Middle East Respiratory Syndrome in Critically Ill Patients with Diabetes: A Multicenter Observational Study of Clinical Presentation, Management and Outcomes

Jesna Jose  
Indian Institute of Technology BHU Varanasi

Hasan Al-Dorzi  
King Saud bin Abdulaziz University for Health Sciences College of Medicine

Awad Al-Omari  
Alfaisal University

Yasser Mandourah  
Prince Sultan Military College of Health Sciences

Fahad Al-Hameed  
King Saud bin Abdulaziz University for Health Sciences College of Medicine

Musharaf Sadat  
King Saud bin Abdulaziz University for Health Sciences College of Medicine

Eman Al-Qasim  
King Saud bin Abdulaziz University for Health Sciences College of Medicine

Basem Alraddadi  
King Faisal Specialist Hospital and Research Center

Abdulrahman Al Harthy  
King Saud Medical City

Ghaleb A Al Mekhlafi  
Prince Sultan Military College of Health Sciences

Abdullah Almotairi  
King Fahad Medical City

Kasim Al Khatib  
Al Noor Specialist Hospital

Ahmed Abdumomen  
King Saud Medical City

Ismael Qushmaq  
King Faisal Specialist Hospital and Research Center

Anees Sindi  
King Abdulaziz Medical City
Ahmed Mady  
King Saud Medical City

Othman Solaiman  
King Faisal Specialist Hospital and Research Center

Rajaa Al-Raddadi  
King Abdulaziz Medical City - Jeddah

Khaled Maghrabi  
King Faisal Specialist Hospital and Research Center

Ahmed Rajab  
King Fahad Hospital

Ayman Kharaba  
King Fahad Hospital

Sara Shalhoub  
King Salman Armed Forces Hospital Northwestern Region

Abdulsalam M Al-Aithan  
King Abdulaziz Medical City

Gajendra K Vishwakarma  
Indian Institute of Technology BHU Varanasi

Atanu Bhattacharjee  
Indian Institute of Technology BHU Varanasi

Yaseen Arabi (✉️ arabi@ngha.med.sa)  
King Saud bin Abdulaziz University for Health Sciences College of Medicine  https://orcid.org/0000-0001-5735-6241

Research article

Keywords: Acute respiratory distress syndrome, coronavirus, diabetes, Middle East respiratory syndrome, COVID-19

DOI: https://doi.org/10.21203/rs.3.rs-57988/v1

License: ☺️ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
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 who developed 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 between critically ill MERS patients who had diabetes and 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 MERS patients, 171 (48.9%) had diabetes, were more likely to be older and have comorbid conditions. Patients with diabetes 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:** Critically ill patients with diabetes constitute half of critically ill patients with MERS, presenting with more severe disease requiring mechanical ventilation compared to those who do not have diabetes. Diabetes is an independent predictor of mortality.

Introduction

The Middle East respiratory syndrome coronavirus (MERS-CoV) is one of the novel zoonotic coronaviruses that can lead to severe acute respiratory illnesses and life-threatening multi-organ dysfunction. It was first isolated from a fatal case of pneumonia in Jeddah, Saudi Arabia in 2012.[1] Since then, community-acquired cases and clusters in healthcare settings have been reported mainly in Saudi Arabia,[2, 3] but also in other 26 countries.[4] 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%.[5] MERS clinical presentation ranges from an asymptomatic infection to rapidly progressive severe respiratory failure with multi organ failure.[6-8] Symptomatic cases manifest after an incubation period of 2-14 days.[7] Fever, cough and dyspnea are common presenting symptoms, [6-9] and admission to intensive care unit (ICU) is frequently needed.[6-8]

Most severe MERS cases have been reported in older adults with chronic comorbidities, including diabetes mellitus, chronic cardiac disease, chronic lung disease, end-stage kidney disease, or immunosuppression.[6, 7, 9-12] One study found that among 47 MERS patients, 68% had diabetes.[6] A case-control study found that diabetes was associated with increased risk of MERS (adjusted OR, 6.99; 95% CI, 1.89–25.86).[11] Diabetes has also been associated with increased mortality in general MERS
patients. Animal studies found that diabetes was associated with a dysregulated immune response resulting in more severe and prolonged lung pathology following MERS-CoV infection.

The objective of this study is to describe clinical presentation and outcomes of critically ill patients with diabetes who developed severe acute respiratory infection due to MERS.

**Methods**

**Patients and settings**

This is a retrospective study of patients admitted to ICUs of 14 referral hospitals in five cities in Saudi Arabia because of severe acute respiratory tract infection (SARI) due to MERS-CoV between September 2012 and October 2015. The characterization of this cohort has been published. SARI was defined as an acute respiratory infection, with fever and cough onset within the preceding 10 days, and evidence of lung involvement based on clinical or radiologic evidence. 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. For infection control purposes, follow-up respiratory samples were collected approximately 1–2 times per week to assess clearance of viral RNA.

**Data collection**

We divided patients into two groups based on preexisting history of diabetes mellitus. We compared their 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. We also described the management in the ICU (use of invasive and noninvasive ventilation, ventilator settings, use of extracorporeal membrane oxygenation (ECMO), prone positioning and medications).

The primary outcome was 90-day mortality. Other studied outcomes were mortality at 14 and 28 days and at ICU and hospital discharge and ICU and hospital length of stay (LOS). We also assessed the time to clearance of MERS-CoV rRT-PCR, 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.

**Statistical analysis**

We compared patients with diabetes to patients with no diabetes using Student t test or the Mann-Whitney U test for continuous variables based on normality assumption and chi-square test or Fisher exact test for categorical variables.
To examine the independent association of diabetes with 90-day mortality, we performed multivariable logistic regression analysis adjusting for selected variables based on clinical significance or statistical difference between the two groups with p values less than 0.1 on univariate testing. These variables included: age, sex, asthma or chronic pulmonary disease, chronic neurological disease, immunosuppressant use prior to 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 multiple imputation technique with 50 imputations. The data set had an arbitrary missing data pattern and it was assumed that the missing data were missing at random (MAR), 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 imputation of BMI, we used the “impute then transform” approach instead of imputing derived variables directly; we imputed the components of derived variables assuming the imputation model was oblivious of the relation between the variables and it would generate imputations that were not consistent with the equation.[16]

Kaplan-Meier curves for the time to viral clearance were constructed censoring by hospital discharge or at 90 days whichever occurred first. Log-rank test was used to compare the median survival time 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 the patients with diabetes and no diabetes. Compared to patients with no diabetes, those with diabetes were older and more likely to have other comorbid conditions such as chronic cardiac and renal disorders. They were more likely present with dyspnea and sputum production. The time from symptom onset to ICU admission was similar.

The laboratory findings are presented in Table 2. There was no difference in white blood cell and platelet counts between the two groups. Patients with diabetes had higher blood glucose, blood urea nitrogen and creatinine.

**Management in the ICU**

Table 3 shows the management interventions performed during the ICU stay. More diabetic patients were treated with non-invasive ventilation (NIV) and with invasive mechanical ventilation (89.5% versus 81.6%,...
than non-diabetics. The time from symptom onset to intubation was similar. There was more use of nitric oxide but less ECMO in patients with diabetes.

For other organ support, more patients with diabetes had shock requiring vasopressors than those with no diabetes (86.0% versus 72.1%, p=0.002). Corticosteroids were given more commonly in patients with diabetes (58.5 versus 41.9%, p=0.002). Renal replacement therapy was provided more often in patients with diabetes (60.2% versus 39.7%, p=0.0001). There was no difference between the number of patients receiving antivirals between the two groups; however, more patients with diabetes received ribavirin and interferon (40.9% vs 26.3%, p=0.02).

**Outcomes of patients**

Table 3 presents the different outcomes of patients. The overall 90-day mortality for the cohort was high. The mortality was higher in patients with diabetes (78.9% versus 54.7%, p<0.0001). On multivariable logistic regression analysis, 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, 1.20; 95% CI, 1.14-1.26) (Table 4).

The ICU LOS, but not that in hospital, was longer for patients with diabetes. The duration of viral shedding was similar in both groups. The median time to clearance of MERS-CoV rRT-PCR was 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 describes the probability of having positive MERS-CoV rRT-PCR after MERS diagnosis and shows no difference between patients with diabetes and no diabetes.

**Discussion**

The main findings of this study were that patients with diabetes constituted around half of critically ill patients with MERS; MERS patients with diabetes presented with dyspnea and sputum production and had respiratory failure requiring mechanical ventilation more often than those with no diabetes; viral shedding was prolonged but of similar duration in patients with diabetes and no diabetes and diabetes was an independent predictor of mortality in MERS.

Diabetes is a global health problem and may lead to significant complications that increase the risk morbidity and development of critical illness. Saudi Arabia is among the countries with the highest prevalence rates (> 30%).[17] This may partly explain the high prevalence of diabetes in our cohort of critically ill MERS patients. 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, needed mechanical ventilation more frequently and were given nitric oxide as rescue therapy more often. They also required vasopressors more often. Multiple antivirals were provided. These included ribavirin and interferon alone or in combination. These antivirals have not been associated with improved outcomes in MERS.[18]
Diabetes is associated with reduced neutrophil chemotaxis after stimulation[19] and blunted inflammatory response to endotoxemia.[20] These abnormalities are thought to be the reasons why diabetics have increased risk of infections. These include infection of the urinary tract, skin and soft tissue and lower respiratory tract.[21] For viral infections, diabetes has been associated with increased risk for hospitalization after H1N1 infection,[22] ICU admission,[22] and death.[23] Comorbidities, including diabetes, have been associated with increased mortality in MERS patients.[24] In a small cohort from two hospitals in Saudi Arabia, diabetes was present in 10.5% of survivors and 70.0% of nonsurvivors (p=0.002).[25] A study that evaluated MERS cases during the Korean outbreak found that diabetes was a risk factor for mortality on multivariate Cox-regression 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 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.[26]

Studies on diabetes prevalence in COVID-19 and its association with disease severity and outcomes have yielded variable results.[27] The prevalence was 5.3-19.5% in studies from China, > 30% in studies from Italy and 10.9-58.0% in studies from the United States.[27] In a study of 140 COVID-19 patients from Wuhan, China, diabetes was prevalent in 12.1% and was not associated with more severe disease (respiratory frequency ≥ 30/min, oxygen saturation ≤ 93% at rest, and oxygenation index ≤ 300 mm Hg). [28] No mortality data were reported.[28] One report of 72314 COVID-19 cases found an overall case-fatality rate of 2.3%. [29] This rate was higher in patients with preexisting comorbid conditions and was 7.3% for diabetes.[29] Another study that included 1099 patients with confirmed COVID-19, diabetes was present in 5.7% of non-severe cases, 16.2% of severe cases and 26.9% in those who had ICU admission, needed mechanical ventilation, or died.[30] However, a meta-analysis of eight studies (N=46,248), the risk of severe COVID-19 was not significantly increased in patients with diabetes (OR, 2.07; 95% CI, 0.89-4.82), unlike hypertension and cardiovascular disease.[31] In a study of 191 patients from two hospitals in Wuhan, China, hypertension was the most common comorbidity (30.4%) followed by diabetes (18.8%). [32] The mortality rate was 28.3% with diabetes being associated with mortality on univariate but not multivariable analysis.[32] Similarly, another study from Wuhan (N=201) found no significant increased mortality risk with diabetes (hazard ratio, 1.58; 95% CI, 0.80-3.13, p = 0.19) in a bivariate cox regression analysis.[33]

It remains unclear clear how diabetes may contribute to increased disease severity and outcome 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-a, IL-6 and IL-12b. [14] This may explain the findings of severe MERS in patients with diabetes. The worse outcome among diabetic patients could be due to the higher prevalence of comorbid underlying medical conditions.
Viral shedding was relatively prolonged in our MERS patients. The time to clearance of rt-PCR for MERS-CoV was similar in patients with diabetes and no diabetes (median: 23 versus 21 days, respectively). Prolonged shedding has been reported in MERS patients in other studies,[34] and has been associated with corticosteroid use.[35] In SARS, early use of hydrocortisone was associated with delayed viral clearance compared with a control group (median: 12 days (range: 11-20 days) versus 8 days (8-15 days), respectively; p=0.11).[36] In 191 COVID-19 patients, the median duration of viral shedding was 20.0 days (Q1, Q3: 17.0-24.0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors (median: 18.5 days; Q1, Q3: 15.0-22.0).[32]

The findings of this study should be interpreted in the light of its strengths and weaknesses. The strengths include that it is the largest cohort of MERS critically ill patients. The limitations include diabetes diagnosis by history, absence of data on glycemic measures such hemoglobin A1c, glucose control during hospitalization and prior or current diabetes medications. In addition, glucose levels in the patients with no diabetes were elevated, suggesting that some patients had stress hyperglycemia or undiagnosed diabetes.

**Conclusions**

In conclusion, diabetes was highly prevalent in a cohort of patients with SARI due to MERS-CoV who were admitted to ICUs in 14 hospitals in Saudi Arabia. Patients with diabetes had more requirement for mechanical ventilation. Diabetes was not associated with longer viral shedding but was an independent predictor of mortality.

**Declarations**

**Acknowledgment**

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

**Ethics approval**

The study was approved by the Ministry of National Guard Health Affairs Institutional Review Board (IRB) and by the IRBs of all participating sites.

**Consent to participants**

Informed consent was waived by the IRB because of the retrospective nature of the study.
Funding source

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

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.

Availability of data and materials

The dataset(s) supporting the conclusions of this article will be made available on the approval of the PI

References

1. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA: Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012, 367(19):1814-1820.

2. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, Alabdullatif ZN, Assad M, Almulhim A, Makhdoom H et al: Hospital outbreak of Middle East respiratory syndrome coronavirus. The New England journal of medicine 2013, 369(5):407-416.

3. Oboho IK, Tomczyk SM, Al-Asmari AM, Banjar AA, Al-Mugti H, Aloraini MS, Alkhaldi KZ, Almohammadi EL, Alraddadi BM, Gerber SI et al: 2014 MERS-CoV outbreak in Jeddah—a link to health care facilities. N Engl J Med 2015, 372(9):846-854.

4. Cho S, Kang J, Ha Y, Park G, Lee J, Ko J, Lee J, Kim J, Kang C, Jo I: MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. Lancet (London, England) 2016, 388(10048):994.

5. Al-Qahtani S, Al-Dorzi HM, Tamim HM, Hussain S, Fong L, Taher S, Al-Knawy BA, Arabi Y: Impact of an intensivist-led multidisciplinary extended rapid response team on hospital-wide cardiopulmonary arrests and mortality*. Crit Care Med 2013, 41(2):506-517.

6. Assiri A, Al-Tawfiq J, Al-Rabeeah A, Al-Rabiah F, Al-Hajjar S, Al-Barrak A, Flemban H, Al-Nassir W, Balkhy H, Al-Hakeem R: Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. The Lancet Infectious diseases 2013, 13(9):752.

7. Alsolamy S: Middle East respiratory syndrome: knowledge to date. Crit Care Med 2015, 43(6):1283-1290.
8. Saad M, Omrani A, Baig K, Bahloul A, Elzein F, Matin M, Selim M, Al Mutairi M, Al Nakhli D, Al Aidaroos A: Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases* 2014, 29:301.

9. Choi WS, Kang C-I, Kim Y, Choi J-P, Joh JS, Shin H-S, Kim G, Peck KR, Chung DR, Kim HO: Clinical Presentation and Outcomes of Middle East Respiratory Syndrome in the Republic of Korea. *Infection & Chemotherapy* 2016, 48(2):118.

10. Al-Tawfiq JA, Hinedi K, Ghandour J, Khairalla H, Musleh S, Ujayli A, Memish ZA: Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. *Clin Infect Dis* 2014, 59(2):160-165.

11. Alraddadi BM, Watson JT, Almarashi A, Abedi GR, Turkistani A, Sadran M, Housa A, Almazroa MA, Alraihan N, Banjar A: Risk factors for primary Middle East respiratory syndrome coronavirus illness in humans, Saudi Arabia, 2014. *Emerging infectious diseases* 2016, 22(1):49.

12. Alqahtani F, Aleanizy F, Mohamed RAEH, Alanazi M, Mohamed N, Alrasheed M, Abanmy N, Alhawassi T: Prevalence of comorbidities in cases of Middle East respiratory syndrome coronavirus: a retrospective study. *Epidemiology and Infection* 2019, 147.

13. Yang Y-M, Hsu C-Y, Lai C-C, Yen M-F, Wikramaratna PS, Chen H-H, Wang T-H: Impact of Comorbidity on Fatality Rate of Patients with Middle East Respiratory Syndrome. *Scientific Reports* 2017, 7.

14. Kulcsar KA, Coleman CM, Beck SE, Frieman MB: Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. *JCI insight* 2019, 4(20).

15. Arabi YM, Al-Omari A, Mandourah Y, Al-Hameed F, Sindi AA, Alraddadi B, Shalhoub S, Almotairi A, Al Khatib K, Abdulmomen A: Critically ill patients with the Middle East respiratory syndrome: a multicenter retrospective cohort study. *Critical care medicine* 2017, 45(10):1683-1695.

16. Von Hippel PT: HOW TO IMPUTE INTERACTIONS, SQUARES, AND OTHER TRANSFORMED VARIABLES. *Sociological Methodology* 2009, 39(1):265-291.

17. Meo S, Usmani A, Qalbani E: Prevalence of type 2 diabetes in the Arab world: impact of GDP and energy consumption. *European review for medical and pharmacological sciences* 2017, 21(6):1303.

18. Arabi Y, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, Jose J, Alraddadi B, Almotairi A, Al Khatib K: Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2019.

19. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B: Impaired leucocyte functions in diabetic patients. *Diabet Med* 1997, 14(1):29-34.

20. Andreasen AS, Pedersen-Skovsgaard T, Berg RM, Svendsen KD, Feldt-Rasmussen B, Pedersen BK, Moller K: Type 2 diabetes mellitus is associated with impaired cytokine response and adhesion molecule expression in human endotoxemia. *Intensive Care Med* 2010, 36(9):1548-1555.

21. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, Rutten GE: Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 2005,
41(3):281-288.

22. Allard R, Leclerc P, Tremblay C, Tannenbaum TN: Diabetes and the severity of pandemic influenza A (H1N1) infection. *Diabetes Care* 2010, 33(7):1491-1493.

23. Hanslik T, Boelle PY, Flahault A: Preliminary estimation of risk factors for admission to intensive care units and for death in patients infected with A(H1N1)2009 influenza virus, France, 2009-2010. *PLoS Curr* 2010, 2:RRN1150.

24. Park J-E, Jung S, Kim A, Park J-E: MERS transmission and risk factors: a systematic review. *BMC Public Health* 2018, 18.

25. Sherbini N, Iskandrani A, Kharaba A, Khalid G, Abduljawad M, Al-Jahdali H: Middle East respiratory syndrome coronavirus in Al-Madinah City, Saudi Arabia: Demographic, clinical and survival data. *Journal of epidemiology and global health* 2017, 7(1):29.

26. Yang J, Feng Y, Yuan M, Yuan S, Fu H, Wu B, Sun G, Yang G, Zhang X, Wang L: Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabetic medicine: a journal of the British Diabetic Association* 2006, 23(6):623.

27. Singh AK, Gupta R, Ghosh A, Misra A: Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. *Diabetes & Metabolic Syndrome* 2020, 14(4):303.

28. Zhang J, Dong X, Cao Y, Yuan Y, Yang Y, Yan Y, Akdis C, Gao Y: Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China. *Allergy* 2020.

29. Wu Z, McGooogan J: Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.

30. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui D: Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine* 2020.

31. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y: Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases* 2020.

32. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)* 2020.

33. Wu C, Chen X, Cai Y, Xia Ja, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C: Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Internal Medicine*.

34. Bin S, Heo J, Song M, Lee J, Kim E, Park S, Kwon H, Kim S, Kim Y, Si Y: Environmental Contamination and Viral Shedding in MERS Patients During MERS-CoV Outbreak in South Korea. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2016, 62(6):755.

35. Arabi Y, Mandourah Y, Al-Hameed F, Sindi A, Almekhlafi G, Hussein M, Jose J, Pinto R, Al-Omari A, Kharaba A: Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome.
36. Lee N, Allen CK, Hui D, Ng E, Wu A, Chiu R, Wong V, Chan P, Wong K, Wong E: Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology* 2004, 31(4):304.

**Tables**

**Table 1:** Baseline characteristics of patients with diabetes who developed Middle East Respiratory Syndrome (MERS) compared to patients with no diabetes.
| Variables                                      | Diabetes N=171 | No Diabetes N=179 | P-value |
|-----------------------------------------------|----------------|------------------|---------|
| Age (yr), Median (Q1, Q3)                     | 61.0 (53.0,72.0) | 54.0 (35.0,67.0) | <0.0001 |
| BMI (Kg/m²), Median (Q1, Q3)                  | 29.3 (24.6,33.3) | 28.3 (24.1,33.0) | 0.31    |
| Male sex – no. (%)                            | 114 (66.7)      | 127 (70.9)       | 0.39    |
| Healthcare worker – no. (%)                   | 4 (2.3)         | 28 (15.6)        |         |
| Community acquired – no. (%)                  | 102 (59.6)      | 83 (46.4)        | <0.0001 |
| Healthcare-associated (Non-healthcare worker) – no. (%) | 65 (38.0) | 68 (38.0) |         |
| Days from onset of symptoms to the emergency room, Median (Q1, Q3) | 5.0 (3.0,8.0)  | 4.0 (2.0,7.0)  | 0.30    |
| Days from symptom onset to ICU admission, Median (Q1, Q3) | 7.0 (4.0,10.5) | 7.0 (4.0,11.0) | 0.66    |
| Days from symptom onset to intubation, Median (Q1, Q3) | 8.0 (5.0,12.0) | 8.0 (5.0,13.0) | 0.37    |
| Presenting symptoms – no. (%)                 |                |
| **Lower respiratory**                         |                |
| Dyspnea                                       | 136 (79.5)      | 123 (68.7)       | 0.02    |
| Cough                                         | 122 (71.3)      | 117 (65.4)       | 0.23    |
| With sputum                                   | 75 (43.9)       | 58 (32.4)        | 0.03    |
| With bloody sputum                            | 11(6.4)         | 18 (10.1)        | 0.22    |
| Chest pain                                    | 36 (21.1)       | 32 (17.9)        | 0.45    |
| Wheezing                                      | 10 (5.8)        | 9 (5.0)          | 0.74    |
| **Upper respiratory**                         |                |
| Earache                                       | 2 (1.2)         | 1(0.6)           | 0.62^   |
| Rhinorhrea                                    | 6(3.5)          | 11(6.1)          | 0.25    |
| Sore throat                                   | 23 (13.5)       | 24 (13.4)        | 0.99    |
| **Systemic symptoms**                         |                |
| Fever (temperature > 38°C)                    | 130 (76.0)      | 131 (73.2)       | 0.54    |
| Condition                                      | Treatment Group 1 | Treatment Group 2 | P-value |
|-----------------------------------------------|-------------------|-------------------|---------|
| Myalgia or arthralgia                         | 32 (18.7)         | 34 (19.0)         | 0.95    |
| Headache                                      | 14 (8.2)          | 21 (11.7)         | 0.27    |
| Fatigue                                       | 66 (38.6)         | 55 (30.7)         | 0.12    |
| Abdominal pain                                | 22 (12.9)         | 25 (14.0)         | 0.76    |
| Lymphadenopathy                               | 1 (0.6)           | 2 (1.1)           | >0.99^  |
| Diarrhea                                      | 20 (11.7)         | 18 (10.1)         | 0.62    |
| Vomiting / Nausea                             | 28 (16.4)         | 30 (16.8)         | 0.92    |
| Altered consciousness- confusion              | 44 (25.7)         | 30 (16.8)         | 0.04    |
| Seizures                                      | 2 (1.2)           | 2 (1.1)           | >0.99^  |

**Other comorbidities – no. (%)**

| Condition                                      | Treatment Group 1 | Treatment Group 2 | P-value |
|-----------------------------------------------|-------------------|-------------------|---------|
| Chronic pulmonary disease (including asthma)  | 22 (12.9)         | 24 (13.4)         | 0.88    |
| Liver disease                                 | 12 (7.0)          | 10 (5.6)          | 0.58    |
| Chronic renal disease                         | 71 (41.5)         | 39 (21.8)         | <0.0001 |
| Chronic cardiac disease                       | 95 (55.6)         | 43 (24.0)         | <0.0001 |
| Chronic neurological disease, Hemiplegia, Paraplegia or Dementia | 22 (12.9) | 16 (8.9) | 0.24 |
| BMI > 30 (Kg/m²)                              | 55 (45.5)         | 60 (40.5)         | 0.42    |
| Any malignancy including leukemia or lymphoma | 12 (7.0)          | 19 (10.6)         | 0.24    |
| Rheumatologic disease                         | 2 (1.2)           | 5 (2.8)           | 0.45^   |
| Any malignancy including leukemia, lymphoma or solid tumors | 14 (8.2) | 20 (11.2) | 0.35 |
| Immunosuppressant use prior to admission      | 6 (3.5)           | 15 (8.4)          | 0.06    |

| SOFA score, Median (Q1, Q3)                   | 9.0 (6.0,12.0)    | 8.0 (5.0,11.0)    | 0.02    |

BMI: Body mass index; SOFA: Sequential Organ Failure Assessment

Denominator of the percentage is the total number of subjects in the treatment group. For continuous 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 unless otherwise noted. ^Fisher’s exact test was used to calculate P-value.
Table 2. Physiological parameters on day 1 admission to ICU in patients with the Middle East Respiratory Syndrome (MERS) coronavirus among patients with diabetes and no diabetes

| 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, 1.0)   | 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 ($\times$ 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 ($\times$10$^9$/L)            | 188.0 (117.0, 253.0) | 168.50 (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 (mmol/L)                     | 12.0 (7.3, 20.8)   | 9.1 (4.1, 16.9)   | 0.0002  |
| Creatinine (mmol/L)                     | 141.4 (91.0, 327.0) | 114.9 (67.0, 217.0) | 0.0004  |
| Bilirubin (mmol/L)                      | 12.3 (7.8, 23.7)   | 12.0 (7.8, 22.9)  | 0.86    |

PaO$_2$: partial pressure of oxygen; SaO$_2$: Oxygen saturation; FiO$_2$: Fraction of inspired oxygen; PaO$_2$/FiO$_2$ ratio: the ratio of partial pressure of oxygen to the fraction of inspired oxygen; ALT: alanine aminotransferase, AST: aspartate transaminase. For continuous variables, Mann-Whitney U test was used to calculate p value. For categorical variables, chi-square test was used to calculate the P value. 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: PaO$_2$: 5 patient and 3 patient, SaO$_2$: 3 patients and 3 patients, FiO$_2$: 8 patients and 17 patient, PaO$_2$/FiO$_2$ 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.
Table 3. Main interventions and outcome in patients with the Middle East Respiratory Syndrome (MERS) coronavirus among Diabetics and non-Diabetics
| Variables                                                                 | Diabetes N=171 | non-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. (%)                                                     | 142 (83.0)     | 145 (81.0)         | 0.62    |
| Both interferon-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 immunoglobulin – no. (%)                                     | 9 (5.3)        | 15 (8.4)           | 0.25    |
| Tracheostomy – no (%)                                                    | 5 (2.9)        | 9 (5.0)            | 0.35    |
| **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

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

For continuous variables, the Mann-Whitney U test was used to calculate p value; For categorical variables, chi-square test was used to calculate the P value unless otherwise noted. ^Fisher’s exact test was used to calculate P-value.

**Table 4: Multivariable model to examine whether diabetes is an independent predictor of mortality**

| Variables                                | Complete case analysis (N=266) | Multiple Imputation (N=350) |
|------------------------------------------|--------------------------------|-----------------------------|
|                                          | OR (95% CI)                    | P-value                     | OR (95% CI)                    | P-value                     |
| Diabetes                                 | 2.09 (1.18, 3.72)              | 0.0050                      | 2.13(1.15, 3.95)               | 0.0161                      |
| SOFA                                     | 1.20 (1.14, 1.26)              | <0.0001                     | 1.17(1.12, 1.23)               | <0.0001                     |
| Female sex                               | 1.68 (1.06, 2.67)              | 0.0150                      | 1.74(1.09, 2.79)               | 0.0214                      |
| Age                                      | 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)             | 0.0695                      | 3.40(1.04, 11.14)              | 0.0434                      |
| BMI (kg/m²)                              | 0.97 (0.90, 1.03)              | 0.2341                      | 0.96(0.91, 1.02)               | 0.2143                      |
| Immunosuppressant use prior to admission | 1.24 (0.29, 5.26)              | 0.7448                      | 1.13(0.35, 3.64)               | 0.8423                      |
| Asthma or chronic pulmonary disease      | 1.20 (0.66, 2.20)              | 0.5062                      | 1.04(0.57, 1.91)               | 0.9028                      |

OR: Odds Ratio ; CI: Confidence Interval; BMI: body mass index; SOFA: Sequential Organ Failure Assessment
Time-to-clearance of the real-time reverse transcription polymerase chain reaction of the Middle East respiratory syndrome (MERS) coronavirus among patients with diabetes and no diabetes. Time to clearance was the time taken from date of admission to negative MERS Test. Log-rank Test is used to calculate the P-value.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.
• SupplementAugust122020.docx