

Critically ill patients with diabetes and Middle East respiratory syndrome: A multi-center observational study

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Research article

Keywords: Acute respiratory distress syndrome, coronavirus, diabetes, Middle East respiratory syndrome

Posted Date: January 14th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-57988/v4>

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Version of Record: A version of this preprint was published on January 19th, 2021. See the published version at <https://doi.org/10.1186/s12879-021-05771-y>.

Abstract

Background: Diabetes is a risk factor for infection with coronaviruses. This study describes the demographic, clinical data, and outcomes of critically ill patients with diabetes and Middle East Respiratory Syndrome (MERS).

Methods: This retrospective cohort study was conducted at 14 hospitals in Saudi Arabia (September 2012-January 2018). We compared the [demographic characteristics](#), underlying medical conditions, presenting symptoms and signs, management and clinical course, and outcomes of critically ill patients with MERS who had diabetes compared to those with no diabetes. Multivariable logistic regression analysis was performed to determine if diabetes was an independent predictor of 90-day mortality.

Results: Of the 350 critically ill patients with MERS, 171 (48.9%) had diabetes. Patients with diabetes were more likely to be older, and have comorbid conditions, compared to patients with no diabetes. They were more likely to present with respiratory failure requiring intubation, vasopressors, and corticosteroids. The median time to clearance of MERS-CoV RNA was similar (23 days (Q1, Q3: 17, 36) in patients with diabetes and 21.0 days (Q1, Q3: 10, 33) in patients with no diabetes). Mortality at 90 days was higher in patients with diabetes (78.9% versus 54.7%, $p < 0.0001$). Multivariable regression analysis showed that diabetes was an independent risk factor for 90-day mortality (odds ratio, 2.09; 95% confidence interval, 1.18-3.72).

Conclusions: Half of the critically ill patients with MERS have diabetes; which is associated with more severe disease. Diabetes is an independent predictor of mortality among critically patients with MERS.

Background

The Middle East respiratory syndrome coronavirus (MERS-CoV) is a novel zoonotic virus that can lead to severe acute respiratory infection (SARI) and life-threatening multi-organ dysfunction. It was first isolated from a fatal case of pneumonia in Jeddah, Saudi Arabia in 2012 [1, 2]. Since then, community-acquired cases and clusters in healthcare settings have been reported mainly in Saudi Arabia [3, 4], but also other countries [5]. By the end of March 2020, the World Health Organization (WHO) reported 2553 confirmed cases in 27 countries (84.3% of cases in Saudi Arabia) with a case fatality rate of 34.4% [6]. *MERS clinical presentation ranges from asymptomatic infection to rapidly progressive severe respiratory failure with multi-organ failure* [7, 8]. Symptoms usually manifest after an incubation period of 2-14 days, with fever, cough, and dyspnea [7-9]. Admission to the intensive care unit (ICU) is frequently needed [7, 8].

Most severe MERS cases have been reported in older adults with chronic comorbidities, including *diabetes mellitus* [2, 7, 9-12]. One cohort study found that among 47 MERS patients, 68% had diabetes [7]. A case-control study demonstrated that diabetes was associated with an increased risk of MERS with an adjusted odds ratio [OR] of 6.99 (95% confidence interval [CI], 1.89–25.86) [11]. Diabetes has also been associated with increased mortality in MERS patients [9, 13]. In animal studies, diabetes was associated with a dysregulated immune response resulting in more severe and prolonged lung pathology following MERS-CoV infection [14].

Previous studies that evaluated diabetes in MERS had relatively small sample sizes, were mostly performed in single centers, and included a mix of critically and non-critically ill patients. We performed this study in a large cohort of critically ill patients with MERS, with the hypothesis that patients with diabetes and viral SARI would have a complicated course of illness and worse outcomes compared with patients with no diabetes. The

objectives of this study are to describe the clinical presentation, management, and outcomes (including mortality and MERS-CoV RNA shedding) of the Middle East Respiratory Syndrome in critically ill patients with diabetes.

Methods

We followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines in reporting our results.

Patients and settings

This is a retrospective cohort study of adult (≥ 14 -year-old) patients with SARI due to MERS-CoV who were admitted to the ICUs of 14 referral hospitals in Saudi Arabia between September 2012 and January 2018. The study was approved by institutional review boards of all participating centers. The characterization of this cohort has already been published earlier [15]. SARI was defined as an acute respiratory infection, with fever and cough onset within the preceding 10 days and clinical or radiologic lung involvement. The presence of MERS-CoV was detected by real-time reverse-transcriptase polymerase chain reaction assay (rRT-PCR) performed on nasopharyngeal swabs or sputum samples in non-intubated patients and tracheal aspirates or bronchoalveolar lavage in intubated patients as recommended by the Saudi Arabian Ministry of Health. Confirmatory laboratory testing required a positive PCR on at least two specific genomic targets (upE and ORF1a) or a single positive target (upE) with sequencing of a second target (RdRpSeq or NSeq). In patients with suspected MERS and negative rRT-PCR, testing was repeated at the discretion of the treating teams. For infection control purposes, follow-up respiratory samples were collected approximately 1–2 times per week in MERS-CoV positive patients [16] to assess clearance of MERS-CoV RNA [15].

Data collection

Data were collected using the standardized International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) tool [17]. In this study, we included patients demographics, baseline characteristics, presenting symptoms, physiologic and laboratory parameters, and severity of illness on ICU admission assessed by the Sequential Organ Failure Assessment (**SOFA**) score [18]. We also described the management in the ICU, including the use of invasive and noninvasive ventilation, extracorporeal membrane oxygenation (ECMO), prone positioning, and selected medications.

The primary outcome was 90-day mortality. Other studied outcomes were mortality at 14 and 28 days and on ICU and hospital discharge and ICU and hospital length of stay (LOS). For patients who survived hospital discharge, the 90-day outcome was assessed by calling the patients. We also assessed the time to clearance of MERS-CoV RNA, which was defined as the time from the first performed rRT-PCR until the test was negative on two occasions, without a positive test afterward [15].

Statistical analysis

In this study, patients were divided into two groups based on the history of preexisting diabetes mellitus, as reported by patients. We compared patients with diabetes to patients with no diabetes using the Student t-test or the Mann-Whitney U test for continuous variables based on normality assumption, and the chi-square test or Fisher's exact test for categorical variables.

To examine the independent association of diabetes with 90-day mortality in MERS patients, we performed multivariable logistic regression analysis adjusting for certain variables selected based on their clinical relevance, excluding the ones which are in the exposure–causal pathway. The variables entered in the model were age, sex, asthma or chronic pulmonary disease, chronic neurological disease, immunosuppressant use before admission, body mass index (BMI), and SOFA score.

For the multivariable logistic regression analysis, 24% (84/350) of patients had missing data (BMI – 81/350, 23%, age – 2/350, 0.5%, and SOFA score – 3/350, 0.8%). Hence missing data were handled using the multiple imputation technique with 50 imputations. Two imputation methods were considered to support the imputation technique: (I) “Predictive mean matching” and (II) “Impute then Transform” approach. The data set had an arbitrary missing data pattern and it was assumed that the missing data were missing at random, such that the probability of a missing observation may depend on observed values but not on unobserved values. Predictive mean matching was used to impute missing values for these variables. For the imputation of BMI, we used the “impute then transform” approach instead of imputing BMI directly, such that we imputed the height and weight assuming the imputation model was oblivious of the relation between these two variables [19]. We reported the results of multivariable analysis without imputation (Model I: Complete case analysis) and with imputation (Model II: Multiple imputation).

Kaplan-Meier curves for the time to MERS-CoV RNA clearance were constructed censoring by hospital discharge or at 90 days whichever occurred first. The log-rank test was used to compare the median survival time between the groups. In addition, Kaplan-Meier curves for survival were also plotted and were censored at 90 days; the log-rank test was used to compare the time to survival between the groups. All statistical tests were two-sided with significance set at $\alpha < 0.05$. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Characteristics of patients

During the study period, 350 patients with MERS SARI were admitted to the participating ICUs. Patients with diabetes constituted 48.9% of the cohort. **Table 1** describes the characteristics and presenting symptoms of patients with diabetes and no diabetes. Compared to patients with no diabetes, those with diabetes were older (median age 61.0 years (Q1, Q3: 53.0, 72.0) versus median age 54.0 years (Q1, Q3: 35.0, 67.0), $p < 0.0001$) and more likely to have other comorbid conditions such as chronic renal disease (71 (41.5%) versus 39 (21.8%), $p < 0.0001$) and cardiac disease (95 (55.6%) versus 60 (40.5%), $p < 0.0001$). They were more likely to present with dyspnea and sputum production. The time from symptom onset to ICU admission was similar.

Baseline characteristics of patients with diabetes and Middle East Respiratory Syndrome (MERS) compared to patients with no diabetes and MERS.

| | Diabetes N=171 | No Diabetes N=179 | P-value |
|--|-------------------|----------------------|--------------------|
|), median (Q1, Q3) | 61.0 (53.0, 72.0) | 54.0 (35.0, 67.0) | <0.0001 |
| m ²), median (Q1, Q3) | 29.3 (24.6, 33.3) | 28.3 (24.1, 33.0) | 0.31 |
| - no. (%) | 114 (66.7) | 127 (70.9) | 0.39 |
| ve worker - no. (%) | 4 (2.3) | 28 (15.6) | |
| ty-acquired - no. (%) | 102 (59.6) | 83 (46.4) | <0.0001 |
| ve-associated (Non-healthcare worker) - no. (%) | 65 (38.0) | 68 (38.0) | |
| 1 the onset of symptoms to the emergency room, median (Q1, Q3) | 5.0 (3.0, 8.0) | 4.0 (2.0, 7.0) | 0.30 |
| 1 symptom onset to ICU admission, median (Q1, Q3) | 7.0 (4.0, 10.5) | 7.0 (4.0, 11.0) | 0.66 |
| 1 symptom onset to intubation, median (Q1, Q3) | 8.0 (5.0, 12.0) | 8.0 (5.0, 13.0) | 0.37 |
| g symptoms - no. (%) | | | |
| spiratory | | | |
| | 136 (79.5) | 123 (68.7) | 0.02 |
| | 122 (71.3) | 117 (65.4) | 0.23 |
| sputum | 75 (43.9) | 58 (32.4) | 0.03 |
| bloody sputum | 11 (6.4) | 18 (10.1) | 0.22 |
| n | 36 (21.1) | 32 (17.9) | 0.45 |
| | 10 (5.8) | 9 (5.0) | 0.74 |
| spiratory | | | |
| | 2 (1.2) | 1 (0.6) | 0.62 [^] |
| a | 6 (3.5) | 11 (6.1) | 0.25 |
| at | 23 (13.5) | 24 (13.4) | 0.99 |
| symptoms | | | |
| mperature > 38°C) | 130 (76.0) | 131 (73.2) | 0.54 |
| r arthralgia | 32 (18.7) | 34 (19.0) | 0.95 |
| | 14 (8.2) | 21 (11.7) | 0.27 |
| | 66 (38.6) | 55 (30.7) | 0.12 |
| l pain | 22 (12.9) | 25 (14.0) | 0.76 |
| enopathy | 1 (0.6) | 2 (1.1) | >0.99 [^] |
| | 20 (11.7) | 18 (10.1) | 0.62 |
| nausea | 28 (16.4) | 30 (16.8) | 0.92 |
| onsciousness/ confusion | 44 (25.7) | 30 (16.8) | 0.04 |
| | 2 (1.2) | 2 (1.1) | >0.99 [^] |
| orbidities - no. (%) | | | |
| ulmonary disease (including asthma) | 22 (12.9) | 24 (13.4) | 0.88 |
| ase | 12 (7.0) | 10 (5.6) | 0.58 |
| renal disease | 71 (41.5) | 39 (21.8) | <0.0001 |
| ardiac disease | 95 (55.6) | 43 (24.0) | <0.0001 |
| urological disease | 22 (12.9) | 16 (8.9) | 0.24 |
| (Kg/m ²) | 55 (45.5) | 60 (40.5) | 0.42 |
| logic disease | 2 (1.2) | 5 (2.8) | 0.45 [^] |
| nancy including leukemia, lymphoma, or solid tumors | 14 (8.2) | 20 (11.2) | 0.35 |
| ppressant use before admission | 6 (3.5) | 15 (8.4) | 0.06 |
| re on ICU day 1, median (Q1, Q3) | 9.0 (6.0, 12.0) | 8.0 (5.0, 11.0) | 0.02 |

ass index; ICU: intensive care unit; Q1: first quartile, Q3: third quartile; SOFA: Sequential Organ Failure Assessment

ator of the percentage is the total number of subjects in the treatment group.

ous variables, Mann-Whitney U test was used to calculate the P-value. For categorical variables, Chi-square test was used to calculate the P-value otherwise noted. [^]Fisher's exact test was used to calculate P-value.

The laboratory findings are presented in **Table 2**. There were no differences in white blood cell and platelet counts between the two groups. Patients with diabetes had higher blood glucose (median 12.1 mmol/L (Q1,Q3: 9.9, 16.1) versus median 8.5 mmol/L (Q1,Q3: 6.5, 11.6), p<0.0001), blood urea nitrogen (median 12.0 mmol/L (Q1,Q3: 7.3, 20.8) versus median 9.1 mmol/L (Q1,Q3: 4.1, 16.9), p=0.0002) and creatinine (median 141.4 mmol/L (Q1,Q3: 91.0, 327.0) versus median 114.9 mmol/L (Q1,Q3: 67.0, 217.0), p=0.0004).

Table 2. Physiological parameters on day 1 of admission to ICU in patients with diabetes and Middle East Respiratory Syndrome (MERS) compared to patients with no diabetes and MERS.

| Variables | Diabetes N=179 | No Diabetes N=171 | P-value |
|--|----------------------|----------------------|---------|
| Respiratory parameters on ICU day 1, median (Q1, Q3) | | | |
| PaO ₂ (mmHg) | 65.1 (56.0, 79.0) | 71.0 (60.2, 86.4) | 0.01 |
| SaO ₂ (%) | 92.0 (87.0, 95.0) | 93.5 (90.0, 95.0) | 0.004 |
| FiO ₂ , | 0.7 (0.45, 1.0) | 0.6 (0.45, 1.00) | 0.24 |
| PaO ₂ /FiO ₂ ratio | 98.0 (64.0, 160.0) | 122.6 (73.4, 187.5) | 0.02 |
| Extrapulmonary parameters on ICU day 1, median (Q1, Q3) | | | |
| Mean arterial pressure (mmHg) | 70.0 (61.0, 83.0) | 70.0 (60.0, 80.0) | 0.72 |
| Leukocyte (× 10 ⁹ /L) | 7.90 (4.50, 11.60) | 6.80 (4.20, 11.20) | 0.31 |
| Hemoglobin (g/dL) | 10.4 (9.0, 12.50) | 11.0 (8.5, 13.0) | 0.48 |
| Hematocrit | 33.0 (28.55, 38.50) | 35.0 (28.0, 40.0) | 0.24 |
| Platelets (x10 ⁹ /L) | 188.0 (117.0, 253.0) | 168.5 (113.0, 253.0) | 0.32 |
| Glucose (mmol/L) | 12.1 (9.9, 16.1) | 8.5 (6.5, 11.6) | <0.0001 |
| Blood urea nitrogen (mmol/L) | 12.0 (7.3, 20.8) | 9.1 (4.1, 16.9) | 0.0002 |
| Creatinine (μmol/L) | 141.4 (91.0, 327.0) | 114.9 (67.0, 217.0) | 0.0004 |
| Bilirubin (μmol/L) | 12.3 (7.8, 23.7) | 12.0 (7.8, 22.9) | 0.86 |

PaO₂: partial pressure of oxygen; SaO₂: Oxygen saturation; FiO₂: Fraction of inspired oxygen; PaO₂: FiO₂ ratio: the ratio of the partial pressure of oxygen to the fraction of inspired oxygen; ALT: alanine aminotransferase, AST: aspartate transaminase; Q1: first quartile, Q3: third quartile.

Data on variables were not available for some patients; the number of patients with missing data in the Diabetes group and the No diabetes group, respectively, were as follows: PaO₂: 5 patients and 3 patients, SaO₂: 3 patients and 3 patients, FiO₂: 8 patients and 17 patients, PaO₂: FiO₂ ratio: 9 patients and 19 patients, MAP: 5 patients and 5 patients, Leukocyte: 5 patients and 9 patients, Hemoglobin: 5 patients and 10

patients, Hematocrit: 7 patients, and 9 patients, Platelets: 6 patients and 5 patients, Glucose: 23 patients and 26 patients, Blood urea: 8 patients and 9 patients, Creatinine: 4 patients and 2 patients, Bilirubin level: 22 patients and 23 patients.

Management in the ICU

Table 3 shows the management interventions performed during the ICU stay. More patients with diabetes were treated with non-invasive ventilation and with invasive mechanical ventilation (89.5% versus 81.6%, $p=0.04$) than non-diabetics. The time from symptom onset to intubation was similar. In comparison to patients with no diabetes, there was more use of nitric oxide in patients with diabetes (28 (16.4%) versus 16 (8.9), $p=0.04$), but less use of ECMO (6 (3.5%) versus 16 (8.9%), $p=0.04$).

3. Main interventions and outcomes in patients with diabetes and Middle East Respiratory Syndrome (MERS) compared to patients with no diabetes and MERS.

| Variables | Diabetes N=171 | No Diabetes N=179 | P-value |
|--|-------------------|----------------------|-------------------|
| Interventions | | | |
| Non-invasive positive pressure ventilation - no. (%) | 64 (37.4) | 43 (24.0) | 0.007 |
| Invasive ventilation - no. (%) | 153 (89.5) | 146 (81.6) | 0.04 |
| Duration, median (Q1, Q3) | 9.5 (4.0,17.0) | 9.0 (4.0, 16.0) | 0.68 |
| Neuromuscular blockade - no. (%) | 55 (32.2) | 78 (43.6) | 0.03 |
| High-frequency oscillation ventilation - no. (%) | 16 (9.4) | 10 (5.6) | 0.18 |
| ECMO - no. (%) | 6 (3.5) | 16 (8.9) | 0.04 |
| Nitric oxide - no. (%) | 28 (16.4) | 16 (8.9) | 0.04 |
| Prone positioning - no. (%) | 14 (8.2) | 19 (10.6) | 0.44 |
| Duration, median (Q1, Q3) | 3.0 (2.0,3.0) | 3.0 (2.0, 3.0) | 0.97 |
| Any oxygen rescue therapy - no. (%) | 73 (42.7) | 84 (46.9) | 0.43 |
| Vasopressors - no. (%) | 147 (86.0) | 129 (72.1) | 0.002 |
| Duration, median (Q1, Q3) | 6.5 (4.0,13.0) | 6.0 (3.0, 14.0) | 0.83 |
| Blood transfusion - no. (%) | 59 (34.5) | 58 (32.4) | 0.68 |
| Antivirals - no. (%) | | | |
| Both interferon and ribavirin - no. (%) | 70 (40.9) | 47 (26.3) | 0.02 [^] |
| Interferon only - no. (%) | 4 (2.3) | 5 (2.8) | |
| Ribavirin only - no. (%) | 10 (5.8) | 8 (4.5) | |
| Oseltamivir - no. (%) | 89 (52.0) | 107 (59.8) | 0.15 |
| Corticosteroids - no. (%) | 100 (58.5) | 75 (41.9) | 0.002 |
| Renal replacement therapy - no. (%) | 103 (60.2) | 71 (39.7) | 0.0001 |
| Duration, median (Q1, Q3) | 8.0 (4.0,14.0) | 8.0 (3.0, 14.0) | 0.92 |
| Intravenous immunoglobins - no. (%) | 9 (5.3) | 15 (8.4) | 0.25 |
| Tracheostomy - no (%) | 5 (2.9) | 9 (5.0) | 0.32 |
| Outcomes | | | |
| ICU mortality - no. (%) | 133 (77.8) | 95 (53.1) | <0.0001 |
| Hospital mortality - no. (%) | 136 (79.5) | 102 (57.0) | <0.0001 |
| 90-day mortality - no. (%) | 135 (78.9) | 98 (54.7) | <0.0001 |
| 28-day mortality - no. (%) | 127 (74.3) | 90 (50.3) | <0.0001 |
| 14-day mortality - no. (%) | 89 (52.0) | 76 (42.5) | 0.07 |
| ICU length of stay (days), median (Q1, Q3) | 11.0 (6.0,19.0) | 8.0 (5.0, 17.0) | 0.05 |
| Hospital length of stay (days), median (Q1, Q3) | 18.0 (10.0,33.0) | 20.0 (10.0, 37.0) | 0.63 |

extracorporeal membrane oxygenation. ICU: Intensive care unit. The denominator of the percentage is the total number of subjects in the group.

Outcomes of patients

The mortality at 90 days was higher in patients with diabetes (78.9% versus 54.7%, $p < 0.0001$) (**Table 3**). On multivariable logistic regression analysis, in both the models (I and II) diabetes was associated with increased mortality (OR, 2.09; 95% CI, 1.18-3.72). Other predictors of mortality were age (OR per 1-year increment, 1.04; 95% CI, 1.02-1.06), female gender (OR 1.68; 95% CI, 1.06-2.67), SOFA (OR per 1-point increment 1.20; 95% CI, 1.14-1.26). (**Table 4**).

I. Multivariable model to examine whether diabetes is an independent predictor of mortality in patients with East Respiratory Syndrome (MERS). We adjusted for age, sex, asthma or chronic pulmonary disease, neurological disease, immunosuppressant use before admission, body mass index (BMI), and SOFA score. **Model I:** Multiple case analysis with no imputation (participants with any missing data are excluded). **Model II:** Multiple imputation (participants with missing data identified and replaced).

| Variables | Model I (N=266) | | Model II (N=350) | |
|--|--------------------|---------|--------------------|---------|
| | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Diabetes | 2.09 (1.18, 3.72) | 0.005 | 2.13 (1.15, 3.95) | 0.02 |
| SOFA (per one-unit increase) | 1.20 (1.14, 1.26) | <0.0001 | 1.17 (1.12, 1.23) | <0.0001 |
| Female sex | 1.68 (1.06, 2.67) | 0.02 | 1.74 (1.09, 2.79) | 0.02 |
| Age (per one-year increase) | 1.04 (1.02, 1.06) | 0.0002 | 1.04 (1.02, 1.06) | <0.0001 |
| Chronic neurological disease | 3.07 (0.80, 11.81) | 0.07 | 3.40 (1.04, 11.14) | 0.04 |
| BMI (kg/m ²) (per one-unit increase) | 0.97 (0.90, 1.03) | 0.23 | 0.96 (0.91, 1.02) | 0.21 |
| Immunosuppressant use before admission | 1.24 (0.29, 5.26) | 0.74 | 1.13 (0.35, 3.64) | 0.84 |
| Asthma or chronic pulmonary disease | 1.20 (0.66, 2.20) | 0.51 | 1.04 (0.57, 1.91) | 0.90 |

Ratio; CI: Confidence Interval; BMI: body mass index; SOFA: Sequential Organ Failure Assessment.

ICU LOS was longer for patients with diabetes (**Table 3**). The time to clearance of MERS-CoV RNA was similar in both groups (23 days (Q1, Q3: 17, 36) in patients with diabetes and 21.0 days (Q1, Q3: 10, 33) in patients with no diabetes). **Figure 1** demonstrates the Kaplan Meir curves for time-to-clearance of MERS-CoV rRT-PCR and shows no difference between patients with diabetes and no diabetes.

Discussion

Our study demonstrates that patients with diabetes constituted around half of the critically ill patients with MERS; MERS patients with diabetes presented with dyspnea and sputum production and were more likely to have respiratory failure requiring mechanical ventilation than those with no diabetes; and diabetes was an independent predictor of mortality in MERS. Viral shedding duration was similar in patients with diabetes and no diabetes

Diabetes is a global health problem and leads to significant complications that increase the risk of morbidity and development of critical illness. Saudi Arabia is among the countries with high prevalence rates (> 30%) [20]. This may partly explain the high prevalence of diabetes in our cohort of critically ill MERS patients. In a Korean cohort of 186 patients with confirmed MERS patients, diabetes was present in 18.8% [9]. In our study, patients with diabetes presented with more severe respiratory symptoms and hypoxia, required mechanical ventilation more frequently, and were given nitric oxide as rescue therapy more often. They also required vasopressors more often. These patients were more likely to receive ribavirin and interferon (alpha or beta-1a) alone or in combination; these antivirals have not been associated with improved outcomes in MERS [21]. Recently, the MIRACLE trial demonstrated a reduction in mortality with the combination of lopinavir-ritonavir and interferon beta-1b; but none of patients in this cohort had received this combination.[22]

Diabetes is associated with reduced neutrophil chemotaxis after stimulation [23] and blunted inflammatory response to endotoxemia [24]. These abnormalities are thought to be the reasons why diabetics have an increased risk of various infections [25]. For viral infections, diabetes has been associated with increased risk for hospitalization after H1N1 infection [26], ICU admission [26], and death [27]. Comorbidities, including diabetes, have been associated with increased mortality in MERS patients [28]. In a small cohort from two hospitals in

Saudi Arabia, diabetes was present in 10.5% of survivors and 70.0% of non-survivors ($p=0.002$) [29]. A study that evaluated MERS cases during the Korean outbreak found that diabetes was a risk factor for mortality on multivariate analysis (OR, 2.47; 95% CI, 1.06-5.72) [9]. Analysis of 1743 MERS cases found that patients with comorbidity (diabetes mellitus, cardiovascular disease, renal disease, or pulmonary disease) had higher mortality risk (adjusted hazard ratio, of 3.7; 95% CI, 2.6-5.7) [13]. In Severe Acute Respiratory Syndrome (SARS), diabetes (OR, 3.0; 95% CI, 1.4-6.3) and fasting blood glucose ≥ 7.0 mmol/L (OR, 3.3; 95% CI 1.4- 7.7) were independent predictors of death [30]. Studies on the association of diabetes with disease severity and outcome in COVID-19 have yielded mixed results [31-36]. In a meta-analysis, the risk of severe COVID-19 was not significantly increased in patients with diabetes (OR, 2.07; 95% CI, 0.89-4.82) [36]. Other studies found no association between diabetes and mortality [32, 35].

It remains unclear how diabetes may contribute to increased disease severity and mortality in people infected with MERS-CoV. In a mouse model of MERS-CoV infection, diabetic mice had a prolonged phase of severe disease and delayed recovery compared to non-diabetic mice [14]. This was associated with delayed inflammation which lasted through 21 days after infection [14]. Diabetic mice exhibited fewer inflammatory monocyte/macrophages and CD4+ T cells and lower levels of TNF- α , IL-6, and IL-12b [14]. This may explain the findings of severe MERS in patients with diabetes.

Viral shedding was relatively prolonged in our MERS patients. However, the time to clearance of MERS-CoV RNA was similar in patients with diabetes and no diabetes. Prolonged shedding has been reported in MERS patients in other studies [37], and has been associated with corticosteroid use [38]. Corticosteroids were used more commonly in patients with diabetes in the current study.

The findings of this study should be interpreted in light of its strengths and weaknesses. The strengths include that it is the largest cohort of critically ill patients with MERS. The limitations are related to the nature of the database and include diabetes diagnosis by history and absence of data on glycemic measures, such as type of diabetes, hemoglobin A1c, glucose control during hospitalization, and prior or current diabetes medications. In addition, glucose levels in patients with no diabetes were elevated, suggesting that some patients had stress hyperglycemia or undiagnosed diabetes. This may affect the associations between diabetes and various outcomes. Given the high prevalence of diabetes in Saudi Arabia, the results of our study may not be generalizable to populations of lower diabetes prevalence.

Conclusion

Diabetes was highly prevalent in a cohort of critically ill patients with MERS. Patients with diabetes had more severe illness. Diabetes was an independent predictor of mortality.

Declarations

Ethics approval and consent to participants

The study was approved by the Ministry of National Guard Health Affairs Institutional Review Board (IRB- RC14-025-R) and by the IRBs of all participating sites (Table S2: Supplement). Informed consent was waived by the IRB because of the retrospective and observational nature of the study.

Consent for publication

All the authors have read the final manuscript and approved its submission

Availability of data and materials

The dataset(s) supporting the conclusions of this article will be made available on the approval of the PI and according to the rules of King Abdullah International Medical Research Center (KAIMRC).

Conflicts of interest

Yaseen Arabi provided nonpaid consultations on therapeutics for MERS for Gilead Sciences and SAB Biotherapeutics and he is a Board Member of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). He is the Lead-Co Chair of the Think-20 Saudi Arabia (T20) Taskforce for COVID-19. Other authors declared that they have no competing interests.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors contribution

JJ and YMA: Conception and design, data acquisition, analytical plan, interpretation of data for the work, drafting of the manuscript, critical revision of the manuscript for important intellectual content, approval of the final version to be published, and agreement to be accountable for all aspects of the work.

HMD, AO, YM, FH, MS, EQ, BAR, ARH, GAM, AA, KK, AAM, IQ, AAS, AM, OS, RR, KM, AR, AK, SS, AMA: Data acquisition, critical revision of the manuscript for important intellectual content, approval of the final version to be published, and agreement to be accountable for all aspects of the work.

GKV and AB: Conception and design, analytical plan, data analysis, critical revision of the manuscript for important intellectual content, approval of the final version to be published, and agreement to be accountable for all aspects of the work

Acknowledgment

We would like to thank the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) for their support in the database construction.

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Figures

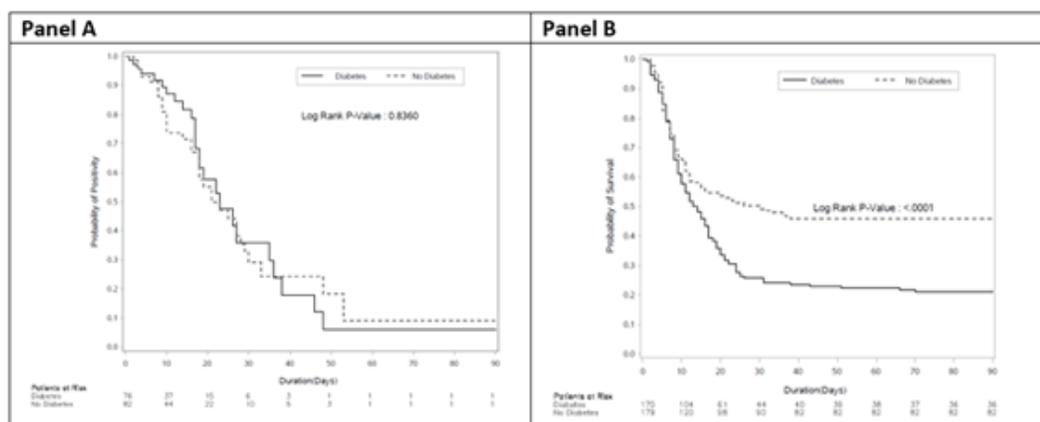


Figure 1

Panel A: Time-to-clearance of the Middle East respiratory syndrome coronavirus (MERS-CoV) RNA among patients with diabetes and no diabetes. Time to clearance was defined as the time taken from the date of ICU admission to having two negative RT-PCR tests not followed by positive test. Log-rank test is used to calculate the P-value. Panel B: Kaplan Meir curves for survival among patients with diabetes and no diabetes and Middle East respiratory syndrome (MERS).

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