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ORIGINAL ARTICLE

# Does ivermectin reduce COVID-19 mortality and progression of disease severity? – A retrospective study.

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**ABSTRACT… Objective:** To investigate the efficacy of ivermectin in the treatment of mild, moderate, and severe COVID-19 infection. **Study Design:** Retrospective Cohort study. **Setting:** COVID-19 Treatment Centre, Dr. Ruth K M Pfau Civil Hospital Karachi. **Period:** July 2020 to December 2020. **Material & Methods:** Medical records of 423 patients during a selected duration of 6 months were reviewed. Patients were stratified into two groups based on whether or not they received a 6-day course of ivermectin in addition to the standard treatment for COVID-19. Primary outcome measures were rate of mortality, days from the start of treatment to negative SARS-CoV-2 PCR, and rate of step-up to the intensive care unit. **Results:** Patients who received ivermectin required a lesser number of days (8.39 days ± 2.04) to become COVID negative than the patients who didn't receive ivermectin (20.38 days ± 6.32), ($p < 0.001$). Multinomial logistic regression showed that the patients who were given ivermectin for COVID 19 infection were four times more likely to be discharged home than stepping up to ICU. The ICU step-up rate in the ivermectin group was found to be 3.7% compared to 13.04% in the non-ivermectin group. No significant differences in mortality were found. **Conclusion:** Treatment with ivermectin in COVID-19 infection is associated with improved outcomes in terms of reduction in duration of illness as well as the progression of disease severity.

**Key words:** Ivermectin, COVID-19, SARS-CoV-2, Mortality.

## INTRODUCTION

The global health emergency; COVID-19 struck 213 countries, affecting more than 47 million people all across the world as of November 2020 with more than 1.2 million deaths attributed to this pandemic.[1] National Institutes of Health(NIH) categorize COVID-19 infection into asymptomatic or presymptomatic infection, mild illness, moderate illness, severe illness, and critical illness based on the severity of symptoms, chest imaging, the saturation of oxygen on room air, and multi-organ involvement.[2] Despite the precise characterization of the disease course and gradation of its severity, however, the world is still in search of an optimal treatment regimen for this disease. Several therapeutic agents have been identified to be of potential benefit in its treatment and many more are anticipated to make their way into the list.[3] However no single option can be stated better than another as of yet.[3] The paramount agents in this exhaustive list that have earned more discussions include azithromycin, hydroxychloroquine, chloroquine, tocilizumab, remdesivir, interferons, methylprednisolone, and ivermectin.[3]

Ivermectin, primarily an antiparasitic drug surprisingly has shown significant anti-viral activity against human immunodeficiency virus, dengue virus, and most importantly the coronavirus; SARS-CoV-2.[4,5] The proposed mechanism of action by which ivermectin seems to show its anti-viral efficacy is the inhibition of Impα/β1 heterodimer which prevents translocation of

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viral proteins into the nucleus. This promotes cellular anti-viral responses by attenuating their inhibition from viral transcription.[5] Several other mechanisms of anti-viral activity have also been proposed for ivermectin.[6,7] Despite the controversy about the high dose of ivermectin that is required for anti-viral efficacy against SARS-CoV-2 which seems impractical to administer without producing severe toxicity, an animal study has shown the accumulation of ivermectin in sufficient concentration in multiple body tissues importantly including the lungs several days after administration.[5,8] A hospital-based matched case-control study conducted in India evaluated the role of ivermectin in the prevention of COVID-19 infection among health care workers. It was shown that two-dose ivermectin prophylaxis at a dose of 300 mcg/kg with an interval of 72 hours produced a 73% reduction in the incidence of COVID-19 infection.[9] The only reported study to our knowledge evaluating the role of ivermectin in the actual treatment of COVID-19 infection was conducted by Rajter JC et al, which demonstrated a significant absolute reduction in the mortality of COVID-19 infected patients.[10]

It is evident that there is a severe scarcity of data as well as a dire need to investigate ivermectin's role in the treatment of COVID-19 infection. Our study aims to evaluate the efficacy of ivermectin in the treatment of mild, moderate, and severe COVID-19 infection.

## MATERIAL & METHODS

The medical records of all patients admitted at the COVID-19 Treatment Centre, Civil Hospital Karachi with the diagnosis of COVID-19 infection were reviewed during the six-month period of July 2020 to December 2020. All information was obtained by chart reviews. Patients of either sex aged 18 years or above with mild, moderate, or severe COVID-19 infection as described by the National Institute of Health (NIH) were included in the study. Patients aged less than 18 years, asymptomatic patients who tested positive for SARS-CoV-2 on nasopharyngeal PCR, and those with critical COVID-19 infection (as described by NIH) at the time of presentation were excluded from the study. The following NIH definitions were used to stratify the patients based on the severity of infection:-

- Asymptomatic infection- Individuals who test positive for SARS-CoV-2 using a virologic test without any symptoms of the infection.
- Mild infection- Individuals who have signs and symptoms of COVID-19 without any shortness of breath or abnormal chest imaging.
- Moderate infection- Individuals who have signs and symptoms of COVID-19 infection along with shortness of breath or lung infiltrates involving less than 50 % of the lung field with oxygen saturation ≥ 94 % on room air
- Severe infection- Individuals who have signs and symptoms of COVID-19 infection along with shortness of breath, lung infiltrates involving more than 50% of the lung field with oxygen saturation < 94 % on room air.
- Critical infection- Individuals who have signs and symptoms of COVID-19 infection along with respiratory failure, septic shock, and/or multi-organ dysfunction.

The study participants were divided into two groups; one that received ivermectin and the other that did not receive ivermectin. The ivermectin group received a 12-milligram once-daily oral dose of ivermectin in the form of tablets for 6 days in addition to the standard therapy which is described below. The non-ivermectin group only received the standard therapy. The standard therapy is detailed as follows:-

- Mild infection- A 7-day course of azithromycin (1000mg 1st dose followed by 500 mg orally once daily for 6 days).
- Moderate infection- A 7 days course of azithromycin (1000mg 1st dose followed by 500 mg orally once daily for 6 days), 5 days course of remdesivir (200 mg 1st dose followed by 100 mg IV once daily for 4 days), 6 mg dexamethasone IV once daily till resolution of respiratory distress (resolution of tachypnea off oxygen with oxygen saturation equal to or greater than 95 % on room air).
- Severe infection- Same as for moderate infection.

The clinical efficacy of ivermectin was assessed

by reviewing death rate, worsening of disease severity (need for stepping up to ICU care), and the number of days it took for nasopharyngeal COVID-19 PCR to become negative in both groups.

Data were entered and analyzed by using the Statistical Package for the Social Sciences (SPSS) software, version 21. Categorical variables were reported as frequencies while continuous data as means and standard deviations. The chi-square test was performed to determine associations between the comorbidities of the patients and severity of COVID-19 infection, the comorbidities and subsequent outcome of the patients (discharge to home, death or stepping up to ICU), the severity of COVID-19 infection and subsequent outcome and the management offered to the infected patients (ivermectin or non -ivermectin group and their outcome. One-way ANOVAs were used to investigate whether the number of days it took for COVID PCR to become negative differed based on comorbidities of the patients, the severity of the infection and management offered to the patients. Multinomial logistic regression was used to determine the difference in the outcome of the infected patients based on the management given to the patients.

## RESULTS

During the above-mentioned 6 months period, 423 patients were included in our study while 107 patients were excluded as they did not meet the inclusion criteria. Out of these, 291 (68.8%) were males while 132 (31.2%) were females. The mean age of our study participants was 51.85 years. Around 40 % of patients in our study population presented with a triad of cough, fever, and shortness of breath, while around 30 % presented with cough and shortness of breath. Most patients in our study population presented with severe COVID-19 infection (45.6%), while 33.57 % had moderate severity, and 20.8 % patients presented with mild severity COVID-19 infection. Around 70 percent of our study population had some other co-morbid illness; most commonly diabetes mellitus, hypertension, and/or ischemic heart disease.

In the ivermectin group, there was a significant association between the comorbidities of the patients and severity of COVID-19 infection $X^2$ (16) = 61.689, $p < 0.001$ (Table-I), the comorbidities and subsequent outcome of the patients $X^2$ (16) = 43.226, $p < 0.001$ (Table-II), the severity of COVID-19 infection and subsequent outcome $X^2$ (4) = 12.163, $p < 0.016$ (Table-III). Table-III shows the outcome of the patients with mild, moderate, and severe COVID-19 infection treated with ivermectin.

In the non-ivermectin group there was a significant association between the comorbidities of the patients and severity of COVID-19 infection $X^2$ (16) = 59.405, $p < 0.001$ (Table-IV), the comorbidities and subsequent outcome of the patients $X^2$ (16) = 66.518, $p < 0.001$ (Table-V), the severity of COVID-19 infection and subsequent outcome $X^2$ (4) = 34.560, $p < 0.016$ (Table-VI). Table-VI shows the outcome of the patients with mild, moderate, and severe COVID-19 infection who were not treated with ivermectin.

| | | Severity | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mild | | Moderate | | Severe | | | |
| | | N | % | N | % | N | % | N | % |
| Comorbid | HTN | 0 | 0.0% | 10 | 13.9% | 14 | 14.0% | 24 | 11.1% |
| | DM | 6 | 13.6% | 4 | 5.6% | 8 | 8.0% | 18 | 8.3% |
| | IHD | 0 | 0.0% | 0 | 0.0% | 4 | 4.0% | 4 | 1.9% |
| | DM+HTN | 2 | 4.5% | 16 | 22.2% | 26 | 26.0% | 44 | 20.4% |
| | DM+IHD | 0 | 0.0% | 2 | 2.8% | 0 | 0.0% | 2 | 0.9% |
| | DM+HTN+IHD | 0 | 0.0% | 12 | 16.7% | 18 | 18.0% | 30 | 13.9% |
| | HTN+IHD | 0 | 0.0% | 4 | 5.6% | 2 | 2.0% | 6 | 2.8% |
| | Others | 8 | 18.2% | 10 | 13.9% | 6 | 6.0% | 24 | 11.1% |
| | None | 28 | 63.6% | 14 | 19.4% | 22 | 22.0% | 64 | 29.6% |
| Total | | 44 | 100.0% | 72 | 100.0% | 100 | 100.0% | 216 | 100.0% |

**Table-I. Crosstabulation between comorbidities and severity of infection**

| | | Outcome | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | | Discharge to Home | | Death | | Step up to ICU | | | |
| | | N | % | N | % | N | % | N | % |
| Comorbid | HTN | 22 | 10.7% | 0 | 0.0% | 2 | 25.0% | 24 | 11.1% |
| | DM | 18 | 8.7% | 0 | 0.0% | 0 | 0.0% | 18 | 8.3% |
| | IHD | 4 | 1.9% | 0 | 0.0% | 0 | 0.0% | 4 | 1.9% |
| | DM+HTN | 44 | 21.4% | 0 | 0.0% | 0 | 0.0% | 44 | 20.4% |
| | DM+IHD | 2 | 1.0% | 0 | 0.0% | 0 | 0.0% | 2 | 0.9% |
| | DM+HTN+IHD | 22 | 10.7% | 2 | 100.0% | 6 | 75.0% | 30 | 13.9% |
| | HTN+IHD | 6 | 2.9% | 0 | 0.0% | 0 | 0.0% | 6 | 2.8% |
| | Others | 24 | 11.7% | 0 | 0.0% | 0 | 0.0% | 24 | 11.1% |
| | None | 64 | 31.1% | 0 | 0.0% | 0 | 0.0% | 64 | 29.6% |
| Total | | 206 | 100.0% | 2 | 100.0% | 8 | 100.0% | 216 | 100.0% |

**Table-II. Crosstabulation between comorbidities and subsequent outcome**

| | | Outcome | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | | Discharge to Home | | Death | | Step up to ICU | | | |
| | | N | % | N | % | N | % | N | % |
| Severity | Mild | 44 | 21.4% | 0 | 0.0% | 0 | 0.0% | 44 | 20.4% |
| | Moderate | 72 | 35.0% | 0 | 0.0% | 0 | 0.0% | 72 | 33.3% |
| | Severe | 90 | 43.7% | 2 | 100.0% | 8 | 100.0% | 100 | 46.3% |
| Total | | 206 | 100.0% | 2 | 100.0% | 8 | 100.0% | 216 | 100.0% |

**Table-III. Crosstabulation between severity of the infection and subsequent outcome in the ivermectin group**

| | | Severity | | | | | |
|---|---|---|---|---|---|---|---|
| | | Mild | | Moderate | | Severe | |
| | | N | % | N | % | N | % |
| Comorbid | HTN | 0 | 0.0% | 10 | 14.3% | 13 | 14.0% |
| | DM | 6 | 13.6% | 4 | 5.7% | 7 | 7.5% |
| | IHD | 0 | 0.0% | 0 | 0.0% | 4 | 4.3% |
| | DM+HTN | 2 | 4.5% | 15 | 21.4% | 24 | 25.8% |
| | DM+IHD | 0 | 0.0% | 2 | 2.9% | 0 | 0.0% |
| | DM+HTN+IHD | 0 | 0.0% | 11 | 15.7% | 16 | 17.2% |
| | HTN+IHD | 0 | 0.0% | 4 | 5.7% | 2 | 2.2% |
| | Others | 8 | 18.2% | 10 | 14.3% | 6 | 6.5% |
| | None | 28 | 63.6% | 14 | 20.0% | 21 | 22.6% |
| Total | | 44 | 100.0% | 70 | 100.0% | 93 | 100.0% |

**Table-IV. Crosstabulation between comorbidities and severity of infection.**

| | | Outcome | | | | | |
|---|---|---|---|---|---|---|---|
| | | Discharge to Home | | Death | | Step up to ICU | |
| | | N | % | N | % | N | % |
| Comorbid | HTN | 16 | 10.0% | 3 | 15.0% | 4 | 14.8% |
| | DM | 13 | 8.1% | 0 | 0.0% | 4 | 14.8% |
| | IHD | 4 | 2.5% | 0 | 0.0% | 0 | 0.0% |
| | DM+HTN | 29 | 18.1% | 8 | 40.0% | 4 | 14.8% |
| | DM+IHD | 2 | 1.3% | 0 | 0.0% | 0 | 0.0% |
| | DM+HTN+IHD | 11 | 6.9% | 5 | 25.0% | 11 | 40.7% |
| | HTN+IHD | 2 | 1.3% | 0 | 0.0% | 4 | 14.8% |
| | Others | 24 | 15.0% | 0 | 0.0% | 0 | 0.0% |
| | None | 59 | 36.9% | 4 | 20.0% | 0 | 0.0% |
| Total | | 160 | 100.0% | 20 | 100.0% | 27 | 100.0% |

**Table-V. Crosstabulation between comorbidities and outcome.**

| | | Outcome | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | Discharge to Home | | Death | | Step up to ICU | | |
| | | N | % | N | % | N | % | N |
| Severity | Mild | 44 | 27.5% | 0 | 0.0% | 0 | 0.0% | 44 |
| | Moderate | 59 | 36.9% | 1 | 5.0% | 10 | 37.0% | 70 |
| | Severe | 57 | 35.6% | 19 | 95.0% | 17 | 63.0% | 93 |
| Total | | 160 | 100.0% | 20 | 100.0% | 27 | 100.0% | 207 |

**Table-VI. Crosstabulation between severity of infection and outcome in the non-ivermectin group.**

ANOVA showed no differences in the number of days for COVID PCR to become negative among different comorbidities F (8, 357) = 1.186, p = 0.307. Whilst, there was a significant difference in the number of days for COVID PCR to become negative among the three grades of severity of COVID 19 infection F (2, 363) = 21.159, p < 0.001. A Tukey post hoc test revealed that the number of days for COVID PCR to become negative was statistically significantly greater in severe infection (16.21 days ± 8.46) as compared to moderate infection (13.10 days ± 6.44, p = 0.02) and mild infection (10.11 days ± 5.00, p < 0.001). Further, there were also statistically significant differences between mild and moderate severity groups (p = 0.006). Additionally, there were statistically significant differences in the number of days for COVID PCR to become negative among ivermectin and non-ivermectin groups F (1, 364) = 651.380, p < 0.001. Patients who received ivermectin required a lesser number of days (8.39 days ± 2.04) to become COVID negative than the patients who didn't receive ivermectin (20.38 days ± 6.32).

Multinomial logistic regression showed that the patients who were given ivermectin during their management for COVID 19 infection were four times more likely to be discharged to home than stepping up to ICU. The ICU step-up rate in the ivermectin group was found to be 3.7% compared to 13.04% in the non-ivermectin group. No significant differences in mortality were found, even though the statistics show a marked reduction in mortality (8.74%) with ivermectin (0.92 %) when compared to the non-ivermectin group (9.66%).

## DISCUSSION

In the present study, the effectiveness of ivermectin in the treatment of COVID-19 infection was evaluated in terms of mortality, rate of step-up to intensive care unit (ICU), and days taken by nasopharyngeal PCR to become negative from the start of treatment. It was found that ivermectin at a dose of 12 milligrams per day in addition to the standard therapy was highly effective and superior to the standard therapy alone in reducing the duration of infection, the rate of ICU step-up as well as the mortality associated with COVID-19. In the ivermectin group, the mortality was only contributed by the patients with severe COVID-19 infection comparable to the non-ivermectin group in which only one patient with moderate severity COVID-19 infection died, while all other patients died from severe infection. Patients treated with ivermectin had an overall mortality of around 1% versus 9.66% in those not treated with ivermectin with an absolute risk reduction of 8.74%. However this difference was not found to be statistically significant by multinomial logistic regression. This is in contrast to the retrospective ICON study that found a statistically significant reduction in mortality of 11.7 percent in patients treated with ivermectin in addition to azithromycin and hydroxychloroquine versus those treated with hydroxychloroquine and azithromycin alone.[10]

In contrast to the ICON study which failed to demonstrate any significant reductions in the rates of extubation or length of hospital stay, our research found ivermectin superior to the usual treatment in reducing the ICU step-up rates by around 9.5 %.[10] In the ivermectin group, only some of the patients with severe COVID-19 infection required ICU care in contrast to the non-ivermectin group in which in addition to the patients with severe COVID-19 infection at least one-third patients that required ICU step-up had moderate severity COVID-19 infection. Summarizing all these results together, it is quite evident that ivermectin was clearly successful in

demonstrating significant in vivo anti-viral activity.

The most marked effect of treatment with ivermectin was found to be on the duration of infection. It reduced the number of days from hospital admission to negative SARS-CoV-2 PCR by roughly 12 days, which decreased the total hospital stay in contrast to the ICON study.[10] It has been shown in several researches that longer duration of COVID-19 illness is strongly associated with increased mortality not only from the complications of disease itself but also because of poor health care delivery for concurrent non-COVID comorbidities.[11-14] Ivermectin was also found superior in reducing the ICU step-up rates by around 9.5 %. In the ivermectin group, only some of the patients with severe COVID-19 infection required ICU care in contrast to the non-ivermectin group in which in addition to the patients with severe COVID-19 infection at least one-third patients that required ICU step-up had moderate severity COVID-19 infection. Summarizing all these results together, it is quite evident that ivermectin was clearly successful in demonstrating significant in vivo anti-viral activity.

Of note, although the dosage of ivermectin (12 milligrams) used in this study was comparable with that used in the ICON study, there was a significant difference in the duration of therapy.[10] The total duration of ivermectin therapy was 6 days in our study in contrast to a single or two-dose treatment of 200 micrograms/kg at first and seventh day of treatment in the ICON study.[10] It may be interpreted that the relatively higher total dose of ivermectin used in our study may be responsible for improved outcomes. It may also be predicted that longer duration of treatment with ivermectin may produce even more better results from the sustained accumulation of the drug in the lung parenchyma reducing the viral replication and the resulting inflammation associated lung injury.[5,8]

An important characteristic of our study population was that the mean age of participants was found to be around 52 years, which shows that most of our participants were well-aged, which is an important risk factor for severe COVID-19 infection and poor prognosis.[15] However, use of ivermectin in this age group still produced a marked reduction in ICU step-up rates as well as the total disease duration. This is in contrast to the ICON study in which a similar age range population was included but only mortality benefit was observed without any reduction in hospital stay or ICU step-up.[10] To add, around 60% of our study population was either diabetic, hypertensive, and/or had ischemic heart disease (comparable with the ICON study), all of which not only contribute to worsening and progression of COVID-19 infection but are also associated with very poor prognosis.[16-18] Therefore, the results of this study may be interpreted with consideration of the high-risk population that made up the majority of our study participants.

There are several important limitations for our study. Most importantly, even though the figures show an absolute reduction in mortality from the use of ivermectin in COVID-19 infected patients, however, the multinomial logistic regression failed to show any significant difference in mortality among the two treatments groups. Moreover, due to the lack of an electronic medical record system in our set-up, we were unable to follow those study participants that were stepped up to ICU care. Similarly, given the urgency of treatment required for COVID-19 infected patients as well as the lack of strong evidence and uncertainty regarding the treatment options available, we were unable to evaluate the effectiveness of ivermectin alone in the treatment of COVID-19 infection. Therefore, it is uncertain whether ivermectin alone or its combination with azithromycin, steroids, and/or remdesivir was responsible for these better outcomes. Arguably also, the relatively smaller number of our study participants may not justify the generalizability of the results and outcomes.

## CONCLUSION

Ivermectin shows promising activity in the management of COVID-19 infection and should attract eyes for future research in its treatment. Multi-center double-blind prospective studies are required to add more evidence.

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