Critically Ill Patients With the Middle East Respiratory Syndrome: A Multicenter Retrospective Cohort Study

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This study was approved by the institutional review boards (IRBs) of all participating centers. Informed consent was waived by the IRBs because of the retrospective nature of the study.

Dr. Arabi disclosed that he was the principal investigator on the a clinical trial for lopinavir/ritonavir and interferon in Middle East respiratory syndrome (MERS) and that he was a nonpaid consultant on antiviral active for MERS-coronavirus (CoV) for Gilead Sciences. Dr. Merson received salary support from Wellcome Trust. Dr. Hayden's institution received funding from GlaxoSmithKline (Data Safety Monitoring Board [DSMB] member for influenza randomized controlled trial [RCT]) and Celltrion (DSMB member for influenza RCT); he received funding from World Health Organization (consultant on influenza and emerging viral infections) and the University of Alabama (Scientific Advisory Board member for National Institutes of Health-sponsored Antiviral Discovery and Development Consortium [honorarium]); he disclosed that he was a nonpaid consultant on antiviral active for MERS-CoV for Gilead Sciences; and he disclosed off-label product use of investigational antivirals for MERS (ribavirin, lopinavir/ritonavir, interferons) and corticosteroids for MERS. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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

Design: Retrospective cohort study.

Setting: Patients admitted to ICUs in 14 Saudi Arabian hospitals.

Patients: Critically ill patients with laboratory-confirmed Middle East respiratory syndrome severe acute respiratory infection ($n = 330$) admitted between September 2012 and October 2015 were compared to consecutive critically ill patients with community-acquired severe acute respiratory infection of non–Middle East respiratory syndrome etiology (non–Middle East respiratory syndrome severe acute respiratory infection) ($n = 222$).

Interventions: None.

Measurements and Main Results: Although Middle East respiratory syndrome severe acute respiratory infection patients were younger than those with non–Middle East respiratory syndrome severe acute respiratory infection (median [quartile 1, quartile 3] 58 yr [44, 69] vs 70 [52, 78]; $p < 0.001$), clinical presentations and comorbidities overlapped substantially. Patients with Middle East respiratory syndrome severe acute respiratory infection had more severe hypoxemic respiratory failure (Pao_2/Fio_2: 106 [66, 160] vs 176 [104, 252]; $p < 0.001$) and more frequent nonrespiratory organ failure (nonrespiratory Sequential Organ Failure Assessment 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%; $p = 0.003$), 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, Middle East respiratory syndrome was independently associated with death compared to non–Middle East respiratory syndrome severe acute respiratory infection (adjusted odds ratio, 5.87; 95% CI, 4.02–8.56; $p < 0.001$).

Conclusions: Substantial overlap exists in the clinical presentation and comorbidities among patients with Middle East respiratory syndrome severe acute respiratory infection from other etiologies; therefore, a high index of suspicion combined with diagnostic testing is essential component of severe acute respiratory infection investigation for at-risk patients. The lack of distinguishing clinical features, the need to rely on real-time reverse transcription polymerase chain reaction from respiratory samples, variability in viral shedding duration, lack of effective therapy, and high mortality represent substantial clinical challenges and help guide ongoing clinical research efforts. (*Crit Care Med* 2017; 45:1683–1695)

Key Words: acute respiratory distress syndrome; coronavirus; Middle East respiratory syndrome; Saudi Arabia; severe acute respiratory infection

As of June 19, 2017, 2,029 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 multiple organ failure. Among hospitalized MERS patients, 53–89% require ICU admission (3, 4) with reported mortality rates of 58–90% among ICU patients (5, 6). A case-control study estimated that hospitalized patients with MERS were five times more likely to require ICU admission and 19 times more likely to die compared with non-MERS controls (3). However, data on the sickest MERS patients remain limited and are 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 five cities in Saudi Arabia with a median of 550 hospital beds (Q1, Q3: 500, 1,200) and 42 ICU beds (Q1, Q3: 34, 64). Organizational features of participating hospitals are summarized in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C764). Of note, three of 14 hospitals (21.4%) reported to perform MERS-coronavirus (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 noninfectious etiology. Diagnostic testing for MERS followed the guidelines set by the Saudi Arabian Ministry of Health; nasopharyngeal swabs or sputum samples, if possible, in nonintubated 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 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 to 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 case report forms (12).

We documented patient demographic features, underlying comorbidities (defined in the **online supplement,** Supplemental Digital Content 1, http://links.lww.com/CCM/C764), 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 and 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 with non-MERS SARI patients using Student *t* test or the Mann-Whitney *U* test for continuous variables based on normality assumption and the chi-square test for categorical variables. Kaplan-Meier curves censored at 90 days and the log-rank test was 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 (vs 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 (Statistical Analysis Software), 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 KAMC-R only, community-acquired cases only and non-MERS SARI who have been tested for MERS. Results were reported in adjusted odds ratios (aORs) with 95% 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 Bonferroni 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 two occasions, without a positive test afterward. We constructed additional Kaplan-Meier curves for the time to clearance, censoring by discharge and at 90 days.

We examined the predictors of mortality among MERS SARI patients by first comparing baseline characteristics, comorbid conditions, and physiologic parameters of MERS SARI survivors and nonsurvivors using univariable analysis, followed by multivariable logistic regression incorporating all variables with p values less than 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-R and to patients with community-acquired infection. Tests were two sided with significance set at α less than 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 with 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]; $p < 0.001$) and 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

TABLE 1. Baseline Characteristics of Patients With the Middle East Respiratory Syndrome Severe Acute Respiratory Infection (MERS SARI) and Non-MERS SARI

Variables	MERS SARI Vs Non-MERS SARI			MERS SARI Survivors Vs Nonsurvivors		
	MERS SARI, *n* = 330	Non-MERS SARI, *n* = 222	*p*	Nonsurvivors, *n* = 217	Survivors, *n* = 113	*p*
Demographics						
Age (yr), median (Q1, Q3)	58 (44, 69)	70 (52, 78)	< 0.001	62 (53.0, 73)	45.5 (35.0, 57.0)	< 0.001
Age excluding healthcare workers (yr), median (Q1, Q3)	59 (47, 71)	70 (52, 78)	< 0.001	62.0 (54.0, 73.0)	48.0 (37.0, 59.0)	< 0.001
Male sex, *n* (%)	225 (68.2)	129 (58.1)	0.02	145 (66.8)	80 (70.8)	0.46
Body mass index (kg/m^2), median (Q1, Q3)	28.3 (24.2, 33.2)	27.4 (23.2, 31.6)	0.06	28.3 (24.2, 32.7)	28.8 (24.1, 33.8)	0.42
Healthcare associated, nonhealthcare worker, *n* (%)	132 (40.0)	0 (0.0)	< 0.001	98 (45.2)	34 (30.1)	< 0.001
Healthcare worker, *n* (%)	32 (9.7)	0 (0.0)		7 (3.2)	25 (22.1)	
Community acquired, *n* (%)	137 (41.5)	222 (100)		92 (42.4)	45 (39.8)	
Unknown, *n* (%)	29 (8.8)	0 (0.0)		20 (9.2)	9 (8.0)	
Comorbidities, *n* (%)						
Diabetes with chronic complications	162 (49.1)	118 (53.2)	0.39	124 (57.1)	38 (33.6)	< 0.001
Chronic cardiac disease	134 (40.6)	126 (56.8)	< 0.001	105 (48.4)	29 (25.7)	< 0.001
Chronic renal disease	100 (30.3)	49 (22.1)	0.06	80 (36.9)	20 (17.7)	< 0.001
Chronic pulmonary disease (including asthma)	46 (13.9)	84 (37.8)	< 0.001	33 (15.2)	13 (11.5)	0.38
Chronic neurologic disease including hemiplegia, paraplegia, and dementia	36 (10.9)	57 (25.7)	< 0.001	32 (14.7)	4 (3.5)	0.004
Any malignancy including leukemia, lymphoma, or solid tumors	34 (10.3)	22 (9.9)	0.98	31 (14.3)	3 (2.7)	0.003
Immunosuppressant use prior to admission	21 (6.4)	26 (11.7)	0.08	14 (6.5)	7 (6.2)	0.07
Liver disease	21 (6.4)	18 (8.1)	0.72	16 (7.4)	5 (4.4)	0.19
Rheumatologic disease	7 (2.1)	7 (3.2)	0.61	3 (1.4)	4 (3.5)	0.24
AIDS	2 (0.6)	1 (0.5)	0.54	0 (0.0)	2 (1.8)	0.05
Any comorbidity	265 (80.3)	203 (91.4)	< 0.001	199 (91.7)	66 (58.4)	< 0.001
Days from onset of symptoms to the emergency department[a], median (Q1, Q3)	5 (3, 8)	3 (2, 6)	0.001	4 (3, 7.5)	5 (3, 8)	0.098
Days from onset of symptoms to ICU admission, median (Q1, Q3)	7 (5, 11)	5 (3, 8)	0.001	7 (5, 12)	6 (4, 9)	0.04
Days from onset of symptoms to intubation, median (Q1, Q3)	8 (5, 12)	6 (3, 11)	< 0.001	8 (5, 12)	8 (5, 12)	0.49

(*Continued*)

TABLE 1. (*Continued*). Baseline Characteristics of Patients With the Middle East Respiratory Syndrome Severe Acute Respiratory Infection (MERS SARI) and Non-MERS SARI

Variables	MERS SARI Vs Non-MERS SARI			MERS SARI Survivors Vs Nonsurvivors		
	MERS SARI, *n* = 330	Non-MERS SARI, *n* = 222	*p*	Nonsurvivors, *n* = 217	Survivors, *n* = 113	*p*
Respiratory symptoms, *n* (%)						
Dyspnea	247 (74.8)	154 (69.4)	0.31	168 (77.4)	79 (69.9)	0.26
Cough	227 (68.8)	141 (63.5)	0.24	147 (67.7)	80 (70.8)	0.42
With sputum	128 (38.8)	100 (45)	0.34	87 (40.1)	41 (36.3)	0.38
With bloody sputum	29 (8.8)	10 (4.5)	0.046	20 (9.2)	9 (8.0)	0.38
Chest pain	66 (20)	25 (11.3)	0.009	44 (20.3)	22 (19.5)	0.25
Sore throat	46 (13.9)	13 (5.9)	< 0.001	29 (13.4)	17 (15.0)	0.89
Wheezing	18 (5.5)	26 (11.7)	0.008	13 (6.0)	5 (4.4)	0.67
Rhinorrhea	15 (4.5)	4 (1.8)	0.02	8 (3.7)	7 (6.2)	0.58
Gastrointestinal symptoms, *n* (%)						
Vomiting/nausea	58 (17.6)	30 (13.5)	0.41	38 (17.5)	20 (17.7)	0.93
Abdominal pain	47 (14.2)	15 (6.8)	0.015	34 (15.7)	13 (11.5)	0.37
Diarrhea	38 (11.5)	18 (8.1)	0.38	23 (10.6)	15 (13.3)	0.52
Other symptoms, *n* (%)						
Fever (temperature ≥ 38°C)	248 (75.2)	93 (41.9)	< 0.001	152 (70.0)	96 (85.0)	0.012
Fatigue	114 (34.5)	69 (31.1)	0.53	73 (33.6)	41 (36.3)	0.86
Altered level of consciousness	70 (21.2)	73 (32.9)	0.004	51 (23.5)	19 (16.8)	0.37
Myalgia or arthralgia	64 (19.4)	22 (9.9)	0.001	30 (13.8)	34 (30.1)	0.002
Headache	34 (10.3)	10 (4.5)	0.001	10 (4.6)	24 (21.2)	< 0.001

MERS SARI = Middle East respiratory syndrome severe acute respiratory infection.

This table includes comparison of MERS SARI vs. non-MERS SARI. In addition, it includes comparison of nonsurvivors and survivors among patients with MERS SARI.

For all percentages, the denominator is the total no. of subjects in the groups unless otherwise specified.

For continuous variables, Mann-Whitney *U* test was used to calculate *p* values.

For categorical variables, chi-square test was used to calculate *p* values.

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 emergency department presentation, ICU admission, and ventilation were approximately 2 days longer for patients with MERS than among patients with non-MERS SARI (Table 1).

Pulmonary Manifestations

At admission to ICU, patients with MERS SARI were more hypoxemic than non-MERS SARI (Pao_2/Fio_2: 106.3 [66.2, 160] vs 176 [104, 252]; $p < 0.001$) 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 (**Tables 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 compared to patients with non-MERS SARI (12 [8, 14] vs 8 [5, 10] cm H_2O; $p < 0.001$) (**Fig. 1**; and **Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C764). 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 compared with non-MERS SARI (**Table 3**).

Nonpulmonary Manifestations

MERS SARI patients had higher nonrespiratory SOFA scores compared to patients with non-MERS SARI (6 [4, 9] vs 5 [3, 7]; $p = 0.002$). 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 (Tables 2 and 3).

TABLE 2. Physiologic Parameters of Patients With the Middle East Respiratory Syndrome Severe Acute Respiratory Infection (MERS SARI) and Non-MERS SARI

	MERS SARI vs Non-MERS SARI			MERS SARI Survivors vs Nonsurvivors		
Variables	MERS SARI, *n* = 330	Non-MERS SARI, *n* = 222	*p*	Nonsurvivors, *n* = 217	Survivors, *n* = 113	*p*
Respiratory parameters on ICU day 1, median (Q1, Q3)						
Pao_2 (mm Hg)	67 (58, 85)	76 (55, 99)	0.02	69 (58, 85)	67 (58, 87)	0.64
Fio_2	0.7 (0.5, 1.0)	0.5 (0.3, 0.6)	< 0.001	0.7 (0.5, 1.0)	0.6 (0.4, 1.0)	0.03
Pao_2/Fio_2 ratio	106 (66, 160)	176 (104, 252)	< 0.001	96 (64, 150)	120 (72, 193)	0.022
$Paco_2$ (mm Hg)	41 (34, 51)	45 (38, 57)	< 0.001	41 (35, 51)	41 (33, 49)	0.56
pH	7.36 (7.26, 7.42)	7.33 (7.26, 7.39)	0.052	7.34 (7.23, 7.41)	7.38 (7.29, 7.42)	0.053
Tidal volume (mL)	400 (350, 440)	400 (340, 436)	0.58	398 (350, 440)	404 (360, 443)	0.32
Tidal volume per kg of predicted body weight (mL/kg)	6.6 (5.8, 7.6)	7.1 (6.0, 8.3)	0.012	6.6 (5.8, 7.5)	6.8 (6.0, 7.8)	0.45
Positive end-expiratory pressure (cm H_2O)	12 (8, 14)	8 (5, 10)	< 0.001	12 (8, 15)	11 (10, 14)	0.96
Plateau pressure (cm H_2O)	28 (22, 30)	23 (17, 26.0)	< 0.001[a]	29 (22, 30)	28 (23, 30)	0.98[a]
Driving pressure (cm H_2O)	15 (12, 18)	15 (11, 18)	0.69	15 (12, 18)	16 (11, 20)	0.98
Number of quadrants with infiltrates on chest radiograph[b]	3 (2, 4)	2 (0, 3)	< 0.001	3 (2, 4)	2 (1, 3)	< 0.001
Extrapulmonary parameters on ICU day 1, median (Q1, Q3)						
Mean arterial pressure (mm Hg)	70 (60, 82)	68 (62, 76)	0.93	67 (58, 79)	73 (61, 84)	0.008
Lactate (mmol/L)	1.8 (1.1, 2.8)	2.0 (1.2, 3.2)	0.18	1.9 (1.3, 3.4)	1.2 (0.9, 2.1)	< 0.001
Blood urea nitrogen (μmol/L)	11 (5.7, 19.0)	9.2 (5.3, 15.5)	0.12	12.9 (7.7, 21.3)	6.1 (3.4, 11.90	< 0.001
Creatinine (μmol/L)	124 (74, 252)	92 (66, 179)	< 0.001	150 (89, 328)	87 (68, 191)	< 0.001
Urine output (mL/d)	1,100 (550, 1,770)	1,224 (710, 1,918)	0.02	960 (450, 1,720)	1,208 (815, 1,870)	0.03
Hemoglobin g/dL	10.7 (8.8, 12.8)	10.7 (9.0, 12.7)	0.59	10.2 (8.7, 11.9)	12.0 (8.9, 13.6)	< 0.001
Platelets ($\times 10^9$/L)	165 (112, 245)	240 (157, 328)	< 0.001	162 (105, 238)	188 (138, 262)	0.039
Leukocyte ($\times 10^9$/L)	7.3 (4.4, 11.6)	10.9 (7.5, 15.4)	< 0.001	8.0 (4.9, 12.0)	6.0 (3.8, 10.5)	0.013
Bilirubin (μmol/L)	12 (7, 23)	11 (7, 20)	0.38	13 (8, 25)	9 (6, 17)	< 0.001
ALT (U/L)	41 (23, 89)	25 (14, 49)	< 0.001	40 (23, 85)	47 (25, 95)	0.32
AST (U/L)	67 (41, 109)	35.5 (22, 64)	< 0.001	70 (43, 119)	63 (38, 95)	0.14
International normalized ratio	1.1 (1.0, 1.3)	1.1 (1.0, 1.4)	0.28	1.2 (1.1, 1.4)	1.0 (1.0, 1.1)	< 0.001
Glasgow Coma Scale	9 (3, 15)	10 (3, 15)	0.79	8 (3, 15)	15 (4, 15)	< 0.001
SOFA score	9 (5, 12)	7 (4, 9)	< 0.001	10 (7, 13)	6 (3, 10)	< 0.001
Respiratory SOFA score	3 (2, 4)	2 (2, 3)	< 0.001	3 (3, 4)	3 (2, 4)	0.018
Nonrespiratory SOFA score	6 (4, 9)	5 (3, 7)	0.002	7 (5, 9)	4 (1, 6)	< 0.001

(*Continued*)

TABLE 2. (*Continued*). Physiologic Parameters of Patients With the Middle East Respiratory Syndrome Severe Acute Respiratory Infection (MERS SARI) and Non-MERS SARI

Variables	MERS SARI vs Non-MERS SARI			MERS SARI Survivors vs Nonsurvivors		
	MERS SARI, *n* = 330	Non-MERS SARI, *n* = 222	*p*	Nonsurvivors, *n* = 217	Survivors, *n* = 113	*p*
Extrapulmonary parameters on day 1, *n* (%)						
Elevated ALT (> 55 U/L)	107/275 (38.9)	31/13 5 (23.0)	0.001	67/185 (36.2)	40/90 (44.4)	0.19
Elevated AST (> 34 U/L)	203/245 (82.9)	76/142 (53.5)	< 0.001	140/164 (85.4)	63/ 81 (77.8)	0.14
Hyperbilirubinemia (> 20.5 μmol/L)	95/279 (34.1)	41/136 (30.1)	0.43	73/189 (38.6)	22/ 90 (24.4)	0.02
Leukopenia (< 4.0 x10^9/L)	63/321 (19.6)	16/219 (7.3)	< 0.001	33/210 (15.7)	30/111 (27.0)	0.02
Thrombocytopenia (< 150 x10^9/L)	124/321 (38.6)	40/219 (18.3)	< 0.001	89/210 (42.4)	35/111 (31.5)	0.06
Extrapulmonary parameters during ICU stay, *n* (%)						
Elevated ALT (> 55 U/L)	142/252 (56.3)	35/93 (37.6)	0.002	93/170 (54.7)	49/82 (59.8)	0.45
Elevated AST (> 34 U/L)	197/227 (86.8))	61/96 (63.5)	< 0.001	137/150 (91.3)	60/77 (77.9)	0.005
Hyperbilirubinemia (> 20.5 μmol/L)	148/252 (58.7)	41/93 (44.1)	0.02	116/169 (68.6)	32/83 (38.6)	< 0.001
Leukopenia (< 4.0 x10^9/L)	58/287 (20.2)	21/204 (10.3)	0.003	37/189 (19.6)	21/ 98 (21.4)	0.71
Thrombocytopenia (< 150 x10^9/L)	169/288 (58.7)	74/204 (36.3)	< 0.001	131/190 (68.9)	38/ 98 (38.8)	< 0.001

ALT = alanine aminotransferase, AST = aspartate transaminase, MERS SARI = Middle East respiratory syndrome severe acute respiratory infection, SOFA = Sequential Organ Failure Assessment.

This table includes comparison of MERS SARI vs. non-MERS SARI. In addition, it includes comparison of nonsurvivors and survivors among patients with MERS SARI.

For continuous variables, Mann-Whitney *U* test was used to calculate *p* value except for *p* values labeled with [a]indicating the use of *t* test.

[b]The no. of patients with data on chest radiograph findings is 316 and 219 in the two groups, respectively.

For categorical variables, chi-square test was used to calculate *p* values.

Viral and Bacterial Testing

Detailed data on MERS-CoV testing were available on 311 of 330 MERS SARI patients. The confirmatory sample for MERS-CoV was from the nasopharynx in 167 of 311 (54%) and from the lower respiratory tract (sputum, endotracheal aspirates, or bronchoalveolar lavage) in 144 of 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 of 311 (76.2%) were diagnosed from the first rRT-PCR test, 51 of 311 (16.4%) after one negative test, 17 of 311 (5.5%) after two negative tests, two of 311 (0.6%) after three negative tests, and four of 311 (1.3%) after four negative tests. The time to clearance of MERS-CoV RNA was significantly shorter in survivors than in nonsurvivors (median 19 d [95% CI, 16–24] vs 37 days [95% CI, lower CI 24, upper CI non-computable]; $p < 0.001$) by survival analysis, **Fig. 2**). Among the non-MERS SARI patients, 129 of 222 patients (58%) were tested for MERS-CoV, 16 of 129 (12.4%) had two negative tests, and 13 of 129 (10.1%) had three 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 (**Fig. S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C764).

Other viral pathogens were identified in 17 of 330 patients (5%) with MERS SARI and 52 of 222 (24%) with non-MERS SARI ($p < 0.001$). In patients with MERS SARI, the most commonly detected viral copathogens included other coronaviruses (5), respiratory syncytial virus (1), and influenza A virus (2), whereas in non-MERS patients, copathogens included influenza A (29) and B (3) viruses, rhinovirus (9), and other coronaviruses (5) (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C764). In the 3 days before and 3 days after ICU admission, bacterial pathogens were identified in

TABLE 3. Main Interventions and Outcomes in Patients With the Middle East Respiratory Syndrome Severe Acute Respiratory Infection (MERS SARI) and Non-MERS SARI

Variables	MERS SARI Vs Non-MERS SARI			MERS SARI Survivors Vs Nonsurvivors		
	MERS SARI, *n* = 330	Non-MERS SARI, *n* = 222	*p*	Nonsurvivors, *n* = 217	Survivors, *n* = 113	*p*
Noninvasive positive pressure ventilation, *n* (%)	100 (30.3)	67 (30.2)	0.98	63 (29)	37 (32.7)	0.49
Duration (d), median (Q1, Q3)	1 (1, 3)	2 (1, 3)	0.38	1 (1, 3)	1 (1, 3)	0.71
Invasive ventilation, *n* (%)	281 (85.2)	162 (73.0)	< 0.001	204 (94.0)	77 (68.1)	< 0.001
Duration (d), median (Q1, Q3)	10 (5, 18)	9 (6, 18)	0.40	8 (5, 16)	14 (6, 26)	0.005
Invasive ventilation-free days (d), median (Q1, Q3)	1 (0, 16)	20 (1, 28)	< 0.001	0 (0, 2)	22 (8, 28)	< 0.001
Neuromuscular blockade, *n* (%)	133 (40.3)	119 (53.6)	0.002	97 (44.7)	36 (31.9)	0.024
Duration (d), median (Q1, Q3)	4 (2, 7)	2 (1, 4)	< 0.001	4 (2, 7)	3 (2, 8.5)	0.64
Nitric oxide, *n* (%)	43 (13)	14 (6.3)	0.011	34 (15.7)	9 (8.0)	0.049
Duration (d), median (Q1, Q3)	4 (2, 5.5)	4 (1.5, 7.5)	0.81	4 (2, 6)	3 (1, 4)	0.22
Prone positioning, *n* (%)	32 (9.7)	2 (0.9)	< 0.001	24 (11.1)	8 (7.1)	0.25
Duration (d), median (Q1, Q3)	3 (2, 3)	2 (2, 2)	0.41	3 (2, 3)	2.5 (2, 3)	0.43
High-frequency oscillation ventilation, *n* (%)	26 (7.9)	0 (0)	< 0.001	24 (11.1)	2 (1.8)	0.003
Duration (d), median (Q1, Q3)	3 (2, 5)	0		4 (2, 7)	1 (1, 1)	0.048
Extracorporeal membrane oxygenation, *n* (%)	19 (5.8)	2 (0.9)	0.003	13 (6.0)	6 (5.3)	0.80
Duration (d), median (Q1, Q3)	8 (3.5, 14)	6.5 (2, 11)	0.78	8 (7, 20)	6 (1, 13)	0.39
Vasopressors, *n* (%)	262 (79.4)	122 (55.0)	< 0.001	199 (91.7)	63 (55.8)	< 0.001
Duration (d), median (Q1, Q3)	6.5 (3, 13)	6 (3, 11)	0.23	6 (4, 12)	8 (3, 15)	0.59
Renal replacement therapy, *n* (%)	161 (48.8)	49 (22.1)	< 0.001	131 (60.4)	30 (26.5)	< 0.001
Duration (d), median (Q1, Q3)	8 (4, 15)	7 (4, 15)	0.48	8 (4, 14)	12 (5, 23)	0.13
Blood transfusion, *n* (%)	114 (34.5)	74 (33.3)	0.77	89 (41)	25 (22.1)	< 0.001
Tracheostomy, *n* (%)	14 (4.2)	30 (13.5)	< 0.001	6 (2.8)	8 (7.1)	0.07
Antivirals, *n* (%)	269 (81.5)	134 (60.4)	< 0.001	177 (81.6)	92 (81.4)	0.97
Oseltamivir	177 (53.6)	121 (54.5)	0.84	112 (51.6)	65 (57.5)	0.31
Ribavirin and interferon	115 (34.8)	0 (0)	NA	85 (39.2)	30 (26.5)	0.039
Interferon only	9 (2.7)	0 (0)		8 (3.7)	1 (0.9)	
Ribavirin only	18 (5.5)	0 (0)		11 (5.1)	7 (6.2)	
Corticosteroids, *n* (%)	177 (53.6)	143 (64.4)	0.039	133 (61.3)	44 (38.9)	< 0.001
IV immunoglobulin, *n* (%)	23 (7.0)	6 (2.7)	0.028	16 (7.4)	7 (6.2)	0.69
ICU mortality, *n* (%)	217 (65.8)	63 (28.4)	< 0.001	213 (98.2)	4 (3.5)	< 0.001
ICU length of stay (d), median (Q1, Q3)	10 (5, 18)	11 (6, 23)	0.04	9 (5, 16)	12 (5, 26.5)	0.057
ICU length of stay among survivors (d), median (Q1, Q3)	12 (5, 26.5)	10 (5, 23)	0.84	NA	NA	
Hospital mortality, *n* (%)	223 (67.6)	82 (36.9)	< 0.001	217 (100)	6 (5.3)	< 0.001

(*Continued*)

TABLE 3. (*Continued*). Main Interventions and Outcomes in Patients With the Middle East Respiratory Syndrome Severe Acute Respiratory Infection and Non–Middle East Respiratory Syndrome Severe Acute Respiratory Infection

Variables	MERS SARI Vs Non-MERS SARI			MERS SARI Survivors Vs Nonsurvivors		
	MERS SARI, *n* = 330	Non-MERS SARI, *n* = 222	*p*	Nonsurvivors, *n* = 217	Survivors, *n* = 113	*p*
Hospital length of stay (d), median (Q1, Q3)	19 (10, 35)	24.5 (13, 62)	< 0.001	16 (10, 26)	33 (14, 67)	< 0.001
Hospital length of stay among survivors (d), median (Q1, Q3)	33 (14, 67)	27 (13, 88)	0.82	NA	NA	NA
28-d mortality, *n* (%)	173 (52.4)	42 (18.9)	< 0.001	173 (79.7)	0	< 0.001
90-d mortality, *n* (%)	217 (65.8)	69 (31.1)	< 0.001	217 (100)	0	< 0.001

MERS SARI = Middle East respiratory syndrome severe acute respiratory infection, NA = not applicable.

This table includes comparison of MERS SARI vs. non-MERS SARI. In addition, it includes comparison of nonsurvivors and survivors among patients with MERS SARI.

Invasive ventilation-free days are calculated based on 28-d observation.

For all percentages, the denominator is the total no. of subjects in the groups unless otherwise specified.

For continuous variables, Mann-Whitney *U* test was used to calculate *p* values.

For categorical variables, chi-square test was used to calculate *p* values.

respiratory samples in 60 of 330 MERS SARI patients (18.5%) and 56 of 222 non-MERS SARI patients (25.2%) ($p = 0.046$) and in blood in 26 of 330 MERS SARI patients (8%) and 29 of 222 non-MERS SARI patients (13%) ($p = 0.046$).

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 $p < 0.001$ for MERS vs non-MERS SARI). Differences in ICU course between MERS SARI survivors and nonsurvivors 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; $p < 0.001$) compared with non-MERS SARI (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C764). Sensitivity analyses were performed by restriction to patients admitted to KAMC-R only, community-acquired cases only and non-MERS SARI who have been tested for MERS did not alter this association (Table S3, Supplemental Digital Content 1). Among patients with MERS SARI, age (per 1 yr 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; $p = 0.008$) were independent predictors of 90-day mortality (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C764). For community-acquired MERS, age (per 1 yr 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. Although 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. Although 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 five- to six-fold increase in death compared with 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 (3) compared 17 MERS patients (eight admitted to ICU) with 82 non-MERS patients (20 admitted to ICU) and reported mortality of 76% among hospitalized MERS patients compared with 15% among non-MERS. Mohd et al (16) compared 80 MERS patients (15 admitted to ICU) with matched 159 non-MERS patients (26 admitted to ICU) and found that none of the presenting symptoms are specific for MERS-CoV infection. Garbati et al (17) 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

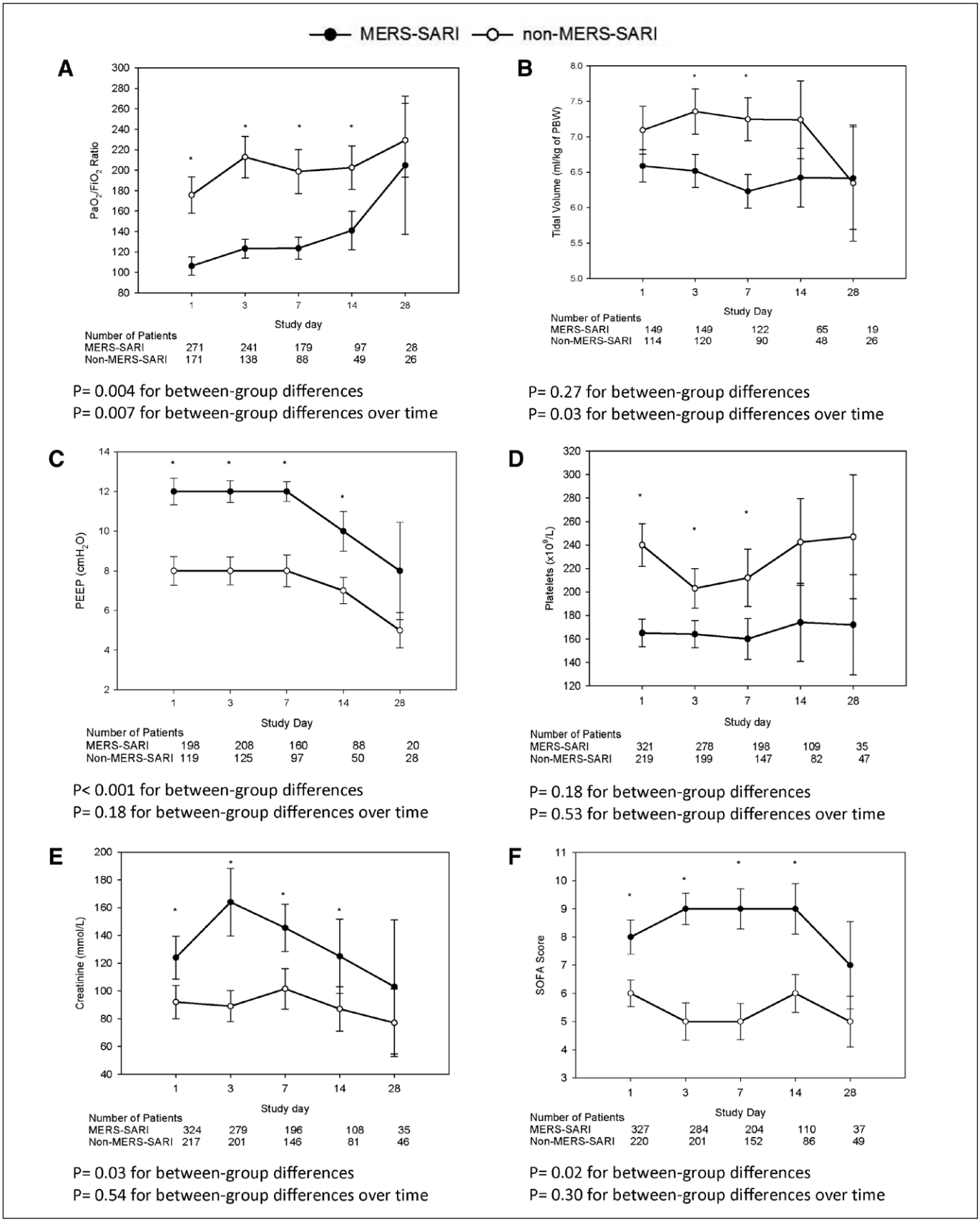

Figure 1. Physiologic parameters among patients with the Middle East respiratory syndrome severe acute respiratory infection (MERS SARI) and non-MERS SARI. Median and 95% CIs are displayed. *Statistical significance for the difference between the two groups on each day. *p* values for the between-group difference and the between-group difference over time using repeated measures analysis of variance are given for each variable. (**A**) Pao_2/Fio_2 ratio, (**B**) tidal volume, (**C**) positive end-expiratory pressure (PEEP), (**D**) platelet count, (**E**) creatinine, (**F**) Sequential Organ Failure Assessment (SOFA) score. PBW = predicted body weight.

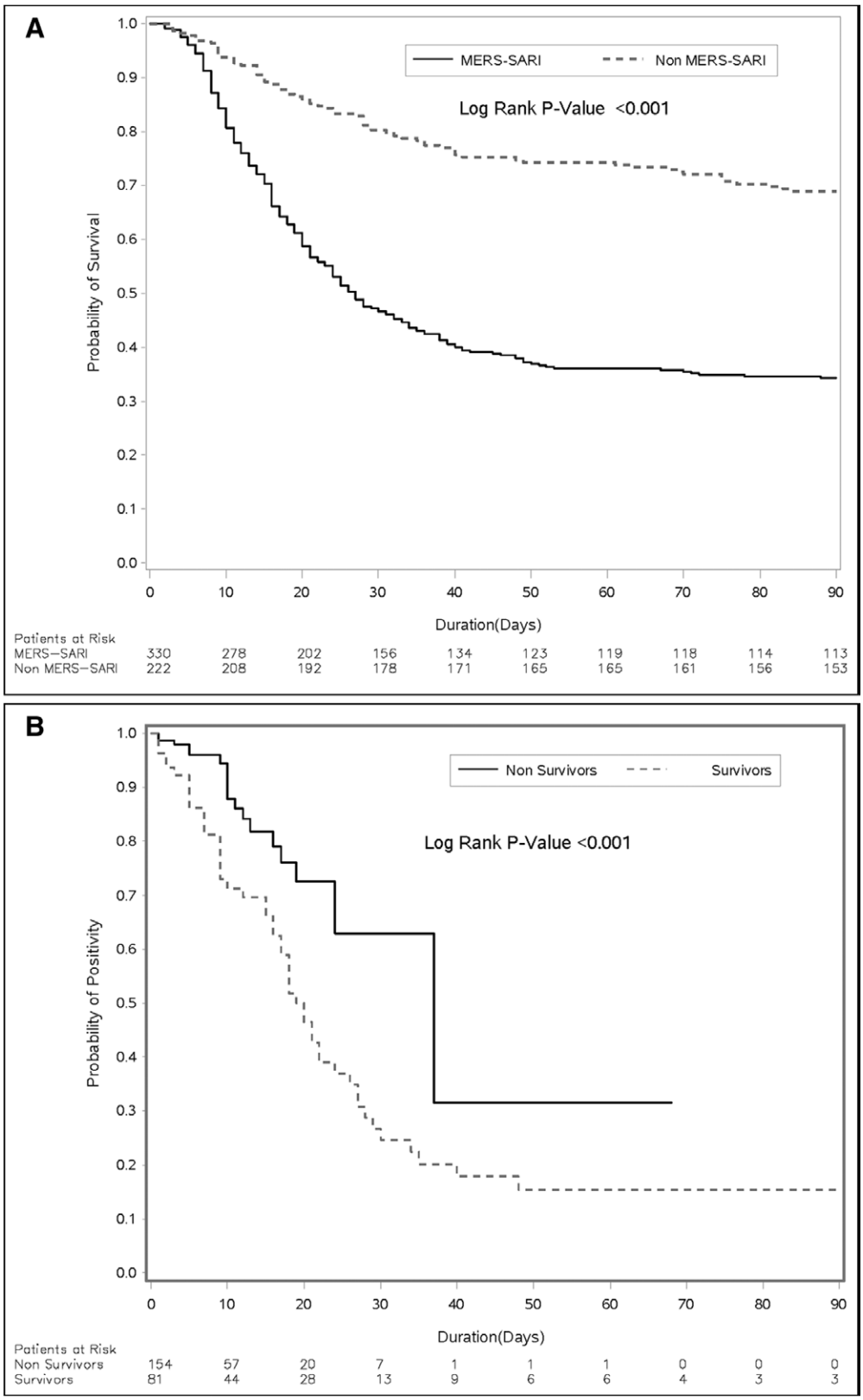

Figure 2. A, Time to clearance of the real-time reverse transcription polymerase chain reaction of the Middle East respiratory syndrome (MERS) coronavirus among survivors and nonsurvivors. **B**, Survival curves for patients with patients with the MERS severe acute respiratory infection (MERS SARI) and non-MERS SARI.

in MERS patients. 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, whereas 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 suggests 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 respiratory syncytial virus. 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 test availability, 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 toward 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 help 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 copathogens 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 do 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 organ-supporting therapy a critical component of MERS care and highlight the pressing need for evaluation of specific antiviral therapies.

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REFERENCES

1. Arabi YM, Balkhy HH, Hayden FG, et al: Middle East respiratory syndrome. *N Engl J Med* 2017; 376:584–594
2. World Health Orgnization: Middle East respiratory syndrome coronavirus (MERS-CoV) – Saudi Arabia. 2017. Available at: http://www.who.int/emergencies/mers-cov/en/. Accessed July 24, 2017
3. Al-Tawfiq JA, Hinedi K, Ghandour J, et al: Middle East respiratory syndrome coronavirus: A case-control study of hospitalized patients. *Clin Infect Dis* 2014; 59:160–165
4. Assiri A, McGeer A, Perl TM, et al; KSA MERS-CoV Investigation Team: Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med* 2013; 369:407–416
5. Saad M, Omrani AS, Baig K, et al: Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: A single-center experience in Saudi Arabia. *Int J Infect Dis* 2014; 29:301–306
6. Arabi YM, Arifi AA, Balkhy HH, et al: Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014; 160:389–397
7. Al-Hameed F, Wahla AS, Siddiqui S, et al: Characteristics and outcomes of Middle East respiratory syndrome coronavirus patients admitted to an intensive care unit in Jeddah, Saudi Arabia. *J Intensive Care Med* 2016; 31:344–348
8. Alraddadi B, Bawareth N, Omar H, et al: Patient characteristics infected with Middle East respiratory syndrome coronavirus infection in a tertiary hospital. *Ann Thorac Med* 2016; 11:128–131
9. Almekhlafi GA, Albarrak MM, Mandourah Y, et al: Presentation and outcome of Middle East respiratory syndrome in Saudi intensive care unit patients. *Crit Care* 2016; 20:123
10. Shalhoub S, Farahat F, Al-Jiffri A, et al: IFN-α2a or IFN-β1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: A retrospective study. *J Antimicrob Chemother* 2015; 70:2129–2132
11. Ministry of Health: Case Definition and Surveillance Guidance. 2015. Available at: http://www.moh.gov.sa/en/CCC/Regulations/CaseDefinition.pdf. Accessed March 31, 2017
12. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Available at: https://isaric.tghn.org/. Accessed March 25, 2017
13. Vincent JL, de Mendonça A, Cantraine F, et al: Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; 26:1793–1800

14. Alraddadi BM, Watson JT, Almarashi A, et al: Risk factors for primary Middle East respiratory syndrome coronavirus illness in humans, Saudi Arabia, 2014. *Emerg Infect Dis* 2016; 22:49–55
15. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, et al: Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. *J Infect Dis* 2014; 210: 1590–1594
16. Mohd HA, Memish ZA, Alfaraj SH, et al: Predictors of MERS-CoV infection: A large case control study of patients presenting with ILI at a MERS-CoV referral hospital in Saudi Arabia. *Travel Med Infect Dis* 2016; 14:464–470
17. Garbati MA, Fagbo SF, Fang VJ, et al: A comparative study of clinical presentation and risk factors for adverse outcome in patients hospitalised with acute respiratory disease due to MERS coronavirus or other causes. *PLoS One* 2016; 11:e0165978
18. Ki M: 2015 MERS outbreak in Korea: Hospital-to-hospital transmission. *Epidemiol Health* 2015; 37:e2015033
19. Al-Dorzi HM, Arabi YM: Outbreaks in the adult ICUs. *Curr Opin Infect Dis* 2017; 30:432–439
20. Mulpuru S, Aaron SD, Ronksley PE, et al: Hospital resource utilization and patient outcomes associated with respiratory viral testing in hospitalized patients. *Emerg Infect Dis* 2015; 21:1366–1371