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Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID-19 (ICON study)

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Running head: Outcomes of Ivermectin use in Covid-19 infection

Abbreviation List:

OR: odds ratio
CI: confidence interval
BMI: body mass index
MAP: mean arteria pressure
SD: standard deviation
IQR: interquartile range
NNT: number needed to treat
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
COVID-19: Coronavirus Disease 2019
IRB: Institutional Review Board
FIO_2: Fraction of Inspired Oxygen

Keywords:

hospitalized COVID-19, survival, mechanical ventilation, severe pulmonary involvement, ivermectin, in-hospital mortality, NNT.

Abstract

Background:

Ivermectin was shown to inhibit SARS-CoV-2 replication in-vitro, which has led to off-label use, but clinical efficacy has not been previously described.

Research Question: Does ivermectin benefit hospitalized 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 through May 11, 2020 treated with or without ivermectin were reviewed. Hospital ivermectin dosing guidelines were provided but treatment decisions were per 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 FiO_2 ≥50%, noninvasive ventilation, or invasive ventilation at study entry. Logistic regression and propensity score matching were used to adjust for confounders.

Results:

280 patients, 173 treated with ivermectin and 107 without ivermectin, were reviewed. Most patients in both groups also received hydroxychloroquine and/or azithromycin. Univariate analysis showed lower mortality in the ivermectin group (15.0% versus 25.2%, OR 0.52, CI 0.29-0.96, P=0.03). Mortality was also lower among ivermectin-

treated patients with severe pulmonary involvement (38.8% vs 80.7%, OR 0.15, CI 0.05-0.47, p=0.001). There were no significant differences in extubation rates (36.1% vs 15.4%, OR 3.11 (0.88-11.00), p=0.07) or length of stay. After multivariate adjustment for confounders and mortality risks, the mortality difference remained significant (OR 0.27, CI 0.09-0.80, p=0.03).

196 patients were included in the propensity-matched cohort. Mortality was significantly lower in the ivermectin group (13.3% vs 24.5%, OR 0.47, CI 0.22-0.99, p<0.05); an 11.2% (CI 0.38%-22.1%) absolute risk reduction, with a number needed to treat of 8.9 (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.

Introduction

Ivermectin has previously been 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 IMP α/β1-mediated nuclear import of viral proteins.[1,2] Wagstaff et al, demonstrated that Ivermectin was a potent in-vitro inhibitor of SARS-CoV-2, showing a 99.8% reduction in viral RNA after 48 hours.[3] There are reports on the internet of physicians worldwide treating COVID-19 empirically with ivermectin since late April, 2020. Per ClinicalTrials.gov, there are currently 37 studies investigating the usefulness of ivermectin in COVID-19. However, in-vivo efficacy of ivermectin in SARS-CoV-2 infection in humans has not previously been reported.

In the late 1970s ivermectin was developed as a new class of drug to treat parasitic infections. Initially used in veterinary Medicine, it was soon found to be safe and effective in humans. It has successfully been used 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 (NDA 50-742/S-022), side effects were uncommon and limited. Reported side effects with greater than 1% occurrence included, elevation in ALT/AST (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%), URI 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 department. Enrollment dates ranged from March 15, 2020 through May 11, 2020. Confirmatory testing was performed by nasopharyngeal swab using an FDA Emergency Use Authorized COVID-19 molecular assay for the detection of SARS-CoV-2 RNA. Patients younger than 18 years old, pregnant, or incarcerated were excluded from data collection based on IRB requirements. Patients who had at least 2 separate admissions placing them in both groups were also excluded.

Study procedures

Records were abstracted by four of the authors and all data were subsequently reviewed 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 at 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 in order 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 categorized as severe or non-severe. Patients were considered to have severe pulmonary involvement if they required an FiO_2 of 50% or greater, high-flow nasal oxygen, noninvasive ventilation, or intubation and mechanical ventilation. The non-severe pulmonary criteria encompassed patients who required no supplemental oxygen, or "low FIO_2" (i.e. 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 micrograms/kilogram 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 FDA-approved for COVID-19. 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 EKG and mandatory cardiac and QTc monitoring for patients receiving hydroxychloroquine (alone or in combination with azithromycin) avoidance of azithromycin if patient's baseline QTc was greater than 460msec, and discontinuation of hydroxychloroquine if there was a concerning elevation in QTc 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. Patient was considered a "survivor" if they left the hospital alive, or if their status in the hospital changed from active care to awaiting transfer to a skilled facility. Two consecutive negative nasopharyngeal swab specimens for SARS-CoV-2, collected ≥ 24 hours 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 Student's t test for parametric continuous variables or Mann-Whitney U test for nonparametric continuous variables as appropriate, and by

Pearson Chi Square test for categorical variables. The method of Hodges-Lehman was used to estimate median differences with 95% confidence intervals.

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, body mass index (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 odds ratio with 95% confidence intervals were computed to show level of certainty. Analyses were based on non-missing data and missing data were not imputed. Missingness of 1% was found for peripheral white blood cell 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 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 less than 0.2 (age, sex, pulmonary condition, hypertension, HIV, severe pulmonary presentation, exposure to corticosteroids, hydroxychloroquine, or azithromycin). Race,

white cell count, absolute lymphocyte count, and need for mechanical ventilation prior to or on the day of study entry were also added as potential clinical confounders.

All tests were 2-sided and a p value <.05 was considered statistically significant.

Statistical analyses were conducted using IBM SPSS v 26.0 software (Armonk, NY), R software v 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria), and SPSS PS-matching software (sourceforge.net).

This study was conducted in accordance with the amended Declaration of Helsinki. The protocol was approved by the Institutional Review Board for the Broward Health Hospital System, protocol approval number 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

307 patients were admitted for COVID-19 during the time period studied. 4 patients were not reviewed due to multiple admissions, 11 did not have COVID-19 confirmed at the time of the study, and 12 were excluded due to either age younger than 18 years old, pregnancy, or incarceration. The remaining cohort of 280 patients was comprised of 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 at day 7 of treatment. Follow up data for all outcomes were

available through May 19th, 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 endpoint 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 due to an unrelated terminal illness, and one patient was awaiting a negative COVID-19 test to proceed with unrelated surgery. In the ivermectin group, five patients were in stable condition, awaiting transfer to skilled facility/rehab, and one patient was clinically improving.

Baseline characteristics and between-group comparisons for unmatched and propensity-matched cohorts are shown in Table 1. Before matching, hypertension and 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 there were no statistically significant differences 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 was also 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 had a higher mortality than those that did not (30.0% vs 13.7%, OR 2.7 (1.47 to 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 (2.78 to 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% (CI 0.38%-22.1%) and a corresponding number needed to treat of 8.9 (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). As race was not a significant predictor after adjustment, a further analysis was performed which showed white patients were significantly older than Black (66.8 vs 59.1 years; mean difference 7.7 years, CI 3.0 –

12.4, p=.001) and Hispanic patients (49.8 years, mean difference 17.0 years, CI 9.6 – 24.4, p<.001).

Discussion

In this multihospital retrospective cohort study, we observed a significant association with ivermectin on improved survival for patients admitted with COVID-19. This association was also 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 white blood cell 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 reported an overall mortality of 21% in their New York City cohort, with a mortality of 88% in intubated patients.[6] Fei Zhou et al reported a 28.2% mortality in their cohort of hospitalized patients in Wuhan, China; their intubated patients had a mortality of 96.9%.[7] In contrast to Ambati et al, we did not see a higher mortality effect for hydroxychloroquine.[8] This may have been due to the small number of patients who were not treated with these agents; our study was thus 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 them from developing fatal arrhythmias. These included baseline EKG and daily QTc monitoring by telemetry for any patient receiving hydroxychloroquine or combination therapy, avoidance of azithromycin if patient's baseline QTc was greater than 460msec, and discontinuation of hydroxychloroquine if there was a concerning elevation in QTc 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 on 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, as the study was performed prior to the results of the RECOVERY trial.[9]

We also did not confirm a higher risk of mortality in Black patients in comparison to white patients after controlling for age. Prior reports have shown lower survival rates among Black and Hispanic patients;[10] however Price et al also found no racial differences in mortality.[11] 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, etc) due to lag 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 outcome of interest, as 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, as overflow conditions during the pandemic placed critically patients in the emergency room and other non ICU environments and we could therefore not accurately determine ICU stay. We did not find a lower mortality in the subgroup of non-severe patients treated with ivermectin; however, our study was not powered to assess these differences as the overall mortality in non-severe 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. Due to 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 due to 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, as only one of the control patients died less 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 less. 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<0.03) cohorts. Most of our patients studied 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 have shown that ivermectin administration was significantly associated 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.

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Juliana C.Rajter, M.D.- lead author, had full access to all of the data in the study, contributed with study design, data collection and interpretation, writing of manuscript

Michael S. Sherman, M.D.- provided data analysis and interpretation, and contributed to writing of the manuscript

Naaz Fatteh, M.D. - contributed with data collection and literature search

Fabio Vogel, Pharm. D. - contributed to the study design and data collection

Jaime Sacks, Pharm. D. - contributed to data collection and data organization

Jean-Jacques Rajter, M.D.- corresponding author, contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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"Take Home Point"

Question: Is Ivermectin associated with lower mortality rate in patients hospitalized with COVID-19?

Results: Retrospective cohort study of consecutive patients hospitalized with confirmed SARS-CoV-2 at a four- hospital consortium in South Florida. Analysis showed statistically significant lower mortality rates in the group treated with ivermectin, as compared to the group treated with “usual care” (15.0% versus 25.2%).

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

Table 1: Patient Characteristics by Treatment Group

	Unmatched Cohort				Matched Cohort			
Demographic characteristics	**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[a], years	59.6 (17.9)	58.6 (18.5)	60.2 (17.6)	0.45	59.6 (17.5)	59.04 (17.7)	60.07 (17.4)	0.68
Female sex	127 (45.4)	43 (41.2)	84 (48.6)	0.17	78 (39.8)	39 (39.8)	39 (39.8)	1.0
Race ethnicity				0.36				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[c]	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)	0.40	31/180 (22.2)	20/90 (22.2)	11/90 (12.2)	0.11
Number of comorbidities[a]	1.66 (1.34)	1.60 (1.46)	1.70 (1.27)	0.57	1.56 (1.33)	1.58 (1.43)	1.53 (1.22)	0.79
Diabetes	90 (32.1)	31 (29.0)	59 (34.1)	0.37	59 (30.1)	30 (30.6)	29 (29.6)	0.88
Cardiac	43 (15.4)	18 (16.8)	25 (14.5)	0.59	27 (13.8)	16 (16.3)	11 (11.2)	0.30
Pulmonary	28 (10.0)	14 (13.1)	14 (8.9)	0.18	18 (10.1)	10 (10.2)	8 (8.2)	0.62
Obesity	114 (40.7)	42 (39.3)	72 (41.6)	0.70	79 (40.3)	39 (39.8)	40 (40.1)	0.88
Renal	24 (8.6)	10 (9.4)	14 (8.1)	0.72	16 (8.2)	9 (9.2)	7 (7.1)	0.60
Cancer	17 (6.1)	8 (7.5)	9 (5.2)	0.44	14 (7.1)	7 (7.1)	7 (7.1)	1.00
Hypertension	50 (17.9)	13 (12.2)	37 (21.4)	0.05	26 (13.2)	12 (12.2)	14 (14.3)	0.67
Neurologic	28 (10.0)	8 (7.5)	20 (11.6)	0.27	17 (8.7)	8 (8.2)	9 (9.2)	0.80
HIV infection	9 (3.2)	1 (1)	8 (4.6)	0.09	3 (1.5)	1 (1.0)	2 (2.0)	0.56
Thyroid	23 (8.2)	7 (6.6)	16 (9.3)	0.42	15 (7.7)	7 (7.1)	8 (8.2)	0.79
BMI[a]	30.0 (7.8)	29.8 (7.2)	30.1 (8.2)	0.81	29.4 (6.6)	29.4 (6.3)	29.4 (6.9)	0.95
Pulmonary severity				0.46				
Severe	75 (26.8)	26 (24.3)	49 (28.3)	0.12	47 (24.0)	22 (22.4)	25 (25.5)	0.62
Intubated at study entry	38 (13.6)	15 (14.0)	23 (13.3)	0.86	25 (12.8)	11 (11.2)	14 (14.3)	0.52
Heart rate[b]	86.0 (75.0, 98.0)	86.0 (74.0, 97.0)	86.0 (75.5, 98.0)	0.65	85.5 (74.0, 98.0)	86.0 (73.0, 97.5)	85.0 (74, 98.0)	0.88
MAP (mm Hg)[b]	93 (82.3, 103.0)	90 (81.0, 103.0)	94 (83, 103)	0.24	92.5 (82.0, 103.0)	91.0 (81.0, 103.2)	93.0 (82.0, 103.0)	0.74
MAP < 70 mm Hg	13/260 (5.0%)	6/89 (6.7%)	7/171 (4.1%)	0.35	7 (3.6)	4 (4.1)	3 (3.1)	0.70
Corticosteroid	90 (32.1)	21 (19.6)	69 (39.8)	0.001	46 (23.2)	21 (21.4)	25 (25.5)	0.5
Hydroxychloroquine	260 (92.9%)	104 (97.2)	156 (90.2)	0.03	190 (96.9)	95 (96.9)	95 (96.9)	1.00
Azithromycin	243 (86.7%)	99 (92.5)	144 (83.2)	0.03	177 (90.3)	90 (91.8)	87 (88.7)	0.47
Peripheral white cell count (X 10^9/L)[b]	7.3 (5.6, 10.2) (n=277)	7.0 (5.7, 8.9) (n=106)	7.6 (5.5, 11.1) (n=171)	0.41	6.9 (5.3, 9.3)	7.0 (5.8, 9.0)	6.9 (5.2, 9.8)	0.69
Lymphocyte count (X	1.15 (0.78, 1.56)	1.14 (0.84, 1.49)	1.20 (0.77, 1.67)	0.62	1.13 (0.77, 1.52)	1.15 (0.87,	1.19 (0.75,	0.88

10^9/L)[b]	(n=260)	(n=102)	(n=158)			1.45)	1.57)	

BMI = body mass index. MAP = mean arterial pressure

[a] mean (± SD)

[b] median (interquartile range)

[c]Asian, Native American, Pacific Islander, or not identified

Table 2: Univariate Clinical Outcomes by Treatment Group

	Unmatched cohort				Matched cohort			
	Number/total number (%) or median (IQR)				Number/total number (%) or median (IQR)			
	Control (n=107)	Ivermectin (n=173)	OR or difference (CI)	P value	Control (n=98)	Ivermectin (n=98)	OR or difference (CI)	P value
Mortality								
Total	27 (25.2)	26 (15.0)	0.52 (0.29 to 0.96)	0.03	24 (24.5)	13 (13.3)	0.47 (0.22 to 0.99)	0.045
Severe	21/26 (80.7)	19/49 (38.8)	0.15 (0.05 to 0.47)	0.001	18/22 (81.8)	8/25 (32.0)	0.27 (0.08 to 0.92)	0.002
Non-severe	6/81 (7.4)	7/124 (5.6)	0.75 (0.24 to 2.3)	0.61	6/76(7.9)	4/74 (5.4)	0.97 (0.61 to 1.54)	0.78
Successful extubation	4/26 (15.4)	13/36 (36.1)	3.11 (0.88 to 11.00)	0.07	3/22 (15.4)	7/18 (38.9)	1.91 (0.43 to 8.46)	0.14
Length of stay (median, IQR)	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

IQR = interquartile range

Table 3: Multivariate analysis of factors associated with mortality

	OR (CI)	P value
Treatment group:		
Ivermectin	0.27 (0.09 to 0.80)	0.03
Control	Reference	
Age	1.05 (1.02 to 1.09)	0.003
Female sex	0.42 (0.24 to 1.82)	0.42
Male sex	Reference	
Current or former smoker	3.49 (0.71 to 17.32)	0.13
Nonsmoker	Reference	
Race		0.18
Black	0.64 (0.21 to 1.94)	0.43
Hispanic	0.14 (0.02 to 1.22)	0.08
Other	0.62 (0.05 to 7.92)	0.71
White	Reference	
Comorbidities		
Diabetes	1.17 (0.39 to 3.55)	0.78
Cardiac	1.51 (0.43 to 5.22)	0.52
Pulmonary	0.15 (0.20 to 1.84)	0.15
Hypertension	0.72 (0.17 to 3.08)	0.66
No comorbidities	Reference	
BMI	0.97 (0.89 to 1.07)	0.58
Severe presentation	11.41 (3.42 to 38.09)	<0.001
Intubated at study entry	2.96 (0.73 to 12.06)	0.13
MAP ≤ 70 mm Hg	1.82 (0.17 to 19.1)	0.62
Corticosteroid treatment	1.71 (0.57 to 5.16)	0.34
Peripheral white cell count	1.08 (0.96 to 1.23)	0.22
Lymphocyte count	3.65 (1.25 to 10.60)	0.02

Abbreviations: BMI – body mass index. MAP – mean arterial pressure.