINAL RESEARCH Estimation Of Direct Medical Costs Of Middle East **Respiratory Syndrome Coronavirus Infection: A** Single-Center Retrospective Chart Review Study

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Background: Among the countries affected by Middle East respiratory syndrome (MERS), Saudi Arabia was impacted the most, with 2,058 cases reported as of June 2019. However, the impact of the MERS epidemic on the Saudi economy is unknown.

Purpose: The present study aimed to evaluate the direct medical costs associated with the management of MERS cases at a tertiary referral hospital in Riyadh, Saudi Arabia.

Methods: The study involved a retrospective chart review of confirmed cases of MERS coronavirus (MERS-CoV) infections in a tertiary care referral center in Riyadh, Saudi Arabia, from January 2015 to October 2018. The collected data included sociodemographic characteristics, medical information, and the cost of hospitalization of each patient as estimated by micro-costing.

Results: A complete set of relevant information was available only for 24 of 44 identified MERS-CoV cases. Patients were mostly females, and the mean age was 52 years. Diabetes, hypertension, and chronic kidney disease were the most frequent comorbidities. The length of hospital stay varied from 1 to 31 days, averaging 4.96 ± 7.29 days. Two of the 24 patients died. The total cost of managing a MERS case at the hospital ranged from \$1278.41 to 75,987.95 with a mean cost of $12,947.03 \pm 19,923.14$.

Conclusion: The findings of this study highlight the enormous expenses incurred by the Saudi health care system due to the MERS-CoV outbreak and the importance of developing an enforceable nationwide policy to control MERS-CoV transmission and infection.

Keywords: Middle East respiratory syndrome coronavirus, costs and cost analysis, Saudi Arabia

Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in 2012 in Saudi Arabia among patients with severe respiratory disease.¹ Since the first cases of MERS emerged, a wide spectrum of disease severity, ranging from asymptomatic infection to fatal pneumonia, has been documented among the confirmed MERS-CoV cases.^{2,3} Initially, MERS-CoV predominantly affected middle-aged males; however, as the epidemic continued to spread, the gap between males and females has narrowed, and all age groups, from children to the elderly, have been affected.⁴⁻⁷ After an average incubation period of approximately 5 days,8 patients typically present with symptoms of lower respiratory tract infection, such as cough and shortness of breath often combined with nonspecific signs of the disease, such as fatigue, myalgia, fever, rhinorrhea, headaches, sore throat, vomiting, or diarrhea.⁹ In patients with pneumonia, MERS can rapidly

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progress to acute respiratory distress syndrome, acute renal failure, multi-organ failure, and death.^{9,10} Moreover, the presence of comorbidities such as diabetes, chronic kidney disease, and cardiovascular disease frequently leads to secondary complications, such as disseminated intravascular coagulation and hyperkalemia.^{11,12} On the other end of the spectrum, healthy immune-competent patients are more likely to have asymptomatic or mild infections which could have gone undetected and unreported.^{6,13}

The MERS-CoV is a positive-strand RNA virus, which through cross species transmission infects both humans and animals.^{14,15} The high propensity of MERS-CoV to cross species barriers is attributed to its ability to recombine and form new variants within the infected organism.¹⁶ This property of MERS-CoV, together with the lack of sufficient knowledge of the pathways by which the virus is transmitted to humans, is a matter of grave concern among virologists, public health researchers, and health activists.^{2,16} Despite a significant research effort in this area, the transmission of MERS-CoV is still puzzling many scientists and clinicians.¹⁷ One of the early hypotheses explaining the transmission of MERS-CoV from its natural host to humans raised the possibility that the virus may have originated in insectivorous bats.¹⁷ However, people do not commonly have contact with these species, particularly in the Arabian Peninsula where most cases have been reported.^{15,17,18} Conversely, human contacts with dromedary camels are commonplace in the Arabian Peninsula, especially in the regions with high reported incidence rates of MERS, suggesting that camels may be the source of human MERS-CoV infections.^{15,18,19} This possibility was supported by the detection of the MERS-CoV in lymph nodes of camels in one of the slaughterhouses in Qatar; this finding suggested that MERS-CoV could be present in the camel meat.²⁰ However, in an experiment involving infection of three camels with MERS-CoV, the virus was undetectable in their organs and the meat.²¹ Even if the camel meat is not associated with the transmission of the virus, almost two-thirds of the camels examined at a slaughterhouse in Qatar were shedding nasal excretion infected with MERS-CoV indicating the possibility of droplet transmission.²⁰ In agreement with this finding, MERS-CoV genomes were detected in nasal swabs collected from dromedaries in Oman, Saudi Arabia, Pakistan, Kuwait, Egypt, Iran, and Israel confirmed the presence of MERS-CoV genomes.¹⁴ Several cases of infection in Saudi Arabia and Qatar have been linked to drinking raw camel milk.^{4,14} Given the potential causal relationship between the consumption of camel-derived food products and MERS, and the fact that the virus can be easily destroyed by pasteurization,¹⁴ the World Health Organization (WHO) advised against the consumption of raw camel milk and uncooked camel meat.^{20,21} Additionally, the WHO strongly discouraged drinking camel urine, which also could represent a risk factor for MERS-CoV infection.^{22,23}

Although camels were implicated as the source of MERS-CoV transmission, the majority of the MERS patients did not come into close contact with camels or other livestock animals.²⁴ Conversely, the vast majority of MERS cases have been associated with health care settings,^{24–26} with a particularly high risk of contracting the infection in overcrowded emergency rooms.²⁷ In fact, most of the reported MERS-CoV cases in Saudi Arabia and South Korea were due to human-to-human transmission, which in most cases happened in the absence of adequate infection control measures in health care facilities.^{28,29} This mode of MERS-CoV transmission was confirmed both epidemiologically and by genetic documentation of the viruses implicated in hospital and household MERS outbreaks.¹⁶ Therefore, the importance of using the appropriate contact and droplet precautions in health care facilities cannot be overestimated.³⁰

According to the WHO, from April 2012 to June 2019, 2,449 laboratory-confirmed cases of MERS were reported, of which 2,058 cases were in Saudi Arabia resulting in a casefatality rate of 37.2%.³¹ The incidence of MERS continues to rise, with seven new cases reported in June 2019 alone from Saudi Arabia.³¹ Overall, the majority of cases occurred in health care facilities, however, the routes of direct or indirect zoonotic transmission of MERS-CoV remain unknown. At present, no vaccine or specific treatment is available, although serious attempts to develop preventive therapy are ongoing.³² According to the World Bank, the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) outbreak resulted in an estimated global economic cost of \$16 billion,⁵ and it is believed that the MERS-CoV infection toll on the overall global economy, and particularly the Saudi economy, will also be enormous. The 2015 MERS-CoV outbreak in South Korea resulted in an estimated economic loss of \$10 billion in the tourism sector alone.33 Although among countries affected by MERS Saudi Arabia was impacted the most, no effort was made to estimate the immense impact of this epidemic on either the macro- or microeconomic levels. Therefore, the aim of the present study was to evaluate the direct medical costs associated with the management of MERS-CoV cases at one of the tertiary referral hospitals in Riyadh, Saudi Arabia.

Materials And Methods

This was a retrospective chart review of confirmed cases of MERS-CoV in King Saud University Medical City, Riyadh, Saudi Arabia. The review covered all cases of MERS from January 2015 to October 2018. All confirmed cases of MERS-CoV that were diagnosed in the hospital or anywhere from the kingdom and were transferred to the hospital were collected. The collected data included sociodemographic characteristics (e.g., age, gender, marital status, nationality, employment in health care sector, and geographic region) as well as medical information (e.g., comorbidities, length of hospital stay, presenting symptoms, exposure to camels or their products or to a MERS case during the preceding 2 weeks, recent (2 weeks) hospitalization, and having H1N1 influenza prior to the admission).

Micro-costing was used to estimate the cost of hospitalization for each patient. These expenses were then used to calculate the mean cost for all of the confirmed MERS cases. The lowest, the highest, and the mean cost were used to project the direct medical cost of all MERS cases in the Kingdom. The information regarding items to be included in the cost analysis was retrieved from electronic medical records.

The expenses composed of the cost of personal protective equipment (e.g., N95 masks, gowns, protective eyewear), intravenous fluids and medications (e.g., antivirals, antibiotics, and other prescription medications), laboratory and diagnostic tests (e.g., CBC, liver and cardiac enzymes, swabs, cultures, chest X-rays and CT scans), room fees (e.g., isolation rooms, intensive care unit, extended care rooms), and health care professionals (physicians and nurses) expenses based on the ministry of health hourly rates. The inpatient costs were obtained from the cost center at the Saudi Arabian Ministry of Health, and the medication costs were obtained from the online drug database of the Saudi Food and Drug Authority (SFDA). The costs in Saudi riyals were converted to US dollars using the exchange rate of 1 USD=3.75 SAR.

The study was approved by the institutional review board of the College of Medicine at King Saud University, Riyadh, Saudi Arabia. The data are presented using descriptive statistics (mean, frequencies, and percentages). All analyses were conducted using the SAS statistical software (version 9.2, SAS Institute Inc., Cary, NC, USA).

Results

Patients

One hundred and forty-six patients reported to the hospital with symptoms consistent with MERS within the study

period. In 44 of them, MERS-CoV was confirmed. However, a complete set of relevant information was available only for 24 patients (Figure 1). Sociodemographic characteristics of the patients are listed in Table 1. The majority of patients were female (62.5%), and the mean age was 52.54 ± 11.27 years. More than half of the patients were married (54.17%), and more than one-third of them were divorced (37.50%). Saudi nationals constituted 62.50% of the study sample, and one-third of the patients were health care workers. Of the 24 MERS patients, 20 were from Riyadh, and one each from Al-Madinah, Al-Qaseem, Aseer, and Tabouk.

Medical Characteristics Of MERS Patients

The most frequent comorbidities among the patients were diabetes (58.33%), hypertension (37.50%), and chronic kidney disease (16.66%) (Table 2). A few number of patients suffered from coronary artery disease, liver disease, asthma, peripheral vascular disease, and cancer. Fever (50.00%), sore throat (41.67%), chills (41.67%), cough (37.50%), and runny nose (25.00%) were the most frequent presenting symptoms. Within the 2 weeks prior to hospital admission, one patient had contact with camels or their products, while 11 (45.83%) were exposed to a MERS case (Table 2). Three patients (12.5%) were hospitalized within the previous 2 weeks, two (8.33%) had acute respiratory distress syndrome, and four had H1N1 influenza. The length of hospital stay varied significantly, ranging from 1 to 31 days, with a mean of 4.96 ± 7.29 days. Two of the 24 patients died, and 22 were discharged (Table 2).

All but six patients were admitted to the hospital due to flu-like symptoms (Table 3). The remaining six patients were admitted for septic arthritis, abdominal pain and dysuria, black discoloration of toes, bleeding during pregnancy, and hyponatremia, which are not typically associated with the MERS-CoV infection. Patients presenting with flu-like symptoms were diagnosed with MERS on the day of admission, while in the other instances the time from admission to the diagnosis of MERS varied from 1 day (abdominal pain and dysuria, bleeding during pregnancy) to 6 days (black discoloration of toes) as shown in Table 3. Notably, 14 patients (58.3%) were discharged home within 24 hrs of their diagnosis.

Hospital Costs

The cost of hospitalization for the 24 patients is detailed in Table 4. The total cost of managing a MERS case at the hospital ranged from \$1278.41 to \$75,987.95 with a mean

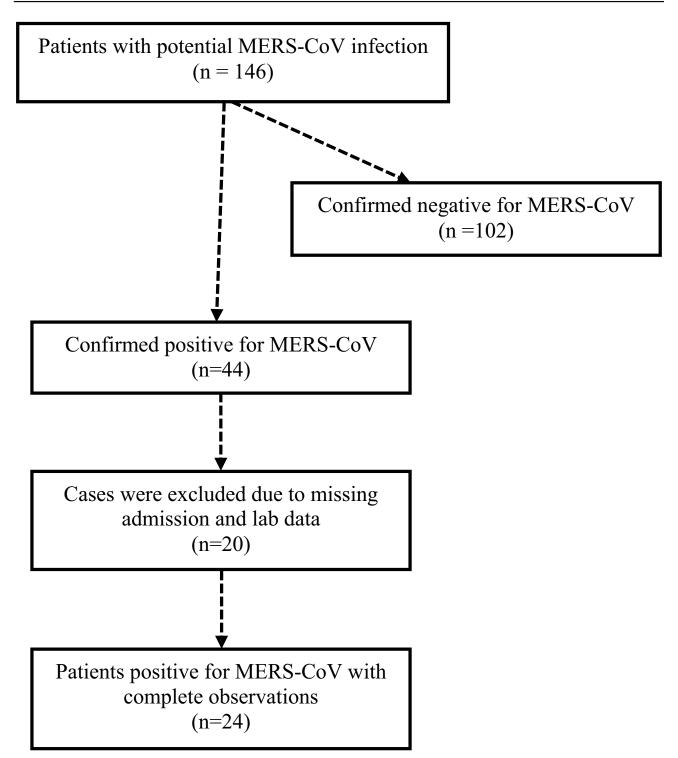


Figure 1 Patient recruitment scheme.

cost of $12,947.03 \pm 19,923.14$. The cost of care was under 20,000 in 75% of the patients, therefore, the median cost, 1867.30, was markedly lower than the mean, and the interquartile range was 2,839.03. Eight cases had hospitalization costs higher than the mean cost (\$12,947.03), which was largely due to the longer length of stay (5–31 days vs 1–5 days). Moreover, the percentage of patients with diabetes (87.5% vs 43.75\%), hypertension (75% vs 18.75\%) as well as those on mechanical ventilation (25% vs 0%), interferon and ribavirin (25% vs 0%),

Characteristics	Patients (N=24)
Gender	
Male, n (%)	9 (37.50)
Female, n (%)	15 (62.5)
Age, years; mean ± SD	52.54 ± 11.27
Marital status	
Single, n (%)	2 (8.33)
Married, n (%)	13 (54.17)
Divorced, n (%)	9 (37.50)
Nationality	
Saudi, n (%)	15 (62.50)
Non-Saudi, n (%)	9 (37.50)
Occupation	
Health care worker, n (%)	8 (33.33)
Other, n (%)	16 (66.67)
Region	
Riyadh, n (%)	20 (83.33)
Al-Madinah, n (%)	I (4.16)
Al-Qaseem, n (%)	I (4.16)
Aseer, n (%)	I (4.16)
Tabouk, n (%)	I (4.16)

 Table I Sociodemographic Characteristics Of The Patients

oseltamivir (50% vs.6.25%), and those with chronic kidney disease (37.5% vs 6.25%), and cancer (25% vs 6.25%) were higher among those cases compared to their counterparts with medical costs lower than the mean cost.

Discussion

Although some efforts in estimating the impact of MERS-CoV outbreak on selected sectors of the economy in some countries like South Korea have been made,³³ the direct medical costs of managing this epidemic that struck more than 24 countries and affected Saudi Arabia the most have not been estimated. The estimated costs of managing MERS cases in this study can be utilized to project the aggregate direct medical cost of managing MERS cases in Saudi Arabia. As of June 2019, 2058 cases of MERS were reported in the Kingdom.³¹ The cost of managing these patients at hospitals would range from \$2,630,967.78 (based on the lowest cost identified in the present analysis, i.e., 1278.41×2058 to 156,383,201.10 (based on the highest cost, i.e., $$75,987.95 \times 2058$) with a mean cost of \$26,644,987.74 (\$12,947.03 × 2058), and a median cost of \$3,842,903.4 (\$1867.30 × 2,058).

Table 2 Medical Characteristics Of The Patients

Characteristics	Patients (N=24)
Comorbidities	
Coronary artery disease, n (%)	l (4.16)
Hypertension, n (%)	9 (37.50)
Diabetes, n (%)	14 (58.33)
Chronic kidney disease, n (%)	4 (16.66)
Liver disease, n (%)	2 (8.33)
Asthma, n (%)	l (4.16)
Peripheral vascular disease, n (%)	l (4.16)
Cancer, n (%)	3 (12.50)
Presenting symptoms	
Fever, n (%)	12 (50)
Headache, n (%)	2 (8.33)
Cough, n (%)	9 (37.50)
Muscle aches, n (%)	l (4.16)
Difficulty breathing, n (%)	3 (12.50)
Runny nose, n (%)	6 (25)
Sore throat, n (%)	10 (41.67)
Weight loss, n (%)	2 (8.33)
Swelling, n (%)	l (4.16)
Pneumonia, n (%)	l (4.16)
Chills (shivering), n (%)	10 (41.67)
Exposure to camels or their products within the past two weeks, n (%)	(4.16)
Exposure to a MERS case within the past two weeks, n (%)	(45.83)
Prior hospitalization in the past two weeks, n (%)	3 (12.5)
Acute respiratory distress syndrome, n (%)	2 (8.33)
HINI influenza, n (%)	4 (16.67)
Length of stay, days; mean ± SD	4.96 ± 7.29
Died, n (%)	2 (8.33)
Discharged, n (%)	22 (91.67)

These estimates include only the cost of inpatient MERS cases management and do not consider the costs associated with the implementation of infection control policies that were implemented right after the MERS-CoV outbreak, such as the cost of shutting down certain hospital wards.³ Moreover, it must be acknowledged that projected cost estimates in managing MERS cases in Saudi Arabia were based on expenses incurred for 24 MERS cases only and do not represent the diverse cases of MERS in the country. Despite these limitations, it should be emphasized that this is the first effort to highlight the direct medical cost of managing MERS cases in Saudi Arabia, a country where more than 80% of MERS cases were reported.³¹

Patient	Reason For Admission	Date Of Diagnosis After Admission	Length Of Stay	Status
1	Flu-like symptoms	Day I	17 days	Died
2	Flu-like symptoms	Day I	l day	Discharged
3	Flu-like symptoms	Day I	l day	Discharged
4	Flu-like symptoms	Day I	l day	Discharged
5	Flu-like symptoms	Day I	l day	Discharged
6	Septic arthritis	Day 3	15 days	Discharged
7	Abdominal pain and dysuria	Day I	2 days	Discharged
8	Flu-like symptoms	Day I	l day	Discharged
9	Black discoloration of toes	Day 6	10 days	Died
10	Flu-like symptoms	Day I	l day	Discharged
11	Flu-like symptoms	Day I	2 days	Discharged
12	Flu-like symptoms	Day I	l day	Discharged
13	Flu-like symptoms	Day I	l day	Discharged
14	Flu-like symptoms	Day I	l day	Discharged
15	Came for a scheduled surgical procedure	Day 4	5 days	Discharged
16	Flu-like symptoms	Day I	l day	Discharged
17	Bleeding during pregnancy	Day I	l day	Discharged
18	Hyponatremia	Day 3	8 days	Discharged
19	Flu-like symptoms	Day I	l day	Discharged
20	Flu-like symptoms	Day I	l day	Discharged
21	Flu-like symptoms	Day I	l day	Discharged
22	Flu-like symptoms	Day I	10 days	Discharged
23	Flu-like symptoms	Day I	5 days	Discharged
24	Flu-like symptoms	Day I	31 days	Discharged

Table 3 Reason For Admission And Time Of Diagnosis

Most of the patients in the study sample had chronic health conditions, such as diabetes (58%), hypertension (37%), chronic kidney disease (17%), and cancer (12%). This is in agreement with the previously published studies which showed a significant relationship between multiple comorbidities and MERS-CoV infection.¹⁷ Moreover, the mean age of the patients was over 50 years which is also consistent with the notion that MERS-CoV rarely affects children and young adults.⁹ Notably, the low rate of mortality among the study sample (8.33%) was significantly lower than the average mortality rate reported in the literature (35–40%).^{9,31} This difference may be largely attributable to the small sample size and relatively short length of hospital stay of patients in the present investigation compared with previously published studies (Table 4).

The findings of this study underscore numerous issues and shortcomings within the Saudi health care system. Onethird of the patients included in the analysis were health care workers. The presence of such a high percentage of health professionals among MERS patients raises serious questions regarding the effectiveness and/or enforcement of infection control policies in hospitals. Moreover, it exposes the lack of response among decision makers to past calls for improvement,^{25,26} providing a grim outlook for the future. The inadequate prevention of nosocomial infections is further underlined by the fact that four of the 24 MERS cases (16.67%) were admitted for symptoms that were not related to MERS infection, and the disease was identified three to 6 days later, suggesting that those patients caught the infection during their hospitalization, which questions again the effectiveness of the hospital infection control policy. Additionally, the unavailability of the data for 20 out of 44 MERS cases unveils poor documentation practices and lack of mandatory management protocols (Figure 1).

Although several studies have pointed to a strong association between the contact with camels and MERS-CoV infection,^{4,9,20} only one of the 24 MERS cases (4.17%) reported an exposure to camels or their products, while 11 cases (45.83%) reported being in contact with a MERS-CoV case within 2 weeks prior to their diagnosis with MERS. The high prevalence of MERS-CoV infections caused by humanto-human contact calls into question the effectiveness of infection control policies at the national level and reveals the inadequacy of the preventive measures taken by the Saudi Ministry of Health that persists after more than 3 years of the MERS-CoV outbreak.²⁵ In fact, the current analysis

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	ICU-Room, days at \$320.00/day	3																							
	Extended Care, days at \$666.67/day	17					15	2		10		2	_			5			8				01	2	31
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	ESR+CRP, \$37.33	17					15									5									
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Table 4 Direct Medical Cost Breakdown For The 24 Cases Of MERS

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estimation. Abbreviations electrocardiogr	estmation. Abbreviations: LOS, length of stay: ISO-Room, isolation room; ICU-Room, intensive care unit; HCW, health care workers; PPE, personal protective equipment; CBC, complete blood count; U&E, urea and electrolytes; ECG, electrocardiogram; RFT, renal function test; LFT, liver function test; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CT, computed tomography; AFB, Acid-Fast Bacilli.	tion ro inction	om; l(test; l	CU-Ro 5SR, er	om, in 'ythroc	tensive :yte sec	diment	unit; H ttion ra	CV, hí íte; CR	salth ca P, C-rea	ire wor active p	kers; PP rotein; C	E, persc CT, com	onal pro puted to	otective Smograp	equipme shy; AFE	∍nt; CB(Acid-F	C, comp ast Baci	lete blc IIi.	noo por	ınt; U&l	E, urea	and ele	ctrolyte	es; ECG

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identified 13 cases (54%) that were discharged within one day of their MERS diagnosis mainly due to the lack of available treatment and the fear of nosocomial transmission. However, the decision to discharge those patients could increase the risk of MERS-CoV transmission outside the hospital, particularly to those at higher risk, such as immunocompromised patients with diabetes and other health conditions prevalent in Saudi Arabia.³⁴ This is concerning given that approximately 46% of the cases were exposed to a MERS case within the past 2 weeks prior to their admission. To control the transmission of MERS-CoV, patients diagnosed with MERS should have been quarantined, an intervention that was successfully implemented in South Korea to contain MERS-CoV outbreak in 2015.^{27,35} The failure to isolate sick patients contributes significantly to the perpetual problem in containing this epidemic that the Saudi health system is still grappling with. Lastly, as a part of the present investigation, a significant effort has been made to review more cases from multiple referral centers. However, these attempts went in vain. The lack of transparency in the management of MERS-CoV infections by some health care facilities in Saudi Arabia is alarming. Notably, the mismanagement of MERS epidemic in Saudi Arabia was highlighted in the press.³⁶

Conclusion

The findings of this study highlight the enormous expenses incurred by the Saudi health system due to the MERS-CoV outbreak. Although the accuracy of the direct medical cost estimation presented in this study is limited since it was merely a review of medical charts for 24 patients, an extensive effort was made to identify all relevant data about each eligible patient and capture every single cost item. To improve the accuracy of the current analysis on direct medical cost estimation for MERS patients, health researchers should be granted access to the medical files of all MERS cases. This may help in highlighting the deficiencies in the infection control policies. Finally, an enforceable nationwide policy for infection control, and standardized protocols for the management of MERS-CoV infections should be implemented.

Abbreviations

MERS-CoV, Middle East respiratory syndrome coronavirus; MERS, Middle East respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; WHO, World Health Organization; SFDA, Saudi Food and Drug Authority; USD, United States dollars.

Table 4 (Continued)

Ethics Statement

Ethical approval for this study was obtained from the institutional review board of the College of Medicine at King Saud University, Riyadh, Saudi Arabia (project number E-18-3008). No personal identifiers were collected and all data were coded to protect the confidentiality of the patients, in compliance with the Declaration of Helsinki. Furthermore, the need for written informed consent was waived, as per the institution policy, since the study was a retrospective chart review and did not involve any patient interviews.

Data Sharing Statement

Study data are available from the authors upon reasonable request.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval for the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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