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Effectiveness and safety of Ivermectin in COVID-19 patients: A prospective study at a safety-net hospital

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Abstract

Ivermectin has been found to inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in vitro. It is unknown whether this inhibition of SARS-CoV-2 replication correlates with improved clinical outcomes. To assess the effectiveness and safety of ivermectin in hospitalized patients with COVID-19. A total of 286 patients with COVID-19 were included in the study. Univariate analysis of the primary mortality outcome and comparisons between treatment groups were determined. Logistic regression and propensity score matching (PSM) was used to adjust for confounders. Patients in the ivermectin group received 2 doses of Ivermectin at 200 μg/kg in addition to usual clinical care on hospital Days 1 and 3. The ivermectin group had a significantly higher length of hospital stay than the control group; however, this significance did not maintain on multivariable logistic regression analysis. The length of intensive care unit (ICU) stay and duration of mechanical ventilation were longer in the control group. However, a mortality benefit was not seen with ivermectin treatment before and after PSM (p values = 0.07 and 0.11, respectively). ICU admission, and intubation rate were not significantly different between the groups (p = 0.49, and p = 1.0, respectively). No differences were found between groups regarding the length of hospital stay, ICU admission, intubation rate, and in-hospital mortality.

KEYWORDS
COVID-19, efficacy, Ivermectin, prospective study, safety profile

1 | INTRODUCTION

Ivermectin is an antimicrobial used to treat parasitic and viral infections, including HIV, influenza, dengue, and Zika virus.[1-3] Recently, ivermectin was found to inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in vitro.[4] The antiparasitic and antiviral mechanisms of ivermectin are different from each other. Ivermectin showed a high binding affinity to the viral S protein,

human cell surface receptors ACE-2, and TMPRSS2.[5] Ivermectin was found to be docked between the viral spike and the ACE2 receptor.[6] This is achieved through its high affinity to the spike protein S1 binding domains of SARS-CoV-2, potentially limiting binding to the ACE-2 receptor or sialic acid receptors, preventing cellular entry of the virus, or preventing hemagglutination.[5] In addition, ivermectin has a binding activity to both the main protease (Mpro) and papain-like protease (PLpro) of SARS-CoV-2; thus, it plays a potential role in

inhibiting the posttranslational processing of viral polyproteins. Ivermectin may also be related to inhibiting nuclear transport. Previous studies reported that ivermectin inhibits IMPα/β1-mediated nuclear import of the N protein.[3,4,7,8] Additionally, the SARS-CoV-2 accessory protein ORF6 has a potential role in the antiviral action of the STAT1 transcription factor by sequestering IMP α/β1 on the rough ER/Golgi membrane.[9] Overall, these findings increased the hope that ivermectin's nuclear transport inhibitory action might be effective against SARS-CoV-2. In efforts to combat the COVID-19 pandemic and in light of limited therapeutic options, ivermectin was utilized off-label early on for treatment of COVID-19 based upon in vitro studies.

To date, there is conflicting data on whether this inhibition of SARS-CoV-2 entry correlates with improved clinical outcomes. The concentrations tested in reported in-vitro assays are equivalent to more than 50-fold the normal C-max achieved with a standard single dose of ivermectin 200 μg/kg. The main concern is that standard doses of ivermectin show a lack of efficacy and tolerability in COVID-19 patients.[10] The most common reported side effects of ivermectin include elevation in transaminases, nausea, diarrhea, dizziness, decreased leukocyte count, allergic reactions, and ocular impairment.[11]

Several studies have been conducted to investigate the clinical outcomes of patients with COVID-19 who received ivermectin treatment. Recent retrospective studies reported that ivermectin treatment in different dose modalities in hospitalized patients had lower mortality than those who did not receive ivermectin.[12,13] There is a lack of randomized controlled trials to support the use of ivermectin in COVID-19 patients. More than a year after the start of the pandemic, a therapeutic medication that would limit the mortality and the course of infection is greatly needed. Therefore, the purpose of this prospective study is to assess the effectiveness and safety profile of ivermectin in addition to standard treatment in hospitalized patients with COVID-19.

2 | MATERIALS AND METHODS

2.1 | Design, setting, and participants

This prospective observational study included 286 patients with COVID-19. Patients were evaluated for inclusion in the study upon admission to the medical or critical care units during the study period of December 2020 and March 2021. Patients were included in the study if they were at least 18 years old, a positive SARS-CoV-2 real-time polymerase chain reaction test, diagnosed with COVID-19 pneumonia, able to be administered ivermectin within 48 h of admission, and provided consent. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Capital Health Regional Medical Center. Two physicians independently verified the data accuracy. The study investigators monitored the patients during the hospital stay and collected all data prospectively. Patients were excluded, If they

had known allergy to ivermectin or some of the components of ivermectin tablets, presence of mal-absorptive syndrome, known history of severe liver disease, need or use of antiviral drugs at the time of admission for another viral pathology other than COVID-19, use of ivermectin up to 7 days before the study, current participation or in the last 30 days in a research study that has included the administration of a drug, current usage of any medication which has strong interaction with CYP3A4 enzymes. In addition, pregnant or breastfeeding female patients were excluded from the study. Epidemiological and demographic information, medical history, co-morbidities, clinical symptoms at admission, treatments, and interventions, including the need for oxygen or invasive mechanical ventilation support during the hospital course, were prospectively collected.

Patients were categorized into two treatment groups based on whether they receive ivermectin plus standard therapy or standard therapy only during the hospitalization. Standard of care alone for COVID-19 consisted of remdesivir 200 mg on Day 1, then 100 mg on Days 2–5, dexamethasone 6 mg PO daily for 10 days OR methyl-prednisolone 0.5 mg/kg q12h, and anticoagulation based on hospital's protocol. We offered the ivermectin treatment to all eligible patients and enrolled those who accepted and signed the informed consent. Patients in the ivermectin group received a total of two doses of ivermectin at 200 μg/kg (maximum dose of 21 mg) in addition to usual clinical care on Days 1 and 3. Informed consent was collected from all patients before enrolling them in the study.

2.2 | Primary and secondary outcomes

The primary endpoint was the comparison of clinical outcomes, measured by the rate of intubation, length of hospital stay, and mechanical ventilation duration. The secondary endpoint was drug safety outcomes (mainly neurological, cutaneous, GI, and ocular), the occurrence of the adverse events requiring discontinuation of the treatment, and clinical and laboratory improvement. The research question was framed before the data collection and database creation.

Venous blood samples for standard biochemistry analysis were collected on admission and during hospitalization based upon the patient's clinical conditions. The age-adjusted Charlson comorbidity index was calculated to assess the comorbidity burden. The severity of pulmonary involvement was evaluated at baseline data collection based on their initial oxygen requirements as nasal cannula up to 6 L, nonrebreather (NRB) Venturi mask or High flow, and mechanical ventilation.

Other variables evaluated as potential confounders were defined. Covariates that could be associated with the outcome was chosen based on clinical judgment and on previously published studies: age, sex, comorbidities assessed by Charlson comorbidity index, the severity of disease evaluated by FiO_2 requirement, white blood cell count (WBC), lymphocytes, platelets count, lactate dehydrogenase (LDH), D-dimer, procalcitonin, fibrinogen, C-reactive

TABLE 1 Baseline characteristics for Ivermectin and control groups before and after propensity score matching

Characteristics	Before propensity score matching			After propensity score matching		
	Ivermectin (%) 60 (21.0)	Control (%) 226 (79.0)	p value	Ivermectin (%) 60 (50.0)	Control (%) 60 (50.0)	p value
Age at diagnosis (median)	66 (19–93)	68 (21–93)	0.48	66 (19–93)	67 (28–91)	0.69
Gender			0.54			0.85
Male	34 (56.7)	118 (52.2)		34 (56.7)	33 (55.0)	
Female	26 (43.3)	108 (47.8)		26 (43.3)	27 (45.0)	
Race			0.53			0.68
White	27 (45.0)	104 (46.0)		27 (45.0)	33 (55.0)	
Hispanic	9 (15.0)	20 (8.8)		9 (15.0)	6 (10.0)	
African American	21 (35.0)	86 (38.1)		21 (35.0)	19 (31.7)	
Asian	3 (5.0)	16 (7.1)		3 (5.0)	2 (3.3)	
Insurance status			<0.001			<0.001
Self pay/charity	3 (5.0)	15 (6.6)		3 (5.0)	4 (6.7)	
Medicare Trad	18 (30.0)	0 (0.0)		18 (30.0)	0 (0.0)	
Medicare MGD	12 (20.0)	177 (78.3)		12 (20.0)	51 (85.0)	
Medicaid Trad	3 (5.0)	24 (10.6)		3 (5.0)	2 (3.3)	
Commercial	24 (40.0)	10 (4.4)		24 (40.0)	3 (5.0)	
Comorbidity score			0.15			0.98
0	18 (30.0)	92 (40.7)		18 (30.0)	17 (28.3)	
1	18 (30.0)	71 (31.4)		18 (30.0)	18 (30.0)	
2+	24 (40.0)	63 (27.9)		24 (40.0)	25 (41.7)	
Clinical presentation						
Fever	21 (35.0)	57 (25.2)	0.13	21 (35.0)	16 (26.7)	0.32
Dyspnea	44 (73.3)	141 (62.4)	0.12	44 (73.3)	41 (68.3)	0.55
Cough	34 (56.7)	97 (42.9)	0.057	34 (56.7)	28 (46.7)	0.27
Abdominal symptom	13 (21.7)	27 (11.9)	0.054	13 (21.7)	6 (10.0)	0.08
Symptom onset (within 10 days)	49 (83.1)	192 (85.3)	0.66	49 (83.1)	45 (76.3)	0.36
Complications						
PE/DVT	8 (13.3)	20 (8.8)	0.30	8 (13.3)	5 (8.3)	0.38
Bacterial PNA	26 (43.3)	64 (28.3)	**0.026**	26 (43.3)	14 (23.3)	**0.02**
ACS	2 (3.3)	9 (4.0)	0.81	2 (3.3)	2 (3.3)	1.0
CVA	1 (1.7)	0 (0.0)	–	1 (1.7)	0 (0.0)	–
VT/Vfib	2 (3.3)	3 (1.3)	0.29	2 (3.3)	0 (0.0)	–
AKI	13 (21.7)	41 (18.1)	0.54	13 (21.7)	12 (20.0)	0.82
Treatments						
Remdesivir	38 (63.3)	126 (55.8)	0.29	38 (63.3)	36 (60.0)	0.71
Conv plasma	4 (6.7)	21 (9.3)	0.52	4 (6.7)	9 (15.0)	0.14
Toculizimab	8 (13.3)	4 (1.8)	<0.001	8 (13.3)	0 (0.0)	**0.006**
Anticoagulation			<0.001			0.05

TABLE 1 (Continued)

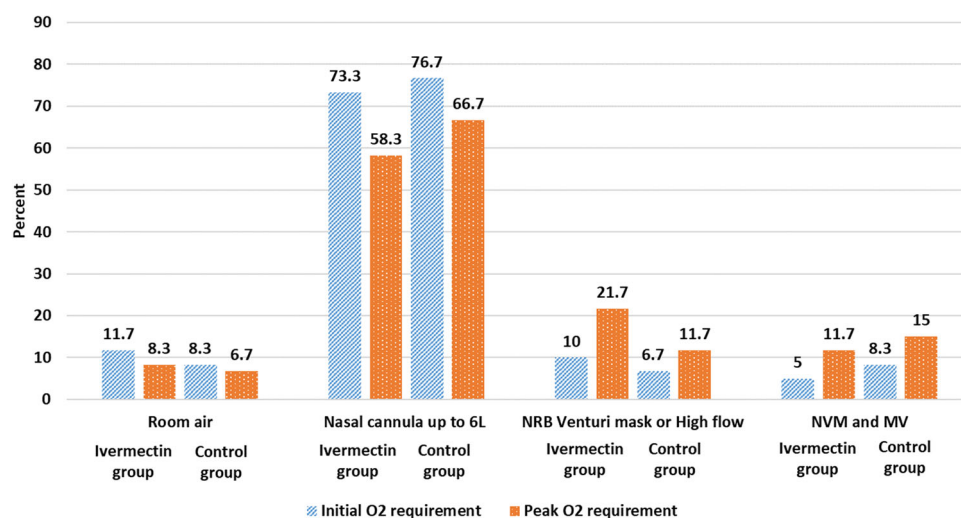|	Before propensity score matching			After propensity score matching		
	Ivermectin (%)	Control (%)		Ivermectin (%)	Control (%)	
Characteristics	60 (21.0)	226 (79.0)	p value	60 (50.0)	60 (50.0)	p value
None or prophylactic	35 (58.3)	183 (81.0)		35 (58.3)	45 (75.0)	
Therapeutic	25 (41.7)	43 (19.0)		25 (41.7)	15 (25.0)	
Dexameth	46 (76.7)	172 (76.1)	0.93	46 (76.7)	48 (80.0)	0.66
Methylpred	28 (46.7)	92 (40.7)	0.41	28 (46.7)	27 (45.0)	0.86
Antibiotics	28 (46.7)	127 (56.2)	0.19	28 (46.7)	34 (56.7)	0.27
Pressors	3 (5.0)	19 (8.4)	0.59	3 (5.0)	8 (13.3)	0.11
Proning	1 (1.7)	0 (0.0)	–	1 (1.7)	0 (0.0)	–
Discharge status			0.076			0.11
Home	49 (81.7)	154 (68.1)		49 (81.7)	41 (68.3)	
Expired	2 (3.3)	26 (11.5)		2 (3.3)	8 (13.3)	
Others	9 (15.0)	46 (20.4)		9 (15.0)	11 (18.3)	

FIGURE 1 Initial and peak oxygen requirement for ivermectin and control groups after propensity score matching. MV, mechanical ventilation; NRB, nonrebreather mask; NVM, noninvasive mechanical ventilation

protein (CRP) on admission was considered as potential confounders and was collected and included in the propensity score matching analysis. Data were collected via an electronic medical record system, and side effects were monitored by the investigator's daily examination.

2.3 | 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 or Fisher exact test for categorical variables. According to their distribution, continuous variables were reported as mean ± SD and medians with interquartile ranges (IQRs). The Kolmogorov–Smirnov test was used to assess the normality of distributions.

Logistic regression and propensity score matching were used to adjust for confounders. Multivariate analysis was performed using binary logistic regression to adjust for confounders between-group differences. Patient variables included in the analysis were age, gender, comorbidities assessed by Charlson comorbidity index, the severity of disease evaluated by FiO_2 requirement, WBC, lymphocytes, platelets count, LDH, D-dimer, procalcitonin, fibrinogen, CRP, a prior plausibility, and documented associations with mortality from previous studies.

TABLE 2 Laboratory findings for ivermectin and control groups before and after propensity score matching

Characteristics	Before propensity score matching			After propensity score matching		
	Ivermectin (%) 60 (21.0)	Control (%) 226 (79.0)	p value	Ivermectin (%) 60 (50.0)	Control (%) 60 (50.0)	p value
Laboratory findings						
Ferritin	560 (25–4586)	382 (17–6517)	0.05	560 (25–4586)	473 (20–2678)	0.57
Lactate dehyrogenase (LDH)	368 (148–2092)	333 (56–3672)	0.18	368 (148–2092)	325 (140–3672)	0.24
Brain natriuretic peptide (BNP)	322 (3–63946)	752 (18–176510)	0.07	322 (3–63946)	817 (18–176510)	0.24
Troponin	0.012 (0–6.9)	0.012 (0–8.9)	0.10	0.012 (0–6.9)	0.012 (0–8.9)	0.30
Sodium	136 (127–146)	136 (121–157)	0.38	136 (127–146)	137 (127–157)	0.25
Aspartate aminotrnsferase (AST)	46 (16–1494)	50 (19–634)	0.67	46 (16–1494)	48 (19–449)	0.70
Alanine aminotransferase (ALT)	30 (10–188)	37 (6–556)	0.23	30 (10–188)	32 (6–556)	0.87
Procalcitonin	0.16 (0–30)	0.23 (0–37)	0.13	0.16 (0–30)	0.25 (0.03–10.2)	0.16
C-reactive protein (CRP)	6.9 (0–38)	6.2 (0–53)	0.29	6.9 (0–38)	6.7 (0.6–39)	0.96
Fibrinogen	601 (38–880)	591 (113–1404)	0.79	601 (38–880)	613 (113–1134)	0.44
D-dimer	1.15 (0–20)	1.23 (0–20)	0.54	1.15 (0–20)	1.26 (0.32–20)	0.45
WBC	7.1 (1.7–92.9)	6.5 (1.8–25.7)	0.94	7.1 (1.7–92.9)	7.2 (1.8–25.7)	0.45
Lymphocytes	8 (0–35)	12.9 (0–304)	**<0.001**	8 (0–35)	12.0 (0.6–37)	**0.002**
Neutrophils	54.2 (1–85)	5.0 (1–87)	**<0.001**	54.2 (1–85)	5.7 (1.5–87)	**<0.001**
Platelets	201 (78–552)	203 (24–505)	0.58	201 (78–552)	203 (55–448)	0.84

We performed the propensity score matching analysis using the R software with the nearest-neighbor algorithm without replacement. According to reporting guidelines on PS analysis, the PS method attempts to balance treated and nontreated groups to reduce confounding by indication in observational designs, thereby creating a quasi-randomized experiment. Propensity score-matched cohorts (1:1 matching ratio) were built. Each patient receiving the Ivermectin treatment was matched with a patient among those admitted at the same period and treated with standard care.

Statistical significance was established at $p < 0.05$. All reported p values were two-tailed. The results were analyzed using statistical software packages (SPSS 22.0, IBM; and R 3.5.1).

2.4 | Role of the funding source

This study has no internal or external funders. No funders role in the design of the study; collection, analysis, or interpretation of the data; or the decision to submit the article for publication.

3 | RESULTS

3.1 | Patients characteristics

A total of 286 patients were included in the study; 60 (21%) patients received ivermectin. In the ivermectin group, the median age was

66 years (IQR: 19–93), 34 (56.7%) patients were male, and the most common race was White (27 patients, 45%), followed by African American (21 patients, 35%) and Hispanic (9 patients, 15%). Most patients had Medicare (50%) and commercial (40%) insurances. In the Ivermectin group, 18 (30%) patients had no comorbidities at the time of diagnosis, while 24 (40%) patients had a comorbidity score of ≥2. Similarly, 17 patients (28.3%) had no comorbidities in the control group and a comorbidity score of ≥2 in 25 patients (41.7%). The comorbidity score did not show a statistical difference between ivermectin and control groups ($p = 0.98$). The most common clinical presentations were dyspnea (44 patients, 73%) and cough (34 patients, 57%), followed by fever (21 patients, 35%) and abdominal symptoms (13 patients, 22%) (Table 1). A total of 49 (83%) patients in the ivermectin group presented with these symptoms within 10 days of diagnosis. A total of 53 (88%) patients required supplemental oxygen therapy, most patients received through nasal cannula up to 6 L (73%), followed by NRB Venturi mask or High flow (10%), and mechanical ventilation (5%) (Figure 1). The median lymphocyte count was higher in the control group (12 vs. 8, $p = 0.002$), while the median neutrophil count was higher in the ivermectin group (54.2 vs. 5.7, $p < 0.001$). Laboratory findings were summarized in Table 2.

3.2 | Primary and secondary outcomes

Ivermectin and control groups were well balanced after 1:1 propensity score matching adjusted by the age of diagnosis, gender, comorbidity
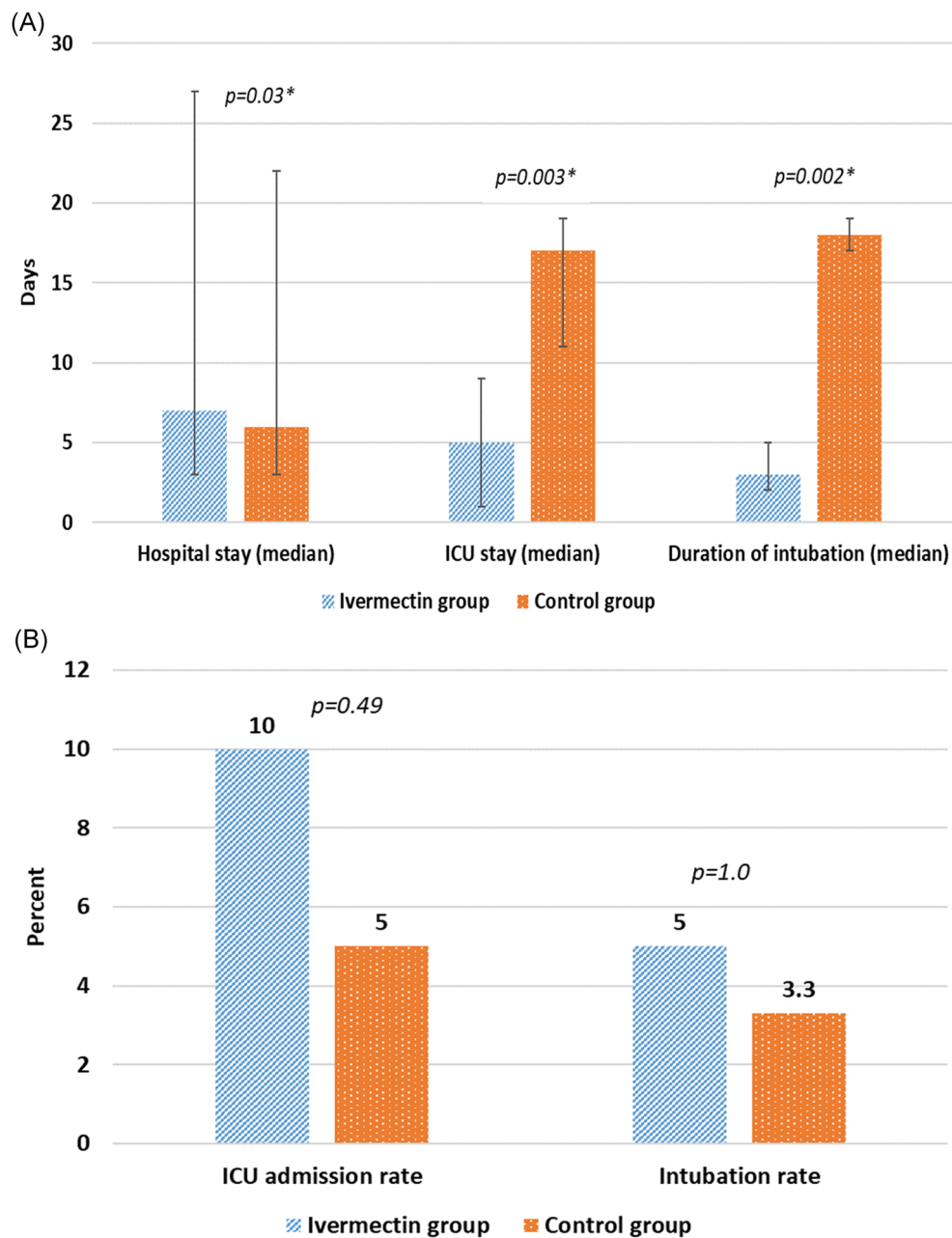
(A)

(B)

FIGURE 2 (A) Median days of hospital stay\, intensive care unit (ICU), and duration of intubation by ivermectin and control groups (B) Rate of ICU admission and intubation by ivermectin and control groups (after propensity score matching)

TABLE 3 Multivariable logistic regression analysis to assess the relationship between the patients who received Ivermectin and variables

Characteristics	OR (95% CI)	p value
Hospital stay[a]	1.09 (0.99–1.22)	0.09
ICU admission[a] (Referance: None)	0.50 (0.09–2.71)	0.42
Intubation[a] (Referance: None)	0.87 (0.11–6.62)	0.20

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]After propensity score matching, adjusted by the age of diagnosis, gender, FiO_2 requirement, white blood count, platelets, LDH, D-dimer, Fibrinogen, and CRP.

score, FiO_2 requirement, WBC, platelets, LDH, D-dimer, Fibrinogen, and CRP (standardized differences were less than 0.1). In the univariate analysis, the ivermectin group had a significantly higher length of hospital stay than the control group (median, 7 vs. 6 days, $p = 0.03$) (Figure 2A). This significance was not maintained on multivariable logistic regression analysis (odds ratio [OR]: 1.09, 95% confidence interval [CI]: 0.99–1.22; $p = 0.09$) (Table 3). The length of intensive care unit (ICU) stay (median, 5 vs. 17 days, $p = 0.003$), and duration of mechanical ventilation (median, 3 vs. 18 days, $p = 0.002$) were longer in the control group (Figure 2A). ICU admission, and intubation rate were not significantly different between the groups ($p = 0.49$, and $p = 1.0$, respectively) (Figure 2B). Also, in the univariate analysis, we did not show the mortality benefit of ivermectin

treatment before and after propensity score matching (p values = 0.07 and 0.11, respectively) (Table 1).

The ivermectin group was more likely to have bacterial pneumonia complications compared to the control group (43% vs. 23%, p = 0.02). Eight patients had a pulmonary embolism or deep vein thrombosis in the ivermectin group, and the ivermectin group more frequently received therapeutic anticoagulation therapy than the control group. In addition, 13 patients had acute kidney injury in the ivermectin group. There were no adverse events that occurred in the ivermectin group.

4 | DISCUSSION

In this prospective observational cohort study, we reported the effectiveness and safety of ivermectin in addition to standard treatment compared to standard therapy alone in hospitalized patients with laboratory-confirmed COVID-19 infection. Also, demographic, clinical, and laboratory findings, as well as treatment outcomes, were reported. In our population, we did not observe a significant association of a two doses modality of 200 μg/kg of ivermectin with improved survival before or after propensity score matching. In terms of the primary endpoints of our study, the ivermectin group had a significantly higher length of hospital stay than the control group; however, this significance was not maintained on multivariable logistic regression analysis after adjustment for comorbidities and main confounders (Table 3). The possible explanations could include delays in discharging patients to other facilities, including inpatient rehabilitation centers and skilled nursing facilities. Also, the ivermectin group had a significantly higher bacterial infection rate which can cause longer hospital stay in that group.

In particular, the length of ICU stay was longer in the control group compared to the ivermectin arm (Figure 2A). Similarly, Rajter et al. reported a trend of higher efficacy of ivermectin in patients who required higher inspired oxygen or ventilatory support.[12] On the other hand, we did not observe a significant difference in ICU admission, intubation rate, and duration of mechanical ventilation between the groups (Figure 2B). These findings were confirmed after multivariate adjustment for comorbidities and differences between groups and a propensity score-matched cohort (Table 3). In terms of laboratory findings of both groups, inflammatory, infectious and coagulation markers were well adjusted and there were no statistical differences between groups before and after propensity score matching except the median lymphocyte and neutrophil counts (Table 2).

To date, several studies have been conducted to investigate the clinical outcomes of ivermectin treatment with different dosing and interval modalities. A randomized, double-blind, placebo-controlled study by Ahmed et al.[14] compared 5 days of 12 mg ivermectin daily treatment alone to ivermectin plus doxycycline versus placebo. In their study, a 5-day course of ivermectin showed earlier virological clearance versus placebo (9.7 vs. 12.7 days; p = 0.02). Another retrospective study by Rajter et al.[12] compared two doses of 200 μg/kg

ivermectin treatment in addition to usual clinical care on Days 1 and 7 plus standard therapy versus standard therapy only. They reported a lower mortality rate in the ivermectin group (15.0% vs 25.2%; OR: 0.52; 95% CI: 0.29–0.96; p = 0.03).

Our study used two doses regimen of 200 μg/kg, with no ivermectin-related adverse events observed. Recent studies have evaluated ivermectin doses up to 800 μg/kg, given in a single dose or three consecutive days, and reported good safety profiles.[15–17] A meta-analysis of the safety profile of higher doses of ivermectin showed no increased risk of adverse events with higher ivermectin doses compared to 200 or 400 μg/kg.[1] To date, the most optimal dose of ivermectin that balances efficacy with tolerability remains unknown.

Our findings are important additions to the limited evidence of ivermectin treatment efficacy in COVID-19 patients during the current pandemic. However, the study also has some limitations. Although it's a prospective cohort, given the observational design of the study, possible residual confounding factors could bias the results of the study. Potential confounders were carefully addressed by selection of a matched control group and propensity score matching. Also, possible differences between groups might not be detected due to the small sample size. Further randomized controlled clinical trials of ivermectin treatment are warranted to validate these important findings.

5 | CONCLUSIONS

Our study did not find a difference in duration of hospitalization, intubation rate, or mortality when a two-dose ivermectin regimen was added to standard therapy of remdesivir, steroids, and anticoagulation for the treatment of COVID-19. Appropriately designed randomized clinical trials with higher doses of ivermectin should be conducted to validate the impact of Ivermectin in patients with COVID-19 infection.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Concept: Muhammet Ozer, Suleyman Yasin Goksu, Reena Conception, Esad Ulker, Rodolfo Magallanes Balderas, Mohammed Mahdi, Manish Gugnani, Marc Whitman; Design: Muhammet Ozer, Suleyman Yasin Goksu, Reena Conception, Manish Gugnani, Marc Whitman; Supervision: Marc Whitman, Rajashree Anandakrishnan, Manish Gugnani; Resources: Muhammet Ozer, Suleyman Yasin Goksu, Reena Conception, Esad Ulker, Rodolfo Magallanes Balderas, Zulfiya Manning; Materials: Muhammet Ozer, Suleyman Yasin Goksu, Reena Conception, Manish Gugnani, Marc Whitman; Data collection and/or processing: Muhammet Ozer, Reena Conception, Esad Ulker, Rodolfo

Magallanes Balderas, Zulfiya Manning, Kim To, Muhammad Effendi, Rajashree Anandakrishnan, Manish Gugnani, Marc Whitman; *Analysis and/or interpretation*: Muhammet Ozer, Suleyman Yasin Goksu, Reena Conception, Manish Gugnani, Marc Whitman; *Literature search*: Muhammet Ozer, Reena Conception, Esad Ulker, Rodolfo Magallanes Balderas, Zulfiya Manning, Kim To, Muhammad Effendi, Rajashree Anandakrishnan, Manish Gugnani, Marc Whitman; *Writing manuscript*: Muhammet Ozer, Suleyman Yasin Goksu, Reena Conception, Esad Ulker, Rodolfo Magallanes Balderas, Manish Gugnani, Marc Whitman; *Critical review*: Muhammet Ozer, Rajashree Anandakrishnan, Kim To, Marc Whitman, Manish Gugnani; *Other*: Esad Ulker, Rodolfo Magallanes Balderas, Mohammed Mahdi.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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