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Impact of Early Corticosteroids on Preventing Clinical Deterioration in Non-critically Ill Patients Hospitalized with COVID-19: A Multi-hospital Cohort Study

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ABSTRACT

Introduction: While guidelines strongly recommend dexamethasone in critical COVID-19, the optimal threshold to initiate corticosteroids in non-critically ill patients with COVID-19 remains unclear. Using data from a state-wide

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COVID-19 registry, we evaluated the effectiveness of early corticosteroids for preventing clinical deterioration among non-critically ill patients hospitalized for COVID-19 and receiving non-invasive oxygen therapy.

Methods: This was a target trial using observational data from patients hospitalized for COVID-19 at 39 hospitals participating in the MI-COVID19 registry between March 16, 2020 and August 24, 2020. We studied the impact of corticosteroids initiated within 2 calendar days of

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hospitalization (“early steroids”) versus no early steroids among non-ICU patients with laboratory-confirmed SARS-CoV2 receiving non-invasive supplemental oxygen therapy. Our primary outcome was a composite of in-hospital mortality, transfer to intensive care, and receipt of invasive mechanical ventilation. We used inverse probability of treatment weighting (IPTW) and propensity score-weighted regression to measure the association of early steroids and outcomes.

Results: Among 1002 patients meeting study criteria, 231 (23.1%) received early steroids. After IPTW, to balance potential confounders between the treatment groups, early steroids were not associated with a decrease in the composite outcome (aOR 1.1, 95%CI 0.8–1.6) or in any components of the primary outcome.

Conclusion: We found no evidence that early corticosteroid therapy prevents clinical deterioration among hospitalized non-critically ill COVID-19 patients receiving non-invasive oxygen therapy. Further studies are needed to determine the optimal threshold for initiating corticosteroids in this population.

Keywords: Corticosteroid therapy; COVID-19 therapeutics; SARS-COV2; Viral infections

Key Summary Points

While corticosteroids are proven beneficial in critical COVID-19, the role of early corticosteroids in non-critically ill hospitalized COVID-19 patients remains unclear.

Using data from a state-wide COVID-19 registry, we studied the impact of “early” corticosteroids (started within 2 days of hospitalization) versus “no early” steroids in preventing clinical deterioration among non-critically ill hospitalized COVID-19 patients.

In our cohort of 1002 COVID-19 patients receiving non-invasive oxygen therapy across 39 hospitals, early steroids were not associated with a decrease in-hospital mortality, transfer to intensive care, or intubation.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to cause substantial morbidity and mortality around the world [1]. Corticosteroids quickly emerged as a potential treatment option in COVID-19 because of their immunomodulatory effects and potential benefits in ARDS and septic shock from other etiologies [2, 3].

While initial guidance regarding corticosteroids was inconsistent, corticosteroids became standard-of-care for patients with severe COVID-19 in June 2020, after results of the RECOVERY randomized clinical trial showed a mortality reduction in oxygen-treated patients, with the greatest benefit for patients receiving invasive mechanical ventilation [4]. Following the RECOVERY trial press release, other steroid trials halted randomization, and the available trial data were pooled through the World Health Organization’s Rapid Evidence Appraisal for COVID-19 Therapies prospective meta-analysis-which confirmed the benefit of steroids in critically ill patients [4, 5]. All major practice guidelines were subsequently updated to recommend corticosteroids in COVID-19 patients receiving supplemental oxygen, with the strongest recommendation for patients receiving invasive mechanical ventilation [6–8].

While corticosteroids are clearly beneficial in critical COVID-19, the precise threshold of illness above which corticosteroids are indicated remains unclear. In particular, it is unclear whether corticosteroids are indicated in non-critically ill patients who are receiving low-flow oxygen therapy [9–11]. Most trials of early steroids in COVID-19 focused either exclusively on critically ill patients [5, 12–14] or included patients with heterogenous respiratory support [4], ranging from nasal canula oxygen to non-invasive ventilation, due to their pragmatic design.

Assessing the benefit of steroids in non-critically ill patients is important because corticosteroid therapy is known to have several potential side effects, including hyperglycemia and fluid retention. Pertinent to COVID-19,

corticosteroids may also prolong viral shedding, as seen in viral pneumonias from severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome [15–17]. Finally, in observational studies of severe pneumonia caused by influenza viruses, corticosteroid therapy has been associated with worse clinical outcomes, including secondary bacterial infection and death [18]. Collectively, these data highlight the need for additional studies to evaluate the benefit of corticosteroids in non-critically ill patients hospitalized with COVID-19 [19, 20].

Therefore, using data from a state-wide, multi-hospital COVID-19 registry, we evaluated the impact of early corticosteroid use on preventing clinical deterioration in patients hospitalized with COVID-19 and receiving non-invasive oxygen therapy. We hypothesized that early corticosteroid treatment would be associated with a reduced mortality, transfer to intensive care, or receipt of invasive mechanical ventilation.

METHODS

Data Source: the MI-COVID19 registry

We utilized data from the MI-COVID 19 registry, a multi-hospital Continuous Quality Initiative sponsored by Blue Cross Blue Shield of Michigan and Blue Care Network, which aims to improve care for hospitalized patients with COVID-19. Over 40 Michigan hospitals voluntarily participate in MI-COVID-19 [21]. Trained abstractors at each hospital collected detailed data on adult patients hospitalized with COVID-19 using a structured data collection template. Patient characteristics, including demographics, medical history, comorbidities, physical findings, laboratory results, imaging studies, and medications, were abstracted directly from medical records. The term “corticosteroid” was harmonized across abstractors and across sites to be systemic (enteral or intravenous) corticosteroid therapy. Data abstracters collected data on the dose, route, type, and duration of systemic steroids directly

from medication administration records in the electronic chart.

For hospitals unable to abstract all COVID-19 hospitalizations because of high volumes, hospitalizations were sorted by day of admission (e.g., Monday–Sunday) and, for each day, a pseudo-random number (minute of hospital discharge) was used to select a sample of patients for abstraction.

Cohort Inclusion/Exclusion Criteria

We identified all patients hospitalized with laboratory-confirmed SARS-CoV-2 infection (between March 16, 2020 and August 24, 2020) from MI-COVID-19 registry hospitals, who received supplemental oxygen during day 1 and/or day 2 of hospitalization, remained alive, and were in a non-ICU hospital location. We excluded patients with: (1) length of hospitalization < 3 days; (2) no supplemental oxygen therapy during day 1 and/or day 2; (3) receipt of invasive mechanical ventilation or ICU level of care during day 1 and/or day 2; (4) admission via inter-hospital transfer; (5) who were pregnant; (6) transitioned to hospice within 3 h of hospital admission; or (7) discharged against medical advice. The goal of the inclusion and exclusion criteria was to emulate a target trial of corticosteroid therapy [22]. Because hospital days 1 and 2 were used for eligibility and strategy assignment, we ensured that no patients either met the study outcome (death, ICU, or invasive mechanical ventilation) or were ineligible for the study outcome (i.e., discharged alive from hospital) during days 1 or 2.

Treatment Assignment

Patients meeting study eligibility criteria were categorized into two treatment groups: early corticosteroids (treatment) and no early corticosteroids (comparison). Patients who received intravenous or oral dexamethasone, prednisone, methylprednisolone, or hydrocortisone within 2 days of arrival to the hospital or emergency department comprised the early steroid group. The comparison group included all patients who received no corticosteroids

during the first 2 days of hospitalization. Pre-hospital corticosteroid use and corticosteroids use after day 2 were not considered in the study group assignment.

Study Outcomes

The primary outcome was clinical deterioration, defined as a composite of hospital mortality, ICU transfer, or receipt of invasive mechanical ventilation. Secondary outcomes included individual components of the composite outcome and hospital length of stay ≥ 7 days.

Subgroups

We examined the primary and secondary outcomes in the overall cohort and for several predefined subgroups by age (<70 vs. ≥ 70 years), duration of symptoms prior to hospitalization (<7 days vs. ≥ 7 days) and maximum oxygen requirement during hospital days 1 and 2 ($\text{FiO}_2 < 40\%$ vs. $\text{FiO}_2 \geq 40\%$).

Statistical Analysis

All variables were summarized with standard descriptive statistics, including mean and standard deviation (SD). Categorical variables were summarized using percentages. Propensity score regression adjustment was used to reduce selection bias. We used an inverse probability of treatment weighting (IPTW) approach based on patients' propensity score (i.e., patients' predicted probability of receiving corticosteroids given their baseline covariates) to balance the differences in baseline variables between treatment groups [23].

A non-parsimonious multivariable logistic regression model was constructed to estimate each patient's propensity score. Variables of the propensity score (PS) model were prespecified before outcome analyses, and included: (1) patient demographics {age, gender, race, body mass index}; (2) co-morbidities {cardiac, pulmonary, diabetes, cancer}; (3) clinical symptoms on hospital presentation {fever, dyspnea}; (4) vital signs during day 1 and 2 of hospitalization {blood pressure, respiratory rate, highest oxygen support}; and (5) laboratory and

radiology features on hospital presentation {creatinine, white blood cell count, and presence of imaging abnormalities}. These covariates were chosen based on clinical experience, review of literature, and data available in the COVID-19 registry [24]. We adjusted for date of admission (measured in half-month epochs) to account for temporal trends in treatment approach (e.g., hydroxychloroquine) and outcomes independent of corticosteroids.

Group distributions were evaluated to determine if the groups were comparable and the IPTW was calculated and normalized. After IPTW, the treatment and comparison groups were similar except for the slight differences in the proportion of admissions occurring during the June 2020 epochs.

We converted different steroids into maximum prednisone equivalents to reduce heterogeneity and to create a standardized framework for comparing steroid dose and duration between treatment and control groups (Steroid Conversion Calculator; MDCalc).

Characteristics between the unadjusted and adjusted groups were compared using *t* tests for continuous variables and Pearson's chi-squared tests for categorical variables. Propensity score-weighted regression models were then fitted to compare primary and secondary outcomes between groups. Odds ratios with 95% confidence intervals (OR, 95% CI) were reported, and overall two-sided alpha-level of 0.05 was used to determine statistical significance. Data were analyzed using SAS software v.9.4 (SAS Institute, Cary, NC, USA).

IRB Statement

MI-COVID-19 was deemed to be quality improvement work and received the designation of non-regulated by the University of Michigan institutional review board. Each hospital participating in the Mi-COVID19 initiative is required to have a signed Data Use Agreement with the Coordinating Center for the collaborative. The data submitted is a limited dataset and is therefore sharable in an aggregated and de-identified format.

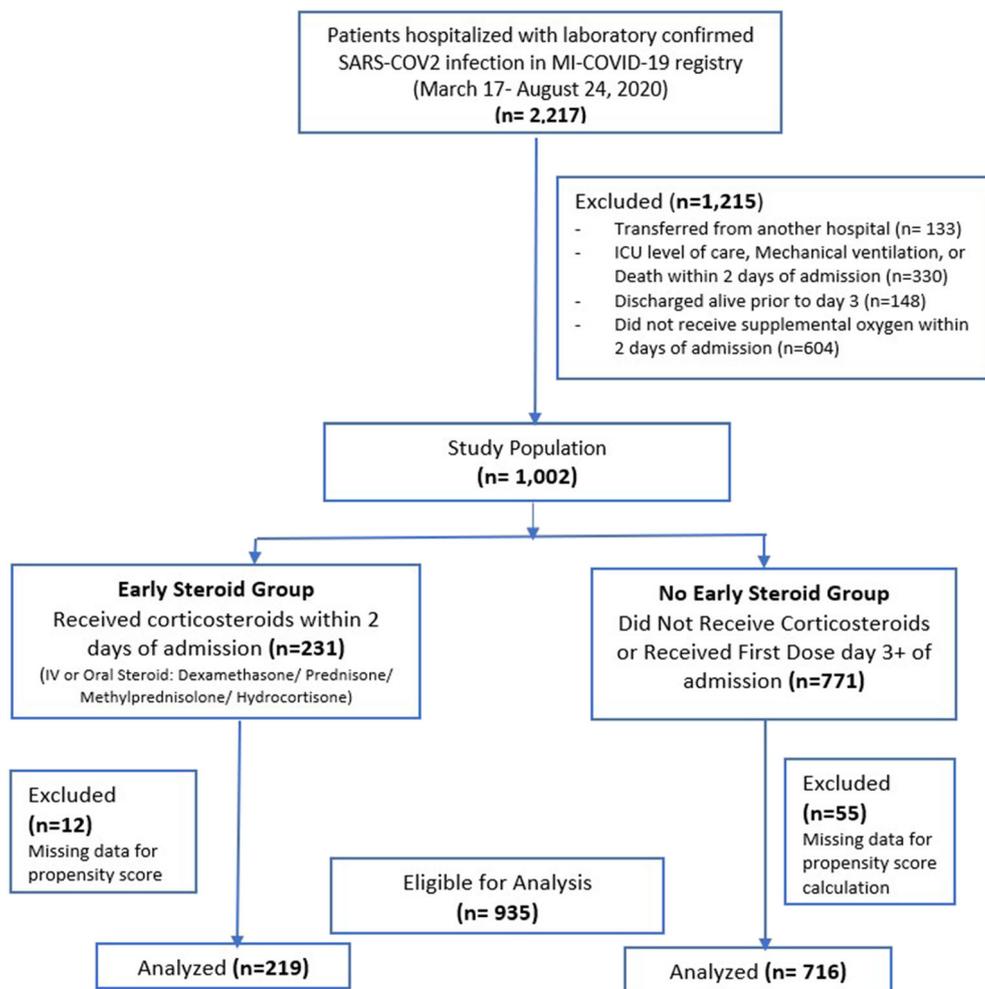


Fig. 1 CONSORT diagram showing the enrollment of subjects, their allocation to treatment, and how they were analyzed in the study

RESULTS

Among 2217 hospitalizations for COVID-19 in the MI-COVID-19 registry during the study period, 1215 were excluded, leaving 1002 patients in our trial emulation (Fig. 1). Of 1002 eligible patients, 231 (23.1%) were treated with corticosteroids within 2 days of presentation (treatment group), while 771 (76.9%) were not (comparison group). Totals of 12 patients in the treatment and 55 patients in the control group had missing data needed for propensity score calculation and were excluded, leaving 935 patients for analysis.

Unadjusted patient characteristics are shown in Supplementary Table 1. Of the patients in the

treatment group, 33% were black compared to 44% in the comparison group. Patients in the treatment group were also more likely to have heart disease or chronic lung disease and to have received corticosteroids prior to hospitalization. Totals of 162 (70.1%) patients in the treatment group and 342 (44.4%) in the comparison group received high-intensity supplemental oxygen therapy during the baseline/enrollment period [i.e., oxygen via nasal prongs or mask at ≥ 6 LPM or $\geq 40\%FIO_2$; heated high flow nasal cannula (HHFNC); or non-invasive positive pressure ventilation (NIPPV)]. After inverse probability weighting, baseline demographic and clinical characteristics were not different between the treatment and comparison groups (Table 1).

Table 1 Characteristics of treatment versus comparison groups after inverse probability weighting

	Treatment (early steroids) (<i>n</i> = 219)	Comparison (no early steroids) (<i>n</i> = 716)	<i>p</i> value
Patient characteristics and comorbidities			
Age, mean (SD)	66.62 (14.40)	65.56 (17.14)	0.41
BMI, mean (SD)	31.29 (8.55)	31.33 (8.37)	0.94
Female	50.4%	47.7%	0.48
Race: Black	39.3%	42.2%	0.44
Self-pay insurance	3.0%	2.4%	0.67
Prior steroids/immunosuppressive therapy	11.6%	11.5%	0.96
Diabetes- complicated	12.5%	11.1%	0.57
Heart disease	40.6%	39.6%	0.79
Chronic lung disease	33.0%	28.3%	0.18
Cancer	9.5%	8.7%	0.70
Moderate/severe kidney disease	27.5%	25.8%	0.63
Vitals, symptoms, and laboratory values during baseline/enrollment period			
Fever (> 100.4 [F])	36.5%	36.9%	0.91
Dyspnea/shortness of breath	80.4%	78.2%	0.48
Elevated respiratory rate (≥ 20)	94.2%	91.5%	0.19
Decreased systolic blood pressure (< 100 mmHg)	26.0%	27.3%	0.70
High supplemental oxygen support first 2 days (low flow NC ≥ 6 l or FiO ₂ $\geq 40\%$, HHFNC, NIPPV)	56.8%	50.2%	0.09
Max. creatinine, mean (SD)	1.68 (4.94)	1.98 (7.17)	0.57
Max. white blood cell (WBC), mean (SD)	7.82 (3.37)	7.86 (6.42)	0.94
Imaging abnormalities on CXR or chest CT	39.6%	37.3%	0.53
Date of hospital admission			
Early March, late March admission	3.3%, 30.3%	0.7%, 43.9%	0.003, < 0.001
Early April, late April admission	42.0%, 12.8%	28.4%, 13.9%	< 0.001, 0.67
Early May, late May admission	6.2%, 2.9%	6.1%, 3.0%	0.95, 0.89
Early June, late June admission	0.1%, 1.8%	3.3%, 0.3%	0.01, 0.01
Early July, late July admission	0.2%, 0.3%	0.2%, 0.3%	0.92, 0.89
Early August admission	0.2%	0.0%	0.21

In the treatment group, the median time between symptom onset and start of corticosteroid therapy was 5 days. A total of 224 (97%) patients in the treatment group received prednisone or methylprednisolone, while 14 (6.1%) patients were treated with dexamethasone. During days with any corticosteroid treatment, patients in the treatment group received a median prednisone-equivalent of 75 mg/day, with a median treatment duration of 4 days. A total of 129 (16.7%) patients in the comparison group also received IV or oral steroids after day 2 of hospitalization. Supplemental Table 2 provides additional information on steroid use in treatment versus comparison groups.

The composite outcome of in-hospital mortality, transfer to the ICU, or receipt of MV occurred 28% in the treatment and 24% in the comparison group. In our IPTW multivariable model, early corticosteroids were not associated with decreased odds of the composite outcome (OR 1.1, 95% CI 0.8–1.6) in the overall cohort (Table 2), nor in any of the pre-specified subgroups defined by age, baseline FIO₂ requirement, or duration of symptoms (Table 3). Early corticosteroids were also not associated with a decrease in any of the individual measures of the primary outcomes of in-hospital mortality (OR 1.3, 95% CI 0.9–1.9), transfer to ICU level of care (OR 1.3, 95% CI 0.8–1.9), or receipt of

invasive mechanical ventilation (OR 1.7, 95% CI 1.1–1.7). Early steroids were also not associated with a decreased odds of hospitalization length of stay ≥ 7 days (OR 0.9, 95% CI 0.6–1.2) (Table 2).

DISCUSSION

In this multi-center observational target trial emulation assessing the impact of early corticosteroid therapy in non-critically ill patients with COVID-19, we found no evidence that early corticosteroids prevent clinical deterioration. Specifically, we were unable to detect an association between early corticosteroids and reduced mortality, ICU transfer, or receipt of invasive mechanical ventilation.

Recommendations for the use of corticosteroids in non-critically ill hospitalized COVID-19 patients requiring oxygen therapy are largely based on data from the RECOVERY trial, a large, multi-hospital, randomized, open-label trial performed in the United Kingdom. This trial compared hospitalized patients who received up to 10 days of dexamethasone to those who received the standard of care. There was no difference in mortality with dexamethasone among patients who did not require oxygen at enrollment (RR 1.2; 95% CI 0.9–1.6). In

Table 2 Association of early steroid treatment with primary and secondary outcomes

	Treatment (early steroids)	Comparison (no early steroids)	Adjusted odds ratio	95% confidence interval
Primary outcome				
Composite of in-hospital mortality, mechanical ventilation, and transfer to ICU level of care	62/219 (28%)	173/716 (24%)	1.1	(0.8, 1.6)
Secondary outcomes				
Individual components of primary outcome				
In-hospital mortality	48 (22%)	123 (17%)	1.3	(0.9, 1.9)
Transfer to ICU level of care	32 (15%)	101 (14%)	1.3	(0.8, 1.9)
Mechanical ventilation	25 (11%)	64 (9%)	1.7	(1.1, 2.7)
Length of stay ≥ 7 days	93/219 (42%)	317/716 (44%)	0.9	(0.6, 1.2)

Odds ratios were generated from inverse probability of treatment weighted multivariable logistic regression models

Table 3 Rate of primary composite outcome of death, mechanical ventilation and ICU transfer by subgroup

	Treatment	Comparison	Adjusted odds ratio	95% confidence interval
All Patients	61/217 (28%)	169/703 (24%)	1.1	(0.8, 1.6)
Duration of symptoms before hospitalization				
< 7 days	43/130 (33%)	120/370 (32%)	1.0	(0.7, 1.6)
≥ 7 days	18/87 (21%)	49/333 (15%)	1.2	(0.6, 2.2)
Age at hospitalization				
< 70 years	23/117 (20%)	66/436 (15%)	1.3	(0.8, 2.2)
≥ 70 years	39/101 (39%)	107/280 (38%)	1.1	(0.6, 1.8)
Max. supplemental oxygen during baseline/enrollment period				
1–6 L (< 40%) low-flow oxygen	17/66 (26%)	87/407 (21%)	1.2	(0.7, 2.1)
All other oxygen	45/152 (30%)	86/309 (28%)	1.0	(0.7, 1.7)

contrast, among patients who received supplemental oxygen (nasal canula, heated high-flow oxygen, and non-invasive positive pressure ventilation), but were not mechanically ventilated at enrollment, 23.3% of patients in the dexamethasone arm died within 28 days compared to 26.2% of patients in the standard of care arm (RR 0.8; 95% CI 0.7–0.9). However, because detailed data on the mode and amount of oxygen therapy were not collected, it is impossible to tease out the threshold at which corticosteroids are indicated from the RECOVERY trial.

The National Institute of Health COVID guidelines suggest dexamethasone can be withheld for hospitalized patients who require “minimal amounts of supplemental oxygen, but be given (either alone or in combination with remdesivir) in patients who require “increasing amounts of supplemental oxygen” [8]. Hence, we wanted to focus specifically on hospitalized COVID-19 patients requiring supplemental oxygen therapy to assess whether early use of steroids would be beneficial, and to identify the threshold of illness at which steroids would be helpful. Our study results are consistent with other observational studies that showed no difference in risk of intubation or mortality between non-critically ill hospitalized patients who received versus those that did not receive corticosteroids [11, 15, 25, 26].

There are many potential reasons for the discrepancy between our results and the findings of the oxygen-treated subgroup in RECOVERY. First, our study focused on a potentially less severely ill hospitalized population than the oxygen-treated patients in RECOVERY. Only 7% of patients in our treatment group received HHFNC therapy and none received NIPPV. Second, the RECOVERY trial specifically evaluated dexamethasone 6 mg orally or intravenously for up to 10 days or until hospital discharge, whichever came first. While the pooled meta-analysis from WHO included patients that received dexamethasone, hydrocortisone, and methylprednisolone, the RECOVERY trial contributed to 59% of patients in this meta-analysis. Many of the trials evaluating alternative glucocorticoids were terminated early after release of results from the RECOVERY trial. Thus, the evidence to support the use of hydrocortisone OR 0.7 (95% CI 0.4–1.1; $P = 0.1$) and methylprednisolone OR 0.9 (95% CI 0.3–2.9; $P = 0.9$) is not as robust as for dexamethasone OR 0.6 (95% CI 0.5–0.8; $P < 0.001$) [5]. Our study mostly evaluated methylprednisolone and prednisone (97% of all steroids used in the treatment group), and notably the average dose of methylprednisolone (75 mg in the treatment group) was twice as high as the equivalent dose of dexamethasone recommended in guidelines. Further, the

median duration of steroids in our study was 4 days in the early steroid group, which was significantly shorter than the recommended duration of 10 days. This may suggest the importance of the choice, dose, and duration of steroids used in COVID-19 to blunt the inflammatory response consistent with results from other studies [27, 28].

Our study should be considered in the context of several limitations. First, it is an observational study in which the decision to administer corticosteroids was at the discretion of the treating clinicians and influenced by local hospital guidelines. We were careful to adhere to best practices for target trial emulation, and did not consider corticosteroid use after day 2 in the study group assignment. Thus, 16.7% patients in the comparison group received IV or oral steroids after day 2, which may have blunted the difference in mortality between treatment and comparison groups. However, because these patients likely received late corticosteroids in response to clinical deterioration, excluding them would have introduced bias. Instead, we used IPTW to balance potential confounders between the treatment and comparison groups. Similar designs have been used in large COVID-19 trials assessing vaccine efficacy and efficacy of COVID 19 therapeutics [29, 30]. While this approach was successful at balancing the a priori confounders (including pre-existing co-morbidities and use of systemic steroids pre-hospitalization), we cannot exclude the possibility of unmeasured confounding. Second, due to small sample sizes, we were unable to evaluate specific steroid regimens, and hence used maximum prednisone equivalents to standardize comparisons between the treatment and control groups. Similarly, inhaled corticosteroid use was out of the scope of this study. Third, while we did not balance on actual bacterial co-infection based on cultures, we balanced on clinical signs and symptoms suggestive of co-infection (fever, dyspnea, vital signs, WBC, imaging abnormalities) to ensure that our treated and untreated populations had equivalent likelihoods of bacterial co-infection. Few patients in our cohort presented with bacterial co-infection, as reported in a separate study [31]. Finally, this study

occurred during the initial U.S. surge, when there was a relatively lower threshold to initiate invasive mechanical ventilation, due to concerns for aerosolization of SARS-CoV-2 with high-flow oxygen, and significant variation in treatments among our hospitals [32]. However, we ensured that the treatment groups were contemporaneous (and therefore subject to similar thresholds for ICU transfer and initiation of invasive mechanical ventilation) by including half-month epoch as a co-variate in our model.

CONCLUSIONS

Using data from a multihospital, state-wide registry, we found no association between early corticosteroid therapy and the composite outcome of in-hospital mortality, transfer to the ICU, and/or receipt of invasive mechanical ventilation in patients hospitalized for COVID-19 and requiring supplemental non-invasive oxygen therapy. Our study highlights the need for additional RCTs to determine the optimal timing, dose, and duration for corticosteroid therapy in non-invasive, mechanically ventilated patients with COVID-19.

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Compliance with ethics guidelines. MI-COVID-19 was deemed to be quality improvement work and received the designation of non-regulated by the University of Michigan institutional review board. Each hospital participating in the Mi-COVID19 initiative is required to have a signed Data Use Agreement with the Coordinating Center for the collaborative. The data submitted is a limited data set and is

therefore sharable in an aggregated and de-identified format.

Data availability. The Mi-COVID19 data registry is proprietary, and all authors abided by the data privacy agreements in place. Statistical code for the study is available on reasonable request. The data sets are not available due to the proprietary nature of MI-COVID 19 data registry. The registry has a process for submitting data requests by participating hospitals. All applications for data analysis vetted by data/design publication committee and prioritized based on alignment with the mission of the collaborative.

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