ORIGINAL ARTICLE

Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome

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Abstract

Rationale: Corticosteroid therapy is commonly used among critically ill patients with Middle East Respiratory Syndrome (MERS), but its impact on outcomes is uncertain. Analyses of observational studies often do not account for patients' clinical condition at the time of corticosteroid therapy initiation.

Objectives: To investigate the association of corticosteroid therapy on mortality and on MERS coronavirus RNA clearance in critically ill patients with MERS.

Methods: ICU patients with MERs were included from 14 Saudi Arabian centers between September 2012 and October 2015. We performed marginal structural modeling to account for baseline and time-varying confounders.

Measurements and Main Results: Of 309 patients, 151 received corticosteroids. Corticosteroids were initiated at a median of 3.0 days (quartile 1 [Q1]–Q3, 1.0–7.0) from ICU admission. Patients who received corticosteroids were more likely to receive invasive ventilation (141 of 151 [93.4%] vs. 121 of 158 [76.6%]; $P < 0.0001$) and had higher 90-day crude mortality (112 of 151 [74.2%] vs. 91 of 158 [57.6%]; $P = 0.002$). Using marginal structural modeling, corticosteroid therapy was not significantly associated with 90-day mortality (adjusted odds ratio, 0.75; 95% confidence interval, 0.52–1.07; $P = 0.12$) but was associated with delay in MERS coronavirus RNA clearance (adjusted hazard ratio, 0.35; 95% CI, 0.17–0.72; $P = 0.005$).

Conclusions: Corticosteroid therapy in patients with MERS was not associated with a difference in mortality after adjustment for time-varying confounders but was associated with delayed MERS coronavirus RNA clearance. These findings highlight the challenges and importance of adjusting for baseline and time-varying confounders when estimating clinical effects of treatments using observational studies.

Keywords: respiratory distress syndrome; coronavirus; pneumonia; Saudi Arabia; corticosteroid

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At Glance Commentary

Scientific Knowledge on the Subject: Corticosteroid therapy is commonly used among critically ill patients with Middle East respiratory syndrome (MERS), but its impact on outcome is uncertain. Analyses of observational studies often do not account for time-varying confounders, such as worsening clinical status and the decision to prescribe corticosteroids, leading to potentially biased estimates of treatment effect.

What This Study Adds to the Field: This multicenter study investigated the association of corticosteroid therapy on mortality and MERS coronavirus RNA clearance accounting for time-varying confounders during critical illness, up to the time of corticosteroid therapy initiation, using marginal structural models. Corticosteroid therapy in patients with MERS was not associated with differences in mortality but was associated with delay in MERS coronavirus RNA clearance.

Middle East respiratory syndrome coronavirus (MERS-CoV) is a pathogenic respiratory virus that often causes severe acute respiratory illness with substantial mortality. To date, there is no specific treatment for MERS, and management is largely supportive (1, 2).

Systemic corticosteroid therapy is commonly used among critically ill patients with MERS, but its impact on the clinical outcomes is uncertain (3). Data from another related coronavirus infection, the severe acute respiratory syndrome (SARS) have been mainly observational and yielded inconsistent results (4, 5). In a systematic review of studies on SARS, of 29 studies documenting corticosteroid use, 25 were inconclusive and 4 were classified as causing possible harm (6). In one randomized controlled trial (RCT) that included 16 non-ICU patients, "early" (<7 d of illness) hydrocortisone therapy was associated with a higher subsequent plasma viral load (7). Similar controversy exists with severe influenza. A meta-analysis of multiple observational studies has shown that corticosteroid therapy was associated with increased mortality in patients with severe influenza (8). Other serious adverse events, including opportunistic infections, prolonged virus replication, and antiviral resistance emergence, have also been observed (9).

Challenging analytic issues with these studies include the risk of immortal time bias and indication bias from time-varying confounding (10–13). Immortal time bias refers to the requirement for patients to survive long enough to receive the intervention of interest, leading to a potential incorrect estimation of a positive treatment effect (11, 13). Indication bias from time-varying confounding refers to having an association related to the indication of the intervention that is evolving during the course of the illness. For example, a patient who becomes sicker has an inherent higher risk of death but may also be more likely to receive second- or third-line therapies because first-line therapies have not led to improvement, possibly leading to an incorrect estimation of a negative or harmful treatment effect. Studies that adjust only for characteristics present at time of hospital or ICU admission do not account for the clinical condition at the time of corticosteroid therapy initiation and thus do not account for potential emerging between-patient time-varying differences that can confound the relationship being investigated. Data from RCTs on corticosteroid therapy in MERS of sufficient size (to have a better chance of balancing such known and unknown confounders between groups receiving or not receiving corticosteroid therapy) are lacking.

The objective of this study is to investigate the association of corticosteroid therapy on mortality and on MERS-CoV RNA clearance accounting for potential immortal time bias and indication bias. Some of this work has been previously presented in abstract form (14).

Methods

Setting

We analyzed data from a multicenter, retrospective cohort study from 14 participating Saudi Arabian tertiary care hospitals (3). The institutional review boards of all participating centers approved the study. Patient-level informed consent was not required.

Patients

We included in this analysis all patients with MERS admitted to the participating ICUs between September 2012 and October 2015. We excluded patients known to be receiving chronic corticosteroid therapy before the onset of critical illness. Details of management and laboratory testing of patients with MERS in the cohort have been reported previously (3). For MERS-CoV–positive patients, follow-up respiratory samples were collected at the discretion of the treating teams approximately one to two times per week to assess clearance of viral RNA for infection control purposes.

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Corticosteroid Therapy

The main exposure was corticosteroid therapy, defined as the use of systemic corticosteroids. We converted all preparations to hydrocortisone-equivalent doses (methylprednisolone 1:5, dexamethasone 1:25, prednisolone 1:4).

Data Collection

Data were collected using standardized International Severe Acute Respiratory and Emerging Infection Consortium case report forms (15). We extracted data on patient demographic features, underlying comorbidities, 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 (15, 16). We collected data on the type, maximum daily dose, and duration of corticosteroids, and we documented the use of antiviral therapy.

The primary outcome was 90-day all-cause mortality. In patients who had at least one follow-up real-time RT-PCR (rRT-PCR) performed after the diagnostic test, we examined the time to MERS-CoV RNA clearance in respiratory secretions by rRT-PCR, defined as the time from ICU admission until the test was negative on two occasions, without a positive test afterward. Secondary outcomes were ICU and hospital mortality and length of stay in the ICU and the hospital.

Statistical Analysis

We compared baseline characteristics, cointerventions, and outcomes of patients who received corticosteroid therapy during ICU admission and those who did not receive any corticosteroid therapy using chi-square test or Fisher exact test for categorical variables and Student *t* test or Mann-Whitney *U* test for continuous variables as appropriate. For serial measurements, we tested differences between the two groups over time using repeated measures analysis of variance with no imputation for missing values or correction for multiple comparisons.

Association of Corticosteroid Therapy and 90-Day Mortality

We tested the associations between corticosteroid therapy and mortality using three approaches: one approach that adjusts for baseline differences only, but does not account for immortal time bias or indication bias from time-varying confounding (*logistic regression*); a second approach—*Cox proportional hazards regression accounting for time-varying exposure*—that adjusts for baseline differences and accounts for immortal time bias (with corticosteroids as a time-varying exposure); and a third approach, using *marginal structural models*, that adjusts for baseline differences and accounts for indication bias (by examining the impact of time-varying confounders on the daily "risk" of prescription of corticosteroids) and immortal time bias (using corticosteroids as a time-varying exposure).

Logistic Regression

To examine the independent association of corticosteroid therapy on 90-day mortality, we performed multivariable logistic regression analysis, with corticosteroid therapy being the independent variable. We included in the multivariable model *a priori*–decided baseline variables of clinical interest and all significant variables at the univariable level ($P \leq 0.2$), which included: age, sex, Day 1 SOFA, asthma/chronic pulmonary disease, chronic cardiac disease, chronic neurological disease, diabetes with chronic complications, obesity, days from onset of symptom to ICU admission, and healthcare worker status, by applying the PROC GENMOD procedure (SAS version 9.4; SAS Institute).

Cox Proportional Hazards Regression Accounting for Time-Varying Exposure

To examine outcomes as a time to event (i.e., death), we performed a Cox proportional hazards model adjusting for the same above-mentioned baseline covariates with corticosteroid therapy as a time-varying covariate.

Marginal Structural Model

Because corticosteroid therapy often was not started at the time of ICU admission, but rather during the course of the disease on the basis of a change in the patient condition, we performed marginal structural model analysis with inverse probability of treatment weighting to account for time-varying confounders that are likely to influence the corticosteroid therapy initiation and at the same time are likely to be correlated with the risk of mortality (10, 17–19). We included the above-mentioned baseline confounding variables as well. In this model, we considered ventilation status and SOFA scores on the day of corticosteroid therapy initiation and the day before as the time-varying variables. We reasoned that these variables capture the patient condition that physicians would most often consider when initiating corticosteroid therapy.

This process involves calculation of two weights for each observation: treatment selection weight and censoring weight. The treatment selection weight at time k is a ratio of two weights. The numerator is the product of probabilities that a patient receives his observed treatment at time k, given the baseline covariates. The denominator is calculated similarly by incorporating also the time-varying covariates (SOFA on the day, SOFA on the previous day, mode of ventilation on the day and mode of ventilation on the previous day) as well (10, 17). The weights are updated until the first day of corticosteroid therapy and kept constant afterward. Because SOFA scores were recorded on Days 1, 3, 7, 14, and 28, we imputed missing values for the remaining days (*see* online supplement). Ventilation status was recorded also on Days 1, 3, 7, 14, and 28, and we coded the mode of ventilation as follows: 0 = no ventilation, 1 = noninvasive ventilation, 2 = invasive ventilation, 3 = advanced ventilation support (e.g., extracorporeal membrane oxygenation, oscillatory, prone, nitric oxide). We imputed the mode of ventilation between these days by the last-observation-carried-forward method.

The same approach is used to calculate the censoring weight for early patient dropout. We have censored patients at hospital discharge or at Day 90, and the weights for censoring are calculated as the ratio of a subject's probability of remaining uncensored up to day k. The final weight for each observation is obtained by multiplying the treatment selection weights and the censoring weights. We used a weight-trimming approach to deal with extreme weights; weights larger than the 95th percentile value were fixed at the 95th percentile value, and weights smaller than the fifth percentile value were fixed at the

fifth percentile value. This process continued until the average weight reached approximately 1. The time-varying intercept was modeled by a smoothing function of time, using restricted cubic splines with five knots for days since beginning of follow-up day (17, 19).

In step 2, weighted pooled logistic regression with robust SE was used to estimate the effect of corticosteroids on mortality after adjusting for baseline characteristics. We modeled the probability of receiving corticosteroid therapy with the assumption that once the patient was started on corticosteroid therapy the patient will remain on that treatment.

Association of Corticosteroid Therapy and MERS-CoV RNA Clearance

We tested the associations between corticosteroid therapy and MERS-CoV RNA clearance in two approaches: one approach—*Cox proportional hazards regression accounting for time-varying exposure*—that adjusts for baseline differences and accounts for immortal time bias (with corticosteroids as a time-varying exposure); and a second approach, using *marginal structural Cox proportional hazards modeling*, that adjusts for baseline differences and accounts for indication bias (by examining the impact of time-varying confounders on the daily "risk" of prescription of corticosteroids) and immortal time bias (using corticosteroids as a time-varying exposure).

Cox Proportional Hazards Regression Accounting for Time-Varying Exposure

We used Cox proportional hazards regression to examine the time to MERS-CoV RNA clearance rRT-PCR. For this analysis, we censored patients if they never cleared MERS-CoV RNA or at hospital discharge if they were discharged alive before they had cleared MERS-CoV RNA. We adjusted for the same baseline covariables used in the logistic regression model, with corticosteroid therapy as a time-varying covariate.

Marginal Structural Cox Proportional Hazards Model

The marginal structural Cox proportional hazards model was performed incorporating the stabilized weights to estimate the effect of corticosteroid therapy on MERS-CoV RNA clearance in a similar approach to the marginal structural model used for 90-day mortality above.

Subgroup and Sensitivity Analyses

Because a corticosteroid therapy effect may be dose dependent and may vary according to the time of initiation (20, 21), we performed all previous models on the following stratified groups: patients who received high-dose corticosteroid therapy (highest daily dose of $>$300 mg of hydrocortisone equivalent), patients who received low-dose corticosteroid therapy (highest daily dose of $\leqslant$300 mg of hydrocortisone equivalent), and patients who had corticosteroid therapy initiated in the first 7 days of ICU admission, each compared with patients who did not receive any corticosteroid therapy. We also compared corticosteroid therapy started after Day 7 compared with no corticosteroid therapy; in this analysis, we only included patients who were alive after Day 7, to ensure that patients in both groups were comparable in having "the opportunity" to receive the treatment, thus minimizing the risk of confounding due to immortal time bias. To further assess the potential effect modification of the time of initiation of corticosteroid therapy on the association between corticosteroid therapy and 90-day mortality, we performed landmark analyses at different time cutoff points by logistic regression analysis and Cox proportional hazards regression model accounting for time-varying exposure. These analyses compared patients who were alive and with/without the exposure (corticosteroid/no corticosteroid) by each time cutoff point. To account for the possible variation by site, we performed a sensitivity analysis using a logistic regression model adjusting for clustering by centers in addition to the previously mentioned baseline variables. To examine whether imputation of missing data had an impact on the association observed in the marginal structural model, and considering that corticosteroid therapy was initiated in 80% of patients in the first 7 days when imputation was relatively limited, we conducted a sensitivity analysis comparing patients who were started on corticosteroid therapy in the first 7 days with patients in the no corticosteroid therapy group with imputation up to Day 7 only. To examine whether the results of the association of corticosteroid therapy and MERS-CoV RNA clearance might have been influenced by the practice of repeating rRT-PCR among different sites, we conducted a sensitivity analysis restricting to centers that had repeated rRT-PCR on more than 50% of their patients.

Tests were two-sided, with significance set at $\alpha < 0.05$. Results from all multivariable analyses are reported as odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CIs) as appropriate. Analyses were conducted using SAS version 9.4.

Results

Patient Characteristics

Within the study period, 309 patients with MERS met the eligibility criteria for this study. Almost, half of these patients, 151 of 309 (48.9%), received corticosteroid therapy. Patients receiving corticosteroid therapy and those not receiving corticosteroid therapy were similar in most baseline characteristics (Table 1). However, patients given corticosteroid therapy were more likely to have one or more comorbidity than those without corticosteroid therapy (132 of 151 [87.4%] compared with 115 of 158 [72.8%]; $P = 0.001$), including diabetes with chronic complications, chronic pulmonary disease, and chronic cardiac disease (Table 1). The use of corticosteroid therapy varied by site (median percentage of patients on corticosteroid therapy, 50%; quartile 1 [Q1]–Q3, 34–70%; *see* Figure E1 in the online supplement).

Corticosteroid Use

Hydrocortisone was the most frequently administered corticosteroid (103 of 151 [68.2%] patients), followed by methylprednisolone (61 of 151 [40.4%]) (Table 2). Corticosteroid therapy was started at a median (Q1–Q3) of 3.0 days (1.0–7.0 d) from ICU admission. The median (Q1–Q3) of the maximum daily hydrocortisone-equivalent dose was 300.0 mg (200.0–400.0 mg), with a median (Q1–Q3) duration of 7.0 days (4.0–14.0 d). Figure 1 shows the distribution of the time to initiate corticosteroid therapy from ICU admission. Before corticosteroid therapy administration, the median (Q1–Q3) Pa_{O_2}/FI_{O_2} was 108.8 mm Hg (68.8–166.2 mm Hg), and the median

Table 1. Baseline Characteristics and Physiological Parameters on Day 1 of Admission to the ICU among Patients with Middle East Respiratory Syndrome in the Corticosteroid Therapy and No Corticosteroid Therapy Groups

Variable	Corticosteroid Group (*N* = *151*)	No Corticosteroid Group (*N* = *158*)	*P* Value
Age, yr, mean ± SD	57.8 ± 17.2	55.3 ± 17.3	0.20*
BMI, kg/m^2	28.9 (24.3–33.8)	28.4 (24.2–33.0)	0.64
Male sex	107 (70.9)	106 (67.1)	0.47
Source of infection			0.25
Community acquired	71 (47.0)	60 (38.0)	
Healthcare worker, hospital acquired	15 (9.9)	17 (10.8)	
Non–healthcare worker, hospital acquired	55 (36.4)	62 (39.2)	
Days from onset of symptoms to the emergency room	5.0 (3.0–8.0)	4.0 (3.0–7.0)	0.03
Days from onset of symptoms to ICU admission	8.0 (5.0–12.0)	6.5 (4.0–11.0)	0.07
Days from onset of symptoms to intubation	8.0 (6.0–12.0)	8.0 (5.0–12.0)	0.40
Comorbidities			
Any comorbidity	132 (87.4)	115 (72.8)	0.001
Diabetes with chronic complications	87 (57.6)	69 (43.7)	0.01
Asthma/chronic pulmonary disease	30 (19.9)	15 (9.5)	0.01
Liver disease	12 (7.9)	9 (5.7)	0.43
Renal disease	43 (28.5)	47 (29.7)	0.81
Chronic cardiac disease	75 (49.7)	53 (33.5)	0.004
Chronic neurological disease/hemiplegia or paraplegia or dementia	20 (13.2)	13 (8.2)	0.15
Obesity	21 (13.9)	15 (9.5)	0.23
Rheumatological disease	2 (1.3)	1 (0.6)	0.62†
HIV/AIDS	1 (0.7)	1 (0.6)	>0.99†
Any malignancy, including leukemia or lymphoma/solid tumors	14 (9.3)	13 (8.2)	0.75
Physiologic parameters			
SOFA score	9.0 (6.0–12.0)	8.0 (5.0–11.0)	0.09
Tidal volume, ml	400 (350–434)	400 (348–454)	>0.99
PEEP, cm H_2O	10.0 (8.0–14.0)	12.0 (10.0–15.0)	0.46
Plateau pressure, cm H_2O	28.0 (22.0–30.0)	28.0 (20.0–31.0)	0.57
$Pa_{O_2}/F_{I_{O_2}}$ ratio, mm Hg	99.0 (64.0–151)	115.5 (73.8–176)	0.12
Mean arterial pressure, mm Hg	68.5 (59.0–80.0)	70.0 (61.0–84.7)	0.05
Lactate, mmol/L	1.8 (1.1–2.7)	1.6 (1.1–2.7)	0.50
INR	1.1 (1.0–1.3)	1.1 (1.0–1.3)	0.88
Creatinine, μmol/L	127.0 (74.0–251.0)	118.0 (72.0–255.0)	0.84
Bilirubin level, μmol/L	12.5 (7.0–24.0)	11.3 (7.8–20.9)	0.70
Platelets, ×10^9/L	180 (111.5–254)	160 (113–241)	0.42
No. of quadrants with infiltrates on chest radiograph	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.19

Definition of abbreviations: BMI = body mass index; INR = international normalized ratio; PEEP = positive end-expiratory pressure; Q = quartile; SOFA = Sequential Organ Failure Assessment.
Data presented as *n* (%) or median (Q1–Q3) unless otherwise noted. For continuous variables, Mann-Whitney *U* test was used to calculate the *P* value unless otherwise noted. For categorical variables, chi-square test was used to calculate the *P* value unless otherwise noted.
**t* test was used to calculate *P* value.
†Fisher exact test was used to calculate *P* value.

(Q1–Q3) positive end-expiratory pressure was 12.0 cm H_2O (10.0–14.0 cm H_2O) (Table 2).

Clinical Course and Outcomes

Throughout their ICU stay, patients in the corticosteroid therapy group received more invasive ventilation, high-frequency oscillation ventilation, nitric oxide, neuromuscular blockers, vasopressors, blood transfusion, and renal replacement therapy and received more ribavirin and IFN than patients who did not receive corticosteroid therapy (Table 3). Changes of physiological parameters over time and between the corticosteroid therapy group and no corticosteroid therapy group are described in Figure E2.

Patients who received corticosteroid therapy compared with those who did not had higher crude 90-day mortality (112 of 151 [74.2%] compared with 91 of 158 [57.6%]; $P = 0.002$), longer ICU length of stay (median [Q1–Q3], 12.5 d [8.0–23.0 d] compared with 7.0 d [5.0–13.0 d]; $P < 0.0001$), and longer hospital length of stay (median [Q1–Q3], 21.0 d [13.0–38.0 d] compared with 15.0 d [8.0–30.0 d]; $P = 0.0006$) (Table 3).

Mortality

After adjustment for baseline variables using multivariable logistic regression, corticosteroid therapy was associated with higher 90-day mortality (adjusted OR [aOR], 1.87; 95% CI, 1.02–3.44; $P = 0.04$). Adjustment for clustering by site did not significantly alter this association (Table E1). Using Cox proportional hazards regression model accounting for time-varying exposures, with adjustment for the

Table 2. Corticosteroid Therapy among Critically Ill Patients with Middle East Respiratory Syndrome ($n = 151$)

Medication Variable	Result
Dexamethasone	9 (6.0)*
Hydrocortisone	103 (68.2)*
Methylprednisolone	61 (40.4)*
Prednisolone	20 (13.2)*
Duration of corticosteroids, d	
All patients	7.0 (4.0–14.0)
Survivors	10.0 (4.0–19.0)
Nonsurvivors	7.0 (4.0–12.0)
Dose, hydrocortisone equivalent/d, mg	300.0 (200.0–400.0)
Duration between onset of illness and corticosteroid initiation, d	10.0 (7.0–17.0)
Duration between hospital admission and corticosteroid initiation, d	7.0 (3.0–15.0)
Duration between ICU admission and corticosteroid initiation, d	3.0 (1.0–7.0)
Duration between onset of ventilation and corticosteroid initiation, d	3.0 (1.0–7.0)
Pa_{O_2}/FI_{O_2} before corticosteroid initiation	108.8 (68.8–166.2)
Positive end expiratory pressure before corticosteroid initiation, cm H_2O	12.0 (10.0–14.0)
SOFA cardiovascular score, before corticosteroid initiation	1.0 (0.0–3.0)

Definition of abbreviations: Q = quartile; SOFA = Sequential Organ Failure Assessment.
Data presented as *n* (%) or median (Q1–Q3).
*Percentages add to more than 100% because some patients received more than one formulation of corticosteroids during ICU stay.

baseline variables, corticosteroid therapy was not associated with mortality difference (adjusted HR [aHR], 1.20; 95% CI, 0.88–1.63; $P = 0.24$). Landmark analyses demonstrated that the associations observed with logistic regression and Cox proportional hazards regression analyses were time dependent, with increasing ORs and HRs when using increasing time cutoff points of initiation of corticosteroid therapy (Figure 2). Using the marginal structural model, there was no significant association between corticosteroid therapy and 90-day mortality (aOR, 0.75; 95% CI, 0.52–1.07; $P = 0.12$). Sensitivity analysis comparing patients who were started on corticosteroid therapy in the first 7 days to patients in the no corticosteroid therapy group and imputing missing data only up to Day 7 did not alter the association ($n = 260$; aOR, 0.76; 95% CI, 0.50–1.15; $P = 0.20$). The dose and time of initiation of corticosteroid therapy were not associated with differences in 90-day mortality (Table 4).

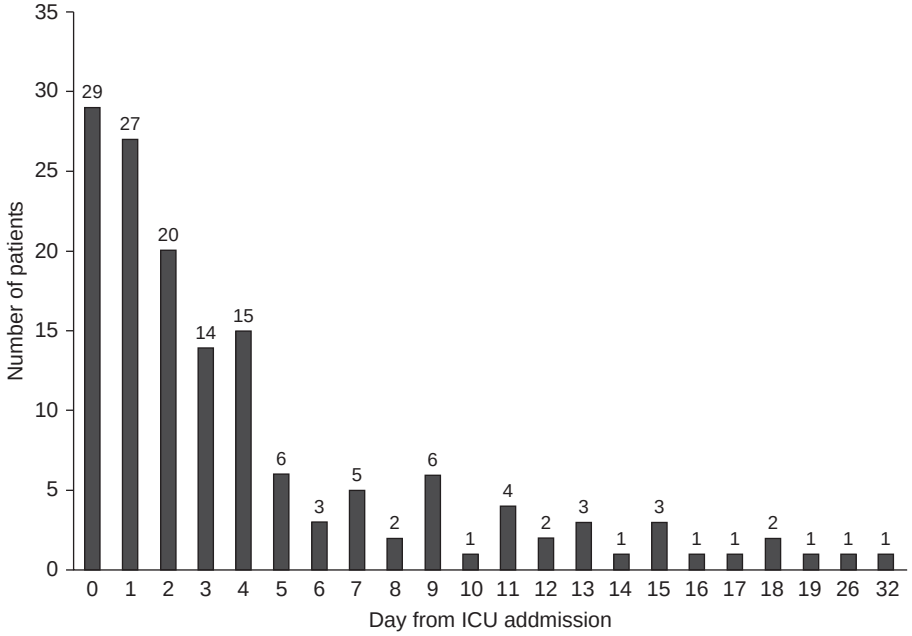


Figure 1. Time to corticosteroid therapy initiation from ICU admission. Day 0 includes patients who were already on corticosteroid therapy when admitted to the ICU. Date of initiation of corticosteroid therapy was missing in three patients.

MERS-CoV RNA Clearance

Crude analyses showed no statistically significant differences in the proportion of patients who had MERS-CoV RNA clearance between the corticosteroid therapy group and the no corticosteroid therapy group, among all patients and among survivors (Table 3). Cox proportional hazards regression accounting for time-varying exposure showed no significant association of corticosteroid therapy with the time to MERS-CoV RNA clearance (aHR, 1.06; 95% CI, 0.61–1.84; $P = 0.84$) (Table 4). However, using marginal structural Cox proportional hazards modeling, corticosteroid therapy was associated with a significant delay in MERS-CoV RNA clearance (aHR, 0.35; 95% CI, 0.17–0.72; $P = 0.005$) (Table 4). Sensitivity analysis restricting to centers who had repeated rRT-PCR on more than 50% of their patients (11 of 14 centers, 168 patients) demonstrated a similar association (aHR, 0.33; 95% CI, 0.15–0.72; $P = 0.005$). A similar association with delayed MERS-CoV RNA clearance was observed when restricting analysis to low-dose, high-dose, and early initiation of corticosteroid therapy. The association of late initiation of corticosteroid therapy (after 7 d) and MERS-CoV RNA clearance was not statistically significant (Table 4).

Discussion

Our study investigates the association of corticosteroid therapy on mortality and MERS-CoV RNA clearance accounting for time-varying confounders during critical illness. Our study shows that corticosteroid

Table 3. ICU Course and Outcomes among Patients with Middle East Respiratory Syndrome in the Corticosteroid Therapy and No Corticosteroid Therapy Groups

Variable	Corticosteroids (*n* = 151)	No Corticosteroids (*n* = 158)	*P* Value
Noninvasive positive pressure ventilation	54 (35.8)	41 (25.9)	0.06
Invasive ventilation	141 (93.4)	121 (76.6)	<0.0001
Neuromuscular blockade	74 (49.0)	46 (29.1)	0.0003
High-frequency oscillation ventilation	17 (11.3)	7 (4.4)	0.03
ECMO	10 (6.6)	8 (5.1)	0.56
Nitric oxide	29 (19.2)	10 (6.3)	0.0007
Prone positioning	20 (13.2)	10 (6.3)	0.04
Vasopressors	134 (88.7)	111 (70.3)	<0.0001
Blood transfusion	74 (49.0)	34 (21.5)	<0.0001
Ribavirin and/or IFN	76 (50.3)	59 (37.3)	0.02
Ribavirin and IFN	64 (42.4)	47 (29.7)	
IFN only	2 (1.3)	6 (3.8)	0.03*
Ribavirin only	10 (6.6)	6 (3.8)	
Oseltamivir	89 (58.9)	80 (50.6)	0.14
Renal replacement therapy	83 (55.0)	69 (43.7)	0.05
ICU mortality	114 (75.5)	89 (56.3)	0.0004
Hospital mortality	117 (77.5)	92 (58.2)	0.0003
90-d mortality	112 (74.2)	91 (57.6)	0.002
ICU length of stay, d	12.5 (8.0–23.0)	7.0 (5.0–13.0)	<0.0001
Hospital length of stay, d	21.0 (13.0–38.0)	15.0 (8.0–30.0)	0.0006
MERS-CoV RNA clearance	34 of 99 (34.3)	31 of 104 (29.8)	0.49
Time to MERS-CoV RNA clearance,† d	21.0 (10.0–31.0)	17.0 (7.0–34.0)	0.31
MERS-CoV RNA clearance among 90-d survivors	20 of 28 (71.4)	24 of 49 (49.0)	0.06
Time to MERS-CoV RNA clearance among 90-d survivors,‡ d	23.0 (11.0–32.5)	17.5 (9.5–36.5)	0.62

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; MERS-CoV = Middle East respiratory syndrome coronavirus; Q = quartile. Data presented as *n* (%) or median (Q1–Q3). For continuous variables, Mann-Whitney *U* test was used to calculate the *P* value. For categorical variables, chi-square test was used to calculate the *P* value unless otherwise noted.

*Fisher exact test was used to calculate *P* value.

†Time to MERS-CoV RNA clearance was calculated for 34 patients in the corticosteroid group and 31 patients in the no corticosteroid group.

‡Time to MERS-CoV RNA clearance among 90-d survivors was calculated for 20 patients in the corticosteroid group and 24 patients in the no corticosteroid group.

therapy in patients with MERS was not associated with significant change in 90-day mortality after adjustment for time-varying confounders but was associated with delayed MERS-CoV RNA clearance.

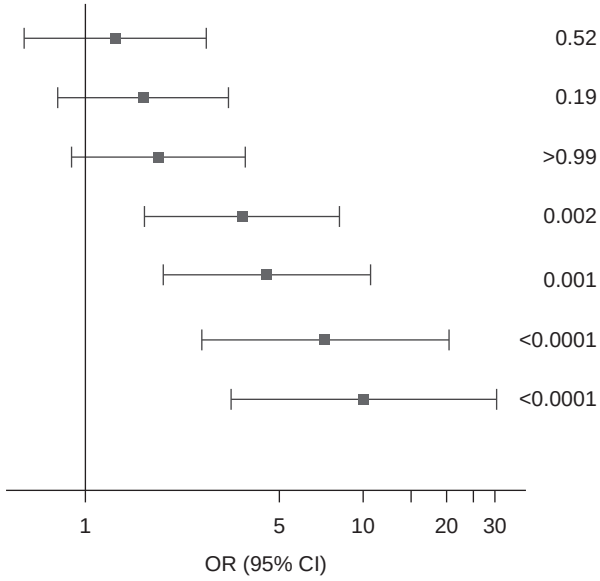
Our study shows that the corticosteroid therapy was commonly used for critically ill patients with MERS. Corticosteroid therapy was initiated at variable times during the course of the disease. Patients were generally hypoxemic and on moderate levels of positive end-expiratory pressure at the time of starting therapy, indicating that corticosteroids were used for patients who were quite ill and/or were not showing signs of improvement. Patients with comorbidities were more likely to receive corticosteroid therapy, as shown in other studies (10, 22–24). The median daily dose in our study was in the range reported by others (10, 20), taking into consideration that we used the maximum daily dose in our analyses. The median time between the onset of critical illness and corticosteroid therapy was longer in our study than what has been reported in other respiratory infection case series (10), which may reflect current recommendations to avoid corticosteroid therapy for patients with MERS unless indicated for other reasons (25), and suggests that physicians used corticosteroids when the clinical condition was not improving.

Studies examining corticosteroid therapy and vital outcomes for patients with community-acquired pneumonia and acute respiratory distress syndrome have yielded conflicting results (26–29). The results of studies on unselected patients with community-acquired pneumonia may not be generalizable to viral pneumonia; a viral etiology was documented in a small number of the included patients in these studies. Observational studies in patients with SARS coronavirus found that high-dose systemic corticosteroid therapy was associated not only with increased subsequent blood viral loads but also with adverse effects and increased mortality (5, 7).

RCTs are the best design to account for confounding factors. Multivariable analysis often uses baseline and not time-varying confounder adjustment, leading to residual confounding from immortal time bias and evolving indication bias from time-varying confounders. The landmark analyses in our study demonstrate the time-dependent nature of associations. Time-varying confounding adjustment, including marginal structural models, has been used fairly extensively in other fields that have longer periods of follow-up, such as studies on treatment of HIV infection (17). In critical care, observational studies have typically not considered time-varying confounding adjustment in shorter follow-up periods. However, such adjustment is particularly relevant when the likelihood of receiving a treatment and the likelihood of the outcome are both influenced by dynamic factors that change between

A

Alive and exposure by	Corticosteroids Events/N (%)		No Corticosteroids Events/N (%)		OR (95% CI)	P Value
Day 3	60/82	(73.2)	75/139	(54.0)	1.28 (0.60, 2.72)	0.52
Day 4	68/94	(72.3)	73/137	(53.3)	1.61 (0.79, 3.28)	0.19
Day 6	66/93	(71.0)	51/115	(44.3)	1.83 (0.89, 3.77)	>0.99
Day 8	64/91	(70.3)	29/93	(31.2)	3.67 (1.63, 8.23)	0.002
Day 10	54/82	(65.9)	23/87	(26.4)	4.48 (1.90, 10.56)	0.001
Day 12	46/77	(59.7)	17/81	(21.0)	7.29 (2.62, 20.35)	<0.0001
Day 14	42/72	(58.3)	12/76	(15.8)	10.1 (3.35, 30.27)	<0.0001



B

Alive and exposure by	Corticosteroids Events/N (%)		No Corticosteroids Events/N (%)		HR (95% CI)	P Value
Day 3	60/82	(73.2)	75/139	(54.0)	0.88 (0.61, 1.28)	0.52
Day 4	68/94	(72.3)	73/137	(53.3)	0.99 (0.69, 1.41)	0.94
Day 6	66/93	(71.0)	51/115	(44.3)	1.22 (0.81, 1.85)	0.34
Day 8	64/91	(70.3)	29/93	(31.2)	2.17 (1.31, 3.60)	0.003
Day 10	54/82	(65.9)	23/87	(26.4)	2.50 (1.42, 4.40)	0.002
Day 12	46/77	(59.7)	17/81	(21.0)	3.15 (1.67, 5.93)	<0.0001
Day 14	42/72	(58.3)	12/76	(15.8)	4.71 (2.26, 9.81)	<0.0001

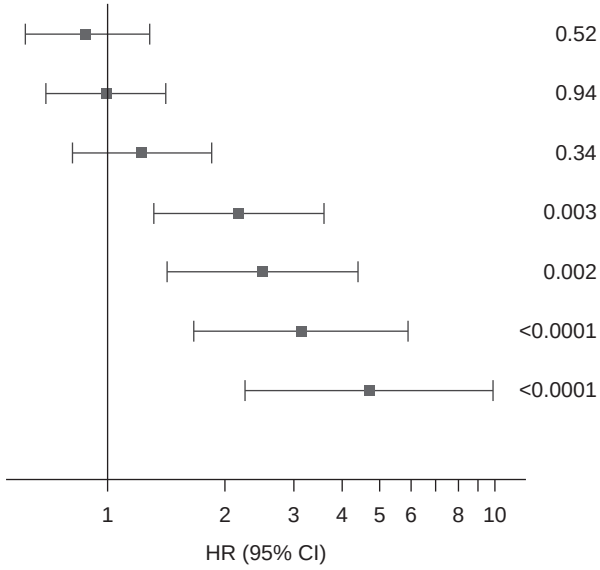


Figure 2. Landmark analyses for 90-day mortality at different time cutoff points by logistic regression analysis (*A*) and Cox proportional hazards regression model accounting for time-varying exposure (*B*) comparing patients who were alive and with/without the exposure (corticosteroid/no corticosteroid) by each time cutoff point. CI = confidence interval; HR = hazard ratio; OR = odds ratio.

baseline and the time at which treatment is received (in those who receive) and every time point at which the treatment might have been administered and was not (in those who do not receive). Our results are in accordance with the results derived from an observational study on influenza A (H1N1) in critically ill patients that showed no association between corticosteroid therapy and mortality when accounting for time-varying confounders using a marginal structural model (10). Our study demonstrates that measures of the association of corticosteroid therapy and mortality are critically dependent on the analytic model chosen and highlights the need for RCTs as the most accurate way to obtain an estimate of the treatment effect. However, as cases of MERS are relatively infrequent and sporadic, analyses of observational

Table 4. Ninety-Day Mortality and Middle East Respiratory Syndrome Coronavirus RNA Clearance of Critically Ill Patients with Middle East Respiratory Syndrome Using Various Adjustment Methodologies

	Day-90 Mortality									MERS-CoV RNA Clearance					
	Logistic Regression			Cox Proportional Hazards Regression Model			MSM			Cox Proportional Hazards Regression Model			Marginal Structural Cox Proportional Hazards Model		
Variables	*n*	aOR (95% CI)	*P* Value	*n*	aHR (95% CI)	*P* Value	*n*	aOR (95% CI)	*P* Value	*n*	aHR (95% CI)	*P* Value	*n*	aHR (95% CI)	*P* Value
All patients treated with corticosteroids vs. patients not treated with corticosteroids (reference)	291	1.87 (1.02–3.44)	0.04	291	1.20 (0.88–1.63)	0.24	290	0.75 (0.52–1.07)	0.12	194	1.06 (0.61–1.84)	0.84	189	0.35 (0.17–0.72)	0.005
Patients treated with >300 mg vs. patients not treated with corticosteroids (reference)	185	1.43 (0.53–3.82)	0.48	185	1.05 (0.65–1.69)	0.84	184	0.99 (0.55–1.80)	0.98	121	0.87 (0.34–2.22)	0.78	118	0.26 (0.09–0.77)	0.02
Patients treated with ⩽300 mg vs. patients not treated with corticosteroids (reference)	241	1.89 (0.94–3.82)	0.08	241	1.21 (0.86–1.71)	0.28	240	0.75 (0.51–1.11)	0.15	164	1.01 (0.54–1.89)	0.98	159	0.41 (0.19–0.88)	0.02
Patients treated for ⩽7 d vs. not treated with corticosteroids (reference)	261	1.81 (0.91–3.59)	0.09	261	1.05 (0.76–1.46)	0.75	260	0.88 (0.61–1.26)	0.48	174	0.59 (0.31–1.13)	0.11	169	0.23 (0.09–0.63)	0.004
Patients treated for >7 d vs. patients not treated with corticosteroids who survived >7 d (reference)	141	2.49 (0.85–7.25)	0.10	142	1.60 (0.88–2.89)	0.12	142	0.51 (0.26–1.00)	0.05	87	3.12 (1.31–7.40)	0.01	85	0.94 (0.36–2.47)	0.90

Definition of abbreviations: aHR = adjusted hazard ratio; aOR = adjusted odds ratio; CI = confidence interval; MERS-CoV = Middle East respiratory syndrome coronavirus; MSM = marginal structural model.

For logistic regression, Hosmer-Lemeshow goodness-of-fit test was used to assess the model fitness, and *P* values were not significant for all analyses except for "patients treated for >7 d versus not treated with corticosteroids and who survived >7 d" data. After removing one observation, which has the highest influence on the chi-square goodness of fit (on the basis of residuals and deviance influence statistics), a nonsignificant *P* value was obtained; we report the results after removing that observation. HR < 1 signifies delay in Middle East respiratory syndrome coronavirus RNA clearance.

data may ultimately provide the best available evidence.

Our results reveal that corticosteroid therapy delayed the MERS-CoV RNA clearance. Similarly, corticosteroid therapy delayed the viral clearance in avian influenza A(H7N9) (20) and SARS (7). This may be related to immune-suppressing effects of corticosteroid therapy, which are mediated mainly by T-cell responses (7). However, it is important to note that persistent positivity of MERS-CoV RNA does not necessarily indicate persistent shedding of live virus.

Our study is the first to address corticosteroid therapy in MERS and is derived from the largest collaborative multicenter observational database on critically ill patients with MERS, using standardized and detailed data collection. The retrospective observational design is a main limitation of our study. We used statistical methods that consider measured baseline and time-varying confounders. However, these adjustments may not be fully account for measured confounders and would not account for indication bias that could occur in the presence of unmeasured confounding. Because follow-up MERS-CoV RNA testing was at the discretion of the treating team, it is possible that patients with persistent viral shedding trajectories were more likely to get repeat RNA testing. This could be a source of bias, because only patients with repeat testing were included in the analysis. However, we do not believe the decision to repeat testing was related to the decision to treat with corticosteroids. In addition, we performed a sensitivity analysis restricting to centers that had repeated testing on more than 50% of patients and found that the association of corticosteroid therapy with MERS-CoV RNA remained the same. We did not assess other associated outcomes with corticosteroid therapy, such as opportunistic infections, hyperglycemia, and neuromyopathy. Marginal structural models require the availability of time-varying data on each time point around when the intervention may be initiated (each day, in our case). Although we used multiple *a priori* selected data time points to adjust for potential changes in severity of illness, we do not have data for each day; we needed to use imputation for days with missing data, and it is possible that additional data points would lead to even more valid estimates. However, 80% of patients were started on corticosteroid therapy in the first 7 days, when missing data were relatively limited, thus minimizing the impact of imputation. Furthermore, sensitivity analysis restricting to the first week showed no change in the estimate of treatment effect. Because of the retrospective observational nature of our study, repeat rRT-PCR testing was not protocolized and varied among centers. However, sensitivity analysis restricting to centers with more frequent testing showed that associations of corticosteroid therapy and viral clearance were robust. Importantly, our findings cannot necessarily be generalized to patients with other types of viral pneumonia or, more broadly, patients with acute respiratory distress syndrome.

Conclusions

Corticosteroid therapy was commonly used in critically ill patients with MERS. After adjustment for baseline and time-varying confounders, the use of corticosteroid therapy was not associated 90-day mortality but was associated with delayed MERS-CoV RNA clearance. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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