IDCases 24 (2021) e01161

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Middle East respiratory syndrome coronavirus infection profile in Qatar: An 8-year experience

Fatma Ben Abid[a,b,*], Nada El-Maki[a], Hussam Alsoub[a,b], Muna Al Masalmani[a,b], Abdullatif Al-Khal[a,b,c], Peter Valentine Coyle[d], Mohamed Ali Ben Hadj Kacem[d], Hafedh AlGazwani[e], Mohammed Al-Thani[f], Hamad Eid Al-Romaihi[f], Mohammed Al-Hajri[f], Farag Elmoubashar[f]

[a] Department of Medicine, Division of Infectious Diseases, Hamad Medical Corporation, Doha, Qatar
[b] Weill Cornell Medical College, Doha, Qatar
[c] College of Medicine, Qatar University, Qatar
[d] Section of Virology and Molecular Biology, Department of Laboratory Medicine and Pathology, Hamad Medical Corporation, Doha, Qatar
[e] Department of Medicine, Hamad Medical Corporation, Doha, Qatar
[f] Ministry of Public Health, Qatar

ARTICLE INFO

Article history:
Received 20 September 2020
Received in revised form 12 May 2021
Accepted 13 May 2021

Keywords:
MERS-CoV
Pneumonia
ARDS
Dromedary camels
Case fatality
RT-PCR

ABSTRACT

The Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in 2012. The objective of the study was to describe the epidemiology, risk factors, clinical characteristics, and outcome of MERS-CoV in Qatar. A total of 28 cases of MERS-CoV were identified, corresponding to an incidence of 1.7 per 1,000,000 population. Most patients had a history of contact with camels 15, travel to Kingdom of Saudi Arabia 7 or known contact with individuals with confirmed MERS-CoV infection 7. Majority of patients had acute kidney injury (AKI) 17 and 9 needed renal replacement therapy. All patients were hospitalized, 14 required critical care support. Overall, total of 10 died. The immediate cause of death was multiorgan failure with acute respiratory syndrome (ARDS) 9. MERS-CoV is a rare infection in the State of Qatar. There was no hospital outbreaks or healthcare worker reported infection. The infection causes severe respiratory failure and acute renal failure. Patients with AKI and on ventilator support carry higher risk of mortality.

Introduction

Middle East Respiratory Syndrome Coronavirus (MERS-CoV), the cause of Middle East Respiratory Syndrome (MERS), is a novel betacoronavirus that was first isolated from a patient with severe pneumonia in Jeddah, Saudi Arabia in 2012 [1]. MERS was subsequently reported from other cities in Saudi Arabia, Qatar, Bahrain, Kuwait, and the United Arab Emirates (UAE). Outside the Middle East, travel-associated MERS was reported with incidents of limited local person-to-person transmission were also reported. In South Korea, a single travel-related case resulted in a large nosocomial MERS outbreak [2]. To date, the total number of MERS cases reported to the World Health Organization (WHO) has exceeded 2,500, nearly 80 % of which were reported from Saudi Arabia.

The reported overall case fatality rate is 35 % [3]. It has been proven that MERS-CoV infection can be transmitted through contact with infected dromedary camels or through human-to-human transmission in particular household contacts, or contact with patients and healthcare workers [4,5]. It is not clear whether asymptomatic patients can transmit the virus or not. We herein describe the epidemiology, risk factors, clinical characteristics and clinical outcomes of MERS in Qatar.

Materials and methods

Study design and population

Laboratory diagnosis of MERS-CoV in Qatar is provided by the National Central Virology Laboratory, Hamad Medical Corporation (HMC) and the registry of the Ministry of Public Health, Qatar. We retrospectively retrieved the demographic data, epidemiological, clinical, laboratory data for all patients with laboratory-confirmed MERS-CoV infection in Qatar diagnosed during the period from

* Corresponding author at: Department of Medicine, PO Box 3050, Doha, Qatar.
E-mail address: bafatma@hotmail.com (F. Ben Abid).

http://dx.doi.org/10.1016/j.idcr.2021.e01161

January 1, 2012, through July 31, 2020. All patients were followed until their discharge or death and their outcome data were collected.

In terms of controlling the viral spread, the Ministry of Public Health (MOPH) in collaboration with Qatar national Outbreak Control Taskforce (OCT) along with animal health sector since the first case in 2012 have done the following:

1 MOPH team had monitored daily all identified contacts of MERS-CoV patients for the appearance of any MERS-CoV related symptoms (such as fever, respiratory or gastrointestinal symptoms . . .) over a period of 14 days following their last exposure. Upon identification of MERS-CoV confirmed cases, all patients were admitted to the hospital and stringent infection prevention and control measures were implemented and followed according to WHO guidelines. The contact and airborne isolation were only removed once two consecutive 48 h apart RT-PCR tests for MERS-CoV were negative.
2 The (OCT) along with animal health sector had put robust camel farm biosecurity measures. For instance, once a confirmed camel contact was reported, the veterinary teams were testing all camels that the patient had possible contact with them in their barns or during camel show competitions or camel market. Once confirmed positive for MERS-CoV infection, the camel was isolated for 2 weeks.
3 Regarding the management of patients, the hospital protocol for pneumonia and acute respiratory distress syndrome were followed. There were no particular established guidelines for MERS-CoV pneumonia during the study period in HMC.

Virology method

Nasal, and/or nasopharyngeal, and/or sputum and/or endotracheal aspirate samples were collected from patients and contacts then sent to virology laboratory in universal or viral transport medium. The test method used is based on a qualitative real time polymerase chain reaction (RT-PCR) with a commercial kit (Fast Track Diagnostics qualitative EMC (MERS-CoV) assay) on ABI 7500 analyzer. The kit is targeting the UpE gene for screening and Orf 1a gene for confirmation. These tests were done in the Section of Virology and Molecular Biology, Department of Pathology and Laboratory Medicine (DPLM) in Hamad Medical Corporation, Qatar.

Definitions

The definition and staging of acute Kidney injury (AKI) was based on the Kidney Disease: Improving Global Outcomes (KIDGO) [6]:

- Definition of AKI:
- Increase in serum creatinine by $\geq$ 0.3 mg/dL within 48 h, or
- AKI staging:
- Stage 1: increase in serum creatinine to 1.5–1.9 times baseline
- Stage 2: increase in serum creatinine to 2–2.9 times baseline
- Stage 3: increase in serum creatinine to $\geq$ 3 times baseline

Statistical methods

Descriptive statistics were performed to summarize patients demographic, epidemiological, clinical and laboratory characteristics. Median and range were described for the continuous variables with normal distribution. Frequencies and proportions were used for categorical variables. Intergroup difference was compared using the *t*-test or Wilcoxon signed-rank test for continuous variables nonparametric variables (e.g., admission length), and the x2 test or Fisher exact test for categorical variables (e.g, gender), as appropriate. Multivariate logistic regression analysis were performed to evaluate the impact of age, gender, comorbidities, EGFR, ventilatory support during hospitalization between patients who died at the end of admission to those who were discharged alive. Correlation between variables was examined using Spearman and Pearson correlation coefficient when appropriate were used to look for any correlations between possible risk factors baseline characteristics, AKI and mortality.

Survival analyses were plotted by using the Kaplan-Meier method to determine the cumulative survival probability, and overall survival time was calculated from the time of hospital discharge to the date of death from any cause or the date at which the patient was last known alive. A p-value of 0.05 or less indicates statistical significance. We used STATA version 12.0 (Statacorp, College Station, TX, USA) for exploratory data analysis and descriptive statistics

Results

A total of 110,823 MERS-CoV RT-PCR tests were performed on all suspected cases of MERS-CoV and all possible contacts of confirmed MERS-CoV cases. We identified a total of 28 laboratory-confirmed MERS-CoV cases during the study period with scattered distribution over the years (Fig. 1). The annual incidence was 1.7 per 1,000,000 population. Patient demographics and clinical characteristics are summarized in (Table 1). Males constituted the vast majority of cases, 25 (89 %), and the median age was 52.5 years (range 22–74), majority of ages were more than 40 years, 19 (68 %). Of note, there were no reported pediatric or pregnant women MERS-CoV infection cases. Furthermore, there have not been any healthcare-associated MERS outbreak in Qatar.

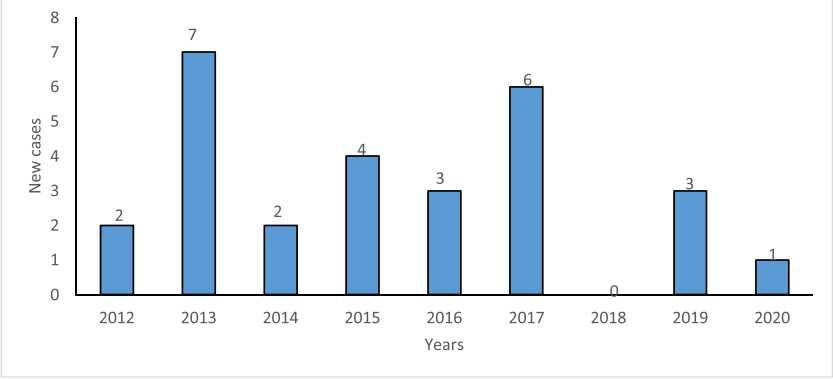

Fig. 1. Yearly distribution of MERS-CoV confirmed cases in Qatar.

Table 1
Demographic, clinical characteristics and outcome of patients with MERS-CoV infection.

Variables	All patients N (%) or median (range)	Survivors N (%) or median (range)	Non-Survivors N (%) or median (range)	*P* value
Total number of MERS-CoV confirmed cases	28	18	10	
Male/Female	25/3	17/1	8/2	0.03
Qataris	15 (54)	8	7	0.42
South East Asia region	8 (29)	6	2	
African region	5 (18)	4	1	
Age, Median/range, years	52.5 (22–73)	43.4 (22–71)	60.5 (29–73)	0.013
Possible risk factors for MERS-CoV infection				
Direct contact with camels	15 (54)	11	4	0.28
Travel KSA	7 (25)	4	3	0.64
Contact with confirmed MERS-CoV case	7 (25)	6	1	0.17
Shepherd at the camel barn	7 (25)	5	2	0.648
Camel race	3 (11)	2	1	0.92
Raw camel milk ingestion	2 (7)	2	0	0.40
Comorbidities				
Presence of $\geq$ 1 comorbidities	17 (60.7)	7	10	0.001
Diabetes Mellitus	10 (36)	4	6	0.048
Hypertension	8 (29)	2	6	0.011
Coronary artery disease	6 (21)	2	4	0.08
Hyperlipidemia	5 (18)	3	2	0.37
Obesity	3 (11)	2	1	0.46
Hypothyroidism	2 (7)	1	1	0.47
Chronic kidney disease	1 (4)	1	0	0.64
Asthma	1 (4)	1	0	0.64
Obstructive sleep apnea	1 (4)	1	0	0.64
Renal transplant recipient	1 (4)	0	1	0.35
Smoking	8 (29)	8	0	0.01
Symptoms on admission				
Fever	24 (85)	15	9	0.80
Cough	22 (79)	14	8	0.81
Shortness of breath	11 (39)	15	7	0.41
Hemoptysis	3 (11)	3	0	0.28
Abdominal pain	4 (14)	3	1	0.39
Diarrhea	2 (7)	0	2	0.11
Vomiting	1 (4)	1	0	0.64
Headache	1 (4)	1	0	0.64
No symptoms	3 (11)	3	0	0.24
Symptoms duration prior to hospital admission, Median/range in days	4.5 (0–12)	4.44 (0–10)	5.7 (1–12)	0.47
Signs on admission				
Oxygen saturation <90 %	14 (50 %)	4	10	< 0.001
Systolic blood pressure <90 mmHg	9 (32 %)	1	8	< 0.001
Laboratory on admission	Median(range)			
Seroconversion from first positive to first 2 negative RT-PCR (days)	14 (4–30)	13.2 (5–25)	17 (4–30)	0.57
Peripheral white blood cell count (WBC) ($x10^3$/uL)	5.2 (2.0–10.3)	7.1 (7.7–21)	7.1(2.7–15.5)	0.911
Platelets count ($< 150 \times 10^3$//uL)	12 (42.8 %)	6	6	0.12
Procalcitonin (ng/mL)	0.41 (0.05–2.42)	0.14 (0.05–0.29)	0.19 (0.05–2.3)	0.624
Creatinine (μmol/L)	69(47–131)	67(51–131)	69(47–129)	0.675
Alanine aminotransferase (ALT) (IU/L)	76(8–6000)	47(8–476)	126(50–6000)	0.548
Aspartate aminotransferase (AST) (IU/L)	102 (18–6309)	65(29–120)	102(18–16309)	0.131
Chest X-ray infiltrates on admission	20 (71 %)	10 (55.5)	10 (100)	0.01
Treatment and Clinical outcome	N (%)			
Admission duration median/range in days	16 (4–97)	19 (4–97)	14 (8–43)	0.356
Intensive care unit admission	15 (53)	5 (28)	10 (100)	0.01
Acute respiratory distress syndrome	13 (46)	4 (14)	9 (90)	< 0.001
Ventilator support	15 (53)			
Mechanical ventilation	9 (32)	2	7	0.04
Extracorporeal	2 (7)	0	2	
membrane oxygenation	4 (14)	3	1	
Non-invasive mechanical ventilation				
Acute kidney injury	17 (61)	7	10	< 0.001
(AKI) total	3 (17.6)	3	0	
AKI stage 1[a]	2 (11.8)	2	0	
AKI stage 2[a]	12 (70.6)	2	10	
AKI stage 3[a]				
Hemodialysis	9 (32)	1	8	< 0.001

[a] Acute kidney injury staging according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

All cases were residents in Qatar. Fifteen (54 %) of the total MERS cases were in Qataris, whereas 8 (29 %) were in individuals of South East Asian nationalities, and 5 (18 %) in individuals of African origin. There were 15 (54 %) cases with history of direct contact with camels, among whom 7 (25 %) were shepherds, 5 (18 %) were camel farm owners and 3 (11 %) were involved in camel racing. Seven (25 %) cases had contact with MERS-CoV-infected patient among whom 5 (18 %) were identified during contact tracing. Seven (25 %) had travel history to Saudi Arabia within two weeks of onset of their MERS symptoms. The first MERS case in Qatar was reported in October 2012. There were no cases from February 2017 to October 2019. In November 2019, a family cluster of three individuals included a fatal case in a 67-year old mother, and cases in her 50-year old son and 32-year old housemaid. The son and the housemaid had mild disease and fully recovered. We were not able to identify any history of contact with camels or travel to endemic MERS-CoV regions. The last case was a reported in February 2020.

Eight patients (29 %) were smokers and 17 (61 %) had at least one comorbidity where diabetes mellitus (DM) was the most common, followed by hypertension (HTN), coronary artery disease, hyperlipidemia and obesity. One patient was a kidney transplant recipient and was on immunosuppressive therapy. The median symptoms duration to health care facility presentation was 4.5 days (range 0–12). Most of the patients presented with fever, followed by cough, dyspnea, hemoptysis and diarrhea. All patients were hospitalized with a median hospital stay 16 days (range 4–97). Median laboratory findings at the time of hospitalization included peripheral white blood cell count (WBC) of 5200/μL (range 2000–10,300/uL), alanine aminotransferase (ALT) of 76 U/L (range 8–6000 U/L), aspartate aminotransferase (AST) IU/L of 102 (18–6309 IU/L), and procalcitonin of 0.41 ng/mL (range 0.05–2.42 ng/mL). Thrombocytopenia was seen in 12 (42.8 %), high liver enzymes, AST > 30 IU/L and ALT > 40 was seen in 23(82 %) and 21(75 %) respectively. The median conversion time from first positive RT-PCR for MERS-CoV to first two consecutive negative RT-PCR results was 14 days (range 4–30 days). Prolonged conversion time was mainly seen in sick and immunocompromised patients.

Twenty patients (71 %) had lung infiltrates on chest x-ray at admission. The chest radiography and computed tomography findings were consisting of patchy to confluent infiltrate primarily involving the lower and mid zones bilaterally and progressing to involve the upper lobes and sometimes complicated by pleural effusion. Twelve patients (43 %) with bilateral lung infiltrates had progressed to acute respiratory distress syndrome (ARDS), multi-organ failure, 15(53 %) needed ventilator support and ICU admission, 9(32 %) were intubated and mechanically ventilated and 2(7%) needed extracorporeal membrane oxygenation. Seventeen (61 %) patients developed acute kidney injury (AKI), where 6 (33.3 %), 1 (5.5 %), and 11 (61.1 %) had stage 1, stage 2 and stage 3 AKI respectively according to the KIDGO criteria. Nine (32 %) patients required hemodialysis, among whom only one survived. We compared characteristics and outcome of patients who developed AKI and non-AKI, summarized in (Table 2). Patients with AKI group were older than patients in non-AKI group ($P < 0.001$), had at least one comorbidity ($P < 0.001$). Longer symptoms duration prior to hospitalization was observed in AKI group ($P < 0.027$). AKI patients had a lower estimated glomerular filtration rate (eGFR) on admission as compared to non-AKI ($P < 0.013$). There were no deaths in non-AKI group.

Twelve (43 %) cases of MERS-CoV infections were complicated by bacterial and fungal infections. 5 (18 %) had bacteremia, two patients had community acquired bacteremia, *Streptococcus intermedius* and *Enterococcus avium*. The former patient died at day 13 from the bacteremia. One patient had polymicrobial bacteremia, *Klebsiella pneumoniae* (*K. pneumoniae*) sensitive strain

Table 2
Comparison of baseline characteristics between acute kidney injury (AKI) and non-AKI groups.

Variables	All patients N = 28 (%)	AKI N = 17(%)	Non-AKI N = 11 (%)	*P* value
Age, Median/range, years	28	51.5+/-14.8	49.6+/-17.7	< 0.001
Male	25 (89)	15	10	0.36
Comorbidities				
Presence of ≥ 1 comorbidities	17	15	2	< 0.001
Diabetes Mellitus	10 (36)	8	2	0.10
Hypertension	8 (29)	8	0	< 0.001
Coronary artery disease	6 (21)	6	0	0.03
Hyperlipidemia	5 (18)	4	1	0.26
Obesity	3 (11)	3	0	0.20
Renal transplant recipient	1 (4)	1	0	0.60
Smoking	8 (29)	8	0	< 0.001
Symptoms duration prior to hospital admission, Median/range in days	4 (1–12)	5.4 (1–12)	3.1(0–10)	0.027
Signs on admission				
Oxygen saturation ≤ 90 %	14 (50 %)	13	1	< 0.001
Systolic blood pressure ≤ 90 mmHg	9 (32 %)	9	0	< 0.001
Laboratory on admission	Median (range)			
eGFR at admission	127(37–144)	86 (37–144)	123 (63–123)	0.013
Lowest eGFR during admission	49(7–117)	13.7 (7–72.9)	90 (58–117)	< 0.001
WBC	5.2 (2.0–9)	4.7 (2–9.5)	5.36 (2–10.3)	0.41
AST > 30	23	19	4	< 0.001
ALT>40	21	20	1	< 0.001
Bilirubin >20	10	9	1	< 0.001
Clinical outcome				
Died	10 (36)	10 (58)	0	< 0.001
Admission duration median/range in days	15 (4–97)	28.6 (6–97)	14.6 (4–36)	0.05
Intensive care unit admission	15 (53)	14 (82)	1(1)	< 0.001
Ventilator support	15 (53)	14 (82)	1 (1)	< 0.001
Mechanical ventilation	9 (32)	11 (65)	0	
Extracorporeal membrane oxygenation	2 (7)	2 (11.7)	0	
Non-invasive mechanical ventilation	4 (14)	3 (17.6)	1 (1)	< 0.001

Table 3
Treatment given during hospitalization, comparison between the two groups of survivors and non-survivors.

Variables	All patients N = 28 (%)	Survivors N = 18 (%)	Non-survivors N = 10 (%)	*P* value
Antibiotics given on admission	20 (71.4)	11 (61)	9 (90)	0.104
Azithromycin alone	3 (10.7)	1(5)	2 (20)	0.68
Moxifloxacin alone	3 (10.7)	2 (11.1)	1 (10)	
Ceftriaxone + Azithromycin	14 (50)	8 (44.4)	6 (60)	
Antibiotic given >1 day from admission				
Piperacillin-tazobactam	3 (10.7)	2 (11.1)	1 (10)	0.39
Meropenem	8 (28.5)	0	8 (80)	
Linezolid	8 (28.5)	1 (5.55)	7 (70)	
Vancomycin	5 (17.8)	2 (11.1)	3 (30)	
Antifungal	7 (42)	2 (11.1)	7 (70)	
Anidulafungin	5 (17.8)	1 (5.55)	4 (40)	0.21
Amphotericin liposomal	1 (3.5)	1 (5.55)	0	
Fluconazole	1 (3.5)	0	1 (10)	
Antiviral				
Oseltamivir	18 (64.2)	9 (50)	9 (90)	0.73
PEGylated interferon alpha	1 (3.5)	1 (5.55)	0	
PEGylated interferon alpha + Ribavirin	1 (3.5)	0	1 (10)	
Corticosteroids				
Hydrocortisone/or methylprednisolone	9 (32.1)	3 (16.6)	6 (60)	0.184
Vasopressors	12 (42.8)	2 (11.1)	10 (100)	< 0.001

and *Stenotrophomonas maltophilia* and died at day 12 post bacteremia. One patient had *K. pneumoniae* and *Leuconostoc lactis*. The *K. pneumoniae* was carbapenem resistant enterobacterales, the patient was treated successfully and discharged at day 97 from admission. One patient had initially *Pseudomonas aeruginosa* bacteremia complicated one week later by *Candida parapsilosis* fungemia which was treated successfully. Antiviral and antibacterial treatments given during hospitalization of MERS-CoV cases are presented in (Table 3). All patients with abnormal chest x-ray on admission, 21 (75 %) were started empirically on one or more antibacterials, 18 (64 %) patients received oseltamivir, one patient received a combination of pegylated interferon alpha and ribavirin and one patient pegylated interferon alpha alone. Both patients had already prolonged stay in intensive care unit and were critically sick and died within few days after the start of treatment. The case fatality rate was 36 % (10 patients). Deceased patient's characteristics were summarized in (Table 5). Compared to survivors, non-survivors were older, had at least one or more underlying comorbidities, all had oxygen saturation below 90 % on room air, 8 (80 %) had hypotension on admission. All deceased patients had stage 3 AKI on admission and 9 (90 %) needed continuous renal replacement therapy (CRRT). All 10 patients needed respiratory support and were admitted to intensive care unit with a median length of stay from admission to death 14 (8–43 range). A multivariate analysis of factors influencing mortality was done and found that ventilator support and AKI was significantly associated with mortality (HR 5.12, 95 % CI (1.57–16.67), *P* value 0.0006 and 4.43 (1.29–15.22), *P* value 0.0018 respectively (Table 4) (Fig. 2).

One of the deceased patients had, at day 17 of admission, subarachnoid hemorrhage and mild subdural hemorrhage noted along the falx (Fig. 3). The patient was having underlying hypertension and coronary artery disease. His blood pressure was well controlled, and his coagulation profile and platelets remained within normal limits during his hospital stay. It was not clear what have caused the subarachnoid hemorrhage.

Discussion

We described the epidemiology, demographics, clinical characteristics and clinical outcomes of patients with confirmed MERS-CoV infection in Qatar. The incidence of MERS-CoV is very low in Qatar as compared to in KSA, 3.49 per 100 000 (95 % CI 3.09–3.95) [5]. This study showed that the total number of confirmed MERS-CoV infection was limited to only 28 cases over the last nine years. Knowing the natural reservoir and the mode of transmission is of paramount importance to control the spread of MERS-CoV. It has proven that dromedary camels are the main reservoir for MERS-CoV, and human can acquire the infection through direct or indirect contact with infected dromedary camels through their nasal secretions or their products such as milk [7,8]. Reusken et al. have found that viable MERS-CoV RNA is present in raw milk expressed from infected camels [8]. It is not clear whether the virus is excreted into milk or just a contamination from other body secretions of infected camels [9]. In the absence of appropriate infection control measures when dealing with infected MERS-CoV camels, the environment surrounding the camel can become contaminated with viable virus [9,10]. Therefore, the WHO advises to avoid consumption of unpasteurized camel milk [11].

Human-to-human MERS-CoV transmission among close contacts has been well documented in previous reports and has occurred mainly in healthcare settings reaching up to 50 % of all confirmed MERS-CoV cases in some reports [7,12]. Hospital outbreaks were mostly attributed to late identification and diagnosis of MERS-CoV cases, hospital's overcrowding and breaching in infection control measures [13–15]. The absence of hospital outbreaks in Qatar was most likely due to early identification of suspected cases, extensive contact tracing, follow

Table 4
Multivariate analysis of factors influencing mortality in all patients.

Variable	HR (95 %)	*P* value
Age	0.97(0.65–1.4)	0.886
Gender	0000	0.99999
CKD	0.24(0.17–3.64)	0.31
Diabetes	7.76(0.07–7.65)	0.82
Hypertension	1.35(0.13–14.03)	0.79
Comorbidities	9.93(0.34–2.87)	0.99
EGFR	0.92(0.06–13.60)	0.95
Hypotension on admission	1.5(0.00–2.87)	1.000
Ventilatory support	5.12(1.57–16.67)	0.0006
AKI	4.43(1.29–15.22)	0.0018

Table 5
Summary of deceased MERS-cases.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Year of MERS infection	2012	2013	2013	2013	2013	2015	2016	2017	2019	2020
Age/gender	49/M	29/M	56/F	48/M	62/M	73/M	66/M	59/M	67/F	64/M
Comorbidities	Hyperlipidemia	Asthma, obesity	DM, HTN, hyperlipidemia	HTN, CAD	HTN	DM, HTN, CAD	DM, HTN, CAD, renal transplant	DM	DM, HTN, hypothyroidism	DM, HTN, CAD, OSA, obese
Duration of hospitalization (days)	43	14	8	21	8	13	14	37	15	25
Symptoms duration before hospitalization	12	3	3	7	7	3	4	10	7	1
Admitting Symptoms	Fever, cough	Fever, cough, SOB	Fever, cough, SOB	Fever	Fever, cough SOB	Fever, cough, SOB, diarrhea	Fever, cough, SOB, diarrhea	Fever, cough, abdominal pain	Fever, cough, SOB	Fever, SOB
BP $\leq$90 mmhg on admission	Yes	yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
SpO2 $\leq$ 90 % on admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AKI/stage	Yes/3	Yes/3	Yes/3	Yes/3	Yes/3	Yes/3	Yes/3	Yes/3	Yes/3	Yes/3
RRT	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Drop of Platelets $\leq$150 from baseline	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Increase of ALT >30	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Increase of AST > 40	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ICU admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Admission's CHEST X-RAY	Bilateral infiltrates	Bilateral infiltrates	Bilateral infiltrates	Bilateral infiltrates	Bilateral infiltrates	Unilateral infiltrate	Unilateral infiltrate	Bilateral infiltrates	Bilateral infiltrates	Bilateral infiltrates
ARDS	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
MV/ECMO/NIV	ECMO	MV	MV	MV	MV	NIV	MV	MV	MV	ECMO
Hospital acquired infection	none	none	none	none	none	Enterococcus avium bacteremia	none	K.pneumonia and STM bacteremia	none	VAP pseudomonas aerogenosa
Antibiotics received on admission	Ceftriaxone +azithromycin	Meropenem+ linezolid	Azithromycin + meropenem	Azithromycin	Ceftriaxone +azithromycin	moxifloxacin	Ceftriaxone +azithromycin	Ceftriaxone +azithromycin	Ceftriaxone +azithromycin	Ceftriaxone +azithromycin
Antibiotics after > 1 day of admission	Piperacillin-Tazobactam +linezolid	Meropenem+ linezolid	Meropenem+ linezolid	Meropenem+ linezolid	Meropenem +linezolid	Meropenem +vancomycin	Meropenem+ linezolid	Meropenem +vancomycin	Meropenem + linezolid	Meropenem +vancomycin
Antiviral	Oseltamivir	Oseltamivir +PEGinterferon	Oseltamivir	Oseltamivir	Oseltamivir		Oseltamivir	Oseltamivir	Oseltamivir	Oseltamivir
Antifungal	none	Anidulafungin	Anidulafungin	none	none	none	none	Anidulafungin	Fluconazole	Anidulafungin
Steroids	none	Hydrocortisone then methylprednisolone	Hydrocortisone then methylprednisolone	None	None	None	Hydrocortisone	Hydrocortisone then methylprednisolone	Hydrocortisone	Hydrocortisone

BP: blood pressure, SpO2: oxygen saturation, AKI: acute kidney injury, RRT: renal replacement therapy, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ICU: intensive care unit, ARDS: acute respiratory distress syndrome, MV: mechanical ventilation, NIV: non-invasive ventilation, ECMO: extracorporeal membrane oxygenation.

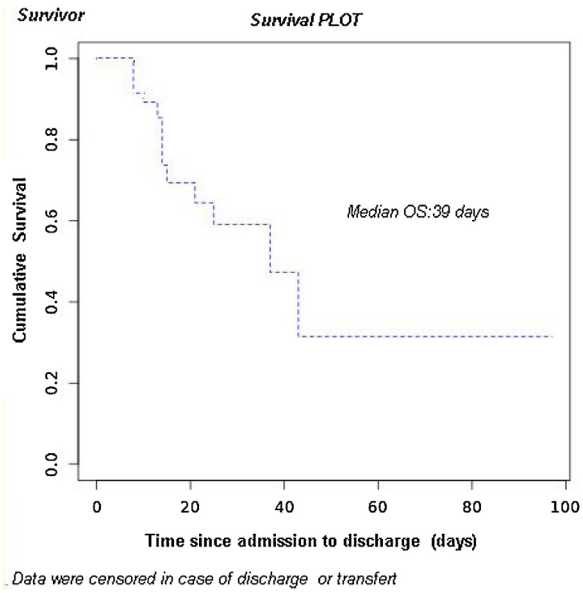

Fig. 2. Kaplan-Meier survival analysis to determine the cumulative survival probability of admitted MERS-CoV infected patients.

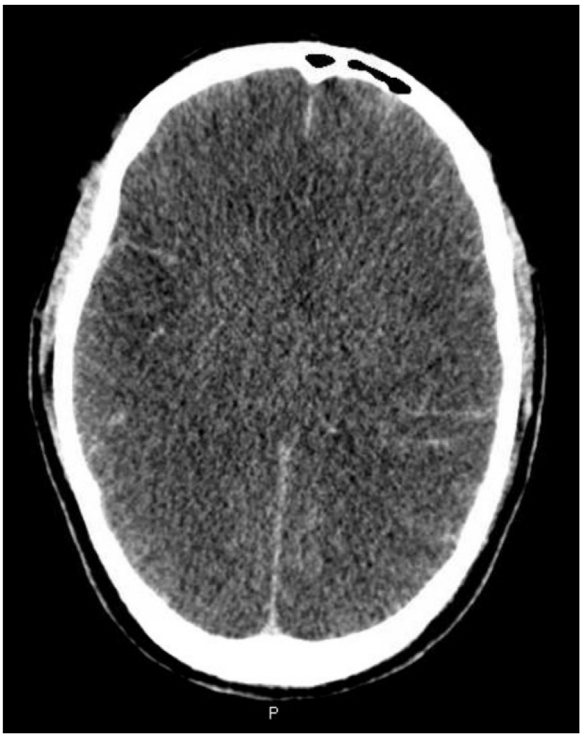

Fig. 3. Computed tomography of the brain showing subarachnoid hemorrhage noted along the bilateral fronto-temporo-parietal cortical sulci and the bilateral sylvian fissures. There is mild subdural hemorrhage also noted along the falx. There is diffuse cerebral edema noted with obliteration of the cortical sulci, basal cisterns and the ventricular system.

up, and use of robust infection control measures in collaboration between the Ministry of Public Health, other healthcare partners and Qatar National Outbreak Control Taskforce. In addition, knowing the natural reservoir of the virus and establishing a clear One Health roadmap along with animal health sector is of paramount importance [16]. This approach has helped in increasing the early screening of all human and camel contacts and their environments in Qatar. Furthermore, the accessibility to molecular tests, the short turnaround time, the relatively large number of screening tests performed in our National virology laboratory, have helped to contain the virus. The MERS-CoV reservoir was well controlled in Qatar which most likely has led to control the epidemic. However, scattered cases and nosocomial outbreaks of MERS-CoV continue to occur in endemic countries including Qatar [7].

MERS-CoV infection is mainly seen among adult males with a median age 53 (36–66) [17,18]. The male predominance and median age of our patients was consisting with previous studies. We did not have any confirmed pediatric or pregnant women MERS-COV cases. The number of pediatric and pregnant women with MERS-COV infection remains very limited [19,20]. As of June 2020, only 11 cases of MERS-CoV infection in pregnant women and 42 cases in pediatric population were reported worldwide. All pregnant women with MERS-CoV infection were symptomatic, with a case fatality rate of 27 % which was not statistically different when compared to the overall fatality rate [20–23]. Whereas most pediatric cases were asymptomatic and had favorable outcome with a case fatality rate of 9.5 % (4 cases died) [24]. The infection was acquired mainly through household contact in children and health care-associated infection in pregnant women [20].

The clinical presentation of Middle East respiratory syndrome coronavirus (MERS-CoV) infection is nonspecific and have ranged from asymptomatic or upper respiratory symptoms to severe acute respiratory distress syndrome and multi-organ failure leading to death [25,26]. Most of our patient were symptomatic at presentation (89 %) with a duration of symptoms of 5–7 days prior to hospital admission. The relation between severity of illness and median time from onset of symptoms to hospital admission was not well described in previous MERS-CoV studies. Whereas, it has been shown to be higher in deceased patients in COVID-19 as compared to recovered patients during the current SARS-CoV-2 pandemic. [4] In addition, it has been reported that common laboratory features of MERS-CoV infection are similar with COVID-19 on admission including lymphopenia and raised amounts of alanine aminotransferase [27]. MERS patients with low albumin, lymphopenia, thrombocytopenia, usually have worse outcome [28]. Majority of our patients had low to normal WBC, thrombocytopenia and low procalcitonin. It is not well established whether low procalcitonin is a factor of good or bad prognosis. The creatinine kinase (CK) was noted to be high in majority of our patients. The radiologic findings in our patients was consisting with previous reports related to MERS-CoV pneumonia were unilateral or bilateral broncho-alveolar shadowing, interstitial infiltrates, reticular opacities, reticulonodular shadowing, nodules, pleural effusions, and/or patchy to confluent consolidation with lower lobes predominance [29,30]. MERS-CoV infection is often complicate by ARDS and extra-pulmonary manifestation in particular AKI. Early and rapid-onset AKI was observed commonly in patients with MERS-CoV infection, affecting the outcome of the disease negatively. AKI was reported in 23.3 % of patients with MERS-CoV infection [31]. AKI was mainly reported in severe MERS-CoV infection cases and can reach up to 70 % of critically ill patients [32,33]. The pathophysiology of MERS-CoV infection and AKI is not well understood. It has been reported that MERS virus is present in renal tissue suggesting renal tissue tropism for the virus [34]. In addition, Yeung et al. have demonstrated that the virus is present in the kidney and the lung and induces apoptosis contributing to tissue damage leading to ARDS and renal failure [35]. In our study the number of patients with AKI on admission is relatively high and is associated with increased mortality.

Of note, one of our patients had neurologic complications with sub-arachnoid hemorrhage and subdural hematoma. MERS-CoV

neurologic complications are very rare findings and were reported only in few case reports where one case of intracerebral hemorrhage was explained by the presence of thrombocytopenia, disseminated intravascular coagulation, and platelet dysfunction and no obvious cause was found in the second case [20,36].

The fatality rate is high and ranged from 24.2%–60%. The high fatality rate can be an overestimate because mild cases might not present to hospital and can be missed [37,38]. Older age, male sex, and the presence of chronic conditions such as obesity, diabetes mellitus, hypertension, malignancies, chronic heart, lung, and kidney disease, and immunocompromised states are associated with poor outcome and higher mortality [37]. On the other hand younger age and occupation (health care workers) were associated with favorable clinical outcome [39]. In our report only presence of comorbidities was statistically significant with increased mortality.

Despite MERS-CoV has emerged since 2012, to date there is neither specific anti- viral treatment nor vaccine available. Several therapies were used for critically ill patients with MERS-CoV pneumonia outside clinical trials. Some treatment options were selected based on their in-vitro cell-culture inhibitory effect against viral replication [40]. For instance, antiviral agents like ribavirin, lopinavir-ritonavir, pegylated interferon alfa-2a were used with no obvious significance in the outcome [41]. In addition, other traditional options like passive antibody treatment with convalescent plasma from previously recovered MERS-CoV patients was tried as well [7]. Convalescent plasma was promising in preclinical animal trial [38]. Zao et al. found that sera from infected dromedary camels can prevent or treat MERS-CoV infected mice especially if the sera are delivered early during the illness [42]. Two patients out of three with severe MERS-CoV pneumonia from South Korea recovered after giving convalescent plasma and showed very good response [3]. In our series, one patient was given ribavirin and another one pegylated interferon alfa-2a without any obvious improvement. Both patients were critically sick at the time of intervention and both patients died. Clinical trials in human are still needed to test safety and efficacy of these experimental treatments.

Conclusion

MERS-CoV is a rare infection in the State of Qatar. Most of the patients had either history of travel to Saudi Arabia or contact MERS-CoV infected cases or contact with camels. There were no hospital outbreaks or healthcare worker reported infections. Extra-pulmonary complications of MERS-CoV infection was marked by large number of patients with AKI. In the absence of targeted therapy and effective vaccine, knowing the reservoir, robust infection control measures and early recognitions of infected MERS cases are of paramount importance to control and prevent the spread of infection.

Study limitations

Besides the limitations inherent in retrospective studies, the small sample size identified during the study period limited the detailed description of the clinical characteristics of the study subjects.

Author-statement

This study was designed, directed, and coordinated by Fatma Ben Abid and Nada El-Maki as the principal investigator. All authors have contributed to the manuscript and have nothing to declare.

Ethical considerations

The study was approved by the Institutional Review Board at Hamad Medical Corporation, IRB register number MRC/0372/2017. A waiver for the requirement to get an informed consent was granted due to the retrospective nature of data collection and analysis.

Funding

Medical Research Center, Hamad Medical Corporation, Qatar.

Declaration of Competing Interest

No potential conflict of interest was reported by the authors.

Acknowledgements

The authors are indebted to Dr. Ali S. Omrani for reviewing the manuscript and his helpful comments.

Special thanks to the Ministry of Public Health, Qatar for providing us the data for contact tracing.

References

[1] Zaki AM, Van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367(19 November)1814–20 8.
[2] Korea Centers for Disease Control and Prevention. Middle east respiratory syndrome coronavirus outbreak in the Republic of Korea, 2015. Osong Public Health Res Perspect 2015;6(4 August):269–78.
[3] World Health Organization. WHO MERS-CoV global summary and risk assessment. Geneva. Switzerland: WHO; 2016 Dec 5.
[4] World Health Organization. WHO MERS-CoV global summary and risk assessment. Geneva. Switzerland: WHO; 2016 Dec 5..
[5] Omrani AS, Shalhoub S. Middle East respiratory syndrome coronavirus (MERS-CoV): what lessons can we learn? J Hosp Infect 2015;91(3 November):188–96.
[6] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–84.
[7] Memish ZA, Perlman S, Van Kerkhove MD, et al. Middle east respiratory syndrome. Lancet 2020;395(10229 March)1063–77 28.
[8] Reusken CB, Farag EA, Jonges M, et al. Middle East respiratory syndrome coronavirus (MERSCoV) RNA and neutralising antibodies in milk collected according to local customs from dromedary camels, Qatar, April 2014. Euro Surveill 2014;19(23 June)20829 12.
[9] Van Doremalen N, Bushmaker T, Karesh WB, et al. Stability of Middle East respiratory syndrome coronavirus in milk. Emerg Infect Dis. 2014;20(7 July):1263–4.
[10] Omrani AS, Jaffar JA, Memish ZA. Middle East respiratory syndrome coronavirus (MERS-CoV): animal to human interaction. Pathog Glob Health 2015;109(8):354–62.
[11] Killerby ME, Biggs HM, Midgley CM, et al. Middle East respiratory syndrome coronavirus transmission. Emerg Infect Dis. 2020;26(2 Febuary):191–8.
[12] Noorwali AA, Turkistani AM, Asiri SI, et al. Descriptive epidemiology and characteristics of confirmed cases of Middle East respiratory syndrome coronavirus infection in the Makkah Region of Saudi Arabia, March to June 2014. Ann Saudi Med 2015;35(3 May-June):203–9.
[13] Conzade R, Grant R, Malik MR, et al. Reported direct and indirect contact with dromedary camels among laboratory-confirmed MERS-CoV cases. Viruses 2018;10(8 August)425 13.
[14] Hui DS, Azhar EI, Kim YJ, et al. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. Lancet Infect Dis 2018;18(8 August):e217–27.
[15] World Health Organization. Global alert and response: Middle east respiratory syndrome coronavirus (MERS-CoV)–update 07 May. 2014.
[16] Farag E, Nour M, Islam MM, et al. Qatar experience on one Health approach for middle-east respiratory syndrome coronavirus, 2012–2017: a viewpoint. One Health 2019;4(7 April):100090.
[17] Aleanizy FS, Mohmed N, Alqahtani FY, et al. Outbreak of Middle East respiratory syndrome coronavirus in Saudi Arabia: a retrospective study. BMC Infect Dis 2017;17(1 January)23 5.
[18] Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. Int J Infect Dis 2016;49(August):129–33.
[19] Thabet F, Chehab M, Bafaqih H, et al. Middle East respiratory syndrome coronavirus in children. Saudi Med J 2015;36(4 April):484–6.

[20] Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: report of two cases & review of the literature. J Microbiol Immunol Infect 2019;52(3 June):501–3.
[21] Alserehi H, Wali G, Alshukairi A, et al. Impact of Middle East Respiratory Syndrome coronavirus (MERS-CoV) on pregnancy and perinatal outcome. BMC Infect Dis 2016;2(16 March):105.
[22] Jeong SY, Sung SI, Sung JH, et al. MERS-CoV infection in a pregnant woman in Korea. J Korean Med Sci 2017;32(10 October):1717–20.
[23] Assiri A, Abedi GR, Al Masri M, et al. Middle East respiratory syndrome coronavirus infection during pregnancy: a report of 5 cases from Saudi Arabia. Clin Infect Dis 2016;63(7 October)951–3 1.
[24] Kindi F, Nair S, Hashmey R. Pediatric Middle east respiratory syndrome coronavirus (MERS-CoV) infection–UAE. 2020. . . 1science. com/item/3000747c8b25b269fce15bd9550174068f277901 https://coronavirus.
[25] WHO. Middle East respiratory syndrome coronavirus (MERS-CoV). https://www.who.int/emergencies/mers-cov/en/ (accessed Feb 12, 2020).
[26] Kim KH, Tandi TE, Choi JW, et al. Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: epidemiology, characteristics and public health implications. J Hosp Infect 2017;95(2 Febuary):207–13.
[27] Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013;13(9 September):752–61.
[28] Choi WS, Kang CI, Kim Y, et al. Clinical presentation and outcomes of Middle East respiratory syndrome in the Republic of Korea. Infect Chemother 2016;48(2 June):118–26.
[29] Das KM, Lee EY, Jawder SE, et al. Acute Middle East respiratory syndrome coronavirus: temporal lung changes observed on the chest radiographs of 55 patients. AJR Am J Roentgenol 2015;205(3 September):W267–74.
[30] Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis 2014;29(December):301–6.
[31] Cha RH, Joh JS, Jeong I, et al. Renal complications and their prognosis in Korean patients with Middle East respiratory syndrome-coronavirus from the central MERS-CoV designated hospital. J Korean Med Sci 2015;30(12 December):1807–14.
[32] Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014;160(6 March)389–97 18.
[33] Alkindi F, Boobes Y, Nair SC, et al. Acute kidney injury associated with middle east respiratory syndrome coronavirus (MERS-CoV) infection. Kidney Intern Rep. 2020;5(3 March)S13 1.
[34] Eckerle I, Müller MA, Kallies S, et al. In-vitro renal epithelial cell infection reveals a viral kidney tropism as a potential mechanism for acute renal failure during Middle East Respiratory Syndrome (MERS) Coronavirus infection. Virol J 2013;23(10 December):359.
[35] Yeung ML, Yao Y, Jia L, et al. MERS coronavirus induces apoptosis in kidney and lung by upregulating Smad7 and FGF2. Nat Microbiol 2016;1(3 Febuary) 16004 22.
[36] Ko JH, Seok H, Cho SY, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther (Lond) 2018;23(7):617–22.
[37] Sherbini N, Iskandrani A, Kharaba A, et al. Middle East respiratory syndrome coronavirus in Al-Madinah City, Saudi Arabia: demographic, clinical and survival data. J Epidemiol Glob Health 2017;7(1 March):29–36.
[38] Habib AM, Ali MA, Zouaoui BR, et al. Clinical outcomes among hospital patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection. BMC Infect Dis 2019;19(1 October)870 22.
[39] Garbati MA, Fagbo SF, Fang VJ, et al. A comparative study of clinical presentation and risk factors for adverse outcome in patients hospitalized with acute respiratory disease due to MERS coronavirus or other causes. PLoS One 2016;11(11 November)e0165978 3.
[40] Zumla A, Chan JF, Azhar EI, et al. Coronaviruses drug discovery and therapeutic options. Nat Rev Drug Discov 2016;15(5 May):327–47.
[41] Momattin H, Al-Ali AY, Al-Tawfiq JA. A systematic review of therapeutic agents for the treatment of the Middle East respiratory syndrome coronavirus (MERS-CoV). Travel Med Infect Dis 2019;30(July-August):9–18.
[42] Zhao J, Perera RA, Kayali G, et al. Passive immunotherapy with dromedary immune serum in an experimental animal model for Middle East respiratory syndrome coronavirus infection. J Virol 2015;89(11 June):6117–20.