ORIGINAL ARTICLE

Clinical characteristics and outcome of ICU admitted MERS corona virus infected patients

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Abstract   Middle East Respiratory Syndrome (MERS) is a novel respiratory illness firstly reported in Saudi Arabia in 2012. It is caused by a new corona virus, called MERS corona virus (MERS-CoV). Most people who have MERS-CoV infection developed severe acute respiratory illness.

Aim of the work: This work is done to determine the clinical characteristics and the outcome of intensive care unit (ICU) admitted patients with confirmed MERS-CoV infection.

Patients and methods: This study included 32 laboratory confirmed MERS corona virus infected patients who were admitted into ICU. It included 20 (62.50%) males and 12 (37.50%) females. The mean age was 43.99 ± 13.03 years. Diagnosis was done by real-time reverse transcription polymerase chain reaction (rRT-PCR) test for corona virus on throat swab, sputum, tracheal aspirate, or bronchoalveolar lavage specimens. Clinical characteristics, co-morbidities and outcome were reported for all subjects.

Results: The main symptoms among the included patients were: fever (96.87%), cough (93.75%), dyspnea (90.62%), sore throat (75%), runny nose (75%), sputum (50%), headache (43.75%), myalgia (40.62%), chest pain (37.50%), hemoptysis (37.50%), nausea and vomiting (34.37%), abdominal pain (21.87%) and diarrhea (15.62%). The presence of abdominal symptoms is significantly ($P < 0.05$) associated with bad prognosis. Out of the included 32 patients, 18 patients (56.25%) survived and 14 patients (43.75%) expired. There was a statistically significant difference in the duration of symptoms before hospitalization, mechanical ventilation and ICU and total hospital stay between the expired group and survivors ($P < 0.01$). Current smoking and smoking severity were statistically significantly ($P < 0.01$) higher in the expired group compared to survivors. Also, there was a statistically ($P < 0.05$) significant positive correlation between mortality and smoking severity ($r = 0.640$). Most of the expired patients presented with bilateral pulmonary infiltrates or unilateral infiltrates, but most of the survivors presented with normal

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radiology or increased bronchovascular markings, and this difference in the results was statistically highly significant ($P < 0.01$). There were statistically highly significant ($P < 0.01$) differences in the mean values of APACHE II score (21.11 ± 3.70 vs 24.21 ± 3.82), SOFA score (5.83 ± 2.64 vs 8.85 ± 2.17) and CPIS (7.55 ± 1.14 vs 8.64 ± 1.39) between the expired group and survivors respectively. Also, there was a statistically significant decrease in PH, PaO_2, O_2 saturation and HCO_3 ($P < 0.05$) among the expired group in comparison with the survivors, but no statistical difference regarding $PaCO_2$ ($P > 0.05$). There was a statistically significant positive correlation between mortality and old age ($r = 0.633$), obesity ($r = 0.712$), diabetes mellitus ($r = 0.685$), renal failure ($r = 0.705$), chronic heart diseases (0.591), COPD ($r = 0.523$), malignancy ($r = 0.692$), kidney transplantation ($r = 0.644$) and liver cirrhosis ($r = 0.525$) ($P < 0.05$). There was a statistically ($P < 0.05$) positive correlation between the number of associated co-morbidities and mortality ($r = 0.735$).

Conclusions: Most MERS corona patients present with fever, cough, dyspnea, sore throat, runny nose and sputum. The presence of abdominal symptoms may indicate bad prognosis. Prolonged duration of symptoms before patients' hospitalization, prolonged duration of mechanical ventilation and hospital stay, bilateral radiological pulmonary infiltrates, and hypoxemic respiratory failure were found to be strong predictors of mortality in such patients. Also, old age, current smoking, smoking severity, presence of associated co-morbidities like obesity, diabetes mellitus, chronic heart diseases, COPD, malignancy, renal failure, renal transplantation and liver cirrhosis are associated with a poor outcome of ICU admitted MERS corona virus infected patients.

Introduction

Middle East Respiratory Syndrome (MERS) is a new viral respiratory infection caused by a newly discovered corona virus, specifically, called Middle East Respiratory Syndrome Corona virus (MERS-CoV). In September 2012, the World Health Organization reported the first case of pneumonia caused by MERS-CoV in Saudi Arabia. All cases of MERS have been linked to countries in and near the Arabian Peninsula. This virus has spread from ill people to others through close contact, such as caring for or living with an infected person. Also, contact with the camels may be a potential source. However, there is no evidence of sustained spread in community settings. Most MERS patients developed a severe acute respiratory illness [1,2].

Aim of the work

This work is done to determine the clinical characteristics and the outcome of ICU admitted patients with confirmed MERS-CoV infection.

Patients and methods

This study included 32 laboratory confirmed MERS corona virus patients who were admitted into ICU. Consent was taken from the patients or their relatives.

All studied cases were subjected to:

(1) Full medical history.
(2) Thorough clinical examination.
(3) Calculation of body mass index (BMI): a BMI of > 30 is considered obese according to WHO [3].
(4) Routine laboratory investigations (complete blood count, kidney and liver functions, and blood sugar testing).

(5) Radiological assessment: chest X-ray (posteroanterior and lateral views) and computed tomography (CT).
(6) Arterial blood gases, including; PH, PaO_2, SaO_2, $PaCO_2$ and HCO_3.
(7) Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the Sequential Organ Failure Assessment score (SOFA) and the Clinical Pulmonary Infection Score (CPIS).
(8) Throat swab (Eurotubo, Deltalab, 08191 Rubí, Barcelona, Spain), sputum, tracheal aspirate or bronchoalveolar lavage specimens were taken and stored at 28 °C, and transported within 72 h to the reference laboratories, where they were subjected to real-time reverse-transcriptase–polymerase-chain-reaction (rRT-PCR) assays to test for MERS-CoV (Altona Diagnostics GmbH, 22767 Hamburg, Germany). For all patients, the results of rRT-PCR tests were confirmed by measuring cycle-threshold values for viral load [4].

Statistical analysis

The statistical analysis was performed with the Statistical Package for the Social Sciences, version 16 for Windows (SPSS Inc., Chicago, IL, USA). Chi-square test was used to measure association. Pearson's correlation test was used to measure correlation. Values of $P < 0.05$ were considered statistically significant.

Results

In this study, there were 20 (62.50%) males and 12 (37.50%) females. The mean age was 43.99 ± 13.03 years.

The main symptoms among the included patients were: fever (96.87%), cough (93.75%), dyspnea (90.62%), sore

throat (75%), runny nose (75%), sputum (50%), headache (43.75%), myalgia (40.62%), chest pain (37.50%), hemoptysis (37.50%), nausea and vomiting (34.37%), abdominal pain (28.12%), abdominal pain (21.87%) and diarrhea (15.62%). The mean duration of symptoms before seeking medical advice was 5.30 ± 3.25 days (Table 1).

The chest radiological findings among the included patients were as follows: 8 (25%) normal chest radiology, 5 (15.63%) increased bronchovascular markings, 7 (21.87%) unilateral infiltrates, and 12 (37.50%) diffuse bilateral infiltrates. Pneumothorax occurred in 5 (15.63%) ventilated patients, for 3 of them it was unilateral and for other 2 patients bilateral (Table 1).

Regarding the ABGs findings in our study: mean PH: 7.26 $\pm$ 0.33, mean PaO_2: 64.04 ± 20.50 mmHg, mean O_2 saturation: 83.92 ± 17.45, mean $PaCO_2$: 38.75 ± 4.17 mmHg, and mean HCO_3 19.44 ± 8.5 meq/L (Table 1).

The mean APACHE II score was 22.46 ± 4.01, the mean SOFA score was 7.15 ± 2.85 and mean CPIS was 8.03 ± 1.35 (Table 1).

Regarding the presence of co-morbidity, 21 (65.62%) patients out of the included 32 patients were associated with one or more co-morbidities and 11 (34.38%) patients were without co-morbidity (Table 2).

All patients were admitted in ICU and a mean duration of ICU stay was 11.32 ± 4.50 days. Regarding mechanical ventilation need, there were 23 (71.87%) ventilated patients and 9 (28.13%) patients without mechanical ventilation. For ventilated patients the mean duration of mechanical ventilation was 6.21 ± 3.76 days. The mean total hospital stay was 15 ± 3.6 days (Table 1).

According to the outcome of 32 patients included in this study, there were two groups:

(1) The survivor group that included 18 patients (56.25%) with a mean age of 37.25 ± 15.50 years.
(2) The expired group that included 14 patients (43.75%) with a mean age of 50.47 ± 13.80 years.

There was a highly statistically significant ($P < 0.01$) difference between the expired group and the survivors regarding the duration of mechanical ventilation (expired: 9.64 ± 2.46, survivors: 3.55 ± 2.00), ICU stay (expired: 13.98 ± 3.50, survivors: 8.66 ± 2.40) and total hospital stay (expired: 17.50 ± 2.92, survivors: 13.06 ± 2.81) (Table 2).

In this study, in spite of a statistically significant ($P < 0.05$) increase in occurrence of corona virus infection among males in comparison with females (62.50% males and 37.50% females), there was no statistically significant difference ($P > 0.05$) in the mortality among them (45% among males and 41.67% among females) ($P > 0.05$) (Table 2).

Current smoking and smoking severity were statistically significantly ($P < 0.01$) higher in the expired group compared to the survivors. Non smoking and ex smoking were statistically significantly ($P < 0.01$) higher among survivors in comparison with the expired group. Also, there was a statistically ($P < 0.05$) significant positive correlation between mortality and smoking severity ($r = 0.640$) (Table 2).

In this study, there were no statistically significant differences between the expired and survivors groups as regards fever, cough, dyspnea, runny nose, sore throat, chest pain, hemoptysis, myalgia or headache ($P > 0.05$), but there was a statistically significant increase in frequency of nausea, vomiting and diarrhea among the expired group than that among the survivors ($P < 0.05$). Also, there was a statistically significant increase in the duration of the symptoms before the hospitalization among the expired group than that among the survivors ($P < 0.05$) (Table 2). There was a statistically significant ($P < 0.05$) positive correlation ($r = 0.681$) between mortality and prolonged duration of illness before hospitalization.

Our study showed that most of the expired patients presented with bilateral pulmonary infiltrates or unilateral infiltrates, but most of the survivors presented with normal radiology or increased bronchovascular markings, and this difference in the results was statistically highly significant ($P < 0.01$) (Table 2).

There were statistically highly significant ($P < 0.01$) differences in the mean values of APACHE II score (21.11 ± 3.70 vs 24.21 ± 3.82), SOFA score (5.83 ± 2.64 vs 8.85 ± 2.17) and

Table 1 Characteristics of the patients included in this study.

Parameters	No (%)
Sex	
Males	20 (62.50%)
Females	12 (37.50%)
Age (years)	43.99 ± 13.03
Symptoms	
Fever	31 (96.87%)
Cough	30 (93.75%)
Dyspnea	29 (90.62%)
Sore throat	24 (75%)
Runny nose	24 (75%)
Sputum	16 (50%)
Headache	14 (43.75%)
Myalgia	13 (40.62)
Chest pain	12 (37.50)
Hemoptysis	12 (37.50%)
Nausea and vomiting	11 (34.37%)
Abdominal pain	7 (21.87)
Diarrhea	5 (15.62)
Radiology	
Normal chest radiology	8 (25%)
Increased bronchovascular markings	5 (15.63%)
Unilateral infiltrates	7 (21.87%)
Diffuse bilateral infiltrates	12 (37.50%)
Pneumothorax	5 (15.63%)
ABGs	
PH	7.26 ± 0.33
PaO_2 (mmHg)	64.04 ± 20.50
O_2 saturation	83.92 ± 17.45
$PaCO_2$ (mmHg)	38.75 ± 4.17
HCO_3 (meq/L)	19.44 ± 8.5
Scores	
APACHE II	22.46 ± 4.01
SOFA score	7.15 ± 2.85
CPIS	8.03 ± 1.35
Duration	
Symptoms before hospitalization	5.30 ± 3.25
Mechanical ventilation	6.21 ± 3.76
ICU stay	11.32 ± 4.50
Total length of hospital stay	15 ± 3.60

Table 2 Comparison between survivor and expired groups.

Parameters	Survivors (N = 18)	Expired (N = 14)	P value
Age (Mean ± SD)	37.25 ± 15.50	50.47 ± 13.80	P < 0.05
Sex			
Males (No = 20)	11 (55%)	9 (45%)	
Females (No = 12)	7 (58.33%)	5 (41.67%)	
P value	P > 0.05	P > 0.05	
Smoking			
Current	4 (22.22%)	10 (71.42%)	P < 0.01
Ex smoker	5 (27.78%)	2 (14.29%)	P < 0.01
Non smoker	9 (50%)	2 (14.29%)	P < 0.01
Radiology			
Normal (No = 8)	6 (33.33%)	2 (14.29%)	P < 0.01
BVMs (No = 5)	4 (22.22%)	1 (7.14%)	P < 0.01
Unilateral infiltrates (No = 7)	6 (33.33%)	1 (7.14%)	P < 0.01
Bilateral infiltrates (No = 12)	2 (11.12%)	10 (71.43%)	P < 0.01
ABGs			
PH	7.32 ± 0.05	7.20 ± 0.031	P < 0.05
PaO_2 (mmHg)	75.81 ± 18.60	52.28 ± 14.60	P < 0.05
$PaCO_2$ (mmHg)	38.20 ± 5.70	39.30 ± 5.37	P > 0.05
HCO_3 (meq/L)	24.11 ± 3.01	14.77 ± 5.50	P < 0.05
O_2 saturation (%)	92.70 ± 8.69	75.14 ± 10.40	P < 0.05
APACHE II	21.11 ± 3.70	24.21 ± 3.82	P < 0.05
SOFA	5.83 ± 2.64	8.85 ± 2.17	P < 0.05
CPIS	7.55 ± 1.14	8.64 ± 1.39	P < 0.05
No co-morbidities	9	2	P < 0.01
Co-morbidities			
Obesity	2	8	P < 0.01
DM	3	10	P < 0.01
Chronic heart diseases	1	7	P < 0.01
COPD	2	4	P < 0.01
Renal failure	1	6	P < 0.01
Malignancy	0	3	P < 0.01
Kidney transplantation	0	1	P < 0.01
Liver cirrhosis	0	1	P < 0.01
Duration			
Duration of symptoms	4.07 ± 2.50	6.54 ± 3.01	P < 0.05
Mechanical ventilation	3.55 ± 2.00	9.64 ± 2.46	P < 0.01
ICU stay	8.66 ± 2.40	13.98 ± 3.50	P < 0.01
Total length of hospital stay	13.06 ± 2.81	17.50 ± 2.92	P < 0.01

CPIS (7.55 ± 1.14 vs 8.64 ± 1.39) between the expired group and survivors respectively (Table 2).

This study found a statistically significant decrease in PH, PaO_2, O_2 saturation and HCO_3 ($P < 0.05$) among the expired group in comparison with the survivors, but no statistical difference regarding $PaCO_2$ ($P > 0.05$) (Table 2).

As regards the correlation between mortality and specific co-morbidities, there was a statistically significant positive correlation between mortality and old age ($r = 0.633$, smoking ($r = 0.640$), obesity ($r = 0.712$), diabetes mellitus ($r = 0.685$), renal failure ($r = 0.705$), chronic heart diseases (0.591), COPD ($r = 0.523$), malignancy ($r = 0.692$), kidney transplantation ($r = 0.644$) and liver cirrhosis ($r = 0.525$) ($P < 0.05$), (Table 3). There was a statistical ($P < 0.05$) positive correlation between the number of associated co-morbidities and mortality ($r = 0.735$).

Table 3 Correlation between the mortality and the co-morbidities in the studied patients.

Co-morbidities	Pearson's correlation	P-value
Age	0.633	<0.05
Smoking severity	0.640	<0.05
Obesity	0.712	<0.05
DM	0.685	<0.05
Chronic heart diseases	0.591	<0.05
COPD	0.523	<0.05
Renal failure	0.705	<0.05
Malignancy	0.692	<0.05
Kidney transplantation	0.644	<0.05
Liver cirrhosis	0.525	<0.05

Discussion

In this study, there were 20 (62.50%) males and 12 (37.50%) females. This sex distribution showed a significant ($P < 0.05$) increase in the occurrence of corona virus infection among males, but there was no statistically significant difference ($P > 0.05$) in the mortality among them (45% among males and 41.67% among females). Our results agree with other workers' results [6,7]. The increased occurrence of corona virus infection among males can be explained by excess movement of the males through community with more exposure to the infected patients.

In this study, there was high mortality (14 patients (43.75%) out of 32) among corona virus infected patients and there was a statistically significant ($P < 0.05$) increase in mortality in middle and old aged patients in comparison to young patients (mean ages: 50.47 ± 13.80 among the expired group vs 37.25 ± 15.50 among survivors). Also, there was a statistically significant ($P < 0.05$) positive correlation ($r = 0.633$) between age and mortality. Other researchers found similar results [5–14]. This high mortality rate among corona virus infected old patients is explained by the high virulence of the new virus in the absence of previous immunity and already compromised immune system among old peoples.

The most common symptoms among the included patients were: fever (96.87%), cough (93.75%), dyspnea (90.62%), sore throat (75%), runny nose (75%), and sputum (50%). There were statistically significant differences between the expired and survivors groups regards fever, cough, dyspnea, runny nose, sore throat, chest pain, hemoptysis, myalgia or headache ($P > 0.05$), but the frequency of nausea, vomiting and diarrhea were statistically significant higher among the expired group in comparison to the survivors ($P < 0.05$). These findings could be explained by the fact that the presence of nausea, vomiting and diarrhoea leads to dehydration (due to poor oral intake and fluid loss) with its detrimental effects. The duration of symptoms before hospitalization, ICU stay, mechanical ventilation and hospital stay in our studied patients were statistically significantly prolonged in the expired group compared to the survivors. Also, there was a statistically significant ($P < 0.05$) positive correlation ($r = 0.681$) between mortality and prolonged duration of illness before hospitalization. Other investigators found similar results [5–8]. These results can be explained by a delay in diagnosis and management of corona infected patients' result in deterioration in their health status with more need for ICU admission, mechanical ventilation, increased total hospital stay and poor outcome. Also, Al-Tawfiq et al. [9] found that corona patients in comparison with controls were more likely to be admitted to the intensive care unit (53% vs 20%; OR, 4.65; $P = .025$) and to have a high mortality rate (76% vs 15%; OR, 18.96; $P < 0.001$).

The chest radiological findings among the included patients were as follows: 8 (25%) normal chest radiology, 5 (15.63%) increased bronchovascular markings, 7 (21.87%) unilateral infiltrates, and 12 (37.50%) diffuse bilateral infiltrates. Pneumothorax occurred in 5 (15.63%) ventilated patients, for 3 of them it was unilateral and for other 2 patients bilateral. Most of the expired patients presented with bilateral pulmonary infiltrates or unilateral infiltrates, but most of the survivors presented with normal radiology or increased bronchovascular markings, and this difference in the results was statistically highly significant ($P < 0.01$). Our findings agree with other investigators who detected similar results [7–9,15]. These extensive radiological shadows are denoting extensive lung pathology with its detrimental effects on pulmonary gas exchange and general condition of the patients with more need for mechanical ventilation and are associated with bad prognosis.

This study found a statistically significant decrease in PH, PaO_2, O_2 saturation and HCO_3 ($P < 0.05$) among the expired group in comparison to the survivors, but no statistical difference regarding $PaCO_2$ ($P > 0.05$). Our results are in accordance with that of Reyes et al. [16] who reported that one of the independent variables that were associated with high mortality was hypoxemia among SARS patients caused by a corona virus.

Current smoking and smoking severity were statistically significantly ($P < 0.01$) higher in the expired group compared to the survivors. Non smoking and ex smoking were statistically significantly ($P < 0.01$) higher among the survivors in comparison with the expired group. Also, there was statistically ($P < 0.05$) significant positive correlation between mortality and smoking severity ($r = 0.640$). These results are in agreement with previous data that showed that smoking is a major determinant of morbidity and mortality in respiratory tract infection, especially in populations that smoke heavily [6–8]. Cigarette smoking is associated with a variety of alterations in cellular and humoral immune system functions. These alterations include a decreased level of circulating immunoglobulins, a depression of antibody responses to certain antigens, a decrease in CD4+ lymphocyte counts, an increase in CD8+ lymphocyte counts, depressed phagocyte activity and a decreased release of pro inflammatory cytokines. [17]. Smoking increases CD8+ lymphocytes in the cell mediated system and suppresses the host defense against infections [18].

There was a statistically significant ($P < 0.05$) positive correlation between mortality and obesity ($r = 0.712$). Several studies indicate that morbid obesity may be an independent risk factor for complications and mortality from MERS corona virus infection [6–9]. There are some explanations for these results. Obesity can impede pulmonary function (reduced functional residual capacity and expiratory volume). A subsequent ventilation–perfusion abnormality may decrease ventilatory reserve and predispose the obese to respiratory failure after even mild pulmonary challenges [19,20]. Obstructive sleep apnea is present in 40% of obese persons and is associated with systemic hypertension, pulmonary hypertension, and cor pulmonale [21,22]. Obese persons are at an increased risk of developing pulmonary emboli and aspiration pneumonia. Morbid obesity is associated with complications in the intensive care unit including prolonged stay, prolonged ventilation and death [23,24]. In addition to its effects on pulmonary function, obesity is frequently, but not always associated with diabetes, hypertension, hyperlipidemia, cardiovascular disease and high overall mortality [20].

Our work found a statistically significant positive correlation between mortality and diabetes mellitus ($r = 0.685$), renal failure ($r = 0.705$), chronic heart diseases (0.591), COPD ($r = 0.523$), malignancy ($r = 0.692$), kidney transplantation ($r = 0.644$) and liver cirrhosis ($r = 0.525$) ($P < 0.05$), (Table 3). There was a statistically ($P < 0.05$) positive correla-

tion between the number of associated co-morbidities and mortality ($r = 0.735$). Our results are in accordance with other workers' results [6–14]. Also, Arabi et al. [25] concluded that people with DM, renal failure, and chronic lung disease and immuno-compromised persons are considered to be at a high risk of severe disease from MERS CoV infection. Also, our results are in agreement with previous data showing that patients who are immuno-compromised as a result of chronic diseases, malignancy, receiving treatment related to solid organ transplants and DM are at a high risk of respiratory tract infection-related complications including mortality [26,27]. Immuno-compromised patients have an increased attention because of the documentation of prolonged viral shedding in critically ill patients, with the subsequent emergence of resistance to neuraminidase inhibitor drugs [28]. Renal failure population has many factors such as overwhelming uremia, neutrophil dysfunction, malnutrition, trace elements' deficiencies, iron overload, impaired glucose metabolism, and hyperparathyroidism, and the use of immunosuppressive drugs to treat and control underlying diseases leads to increased morbidity and mortality of infection [29]. Casqueiro et al. [30] concluded that the infectious diseases are more frequent and/or serious in patients with DM, which potentially increases their morbidity and mortality due to many factors as a deficiency of the C4 component in DM, this reduction of C4 is probably associated with polymorphonuclear dysfunction and reduced cytokine response decrease secretion of inflammatory cytokines as interleukin-1 (IL-1) and IL-6 decreased mobilization of polymorphonuclear leukocytes, chemotaxis and phagocytic activity. CD4 T-lymphocytes and their response to antigens are impaired.

Conclusions

Most MERS corona patients present with fever, cough, dyspnea, sore throat, runny nose and sputum. The presence of abdominal symptoms may indicate bad prognosis. Prolonged duration of symptoms before patients' hospitalization, prolonged duration of mechanical ventilation and hospital stay, bilateral radiological pulmonary infiltrates, and hypoxemic respiratory failure were found to be strong predictors of mortality in such patients. Also, old age, current smoking, smoking severity, presence of associated co-morbidities like obesity, diabetes mellitus, chronic heart diseases, COPD, malignancy, renal failure, renal transplantation and liver cirrhosis associated with a poor outcome of ICU admitted MERS corona virus infected patients.

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