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ORIGINAL ARTICLE

The prognosis of MERS cases with comorbidities in Saudi Arabia 2012-2019

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ABSTRACT

Background: Middle East respiratory syndrome (MERS) is a severe respiratory illness that was first identified in 2012, following the outbreaks in the Kingdom of Saudi Arabia (KSA). The main aim of this study was to determine the prognosis of MERS patients with comorbidities, through the measurement of the fatality rate.

Methods: This is a retrospective cohort study that included patients diagnosed with MERS, from 2012 to 2019, within the KSA. The fatality rate was measured for cases with and without comorbidities, based on various classifications of chronic disease.

Results*:* Of the patients diagnosed with MERS and comorbidities, 327 (45%) patients were deceased, whereas only 49 (21%) of the MERS cases without comorbidities died. Based on the fatality rates, MERS cases with endocrine diseases, renal diseases, other comorbidities (including septic shock and obesity), and cardiovascular diseases were the most vulnerable, with fatality rates of 49% (247), 48% (41), 47% (77), and 41% (558), respectively.

Conclusion: This study suggests that the prognosis for MERS cases with comorbidities is poorer than for cases without comorbidities. Male gender and older age were associated with increased cases of fatality rate.

Keywords: MERS, comorbidities, fatality rate, public health.

Introduction

Middle East respiratory syndrome (MERS) is a severe respiratory illness that was first identified in 2012, following the outbreaks in the Kingdom of Saudi Arabia (KSA). Cases were reported in the regions of Hassa, Jeddah, Riyadh, and Taif. Most of those who contracted MERS suffered from comorbidities, where it has been reported by Alqahtani et al. [1] that 57% of the MERS cases were suffering from different comorbidities including congestive heart failure, chronic kidney disease, diabetes mellitus, hypertension, ischemic heart disease, and end-stage renal disease.

In Saudi Arabia, the case fatality rate (CFR) was reported to be ranging from 20%, among confirmed cases reported from the Saudi Ministry of Heath to the World Health Organization between April 2014 and June 2016 [1], to 75% among MERS cases admitted to the intensive care unit in the King Fahad Hospital, Jeddah, Saudi Arabia [2]. A systematic review conducted by Park et al. [3] reported the CFR among MERS cases in Saudi Arabia to be ranging from 22% to 69.2%. The reported rates in the KSA are higher than what was reported in Korea in 2015, where Cowling et al. [4] reported the CFR as 21%.

The risk of mortality among MERS cases was reported to be significantly increasing with advanced age and the presence of multiple comorbidities [1], including diabetes, chronic kidney disease, respiratory disease, pneumonia, cardiac disease, and cancer [3]. Additionally, the male gender was reported to be associated with increased morality.

Although there are several studies in the KSA that have addressed the CFR for MERS among Saudi patients, to the best of our knowledge, recent data on the prognosis of MERS cases with comorbidities are lacking. Therefore, the current study aimed to estimate the CFR among

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MERS patients with comorbidities compared with patients without comorbidities.

Methods

The current study is a retrospective cohort study including patients diagnosed with MERS during the period from 2012 to 2019. All patients were followed-up through the study period till one of the study's end points, which is either death or recovery.

The study was conducted in the KSA which has 13 administrative regions (Figure 1). The data for MERS cases were collected from the national situation room (NSR) forms, referred to as MERS database. The NSR is responsible for the management of data within the scope of practice of the command and control center for the KSA's Ministry of Health and regional health directorates. The MERS database is used by the NSR to update or generate reports and shared nationally and internationally with the World Health Organization-International Health Regulations (WHO-IHR) via the MERS daily update report.

The current study included confirmed MERS cases registered in the MERS database regardless of their age or gender. All included cases were either citizens or residents of the KSA during the study period.

The data for the current study were collected from the MERS database. The data elements included the following variables: demographic data, clinical data, originating hospital, current hospital, current case status, either deceased or recovered, and source of infection. Additionally, data on comorbidities were collected from the MERS database from the public health department, including endocrine diseases, renal diseases, other comorbidities (including septic shock and obesity), and cardiovascular diseases. The disease classification was based on the international classification of disease version 10. The study team maintained both internal and external validity. Regarding internal validity, where the data had passed through multiple layers of validation before final approval by the KSA Ministry of Health included regional health directorates' validation, consolidation of all regional health platforms' MERS data by the national public health platform, and review by the National Health Emergency Operations Center.

Descriptive and frequency analyses were used to assess clinical data of all participants, and different subcategories. Data were analyzed using Microsoft Office Excel and an open source software package (Epidemiologic Statistics for Public Health [online], which is available at http://openepi.com/Menu/OE_Menu.htm). Tableau software version 8.2, which is the software used by the NSR,

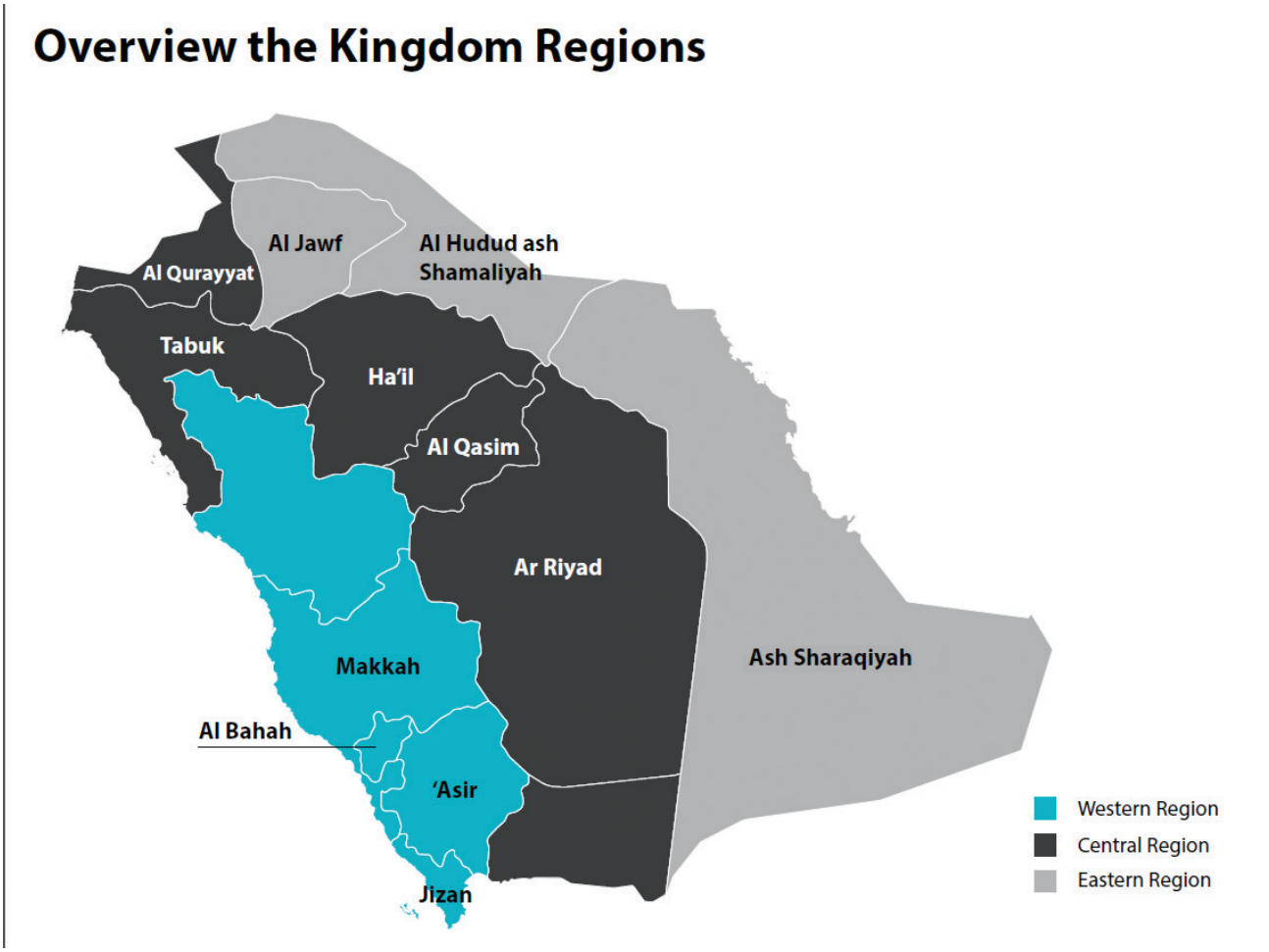

Figure 1. *Thirteen administrative regions in the Kingdom of Saudi Arabia.*

was used for data visualization. The odds ratio (OR), its standard error, and 95% confidence interval (CI) were calculated according to Altman (1991). *p*-value < 0.05 was considered to be significant.

Results

Of the total 1,060 confirmed MERS cases, 731 were with comorbidities, while 329 were without comorbidities. As shown in Table 1, 44.73% (327 cases) of MERS cases with comorbidities deceased. Of the 329 MERS cases without comorbidities, only 14.89% (49 cases) died.

Further examination of the CFR shows the highest fatality rate was reported in MERS cases with endocrine diseases as comorbidities at 49% (247). This was followed by renal comorbidities at 48% (41), cardiovascular system (CVS) at 41% (229), central nervous system (CNS) at 40% (23), reproductive system/pregnancy at 40% (6), gastrointestinal system (GIT) comorbidities at 39% (11), respiratory comorbidities at 38% (33), hematology comorbidities at 31% (4), and musculoskeletal comorbidities 27% (3). The CRF among other comorbidities was reported accumulatively at 47% (36) (see Table 2).

Table 3 shows that the CFR was higher among males than females at 38.71% versus 27.18%. Since most of the affected cases were male, further breakdown and analysis of this group was undertaken and is shown in Table 4, whereas males with comorbidities had a fatality rate of 45.65% versus 20.48% among male cases without comorbidities.

Table 1. *Number of deceased and recovered cases in MERS patients with and without comorbidities (n = 1,060).*

Groups	Deceased *n*(%)	Recovered *n*(%)
MERS with comorbidities	327 (44.73)	404 (55.25)
MERS without comorbidities	49 (14.89)	280 (85.10)
Total	376	684

Table 2. *Fatality rates in MERS cases with comorbidities (n = 1060), by comorbidity type.*

System involved	Number of cases	Number of deaths	% Fatality
Endocrine	501	247	49%
Renal	86	41	48%
Others	77	36	47%
CVS	558	229	41%
CNS	57	23	40%
Reproductive system/ pregnancy	15	6	40%
GIT	28	11	39%
Respiratory	86	33	38%
Hematology	13	4	31%
Musculoskeletal	11	3	27%

Table 3. *Deceased and recovered MERS cases by gender (n = 1,060).*

Male\Female	Deceased *n*(%)	Recovered *n*(%)
Male	295 (38.71)	467 (61.29)
Female	81 (27.18)	217 (72.82)

This was the same observation among female gender, where MERS cases with comorbidities had CFR higher than cases without comorbidities at 41.90% versus 5.04%% respectively as shown in Table 5. Advancing age was also associated with increased fatality rate, where patients aged above 65 years, who had comorbidities, had a reported 64.07% fatality rate, while the corresponding statistics for those from the same age group but without comorbidities was 4.45% as shown in Table 6.

As shown in Table 7, age more than 65 years was associated with almost five times increased risk of mortality among MERS cases compared with younger population; OR (95% CI) at 4.94 (3.72-6.57), *p* value < 0.0001. The presence of comorbidities was also associated with more than four times increased risk of mortality among MERS cases; OR (95% CI) at 4.62 (3.30-6.47), p value < 0.0001. Male gender was associated with 69% increased risk of mortality among MERS cases.

Discussion

This study considered 1,060 MERS cases, of which 731 (69%) were with comorbidities and 329 (31%) were without comorbidities. The results show that 45% of the MERS patients with comorbidities died, versus only 15% of MERS patients without comorbidities died. In contrast to Alqahtani et al. [1], our data show a clear difference in fatality rates between MERS generally and within the group of mortality. This is attributable to our larger sample and more recent data.

This study reported CFR in MERS cases less than what was reported by Garout et al. [2], where they

Table 4. *Deceased and recovered male MERS cases with and without comorbidities.*

Males	Deceased *n*(%)	Discharged *n*(%)
With comorbidity	252 (45.65)	300 (54.35)
Without comorbidity	43 (20.48)	167 (79.52)

Table 5. *Deceased and recovered female MERS cases with and without comorbidities.*

Females	Deceased *n*(%)	Discharged *n*(%)
With comorbidity	75 (41.90)	104 (58.10)
Without comorbidity	6 (5.04)	113 (94.69)

Table 6. *Patients above 65 years with MERS - deceased and recovered cases.*

Above 65	Deceased n(%)	Discharged n(%)
With comorbidity	173 (64.07)	97 (35.93)
Without comorbidity	15 (45.45)	18 (54.55)

Table 7. *Factors associated with increased case fatality.*

Variable	OR (95% CI)	*p* value
Presence of comorbidities	4.62 (3.30-6.47)	< 0.0001
Male gender	1.69 (1.26-2.27)	0.0005
Age older than 65 years	4.94 (3.72-6.57)	<0.0001

OR = odds ratio; CI = confidence interval.

reported 75% of case fatality (39 patients died out of 52 confirmed MERS cases). This higher rate could be explained by the fact that majority of the studied cases were suffering from underlying comorbidities. On the other hand, the CFR reported by our study is higher than what was estimated by Cowling et al. [4] in South Korea at 21% or what was reported by Cauchemez et al. [5] for secondary cases with the exclusion he made for sporadic cases identified after presenting with serious disease at also 21%. This difference could be attributable to our larger sample and more recent data. However, the current study's findings are within the fatality rate range reported in recent review, where it was reported to range from 22% to 69% [3].

Majumder et al. [6], on their attempt on the estimation of MERS-Coronavirus (MERS-CoV) reproductive number and CFR for the spring 2014 Saudi Arabia outbreak, state that the overall CFR for MERS is 40%, whereas they estimated non-attributed death data using Monte Carlo simulation, a gap which we consider in this study using more recent data that support further analytics beyond the measurement of the overall CFR.

Recently, Alanazi et al. [10], in their study of 32 MERS patients, have reported that fatality and severity correspond to the severity of underlying conditions focusing on diabetes mellitus and hypertension. Our data show that MERS fatality rates in cases with comorbidities are highest in cases with comorbid endocrine diseases such as diabetes mellitus reaching 49%. This is similar to what has been reported in another study, where the fatality rate among cases with diabetes was 50.9% [1]. This finding could be explained by the observation of Kulcsar et al. [11], wherein they have reported that the increased disease severity observed in individuals with MERS and comorbid type 2 diabetes is likely due to a dysregulated immune response, which results in more severe and prolonged lung pathology. The second comorbidity that was associated with high fatality rate among MERS cases was comorbid renal diseases with a CFR of 48%. This was also the finding of Alraddadi et al. [12] where the fatality rate was 71% among cases with chronic kidney disease. Patients with comorbid cardiovascular diseases had a fatality rate of 41%, the mechanisms that could be behind the worse clinical outcomes in patients with cardiovascular disease could be more advanced age, reduced cardiopulmonary reserves, dysregulation of the immune system, and intolerance of viral-mediated cytokine storm [13].

On the other hand, patients with central nervous system diseases, reproductive system diseases, and pregnancy had a fatality rate of 40%. Patients with hematological diseases had a fatality rate of 31% and those with musculoskeletal diseases had fatality rate of 27%. The group categorized as 'other comorbidities' had a fatality rate of 47% (36 patients).

These results also support Garout et al.'s [2] study, whose results found the most common comorbidities among diabetes mellitus (52%), hypertension (46%), and chronic renal disease (21%). The values given in Garout et al.'s results differed slightly from our own.

In terms of gender, male cases of MERS with comorbidities had a fatality rate of 45.65% and 41.90% in females. The current analysis showed that the male gender is associated with a 69% increase in mortality risk among MERS cases. This finding is in line with what has been previously reported from recent MERS outbreaks where there was a high incidence and CFRs among men, with the sex-dependent increase in disease severity being more pronounced with older age [14]. Male predominance could be explained by the facts that males and females respond differently to many RNA and DNA virus infections, wherein males generate less robust immune responses, while in contrast, females mount stronger innate and adaptive immune responses and are relatively resistant to virus infections [15]. Another explanation could be the increased risk of exposure to infection among men, especially in Saudi Arabia, where men are primarily responsible for outdoor activities, while women are primarily housewives and are less susceptible to infection.

Furthermore, our analysis supports the argument that MERS fatality rates increase with advanced age. Our data show the overall fatality rate in cases aged below 65 years to be 36%, while there was a 64% fatality rate among those older than 65 years and with comorbidities. Additionally, old patients with MERS-CoV infection had almost five times increased risk of mortality. This supports the results given by Alqahtani et al. [1]. This could be due to the fact that older age is usually associated with vascular aging, diminished renal function, and the presence higher number of comorbidities [13]. Additionally, the age-associated immune-senescence, which results in a suboptimal immune response, could be behind the severity of MERS infection among old age subjects [16].

Limitations of the study

The main limitation in our study is the absence of data regarding comorbidities in confirmed MERS-CoV cases. Some of the cases in our record did not specify whether comorbidities existed or not, but this would not have affected the significance of the results, since we assumed that the pattern of available data would generate similar results if applied to the group with missing data, since all other variables are available. Our knowledge base is built by uncovering each piece of the puzzle of MERS-CoV, one at a time, and limitations show us where new efforts should be made. Thus, we invite colleagues to extend study of the outcomes of MERS with comorbidities. On the other hand, our study's main strength was the maintenance of the external validity that made the study's results widely applicable and extendable. Another strength of the current study was the quality and reliability of the collated data which was revised and corrected according to the main health electronic surveillance network used in the KSA.

Conclusion

We conclude that MERS shows poor prognosis in patients with comorbidities, mainly diabetes, cardiovascular disease, and renal disease. Male gender and older age are associated with high fatality rates.

Disaster Medicine and Public Health Implications

This study attempts to close the knowledge gap that has restricted basic epidemiology, particularly in terms of CFR(s) among MERS cases with comorbidities. We expect the results to have a positive impact on the quality and costs of medical services, and believe that this work will direct education and awareness efforts in the context of MERS and disaster medicine literature specifically, and public health issues related to Disaster Medicine in general.

List of abbreviations

CFR	Case fatality rate
KSA	Kingdom of Saudi Arabia
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
NSR	National situation room

Conflict of interest

The authors declared that they have no conflict of interest.

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Consent for publication

Consent for publication was provided by the general directorate of emergencies, disasters, and ambulance services. Due to the retrospective nature of the study, patients' consents were not obtained for the data used in this publication because this study did not compromise anonymity or confidentiality or breach of local data protection laws.

Ethical approval

Ethical approval was granted by Institutional Review Board via reference number 20-136M dated: 13-July-2020.

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