Journal of Young Pharmacists, 2023; 15(4):716-724.
https://www.jyoungpharm.org

Original Article

Efficacy and Cardiovascular Safety of Remdesivir in COVID-19: A Case-Control Study

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ABSTRACT

Background: The Food and Drug Administration (FDA) has approved remdesivir under emergency use authorization for the management of the early stage of Coronavirus Disease (COVID-19). Since remdesivir has been approved on a 'fast-track' basis, the real-life efficacy and its safety on different population subsets have not been studied in detail so far. This study aimed to investigate the real-life efficacy with a special focus on the cardiovascular safety of remdesivir in the management of COVID-19. **Materials and Methods:** This is a single-centered, case-control study conducted from April 2022 to March 2023 in 427 case records and 301 records (181 under remdesivir and 120 in the control group) were analyzed. **Results:** In the severe COVID-19 category, the remdesivir group has significant AST, ALT, blood urea, and serum creatinine elevation when compared to the baseline values. Remdesivir is associated with a significant increase in the occurrence of QT prolongation during therapy (Odds ratio [QT]=3.18 (95% Confidence Interval [CI] 1.13 to 8.93; *p*=0.038). The Remdesivir group does not differ significantly in all-cause mortality in COVID-19 when compared with that of the control group (35.4% Vs. 33.3%; *p*=0.804). **Conclusion:** The use of remdesivir in COVID-19 patients did not reduce all-cause mortality and it is not associated with protective mortality outcomes. Remdesivir causes increased incidence of QT prolongation, bradycardia, and elevation of AST, ALT, Blood urea, and serum creatinine levels in COVID-19 patients.

Keywords: COVID-19, Coronavirus, Mortality, QT prolongation, Remdesivir.

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Received: 04-09-2023;
Revised: 23-09-2023;
Accepted: 29-09-2023.

INTRODUCTION

Coronavirus Disease (COVID-19), caused by the novel coronavirus, was declared a pandemic by the World Health Organization in 2020 after three months of its emergence in Wuhan, China.[1] The Acute Respiratory Distress (ARDS) caused by COVID-19 has accounted for millions of deaths worldwide. Since no specific antiviral drugs targeting Coronavirus existed in 2019, a spectrum of drugs from various groups has been tried. Corticosteroids, anticoagulants (Low Molecular Weight Heparin [LMWH]), anthelminthic (Ivermectin), antibiotics (azithromycin), anti-rheumatoid drugs (hydroxychloroquine), antimalarial (chloroquine), and other various antiviral drugs (lopinavir, ritonavir, etc) have been repurposed to prevent the catastrophic development of ARDS in COVID-19.[2-7] Later in May 2020, FDA approved remdesivir under emergency use authorization for the management of the early stage of COVID-19. Later in October 2020, based on three RCTs, the Food and Drug Administration (FDA) approved remdesivir for the early management of COVID-19 in adults and pediatrics (older than 12 years and weighing ≥40kg).[8] Thus as a standard protocol, remdesivir was administered along with corticosteroids and anticoagulants in the early stages of COVID-19. Various studies also encouraged the use of azithromycin and ivermectin in the management of COVID-19 besides standard protocol.[5,8-10] Since remdesivir has been approved on a 'fast-track' basis, the real-life efficacy and its safety on different population subsets have not been studied in detail so far. A meta-analysis of nine studies conducted in 2021 has shown that remdesivir has no significant impact on the improvement of clinical outcomes in COVID-19.[11] In contrast, a meta-analysis of eight randomized controlled trials in 2021-2022 has shown significant mortality reduction in COVID-19 by remdesivir.[12] Therefore a lacuna exists about the real-life efficacy of remdesivir in COVID-19 management. Moreover, additional studies are required to establish the safety of remdesivir in different population subsets. Hence our study aimed to investigate the real-life efficacy with a special focus on the cardiovascular safety of remdesivir in the management of COVID-19.

DOI: 10.5530/jyp.2023.15.98

MATERIALS AND METHODS

Study setting and design

This is a single-centered, retrospective case-control study conducted from April 2022 to March 2023 in Thanjavur Medical College, Thanjavur, Tamil Nadu, India. The study protocol was submitted to the Institutional Ethical Committee (IEC) of our institute, and approval for the same was obtained (Certificate No: IEC/2022/791). The case records were accessed in the Department of Medical Records, Thanjavur Medical College, Thanjavur, Tamil Nadu, India. Since this study involves case records, an exemption for obtaining informed consent for the patient has been obtained from the IEC. The undertaking was given to the IEC regarding the non-disclosure of the identity of the patients.

Inclusion criteria

The records of the patients (≥18 years of age) who were confirmed with COVID-19 by RT-PCR and radiological evidence of viral pneumonia from April 2022 to March 2023 were included in the study.

Exclusion criteria

The case records that showed discharged against medical advice, absconded, RT-PCR positive but radiological investigation not done, initial presentation with severe shock, multi-organ failure, immediate need for intubation/ ventilator support, not completed five days remdesivir course were excluded.

Groups

The cases are defined as COVID-19 patients (confirmed with RT-PCR and radiological investigation) who were treated with a five-day course of intravenous remdesivir. The course of remdesivir is intravenous administration of 200mg O.D. on the first day followed by intravenous administration of 100 mg O.D. for the next four days. The case group also received other drugs as per the standard protocol for the management of COVID-19. The controls are defined as the COVID-19 patients (confirmed with RT-PCR and radiological investigation) who were not administered remdesivir but received other drugs as per the standard protocol for the management of COVID-19. Both cases and control groups received LMWH and dexamethasone uniformly.

Parameters Analyzed

From the case records, the baseline parameters like age, gender, COVID Severity score by chest Computed Tomography (CT), comorbidity status, drugs administered, blood pressure, liver function test (Aspartate Aminotransferase [AST], Alanine Aminotransferase [ALT], total bilirubin, and Alkaline Phosphatase (ALP), Renal function test (blood urea, serum creatinine), Random blood glucose, and Complete Blood Count (CBC) were noted. For the case group, the above laboratory investigation values were noted again after 7 days. ECG taken on the 7th day was analyzed for the presence or absence of QT prolongation and bradycardia for both case and control groups.

Statistical analysis

Data were coded, entered in Excel-MS Office, and analyzed using SPSS version 16. Quantitative data were analyzed for normality distribution. Categorical data, parametric and non-parametric data were summarized as n (%), mean ± Standard Deviation (SD), and median with interquartile range, respectively. Unpaired *t*-test, Mann-Whitney U test, and Chi-square test were used to compare the mean, median, and frequency between case and control groups, respectively. Wilcoxon signed-rank test was used to compare the median values of parameters before and after remdesivir in the case group. Friedman test with Dunn's post hoc test was used to compare the median values for parameters between six subgroups (before and after remdesivir Vs. severity of COVID-19 based on CT score). Univariate analysis of various parameters in predicting the mortality in COVID-19 was performed and crude Odds Ratio (OR) was derived. Multivariate logistic regression analysis by forward LR method was performed for factors predicting COVID-19 mortality and adjusted OR was derived. $p<0.05$ was considered statistically significant.

RESULTS

Record selection and baseline characteristics

A total of 427 case records of patients admitted with COVID-19 from April 2022 to March 2023 were retrieved from the Medical Records department of our institute. Out of 427 records, 34 were discharged against medical advice, 8 absconded, 17 had no CT chest taken, 37 presented initially with shock/multi-organ failure, 21 presented with the immediate need for a ventilator, and 9 did not complete 5-day course of remdesivir. Thus 301 case records were included in the study. Out of these 301 records, 181 received remdesivir (case group) and 120 did not receive remdesivir (control group). Power analysis was performed using openepi.com for this sample size. From the previous study,[13] the percentage of death in the remdesivir group is 2.4% while in the control group is 24.8%. Using these values, the power of this case-control study was calculated to be 99%. Table 1 shows the baseline characteristics of the case and control groups. No significant difference was observed in age, AST, ALT, Total bilirubin, ALP, blood urea, serum creatinine, total count, hemoglobin, platelet count, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and proportion of azithromycin received between case and control groups. Male gender, CT severity score, presence of comorbidity, RBS, and person who received ivermectin were significantly higher in the remdesivir group than the control group.

Table 1: Comparison of baseline characteristics between remdesivir and no-remdesivir group in the study.

Sl. No.	Parameter	Remdesivir group (*n*=181)	No remdesivir group (*n*=120)	Statistical test	Statistic	*p* value
1	Age in years (Mean±SD)	59.6 ± 13.5	56.9 ± 13.3	Unpaired t	t=1.66	0.096 (NS)
2	Gender ratio (M:F)	110:71	57:63	Chi-square	$\chi 2$=5.14	0.025*
3	CT severity score	14 (10 – 17)	7 (4 – 14)	Mann Whitney U	U=5625	<0.001*
4	Presence of comorbidity n (%)	128 (66.3)	65 (33.7)	Chi-square	$\chi 2$=8.59	0.005*
5	AST (IU/L)	32 (26 – 45)	36 (24 – 47)	Mann Whitney U	U=12128	0.086 (NS)
6	ALT (IU/L)	32 (25 – 41)	30 (22 – 42)	Mann Whitney U	U=11125	0.719 (NS)
7	Total bilirubin (mg/dL)	0.9 (0.8 – 1)	0.9 (0.8 – 1)	Mann Whitney U	U=10341	0.464 (NS)
8	ALP (IU/L)	74 (51 – 89)	62 (51 – 92)	Mann Whitney U	U=10433	0.563 (NS)
9	RBS (mg/dL)	148 (91 – 257)	105 (78 – 204)	Mann Whitney U	U=9106	0.018*
10	Blood urea (mg/dL)	42 (31 – 51)	36 (28 – 53)	Mann Whitney U	U=9419	0.051 (NS)
11	Sr. Creatinine (mg/dL)	1.1 (0.9–1.5)	1 (0.8 – 1.2)	Mann Whitney U	U=9513	0.059 (NS)
12	Total count (1000 cells/cc)	9.5 (6.8 – 13.1)	8.25 (5.9 – 11.5)	Mann Whitney U	U=9489	0.053 (NS)
13	Hemoglobin (g/dL)	12.1 (10.8 – 13.5)	12 (10.5 – 13.1)	Mann Whitney U	U=10145	0.334 (NS)
14	Platelet count (1000 cells/cc)	233 (189 – 298)	239 (195 – 310)	Mann Whitney U	U=11646	0.287 (NS)
15	Systolic BP (mm Hg)	127.8 ± 14.9	131 ± 14.8	Unpaired *t*	t=-1.82	0.071 (NS)
16	Diastolic BP (mm Hg)	82.2 ± 10.1	84 ± 10.3	Unpaired *t*	t=-1.49	0.136 (NS)
17	Azithromycin given n (%)	57 (31.5)	41 (34.2)	Chi-square	$\chi 2$=0.235	0.706 (NS)
18	Ivermectin given n (%)	68 (37.6)	61 (50.8)	Chi-square	$\chi 2$=27.7	0.024*

Data are expressed as median with interquartile range except for age (mean ± SD), gender (ratio), CT severity score n (%), presence of comorbidity n (%), Azithromycin n (%), anti-coagulant n (%), and ivermectin n (%). *indicates $p<0.05$ and considered statistically significant. NS=Not significant.

Safety of remdesivir

Table 2 shows the change of Renal Function Tests (RFT), Liver Function Test (LFT), and CBC parameters before and after receiving remdesivir in the case group. The median values of AST, ALT, ALP, blood urea, and serum creatinine are significantly elevated after 5 days of receiving remdesivir. Median values of platelet count and total count were elevated and the median value of hemoglobin was reduced after receiving remdesivir in the case group. Table 3 shows the changes in the above parameters with respect to the severity of COVID. The median values of AST, ALT, blood urea, and serum creatinine are significantly higher in severe COVID-19 after receiving remdesivir. Significant elevation of median values of blood urea and serum creatinine are also noted in moderate COVID severity after receiving remdesivir. The

Table 2: Comparison of various parameters before and after remdesivir therapy observed in the study (*n*=181).

Sl. No.	Parameter	Before remdesivir (*n*=181)	After remdesivir (*n*=181)	Statistic	*p* value
1	AST (IU/L)	32 (26 – 45)	34 (28 – 54)	W=6271	<0.0001*
2	ALT (IU/L)	32 (25 – 41.5)	36 (26 – 53)	W=8700	<0.0001*
3	Total bilirubin (mg/dL)	0.9 (0.8 – 1)	0.9 (0.9 – 1)	W=1104	0.066 (NS)
4	ALP (IU/L)	74 (51 – 89)	78 (54 – 95.5)	W=3388	0.0144*
5	RBS (mg/dL)	148 (91.5 – 257)	196 (119.5 – 272)	W=6691	<0.0001*
6	Blood urea (mg/dL)	42 (31 – 51)	48 (38 – 63)	W=10197	<0.0001*
7	Sr. Creatinine (mg/dL)	1.1 (0.9 – 1.45)	1.2 (1 – 1.6)	W=5923	<0.0001*
8	Total count (1000 cells/cc)	9.5 (6.8 – 13.2)	10.7 (7.4 – 14)	W=4697	0.0006*
9	Hemoglobin (g/dL)	12.1 (10.8 – 13.5)	11.8 (10.4 – 13.3)	W=-8989	<0.0001*
10	Platelet count (1000 cells/cc)	233 (189 – 298.5)	251 (201 – 326)	W=5544	<0.0001*

Data are expressed as median with interquartile range. Wilcoxon signed Rank test was used to compare the median between the groups. *indicates $p<0.05$ and considered statistically significant. NS=Not significant.

median values of ALP did not change with respect to the severity of COVID-19 after receiving remdesivir.

Cardiovascular safety

The ECG was analyzed for both cases and controls in the study. QT prolongation was noted in 20.4% (37 out of 181) in the remdesivir group while it was only 3.3% (4 out of 120) in the control group. Amongst 37 who developed QT prolongation in the remdesivir group, 19 patients have received azithromycin also. Thus, after eliminating the patients who received azithromycin (57 in the case and 41 in the control group), the QT prolongation in the remdesivir group was 14.5% (18 out of 124) and it was 5.06% (4 out of 79) in the control group. The OR of developing QT prolongation with remdesivir and azithromycin was 7.45 (95% Confidence Interval [CI] 2.67 to 19.9; $p<0.0001$). The OR of developing QT prolongation with remdesivir alone was 3.18 (95% CI 1.13 to 8.93; $p=0.038$). Bradycardia was noted in 8.8% (16 out of 181) in the remdesivir group and none in the control group. Other ECG changes like PVC have been noted in 2 patients and acute ST changes in one patient in the remdesivir group.

Efficacy and mortality rate with remdesivir in COVID-19

The all-cause mortality observed in the remdesivir group was 35.4% (64 out of 181) while it was 33.3% in the control group (40 out of 120). No significant difference was noted in the all-cause mortality rate between remdesivir and the control group ($p=0.804$).

Univariate analysis of factors predicting mortality in COVID-19

Table 4 shows the univariate analysis of various factors predicting mortality in COVID-19. Aged more than 60 years, patients with two comorbid conditions and severe COVID-19 category have the OR of 2.51 (95% CI: 1.54 to 4.03, $p<0.0001$), 1.91 (95% CI: 1.07 to 3.53, $p=0.039$), and 3.82 (95% CI: 2.2 to 6.5, $p<0.0001$), respectively for mortality in COVID-19. In contrast, receiving ivermectin (OR=0.52, 95% CI: 0.3 to 0.85, $p=0.011$) and mild COVID-19 severity (OR=0.21, 95% CI: 0.1 to 0.38, $p<0.0001$) have a protective effect in COVID-19. Other factors like male gender, one comorbid condition, presence of diabetes, systemic hypertension, CAD, receiving remdesivir, receiving azithromycin, and moderate COVID-19 severity have failed to predict the mortality in COVID-19.

Multivariate analysis of factors predicting mortality in COVID-19

The above five factors in univariate analysis (age more than 60, patients with two comorbid conditions, Mild and Severe COVID-19 category, and received ivermectin) were subjected to multivariate logistic regression analysis by forward stepwise LR method (Table 5). The overall predictability of the model was 70.8%. In the final multivariate logistic regression analysis only the following three factors predict the mortality in COVID-19; age > 60 years (Wald=7.23; β=0.718; Standard Error [SE]=0.267, $p=0.007$, adjusted OR=2.04), Mild COVID severity category (Wald=8.106; β=-0.995; SE=0.349, $p=0.001$, adjusted OR=0.37), and Severe COVID-19 category (Wald=6.678; β=0.789; SE=0.305, $p=0.006$, adjusted OR=2.25).

Table 3: Comparison of change in levels of LFT and RFT parameters before and after remdesivir group with respect to CT severity score.

Sl. No.	Parameter		Severity of Covid based on CT severity score			Friedman Statistic	*P* value	Dunn post hoc test (significant group comparison)	Adjusted *p* value
			Mild (*n*=34)	Moderate (*n*=81)	Severe (*n*=66)				
1	AST (IU/L)	Bef Rem	32 (26-45)	31 (24-42)	39.5 (28 – 69.5)	Fr=19.95 D_f=5	0.001*	Severe bef Vs Aft Rem	0.011*
		Aft Rem	38.5 (28 – 53.25)	30 (25 – 44.5)	41 (27.5-52.5)				
2	ALT (IU/L)	Bef Rem	30.5 (24.5 – 36.75)	31 (21.5 – 41.5)	34 (29 – 46.75)	Fr=22.05 D_f=5	0.001*	Severe bef Vs Aft Rem	0.004*
		Aft Rem	34.5 (26 – 49)	33 (24.5 – 51.5)	44.5 (29 – 63.25)				
3	ALP (IU/L)	Bef Rem	74 (43.75 – 93.5)	74 (51.5 – 89)	74 (55.5 – 89.75)	Fr=8.61 D_f=5	0.126 (NS)	----	
		Aft Rem	69.5 (48 – 84.5)	76 (54.5 – 92.5)	83.5 (69.75 -101)				
4	Blood urea (mg/dL)	Bef Rem	41 (32.25 – 54.5)	39 (29 – 49.5)	46 (36 – 54.75)	Fr=34.6 D_f=5	<0.0001*	Mod Bef Vs aft Rem	0.009*
		Aft Rem	42 (31.5 – 51.75)	45 (35 – 60)	53 (43.75 – 75)			Severe bef Vs Aft Rem	0.035*
5	Sr. Creatinine (mg/dL)	Bef Rem	1.1 (0.9 – 1.4)	1.1 (0.9 – 1.3)	1.2 (1 – 1.5)	Fr=26.8 D_f=5	<0.0001*	Mod Bef Vs aft Rem	0.004*
		Aft Rem	1.05 (0.9 – 1.4)	1.3 (1 – 1.55)	1.3 (1.2 – 1.8)			Severe bef Vs Aft Rem	0.01*

Data are expressed as median with interquartile range. Friedman test with Dunn's post hoc test was performed to compare the distribution between the six groups (severity of Covid and timing of remdesivir). *indicates $p<0.05$ and considered statistically significant. NS=Not significant.

DISCUSSION

The study aimed to investigate the real-life efficacy and safety of remdesivir in COVID-19 management. We observed a significant elevation of median values of various LFT and RFT parameters in the remdesivir group after five days of therapy from the baseline. In the severe COVID-19 category, the remdesivir group has significant AST, ALT, blood urea, and serum creatinine elevation when compared to the baseline values. Remdesivir is associated with a significant increase in the occurrence of QT prolongation during therapy. After eliminating the potential interaction by azithromycin in causing QT prolongation, remdesivir has an independent effect on QT prolongation (OR=3.18 (95% CI 1.13 to 8.93; p=0.038). Moreover, the remdesivir group does not differ significantly in all-cause mortality in COVID-19 when compared with that of the control group (35.4% Vs. 33.3%; p=0.804).

Remdesivir, an adenosine nucleoside analog developed by Gilead Science Inc, is a viral RNA polymerase inhibitor.[14] The approval of remdesivir by the FDA in adults and paediatrics (older than 12 years of age and weighing at least 40kg) was based on the results from three RCTs.[15] The first RCT sponsored by the National Institute of Allergy and Infectious Disease (NIAID) was an Adaptive COVID-19 treatment trial-1 (ACCT-1)conducted as an adaptive, placebo-controlled, double-blind trial for three months duration in 1062 COVID-19 patients. The difference in the proportion of all-cause mortality observed between placebo and remdesivir was 3.8% (10.9% in remdesivir Vs. 14.7% in placebo). The proportion of SAE observed in ACCT-1 were 31.6% (163 out of 516 patients) and 24.6% (131 out of 532 patients) in the placebo and remdesivir group, respectively. Non-serious AE-like elevation of AST (3.4%), the elevation of serum creatinine (5.9%), and anemia (7.9%) were also noted in the remdesivir group in ACCT-1 trial.[16] The total non-serious AE observed in the placebo was 57% while it was 51% in the remdesivir group in ACCT-1 trial. The second RCT sponsored by Gilead Science was a parallel, open-labeled, multicentre RCT conducted for 45 days in 1113 COVID-19 participants. The all-cause mortality observed in this trial with a five-days-remdesivir treatment arm, 10-days-remdesivir treatment arm, extension-treatment-10-days remdesivir arm and standard-of-care arm were 1.05% (2 out of 191 patients), 1.55% (3 out of 193 patients), 2.58% (13 out of 503 patients), and 2% (4 out of 200), respectively.[17] The proportion of SAE observed in the five-days-remdesivir treatment arm, 10-days-remdesivir treatment arm, extension-treatment-10-days

Table 4: Univariate analysis of factors determining the mortality in the COVID-19 patients.

Sl. No.	Variable	Died N (%)	Alive n (%)	Chi square value	*P* value	Crude OR	95% confidence interval of OR
1	Age >60 years (*n*=135)	62 (45.9)	73 (54.1)	$\chi2=14$	<0.0001*	2.51	1.54 to 4.03
2	Male gender (*n*=167)	62 (37.1)	105 (62.9)	$\chi2=1.1$	0.33 (NS)	--	--
3	With 1 comorbidity (*n*=104)	38 (36.5)	66 (63.5)	$\chi2=0.277$	0.612 (NS)	--	--
4	With 2 comorbidity (*n*=53)	25 (47.2)	28 (52.8)	$\chi2=4.52$	0.039*	1.91	1.07 to 3.53
5	With Diabetes (*n*=137)	50 (36.5)	87 (63.5)	$\chi2=0.421$	0.544 (NS)	--	--
6	With Hypertension (*n*=92)	38 (41.3)	54 (58.7)	$\chi2=2.67$	0.115 (NS)	--	--
7	With CAD (*n*=72)	30 (41.7)	42 (58.3)	$\chi2=2.2$	0.157 (NS)	--	--
8	Received remdesivir (*n*=181)	64 (35.4)	117 (64.6)	$\chi2=0.131$	0.805 (NS)	--	--
9	Received azithromycin (*n*=98)	38 (38.7)	60 (61.3)	$\chi2=0.453$	0.501(NS)	--	---
10	Received Ivermectin (*n*=129)	34 (26.4)	95 (73.6)	$\chi2=6.7$	0.011*	0.52	0.3 to 0.85
11	Mild covid severity (*n*=103)	15 (14.6)	88 (85.4)	$\chi2=27.6$	<0.0001*	0.21	0.1 to 0.38
12	Moderate Covid severity (*n*=128)	43 (36.4)	75 (63.6)	$\chi2=0.31$	0.652 (NS)	--	--
13	Severe Covid (*n*=80)	46 (57.5)	34 (42.5)	$\chi2=25.3$	<0.0001*	3.82	2.2 to 6.5

Data are expressed as n (%). Chi square test was used to compare the proportions between the outcomes. 2X2 table was constructed to derive the Odd's ratio (crude) and 95% confidence interval. *indicates $p<0.05$ and considered statistically significant.

remdesivir arm, and standard-of-care arm were 4.7% (9 out of 191 patients), 5.18% (10 out of 193 patients), 7.95% (40 out of 503 patients), and 9% (18 out of 200), respectively. The third RCT sponsored by Gilead Science was also a multi-centred, parallel-arm, open-labelled RCT conducted for three months in 4891 COVID-19 patients.[18] The all-cause mortality observed in this trial with five-days-remdesivir treatment arm, 10-days-remdesivir treatment arm, extension-treatment-10-days remdesivir arm and mechanically-ventillated-10-days-remdesivir treatment arm were 12.5% (25 out of 200 patients), 14.2% (28 out of 197 patients), 11.7% (422 out of 3597 patients), and 25.2% (213 out of 844), respectively. The proportion of SAE observed in five-days-remdesivir treatment arm, 10-days-remdesivir treatment arm, extension-treatment-10-days remdesivir arm and mechanically-ventillated-10-days-remdesivir treatment arm were 21.5% (43 out of 200 patients), 34.5% (68 out of 197 patients), 23.6% (851 out of 3597 patients), and 42.9% (362 out of 844), respectively.[18] Therefore, in all the above three RCTs on which remdesivir approval was approved, it is evident that remdesivir has a substantial ability to cause various SE in COVID-19 patients. Since remdesivir decreased the time to recovery in COVID-19 and reduced the mortality rate in COVID-19, 'fast-track' approval was given to remdesivir by FDA in October 2020.[15] Similar to the other early trials conducted in 2020, in our study also remdesivir group has an increase in AST, ALT, ALP, RBS, total count, platelet count, serum creatinine, and blood urea levels and a decrease in hemoglobin level after 5 days of treatment. To rule out the interaction of COVID-19 severity in the elevation of the above lab parameters, data were analyzed by subgrouping based on COVID-19 severity. We found that ALP, RBS, total count, platelet count, and hemoglobin showed no difference in subgroup comparison indicating the potential confounding of disease severity in the elevation of the parameters. However, parameters like AST, ALT, serum creatinine, and blood urea are elevated significantly in the severe and moderate COVID-19 categories after 5 days of treatment with remdesivir. Therefore,

Table 5: Multivariate logistic regression analysis of factors determining the mortality in Covid-19 patients.

Sl. No.	Variable	Crude OR for mortality	*P* value	Wald	B	SE	Adjusted OR Exp (B)	95% Confidence interval
1	Age > 60 years	2.51	0.007*	7.233	0.718	0.267	2.04	1.21 to 3.44
2	With 2 comorbidity	1.91	0.431 (NS)	1.24	0.383	0.343	--	--
3	Received Ivermectin	0.52	0.072 (NS)	3.803	-0.549	0.282	--	--
5	Mild covid severity	0.21	0.001*	8.106	-0.995	0.349	0.37	0.18 to 0.73
5	Severe Covid	3.82	0.006*	6.678	0.789	0.305	2.25	1.25 to 4.1

Total *N*=301. Multivariate logistic regression analysis was performed using forward LR method. *indicates $p<0.05$ and considered statistically significant. NS=Not significant.

based on our study observation, we recommend monitoring the LFT and RFT parameters frequently during remdesivir therapy. In addition to this, the use of remdesivir in CKD and liver failure patients should be avoided and warranted only when the benefit outweighs the risk.

Various case reports have mentioned the occurrence of QT prolongation and bradycardia with remdesivir therapy.[19-22] In ACCT-1 trial also cardiac arrest was noted in 1.1% of the remdesivir group and 1% of the placebo group.[16] Thus the cardiotoxic effects of remdesivir were under-studied in COVID-19 patients. We observed QT prolongation of 20.4% (37 out of 181) in the remdesivir group but only 3.3% (4 out of 120) in the control group. In our study, the OR of developing QT prolongation with remdesivir and azithromycin was found to be 7.45 (95% CI 2.67 to 19.9; $p<0.0001$). Since azithromycin is a proven drug to cause QT prolongation,[23] after eliminating the azithromycin-administered patients, the OR of developing QT prolongation with remdesivir alone was found to be 3.18 (95% CI 1.13 to 8.93; $p=0.038$). Bradycardia was the second most common ECG abnormality noted in our study. Bradycardia was noted in 8.8% (16 out of 181) of the remdesivir group and none of the control group. Remdesivir, being an adenosine nucleoside analog, will be converted to its triphosphate form for inhibition of viral RNA polymerase. Even though the remdesivir triphosphate has low interaction with human mitochondrial RNA polymerase (h-mtRNAP), a possible cross-reaction of remdesivir with h-mtRNAP could not be avoided. It has been postulated that the inhibition of myocardial h-mtRNAP might account for the cardiotoxic effect of remdesivir thereby causing QT prolongation.[19] In our study, we also observed a significantly higher occurrence of bradycardia with remdesivir than the control group. It is a proven fact that adenosine causes bradycardia by acting on the adenosine-1 receptor in the SA node and AV node. Since activated remdesivir triphosphate also has adenosine moiety in its structure, we speculate that the possible interaction with adenosine receptors in the SA node or AV node can cause bradycardia. Since our study findings of remdesivir-induced QT prolongation and bradycardia corroborate with other studies,[19-22] it warrants future in-vitro research for elucidating the molecular level mechanism for the same.

Systematic reviews have shown that remdesivir has no effect in decreasing the need for mechanical ventilation and mortality in COVID-19.[11] Nevertheless, remdesivir decreases the time to recovery and increases the rates of clinical improvement.[11,12] In our study, the all-cause mortality observed in the remdesivir group was 35.4% (64 out of 181) while it was 33.3% in the control group (40 out of 120). No significant difference was noted in the all-cause mortality rate between remdesivir and the control group ($p=0.804$) which is comparable to meta-analysis conducted in 2021. We performed univariate analysis to predict the mortality in COVID-19 patients. Remarkably, male gender, patients with one comorbidity, remdesivir therapy, and azithromycin therapy did not predict the mortality in univariate analysis. On the other hand, age > 60 years, patients with two comorbid conditions, mild and severe COVID-19 category, and ivermectin therapy were found to predict mortality outcomes in COVID-19. Upon subjecting to multivariate logistic regression, only three factors namely, age > 60 years (Wald=7.23; β=0.718; SE=0.267, $p=0.007$, adjusted OR=2.04), mild COVID-19 severity category (Wald=8.106; β=-0.995; SE=0.349, $p=0.001$, adjusted OR=0.37), and Severe COVID category (Wald=6.678; β=0.789; SE=0.305, $p=0.006$, adjusted OR=2.25) were found to predict mortality outcome in COVID-19. Various studies have also predicted age>60 as a risk factor for mortality in COVID-19 similar to our study.[11,12] Interestingly we observed that remdesivir, azithromycin, and ivermectin therapy were not associated with protective mortality outcomes. The severity of the COVID category and age factors were the only two factors that determined the mortality outcome of COVID-19 in our study. The major limitation of our study is that it has been conducted as a case-control study. Nevertheless,

all the records of COVID-19 patients from April 2022 to March 2023 have been scrutinized for eligibility and included in the study. Moreover, we have achieved 99% power for this study with the arrived sample size thus eliminating the potential type II error possibility. The major strength of our study is the data has been collected in later phases of the COVID-19 pandemic (2022-2023) wherein the standard of care protocol for COVID-19 management has been refined. Multiple inefficacious drugs used in the early phases of the COVID-19 pandemic have been removed in the 2022-2023 treatment protocol and all patients received corticosteroid and LMWH uniformly. Thus, our study data has minimal confounding factors in estimating the all-cause mortality with remdesivir.

CONCLUSION

The use of remdesivir in COVID-19 patients did not reduce all-cause mortality and it is not associated with protective mortality outcomes. Remdesivir causes increased incidence of QT prolongation, bradycardia, and elevation of AST, ALT, blood urea, and serum creatinine levels in COVID-19 patients. Only the age of the patient and the severity of the COVID-19 category predict the mortality outcome of COVID-19.

ACKNOWLEDGEMENT

The authors thank the Medical Records Department, Thanjavur Medical College, Tamil Nadu, India for providing the case records for collecting the data for this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL

The study protocol was submitted to the Institutional Ethical Committee-Thanjavur Medical College, Tamil Nadu, India, and approval for the same was obtained (Certificate No: IEC/2022/791).

CONSENT TO PARTICIPATE

Since this study involves case records, an exemption for obtaining informed consent for the patient has been obtained from the IEC. The undertaking was given to the IEC regarding the non-disclosure of the identity of the patients.

ABBREVIATIONS

ALP: Alkaline phosphatase; **ALT:** Alanine aminotransferase; **ARDS:** Acute respiratory distress; **AST:** Aspartate aminotransferase; **CBC:** Complete blood count; **CI:** Confidence interval; **COVID-19:** Coronavirus disease; **CT:** Chest computed tomography; **DBP:** Diastolic blood pressure; **FDA:** Food and Drug Administration; **IEC:** Institutional Ethical Committee; **LFT:** Liver function test; **LMWH:** Low molecular weight heparin; **OR:** Odds ratio; **RFT:** Renal function tests; **SBP:** Systolic blood pressure; **SE:** Standard error.

REFERENCES

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA,. 2020;323(11):1061-9. doi: https://doi.org/10.1001/jama.2020.158510.1001/jama.2020.1585.
2. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al.* RECOVERY Collaborative Group, Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021;384(8):693-704. doi: https://doi.org/10.1056/NEJMoa202143610.1056/NEJMoa2021436.
3. Kow CS, Hasan SS. Use of low-molecular-weight heparin in COVID-19 patients. J Vasc Surg Venous Lymphat Disord. 2020;8(5):900-1. doi: https://doi.org/10.1016/j.jvsv.2020.06.00610.1016/j.jvsv.2020.06.006.
4. Hennekens CH, Rane M, Solano J, Alter S, Johnson H, Krishnaswamy S, *et al.* Updates on hydroxychloroquine in prevention and treatment of COVID-19. Am J Med. 2022;135(1):7-9. doi: https://doi.org/10.1016/j.amjmed.2021.07.03510.1016/j.amjmed.2021.07.035.
5. Gyselinck I, Janssens W, Verhamme P, Vos R. Rationale for azithromycin in COVID-19: an overview of existing evidence. BMJ Open Respir Res. 2021;8(1):e000806. doi: https://doi.org/10.1136/bmjresp-2020-00080610.1136/bmjresp-2020-000806.
6. Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, *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;103:214-6. doi: https://doi.org/10.1016/j.ijid.2020.11.19110.1016/j.ijid.2020.11.191.
7. Patel TK, Patel PB, Barvaliya M, Saurabh MK, Bhalla HL, Khosla PP. Efficacy and safety of lopinavir-ritonavir in COVID-19: A systematic review of randomized controlled trials. J Infect Public Health. 2021;14(6):740-8. doi: https://doi.org/10.1016/j.jiph.2021.03.01510.1016/j.jiph.2021.03.015.
8. Cascella M, Rajnik M, Aleem A, et al. Features, Eevaluation, and Ttreatment of Ccoronavirus (COVID-19) Updated 2023. In:. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776.
9. Andreani J, Le Bideau M, Duflot I, Jardot P, Rolland C, Boxberger M, *et al. In vitro* testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. Microb Pathog. 2020;145:104228. doi: https://doi.org/10.1016/j.micpath.2020.10422810.1016/j.micpath.2020.104228.
10. Hache G, Rolain JM, Gautret P, Deharo JC, Brouqui P, Raoult D, *et al.* Combination of hydroxychloroquine plus azithromycin as potential treatment for COVID-19 patients: safety profile, drug interactions, and management of toxicity. Microb Drug Resist. 2021;27(3):281-90. doi: https://doi.org/10.1089/mdr.2020.023210.1089/mdr.2020.0232.
11. Tanni SE, Silvinato A, Floriano I, Bacha HA, Barbosa AN, Bernardo WM. Use of remdesivir in patients with COVID-19: a systematic review and meta-analysis. J Bras Pneumol. 2022;48(1):e20210393. doi: https://doi.org/10.36416/1806-3756/e20210393.
12. Boglione L, Meli G, Poletti F, Rostagno R, Moglia R, Cantone M, *et al.* Risk factors and incidence of long-COVID syndrome in hospitalized patients: does remdesivir have a protective effect? QJM: Int J Med. 2022;114(12):865-71. doi: https://doi.org/10.1093/qjmed/hcab29710.1093/qjmed/hcab297.
13. Boglione L, Dodaro V, Meli G, Rostagno R, Poletti F, Moglia R, *et al.* Remdesivir treatment in hospitalized patients affected by COVID-19 pneumonia: A case-control study. J Med Virol. 2022;94(8):3653-60. doi: https://doi.org/10.1002/jmv.2776810.1002/jmv.27768.
14. Remdesivir |, Gilead [linternet]. [cited 2023 Jun 19Jun 19 2023]. Available from: https://www.gilead.com/remdesivir.
15. FDA Aapproves Ffirst Ttreatment for COVID-19 [linternet]. FDA. FDA; 2020 [cited 2023 Jun 19]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19.
16. National Institute of Allergy and Infectious Diseases (NIAID). A multicenter, adaptive, randomized blinded controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in Hospitalized Adults [Internet]. clinicaltrials.gov; 2022 Mar [cited 2023 Jun 17]. Report No.: results/NCT04280705. Available from: https://clinicaltrials.gov/ct2/show/results/NCT04280705. Hospitalized Adults. clinicaltrials.gov; 2022 Mar. In:.
17. Gilead Sciences., A Phase A. 3 randomized study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with moderate COVID-19 compared to standard of care treatment [linternet]; 2021 Jan. clinicaltrials.gov; 2021 Jan [cited 2023 Jun 17]. Report No.: NCT04292730. Available from: https://clinicaltrials.gov/ct2/show/NCT04292730.
18. Gilead Sciences., A Phase A. 3 randomized study to evaluate the safety and Aantiviral activity of remdesivir (GS-5734™) in participants with severe COVID-19 [linternet]; 2020 Dec. clinicaltrials.gov; 2020 Dec [cited 2023 Jun 17]. Report No.: NCT04292899. Available from: https://clinicaltrials.gov/ct2/show/NCT04292899.

19. Singla K, Kumar S, Behl A, Puri GD. Remdesivir induced bradycardia and QT prolongation: A rare side effect of a ubiquitous drug of the COVID-19 era. J Anaesthesiol Clin Pharmacol. 2022;38;(Suppl 1):S148-9. doi: https://doi.org/10.4103/joacp.joacp_305_2110.4103/joacp.joacp_305_21.
20. Haghjoo M, Golipra R, Kheirkhah J, Golabchi A, Shahabi J, Oni-Heris S, *et al.* Effect of COVID-19 medications on corrected QT interval and induction of torsade de pointes: results of a multicenter national survey. Int J Clin Pract. 2021;75(7):e14182. doi: https://doi.org/10.1111/ijcp.1418210.1111/ijcp.14182.
21. Harbi SA, AlFaifi M, Al-Dorzi HM, Aljuhani O, Alenazi AA, Alalawi M, *et al.* A case report on the association between QTc prolongation and remdesivir therapy in a critically ill patient. IDCases. 2022;29:e01572. doi: https://doi.org/10.1016/j.idcr.2022.e01572 10.1016/j.idcr.2022.e01572.
22. Gupta AK, Parker BM, Priyadarshi V, Parker J. Cardiac adverse events with remdesivir in COVID-19 infection. Cureus,. 2020;12(10):e11132. doi: https://doi.org/10.7759/cureus.1113210.7759/cureus.11132.
23. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, *et al.* Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiology. 2020;5(9):1036-41. doi: https://doi.org/10.1001/jamacardio.2020.183410.1001/jamacardio.2020.1834.

Cite this article: Lakshmanan M, Chittaranjan V, Raju SA, Palanisamy P. Efficacy and Cardiovascular Safety of Remdesivir in COVID-19–A Case-Control Study. J Young Pharm. 2023;15(4):716-24.