Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Research Letters

The Effect of Ivermectin on Cases of COVID-19☆

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ABSTRACT

Ivermectin is an antiviral agent that has historically had a wide variety of uses. Recently, it has gained popularity in the mainstream media for use in treating and preventing COVID-19 infection, prompting high sales in veterinary grade Ivermectin. Studies are increasingly looking at Ivermectin as a possible agent for prevention and treatment of COVID-19, however further information is needed to assess efficacy and safety. Our project aimed to evaluate mortality differences in patients with COVID-19 infection who were prescribed Ivermectin vs. those not prescribed Ivermectin. Adult patients with active COVID-19 infection who were not prescribed Ivermectin (n = 797,285 Outpatient, n = 481,705 Inpatient, and n = 58,050 Intensive care unit), and those prescribed Ivermectin (n = 804 Outpatient, n = 1774 Inpatient, and n = 107 Intensive care unit) were evaluated. The cohorts were then evaluated for mortality comparing patients prescribed Ivermectin and those not prescribed Ivermectin in the Outpatient (7.7 % vs 2.2 %, $P < 0.001$), Inpatient not requiring Intensive Care (15.6 % vs 7.2 %, $P \leq 0.001$), and Intensive care (20.6 % vs 19.6 %, $P = 0.86$) treatment settings.

1. Background

Ivermectin has been cited as a "wonder drug" with its wide range of activities of antimicrobial, anti-viral, and anti-cancer properties [1]. Regarding its role as an antiviral agent, it has shown efficacy in both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) viruses. Ivermectin acts as an inhibitor of nuclear transport mediated by the importin α/β1 heterodimer, responsible for the translocation of various viral species proteins and therefore blocking their replication [2]. Ivermectin has been shown to have activity against DNA viruses, such as pseudorabies, as well as several RNA viruses, such as Zika, Influenza, Venezuelan equine encephalitis, West Nile and Dengue [2]. Ivermectin use has increased with the aim of treating the virus SARS-CoV-2, the culprit of COVID-19; however, its activity against the virus has yet to be established.

Caly et al. tested the activity of Ivermectin on SARS-CoV-2 in vitro and found a 99.8 % reduction in cell-associated viral RNA at 24 h; by 48 h this effect increased to a 5000-fold reduction of viral RNA compared to controls [3]. The drug concentrations used in this study were up to 100-fold the peak concentration achieved in plasma using the dose for onchocerciasis [4].

The prophylactic use of ivermectin has also been studied for the prevention of COVID-19 infection. As Ivermectin is used prophylactically against parasitic infections commonly in Africa, one study compared the incidence of COVID-19 in areas of its prophylactic use to other countries that do not. It was found that indeed those that were administering Ivermectin did have significantly lower incidence of COVID-19, however, the sample sizes varied greatly [5].

Though Ivermectin has a good safety profile with minimal adverse effects when appropriately prescribed [1], the general public has been self-medicating veterinary-grade Ivermectin which has led to many adverse effects and further strain on our healthcare system; prompting the FDA to emphasize that it is has not authorized or approved ivermectin for use in preventing or treating COVID-19 in humans or animals [6]. Our study aimed to evaluate mortality in patients with COVID-19 who were treated with Ivermectin.

2. Methods

We queried the TriNetX database, a de-identified clinical database comprising 65 health care organizations primarily from U.S.-based healthcare organizations. We identified adult patients aged 18–90 years with laboratory confirmed Covid-19 infection from Jan 20, 2020 to Feb 14 2022. Patients were divided into those who were taking

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Ivermectin and had no previous history of Ivermectin use prior to COVID-19 diagnosis and those without Ivermectin use. We created additional cohorts of Outpatient, Inpatient (without requiring Intensive care), and Intensive care treatment. These cohorts were analyzed for differences in mortality. Descriptive statistics were used to measure associations and to create Kaplan-Meier survival curves to assess the endpoint of mortality. A propensity score matching of 1:1 was performed to account for differences in baseline characteristics between the 2 groups. The 1:1 propensity score was developed using a logistic regression to create two matched cohorts using the covariates Age, Male, Female, White, Black, Hispanic, Asian, American Indian-Alaska Native, Hypertension, Chronic Heart Failure, Chronic Obstructive Pulmonary Disease, Chronic Kidney Disease, History of Smoking, Heart Failure, Remdesivir use, Hydroxychloroquine use, Transfusion of Convalescent Plasma, Steroid use, Alcohol Dependence, and Body Mass Index. To reduce possible differences, the authors created several matched cohorts over a 30-day period (Outpatient n = 803/803, Inpatient n = 1773/1773, and Intensive care unit n = 107/107).

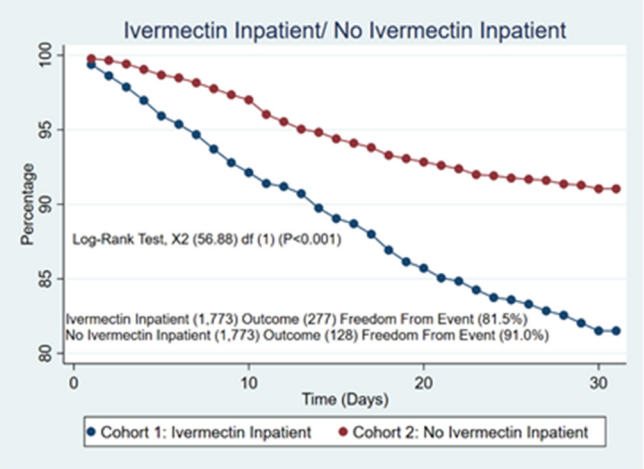

Fig. 2. Survival in Ivermectin use vs. no Ivermectin use in the inpatient (not ICU) cohort.

3. Results

Adult patients with active COVID-19 infection who were not prescribed Ivermectin (n = 797,285 Outpatient, n = 481,705 Inpatient, and n = 58,050 Intensive care unit), and those prescribed Ivermectin (n = 804 outpatient, n = 1774 inpatient, and n = 107 intensive care unit) were evaluated. Mortality within 30 days (defined by the use of the social security database provided through Trinetx) was then measured. The Outpatient treatment cohort had higher 30-day mortality in patients treated with Ivermectin compared to no Ivermectin treatment (7.7 % vs 2.2 %, P < 0.001), (Fig. 1) and the Inpatient treatment cohort with Ivermectin had higher mortality in the Ivermectin treatment cohort compared to without Ivermectin (15.6 % vs 7.2 %, P ≤ 0.001) (Fig. 2). The Intensive care treatment cohort did not see a statistically significant difference between the cohorts treated with Ivermectin and those without Ivermectin treatment. (20.6 % vs 19.6 %, P = 0.86) (Fig. 3).

4. Discussion

Our results showed no statistically significant mortality benefit with using Ivermectin in any setting for patients with COVID-19. The mortality in patients requiring intensive care did not note a statistically significant difference, however in the Inpatient setting not requiring Intensive (ICU) care, as well as the outpatient setting, there was a drastically increased mortality in patients with COVID-19 taking Ivermectin. In the outpatient setting, the mortality difference of 7.7 % in comparison to 2.2 % met statistical significance, and the difference in mortality was even more drastic in the Inpatient treatment group, with a mortality of 15.6 % compared to 7.2 % in the cohort without Ivermectin use. This was an unexpected finding of harm associated with the use of Ivermectin which needs further evaluation with additional studies.

There was a decreased use of Ivermectin in both the Outpatient and Inpatient without requiring ICU level care cohorts among patients who identify as Black or African American when compared to patients of White, Asian, Hispanic or Latino, and American Indian or Alaska Native heritage. We noticed in all demographics an increased use of Ivermectin in the Intensive care setting as well as additional therapies, suggesting that Ivermectin may have been used after all other treatments had been exhausted. In all cohorts, increased use of steroids was noted in patients also prescribed Ivermectin compared to those not prescribed Ivermectin. Additionally, mortality in patients identifying as Black or African American was increased from their White counterparts in the Outpatient and Inpatient cohorts both with and without the use of Ivermectin. Mortality was unable to be assessed by demographic in many instances due to small sample size (Figs. 1–3).

Our study had the limitations of being retrospective in nature, having the inherited limitations of selection bias and inability to assess incidence. We were also not able to distinguish the use of any COVID-19 vaccine. This study has the strengths of a large sample size and use of

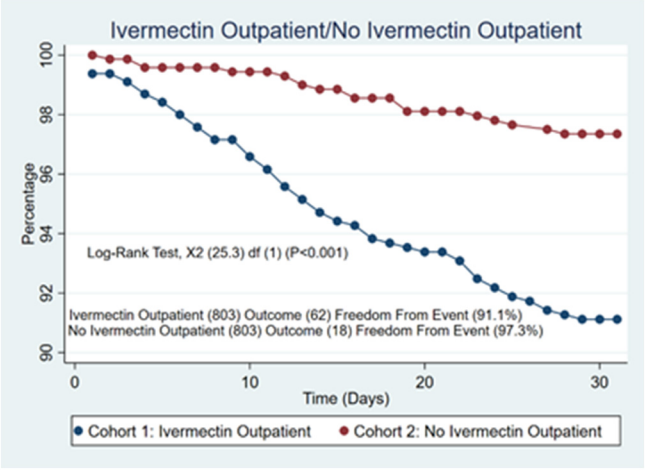

Fig. 1. Survival in Ivermectin use vs. No Ivermectin use over time in the outpatient cohort.

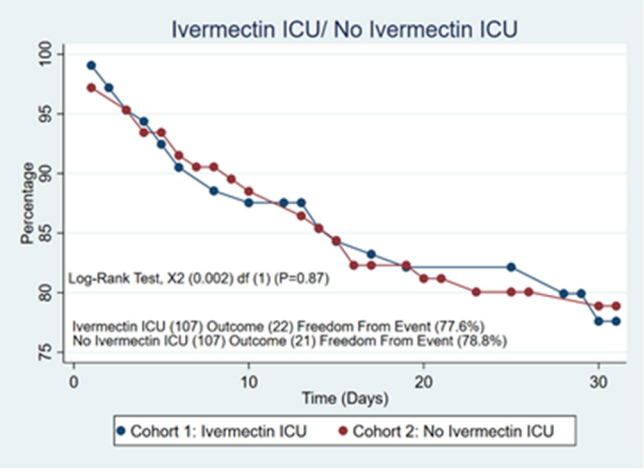

Fig. 3. Survival in Ivermectin use vs. no Ivermectin use in the intensive care cohort.

Table 1
Demographic information.

Demographics table	Outpatient - Ivermectin	Outpatient - no Ivermectin	Inpatient - Ivermectin	Inpatient – no Ivermectin	ICU – Ivermectin	ICU – no Ivermectin
Age at index	56.1 ± 16.0	49.3 ± 17.9	58.4 ± 15.5	55.8 ± 18.4	60 ± 12.9	60.5 ± 16.2
White	69.8 %	61.5 %	44.1 %	62.9 %	62.6 %	67.2 %
Male	58.3 %	59.3 %	54.6 %	45.5 %	59.8 %	56.0 %
Female	41.7 %	40.7 %	45.4 %	54.5 %	40.2 %	44.0 %
Hispanic or Latino	10.2 %	11.8 %	13.4 %	13.2 %	18.7 %	11.2 %
Black or African American	5.5 %	14.1 %	4.8 %	14.7 %	18.7 %	18.8 %
Asian	2.6 %	1.7 %	1.6 %	1.8 %	9.3 %	2.2 %
American Indian or Alaska Native	1.2 %	0.4 %	0.6 %	0.8 %	9.3 %	0.6 %
Hypertensive diseases	54.6 %	41.4 %	39.0 %	46.1 %	71.0 %	65.0 %
Chronic kidney disease (CKD)	19.2 %	17.6 %	9.4 %	15.1 %	36.4 %	28.9 %
Personal history of nicotine dependence	13.3 %	10.3 %	9.8 %	18.9 %	33.6 %	32.1 %
Heart failure	12.9 %	7.9 %	7.9 %	13.6 %	29.9 %	29.5 %
chronic obstructive pulmonary disease	10.8 %	7.2 %	5.6 %	11.1 %	15.0 %	20.9 %
Alcohol dependence	3.5 %	2.4 %	1.8 %	3.7 %	9.3 %	7.0 %
remdesivir	8.7 %	1.4 %	11.0 %	2.5 %	38.3 %	17.1 %
hydroxychloroquine	6.3 %	2.2 %	4.1 %	1.9 %	9.3 %	3.3 %
Transfusion of Convalescent Plasma	1.2 %	0.13 %	0.8 %	0.2 %	9.3 %	1.7 %
Corticosteroids	68 %	50 %	71 %	48 %	86 %	61 %
BMI	30.3 ± 7.2	30.6 ± 7.2	30.4 ± 6.5	30.7 ± 7.3	31.3 ± 7.8	30.4 ± 7.7

Table 2
Mortality among treatment cohorts.

Demographics table	Outpatient - Ivermectin	Outpatient - no Ivermectin	Inpatient - Ivermectin	Inpatient – no Ivermectin	ICU – Ivermectin	ICU – no Ivermectin
Mortality	7.7 %	2.2 %	15.6 %	7.2 %	20.6 %	19.6 %
Male	8.2 %	2.9 %	17.9 %	7.4 %	31.7 %	21.8 %
Female	5.5 %	1.7 %	14.4 %	4.3 %	35.6 %	23.2 %
White	6.9 %	2.0 %	13.2 %	4.5 %	38.3 %	27.7 %
Hispanic or Latino	NA	NA	NA	NA	NA	NA
Black or African American	19.6 %	1.14 %	26.3 %	3.8 %	NA	NA
Asian	45.4 %	0.86 %	NA	NA	NA	NA
American Indian or Alaska Native	NA	NA	NA	NA	NA	NA

a large national database giving a broad array of patients across many health systems for greater diversity of patient populations (Tables 1 and 2).

5. Conclusion

Ivermectin currently has no approved indication for treatment of COVID-19 and the FDA has warned physicians and the public about the widespread misinformation spreading in the media regarding Ivermectin use [7]. The aim of this study was not to dismiss the use of Ivermectin as a treatment of COVID-19 but to signify the need for further investigation.

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