CHEST

Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019

The Ivermectin in COVID Nineteen Study

Juliana Cepelowicz Rajter, MD; Michael S. Sherman, MD, FCCP; Naaz Fatteh, MD; Fabio Vogel, PharmD, BCPS; Jamie Sacks, PharmD; and Jean-Jacques Rajter, MD

BACKGROUND: Ivermectin was shown to inhibit severe acute respiratory syndrome coronavirus 2 replication in vitro, which has led to off-label use, but clinical efficacy has not been described previously.

RESEARCH QUESTION: Does ivermectin benefit hospitalized coronavirus disease 2019 (COVID-19) patients?

STUDY DESIGN AND METHODS: Charts of consecutive patients hospitalized at four Broward Health hospitals in Florida with confirmed COVID-19 between March 15 and May 11, 2020, treated with or without ivermectin were reviewed. Hospital ivermectin dosing guidelines were provided, but treatment decisions were at the treating physician's discretion. The primary outcome was all-cause in-hospital mortality. Secondary outcomes included mortality in patients with severe pulmonary involvement, extubation rates for mechanically ventilated patients, and length of stay. Severe pulmonary involvement was defined as need for $F_{IO_2} \geq 50\%$, noninvasive ventilation, or invasive ventilation at study entry. Logistic regression and propensity score matching were used to adjust for confounders.

RESULTS: Two hundred eighty patients, 173 treated with ivermectin and 107 without ivermectin, were reviewed. Most patients in both groups also received hydroxychloroquine, azithromycin, or both. Univariate analysis showed lower mortality in the ivermectin group (15.0% vs 25.2%; OR, 0.52; 95% CI, 0.29-0.96; $P = .03$). Mortality also was lower among ivermectin-treated patients with severe pulmonary involvement (38.8% vs 80.7%; OR, 0.15; 95% CI, 0.05-0.47; $P = .001$). No significant differences were found in extubation rates (36.1% vs 15.4%; OR, 3.11; 95% CI, 0.88-11.00; $P = .07$) or length of stay. After multivariate adjustment for confounders and mortality risks, the mortality difference remained significant (OR, 0.27; 95% CI, 0.09-0.80; $P = .03$). One hundred ninety-six patients were included in the propensity-matched cohort. Mortality was significantly lower in the ivermectin group (13.3% vs 24.5%; OR, 0.47; 95% CI, 0.22-0.99; $P < .05$), an 11.2% (95% CI, 0.38%-22.1%) absolute risk reduction, with a number needed to treat of 8.9 (95% CI, 4.5-263).

INTERPRETATION: Ivermectin treatment was associated with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement. Randomized controlled trials are needed to confirm these findings. CHEST 2021; 159(1):85-92

KEY WORDS: hospitalized COVID-19; in-hospital mortality; ivermectin; mechanical ventilation; number needed to treat; severe pulmonary involvement; survival

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; IQR = interquartile range; MAP = mean arteria pressure; QTc = corrected QT interval; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

AFFILIATIONS: From the Broward Health Medical Center, Fort Lauderdale, FL (J. C. R., N. F., F. V., J. S., and J.-J. R.); the Drexel University College of Medicine (M. S. S.),

Take-home Points

Study Question: Is ivermectin associated with lower mortality rate in patients hospitalized with coronavirus disease 2019 (COVID-19)?

Results: A retrospective cohort study of consecutive patients hospitalized with confirmed severe acute respiratory syndrome coronavirus 2 infection at a four-hospital consortium in South Florida. Analysis showed statistically significant lower mortality rates in the group treated with ivermectin as compared with the group treated with usual care (15.0% vs 25.2%).

Interpretation: Ivermectin was associated with lower mortality during treatment of COVID-19 patients, especially in patients who required higher inspired oxygen or ventilatory support.

Ivermectin previously was studied as a therapeutic option for viral infections, with data showing some in vitro activity against a broad range of viruses, including HIV, dengue, influenza, and Zika virus, likely through inhibition of importin α/β1-mediated nuclear import of viral proteins.[1-3] Wagstaff et al[4] demonstrated that ivermectin was a potent in vitro inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), showing a 99.8% reduction in viral RNA after 48 h. Reports can be found on the Internet of physicians worldwide treating Coronavirus disease 2019 (COVID-19) empirically with ivermectin since late April 2020.

According to ClinicalTrials.gov, currently 37 studies are investigating the usefulness of ivermectin in COVID-19. However, in vivo efficacy of ivermectin in SARS-CoV-2 infection in humans has not been reported previously.

In the late 1970s, ivermectin was developed as a new class of drug to treat parasitic infections. Initially used in veterinary medicine, it soon was found to be safe and effective in humans. It has been used successfully to treat onchocerciasis and lymphatic filariasis in millions of people worldwide as part of a global drug donation program. About 3.7 billion doses of ivermectin have been distributed in mass drug administration campaigns globally over the past 30 years. Presently, ivermectin is approved for use in humans in several countries to treat onchocerciasis, lymphatic filariasis, strongyloidiasis, and scabies.[1]

Based on the data drug safety sheet for ivermectin (New Drug Application Identifier: 50-742/S-022), side effects were uncommon and limited. Reported side effects with more than 1% occurrence included elevation in alanine aminotransferase and aspartate aminotransferase (2%), nausea (2%), diarrhea (2%), decreased leukocyte count (3%), peripheral edema (3%), tachycardia (3%), dizziness (3%), and pruritus (3%). A pharmacokinetic study of 166 patients reported side effects of headache (6%), dysmenorrhea (5.5%), upper respiratory infection symptoms (1.8%), and diarrhea (1.8%).[5]

Methods

Patients

Sequentially consecutive hospitalized patients at four Broward Health-associated hospitals in South Florida with laboratory-confirmed infection with SARS-CoV-2 during their admission were reviewed in this study. The list of confirmed cases was provided by the hospitals' epidemiology departments. Enrollment dates ranged from March 15, 2020, through May 11, 2020. Confirmatory testing was performed by nasopharyngeal swab using a Food and Drug Administration Emergency Use Authorized COVID-19 molecular assay for the detection of SARS-CoV-2 RNA. Patients younger than 18 years and those who were pregnant or incarcerated were excluded from data collection based on institutional review board requirements. Patients who had at least two separate admissions placing them in both groups also were excluded.

Study Procedures

Records were abstracted by four of the authors (J. C. R., N. F., J. S., and J.-J. R.), and all data were reviewed subsequently and confirmed by the lead author. Baseline data were collected at the time of ivermectin administration for the ivermectin group; for the usual care group, baseline was either the time of administration of hydroxychloroquine or, if not used, at the time of admission. Information collected included COVID-19 testing results, patient demographics, pre-existing comorbid conditions, initial vital signs, laboratory results, and the use of corticosteroids, hydroxychloroquine, and azithromycin to describe the cohort and to identify potential confounders between groups. Severity of pulmonary involvement was assessed at the time of baseline data collection and was categorized

Philadelphia, PA; and the Florida International University (J.-J. R.), Miami, FL.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: Jean-Jacques Rajter, MD; e-mail: covid19@pscflorida.com

DOI: https://doi.org/10.1016/j.chest.2020.10.009

as severe or nonsevere. Patients were considered to have severe pulmonary involvement if they required an F_{IO_2} of 50% or more, high-flow nasal oxygen, noninvasive ventilation, or intubation and mechanical ventilation. The nonsevere pulmonary criteria encompassed patients who required no supplemental oxygen or low F_{IO_2} (ie, venturi mask 40% or less or up to 6 L/min of low-flow nasal cannula), independent of laboratory findings.

Patients were categorized into two treatment groups based on whether they received ivermectin at any time during the hospitalization. Patients in the ivermectin group received at least one oral dose of ivermectin at 200 μg/kg in addition to usual clinical care. A second dose could be given at the discretion of the treating physician at day 7 of treatment. Ivermectin is not currently approved by the Food and Drug Administration for COVID-19 treatment. The decision to prescribe ivermectin, hydroxychloroquine, azithromycin, or other medications was at the discretion of the treating physicians; however, hospital guidelines were established for the safe use and dosing of these agents. These guidelines included a baseline ECG and mandatory cardiac and corrected QT interval (QTc) monitoring for patients receiving hydroxychloroquine (alone or in combination with azithromycin), avoidance of azithromycin if patient's baseline QTc was more than 460 msec, and discontinuation of hydroxychloroquine if a concerning elevation in QTc occurred or if the patient's cardiologist recommended discontinuation. Oxygen and ventilatory support were applied per the customary care. Empiric use of ivermectin was given explicitly for COVID-19.

Outcomes

The primary outcome was all-cause in-hospital mortality. A patient was considered a survivor if he or she left the hospital alive or if his or her status in the hospital changed from active care to awaiting transfer to a skilled facility. Two consecutive nasopharyngeal swab specimens showing negative results for SARS-CoV-2, collected $\geq$ 24 h apart, were necessary for a patient to be accepted to the local skilled nursing facilities.

Secondary outcomes included subgroup mortality of patients with severe pulmonary involvement, extubation rates for patients requiring mechanical ventilation, and length of hospital stay. Length of stay was calculated from day of admission to either the day of discharge or to patient death.

Statistical Analysis

Univariate analysis of the primary mortality outcome and comparisons between treatment groups were determined by the Student t test for parametric continuous variables or the Mann-Whitney U test for nonparametric continuous variables as appropriate, and by the Pearson χ^2 test for categorical variables. The method of Hodges-Lehman was used to estimate median differences with 95% CIs.

To adjust for confounders and between-group differences, a multivariate analysis was performed using stepwise binary logistic regression. Patient variables included in the analysis were age, sex, comorbidities of diabetes, chronic lung disease, cardiovascular disease, and hypertension, smoking status, severity of pulmonary involvement, need for mechanical ventilation at study entry, BMI, peripheral white blood count, absolute lymphocyte count, and use of corticosteroids based on bivariate associations within our data, a priori plausibility, and documented associations with mortality from previous studies. Adjusted ORs with 95% CIs were computed to show level of certainty. Analyses were based on nonmissing data, and missing data were not imputed. Missingness of 1% was found for peripheral WBC count, 5% for smoking status, and 7% for absolute lymphocyte count.

We performed a secondary analysis using propensity score matching to reduce the effects of confounding and the likelihood of selection bias. Propensity matching was performed using a nearest-neighbor algorithm with 1:1 matching without replacement and a caliper distance of less than 0.2. Variables for propensity scoring included those variables from the univariate between-groups analysis of the unmatched cohort that had a P value of less than .2 (age, sex, pulmonary condition, hypertension , HIV status, severe pulmonary presentation, and exposure to corticosteroids, hydroxychloroquine, or azithromycin). Race, WBC count, absolute lymphocyte count, and need for mechanical ventilation before or on the day of study entry also were added as potential clinical confounders.

All tests were two-sided and a P value $< .05$ was considered statistically significant. Statistical analyses were conducted using IBM SPSS version 26.0 software, R version 3.5.3 software (R Foundation for Statistical Computing), and SPSS PS-matching software (sourceforge.net).

This study was conducted in accordance with tenets of the amended Declaration of Helsinki. The protocol was approved by the institutional review board for the Broward Health Hospital System (Identifier: 2020-034-BHMC). The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the study.

Results

Characteristics of the Patients

Three hundred seven patients were admitted for COVID-19 during the period studied. Four patients were not reviewed because of multiple admissions, 11 did not have COVID-19 confirmed at the time of the study, and 12 were excluded because their age was younger than 18 years, they were pregnant, or they were incarcerated. The remaining cohort of 280 patients comprised 173 treated with ivermectin and 107 in the usual care group. Most patients received a single dose of ivermectin; however, 13 patients received a second dose of ivermectin for ongoing signs or symptoms on day 7 of treatment. Follow-up data for all outcomes were available through May 19, 2020. No patients were lost to follow-up for the primary outcome. At the time of analysis, all patients in both groups had met the end point of death, discharge alive, or awaiting transfer to a skilled facility. Of those awaiting transfer, in the control group, one patient was awaiting transfer to hospice because of an unrelated terminal illness and one patient was awaiting negative COVID-19 test results to proceed with unrelated surgery. In the ivermectin group, five patients were in stable condition, awaiting transfer to skilled facility or rehabilitation, and one patient was improving clinically.

Baseline characteristics and between-group comparisons for unmatched and propensity-matched cohorts are shown in Table 1. Before matching, hypertension and

TABLE 1] Patient Characteristics by Treatment Group

Demographic Characteristic	Unmatched Cohort				Matched Cohort			
	Total (N = 280)	Usual Care (n = 107)	Ivermectin (n = 173)	*P* Value	Total (N = 196)	Usual Care (n = 98)	Ivermectin (n = 98)	*P* Value
Age, y	59.6 ± 17.9	58.6 ± 18.5	60.2 ± 17.6	.45	59.6 ± 17.5	59.04 ± 17.7	60.07 ± 17.4	.68
Female sex	127 (45.4)	43 (41.2)	84 (48.6)	.17	78 (39.8)	39 (39.8)	39 (39.8)	1.0
Race or ethnicity			.36				1.0	
Black	153 (54.6)	55 (51.4)	98 (56.6)		108 (55.1)	54 (55.1)	54 (55.1)	
White	76 (27.1)	35 (32.7)	41 (23.7)		55 (28.1)	27 (27.6)	28 (28.6)	
Hispanic	33 (11.7)	12 (11.2)	21 (12.1)		23 (11.7)	12 (12.5)	111 (11.2)	
Other or not identified[a]	13 (4.6)	5 (4.7)	13 (7.5)		10 (5.1)	5 (5.1)	5 (5.1)	
Current or former smoker	46/255 (18.0)	22/99 (22.3)	24/156 (15.6)	.40	31/180 (22.2)	20/90 (22.2)	11/90 (12.2)	.11
No. of comorbidities	1.66 ± 1.34	1.60 ± 1.46	1.70 ± 1.27	.57	1.56 ± 1.33	1.58 ± 1.43	1.53 ± 1.22	.79
Diabetes	90 ± 32.1	31 ± 29.0	59 ± 34.1	.37	59 ± 30.1	30 ± 30.6	29 ± 29.6	.88
Cardiac	43 ± 15.4	18 ± 16.8	25 ± 14.5	.59	27 ± 13.8	16 ± 16.3	11 ± 11.2	.30
Pulmonary	28 ± 10.0	14 ± 13.1	14 ± 8.9	.18	18 ± 10.1	10 ± 10.2	8 ± 8.2	.62
Obesity	114 ± 40.7	42 ± 39.3	72 ± 41.6	.70	79 ± 40.3	39 ± 39.8	40 ± 40.1	.88
Renal	24 ± 8.6	10 ± 9.4	14 ± 8.1	.72	16 ± 8.2	9 ± 9.2	7 ± 7.1	.60
Cancer	17 ± 6.1	8 ± 7.5	9 ± 5.2	.44	14 ± 7.1	7 ± 7.1	7 ± 7.1	1.00
Hypertension	50 ± 17.9	13 ± 12.2	37 ± 21.4	.05	26 ± 13.2	12 ± 12.2	14 ± 14.3	.67
Neurologic	28 ± 10.0	8 ± 7.5	20 ± 11.6	.27	17 ± 8.7	8 ± 8.2	9 ± 9.2	.80
HIV infection	9 ± 3.2	1 ± 1	8 ± 4.6	.09	3 ± 1.5	1 ± 1.0	2 ± 2.0	.56
Thyroid	23 ± 8.2	7 ± 6.6	16 ± 9.3	.42	15 ± 7.7	7 ± 7.1	8 ± 8.2	.79
BMI	30.0 ± 7.8	29.8 ± 7.2	30.1 ± 8.2	.81	29.4 ± 6.6	29.4 ± 6.3	29.4 ± 6.9	.95
Pulmonary severity				.46				
Severe	75 (26.8)	26 (24.3)	49 (28.3)	.12	47 (24.0)	22 (22.4)	25 (25.5)	.62
Intubated at study entry	38 (13.6)	15 (14.0)	23 (13.3)	.86	25 (12.8)	11 (11.2)	14 (14.3)	.52
Heart rate	86.0 (75.0-98.0)	86.0 (74.0-97.0)	86.0 (75.5-98.0)	.65	85.5 (74.0-98.0)	86.0 (73.0-97.5)	85.0 (74-98.0)	.88
MAP (mm Hg)	93 (82.3-103.0)	90 (81.0-103.0)	94 (83-103)	.24	92.5 (82.0-103.0)	91.0 (81.0-103.2)	93.0 (82.0-103.0)	.74
MAP ≤ 70 mm Hg	13/260 (5.0)	6/89 (6.7)	7/171 (4.1)	.35	7 (3.6)	4 (4.1)	3 (3.1)	.70
Corticosteroid	90 (32.1)	21 (19.6)	69 (39.8)	.001	46 (23.2)	21 (21.4)	25 (25.5)	.5
Hydroxychloroquine	260 (92.9)	104 (97.2)	156 (90.2)	.03	190 (96.9)	95 (96.9)	95 (96.9)	1.00
Azithromycin	243 (86.7)	99 (92.5)	144 (83.2)	.03	177 (90.3)	90 (91.8)	87 (88.7)	.47

(Continued)

TABLE 1 *(Continued)*

Demographic Characteristic	Unmatched Cohort				Matched Cohort			
	Total (N = 280)	Usual Care (n = 107)	Ivermectin (n = 173)	*P* Value	Total (N = 196)	Usual Care (n = 98)	Ivermectin (n = 98)	*P* Value
Peripheral WBC count ($\times 10^9$/L)	7.3 (5.6-10.2; n = 277)	7.0 (5.7-8.9; n = 106)	7.6 (5.5-11.1; n = 171)	.41	6.9 (5.3-9.3)	7.0 (5.8-9.0)	6.9 (5.2-9.8)	.69
Lymphocyte count ($\times 10^9$/L)	1.15 (0.78-1.56; n = 260)	1.14 (0.84-1.49; n = 102)	1.20 (0.77-1.67; n = 158)	.62	1.13 (0.77-1.52)	1.15 (0.87-1.45)	1.19 (0.75-1.57)	.88

Data are presented as No. (%), mean ± SD, or median (interquartile range), unless otherwise indicated. Current and former smoker is given as a proportion of the population with known smoking status documented in their medical records. MAP = mean arterial pressure.
[a]Asian, Native American, Pacific Islander, or not identified.

corticosteroid use were more prevalent in the ivermectin group, whereas the use of hydroxychloroquine and hydroxychloroquine plus azithromycin were higher in the usual care group.

Propensity score matching created a total of 98 matched pairs. After matching, no statistically significant differences were found between the two groups. Eight patients in the propensity-matched group received a second dose of ivermectin on day 7.

Outcomes

Unadjusted outcomes for the unmatched cohort and outcomes in the propensity-matched cohort are shown in Table 2. For the unmatched cohort, overall mortality was significantly lower in the ivermectin group than in the usual care group (15.0% vs 25.2% for ivermectin and usual care, respectively; $P = .03$). Mortality also was lower for ivermectin-treated patients in the subgroup of patients with severe pulmonary involvement (38.8% vs. 80.7% for ivermectin and usual care, respectively; $P = .001$). On univariate analysis, patients receiving corticosteroids showed a higher mortality than those who did not receive corticosteroids (30.0% vs 13.7%; OR, 2.7; 95% CI, 1.47-4.99; $P = .001$); however, corticosteroids were more likely to have been prescribed for severe patients (58.6% vs 22.4% for severe and nonsevere, respectively; OR, 4.91; 95% CI, 2.78-8.63; $P < .001$).

Results were similar, with lower mortality in the ivermectin-treated patients for the matched cohort for the group as a whole and for the subgroup with severe pulmonary involvement (Table 2). In the matched cohort, ivermectin was associated with an absolute risk reduction of 11.2% (95% CI, 0.38%-22.1%) and a corresponding number needed to treat of 8.9 (95% CI, 4.5-263) to prevent one death. We found no difference in median hospital length of stay or in extubation rates in either the unmatched or matched cohorts. Of note, 1 of the 13 patients who received a second dose of ivermectin died; this patient was not in the propensity-matched cohort.

Multivariate analysis was performed on the unmatched cohort, adjusting for demographic factors and between-group differences in mortality risks. Independent predictors of in-hospital mortality included treatment group, age, severe pulmonary disease category, and reduced lymphocyte count (Table 3). Because race was not a significant predictor after adjustment, a further analysis was performed that showed that White patients were significantly older than Black patients (mean age, 66.8 vs 59.1 y; mean difference, 7.7 y; 95% CI, 3.0-12.4 y;

TABLE 2] Univariate Clinical Outcomes by Treatment Group

Outcome	Unmatched Cohort				Matched Cohort			
	Control Subjects (n = 107)	Ivermectin (n = 173)	OR or Difference (95% CI)	*P* Value	Control Subjects (n = 98)	Ivermectin (n = 98)	OR or Difference (95% CI)	*P* Value
Mortality	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Total	27 (25.2)	26 (15.0)	0.52 (0.29-0.96)	0.03	24 (24.5)	13 (13.3)	0.47 (0.22-0.99)	0.045
Severe	21/26 (80.7)	19/49 (38.8)	0.15 (0.05-0.47)	0.001	18/22 (81.8)	8/25 (32.0)	0.27 (0.08-0.92)	0.002
Nonsevere	6/81 (7.4)	7/124 (5.6)	0.75 (0.24-2.3)	0.61	6/76(7.9)	4/74 (5.4)	0.97 (0.61-1.54)	0.78
Successful extubation	4/26 (15.4)	13/36 (36.1)	3.11 (0.88-11.00)	0.07	3/22 (15.4)	7/18 (38.9)	1.91 (0.43-8.46)	0.14
Length of stay	7.0 (4.0-10.0)	7.0 (4.0-13.3)	0 (-1 to 2)	0.34	7.0 (4.0-10.0)	7.0 (3.0-13.0)	0 (-2 to 1)	0.88

Data are presented as No./Total No. (%) or median (interquartile range) unless otherwise indicated.

$P = .001$) and that Hispanic patients (mean age, 49.8 y; mean difference, 17.0 y; 95% CI, 9.6-24.4 y; $P < .001$).

Discussion

In this multihospital retrospective cohort study, we observed a significant association of ivermectin with improved survival for patients admitted with COVID-19. This association also was seen in the subset of patients with severe pulmonary disease. These findings were confirmed after multivariate adjustment for comorbidities and differences between groups, and also in a propensity score-matched cohort. Similar to other studies, we noted that older age, cardiac disease, current or former smoking, more severe pulmonary involvement at presentation, higher WBC counts, and lower lymphocyte counts emerged as risk markers for in-hospital mortality.

The overall mortality, and mortality in intubated patients, in our usual care group was similar to what was reported in previous studies. Richardson et al[6] reported an overall mortality of 21% in a New York City cohort, with a mortality of 88% in intubated patients. Zhou et al[7] reported 28.2% mortality in a cohort of hospitalized patients in Wuhan, China; the intubated patients showed a mortality of 96.9%. In contrast to Magagnoli et al,[8] we did not see a higher mortality effect for hydroxychloroquine. This may have been because of the small number of patients who were not treated with this agent; thus, our study was underpowered to detect a difference in mortality from hydroxychloroquine treatment. We also hypothesize that precautionary measures in the hospitals' protocol for hydroxychloroquine use could have prevented fatal arrhythmias from developing. These included baseline electrocardiography and daily QTc monitoring by telemetry for any patient receiving hydroxychloroquine or combination therapy, avoidance of azithromycin if patient's baseline QTc was more than 460 msec, and discontinuation of hydroxychloroquine if a concerning elevation in QTc occurred or if the patient's cardiologist recommended discontinuation. In contrast to Horby et al,[9] we did not find a mortality benefit for patients who were prescribed corticosteroids in our multivariate analysis, which included several severity covariates. These findings are likely explainable by physicians' choice to reserve use of corticosteroids for the most seriously ill patients, because the study was performed before the results of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial were published.[9]

TABLE 3] Multivariate Analysis of Factors Associated With Mortality

Variable	OR (95% CI)	*P* Value
Treatment group	. . .	. . .
Ivermectin	0.27 (0.09-0.80)	.03
Control subject	Reference	. . .
Age	1.05 (1.02-1.09)	.003
Sex	. . .	. . .
Female	0.42 (0.24-1.82)	.42
Male	Reference	. . .
Smoking status	. . .	. . .
Current or former smoker	3.49 (0.71-17.32)	.13
Nonsmoker	Reference	. . .
Race	. . .	.18
Black	0.64 (0.21-1.94)	.43
Hispanic	0.14 (0.02-1.22)	.08
Other	0.62 (0.05-7.92)	.71
White	Reference	. . .
Comorbidities	. . .	. . .
Diabetes	1.17 (0.39-3.55)	.78
Cardiac	1.51 (0.43-5.22)	.52
Pulmonary	0.15 (0.20-1.84)	.15
Hypertension	0.72 (0.17-3.08)	.66
No comorbidities	Reference	. . .
BMI	0.97 (0.89-1.07)	.58
Severe presentation	11.41 (3.42-38.09)	< .001
Intubated at study entry	2.96 (0.73-12.06)	.13
MAP ≤ 70 mm Hg	1.82 (0.17-19.1)	.62
Corticosteroid treatment	1.71 (0.57-5.16)	.34
Peripheral WBC count	1.08 (0.96-1.23)	.22
Lymphocyte count	3.65 (1.25-10.60)	.02

MAP = mean arterial pressure.

We also did not confirm a higher risk of mortality in Black patients in comparison with White patients after controlling for age. Prior reports showed lower survival rates among Black and Hispanic patients[10]; however, Price et al[11] also found no racial differences in mortality. In our hospital population, White patients were significantly older, which is reflective of our catchment area and may be responsible for the discrepancy.

We did not observe a significant difference in hospital length of stay between the groups (median, 7 days for both groups) despite the lower mortality. Possible explanation could include delay in discharging patients to other facilities (skilled nursing facilities, inpatient rehabs, and so forth) because of a delay in obtaining required repeat COVID-19 testing results. Patients who died were included in length-of-stay measurements.

Use of mechanical ventilation was not adopted as an outcome of interest, because guidelines and practice patterns for intubation criteria changed throughout the length of the study. We were unable to determine ICU length of stay and ventilatory-free days in the ICU because overflow conditions during the pandemic placed critically ill patients in the emergency room and other non-ICU environments, and therefore, we could not determine ICU stay accurately. We did not find a lower mortality in the subgroup of nonsevere patients treated with ivermectin; however, our study was not powered to assess these differences because the overall mortality in nonsevere patients was low. Similarly, the study was not powered to determine whether extubation rates were higher in the ivermectin group. These should be investigated further with a larger randomized controlled trial.

Interpretation

Our study has several limitations. Because of the retrospective observational nature of the study, despite adjustment for known confounders and propensity score matching, we cannot exclude the possibility of unmeasured confounding factors. Although more of the control group was enrolled in the first weeks of the study, suggesting the possibility of timing bias, this may be offset by preferential treatment of more severe patients with ivermectin early in the study because of low initial availability. We also did not find consistently different mortality outcomes with time over the short duration of this study. We also did not find evidence of immortal time bias, because only one of the control patients died fewer than 5 days from admission, the average time from admission to death was 11 days, and the vast majority of patients received ivermectin in 2 days or fewer. If we omit the patient with potential immortal time from the analysis, the mortality difference remains significant in both unmatched (15.0% vs 24.5% for ivermectin and usual care, respectively; $P < .05$) and matched (12.4% vs 25.0% for ivermectin and usual care, respectively; $P < .03$) cohorts. Most of the studied patients received hydroxychloroquine with or without azithromycin, and we are unable to determine whether these medications had an added benefit or whether mortality would have been better in both groups without these agents.

We showed that ivermectin administration was associated significantly with lower mortality among patients with COVID-19, particularly in patients with more severe pulmonary involvement. Interpretation of these findings are tempered by the limitations of the retrospective design and the possibility of confounding. Appropriate dosing for this indication is not known, nor are the effects of ivermectin on viral load or in patients with milder disease. Further studies in appropriately designed randomized trials are recommended before any conclusions can be made.

Acknowledgments

Author contributions: J. C. R., lead author, had full access to all of the data in the study and contributed to the study design, data collection and interpretation, and writing of manuscript. M. S. S. provided data analysis and interpretation and contributed to writing of the manuscript. N. F. contributed to data collection and literature search. F. V. contributed to the study design and data collection. J. S. contributed to data collection and data organization. J.-J. R., corresponding author, contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Financial/nonfinancial disclosures: None declared.

Other contributions: The authors thank Edward Gracely, PhD, for his support and advice with the statistical analysis, and William Rifkin, MD, for reviewing the manuscript.

References

1. Navarro M, Camprubí D, Requena-Méndez A, et al. Safety of high-dose ivermectin: a systematic review and meta-analysis. *J Antimicrobial Chemother*. 2020;75:827-834.
2. Boldescu V, Behnam MAM, Vasilakis N, Klein CD. Broad-spectrum agents for flaviviral infections: dengue, Zika and beyond. *Nat Rev Drug Discov*. 2017;16:565-586.
3. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J*. 2012;443:851-856.
4. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020;178:104787.
5. Munoz J, Ballester MR, Antonijoan RM, et al. Safety and pharmacokinetic profile of fixed dose ivermectin with an innovative 18 mg tablet in healthy adult volunteers. *PLoS Negl Trop Dis*. 2018;12(1):e0006020.
6. Richardson S, Hirsch JS, Narasimha M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323(20):2052-2059.
7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
8. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19 [published online ahead of print April 23, 2020]. *medRxiv*. https://doi.org/10.1101/2020.04.16.20065920.
9. Horby P, Lim WS, Emberson JR, et al. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19-preliminary report [published online ahead of print July 7, 2020]. *N Engl J Med*. https://doi.org/10.1056/NEJMoa2021426.
10. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 states, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(15):458-464.
11. Price CC, Altice FL, Shyr Y, et al. Tocilizumab treatment for cytokine release syndrome in hospitalized COVID-19 patients: survival and clinical outcomes. *Chest*. 2020;158(4):1397-1408.