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

Muhammet Ozer1 | Suleyman Yasin Goksu2 | Reena Conception3 | Esad Ulker1 | Rodolfo Magallanes Balderas1 | Mohammed Mahdi1 | Zulfiya Manning1 | Kim To3 | Muhammad Effendi3 | Rajashree Anandakrishnan4 | Marc Whitman4 | Manish Gugnani5

1Department of Internal Medicine, Capital Health Medical Center, Trenton, New Jersey, USA
2Department of Internal Medicine, UT Southwestern Medical Center, Dallas, Texas, USA
3Department of Pharmacology, Capital Health Medical Center, Trenton, New Jersey, USA
4Department of Infectious Diseases, Capital Health Medical Center, Trenton, New Jersey, USA
5Department of Pulmonology and Critical Care, Capital Health Medical Center, Trenton, New Jersey, USA

Correspondence
Muhammet Ozer, Department of Internal Medicine, Capital Health Medical Center, Trenton, NJ 08638, USA.
Email: muh.ozer@gmail.com

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.\(^7\) 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 200μg/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, comorbidities, 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 methylprednisolone 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 FiO₂ requirement, white blood cell count (WBC), lymphocytes, platelets count, lactate dehydrogenase (LDH), D-dimer, procalcitonin, fibrinogen, C-reactive
| Characteristics          | Before propensity score matching | After propensity score matching |
|--------------------------|----------------------------------|----------------------------------|
|                          | Ivermectin (%)                  | Control (%)                      | Ivermectin (%) | Control (%) | p value | Ivermectin (%) | Control (%) | 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)   | 0.54    |
| Female                   | 26 (43.3)                       | 108 (47.8)                      | 26 (43.3)      | 27 (45.0)   | 0.53    |
| Race                     |                                  |                                  | 0.53           | 0.68        |
| White                    | 27 (45.0)                       | 104 (46.0)                      | 27 (45.0)      | 33 (55.0)   | 0.48    |
| Hispanic                 | 9 (15.0)                        | 20 (8.8)                        | 9 (15.0)       | 6 (10.0)    | 0.35    |
| African American         | 21 (35.0)                       | 86 (38.1)                       | 21 (35.0)      | 19 (31.7)   | 0.62    |
| Asian                    | 3 (5.0)                         | 16 (7.1)                        | 3 (5.0)        | 2 (3.3)     | 0.68    |
| Insurance status         |                                  |                                  | <0.001         | <0.001      |
| Self pay/charity         | 3 (5.0)                         | 15 (6.6)                        | 3 (5.0)        | 4 (6.7)     | <0.001 |
| Medicare Trad            | 18 (30.0)                       | 0 (0.0)                         | 18 (30.0)      | 0 (0.0)     | <0.001 |
| Medicare MGD            | 12 (20.0)                       | 177 (78.3)                      | 12 (20.0)      | 51 (85.0)   | <0.001 |
| Medicaid Trad            | 3 (5.0)                         | 24 (10.6)                       | 3 (5.0)        | 2 (3.3)     | <0.001 |
| Commercial              | 24 (40.0)                       | 10 (4.4)                        | 24 (40.0)      | 3 (5.0)     | <0.001 |
| Comorbidity score        |                                  |                                  | 0.15           | 0.98        |
| 0                        | 18 (30.0)                       | 92 (40.7)                       | 18 (30.0)      | 17 (28.3)   | 0.15    |
| 1                        | 18 (30.0)                       | 71 (31.4)                       | 18 (30.0)      | 18 (30.0)   | 0.15    |
| 2+                       | 24 (40.0)                       | 63 (27.9)                       | 24 (40.0)      | 25 (41.7)   | 0.15    |
| 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                          |                                  |                |             |

(Continues)
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 χ² 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 FiO₂ requirement, WBC, lymphocytes, platelets count, LDH, D-dimer, procalcitonin, fibrinogen, CRP, a prior plausibility, and documented associations with mortality from previous studies.

| Characteristics | Before propensity score matching | | After propensity score matching |
|-----------------|---------------------------------|-----------------|---------------------------------|
|                 | Ivermectin (%) | Control (%) | p value | Ivermectin (%) | Control (%) | p value |
| None or prophylactic | 35 (58.3) | 183 (79.0) | | 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 |

|                  | Before propensity score matching | | After propensity score matching |
|-----------------|---------------------------------|-----------------|---------------------------------|
|                 | Ivermectin (%) | Control (%) | p value | Ivermectin (%) | Control (%) | p value |
| Room air        | 11.7 | 8.3 | 6.7 | | | |
| Ivermectin group | 8.3 | 8.3 | 6.7 | | | |
| Control group | | | | | | |
| Nasal cannula up to 6L | 73.3 | 76.7 | | | |
| Ivermectin group | 58.3 | 66.7 | | | |
| Control group | | | | | | |
| NRB Venturi mask or High flow | 10 | 21.7 | | | |
| Ivermectin group | 6.7 | 11.7 | | | |
| Control group | | | | | | |
| NVM and MV | 5 | 11.7 | 8.3 | 15 | | |

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

TABLE 1 (Continued)
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...
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.

| Characteristics      | OR (95% CI)       | \( p \) value |
|----------------------|-------------------|--------------|
| Hospital stay         | 1.09 (0.99–1.22)  | 0.09         |
| ICU admission         | 0.50 (0.09–2.71)  | 0.42         |
| Intubation            | 0.87 (0.11–6.62)  | 0.20         |

Abbreviations: CI, confidence interval; OR, odds ratio.

*After propensity score matching, adjusted by the age of diagnosis, gender, \( \text{FiO}_2 \) requirement, white blood count, platelets, LDH, D-dimer, Fibrinogen, and CRP.

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.

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

---

**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).
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.13 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.

FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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
DATA AVAILABILITY STATEMENT

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

ORCID

Muhammet Ozer http://orcid.org/0000-0002-9579-1372

REFERENCES

1. Navarro M, Camprubí D, Requena-Méndez A, et al. Safety of high-dose ivermectin: a systematic review and meta-analysis. J Antimicrob Chemother. 2020;75(4):827-834.

2. Boldescu V, Behnam M, Vasilakis N, Klein CD. Broad-spectrum agents for flaviviral infections: dengue, Zika and beyond. Nat Rev Drug Discovery. 2017;16(8):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(3):551-556.

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. Eweas AF, Alhossary AA, Abdel-Moneim AS. Molecular docking reveals Ivermectin and Remdesivir as potential repurposed drugs against SARS-CoV-2. Front Microbiol. 2021;11:3602.

6. Lehrer S, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2. In Vivo. 2020;34(5):3023-3026.

7. Timani KA, Liao Q, Ye L, et al. Nuclear/nucleolar localization properties of C-terminal nucleocapsid protein of SARS coronavirus. Virus Res. 2005;114(1-2):23-34.

8. Yang S, Atkinson SC, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res. 2020;177:104760.

9. Rowland RR, Chauhan V, Fang Y, Pekosz A, Kerrigan M, Burton MD. Intracellular localization of the severe acute respiratory syndrome coronavirus nucleocapsid protein: absence of nucleolar accumulation during infection and after expression as a recombinant protein in vero cells. J Virol. 2005;79(17):11507-11512.

10. Camprubí D, Almuedo-Riera A, Martí-Soler H, et al. Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients. PLoS One. 2020;15(11):e0242184.

11. Muñoz J, Ballester MR, Antonijoan RM, et al. Safety and pharmacokinetic profile of fixed-dose ivermectin with an innovative 18mg tablet in healthy adult volunteers. PLoS Neglected Trop Dis. 2018;12(1):e0006020.

12. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. Use of ivermectin is associated with lower mortality in hospitalized patients with Coronavirus Disease 2019: The ivermectin in COVID nineteen study. Chest. 2021;159(1):85-92.

13. Kory P, Meduri GU, Iglesias J, et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. 2020;28(3):e299-e318.

14. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2021;103:214-216.

15. Wimmersberger D, Coulibały JT, Schulz JD, et al. Efficacy and safety of ivermectin against Trichuris trichiura in preschool-aged and school-aged children: a randomized controlled dose-finding trial. Clin Infect Dis. 2018;67(8):1247-1255.

16. Smit MR, Ochomo EO, Aljayyoussi G, et al. Human direct skin feeding versus membrane feeding to assess the mosquitocidal efficacy of high-dose Ivermectin (IVERMAL Trial). Clin Infect Dis. 2019;69(7):1112-1119.

17. Kamng J, Gardon J, Gardon-Wendel N, Demanga-Ngangu, Duke BO, Boussinesq M. Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. Trans R Soc Trop Med Hyg. 2004;98(8):496-504.

How to cite this article: Ozer M, Goksu SY, Conception R, et al. Effectiveness and safety of Ivermectin in COVID-19 patients: A prospective study at a safety-net hospital. J Med Virol. 2022;94:1473-1480. doi:10.1002/jmv.27469