Development of a risk-prediction model for Middle East respiratory syndrome coronavirus infection in dialysis patients

Anwar E. AHMED [ORCID],[1] Abeer N. ALSHUKAIRI,[2] Hamdan AL-JAHDALI,[1]
Mody ALAQEEL,[1] Salma S. SIDDIQ,[3] Hanan A. ALSAAB,[4] Ezzeldin A. SAKR,[3]
Hamed A. ALYAHYA,[3] Munzir M. ALANDONISI,[3] Alaa T. SUBEDAR,[3]
Nouf M. ALOUDAH,[5] Salim BAHAROON,[1] Majid A. ALSALAMAH,[1]
Sameera AL JOHANI,[1] Mohammed G. ALGHAMDI[3]

[1]*King Saud bin Abdulaziz University for Health Sciences (KSAU-HS)/King Abdullah International Medical Research Center (KAIMRC)/King Abdulaziz Medical City (KAMC), Ministry of National Guard - Health Affairs, Riyadh;* [2]*King Faisal Specialist Hospital and Research Centre, Jeddah;* [3]*King Fahad General Hospital, Jeddah;* [4]*Medical Records Department, Ministry of Health, Jeddah;* [5]*King Saud University, Riyadh, Saudi Arabia*

Abstract

Introduction: The Middle East respiratory syndrome coronavirus (MERS-CoV) infection can cause transmission clusters and high mortality in hemodialysis facilities. We attempted to develop a risk-prediction model to assess the early risk of MERS-CoV infection in dialysis patients.

Methods: This two-center retrospective cohort study included 104 dialysis patients who were suspected of MERS-CoV infection and diagnosed with rRT-PCR between September 2012 and June 2016 at King Fahd General Hospital in Jeddah and King Abdulaziz Medical City in Riyadh. We retrieved data on demographic, clinical, and radiological findings, and laboratory indices of each patient.

Findings: A risk-prediction model to assess early risk for MERS-CoV in dialysis patients has been developed. Independent predictors of MERS-CoV infection were identified, including chest pain (OR = 24.194; P = 0.011), leukopenia (OR = 6.080; P = 0.049), and elevated aspartate aminotransferase (AST) (OR = 11.179; P = 0.013). The adequacy of this prediction model was good (P = 0.728), with a high predictive utility (area under curve [AUC] = 76.99%; 95% CI: 67.05% to 86.38%). The prediction of the model had optimism-corrected bootstrap resampling AUC of 71.79%. The Youden index yielded a value of 0.439 or greater as the best cut-off for high risk of MERS infection.

Discussion: This risk-prediction model in dialysis patients appears to depend markedly on chest pain, leukopenia, and elevated AST. The model accurately predicts the high risk of MERS-CoV infection in dialysis patients. This could be clinically useful in applying timely intervention and control measures to prevent clusters of infections in dialysis facilities or other health care settings. The predictive utility of the model warrants further validation in external samples and prospective studies.

Key words: Hemodialysis, Middle East respiratory syndrome coronavirus (MERS-CoV), chest pain, leukopenia, aminotransferase (AST), Saudi Arabia

INTRODUCTION

An important lesson was learned from the world's largest Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks that occurred in Saudi Arabia and South Korea: that health care-associated infection is a major cause of rapid pathogen spread in health care settings with a high risk of cluster infections. In particular it was discovered that they spread rapidly in hemodialysis, inpatient, emergency, and intensive care facilities.[1–6] Dialysis patients were associated with a high risk of mortality[6] compared to the national mortality estimates in the MERS-CoV population.[7,8]

Assiri et al. were able to track hospitals, units, rooms, beds, symptoms onset, and diagnoses status to map a large cluster of infections between April 1 and May 23, 2013.[1] According to the authors, the clusters developed in the hemodialysis facility, where 1 health care-associated infected patient who underwent long-term hemodialysis transmitted the virus to 7 dialysis patients and the transmission then continued to other hospital settings.[1]

In a recent study, Assiri et al. reported a high likelihood of transmission in dialysis patients and health care workers within the outpatient dialysis facility.[6] Among 186 laboratory-confirmed MERS-CoV patients in South Korea, only 1 dialysis patient was identified, but no cluster viral transmissions were identified in other patients who utilized the same hemodialysis facility.[9] Park et al. developed a guideline to control cluster infections and prevent MERS outbreaks in hemodialysis facilities.[9]

Earlier studies on dialysis patients focused on virus transmission and clinical outcomes, while limited by the small number of MERS cases. Our understanding of early diagnoses of MERS and identifying patients at high risk of infection is incomplete,[10] particularly in a hemodialysis facility. A MERS-CoV risk assessment tool is urgently needed to accurately identify dialysis patients at high risk of infection and apply infection control measures to prevent future cluster transmission in these patients and patients in other health care facilities.

Exploring an efficient screening system to detect MERS-CoV infection at an earlier stage may result in immediate isolation[11] and improve clinical outcomes and economic burdens.[12,13] A valid risk-predictive model for MERS-CoV infection in dialysis patients may increase the likelihood of early virus detection. The authors attempt to develop an algorithm that combines demographic, clinical, radiological, and laboratory data to assess the early risk of MERS-CoV infection in dialysis patients who are suspected of having MERS-CoV infection and were diagnosed by real-time reverse transcription-PCR (rRT-PCR) between September 2012 and June 2016. The authors hypothesized that MERS-CoV infection in dialysis patients could be predicted by a set of clinical, radiological, and laboratory indices.

METHODS

This two-center retrospective cohort study included 104 dialysis patients who were suspected of having MERS-CoV, according to the Saudi Ministry of Health Guidelines,[14] and were diagnosed with rRT-PCR between September 2012 and June 2016 at King Fahd General Hospital in Jeddah (KFGH-JED) and King Abdulaziz Medical City in Riyadh (KAMC-R). These hospitals are the largest to provide health care in Saudi Arabia, and both hospitals experienced MERS outbreaks.[15,16] The Institutional Review Board (IRB) approval was obtained from both hospitals: the Saudi Ministry of Health (IRB Log Number: 16–230E) and the Ministry of National Guard Health Affairs (Study Number: RC17/061), Riyadh Saudi Arabia. Inclusion criteria were dialysis patients aged 14 years or older and their clinical specimens that were diagnosed with rRT-PCR for MERS-CoV infection during the study period.

The case definition of Saudi Ministry of Health is used in all local health facilities as a guideline to classify patients with suspected MERS-CoV infection. A suspected case defined as a person with:

1. Acute respiratory illness and/or chest radiological findings of pneumonia,
2. Hospitalized with health care associated-pneumonia,
3. Upper or lower respiratory tract illness within 14 days after exposure to a confirmed/probable case of MERS-CoV infection, and
4. High fever (≥38°C), headache, body aches, nausea/vomiting, diarrhea, or with or without respiratory symptoms, leucopenia, and thrombocytopenia.[14]

Data were abstracted into 15 potential predictors of MERS, including demographic data (age and gender); clinical presentations (fever, cough, short breath, *chest pain*, abdominal pain, diarrhea, vomiting, diabetes); radiology findings in chest (abnormal CT scan or x-ray); baseline laboratory measurements (number of white cells) (WBC) 109/L in the blood, blood platelet count 10^9/L, alanine transaminase (ALT) U/L, and aspartate transaminase (AST) U/L. In order to evaluate whether MERS-CoV infection was associated with a decrease in WBC count, a cut-off of less than 4 (10^9/L) indicates leukopenia.[14] Similarly, platelet count of less than 150 (10^9/L) indicates

Table 1 Characteristics of dialysis patients who underwent rRT-PCR screening by MERS-CoV status (N = 104)

Characteristics	Overall Mean	SD	Non-MERS 56 (53.8%) Mean	SD	MERS 48 (46.2%) Mean	SD	P	OR	95% CI for OR	
Age (14–95 years)	60.3	16.7	61.3	18.5	59.1	14.5	0.503	0.992	0.969	1.015
	n	%	n	%	n	%	P	OR	95% CI for OR	
Male gender	75	72.1	39	69.6	36	75.0	0.544	1.308	0.550	3.111
Fever	50	51.5	24	48.0	26	55.3	0.471	1.341	0.603	2.982
Cough	59	60.2	27	52.9	32	68.1	0.128	1.896	0.832	4.321
Short breath	71	72.4	35	68.6	36	76.6	0.379	1.496	0.610	3.671
Chest pain	21	21.6	4	8.0	17	36.2	0.001[a]	6.517	1.998	21.257
Abdominal pain	14	14.3	7	13.7	7	14.9	0.869	1.100	0.355	3.411
Diarrhea	12	12.5	3	6.1	9	19.1	0.054	3.632	0.918	14.370
Vomiting	14	14.3	8	15.7	6	12.8	0.680	0.787	0.251	2.464
Diabetes	59	61.5	24	49.0	35	74.5	0.010[a]	3.038	1.283	7.196
Abnormal radiology	36	42.4	10	26.3	26	55.3	0.007[a]	3.467	1.377	8.725
Leukopenia	17	16.3	6	10.7	11	22.9	0.093	2.477	0.840	7.308
Thrombocytopenia	40	40.8	22	41.5	18	40.0	0.880	0.939	0.418	2.109
ALT elevated	27	40.9	8	30.8	19	47.5	0.177	2.036	0.721	5.751
AST elevated	56	83.6	19	70.4	37	92.5	0.022[a]	5.193	1.233	21.865

[a]Significant at α = 0.05.

thrombocytopenia,[14] ALT greater than 55 (U/L) indicates elevated ALT, and AST greater than 34 (U/L) indicate elevated AST.

STATISTICAL ANALYSIS

Data were analyzed using STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). Overall sample summary and subgroup analysis were provided in Table 1. P value of independent samples t test/chi-square test and unadjusted odds ratio (OR) were reported to test whether specific characteristics were associated with MERS-CoV infection in dialysis patients (Table 1). The area under the curve (AUC) and 95% confidence interval (CI) were used to evaluate the accuracy of each predictor in identifying MERS-CoV infection (Table 2). We developed the MERS risk-prediction model in dialysis patients using the stepwise logistic regression model. Fifteen potential predictors of MERS-CoV were evaluated at α ≤ 0.05. The goodness-of-fit of the final model was evaluated using the Hosmer-Lemeshow test. A P value of greater than 5% (α > 0.05) indicates the model fit the data well. The discrimination of the model was evaluated by the receiver operator characteristic curve and was compared with the each of the most important predictors (Figure 1). The risk model was internally validated in 100 bootstrap samples drawn with

replacement from the study sample (N = 104). The model was presented in the form of the predictive probability of MERS-CoV infection in dialysis, which is a function of the important selected variables, refer to the supplement

Table 2 Area under the receiver operator characteristic curve for predicting MERS

| Factor	AUC	SE	95% CI for AUC Lower	Upper
Age	0.436	0.057	0.324	0.549
Gender	0.527	0.044	0.440	0.614
Fever	0.537	0.051	0.436	0.637
Cough	0.576	0.049	0.479	0.672
Short breath	0.540	0.045	0.451	0.629
Chest pain	0.641	0.040	0.562	0.720
Abdominal pain	0.506	0.036	0.436	0.576
Diarrhea	0.565	0.034	0.499	0.631
Vomiting	0.485	0.036	0.416	0.555
Diabetes	0.627	0.048	0.533	0.722
Abnormal radiology	0.645	0.052	0.544	0.746
Leukopenia	0.561	0.037	0.488	0.634
Thrombocytopenia	0.493	0.050	0.394	0.591
ALT elevated	0.584	0.061	0.464	0.703
AST elevated	0.611	0.050	0.514	0.708
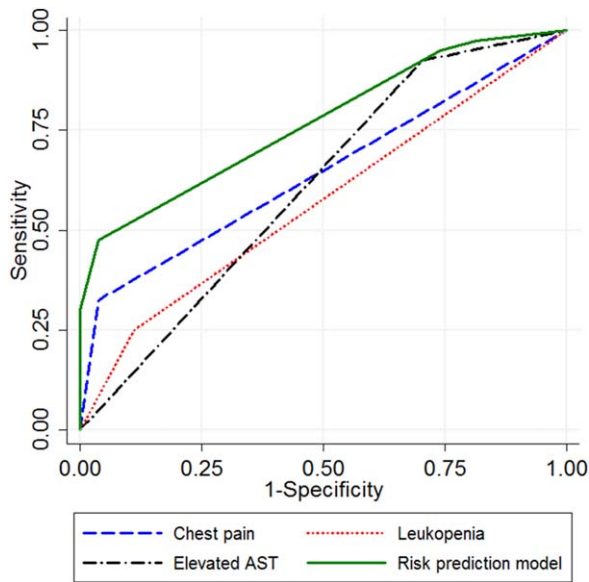
Figure 1 ROC curve of the risk prediction model as compared to individual predictor. [Color figure can be viewed at wileyonlinelibrary.com]

file. The Youden index was used to identify optimal probability cut-off value for the MERS risk stratification.

RESULTS

Of the 104 dialysis patients studied, 76% had respiratory symptoms, and 26.9% had gastrointestinal symptoms at presentation. The sample age was relatively older at 60.3 ± 16.7 years and 72.1% were males (Table 1). Among the samples, 48 (46.2%) were diagnosed by rRT-PCR as having MERS-CoV infection and 56 (53.8%) as having no MERS-CoV infection. MERS-CoV was associated with mortality in dialysis patients (39.3% in non-MERS-CoV vs. 91.7% in MERS-CoV, P = 0.001). In the dialysis patients studied, MERS-CoV infection was not associated with age (P = 0.503) or gender (P = 0.544). However, MERS dialysis patients were more likely to have chest pain (OR = 6.517; P = 0.001), diabetes (OR = 3.038; P = 0.010), abnormal radiology findings (OR = 3.467;

Table 4 Probability cut-off values for discriminating between high-risk and low-risk MERS in dialysis patients

Probability cut-off	Sensitivity	Specificity
0.225	0.975	0.185
0.439	0.950	0.259
0.604	0.500	0.926
0.780	0.475	0.963
0.914	0.300	1.000
0.978	0.050	1.000

P = 0.007), and elevated AST (OR = 5.193; P = 0.022). The AUC in Table 2 shows the predictors of MERS infections. It indicates that chest pain, diabetes, abnormal radiology findings, and elevated AST (AUC $\geq$ 0.60) were the most powerful predictors of discriminating MERS.

When controlled for 15 potential predictors (Table 3), the final risk-prediction model retained 3 independent variables (at $\alpha \leq 0.05$) that increased the risk of MERS-CoV infection. MERS dialysis patients were more likely to have chest pain (OR = 24.194; P = 0.011), leukopenia (OR = 6.080; P = 0.049), and elevated AST (OR = 11.179; P = 0.013). According to the Hosmer-Lemeshow test, the adequacy of this prediction model was good (P = 0.728). The model shows high potential for predicting MERS (AUC = 76.99%; 95% CI: 67.05% to 86.38%). The prediction of the model had optimism-corrected bootstrap resampling AUC of 71.79%. Figure 1 shows that the risk-prediction model improved the accuracy of risk classification as compared to the individual predictors. The predicted probability of MERS can be calculated by: $[1 + \exp(2.362 - 3.186 \times \text{Chest pain} - 1.805 \times \text{leukopenia} - 2.414 \times \text{elevated AST})]^{-1}$. Table 4 presents cut-off values for risk probability.

DISCUSSION

This is the first study to develop a risk-prediction model in dialysis patients who screened for MERS-CoV infection by rRT-PCR. The study included data on 104 dialysis

Table 3 Risk-prediction model of MERS-CoV infection in dialysis patients

Factor	B	SE	P	OR	[95% CI]	
Chest pain	3.186	1.251	0.011[a]	24.194	2.084	280.917
Leukopenia	1.805	0.918	0.049[a]	6.080	1.007	36.726
Elevated AST	2.414	0.974	0.013[a]	11.179	1.656	75.484
Constant	−2.362	0.980	0.016[a]	0.094	0.014	0.643

[a]Stepwise selection significant at $\alpha = 0.05$.

patients from 2 centers, KFGH-JED and KAMC-R. MERS-CoV infection is common in dialysis patients,[1,5,6] and is associated with increased rapid spread,[1] which can be prevented through early detection, isolation, and monitoring individuals at risk. Subsequently, a predictive model was developed for MERS-CoV infection in hemodialysis facilities. The model shows promising accuracy in detecting high-risk dialysis patients with an AUC of 76.99%.

The model identified the 3 most important clinical and laboratory characteristics that could help in distinguishing MERS-CoV infection from other respiratory illnesses. Dialysis patients with chest pain were associated with a 24-times higher risk of MERS-CoV infection than dialysis patients without chest pain. Earlier studies reported that chest pain was one of the most common symptoms in the MERS-CoV population.[17,18] In agreement with a matched case-control study,[19] we found no differences between MERS and non-MERS groups in regards to fever, shortness of breath, cough, and other gastrointestinal symptoms.

Dialysis patients with low WBC count or leukopenia was associated with a 6-times higher risk of MERS-CoV infection as compared to dialysis patients without leukopenia. This finding is in agreement with Saudi Ministry of Health Guidelines, as they developed a tool to identify and evaluate individuals for MERS-CoV infection,[14] and several other reports,[17,20,21] where the WBC was found to be lower in patients with MERS-CoV infection. Our findings support the matched case-control study[19] which showed that MERS-CoV patients are more likely to have leucopenia and transaminitis.

In concordance with earlier studies,[17,19,22] elevated AST was found to be a feature of MERS-CoV infection, where dialysis patients with elevated AST were associated with 11-times higher risk of MERS-CoV infection as compared with dialysis patients with no elevated AST. According to our risk-prediction model, ALT has poor predictive utility. This association was also described by Ajlan et al.,[22] where normal ALT levels have been frequently encountered in MERS patients. A prospective study is needed to understand further the link between abnormal AST and MERS-CoV infection in dialysis patients.

The model with the 3 mentioned predictors can be useful in clinical decision to identify high-risk dialysis patients for further investigations and interventions. We presented a simple form of a probability prediction model to calculate the potential risk of infection. For instance, a randomly selected dialysis patient who presented with chest pain, leukopenia, and elevated AST has a probability of MERS of 0.994. Another case, a randomly selected dialysis patient who did not present with chest pain, leukopenia, or elevated AST has a probability of MERS of 0.086. The cut-off values of the probabilities that discriminate between the high-risk and low-risk MERS were provided in Table 4. According to the Youden index, a cut-off value ($P \geq 0.439$) produces sensitivity and specificity of 0.950 and 0.259, respectively was found optimal to identify high-risk MERS infection.

Diabetes and abnormal radiology were risk factors for MERS-CoV infection when we presented the unadjusted analysis. However, these 2 factors were not significant after adjustment for other confounding factors.

Several limitations should be reported that could influence the prediction of the risk model. The model needs to be validated in a prospective MERS-CoV investigation. The study included two of the largest hospitals in Saudi Arabia, yet the model may not be generalizable to dialysis patients in other hospitals. Although this study is the largest rRT-PCR study on dialysis patients who screened for MERS-CoV infection, yet it is limited by the small number of cases screened. The authors were not able to include many other potential confounding factors in the analysis because they were not available. We also acknowledge that the small number of dialysis patients and unequal distribution of MERS between hospitals limit our report.

Despite the limitations mentioned, the prediction ability of the model appears to be promising in clinical decision making to identify suspected dialysis patients with MERS-CoV infection at an early stage of the infection.

In summary, this risk-prediction model in dialysis patients appears to depend markedly on chest pain, leukopenia, and elevated AST. The model accurately predicts high-risk of MERS-CoV infection in dialysis patients. This could be clinically useful in applying timely intervention and control measures to prevent clusters of infections in dialysis facilities or other hospital settings. The predictive utility of the model warrants further validation in an external sample and a prospective study.

ACKNOWLEDGMENTS

REFERENCES

1 Assiri A, McGeer A, Perl TM, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med.* 2013; **369**:407–416.

2 Al-Tawfiq JA, Memish ZA. Managing MERS-CoV in the healthcare setting. *Hosp Pract (1995).* 2015; **43**: 158–163.

3 Memish ZA, Al-Tawfiq JA, Alhakeem RF, et al. Middle East respiratory syndrome coronavirus (MERS-CoV): A cluster analysis with implications for global management of suspected cases. *Travel Med Infect Dis.* 2015; **13**:311–314.

4 Lee H, Ki CS, Sung H, et al. Guidelines for the laboratory diagnosis of Middle East respiratory syndrome coronavirus in Korea. *Infect Chemother.* 2016; **48**: 61–69.

5 Hastings DL, Tokars JI, Aziz IZ, et al. Outbreak of Middle East respiratory syndrome at tertiary care hospital, Jeddah, Saudi Arabia, 2014. *Emerg Infect Dis.* 2016; **22**:794.

6 Assiri A, Abedi GR, Saeed AA, et al. Multifacility outbreak of Middle East respiratory syndrome in Taif, Saudi Arabia. *Emerg Infect Dis.* 2016; **22**:32.

7 Ahmed AE. The predictors of 3-and 30-day mortality in 660 MERS-CoV patients. *BMC Infect Dis.* 2017; **17**:615.

8 Ahmed AE. Estimating survival rates in MERS-CoV patients 14 and 45 days after experiencing symptoms and determining the differences in survival rates by demographic data, disease characteristics, and regions: A worldwide study. *Epidemiol Infect.* 2018; **146**: 489–495.

9 Park HC, Lee YK, Lee SH, et al. Middle East respiratory syndrome clinical practice guideline for hemodialysis facilities. *Kidney Res Clin Pract.* 2017; **36**:111.

10 Ahmed AE. Diagnostic delays in 537 symptomatic cases of Middle East respiratory syndrome coronavirus infection in Saudi Arabia. *Int J Infect Dis.* 2017; **62**:47–51.

11 Koenig KL. Identify-Isolate-Inform: A modified tool for initial detection and management of Middle East respiratory syndrome patients in the emergency department. *West J Emerg Med.* 2015; **16**:619.

12 Ahmed AE, McClish DK, Schubert CM. Accuracy and cost comparison in medical testing using sequential testing strategies. *Statist Med.* 2011; **30**:3416–3430.

13 Ahmed AE, Schubert CM, McClish DK. Reducing cost in sequential testing: a limit of indifference approach. *Statist Med.* 2013; **32**:2715–2727.

14 Case Definition and Surveillance Guidance - Updated June 2015. Available from: www.moh.gov.sa/en/CCC/Regulations/Case%20Definition.pdf (accessed date: March 15, 2017).

15 Oboho IK, Tomczyk SM, Al-Asmari AM, et al. 2014 MERS-CoV outbreak in Jeddah—A link to health care facilities. *N Engl J Med.* 2015; **372**:846–854.

16 Al-Dorzi HM, Aldawood AS, Khan R, et al. The critical care response to a hospital outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection: an observational study. *Ann Intensive Care.* 2016; **6**:101.

17 Ahmed AE, et al. Early identification of pneumonia patients at increased risk of MERS-CoV infection in Saudi Arabia. *Int J Infect Dis.* 2018; **69**:68–74.

18 Moniri A, Marjani M, Tabarsi P, Yadegarynia D, Nadji SA. Health care associated Middle East respiratory syndrome (MERS): A Case from Iran. *Tanaffos.* 2015; **14**: 262.

19 Mohd HA, Memish ZA, Alfaraj SH, et al. Predictors of MERS-CoV infection: A large case control study of patients presenting with ILI at a MERS-CoV referral hospital in Saudi Arabia. *Travel Med Infect Dis.* 2016; **14**:464–470.

20 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**: 118–126.

21 Yousefi M, Dehesh MM, Farokhnia M. Epidemiological and clinical characteristics of patients with Middle East respiratory syndrome coronavirus in Iran in 2014. *Jpn J Infect Dis.* 2017; **70**:115–118.

22 Ajlan AM, Ahyad RA, Jamjoom LG, Alharthy A, Madani TA. Middle East respiratory syndrome coronavirus (MERS-CoV) infection: Chest CT findings. *Ajr Am J Roentgenol.* 2014; **203**:782–787.