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Early identification of pneumonia patients at increased risk of Middle East respiratory syndrome coronavirus infection in Saudi Arabia



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ABSTRACT

Background: The rapid and accurate identification of individuals who are at high risk of Middle East respiratory syndrome coronavirus (MERS-CoV) infection remains a major challenge for the medical and scientific communities. The aim of this study was to develop and validate a risk prediction model for the screening of suspected cases of MERS-CoV infection in patients who have developed pneumonia.

Methods: A two-center, retrospective case-control study was performed. A total of 360 patients with confirmed pneumonia who were evaluated for MERS-CoV infection by real-time reverse transcription polymerase chain reaction (rRT-PCR) between September 1, 2012 and June 1, 2016 at King Abdulaziz Medical City in Riyadh and King Fahad General Hospital in Jeddah, were included. According to the rRT-PCR results, 135 patients were positive for MERS-CoV and 225 were negative. Demographic characteristics, clinical presentations, and radiological and laboratory findings were collected for each subject.

Results: A risk prediction model to identify pneumonia patients at increased risk of MERS-CoV was developed. The model included male sex, contact with a sick patient or camel, diabetes, severe illness, low white blood cell (WBC) count, low alanine aminotransferase (ALT), and high aspartate aminotransferase (AST). The model performed well in predicting MERS-CoV infection (area under the receiver operating characteristics curves (AUC) 0.8162), on internal validation (AUC 0.8037), and on a goodness-of-fit test ($p = 0.592$). The risk prediction model, which produced an optimal probability cut-off of 0.33, had a sensitivity of 0.716 and specificity of 0.783.

Conclusions: This study provides a simple, practical, and valid algorithm to identify pneumonia patients at increased risk of MERS-CoV infection. This risk prediction model could be useful for the early identification of patients at the highest risk of MERS-CoV infection. Further validation of the prediction model on a large prospective cohort of representative patients with pneumonia is necessary.

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Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in 2012. The diagnosis of this infection remains complex (Al Johani and Hajeer, 2016; Sung et al., 2016; Ahmed, 2017a) and it has a high fatality rate (Ahmed, 2017b, c; Aleanizy et al., 2017; Sherbini et al., 2017; Kim et al., 2017). The early detection and identification of individuals at high risk of a

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disease is the most effective strategy to improve patient clinical outcomes (Ahmed, 2017a) and reduce the costs of testing, both physical and economic (Ahmed et al., 2011, 2013). The real-time reverse transcription polymerase chain reaction (rRT-PCR) has been found to be valid and accurate for the evaluation of respiratory swabs, sputum, and other endotracheal aspirate material (Corman et al., 2012a, b). However, although rRT-PCR is the most accurate and sensitive test available at the authors' centers, absolute identification of MERS-CoV may require multiple clinical specimens from different sources and take days (Corman et al., 2012a, b; Anon, 2018a).

The Saudi Ministry of Health (MOH) has developed MERS-CoV visual triage guidelines to identify suspected cases (Anon, 2018b). The current guidelines include fever, respiratory symptoms, gastrointestinal symptoms, chronic diseases, and risk of exposure to MERS-CoV. In clinical practice, identifying high-risk individuals can be challenging, since most laboratory-confirmed MERS-CoV patients report common clinical risk indices to patients with other respiratory conditions. For instance, respiratory and gastrointestinal symptoms are common for both MERS-CoV and non-MERS-CoV patients (Mohd et al., 2016). Thus, further exploration must take place to reduce the risk of MERS-CoV infection. A risk prediction model is urgently needed to stratify patients with suspected MERS-CoV. This may decrease the risk of virus transmission to others who are in close contact, for example healthcare workers, patients, and hospital visitors, by allowing the careful management of those who are potentially infected at an early stage of infection. Developing a MERS-CoV prediction model may more efficiently aid physicians in identifying individuals at high risk and selecting the necessary test(s) to improve prevention and control measures.

Several methodological studies have shown that combining demographic characteristics with clinical, radiological, and laboratory information can improve risk assessment and diagnostic accuracy (Ahmed et al., 2011, 2013; Sidransky, 2002; Etzioni et al., 2003). These previous studies used a linear combination to develop an algorithm that combines demographic characteristics, symptoms, and clinical, radiological, and laboratory findings to identify the highly suspected MERS-CoV cases.

MERS-CoV was initially identified in a patient being treated for pneumonia in 2012 (Zaki et al., 2012), and since then, pneumonia and its symptoms have remained common characteristics in MERS-CoV patients (Saad et al., 2014; Choi et al., 2016).

The aim of this study was to develop and validate a reliable risk prediction model for the screening of suspected cases of MERS-CoV infection in patients who have developed pneumonia.

Methods

A two-center, retrospective case-control study was conducted utilizing data from King Abdulaziz Medical City in Riyadh (KAMC-R) and King Fahad General Hospital in Jeddah (KFGH-JED), Saudi Arabia. The data were obtained between September 1, 2012 and June 1, 2016. KFGH-JED experienced a MERS outbreak between March and May 2014 (Obobo et al., 2015), and KAMC-R experienced a large MERS outbreak between June and August 2015 (Al-Dorzi et al., 2016). Both study centers applied the Saudi MOH case definitions (Anon, 2018b) to identify suspected individuals in the population studied, and rRT-PCR was used as the gold standard test to diagnose MERS-CoV in multiple and different clinical specimens when necessary. MERS-CoV-related symptoms were common at both centers.

The project received ethical approval from two independent ethics committees: the Saudi MOH (IRB log number 16-230E) and King Abdullah International Medical Research Center (study number RC17/061), Riyadh Saudi Arabia.

During the study, the medical records of 829 subjects who were being assessed by rRT-PCR for suspected MERS-CoV were reviewed. The suspicion of MERS-CoV infection at both KAMC-R and KFGH-JED was determined based on the Saudi MOH guidelines (Anon, 2018b). Two groups were compared: patients who were positive and patients who were negative for MERS-CoV infection. In an effort to reduce heterogeneity between the study groups, only subjects with a lung infiltrate on chest X-ray and/or computed tomography (CT) scan of the chest were included in the analysis. Thus, subjects who had no available results of a chest X-ray or CT scan of the chest were excluded. The initial screening for suspected MERS-CoV patients includes pneumonia (Anon, 2018b). Most of the patients studied were evaluated for pneumonia immediately after presentation.

The study excluded subjects who were less than 15 years of age (pediatrics/children), as defined in the Saudi MOH guidelines (Anon, 2018b), and excluded subjects who had upper respiratory tract infections (respiratory symptoms, positive or negative MERS-CoV rRT-PCR, and normal chest X-ray and CT scan of the chest).

The final sample comprised a cohort of 360 subjects who had a lung infiltrate on chest X-ray and/or a CT scan of the chest, who were classified according to the results of MERS-CoV rRT-PCR. The case group consisted of 135 pneumonia patients who were positive for MERS-CoV infection, and the control group consisted of 225 pneumonia patients who were negative for MERS-CoV infection.

Cases were defined as patients with MERS-CoV pneumonia who had positive MERS-CoV rRT-PCR on nasopharyngeal aspirate and/or bronchoalveolar lavage in addition to a lung infiltrate on chest X-ray and/or CT scan of the chest. Controls were defined as patients with respiratory symptoms, a lung infiltrate on chest X-ray and/or CT scan of the chest, pneumonia, and negative MERS-CoV rRT-PCR result of nasopharyngeal aspirate and/or bronchoalveolar lavage.

Nineteen predictive variables were included: age, sex, fever (temperature $\geq 38^\circ\text{C}$), one composite respiratory symptom (the presence of cough, bloody cough, shortness of breath, or chest pain), one composite gastrointestinal symptoms (the presence of diarrhea, vomiting, or nausea), seven MERS-CoV potential risk factors (contact with sick patients or camels, severe illness (defined according to the patient's clinical status, 'yes/no', which is based on clinical judgment), diabetes, lung disease, liver disease, renal disease, and heart disease), and seven laboratory measurements (white blood cell (WBC) count ($\times 10^9/\text{l}$), platelets ($\times 10^9/\text{l}$), creatinine ($\mu\text{mol/l}$), bilirubin ($\mu\text{mol/l}$), alanine aminotransferase (ALT; U/l), aspartate aminotransferase (AST; U/l), and albumin (g/l)). The reference ranges for the laboratory measures were as follows: WBC count, $4\text{--}11 \times 10^9/\text{l}$; platelets, $150\text{--}400 \times 10^9/\text{l}$; creatinine, $50\text{--}98 \mu\text{mol/l}$; bilirubin, $3.4\text{--}20.5 \mu\text{mol/l}$; ALT, $5\text{--}55 \text{U/l}$; AST, $5\text{--}34 \text{U/l}$; albumin, $35\text{--}55 \text{g/l}$. No serological tests were available at the centers for these patients.

Statistical analysis

Stata statistical software release 15, 2017 (StataCorp. LLC, College Station, TX, USA) was used for the data analysis. The sample characteristics were recorded as the frequency and percentage, or as the mean \pm standard deviation (SD). Laboratory measurements were summarized as the median and 25th–75th percentiles. A subgroup analysis (Chi-square test, independent samples *t*-test, or Mann–Whitney *U*-test) was used to identify unadjusted associations between demographic, clinical, and laboratory measurements according to MERS-CoV status. The performance of each bivariate predictor was further assessed by unbiased estimate, the area under the curve (AUC), and its 95% confidence interval (CI).

Stepwise binary logistic regression was employed to develop a MERS-CoV risk prediction model and identify factors that could be used to estimate the probabilities of MERS-CoV infection.

The goodness-of-fit of the final model was tested by Hosmer–Lemeshow procedure: a large p -value indicates that a model has a good fit. The discrimination ability between high and minimal risk of MERS-CoV infection of the final model was assessed by the AUC and its 95% CI. A receiver operating characteristics (ROC) curve was generated for the risk prediction model. Two hundred random samples were drawn with replacements from the original study sample ($N = 360$). The model internal validity was assessed in these 200 samples by the AUC and its 95% CI. Optimal cut-off values of the probabilities for each model were determined using a generalized Youden index (Youden, 1950). At these thresholds, it was possible to achieve the best balance between specificity and sensitivity.

Results

A total of 360 pneumonia patients were included in the analysis: 37.5% were confirmed MERS-CoV-positive and 62.5% were confirmed MERS-CoV-negative. The mean age at presentation was 55.9 years, with a standard deviation of 20.2 years; age ranged between 16 and 109 years. Of the total sample, 6.9% had been in contact with a sick patient or camel, 60% had fever, 84.2% had at least one respiratory symptom, and 18.6% had at least one gastrointestinal symptom. The two groups were similar in the distribution of age ($p = 0.220$) and sex ($p = 0.079$). The characteristics of the sample can be found in Table 1.

Subgroup analyses are presented in Tables 1 and 2. The Chi-square test or the independent samples t -test revealed that sex ($p = 0.079$) and age ($p = 0.220$) were similar in the two groups. The risk of MERS-CoV infection was similar in patients with and without fever ($p = 0.267$), respiratory symptoms ($p = 0.080$), or gastrointestinal symptoms ($p = 0.382$). Severe illness ($p = 0.001$), contact with a sick patient or camel ($p = 0.001$), diabetes ($p = 0.001$), heart disease ($p = 0.007$), and renal disease ($p = 0.025$) were significantly associated with an increased risk of MERS-CoV infection.

The independent samples Mann–Whitney U -test revealed that the WBC count ($p = 0.001$) and platelet count ($p = 0.006$) were significantly lower in patients who were positive for MERS-CoV than in those who were negative for MERS-CoV infection. In contrast, creatinine ($p = 0.001$), bilirubin ($p = 0.001$), AST ($p = 0.001$), and albumin ($p = 0.004$) were significantly higher in patients who were positive for MERS-CoV than in those who were negative for MERS-CoV infection. ALT ($p = 0.352$) was insignificantly higher in patients who were positive for MERS-CoV than in those who were negative for MERS-CoV infection.

According to the individual ROC curve analysis (Table 3), severe illness, diabetes, WBC count, creatinine, bilirubin, albumin, and AST were the most important predictors of MERS-CoV infection.

A risk prediction model was developed using stepwise binary logistic regression ($p \leq 0.05$). The model retained seven independent variables that were associated with increased odds of MERS-CoV (Table 4). Male sex (adjusted odds ratio (aOR) 1.883, $p = 0.043$), contact with a sick patient or camel (aOR 21.915, $p = 0.001$), diabetes (aOR 2.703, $p = 0.002$), severe illness (aOR 6.312, $p = 0.001$), low WBC count (aOR 0.897, $p = 0.001$), high AST (aOR 1.007, $p = 0.007$), and low ALT (aOR 0.995, $p = 0.024$) were found to have a significant impact on the prediction of MERS-CoV.

The Hosmer–Lemeshow test indicated that this model fitted the data well ($p = 0.592$). This model showed substantial discrimination, with an AUC of 0.8162 and a 95% CI of 0.7651–0.8674 (Figure 1). The prediction model was validated using the bootstrap procedure. A total of 200 random samples were drawn with replacements from the original sample, and the model showed a substantial ability to assess MERS-CoV infection in this study population (AUC 0.804, 95% CI 0.7838–0.8235).

The findings in Table 4 were used to create a risk-probability model. The risk prediction for the model can be expressed by the following equation: predicted probability = $[1 + \exp(1.409 - (0.633 \times \text{male}) - (3.087 \times \text{sick patient or camel contact}) - (0.995 \times \text{diabetes}) - (1.842 \times \text{severe illness}) + (0.109 \times \text{WBC count}) - (0.007 \times \text{AST}) + (0.005 \times \text{ALT}))]^{-1}$. A calculator was developed

Table 1

Demographic characteristics and clinical parameters of patients who developed pneumonia, according to MERS-CoV status.

Predictor	Levels	Overall N = 360		Negative MERS-CoV n = 225 (62.5%)		Positive MERS-CoV n = 135 (37.5%)		p-Value
		Mean	±SD	Mean	±SD	Mean	±SD	
Age (16–109) years		56	20.2	55	21.4	57.5	18.1	0.220
		n	%	n	%	n	%	
Male	No	134	37.4	92	40.9	42	31.6	0.079
	Yes	224	62.6	133	59.1	91	68.4	
Severe illness ^a	No	259	71.9	193	85.8	66	48.9	0.001*
	Yes	101	28.1	32	14.2	69	51.1	
Fever	No	144	40.0	85	37.8	59	43.7	0.267
	Yes	216	60.0	140	62.2	76	56.3	
Respiratory symptoms ^a	No	54	15.0	28	12.4	26	19.3	0.080
	Yes	306	85.0	197	87.6	109	80.7	
Gastrointestinal symptoms ^a	No	293	81.4	180	80.0	113	83.7	0.382
	Yes	67	18.6	45	20.0	22	16.3	
Sick patient or camel contact	No	335	93.1	220	97.8	115	85.2	0.001*
	Yes	25	6.9	5	2.2	20	14.8	
Diabetes	No	202	56.1	144	64.0	58	43.0	0.001*
	Yes	158	43.9	81	36.0	77	57.0	
Lung disease	No	331	91.9	209	92.9	122	90.4	0.395
	Yes	29	8.1	16	7.1	13	9.6	
Heart disease	No	271	75.3	180	80.0	91	67.4	0.007*
	Yes	89	24.7	45	20.0	44	32.6	
Liver disease	No	345	95.8	217	96.4	128	94.8	0.454
	Yes	15	4.2	8	3.6	7	5.2	
Renal disease	No	298	82.8	194	86.2	104	77.0	0.025*
	Yes	62	17.2	31	13.8	31	23.0	

MERS-CoV, Middle East respiratory syndrome coronavirus; SD, standard deviation. *Significant at $\alpha = 0.05$.

^a Respiratory symptoms: the presence of cough, bloody cough, shortness of breath, or chest pain. Gastrointestinal symptoms: the presence of diarrhea, vomiting, or nausea. Severe illness, defined according to the patient's clinical status: yes/no.

Table 2
Laboratory parameters of patients who developed pneumonia, according to MERS-CoV status.

Predictor ^a	Overall N = 360			Negative MERS-CoV n = 225 (62.5%)			Positive MERS-CoV n = 135 (37.5%)			p-Value
	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile	
WBC count ($\times 10^9/l$)	8.2	5.8	12.5	9.4	6.2	13.7	6.8	5.1	10.8	0.001*
Platelets ($\times 10^9/l$)	230.0	159.0	305.0	246.0	174.0	330.0	203.5	146.5	282.0	0.006*
Creatinine ($\mu\text{mol/l}$)	64.0	1.1	111.0	10.2	1.0	88.0	82.0	39.1	151.0	0.001*
Bilirubin ($\mu\text{mol/l}$)	6.3	0.7	11.8	4.7	0.5	11.0	8.0	4.8	13.4	0.001*
ALT (U/l)	33.5	20.5	54.5	31.0	20.0	52.0	35.0	21.0	64.0	0.352
AST (U/l)	35.0	22.0	61.0	29.5	21.0	53.0	48.0	24.0	84.0	0.001*
Albumin (g/l)	27.0	3.3	34.0	21.0	3.2	34.0	30.0	20.5	35.0	0.004*

MERS-CoV, Middle East respiratory syndrome coronavirus; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase. *Significant at $\alpha = 0.05$.
^a WBC count, normal range: $4\text{--}11 \times 10^9/l$. Platelets, normal range: $150\text{--}400 \times 10^9/l$. Creatinine, normal range: $50\text{--}98 \mu\text{mol/l}$. Bilirubin, normal range: $3.4\text{--}20.5 \mu\text{mol/l}$. ALT, normal range: $5\text{--}55 \text{U/l}$. AST, normal range: $5\text{--}34 \text{U/l}$. Albumin, normal range: $35\text{--}55 \text{g/l}$.

Table 3
Individual ROC curve analysis.

Predictor	AUC	SE	95% CI	
			Lower	Upper
Age	0.523	0.031	0.463	0.582
Male	0.547	0.026	0.495	0.598
Severe illness	0.684	0.025	0.636	0.733
Fever	0.470	0.027	0.418	0.523
Respiratory symptoms	0.467	0.021	0.426	0.507
Gastrointestinal symptoms	0.500	0.024	0.454	0.546
Sick patient or camel contact	0.563	0.016	0.531	0.595
Diabetes	0.605	0.027	0.553	0.658
Lung disease	0.513	0.015	0.482	0.543
Heart disease	0.563	0.024	0.515	0.611
Liver disease	0.508	0.011	0.486	0.530
Renal disease	0.546	0.022	0.504	0.588
WBC count ($\times 10^9/l$)	0.617	0.031	0.557	0.677
Platelets ($\times 10^9/l$)	0.589	0.032	0.527	0.651
Creatinine ($\mu\text{mol/l}$)	0.666	0.030	0.607	0.725
Bilirubin ($\mu\text{mol/l}$)	0.635	0.035	0.567	0.703
ALT (U/l)	0.533	0.036	0.462	0.603
AST (U/l)	0.622	0.035	0.553	0.690
Albumin (g/l)	0.604	0.035	0.535	0.672

ROC, receiver operating characteristics; AUC, area under the ROC curve; SE, standard error; CI, confidence interval; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4
MERS-CoV risk prediction model and its accuracy (AUC 0.8162, 95% CI 0.7651–0.8674).

Predictor	B	SE	p-Value	OR	95% CI	
					Lower	Upper
Male	0.633	0.313	0.043	1.883	1.021	3.475
Sick patient or camel contact	3.087	0.682	0.001	21.915	5.759	83.387
Diabetes	0.995	0.315	0.002	2.703	1.458	5.011
Severe illness	1.842	0.324	0.001	6.312	3.342	11.922
WBC count ($\times 10^9/l$)	−0.109	0.030	0.001	0.897	0.846	0.951
AST (U/l)	0.007	0.003	0.007	1.007	1.002	1.013
ALT (U/l)	−0.005	0.002	0.024	0.995	0.990	0.999
Constant	−1.409	0.375	0.001	0.244	0.117	0.509

MERS-CoV, Middle East respiratory syndrome coronavirus; AUC, area under the receiver operating characteristics curve; CI, confidence interval; SE, standard error; OR, odds ratio; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

to calculate the potential risk of MERS-CoV infection in pneumonia patients.

We determined the optimal cut-off or threshold values of the probabilities to mark the differences between the high-risk and low-risk groups. When an equal weight was given for sensitivity and specificity ($m = 1$), the optimal cut-off value (probability

≥ 0.33) produced sensitivity and specificity of 0.716 and 0.783, respectively. When more weight was given for sensitivity than specificity ($m = 0.50$), the optimal cut-off value (probability ≥ 0.20) produced sensitivity and specificity of 0.902 and 0.550, respectively. When more weight was given for specificity than sensitivity ($m = 1.50$), the optimal cut-off value (probability ≥ 0.39) produced sensitivity and specificity of 0.647 and 0.831, respectively.

Discussion

Based on data from the two largest hospitals in Saudi Arabia, a risk prediction model was developed for MERS-CoV infection in pneumonia patients. This model was generated from a retrospective study and should be assessed prospectively for external validation. Seven variables were identified as having a great impact on the MERS-CoV risk assessment prediction. The risk prediction model highlights the strong potential impact of male sex, contact with a sick patient or camel, severe illness, diabetes, low WBC count, high AST, and low ALT on MERS-CoV infection. These few important parameters could be part of routine medical examinations to be performed (for the purpose of identifying highly suspected individuals) in daily clinical practice in order to make a prompt and timely clinical decision.

According to the model, high AST was associated with an increased risk of being infected with MERS-CoV. This finding is similar to that of Mohd et al., who noted high AST levels in MERS-CoV patients (Mohd et al., 2016). Unlike their findings, it was noted in the present study that the impact of ALT became significantly negative after controlling for several confounders. However, this type of association should be evaluated further in a prospective study in the presence of other unmeasured confounders.

Although sex was found to have no impact on MERS-CoV infection in the unadjusted analysis, the multivariate analysis revealed that the risk of MERS-CoV infection was 88.3% times higher in males than in females. This may be because other factors are playing a role in the development of MERS-CoV in males, such as camel contact, since males are more likely than females to have contact with camels.

In agreement with the recent Saudi MOH MERS-CoV visual triage guidelines for the identification of suspected cases (Anon, 2018b), it was found that the odds of being infected with MERS-CoV were higher in patients with diabetes as compared to those with no diabetes. This also supports the findings of previous studies (Badawi and Ryoo, 2016; Assiri et al., 2013; Al-Tawfiq et al., 2014; Alraddadi et al., 2016) in which researchers systematically recognized that diabetes is a risk factor for MERS-CoV infection. These findings indicate that more attention should be given to assessing the risk of MERS-CoV infection in diabetic patients and whether the risk depends on a specific diabetes type or condition in these patients.

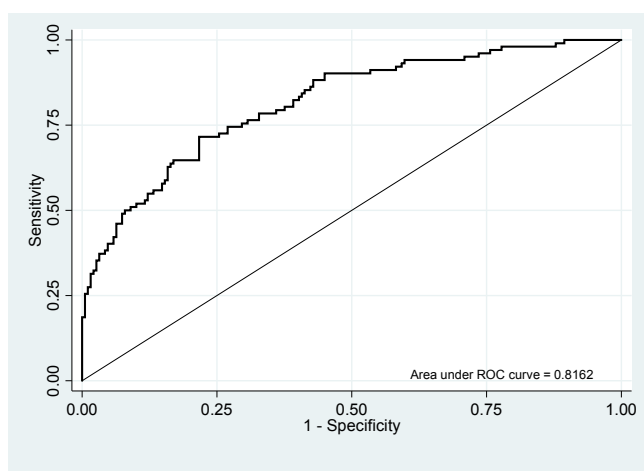


Figure 1. The performance of proposed algorithm.

As asserted in the Saudi MOH MERS-CoV visual triage guidelines and many other studies (Muhairi et al., 2016; Younan et al., 2016; Reeves et al., 2015; Sabir et al., 2016; Azhar et al., 2014a, b), contact with a sick patient or camel was identified as an independent predictor of MERS-CoV infection, according to the risk prediction model. It must be noted that the finding in the present study could have been limited by combining camel contact and sick patient contact due to the small sample size of each category.

This study shows the importance of incorporating various types of information to improve the performance of the risk prediction. According to the linear combination model, it was found that several of the parameters highlighted in the Saudi MOH MERS-CoV visual triage guidelines were not able to distinguish between 'high-risk' and 'low-risk' groups, nor did they help in predicting MERS-CoV infection. For instance, fever, respiratory symptoms, gastrointestinal symptoms, heart disease, and renal disease were noted to have an insignificant impact on MERS-CoV infection.

However, in agreement with the Saudi MOH MERS-CoV guidelines and two other reports (Mohd et al., 2016; Arabi et al., 2017), the odds of being infected with MERS-CoV were associated with a significant risk reduction of 10.3% for each unit increase in WBC count.

These results suggest that demographic, clinical, radiological, and laboratory data should be used in routine practice to identify suspected MERS-CoV cases, as such data could serve as the first line of prevention strategies. It was found that the accuracy of prediction (Figure 1) was further improved when combining various medical and patient variables as opposed to relying on a single factor (Table 3). This has been proven theoretically and in application (Ahmed et al., 2013, 2011, 2015; Etzioni et al., 2003; Shen, 2008; Pepe and Thompson, 2000; Su and Liu, 1993; Thompson, 2003), where a linear combination has been used to maximize the diagnostic accuracy of a disease of interest.

The strength of this study lies in the fact that a simple and applicable predictive model was developed that incorporates demographic, clinical, radiological, and laboratory data, where these were functionally associated and contributed greatly to stratifying and distinguishing between a high and a minimal risk of MERS-CoV infection. This simple evaluation of suspected MERS-CoV cases appears promising and could be implemented easily in routine clinical practice. This model could be used as a risk stratification method or a triage tool to help physicians in making an informed decision and planning the next step when deciding whether an rRT-PCR or further investigation is necessary.

It was possible to derive a risk probability algorithm (range 0–1), a generalized Youden index (Choi et al., 2016) was used to determine an optimal cut-off to stratify the risk, and a risk probability of ≥ 0.41 was identified as being the optimal cut-off, with a sensitivity of 0.688 and specificity of 0.789.

Several limitations to the proposed risk prediction model were identified. The study findings were based on a retrospective design; therefore this prediction model should be interpreted with caution. Limited information was available on patient variables, clinical variables, and transmission routes. For example, information on primary cases and secondary cases may be supplemented by the results of clinical, radiological, and laboratory data. In this study, 'contact with a sick patient' and 'contact with a sick camel' were combined into one variable due to the small number in each category. Severe illness was based on a subjective judgment. An additional potential limitation was that the duration of symptoms was not available for these patients. This study investigated a very specific population (pneumonia) at only two centers, which could compromise the applicability and generalizability of the risk prediction model. Moreover, the prediction model may not be generalizable to patients who do not fulfill the MOH guidelines. Further validation of the prediction model on an external sample and prospective cohort of representative patients with pneumonia is necessary, specifically in relevant settings: emergency, outpatient, inpatient, and community.

Despite these limitations, the model developed shows promise for the identification of suspected MERS-CoV cases in clinical practice. This model could be applicable in various healthcare settings – inpatient, outpatient, and emergency departments – because no extensive laboratory testing is required and samples may be available within short turnaround times. This may allow rapid evaluation and improve clinical decision-making.

In conclusion, this study provides a simple, practical, and valid algorithm to identify individuals at increased risk of MERS-CoV infection among patients who have developed pneumonia. This risk model is not only useful for risk stratification and decision-making in clinical practice, but it could also be useful in preventing and managing the possible spread of MERS-CoV. The usefulness of this newly developed tool must be validated in an external prospective study.

Ethical approval

The project received ethical approval from two independent ethics committees: the Saudi Ministry of Health (IRB log number 16-230E) and King Abdullah International Medical Research Center (study number RC17/061), Riyadh Saudi Arabia.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ijid.2018.03.005>.

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