Critically Ill Patients with the Middle East Respiratory Syndrome (MERS): A

Multicenter Retrospective Cohort Study

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Abstract

Objective: To describe patient characteristics, clinical manifestations, disease course including viral replication patterns and outcomes of critically ill patients with severe acute respiratory infection (SARI) from the Middle East Respiratory Syndrome (MERS SARI) and to compare these features to patients with SARI due to other etiologies.

Design: Retrospective cohort study.

Setting: Patients admitted to intensive care in 14 Saudi Arabian hospitals.

Patients: Critically ill patients with laboratory-confirmed MERS SARI (n= 330) admitted between September 2012 and October 2015 were compared to consecutive critically ill patients with community-acquired SARI of non-MERS etiology (non-MERS SARI) (n=222).

Interventions: None.

Measurements and Results: Although MERS SARI patients were younger than those with non-MERS SARI from all etiologies (median (quartile Q1, Q3) 58 years (44, 69) vs. 70 (52, 78) , p<0.001), clinical presentations and co-morbidities overlapped substantially. Patients with MERS SARI had more severe hypoxemic respiratory failure (PaO2/FiO2 106.3 (66.2, 160.0) vs. 175.7 (104.2, 252.0), p<0.001) and more frequent non-respiratory organ failure (non-respiratory SOFA score: 6 (4, 9) vs. 5 (3, 7), p= 0.002); thus required more frequently invasive mechanical ventilation (85.2% vs. 73.0%, p<0.001), oxygen rescue therapies (extracorporeal membrane oxygenation 5.8% vs. 0.9%, p=0.02), vasopressor support (79.4% vs. 55.0%, p<0.001) and renal replacement therapy (48.8% vs. 22.1, p<0.001). After adjustment for potential confounding factors, MERS was independently associated with death compared to non-MERS SARI (aOR 5.87, 95% CI 4.02, 8.56, p<0.001).

Conclusions: Substantial overlap exists in the clinical presentation and co-morbidities among patients with MERS SARI from SARI from other etiologies; therefore, a high index of suspicion combined with diagnostic testing is essential component of SARI investigation for

at-risk patients. The lack of distinguishing clinical features, the need to rely on rt-PCR from respiratory samples, variability in viral shedding duration, lack of effective therapy, and high mortality, represent substantial clinical challenges and help to guide ongoing clinical research efforts.

Introduction

As of June 19, 2017, 2029 laboratory-confirmed cases of the Middle East Respiratory Syndrome (MERS) were reported from 27 countries (80% from Saudi Arabia), with an overall case fatality proportion of 35%.[1,2] The clinical spectrum ranges from asymptomatic or mildly symptomatic cases to critical illness due to respiratory and multi-organ failure. Among hospitalized MERS patients, 53-89% require Intensive Care Unit (ICU) admission[3,4] with reported mortality rates of 58-90% among intensive care unit (ICU) patients.[5,6] A case-control study estimated that hospitalized patients with MERS were 5 times more likely to require ICU admission and 19 times more likely to die compared to non-MERS controls.[3] However, data on the sickest MERS patients remains limited and is based mostly on single-center studies, without comparison to appropriate controls – patients with severe acute respiratory infection (SARI) of non-MERS etiologies[5-7]. Therefore, the objective of this study was to describe patient characteristics, clinical manifestations, disease course including viral replication patterns and outcomes of critically ill patients with MERS SARI and to compare these features to patients with SARI due to other etiologies.

Materials and Methods

Setting

In this retrospective cohort study, we included patients from 14 referral hospitals in 5 cities in Saudi Arabia with a median of 550 hospital beds (Q1-Q3: 500, 1200) and 42 ICU beds (Q1-Q3: 34, 64). Organizational features of participating hospitals are summarized in the Supplementary Appendix (Table S1). Of note, 3/14 (21.4%) hospitals reported to perform MERS-CoV real-time reverse transcription polymerase chain reaction (rRT-PCR) although confirmation was required for all hospitals at the central laboratory of the Saudi Ministry of Health. The Institutional Review Boards of all participating centers approved the study. Patient-level informed consent was not required. Some of the patients described in this study have been reported previously in single-center studies.[6-10]

Patients and Diagnostic Testing

SARI was defined as an acute respiratory infection, including a history of fever and cough with onset within the last 10 days; clinical suspicion or documented pulmonary parenchymal disease (e.g. unilateral of bilateral infiltrates on chest radiograph or computed tomographic scan) and illness not already explained by non-infectious etiology. Diagnostic testing for MERS followed the guidelines set by the Saudi Arabian Ministry of Health; nasopharyngeal swabs or sputum samples, if possible, in non-intubated patients and tracheal aspirates or bronchoalveolar lavage in intubated patients were tested by MERS-CoV rRT-PCR which targeted amplifications of the upstream E protein (upE gene) and open reading frame (ORF)1a.[11] In patients with suspected MERS and negative rRT-PCR, testing was repeated at the discretion of the treating teams. For MERS-CoV positive patients, follow-up respiratory samples were collected approximately 1-2 times per week to assess clearance of viral RNA for infection control purposes. Patients were also tested with common viral panels and bacterial cultures from respiratory and blood samples at the discretion of the treating teams. Serology testing for MERS was not used as a standard diagnostic test. MERS SARI was defined as SARI with a positive rRT-PCR respiratory sample; otherwise, SARI case was considered non-MERS SARI.

Data Collection

We included all MERS SARI patients admitted to the participating ICUs between September 2012 and October 2015. We compared critically ill patients with laboratory-confirmed MERS SARI to all consecutive cases of critically ill patients with community-acquired SARI of non-MERS etiology (non-MERS SARI) during January 2014-October 2015, using the same eligibility criteria otherwise, and captured in a SARI database at King Abdulaziz Medical City-Riyadh (KAMC-R), Saudi Arabia. Data were collected by using standardized International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) case report forms.[12]

We documented patient demographic features, underlying co-morbidities (defined in the online Supplement), radiographic findings and the durations from symptom onset to presentation to the emergency department, ICU admission and intubation. We assessed severity of illness using the sequential organ failure assessment (SOFA) score, as well as laboratory and ventilator parameters on days 1, 3, 7, 14 and 28 of ICU admission based on the most abnormal values for each day.[13] We recorded the results of virology and microbiology testing and treatments received, including aspects of mechanical ventilation, hemodynamic and renal support during ICU stay. The primary outcome was 90-day mortality. Secondary outcomes were ICU, hospital and 28-day mortality and mechanical ventilation duration, length of stay in the ICU and the hospital.

Statistical Analysis

We compared MERS SARI to non-MERS SARI patients using Student's t-test or the Mann Whitney U Test for continuous variables based on normality assumption and the Chi-square test or Fisher's exact test for categorical variables. Kaplan-Meier curves censored at 90 days, and the log-rank test were used to compare the median survival time between the two groups. We reported continuous variables as medians and quartiles 1 and 3 (Q1, Q3).

To examine the independent association of MERS on 90-day mortality, we performed multivariable logistic regression analysis with the following variables: MERS SARI (versus non-MERS SARI), age, sex and chronic comorbidities (diabetes, cardiac, renal, pulmonary, obesity, neurologic and immunosuppression). We also adjusted for clustering by centers by applying the PROC SURVEYLOGISTIC procedure with a "cluster" statement (SAS), in addition to year, using two variables reflecting early (before July 2014) and more contemporary (July 2014-2015) experience. We carried multiple sensitivity analyses to ensure the robustness of the independent association of MERS and mortality by restriction to patients admitted to King Abdulaziz Medical City-Riyadh (KAMC-R) only, community-acquired cases only and non MERS-SARI who have been tested for MERS. Results were reported in adjusted odds ratios (aOR) with 95% confidence intervals (CI). For serial

measurements, we tested differences between the two groups over time using repeated measures analysis of variance with no imputation for missing values. We tested the difference between the groups at each study day using t-test or the Mann Whitney U Test and we accounted for multiple testing by Benferroni correction.

We examined the time to clearance of MERS-CoV rRT-PCR defined as the time from the first performed rRT-PCR until the test was negative on 2 occasions, without a positive test afterwards. We constructed additional Kaplan-Meier curves for the time to clearance, censoring by death and at 90 days.

We examined the predictors of mortality among MERS SARI patients by first comparing baseline characteristics, co-morbid conditions and physiologic parameters of MERS SARI survivors and non-survivors using univariable analysis, followed by multivariable logistic regression incorporating all variables with p values <0.1 on univariable testing and adjusting for clustering by center and for year. We carried out sensitivity analyses by restricting the logistic regression analysis to patients from KAMC and to patients with community-acquired infection. Tests were two-sided with significance set at α <0.05. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient characteristics

During the study period, 330 MERS SARI patients were admitted to the participating ICUs and were compared to 222 non-MERS SARI patients. Patients with MERS SARI were younger than non-MERS SARI patients (median (Q1, Q3) 58 (44, 69) vs. 70 (52, 78), p= <0.001), were more likely to be males (68.2% vs 58.1%, p= 0.02) and to be healthcare workers (9.7% vs. 0.0%, p= <0.001) (Table 1). Chronic comorbidities were highly prevalent (any comorbidity, 80.3% in MERS SARI, 91.4% in non-MERS SARI).

MERS SARI patients presented to emergency department after a median of 5 days (Q1, Q3: 3, 8) from the onset of symptoms, and were admitted to the ICU after 7 days (Q1, Q3: 5, 11) from symptom onset. Invasive mechanical ventilation was initiated in 85.2% of patients, after a median of 8 days (Q1, Q3: 5, 12) from their first symptom. The durations from symptom onset to ER presentation, ICU admission and ventilation were approximately 2-4 days longer for patients with MERS than among patients with non-MERS SARI (Table 1).

Pulmonary manifestations

On admission to ICU, patients with MERS SARI were more hypoxemic than non-MERS SARI (PaO2/FiO2: 106.3 (66.2, 160.0) vs 175.7 (104.2, 252.0), p<0.001) and had more extensive chest radiograph infiltrates compared to patients with non-MERS SARI (number of quadrants with infiltrates on chest radiograph 3 (2, 4) vs 2 (0, 3), p= <0.001). More MERS SARI patients required invasive mechanical ventilation (Table 2 and 3) and needed higher FiO_2 (0.7 (0.5, 1.0) vs 0.5 (0.3, 0.6), p= <0.001) and positive end expiratory pressure (PEEP) compared to patients with non-MERS SARI (12 (8, 14) vs 8 (5, 10) cmH2O, p= <0.001) (Figures 1 and S1). MERS SARI patients were more likely to receive rescue oxygenation therapies, including neuromuscular blockade, nitric oxide, prone positioning, high-frequency oscillation ventilation and extracorporeal membrane oxygenation (ECMO) compared to non-MERS SARI (Table 3).

Non-Pulmonary manifestations

MERS SARI patients had higher SOFA scores compared to patients with non-MERS SARI 3 (2, 4) vs. 2 (2, 3), p= 0.002). MERS SARI patients were more likely to develop shock requiring vasopressor therapy, renal failure requiring renal replacement therapy, elevated liver enzymes, leukopenia and thrombocytopenia compared to patients with non-MERS SARI (Table 2 and 3).

Viral and bacterial testing

Detailed data on MERS-CoV testing was available on 311/330 MERS SARI patients. The confirmatory sample for MERS-CoV was from the nasopharynx in 167/311 (54%) and from the lower respiratory tract (sputum, endotracheal aspirates or brochoalveolar lavage) in 144/311(46%). Initial negative samples collected before positive ones were predominantly from the upper respiratory tract (88/108, 81.5%). Of all MERS SARI patients, 237/311 (76.2%) were diagnosed from the first rRT-PCR test; 51/311 (16.4%) after one negative test, 17/311 (5.5%) after 2 negative tests, 2/311 (0.6%) after 3 negative tests and 3/311 (1.3%) after 4 negative tests. The time to clearance of MERS-CoV RNA was significantly shorter in survivors compared to non-survivors (median 20 days (95% CI 17, 26) vs 37 days (95% CI 24, -), p value= 0.0005 by survival analysis, Figure 2). Among the non-MERS SARI patients, 129/222 patients (58%) were tested for MERS-CoV, 16/129(12.4%) had 2 negative tests and 13/129 (10.1%) had 3 or more negative tests. Testing for MERS-CoV among SARI patients increased with time, from 43% before July 2014, to 79% in the second half of 2014 to 100% in 2015. (Figure S2).

Other viral pathogens were identified in 17/330 (5%) patients with MERS SARI and 52/222 (24%) with non-MERS SARI (p <0.001). In patients with MERS SARI the most commonly detected viral co-pathogens included other coronaviruses (5), respiratory syncytial virus (1) and influenza A virus (4), whereas in non-MERS patients co-pathogens included influenza A (39) and B (3) viruses, rhinovirus (9), and other coronaviruses (5), (Table S2). In the first 3 days before and after ICU admission, bacterial pathogens were identified in respiratory samples in 60/330 (18.5%) MERS SARI patients and 56/222 (25%) non-MERS SARI (p= 0.046) and in blood in 26/330 (8%) of MERS SARI and 29/222 (13%) of non-MERS SARI (p= 0.046).

Outcomes

Crude 90-day mortality was higher in patients with MERS SARI compared to non-MERS

SARI (65.8% vs 31.1%, p< 0.001). Survival curves are shown in Figure 2 (log-rank test p <0.0001 for MERS vs non-MERS SARI). Differences in ICU course between MERS SARI survivors and non-survivors are reported in Table 2. Multivariate logistic regression showed that MERS was an independent risk for death (aOR 5.87, 95%CI 4.02, 8.56, p value <0.001) compared to non-MERS SARI (Table S3). Sensitivity analyses were performed by restriction to patients admitted to King Abdulaziz Medical City-Riyadh (KAMC-R) only, community acquired cases only and non MERS-SARI who have been tested for MERS did not alter this association (Table S3). Among patients with MERS SARI, age (per one year increase) (aOR 1.05, 95%CI 1.03, 1.07, p <0.001) and chronic renal disease (aOR 2.48, 95% CI 1.26, 4.89, p=0.01) were independent predictors of 90-day mortality (Table S4). For community-acquired MERS, age (per one year increase) (aOR= 1.10, 95% CI= 1.07, 1.14. p=<0.001) and diabetes with chronic complications (aOR 4.20, 95% CI 1.06,16.60, p=0.04) were independent predictors of 90-day mortality.

Discussion

This is the largest study of critically Ill patients with MERS to date and the first to compare MERS with a large cohort of similar patients with SARI of diverse etiologies. While there are important differences in clinical course and outcome, this study also highlights the overlap in the initial clinical presentation and underlying conditions of MERS and non-MERS SARI. This overlap has important implications for practice, as a MERS diagnosis based on clinical, radiologic and standard laboratory data alone is not possible. While epidemiologic risk factors should be sought[14], timely testing with rRT-PCR for MERS-CoV is essential in patients at-risk. Our study also confirms that initial negative rRT-PCR does not exclude the diagnosis of MERS with the initial rRT-PCR test being positive only in 76.2% of patients ultimately found to have MERS SARI. Specimens from upper respiratory tract were more likely to be negative and accounted for 81.5% of initial negative samples before positive ones. This is consistent with earlier studies of seriously ill MERS patients that have shown

that viral loads are often higher in lower than upper respiratory tract specimens.[15] As we found, repeated sampling is important to improve the sensitivity of testing, when there is a high index of clinical suspicion. Our study demonstrates that MERS was independently associated with almost 5-6 fold increase in death compared to non-MERS SARI; a finding that was found to be robust on different sensitivity analyses, including restriction to only community acquired cases.

Three single-center studies examined the differences of MERS and non-MERS illness among hospitalized patients. Al-Tawfiq et al compared 17 MERS patients (8 admitted to ICU) to 82 non-MERS patients (20 admitted to ICU) and reported mortality of 76% among hospitalized MERS patients compared to 15% among non-MERS.[3] Hamzah et al compared 80 MERS patients (15 admitted to ICU) to matched 159 non-MERS patients (26 admitted to ICU) and found that none of the presenting symptoms are specific for MERS-CoV infection.[16] Garbati et al studied 48 MERS patients (25 admitted to ICU) and 111 non-MERS patients (62 admitted to ICU) and found that MERS and non-MERS were not distinguishable although diarrhea was more common in MERS patients.[17] The three single-center studies included hospitalized patients with acute respiratory infection with heterogeneous severity. Data on severity of illness, physiology and ICU therapies among the subset of ICU patients were not available. In the three studies, the control group was selected based on having a negative MERS-CoV test; while we used a pragmatic but protocolized approach in selecting non-MERS SARI by including those who met the clinical definition of SARI and never diagnosed with MERS. In the three reported studies, it is unknown how many patients met criteria for the testing and were not actually tested. Our approach mimics real-life practice, provides insight to testing practices and provides a more accurate approximation of the denominator of all ARI or SARI cases, which is defined based on clinical and not laboratory criteria.

Viral pathogens (other than MES-CoV) were found in approximately 4% of patients with MERS SARI and 24% of non-MERS SARI patients, with influenza being the most common.

In addition, bacterial pathogens from respiratory samples were found in 20-25% of patients, and from bloodstream in 8-10% of patients with MERS SARI and non-MERS SARI, emphasizing the likely importance of empiric therapy directed against appropriate community- or hospital-acquired bacterial or viral pneumonia, and close follow-up for potential secondary infections among patients presenting with SARI.

We observed that more than one third of patients with non-MERS SARI were not tested for MERS-CoV; although this occurred mainly before July 2014 and improved in 2015 to 100%. There are several reasons that may explain not testing SARI patients for MERS-CoV before July 2014, including the limited awareness about MERS, the sporadic and rare nature of the disease combined with the unavailability of rRT-PCR in the treating hospitals and long turn-around time of testing. This also may reflect the reliance of some physicians on "clinical suspicion" to request MERS testing. The higher percentage of isolated pathogens in the non-MERS SARI patients suggest that the presence of an alternative pathogen may have persuaded physicians away from MERS testing. Our study shows however, that such a strategy is not justified in that MERS cannot be ruled out on either clinical findings or based on the presence of other pathogens. Our data underscore the need for timely diagnostic testing for MERS, as delayed diagnosis has been implicated as a major contributing factor to hospital outbreaks.[18,19] Testing for other viral pathogens was also variable; 75% of patients were tested for influenza A and 25% for other viruses, such as rhinovirus and RSV. This may have been related to the lack of availability of viral PCR multiplex in earlier years, but it may also be a reflection of uncertain value of viral testing. A recent Canadian study found that viral testing was performed in only 11% of patients hospitalized with respiratory symptoms.[20] The practices of viral testing around the globe vary considerably, are highly dependent upon clinical suspicion, individual and local practice patterns and likely lead to poor sensitivity in detecting well-established, seasonal and emerging pathogens.

Our study has several strengths. It is the largest collaborative multicenter study on MERS SARI, incorporating a contemporary comparator group and using the same eligibility criteria

in addition to a standardized data collection format. Limitations include the retrospective nature and the inclusion of non-MERS SARI patients from only one center and a different period of time. However, a sensitivity analysis restricting comparisons to non-MERS SARI from the same center found a similar independent association of MERS with mortality in comparison to non-MERS SARI. Because serology testing was not routinely performed and because rRT-PCR for MERS-CoV was not done on all patients in the non-MERS SARI cohort, it is possible that some MERS patients may have been undiagnosed. If there were misclassification of non-MERS patients, it would tend to bias our findings towards showing no between-group differences, so that differences in presentation, clinical course and outcomes may be more extreme than what we have reported. The multicenter nature and relatively large sample size of this study helps to improve the likely generalizability of the findings. On the other hand, variability in screening practices, follow-up of suspected cases with repeat testing, discharge criteria and case management may have varied among centers and over time. Therefore, we adjusted for clustering by center and for the study period. As the bacterial and viral diagnostic testing was not protocolized, the prevalence of other viral and bacterial co-pathogens may have been underestimated. Similar to many cohort studies of patients with SARI, we could not determine the cause of illness in many of the non-MERS patients. Finally, the data does not allow inferences about the incidence of MERS.

Conclusions:

Our study demonstrates that SARI of MERS and of non-MERS etiologies cannot be reliably distinguished by clinical presentation, making diagnostic testing for MERS an essential component of SARI investigation for at-risk patients. Severe respiratory illness, common multisystem organ dysfunction and a high risk of death make supportive organ-supporting therapy a critical component of MERS care and highlight the pressing need for evaluation of specific antiviral therapies.

Conflict of interest

The authors declare that they have no competing interests.

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Not applicable.

Ethics approval

The study was approved by the National Guard Health Affairs Institutional Review Board(IRB).

Consent to participants

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

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Figure legends

Figure 1. Physiologic parameters among patients with the Middle East Respiratory Syndrome severe acute respiratory infection (MERS SARI) and non-Middle East Respiratory Syndrome severe acute respiratory infection (Non-MERS SARI). Median and 95% confidence intervals are displayed. * denotes statistical significance for the difference between the two groups on each day. P values for the change over time and for the diffrence between the two groups over time using repeated measures analysis of variance are given for each variable. **A.** The ratio of partial pressure of oxygen in arterial blood/ the fraction of inspired oxygen (PaO2/FiO2), **B.** Tidal volume, **C.** Positive end expiratory pressure (PEEP), **D.** Platelet count, **E.** Creatinine, **F.** Sequential Organ Failure Assessment (SOFA) score.

Figure 2.

Panel A. Time to clearance of the real-time reverse transcription polymerase (rRT-PCR) of the Middle East Respiratory Syndrome coronavirus (MERS-CoV) among survivors and non-survivors.

Panel B. Survival curves for patients with patients with the Middle East Respiratory Syndrome severe acute respiratory infection (MERS SARI) and non-Middle East Respiratory Syndrome severe acute respiratory infection (Non-MERS SARI).