

The effect of ivermectin on non-severe and severe COVID-19 disease and gender-based difference of its effectiveness

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Abstract

The COVID-19 pandemic has led to mortality and morbidity since December 2019. Many possible treatment options have

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been advised till date. The role of ivermectin in the treatment of COVID-19 disease remains controversial. The aim of our study was to evaluate the effect of ivermectin in hospitalized patients with non-severe and severe COVID-19 disease. We conducted a retrospective cohort study that compared outcomes in 2 groups of COVID-19 patients hospitalized at the largest tertiary care center of Pakistan. The study group was given ivermectin along with standard treatment of covid-19 disease; the comparison group was not. Data on mortality, inflammatory markers such as C-reactive protein (CRP) and ferritin, length of hospital stay and baseline characteristics were collected from Aga Khan University's database from October 2020 till February 2021. Statistical analysis was done to determine the effectiveness of ivermectin in non-severe and severe COVID-19. Comparison of effectiveness of ivermectin in both genders was also conducted. The cohort included 188 patients out of which 90 were treated with ivermectin. Mortality and length of hospitalization was not found to be significantly different in the study group compared with the control group (5.6% vs 5.1%; $p=0.87$ and 5 days vs 4 days; $p=0.27$). Analysis of secondary outcomes did not yield statistically significant results, apart from ferritin levels which were significantly less in patients treated with ivermectin (547.1 vs 756.7; $p=0.03$). The ferritin and CRP levels in affected males were higher than in females on admission and discharge. Our findings suggest ivermectin does not significantly affect all-cause mortality, length of hospitalization and CRP levels in hospitalized COVID-19 patients. Large scale randomized controlled trials (RCTs) are required to further evaluate the role of ivermectin in covid-19 disease.

Introduction

The SARS-CoV-2 pandemic that we are currently going through, started in the city of Wuhan in China towards the end of 2019. The pandemic since then has continued to affect the lives of the people throughout the globe. A total of over 162 million people have been infected whereas over 3.3 million lives were claimed by COVID-19 as of 16 May, 2021 [1]. In Pakistan alone 900,552 cases have been confirmed while over 20,000 people passed away due to COVID-19 [2].

Many medications have been proposed as probable treatment but the scientific evidence does not seem to support the use of majority of them. This includes interferon, hydroxychloroquine, chloroquine, conventional anti-virals, mono-clonal antibody, convalescent plasma therapy, and antirheumatics like tocilizumab [3-6]. Treatment, is largely based on symptomatic management of the patient and prevention of complications. Steroids and remdesivir

have shown positive outcomes such as decreased mortality or recovery time in patients with COVID-19 [7,8].

Ivermectin seems to be a promising drug for COVID-19. Its ability to impede protein transport into host nucleus via inhibition of importin (IMP) α/β receptor are behind its antiviral properties. It can therefore inhibit the replication processes in various RNA and DNA viruses, e.g., influenza, Zika virus, Dengue virus, Porcine circovirus and others [9,10]. Another possible contributing mechanism is allosteric modulation of the P2X4 receptor, which leads to the secretion of a chemotactic-chemokine ligand 5 (CCL-5) [11]. Some studies suggest that ivermectin might have immunosuppressive effects [12]. This is particularly important since it indicates mitigation of inflammatory response during SARS by the drug. Indeed in-vitro models support the theory that in SARS-CoV-2 a similar inhibitory effect leading to decreased replication will be seen [13]. This has spurred clinicians to consider using ivermectin as treatment in COVID-19. Peru has even restarted to prescribe ivermectin to their out-patients – even with arguably insufficient evidence [14]. To the best of our knowledge, gender-based role of ivermectin in COVID-19 has not been discussed in literature as yet. The aim of our study was to evaluate the effect of ivermectin on non-severe and severe COVID-19 disease and to see gender-based difference of its effectiveness.

Materials and Methods

A retrospective cohort study was conducted on hospitalized patients with COVID-19 disease confirmed by nasopharyngeal RT-PCR at the Aga Khan University Hospital (AKUH) located in largest cosmopolitan city of Karachi, in Pakistan between Oct 2020 and Feb 2021. The study protocol was approved by the Ethics Review Committee (ERC) of the AKUH.

AKUH is a tertiary care hospital in Karachi in the largest city of Pakistan. We have recruited non-severe and severe hospitalized patients of COVID-19 disease during study period and divided them in a study group; who received two doses of 12mg ivermectin 24 h apart and control group; who had not received ivermectin. Both groups had received other standard treatment according to hospital protocol for management of COVID-19 disease. We have excluded critical COVID-19 patients and patients who were discharged from Emergency Department or those seen in outpatient clinics.

The disease severity was classified according to the WHO classification into non-severe, severe and critically ill patients. Severe COVID-19 was defined as patients having respiratory distress with a respiratory rate of 30 breaths per minute or more and oxygen saturations below 90% on room air whereas non-severe COVID-19 was defined as absence of signs of severe COVID-19 [15]. Along with the analysis of effect of ivermectin on the study and comparison group, we also analyzed the effect of ivermectin on both the genders to see if there is a gender difference of its effectiveness or not, as this has not been seen and analyzed in literature previously. Our primary outcome was to investigate the effect of ivermectin on all-cause mortality and length of hospitalization in said patients while inflammatory marker levels (CRP and ferritin) at discharge & differences in the two genders were considered as secondary outcomes.

The data was collected from AKU's Health Information Management Services (HIMS) department on a pre-designed questionnaire. Data on age, disease severity (severe or non-severe), comorbidities, requirement of oxygen post-discharge and exposure to steroids (dexamethasone or prednisone) and/or remdesivir were noted.

Statistical analysis

All statistical analysis was done using the SPSS (Release 19.0, standard version). A descriptive analysis was performed for demographic features presented as mean \pm SD for quantitative variable like age, gender and comorbidities. Disease severity, inflammatory markers and length of hospital stay were compared between both the groups using Mann-Whitney U test and chi-square test where necessary. Odds ratios with 95% confidence interval were computed. In all analyses, p-value <0.05 was considered statistically significant.

Results

A total of 188 subjects of non-severe and severe COVID-19 disease were included. Out of 188 patients, 90 patients were a part of the study group whereas the remaining 98 were in the control group. The baseline characteristics of both groups are summarized in Table 1.

There was a male predominance in both groups (68.9% in study and 65.3% in control group). There was no significant difference of age and other comorbidities in both groups. Overall, 61.7% had severe disease and patients in study group had a slightly more severe disease than the control group (65.6% vs 58.2%; $p=0.37$). Likewise, steroids and remdesivir were used more in the study group (66.7% vs 48%). There was no significant difference noted on CRP levels at discharge (20.4 mg/L (interquartile range, 10.3-36 mg/L) in study group while 18.5 mg/L (interquartile range, 8.5-47.5 mg/L) in the control group ($p=0.96$). We noted an increase in ferritin as the treatment went on across both groups, however the increase in the ivermectin exposed group was significantly less than that in the control group. Median ferritin levels at discharge in the study group was 547.1 mg/L (interquartile range, 247.5-868.1 mg/L) while 756.7 mg/L (interquartile range, 313.2-1370.6 mg/L) in the control group ($p=0.03$) (Table 2). There were 5 mortalities in each group (5.6% vs 5.1%; $p=0.87$). Age [OR = 1.15 (95%CI, 1.06 to 1.25); $p<0.001$] and disease severity [OR=5.93 (95% CI 0.74-48.17; $p=0.048$) was found to be an independent factor of mortality in both groups. Mortality in the two genders was not found to be significantly different [odds ratio = 1.16 (95%CI, 0.25 to 7.17); $p=1$] (Table 3).

The median length of stay of study group was 5 days (interquartile range, 3-6 days) whereas it was 4 days (interquartile range, 3-6 days) in the control group ($p=0.27$) (Table 2). Length of hospitalization in females was found to be 4 days (interquartile range, 1-10 days) and in males 4 days (interquartile range, 1-18 days) as well ($p=0.40$) (Table 3).

It was also seen that ferritin and CRP levels in affected males were higher than in females at both admission and discharge. Analysis did reveal a significant difference in ferritin on admission ($p<0.001$), ferritin on discharge ($p<0.001$) and CRP on admission ($p=0.021$) between the two genders. The difference in CRP on discharge was insignificant ($p=0.866$) (Table 3 and Figure 1). No side effects of ivermectin were seen in the study group.

Discussion

The role of ivermectin in the treatment of COVID-19 still remains controversial with some studies showing favorable results

[16,17] while others opposing its use [18]. Our study did not show any statistically significant changes in outcomes like patient mortality, length of hospital stay and differences in CRP levels.

Earlier a study by Caly *et al.* sparked interest in health professionals across the whole world showing the antiviral properties of ivermectin [13]. This compelled researchers to conduct studies exploring the potential of the drug. There was an influx of studies earlier that claimed ivermectin as an effective option against the pathogen [16,17,19-23]. Concerns regarding power of these tests, biases and designs have existed, demanding more solid evidence for the use of ivermectin in COVID-19 - this study opposes that claim.

These findings are also corroborated by a randomized clinical trial which failed to find a decreased time of resolution of symptoms in said patients against placebo [18]. As for some studies which show a positive impact of ivermectin in the disease, many

studies have limitations as summarized by National Institutes of Health (NIH) [24].

We agree with Camprubi *et al.* [25] about the dosage of ivermectin which might be a vital factor. However, its toxicity is a plausible concern, even though studies has shown safety of ivermectin. [26-28]. In the study by Caly *et al.* [13] the doses used are ten-fold greater than those approved by FDA. This concern, along with noted variable results upon reviewing studies, trials and analyses exploring the use of ivermectin in COVID-19, made the European Medicines Agency advised against its use in COVID-19 [29]. Similarly the COVID-19 Treatment Guidelines Panel at NIH seems to be hesitant, and rightly so, to suggest ivermectin as a treatment option in the disease. In fact recently, they released a statement putting forward concerns related to the quality of studies and trials [30].

A meta-analysis of 3 observational studies by Padhy *et al.*

Table 1. Characteristics of study and control group.

	Study group		Control group		Total	
	Female (n=28)	Male (n=62)	Female (n=34)	Male (n=64)	Female (n=62)	Male (n=126)
Age (years)						
Mean (SD)	58.7 (13.2)	57.7 (12.8)	57.4 (15.3)	54.6 (14.9)	58.0 (14.3)	56.2 (14.0)
Median (min, max)	57.5 (31.0, 85.0)	58.5 (32.0, 91.0)	58.5 (25.0, 88.0)	54.5 (26.0, 96.0)	58.0 (25.0, 88.0)	56.0 (26.0, 96.0)
Comorbidities						
None	10.0 (35.7%)	22.0 (35.5%)	13.0 (38.2%)	32.0 (50.0%)	23.0 (37.1%)	54.0 (42.9%)
DM	1.00 (3.6%)	8.00 (12.9%)	4.00 (11.8%)	4.00 (6.3%)	5.00 (8.1%)	12.0 (9.5%)
HTN	8.00 (28.6%)	12.0 (19.4%)	8.00 (23.5%)	7.00 (10.9%)	16.0 (25.8%)	19.0 (15.1%)
IHD	0 (0%)	1.00 (1.6%)	0 (0%)	1.00 (1.6%)	0 (0%)	2.00 (1.6%)
HTN/IHD	1.00 (3.6%)	2.00 (3.2%)	0 (0%)	0 (0%)	1.00 (1.6%)	2.00 (1.6%)
DM/IHD	1.00 (3.6%)	1.00 (1.6%)	0 (0%)	1.00 (1.6%)	1.00 (1.6%)	2.00 (1.6%)
DMIHTN	7.00 (25.0%)	13.0 (21.0%)	9.00 (26.5%)	14.0 (21.9%)	16.0 (25.8%)	27.0 (21.4%)
DM/HTN/IHD	0 (0%)	3.00 (4.8%)	0 (0%)	5.00 (7.8%)	0 (0%)	8.00 (6.3%)
MedsSupportive care	1.00 (3.6%)	1.00 (1.6%)	11.0 (32.4%)	7.00 (10.9%)	12.0 (19.4%)	8.00 (6.3%)
Steroids	12.0 (42.9%)	16.0 (25.8%)	8.00 (23.5%)	25.0 (39.1%)	20.0 (32.3%)	41.0 (32.5%)
Remdesivir and steroids	15.0 (53.6%)	45.0 (72.6%)	15.0 (44.1%)	32.0 (50.0%)	30.0 (48.4%)	77.0 (61.1%)
Disease severity						
Non-severe	10.0 (35.7%)	21.0 (33.9%)	15.0 (44.1%)	26.0 (40.6%)	25.0 (40.3%)	47.0 (37.3%)
Severe Oxygen supplementation on discharge	18.0 (64.3%)	41.0 (66.1%)	19.0 (55.9%)	38.0 (59.4%)	37.0 (59.7%)	79.0 (62.7%)
Not required	27.0 (96.4%)	47.0 (75.8%)	29.0 (85.3%)	58.0 (90.6%)	56.0 (90.3%)	105 (83.3%)
Required	1.00 (3.6%)	15.0 (24.2%)	5.00 (14.7%)	6.00 (9.4%)	6.00 (9.7%)	21.0 (16.7%)

DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease.

Table 2. CRP, ferritin levels, length of hospitalization and outcome in both study and control group.

	Total	Study group; n=90	Control group; n=98	p-value
Ferritin on admission	465.2(233.8-1009.7)	464.8(216.9-846.9)	465.6(256.1-1140.5)	0.58*
Ferritin on discharge	640.9(271.1-1160.6)	547.1(247.5-868.1)	756.7(313.2-1370.6)	0.03*
CRP on admission	63.1(28.4-122.9)	67.6(35.5-130.5)	58.6(24-119.2)	0.21*
CRP on discharge	19(9.2-40)	20.4(10.3-36)	18.5(8.5-47.5)	0.96*
Length of hospital stay	4(3-6)	5(3-6)	4(3-6)	0.27*
OutcomeDischargedMortality	179(94.7)10(5.3)	85(94.4)5(5.6)	94(94.9)5(5.1)	0.87

*Mann-Whitney U test.

[31] showed that ivermectin, as an adjunct to other prospective drugs, reduced mortality and resulted in clinical improvement. Furthermore Okumuş *et al.* also found ivermectin to be beneficial

as an add-on therapy [32]. However, the use of other drugs can interfere with ivermectin metabolism. Antiretrovirals such as lopinavir/ritonavir and darunavir/cobicistat which inhibit

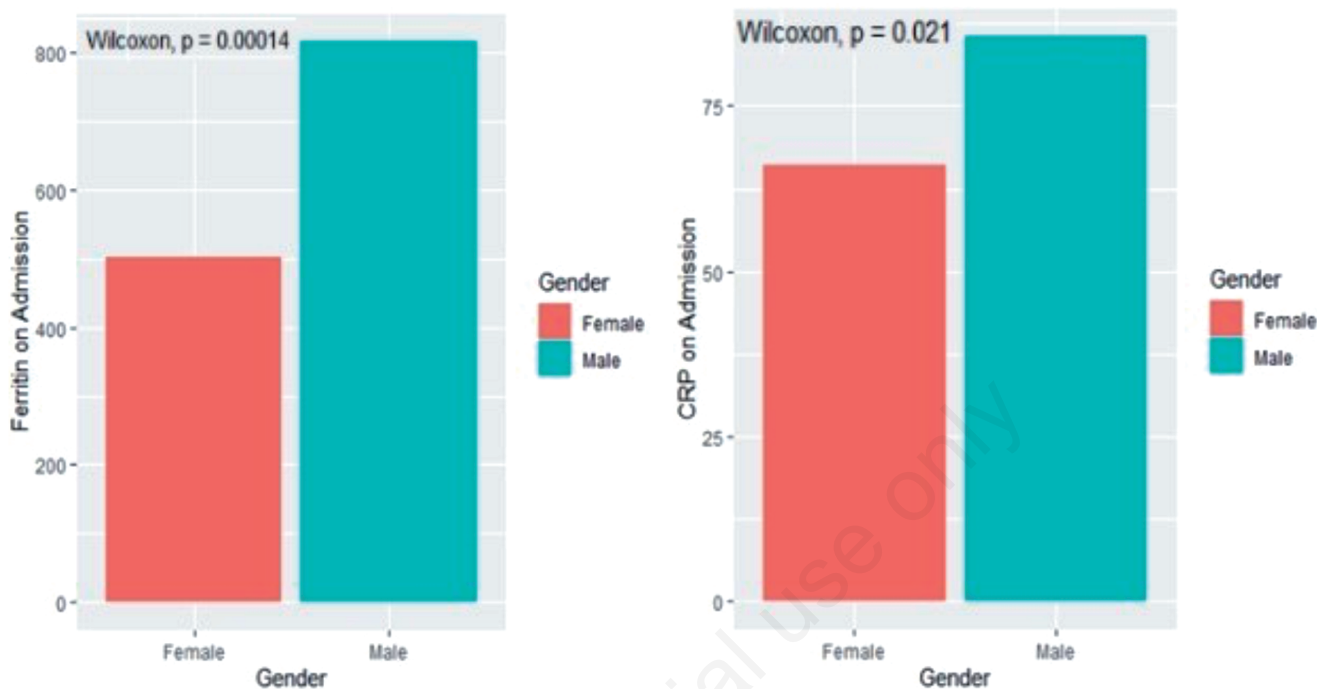


Figure 1. Gender base difference of serum ferritin and C-reactive protein levels on admission.

Table 3. Gender base difference on C-reactive protein, ferritin level, length of hospitalization and outcome in both study and control group.

	Study group		Control group		Total		p-value (OR)
	Female (n=28)	Male (n=62)	Female (n=34)	Male (n=64)	Female (n=62)	Male (n=126)	
CRP on admission (mg/L)							
Mean (SD)	74.9 (57.8)	86.2 (59.5)	58.2 (65.8)	84.9 (63.6)	66.0 (62.2)	85.5 (61.4)	0.021
Median (min, max)	61.2 (3.58, 249)	76.4 (5.06, 200)	40.4 (0.400, 306)	75.4 (0.26, 264)	48.0 (0.400, 306)	75.9 (0.260, 264)	
CRP on discharge (mg/L)							
Mean (SD)	29.0 (24.4)	26.9 (30.0)	26.8 (30.0)	35.5 (40.4)	27.7 (27.5)	31.1 (35.6)	0.866
Median (min, max)	23.3 (1.16, 88.1)	20.4 (0.300, 187)	18.7 (0.140, 122)	18.0 (0.450, 166)	19.2 (0.140, 122)	18.8 (0.300, 187)	
Ferritin on admission (mg/L)							
Mean (SD)	589 (686)	753 (845)	426 (540)	880 (648)	502 (612)	815 (755)	
Median (min, max)	401 (44.6, 3380)	530 (49.1, 5090)	262 (3.10, 2590)	615 (28.6, 2970)	301 (3.10, 3380)	555 (28.6, 5090)	<0.001
Ferritin on discharge (mg/L)							
Mean (SD)	571 (677)	749 (671)	460 (469)	1050 (649)	523 (591)	879 (675)	<0.001
Median (min, max)	435 (65.1, 3270)	597 (30.3, 3630)	271 (29.6, 1720)	1040 (140, 2930)	304 (29.6, 3270)	708 (30.3, 3630)	
Length of hospitalization (days)							
Mean (SD)	4.89 (2.08)	4.85 (2.99)	3.88 (1.65)	4.83 (2.56)	4.34 (1.91)	4.84 (2.77)	0.40
Median (min, max)	4.50 (2.00, 10.0)	5.00 (1.00, 18.0)	4.00 (1.00, 8.00)	4.00 (1.00, 15.0)	4.00 (1.00, 10.0)	4.00 (1.00, 18.0)	
Outcome							
Discharged	26.0 (92.9%)	59.0 (95.2%)	33.0 (97.1%)	60.0 (93.8%)	59.0 (95.2%)	119 (94.4%)	1.00
Expired	2.00 (7.1%)	3.00 (4.8%)	1.00 (2.9%)	4.00 (6.3%)	3.00 (4.8%)	7.0 (5.6%)	

CRP, C-reactive protein; SD, standard deviation.

cytochrome P450 3A4 – metabolizes ivermectin. Ritonavir and cobicistat also inhibit the P-glycoprotein which usually takes ivermectin out of the CNS, thereby facilitating toxic doses [33,34].

Differences in inflammatory markers in the two genders were noted. Higher ferritin and CRP levels in men compared to women might point to a worse prognosis in males. Similar results have been noted in other studies [35,36]. These two studies go on to propose that testosterone has an immunosuppressive effect which leads to greater susceptibility. Indeed, a reduction in testosterone has been linked to greater susceptibility such as in men of old age [37]. A study from China in 2020 concluded that males are ‘at risk for worse outcomes and death’ independent of age [38]. A study from Italy corroborates this notion by reporting an increased mortality rate in men [39]. However, the same study did also report a higher incidence in women, which is in contrast to studies suggesting the opposite [40]. In a large US cohort where comorbidities were matched, males were observed to be at risk for worse outcomes [40]. Other possible explanations have been offered - one of which is a higher ACE2 concentration in men [41]. Attitudes have also been shown to differ amongst men and women [42]. Our study though does not provide evidence for a higher mortality or longer stay in males as explained below. We do encourage researchers to look into these differences.

Our study supports the hypothesis that increased age is related to higher mortality in COVID-19 patients as in other studies [43]. Ferritin has been shown to be related to fatal outcomes in COVID-19 due to its involvement with the cytokine storm [44,45]. Our results show significantly less ferritin levels were observed in the ivermectin arm, which would suggest ivermectin did positively affect in the therapy of SARS-CoV-2. It might still be possible that the effect of ivermectin might not translate into improvement in length of hospital stay. This could explain why the difference in inflammatory marker levels did not seem to affect length of stay or mortality in the two genders as well. Literature on the effect of ivermectin on these parameters is variable [18,46].

We recommend that high-powered randomized controlled trials to determine the role of ivermectin in the treatment of SARS-CoV-2.

Limitations

Retrospective cohorts are prone to informational bias. Potential differences between groups might not be detected due to smaller sample size. Other treatment for COVID-19 like the use of steroids and remdesivir, was more pronounced in the study group. The dosage of ivermectin across all subjects in the study was not standardized.

Conclusions

This study does not provide evidence for the use of ivermectin in the treatment of COVID-19 in severe and non-severe hospitalized patients. Furthermore, there was no significant difference seen in any gender with respect to effect of ivermectin. Large scale RCTs are required to evaluate the role of ivermectin in the COVID-19 disease.

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