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Clinical predictors of mortality of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: A cohort study

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A B S T R A C T

Background: Since the emergence of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012, the virus had caused a high case fatality rate. The clinical presentation of MERS varied from asymptomatic to severe bilateral pneumonia, depending on the case definition and surveillance strategies. There are few studies examining the mortality predictors in this disease. In this study, we examined clinical predictors of mortality of Middle East Respiratory Syndrome (MERS) infection.

Methods: This is a retrospective analysis of symptomatic admitted patients to a large tertiary MERS-CoV center in Saudi Arabia over the period from April 2014 to March 2018. Clinical and laboratory data were collected and analysis was done using a binary regression model.

Results: A total of 314 symptomatic MERS-CoV patients were included in the analysis, with a mean age of 48 (± 17.3) years. Of these cases, 78 (24.8%) died. The following parameters were associated with increased mortality, age, WBC, neutrophil count, serum albumin level, use of a continuous renal replacement therapy (CRRT) and corticosteroid use. The odd ratio for mortality was highest for CRRT and corticosteroid use (4.95 and 3.85, respectively). The use of interferon-ribavirin was not associated with mortality in this cohort.

Conclusion: Several factors contributed to increased mortality in this cohort of MERS-CoV patients. Of these factors, the use of corticosteroid and CRRT were the most significant. Further studies are needed to evaluate whether these factors were a mark of severe disease or actual contributors to higher mortality.

1. Introduction

The emergence of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in late 2012 caused a significant global public and clinical concern due to the disease high case fatality rate and the inability to distinguish cases of MERS-CoV from other severe respiratory tract infections caused by other pathogens [1–4]. One study found that monocytosis with normal WBC and lower C-reactive protein (CRP) are useful predictors of MERS-CoV infection [4]. The clinical presentation of MERS varied from asymptomatic to severe bilateral pneumonia, depending on the case definition and surveillance strategies [5–7]. The case fatality rate of MERS-CoV has changed over the last 6 years, depending on the outbreak and its timing, comprehensiveness of the surveillance program (to include mild and asymptomatic cases) and the country of the report from 28.6% to 63.6% [8]. A lower case fatality rates were reported from a MERS-CoV reference center in Riyadh, Saudi Arabia [9] and from the South Korea's outbreak [10,11]. When compared to severe respiratory infections caused by non-MERS-CoV, the case fatality rate was higher in MERS than non-MERS cases [1,9]. Six years into the MERS-CoV epidemic, there are few studies addressing the clinical predictors of mortality in MERS-CoV cases [11,12]. MERS-CoV had caused concern among travelers, however, MERS-CoV infection was reported infrequently among pilgrims performing Umrah [13,14]. There were reports of more than 20 travel-related MERS-CoV cases [13]. A single case of travel associated MERS-CoV infections caused the largest outbreak outside the Arabian Peninsula in South Korea [13,15–17]. In a systematic review of pilgrims, acquisition of MERS-CoV was very limited and systematic screening of

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Table 1
Base line characteristics in patients with Middle East respiratory syndrome Coronavirus (MERS-CoV) infection.

	Alive	Deceased	P value
Age (years)	45.7 ± 16.5	56.3 ± 17.6	0.0001
Temperature (^{0}C)	37.1 ± 0.8	37.3 ± 0.6	0.1037
WBC (×10^9/L)	6.8 ± 3.8	9.5 ± 5.9	0.0001
Hgb (g/dl)	13.3 ± 2.5	11.3 ± 2.6	0.0001
Platelet (×10^9/L)	227.3 ± 102.8	216.8 ± 113.8	0.405
Neutrophil (×10^9/L)	4.5 ± 3.2	8.1 ± 5.7	0.0001
CK (U/l)	1051.7 ± 4565	712.7 ± 1132.6	0.537
ALT (U/l)	68 ± 171	72.7 ± 124	0.815
AST (U/l)	88.75 ± 184	162.9 ± 25	0.0028
Creatinine (mg/dl)	126.8 ± 216	253.6 ± 273	0.0001
Albumin (g/dl)	35.1 ± 6.4	28.29 ± 6	0.0001

WBC = White Blood Cell count; Hgb = hemoglobin; CK = creatinine kinase; ALT = alanine aminotransferase; AST = Aspartate aminotransferase

pilgrims showed no infections [18]. There had been no asymptomatic MERS-CoV cases among travelers despite a high proportion in non-travelers [19]. A recent study included confirmed cases who were admitted to this hospital in 2014–2015 and found independent predictors of survival as younger age, not being transferred to the ICU and not receiving renal replacement therapy [20]. Here, we evaluate a larger number of cases over a longer period of time.

2. Materials and methods

All symptomatic MERS-CoV confirmed patients who were admitted to a referral hospital in the central part of Saudi Arabia from April 2014 to March 2018 were included in the study. Asymptomatic cases (N = 38) were excluded. Prince Mohammed bin Abdulaziz Hospital (PMAH) is a referral center for all MERS-CoV patients diagnosed in the central region based in Riyadh, Saudi Arabia. All infections were confirmed using real time RT-PCR of respiratory samples as described previously [21,22]. Data on the following parameters were collected: demographic data: age, gender, height and weight, clinical: presence of shortness of breath, cough, sore throat and fever, laboratory results (WBC, hemoglobin, platelet, neutrophil, hepatic function tests (ALT, AST), Creatinine and Albumin, and medical interventions: plasmapheresis, use of intravenous immunoglobulin, Extra Corporal Mechanical Oxygenation (ECMO), and a continuous renal replacement therapy (CRRT), interferon-ribavirin, and corticosteroid use.

3. Statistics

Statistical analysis was done using Minitab® (Minitab Inc. Version 17. PA 16801, USA; 2017). Descriptive analyses were used for demographic, clinical and laboratory data. Bivariate analysis described the association of status of outcome and various clinical and laboratory parameters. We then utilized the binary logistic regression analysis with a backward stepwise approach to analyze the outcome in relation to continuous and categorical variables. The odds ratio was calculated for significantly associated variables. A P-value of less than 0.05 indicates statistical significance.

4. Results

A total of 314 symptomatic MERS patients were included in the analysis, with a mean age of 48 (± 17.3) years. Of these cases, 78 (24.8%) died. Table 1 shows identified parameters to be associated with mortality. In binary logistic regression analysis with a backward stepwise approach the following parameters were associated with increased mortality, age, increased WBC, and neutrophil count, lower serum albumin level, use of CRRT and corticosteroid use. The odd ratio for mortality was highest for CRRT and corticosteroid use (4.95 and 3.85, respectively). The use of interferon-ribavirin was not associated with mortality in this cohort. The majority of patients received methyl-prednisone with variable doses and duration (see Table 2).

5. Discussion

In this study, we analyzed predictors of MERS survival among a cohort of patients admitted to a referral center for MERS-CoV therapy in the capital city of Riyadh, Saudi Arabia. In this study, we included only symptomatic cases in analysis as all asymptomatic cases recovered. The reason for this exclusion is that we attempted to investigate the factors contributing to mortality in symptomatic cases. In previous studies, mild or asymptomatic disease was observed in secondary cases, in young patients, and in previously healthy individuals [23]. It was described that as the percentage of asymptomatic patients increased to 29%, the case fatality rate decreased to 30% [7,12,23–26]. Of the 314 symptomatic MERS patients, 24.8% died. This rate is lower than the previously published range of 28.6%–63.6% [8–11]. Earlier studies showed high case fatality rate among symptomatic and critical ill patients [8–11].

In this study we found that there are few predictors of mortality in MERS-CoV patients. Increasing age was a predictor and this is in agreement with a previous study where age ≥65 years was associated with increased mortality with an OR of 4.39 [12]. However, in that study age was the only predictor of mortality. Older age may be associated with concurrent comorbidities and thus increasing case fatality rate. In one study, predictors of 30-day mortality included older age, non-healthcare workers, pre-existing illness, severity of illness, and hospital-acquired infections [27]. We found that corticosteroid was associated with increased mortality. In one study, patients who received corticosteroids had a higher 90-day crude mortality of 74.2% compared to 57.6% among the comparator group [28]. In that study, authors compared 151 MERS patients in the corticosteroid group derived from 14 different healthcare facilities and patients who received corticosteroid therapy had delayed clearance of viral RNA [28]. It is probably the practice to use corticosteroid for patients who were not showing clinical improvements and thus might be at a higher rate of mortality to begin with.

Baseline data showed that deceased patients had higher initial WBC of 9.5 ± 5.9 compared to 6.8 ± 3.8 (P = 0.0001) and had lower hemoglobin level of 11.3 ± 2.6 g/dl compared to those who survived (13.3 ± 2.5 g/dl) (P = 0.0001). In addition, deceased MERS cases had

Table 2
Fcators associated with mortality from binary logistic regression analysis with a backward stepwise approach.

Source	Adjusted Dev	Adjusted Mean	Odds Ratio	95% CI	Chi-Square	P-Value
Age (years)	8.356	8.3557	1.0293	(1.0090, 1.0500)	8.36	0.004
WBCS X 10^9/L	3.298	3.2978	0.7515	(0.5432, 1.0396)	3.3	0.069
NEUT X 10^9/L	6.393	6.3929	1.5234	(1.0714, 2.1660)	6.39	0.011
Albumin 33 g/L	11.941	11.9406	0.9031	(0.8502, 0.9592)	11.94	0.001
CRRT	11.866	11.866	4.9475	(1.9660, 12.4507)	11.87	0.001
Corticosteroid use	15.687	15.6869	3.8449	(1.9533, 7.5685)	15.69	0.0001

WBC = White Blood Cell count; NEUT = neutrophil count; CRRT = continuous renal replacement therapy.

a lower albumin level of 28.29 ± 6 compared to survival group (35.1 ± 6.4) (P = 0.0001). Similarly, a previous study showed that low serum albumin was associated with severe MERS-CoV infection and may reflects nutritional status of the patients [29].

We found that CRRT was associated with higher rate of mortality among MERS patients. In a previous study, the application of CRRT was a risk factor for MERS-CoV-related mortality [30]. Another study showed that MERS patients were more likely to require ECMO (5.8% vs 0.9%; p = 0.003) [31]. However, one study showed that the ECMO group had lower in-hospital mortality (65 vs. 100%, P = 0.02) [32]. Thus, it was suggested that ECMO therapy could be used as a rescue therapy for MERS-CoV patients who develop refractory hypoxia as the therapy needs a specialized center.

In conclusion, we do not yet know if all factors contributed to mortality or were simply markers of pre-mortal last interventions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2019.03.004.

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