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EFFICACY OF IVERMECTIN AND DOXYCYCLINE AS AN ADJUNCT TO REMDESIVIR IN SEVERE COVID-19 CASES – A RETROSPECTIVE ANALYSIS

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ABSTRACT: Introduction: Covid-19 pandemic has posed new challenges to humanity. The definitive cure is yet to be found, while drug repurposing holds the key so far. Remdesivir had been used for the treatment of novel corona-virus. Ivermectin and Doxycycline have also been recommended for treating Covid-19, but their efficacy has not been studied extensively. **Methods:** We conducted a retrospective study during the second wave of the pandemic. Data were retrieved and 162 patients who had received Remdesivir were divided into 2 groups. Group I (101 patients) received Tab Ivermectin and Cap Doxycycline and Group R (61 patients) received only Remdesivir. The standard treatment was common for both groups. Mortality, duration of intensive care unit stay, and oxygen requirement were compared between the groups. **Results:** There was no statistically significant difference observed in demography, vaccination status, investigations on admission, comorbidity, and APACHE scoring between both groups. Group R had higher mortality with 75.41% as compared to Group I with a mortality rate of 55.45%, which was statistically significant. The mean duration of ICU stay in group I was 6.98 ± 4.78 days, and in Group R was 4.58 ± 3.82 days, and the mean total days of oxygen support needed in group I was 8.57 ± 5.5 days, and in Group R was 5.33 ± 4.82 days which were also statistically significant. **Conclusion:** Ivermectin Doxycycline and Remdesivir may be associated with lower mortality in critically ill Covid-19 patients compared to patients treated with Remdesivir alone.

INTRODUCTION: Spanish-Flu pandemic struck the world in 1918-1919, caused by H1N1 influenza virus [1]. With no vaccine to protect against influenza infection and no specific treatment for this virus, control efforts worldwide were limited to non-pharmacological interventions such as isolation, quarantine, good personal hygiene, disinfectants, and limitations of public gatherings.

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A century later, when Severe Acute Respiratory Syndrome Corona Virus-2 (SARS Co-V2) virus emerged, history repeated itself. Despite numerous scientific advancements in the last century, we are not in a very different position today. With antigenic shifts and drifts, common in the influenza virus, definitive treatment was difficult to find [2].

Coronaviruses are a large family of enveloped, positive-sense, single-stranded RNA viruses. This group of viruses has earlier caused severe acute respiratory syndrome (SARS), Middle East respiratory syndrome-related coronavirus (MERS), and recently SARS-CoV-2, the pathogen causing Covid-19 [3]. Since, the onset of the pandemic in December 2019, several medications have been

tried to treat novel coronavirus with drug repurposing and drug repositioning [4]. They include Remdesivir, Azithromycin, Oseltamavir, Ivermectin -Doxycycline combination, Hydroxy-chloroquine, *etc*. However, none have given promising results, especially when used alone. Several empirical treatments have now become the order of the day for the treatment of SARS-CoV-2. Researchers worldwide have put their experience, skills and expertise into finding a viable, sustainable, reproducible treatment. Gilead Sciences developed Remdesivir (GS-5734) [5] which inhibits RNA polymerases. *In-vitro* and preclinical *in-vivo* animal models supported the effectiveness of Remdesivir against SARS-CoV-2 and related coronavirus. It got its approval for Emergency use in Covid- 19 disease by Food and Drug Administration (FDA) in 2020.

Ivermectin, a FDA-approved antiparasitic drug [6] was found to have inhibitory effects on the replication of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Ivermectin has broad antiviral activity through inhibition of viral proteins, including importin α/β1 heterodimer and integrase protein [1]. The addition of Ivermectin at a concentration of 5μM (twice the reported IC50) to Vero-hSLAM cells, 2 h post-infection with SARS-CoV-2, resulted in a reduction in the viral RNA load by 99.98% at 48 h. Caly *et al* suggested that this drug could reduce the viral load in infected patients, with a potential effect on disease progression and spread [6].

Thereby, a single dose of Ivermectin can limit person–to–person transmission of SARS-CoV-2. Ivermectin in the dose of 12 mg b.i.d. alone or in combination with other therapy for 5 to 7 days was considered a safe therapeutic option for mild, moderate or severe cases of Covid-19 infection [7]. It is cost-effective, especially when the other drugs are expensive & not easily available [7]. Ivermectin has been demonstrated to be generally well tolerated. For the most part, side effects have been mild and transient. Doxycycline is a tetracycline class of antibiotics that acts via inhibition of bacterial ribosomes [8]. It is a well-tolerated bacteriostatic drug that has been used for a very long time. Ivermectin and Doxycycline were used in an earlier study of Onchocerciasis where their efficacy and tolerability were established as a combination [9]. Several recent studies have suggested a therapeutic role of Doxycycline in Covid-19 [10, 11]. A combination of Ivermectin and Doxycycline was recommended for Covid-19 patients by Alam MT *et al.* [11]. However, clinical studies to evaluate the efficacy of this combination have been scarce. We wished to determine if the combination of oral Ivermectin and Doxycycline started before Injection (Inj) Remdesivir was associated with lower mortality rate in patients hospitalized with Covid-19 than in patients treated with Remdesivir alone. Our secondary objectives were to observe the total duration of Intensive Care Unit (ICU) stay in both the groups and the duration of oxygen requirement.

MATERIALS AND METHODS: This retrospective observational study was conducted after Institutional ethical committee approval, and the study was registered with CTRI (registration number CTRI/2021/06/034344). Data were collected from medical records of laboratory-confirmed Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) positive Covid-19 patients admitted to the ICU during the second pandemic wave between 9th April 2021 till 15th July 2021 in a Tertiary Care Hospital.

Patients aged > 18 years of either sex requiring oxygen therapy received Inj. Remdesivir in the ICU were included in this study. Patients < 18 years, pregnant and lactating mothers, patients who have not taken a single dose of Remdesivir and expired within a few hours of admission to ICU, patients who have been given additional treatment like plasma therapy, and referred patients to other centers were excluded from our study.

Information collected includes brief history regarding the onset of symptoms and comorbidities of the patient, confirmed Covid-19 testing report, patient demographics, vaccination status, initial vital signs, laboratory reports on admission, and use of treatment other than standard regimen like plasma therapy. Investigation on admission to ICU like Total Leukocyte count (TLC), Procalcitonin (PCT), Serum Lactate Dehydrogenase (Sr LDH), Serum Ferritin was noted for all patients. Calculated acute physiology and chronic health evaluation score (APACHE score) on admission was noted for all patients. Information regarding

the drugs taken or started before admission to our ICU was noted. Patients were categorized into 2 groups based on the drugs taken by the patients into Group I (Ivermectin-Doxycycline and Remdesivir) and Group R (Remdesivir)

Group I: Patients who received Tab Ivermectin, Cap Doxycycline, and Inj. Remdesivir.

Group R: Patients who received only Remdesivir. Patients in both groups had also received Inj. Ceftriaxone 1g intravenous(IV) b.i.d and escalated or de-escalated according to patient's clinical condition, Inj. Enoxaparin 40mg subcutaneous b.i.d, Inj. Methylprednisolone 40mg IV b.i.d or Inj. Dexamethasone 8mg IV b.i.d depending on the requirement of the patient, Inj. Vitamin C 1.5g IV b.i.d, Tab Zinc 50mg OD, Tab N-acetylcysteine 600mg TID, metered dose inhaler of Salbutamol 2 puffs TID and supportive treatment as per institutional protocol.

Statistical Analysis: Data was entered into a Microsoft Excel datasheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. The Chi-square test was used as a test of significance for qualitative data. Continuous data were represented as mean and standard deviation. An independent t-test was used as a test of significance to identify the mean difference between two quantitative and qualitative variables, respectively [12, 13, 14].

Graphical Representation of Data: MS Excel and MS word were used to obtain graphs such as bar diagrams, column diagrams, and line diagrams. *P-value* (Probability that the result is true) of <0.05 was considered statistically significant after assuming all the rules of statistical tests.

Statistical Software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS: Two hundred and sixty-two patients were assessed for eligibility in Covid ICU during the period studied. After exclusion, 162 patients were analyzed, of which 101 patients were included in group I and 61 patients were included in Group R. **Fig. 1.**

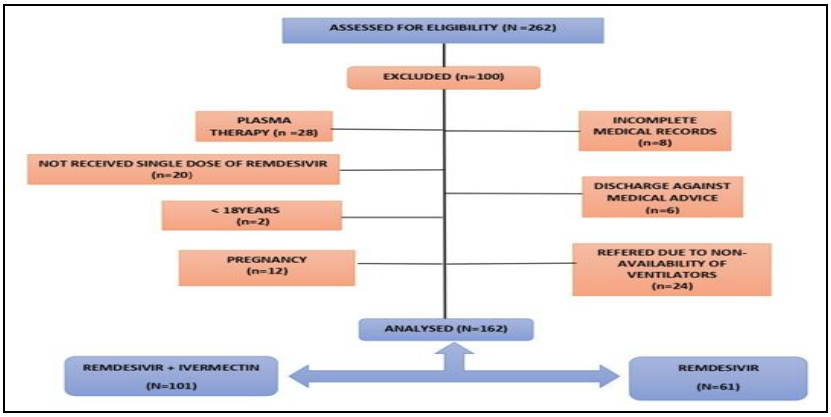

FIG. 1: CONSSORT DIAGRAM

In Group I, mean Age was 51.55 ± 14.83 years and in Group R was 49.7 ± 15.35 years, which was comparable between the groups.

There was no statistically significant difference in gender and vaccination status between the two groups **Table 1.**

TABLE 1: GENDER DISTRIBUTION AND VACCINATION STATUS

Parameter		Group I Remdesivir+ Ivermectin & Doxycycline		Group R Remdesivir		*P*
		Count	Column N%	Count	Column N%	
Gender	Female	35	34.65%	26	42.62%	0.31*
	Male	66	65.35%	35	57.38%	
Vaccination Status	1st Dose	10	9.90%	12	19.67%	
	2nd Dose	2	1.98%	0	0.00%	0.125*
	No	89	88.12%	49	80.33%	

*Chi-square test

Regarding co-morbidities, in Group I, 0.99% had Epilepsy, 0.99% had HIV, 46.5% had DM, 0.99% had TB, 26.73% had HTN, 0.99% had IHD, 1.98% had Asthma, 0.99% had Anemia and 3.96% had CKD. In Group R, 54.9% had DM, 1.64% had S/P Craniotomy, 29.51% had HTN, 1.64% had IHD, 1.64% had CKD and 4.92% had Hypothyroidism. The most common comorbidity in both groups was Diabetes Mellitus with 46.5% of patients in Group I and 54.91%in group R followed by Hypertension which was seen in 26.73% in group I and 29.51% in Group R. 3 patients were incidentally diagnosed with Hypothyroidism in Group R which was well controlled. On admission, there was no significant difference in mean TLC, PCT, Serum LDH, Serum Ferritin, and APACHE SCORE comparison between the two groups **Table 2.**

TABLE 2: INVESTIGATIONS ON ADMISSION

	Group				*P*
	Remdesivir + Ivermectin & Doxycycline [Group I]		Remdesivir [Group R]		
	Mean	SD	Mean	SD	
TLC	11.86	7.95	12.92	6.77	0.492 *
PCT	0.5	0.81	0.68	1.12	0.314*
Sr. LDH	471.14	226.32	532.37	306.22	0.271*
Sr Ferritin	423.53	305.28	507.34	383.55	0.194*
APACHE Score	45.23	166.05	26.35	6.44	0.51*

*****Two sample t-test, SD – standard deviation

Group R had a higher mortality **Fig. 2** of 75.41% as compared to Group I, with a mortality rate of 55.45%. There was a significant difference in Mortality Distribution between the two groups. In group I, among 101 patients, 56 patients died and in Group R, among 61 patients, 46 patients died. Amongst patients who survived, 43.34% were diabetics, and among subjects who died, 52.94% were diabetics. There was no significant difference in other comorbidities and mortality distribution between groups **Fig 3.**

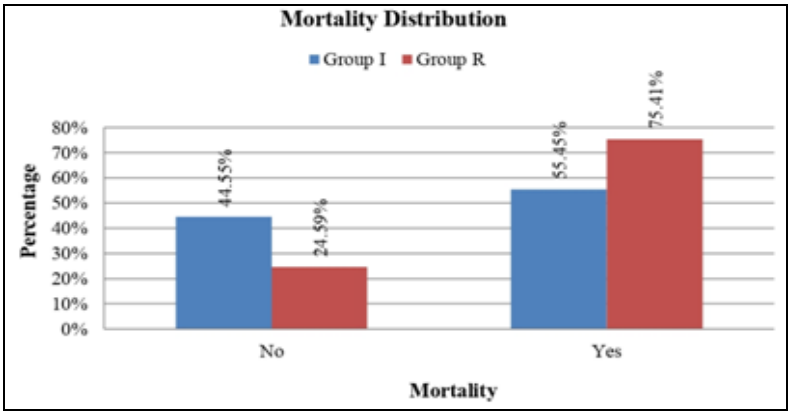

FIG. 2: BAR DIAGRAM SHOWING MORTALITY DISTRIBUTION BETWEEN TWO GROUPS

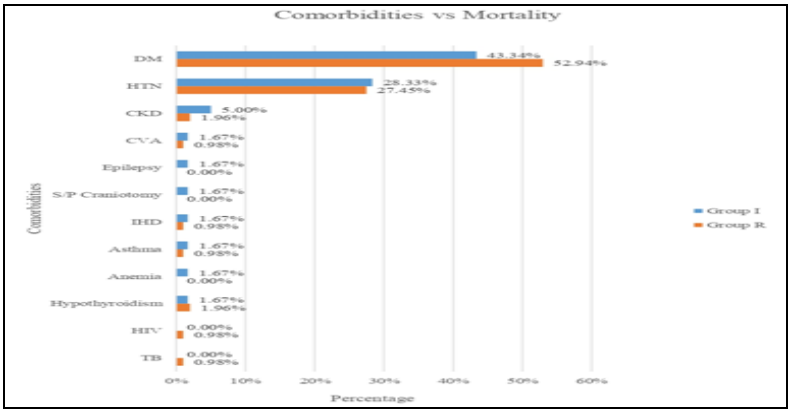

FIG. 3: COLUMN DIAGRAM SHOWING COMORBIDITIES AND MORTALITY DISTRIBUTION BETWEEN TWO GROUPS

There was a significant difference in the mean duration of ICU stay and mean total days of oxygen support needed between the two groups. Duration of ICU stay and total days of oxygen support was more in Group I than in Group R **Table 3.**

TABLE 3: MEAN DURATION OF ICU STAY AND OXYGEN SUPPORT REQUIRED IN BOTH THE GROUPS

	Group				*P*
	Remdesivir+ Ivermectin & Doxycycline Group I		Remdesivir Group R		
	Mean	SD	Mean	SD	
Duration of ICU stay	6.98	4.78	4.58	3.82	0.001*
Total days of oxygen support	8.57	5.5	5.33	4.82	0.001*

DISCUSSION: The Covid-19 pandemic has touched almost every family during the second pandemic wave. Few studies are done worldwide for definitive treatment of Covid-19 with drug repurposing [10, 15, 16]. Retrospective analysis and some randomized controlled trials are done to evaluate the efficacy of Ivermectin [17, 18]. There was no significant difference observed between age and gender distribution between the groups in our study. We observed that 88.12% in group I and 80.33% in Group R were not vaccinated.

Non-vaccination was probably due to the non-availability of the vaccine and hesitancy among the public during the initial period of the pandemic. Although the percentage of people of non-vaccinated in group I was higher than in group R, the difference was not statistically significant. Vaccination status has not been observed in any other studies. Abd-Elsalam *et al.* and Alberto Cundapi Nunez *et al*., and in their study, observed Hypertension followed by Diabetes Mellitus as the most common comorbidity associated with Covid-19 [15, 19].

In our study, we observed that in both groups, Diabetes Mellitus followed by Hypertension as the most common comorbidity associated with Covid-19. Investigations like TLC, PCT, Serum LDH, Serum Ferritin and APACHE SCORE at admission were noted, and no statistically significant difference was observed. Juliana Cepelowicz Rajter *et al.* also observed higher WBC Counts and lower lymphocyte counts as a risk factors for in-hospital mortality [17].

In our study, we observed higher WBC counts in both groups. In the study by Abd-Elsalam *et al.*, univariable regression analysis showed that the patient's age, ALT, creatinine, ferritin, and CRP were independently related to the patient's mortality [15]. Alberto Cundapí Núñez *et al.* [19] studied the therapeutic efficacy of Ivermectin as an adjuvant in the treatment of patients with Covid-19. They studied 107 patients where 24 were outpatient, 41 patients were severely hospitalized and 42 were critically ill, hospitalized in the ICU. Patients with clinical suspicion and/or SARS-CoV-2 pneumonia received outpatient treatment with Tab Ivermectin 12 mg on days 1 and 2, severe hospitalized patients received Ivermectin on days 1,3 and 5 and critically ill ICU patients received Tab Ivermectin on days 1,2,3,4 and 5, along with other standard treatment.

Ivermectin given in the early stages of the disease was highly effective as symptoms were relieved and severity was reduced. They concluded that Ivermectin as an adjuvant in the treatment of Covid-19 patients is more effective in outpatient patients. In critically ill hospitalized and severely hospitalized patients, Ivermectin had a significant impact on both improving patients' health and decreasing lethality [19].

Our study involved only critical patients where we observed decreased mortality (55.45%) in patients who were treated with Tab Ivermectin , Cap Doxycycline and Inj. Remdesivir, with as compared to 75.41% in patients treated with Inj. Remdesivir alone, along with other standard treatments. Juliana Cepelowicz Rajter *et al* [17] conducted a retrospective study on 280 patients at four hospitals in South Florida. Patients were divided into 2 groups based on whether they received Tab Ivermectin and other standard treatments at the time of admission or usual standard care.

Here 173 patients were treated with Ivermectin, and 107 patients were given the usual standard care. Patients with severe pulmonary involvement were also included in this study.

They observed that Ivermectin group had lower mortality of 15.0% vs. 25.2% in the usual standard care group. Mortality was also lower for Ivermectin-treated patients in the subgroup of patients (48 patients) with severe pulmonary involvement (38.8% vs 80.7%for Ivermectin and usual care group, respectively). Since our study involves only critically ill patients, these findings correlate with our research, where we observed lower mortality of 55.45% in Ivermectin group *vs* 75.41% in only the Remdesivir group. Byrant *et al* in his meta-analysis and systemic review regarding Ivermectin in the prevention and treatment of Covid -19, treatment suggested that early use of Ivermectin may reduce morbidity and mortality from Covid-19.

This is based on a reduction in Covid-19 infections when Ivermectin was used as prophylaxis; the more favorable effect was seen in mild to moderate disease compared with severe disease [20]. Sherief Abd-Elsalam *et al.* conducted a randomized controlled study evaluating the efficacy of Ivermectin in COVID-19 treatment [15]. In this study, 164 patients were randomized into 2 groups with Tab Ivermectin 12mg per day for 3 days, with standard treatment in Group I and standard treatment alone in Group II. Although there was no statistically significant difference in endpoints by Ivermectin doses (12 mg/day for 3 days); there was an observed trend to reducing hospital stay in the Ivermectin-treated group.

However, this observation did not correlate with our study. The mean duration of ICU stay in Ivermectin / Doxycycline group was 6.98 ± 4.78 days and in the Remdesivir group was 4.58 ± 3.82 days which was statistically significant. The longer duration of ICU stay in the Ivermectin group could be attributed to higher survival rate seen in Ivermectin group. In contrast to our study Juliana Cepelowicz Rajter *et al* [17] who did a retrospective analysis to find out whether the use of Ivermectin was associated with lower mortality in hospitalized Covid-19 patients, did not find any significant difference in the length of hospital stay between Ivermectin and usual care group.

M Talam *et al* [12] conducted a case series where 100 Covid-19 Positive with mild to moderate categories were included in the study. They included patients who were treated with a combination of Tab Ivermectin 0.2mg/kg single dose and Doxycycline 100mg OD for 10 days. Retesting was done between 4 and 18 days of starting medication. All patients tested negative, and their symptoms improved within 72 h. There were no noticeable side effects. A combination of Ivermectin and Doxycycline was found to be very effective in viral clearance in mild and moderately sick Covid-19 patients. The use of mechanical ventilation was not adopted as an outcome of interest because guidelines and practice patterns for intubation criteria kept changing throughout the length of the study. However mean total days of oxygen support needed in group I was 8.57 ± 5.5 days, and in Group R was 5.33 ± 4.82 days.

There was a statistically significant difference between the groups with the Ivermectin group requiring an increased number of days of oxygen support compared to Group R. This can be explained as more deaths were seen in the Remdesivir alone group patients have likely died in the early period of ICU admission. A systematic review by Popp M *et al.* [21] investigating Ivermectin for preventing and treating Covid-19 disease compared to no treatment, placebo, and standard of care concluded that, the completed studies were small and only very few were considered high quality. They suggested that more randomized controlled studies are required to come to any conclusive evidence.

Choudhury *et al.* [10] conducted a randomized controlled trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on mild to moderate Covid-19 patients. It concluded that Ivermectin-Doxycycline combination showed a trend toward superiority to the Hydroxychloroquine-Azithromycin combination therapy in the case of patients with mild to moderate Covid-19 disease. However, the difference in time to becoming symptom-free and the difference in time to negative PCR was not statistically significant. Since there is no confirmed treatment for novel coronavirus, appropriate Covid-19 behavior like social distancing and face masks remain the mainstay of controlling the disease.

There were some limitations in our study. Since all the enrolled patients were from one center, there

may be chances of selection bias. The exact number of days of the weaning process with intubation- Non-invasive ventilation- Non-rebreathing mask-Venti-mask could not be calculated for each patient. Investigations were taken only on admission. Our case sheets had recorded APACHE Scores on admission as per government protocol. Subsequent APACHE Score was not uniformly documented as the severity of the pandemic increased and the workforce was severely strained. There was no repeat RT-PCR report available to see for viral clearance. Lastly, since it was a retrospective observational study, the results were not conclusive in proving the appropriate treatment for Covid-19. Extensive multicentric randomized controlled studies are needed to determine the outcomes of both drugs.

CONCLUSION: Ivermectin Doxycycline and Remdesivir may be associated with lower mortality compared to patients treated with Inj. Remdesivir alone, along with other standard treatments. With no conclusive treatment for Covid-19, drug repurposing holds the key so far. Further studies with appropriately designed randomized trials are recommended to be prepared for any future pandemics.

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CONFLICTS OF INTEREST: NIL

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