ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 01 | January - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFICACY AND SAFETY OF REMDESIVIR IN INDIAN PATIENTS WITH MODERATE TO SEVERE COVID-19: RESULTS FROM THE OPEN LABEL PERIOD OF A PHASE II, RANDOMIZED CONTROLLED TRIAL

General Medicine

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ABSTRACT

BACKGROUND: Remdesivir has proved its antiviral efficacy on COVID-19 virus in-vitro, but its role in infected patients is still obscure.
OBJECTIVE: To evaluate the efficacy and safety of Remdesivir in COVID-19 patients with significant pulmonary involvement.
STUDY DESIGN AND METHOD: We conducted a single center, two-arm, prospective, open-label, phase II study from June 2020 to December 2020 on COVID-19 patients (≥18 years), admitted at Jagjivan Ram Railway Hospital, Mumbai. The primary outcome was to evaluate the all-cause mortality up to 28 days in COVID-19 patients; secondary outcome was to assess the length of hospital stay (LOHS) and duration of respiratory supports, using PASS v11.0 software (19).
RESULTS: Overall mortality status at 28 days was not significant (62 (31.2%) in the remdesivir group vs 65 (32.5%) in the control group), and the mean LOHS was less in remdesivir arm which was statistically significant in the female subgroup although the remdesivir group had delay in hospital admission from the onset of the symptoms and statistically higher index IL6 values. Duration of invasive mechanical ventilation showed significant statistical difference among the study groups (4.7±1.18 days in control vs 2.8±1.88 days in remdesivir), and across both the genders. Hypertension and diabetes mellitus found to be the most common comorbidities in COVID-19. No safety concerns were reported in Remdesivir group.
CONCLUSION: Remdesivir was well tolerated without any adverse events, but did not show any significant effect on COVID-19 survival rate, however it decreases the length of hospital stay and duration of invasive ventilator support. More studies are needed to understand the effects of Remdesivir in larger populations.

KEYWORDS

COVID-19, Mortality, Remdesivir (GS-5734) SARS-CoV-2

INTRODUCTION

The ongoing COVID-19 pandemic have afflicted millions of general population and the healthcare system worldwide [1]. Since the emergence of the virus, there have been increasing number of cases and associated deaths with the major cause being respiratory system failure [2]. As per the WHO records, 34,615,757 cases of COVID-19 have been reported in India with 470,115 deaths as of 3 December 2021 [3]. The pandemic has set an unprecedented challenge to the medical and scientific community, inflicting emergency need to develop treatments, both for management and prevention. To date, the mainstay of clinical management is largely the treatment of the symptoms and no specific anti-viral approach has proven successful. Several

therapies have been tried and tested for COVID-19 treatment and detecting effective antiviral option against SARS-CoV-2 remains challenge.

Remdesivir was identified early as a strong therapeutic player for the infection due to its ability to inhibit the virus in vitro [4]. This is attributed to the fact that remdesivir is a broad spectrum antiviral drug that has proven its strong ability against many RNA viruses' in-vivo and in-vitro [5]. Remdesivir provided positive results in COVID-19 infection in animals and in-vitro studies, but the findings from several clinical trials concluded with inconsistent results. Few studies showed significantly positive results of remdesivir in COVID-19 treatment in relation to time of recovery, oxygen requirement, death rate, and clinical improvement while some studies did not show any positive outcome of remdesivir in COVID-19 treatment [6]. Although, a meta-analysis study concluded that the patients treated with remdesivir had a better recovery and thus better rates of discharge from the hospital, limited evidence exists on the significant effect of remdesivir on the mean time to clinical improvement or death rate in COVID-19 [7]. In addition, a study reported highly significant results with the use of remdesivir in severe COVID-19 patients, although high chances of false-positive results were suspected due to small patient cohort [8]. In a double-blind clinical trial, COVID-19 patients with severe symptoms treated with a 10-day course of remdesivir showed a significantly shorter time to recovery than those receiving placebo (11 days vs 15 days) [9].

Subsequently, similar reported results by other studies encouraged US Food and drug administration (FDA) to grant approval to remdesivir for the emergency use in COVID-19 adults and younger patients, , making it the first antiviral drug to gain permission for the use in COVID-19 treatment [9,10]. In India, compassionate provision of remdesivir allowed its use in COVID 19 patients with moderate to severe symptoms. To provide further evidence and quantify the beneficial effects of remdesivir, this phase II, open-label, randomised control trial was conducted to access the efficacy and safety of Remdesivir in COVID-19 infection with significant pulmonary involvement.

Patients and Methods

Study design

This was a single center, two-arm, prospective, open-label, phase II study conducted over a period of 6 months, from June 2020 to December 2020. The primary objective of this study is to assess the all-cause mortality up to 28 days on COVID-19 patients (≥18 years), admitted at Jagjivan Ram Railway Hospital, Western Railway, Mumbai. The secondary objectives were to assess the length of hospital stay (LOHS) and duration of respiratory supports. The safety objective is to evaluate the percentage of any adverse events associated with the Remdesivir treatment or other events which led to discontinuation of the drug.

Prior to participation, all patients provided written informed consent and the study processed were approved by the institutional review board of Jagjivan Ram Railway Hospital. The study was conducted in accordance with the ethical principles laid out in the Declaration of Helsinki and ICH GCP guidelines

Participants

Eligible patients were males and non-pregnant females, aged 14 years and above, admitted with COVID-19 disease as confirmed with RT-PCR test (PCR positive, sample collected < 72 hours before randomization). All patients had existing comorbidity, and fulfilled at least one of the mentioned criteria: radiographic infiltrates by imaging (X-Ray, CT), SpO2 < 94% on room air with/without hypotension (MAP<65 mmHg), or requiring supplementation oxygen (PaO2/FiO2 :< 300). Eligible women of childbearing potential agreed to use at least one primary form of contraception (excluding hormonal contraception) from the time of screening through day 28 and at least 7 days after the study. All participants were agreed upon not to participate in any other clinical study related to COVID-19 or SARS-CoV-2 through day 28.

Exclusion criteria included pregnant women or breastfeeding women; patients with hepatic cirrhosis with ALT/AST more than 5 times UNL; patients with severe renal impairment or patient (<30 ml/min/ 1.73 m^2) on renal replacement therapy. Patients who were anticipated to be discharged from the hospital or transfer to another hospital which was not the study site within 72 hours were also excluded from the study.

Randomization and intervention

A total of 399 patients were enrolled in the study out of which 199 were randomized to Remdesivir group, and 200 were randomized to control group. In the Intervention arm, patients had received intravenous Remdesivir (200 mg on day 0, followed by 100 mg for 4-9 days, in a single day infusion as per clinical profile of patients) along with all the medications in controlled arm. Drug was administered in 100 ml of normal saline (NS), transfused over 2-3 hours. In the control arm, the patients received the standard care for COVID-19 disease. For each patient, study endpoints were considered as 28 days post enrolment or death, whichever came earlier.

Statistical Analysis Plan

Sample size calculation

Sample size calculation for standard of care was based on a cut off of 18% patients if faced mortality and a relative effectiveness of 50% was considered. Calculations were executed using PASS v11.0 software (19).

Group sample sizes of 226 in the intervention group and 226 in the control group achieve 80 % power to detect the absolute difference of -0.09 between the group proportions. The proportion of participants not meeting the primary outcome in group one (the treatment group) was assumed to be 0.18 under the null hypothesis and 0.09 under the alternative hypothesis. The proportion of participants in group two (the control group) who would not meet the primary outcome is assumed to be 0.18 based on current evidence. The test statistics used was the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.05, with a power of 0.8. Total patients would be enrolled for at least 100 per group.

Data capture method

Paper CRFs were used to collect data. The data were then entered on an electronic system. A data entry system with electronic tracking, password-restricted access, audit trail, with time and date stamps on data entry and edits were developed, and SOP for data collection were followed.

Analysis plan

Baseline data about demography, clinical presentation, ongoing medical therapy, and clinical history of participants in both arms were compared. Adverse events associated with the infusion of Remdesivir were also descriptively summarized and compared with the adverse events experienced by participants receiving standard of care (/Control group). Continuous variables were expressed as mean ± standard deviation and categorical data were expressed as numbers and percentages. Based on whether continuous variables were normally distributed, Student's t-test was used for comparison among groups. Categorical variables were compared using the 2 test. Fisher's exact test was employed instead of the 2 test when >20% of cells had expected frequencies <5. The all-cause mortality within 28 days was portrayed by Kaplan-Meier plot and compared with a log rank and Breslow test. The hazard ratio for mortality were calculated by cox proportional hazards model. Gender sub-group analysis was also been applied wherever applicable. For all analyses, a two-tailed P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Among the 399 eligible participants, 260 (65.2%) were males, and 139 (34.8%) were females. Gender distribution in the remdesivir group was 137 (68.8%) men versus 62(31.2%) women, compared to123 (61.5%) versus 77 (38.5%) in the control group with no statistical difference (P>0.05)..

The mean age of the eligible patients was 55.61 ± 14.20 years with a statistical indication of higher age in remdesivir group as compared to control group (p<0.001). Hypertension (41.1%) and type 2 diabetes mellitus (32.8 %) were the most common comorbidities found in all the patients, significantly high among remdesivir group, followed by ischemic heart disease (4.8%), chronic kidney diseases (1.5%), asthma (1.3%), COPD (0.8%), and obesity (0.2%) (Table 1).

Table 1: Baseline characteristics of the study population

Demographics	N	Values Mean ±SD	Range Min - Max	P-Value
Age (In Years)	399	55.61 ± 14.20	18 - 92	
Remdesivir Arm	199	58.05 ± 11.32	26 - 86	<0.001

Control Arm	200	53.19 ± 16.25	18 - 92	
		n (%)		
Gender (Male : Female)	399	260 (65.2%): 139 (34.8%)		
Remdesivir Arm	199	137 (68.8%): 62(31.2%)		0.124
Control Arm	200	123 (61.5%): 77 (38.5%)		
Comorbidities				
Hypertension	399	164 (41.1%)		
Remdesivir Arm	199	109 (54.8%)		<0.001
Control Arm	200	55 (27.5%)		
T2DM	399	131 (32.8%)		
Remdesivir Arm	199	82 (41.2%)		<0.001
Control Arm	200	49 (24.5%)		
IHD	399	19 (4.8%)		
Remdesivir Arm	199	10 (5%)		0.805
Control Arm	200	9 (4.5%)		
COPD	399	3 (0.8%)		
Remdesivir Arm	199	3 (1.5%)		0.081
Control Arm	200	0 (0%)		
Asthma	399	5 (1.3%)		
Remdesivir Arm	199	5 (2.5%)		0.024
Control Arm	200	0 (0%)		
CKD	399	6 (1.5%)		
Remdesivir Arm	199	4 (2%)		0.407
Control Arm	200	2 (1%)		
Malignancy	399	0 (0%)		
Remdesivir Arm	199	0 (0%)		-
Control Arm	200	0 (0%)		
Obesity	399	1(0.2%)		
Remdesivir Arm	199	1(0.5%)		0.499
Control Arm	200	0 (0%)		

Difference in overall mortality status at 28 days (62 (31.2%) in the remdesivir group vs 65 (32.5%) in the control group), and the gender mortality difference between both the study groups, resulted to be statistically not significant. In the remdesivir arm, the overall mortality is found to be low in females compared to the control arm, though there is no clinically meaningful differences between two groups. However, with the increasing age, the mortality was found to be statistically significant in both the study groups, as well as for overall study population. In remdesivir group, hypertension was found to be statistically significant ($p<0.05$) and to be associated with the most number of deaths. IHD in control group, and CKD in remdesivir group, and overall had higher number of mortalities ($p<0.05$). Other pre-existing comorbidities like T2DM, COPD, asthma, and obesity showed no statistical relation with the mortality status in any of the study groups ($p> 0.05$) (Table 2).

Table 2: All-cause mortality status of the study participants at 28 days

Characteristics	Total		Mortality-Remdesivir		Mortality-Control	
	N (%)	P-Value	N (%)	P-Value	N (%)	P-Value
Mortality-Overall	127 (31.8%)		62 (31.2%)		65 (32.5%)	0.773
Male	90 (34.6%)	0.102	47 (34.3%)	0.154	43 (35.0%)	0.348
Female	37 (26.6%)		15 (24.2%)		22 (28.6%)	
Age						
≤ 35 Years	1 (2.5%)	<0.001	0 (0%)	0.05	1 (3.1%)	<0.001
36-59 Years	47 (23%)		30 (28%)		17 (17.5%)	
≥60 Years	79 (51%)		32 (38.1%)		47 (66.2%)	
Duration from Onset of symptoms to Hospitalization						
≤3 Days	50 (33.6%)	0.489	24 (30.8%)	0.961	26 (36.6%)	0.14
4 – 7 Days	70 (32.0%)		31 (32%)		39 (32%)	
≥ 8 Days	7 (31.8%)		7 (29.2%)		0 (0%)	
Hypertension						
Absent	61 (26.0%)	0.003	15 (16.7%)	<0.001	46 (31.7%)	0.704
Present	66 (40.2%)		47 (43.1%)		19 (34.5%)	
T2DM						
Absent	78 (29.1%)	0.095	32 (27.4%)	0.166	46 (30.5%)	0.28
Present	49 (37.4%)		30 (36.6%)		19 (38.8%)	
IHD						
Absent	119 (31.3%)	0.324	60 (31.7%)	0.434	59 (30.9%)	0.025
Present	8 (42.1%)		2 (20%)		6 (66.7%)	
COPD						
Absent	126 (31.8%)	0.955	61 (31.1%)	0.935	65 (32.5%)	NA
Present	1 (33.3%)		1 (33.3%)			
Asthma						
Absent	125 (31.7%)	0.693	60 (30.9%)	0.665	65 (32.5%)	NA
Present	2 (40.0%)		2 (40%)			
CKD						
Absent	123 (31.3%)	0.065	58 (29.7%)	0.003	65 (32.8%)	0.324
Present	4 (66.7%)		4 (100%)		0 (0%)	
Obesity						
Absent	127 (31.9%)	0.494	62 (31.3%)	0.500	65 (32.5%)	NA
Present	0 (0%)		0 (0%)			
Log Rank (Mantel-cox) test	0.264					
Breslow test (Generalized Wilcoxon)	0.048					

The survival analysis of the two study groups revealed that all-cause mortality was not significant at the end of 28 days from the time of randomization. Similar results were noticed in the log-rank test as this was also not significant ($p>0.05$), suggesting that both the survival curves have no difference at 28 days. However, Breslow test was statistically significant ($p<0.05$) suggesting that there exists some difference among control and remdesivir group during the initial time of treatment (Fig. 1)

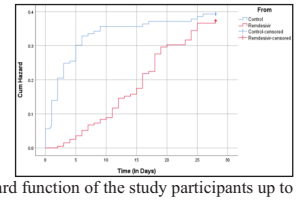

Figure 1: Hazard function of the study participants up to 28 days from start of study

The mean duration of onset of symptoms of covid-19 to hospitalization in remdesivir group was 4.8 ± 3.11 days, and 4.2 ± 1.9 days in control group which came out to be statistically significant showing that in spite of delay in admission, remdesivir had no significant difference in overall mortality. Numerically the mean length of hospital stay was higher in control group (16.2 ± 9.37 days vs 14.6 ± 9.28 days, p=0.079) than remdesivir group, but statistically it was not significant. However, the length of stay for females in control group was found to be significantly higher as compared to remdesivir group (Table 3).

Table 3: Hospitalization characteristics of the study participants

Characteristics	Sample	Total	Remdesivir (n=199)	Control (n=200)	P-Value
Duration from Onset of symptoms to Hospitalization (in days)	399	4.5 ± 2.58	4.8 ± 3.11	4.2 ± 1.90	0.04
Length of stay (in days)	393	15.4 ± 9.35	14.6 ± 9.28	16.2 ± 9.37	0.079
Male	256	15.6 ± 8.95	15.3 ± 9.57	16.0 ± 8.23	0.495
Female	137	15.0 ± 10.08	13.0 ± 8.47	16.5 ± 11.00	0.041
No of dosed of Remdesivir	199	NA	4.79 ± 1.81	NA	
Male	137	NA	5.30 ± 1.98	NA	0.295
Female	62	NA	4.79 ± 1.81	NA	
Death	62	NA	5.44 ± 2.32	NA	0.149
Alive	137	NA	5.01 ± 1.73	NA	
Time from symptom onset to starting remdesivir (In days)	199	NA	7.12 ± 4.91	NA	NA
Death	62	NA	7.5 ± 6.00	NA	0.484
Alive	137	NA	7.0 ± 4.34	NA	
Invasive Mechanical Ventilation	399	95 (23.8%)	46 (23.1%)	49 (24.5%)	0.745
Male	260	60 (23.1%)	28 (20.4%)	32 (26%)	0.286
Female	139	35 (25.2%)	18 (29.0%)	17 (22.1%)	0.348
Non-Invasive Mechanical Ventilation	399	117 (29.3%)	57 (28.6%)	60 (30%)	0.766
Male	260	75 (28.8%)	38 (27.7%)	37 (30.1%)	0.677
Female	139	42 (30.2%)	19 (30.6%)	23 (29.9%)	0.921
Duration of invasive ventilation (in days)	95	3.7 ± 1.83	2.8±1.88	4.7±1.18	<0.001
Male	60	3.7 ± 1.87	3.1 ± 1.98	4.7±1.17	<0.001
Female	35	3.6 ± 1.76	1.7 ± 0.82	4.6 ± 1.22	<0.001
Duration of non-invasive ventilation (in days)	117	4.5±3.37	4.4 ± 4.56	4.6±1.25	0.693
Male	75	4.1 ± 2.85	3.8 ± 3.66	4.5 ± 1.26	0.244
Female	42	5.3 ± 4.28	6.1 ± 6.43	4.8 ± 1.25	0.376

NA-Not applicable

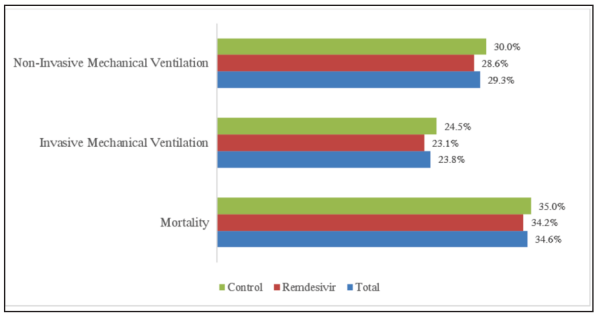

Figure 2: Mortality and respiratory supports in the study participants

The mean number of doses of remdesivir administered was 4.79 ± 1.81 times which was reported to be statistically insignificant across gender and mortality status. Mean time between the onset of symptoms and the start of study treatment was 7.12 ± 4.91 days. Numerically this time gap was seen to be little less in alive group (7.0 ± 4.34) as compared to mortality group (7.5 ± 6.00), but statistically it was not significant. Requirement of invasive mechanical ventilation and non- invasive mechanical ventilation had no statistical difference among both the study groups. However, duration of invasive mechanical ventilation (IV) showed significant statistical difference among the study groups (4.7±1.18 control vs 2.8±1.88 remdesivir), and across both the genders, suggesting that the invasive mechanical ventilation days were significantly higher in control group as compared to remdesivir group advocating that remdesivir administration was helpful in early onset of clinical improvement in COVID-19 patients. Duration of non-invasive mechanical ventilation showed no statistical difference (Table 3, Figure 2).

No adverse events were reported in patients receiving remdesivir treatment (Table 4).

Table 4: Proportion of various drug related adverse events among remdesivir participants

Characteristics	Sample	Remdesivir (n=199)
Adverse event	399	0 (0%)
Male	260	0 (0%)
Female	139	0 (0%)

Clinical biomarker analysis showed the mean change in neutrophil-to-lymphocyte (NL) ratio in all participants to be statistically significant from baseline to date of discharge/death. Likewise, the mean level of blood urea nitrogen (BUN) was found to be increased during the course and showed significant difference at day 3 and day of discharge or death from baseline. In addition, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and C-reactive protein (CRP) values showed statistical difference at day 1 and at the end of follow up from baseline. The index interleukin 6 (IL6) values, one of the best inflammatory markers, were found to be higher in mortality group as compared to alive group (108.4 ± 92.2 vs 72.4 ± 47.6, p=0.004) (Table 5).

Table 5: Change in clinical biomarkers for all the participants

Biomarkers- Overall	Baseline	Day 1		Day 3		Date of Discharge/Death	
Parameter	**Mean ± SD**	**Mean ± SD**	**P-Value**	**Mean ± SD**	**P-Value**	**Mean ± SD**	**P-Value**
CBC							
NL ratio	27.8 ±149.2	15.6 ±13.5	0.002	32.7 ±27.7	<0.001	24.9 ±18.1	<0.001
Hb	16.6 ± 62.5	19 ±56.5	0.309	12.2 ±1.8	0.225	18.0 ±23.1	0.338
TLC	8745.6 ±4255.2	11786.5 ±6087.1	<0.001	15909.8 ±7158.8	<0.001	15209.8 ±9630	<0.001
Platelet count	222491 ±119956	211215.5 ±118333.7	0.971	287443 ±512794.8	0.364	230930.6 ±131980.9	0.220
RFT							
BUN	19 ±14.2	24.3 ±14.7	0.480	27.7 ±16.4	0.045	30.2 ±27.4	<0.001
Creatinine	1.4 ±2.1	2.2 ±4.0	0.191	1.8 ±4.2	0.224	1.7 ±3.0	0.208
LFT							
Bilirubin	0.7 ±1.1	1.3 ±6.9	0.401	0.8 ±0.7	0.631	0.9 ±1	0.094

SGOT	39.6 ±43.2	34.4 ±23.7	0.001	39.7 ±53.9	0.920	57.7 ±87.7	<0.001
SGPT	44.6 ±103.5	36.5 ±26.1	0.150	35 ±22.9	0.215	51.8 ±88.3	0.012
ALK Phos	80.4 ±35.8	83.5 ±41	0.745	72.7 ±37.5	0.270	82.3 ±33.1	0.376
CRP	11.8 ±83.2	5.7 ±7.7	<0.001	11.5 ±12.2	0.571	10.3 ±13.9	0.62
IL 6*	92.3 ± 77.50	-	-	-	-	-	-
Alive	72.4 ± 47.6	-	-	-	-	-	-
Dead	108.4 ± 92.2	-	-	-	-	-	-
Ferritin	797 ±1434.3	-	-	-	-	-	-
Alive	802.3 ± 1332.8	-	-	-	-	-	-
Dead	785.4 ± 1644.5	-	-	-	-	-	-
D-DIMER*	1099.3 ±1988.7	-	-	-	-	-	-
Alive	1294.8 ± 2160.1	-	-	-	-	-	-
Dead	630.2 ± 1405.4	-	-	-	-	-	-
LDH	406 ±300.9	-	-	-	-	-	-
Alive	412.7 ± 275.1	-	-	-	-	-	-
Dead	387.8 ± 363.3	-	-	-	-	-	-

In Remdesivir receiving group, the mean change in NL ratio was found to be statistically significant from baseline to day of discharge/death in all participants, and BUN was found to be more during the course and showed significant difference at day 3 and day of discharge/death from baseline. In addition, SGOT, SGPT, and CRP values showed statistical difference at day 1 and at the end of follow up from baseline (Table 6).

Table 6: Change in clinical biomarkers for all the Remdesivir group patients

Biomarkers- Remdesivir	Baseline	day 1		Day 3		Date of Discharge/Death	
Parameter	**Mean ± SD**	**Mean ± SD**	**P-Value**	**Mean ± SD**	**P-Value**	**Mean ± SD**	**P-Value**
CBC							
NL ratio	12.9 ±9.7	20.5 ±10.8	0.048	50.8 ±29	0.001	36 ±10.5	<0.001
Hb	13.3 ±1.4	12.9 ±1	0.208	12 ±1.8	0.111	13.1 ±2	0.003
TLC	11392.9±5431.3	14002±6211.7	<0.001	16622.9±7465.3	0.000	17145.4±10628.3	0.000
Platelet count	284142.9±215418.5	215142.9±142223.3	0.486	191524.8±105750.4	0.030	263869.6±152716.4	0.256
RFT							
BUN	30.6 ±18	28.1 ±13.1	0.186	28.1±17.1	0.352	35.2 ±30.3	<0.001
Creatinine	1.6 ±1.6	1.2 ±0.6	0.040	2.3 ±6	0.485	1.9 ±3.1	0.233
LFT							
Bilirubin	1.2 ±2.6	0.8 ±1	0.338	0.8 ±0.7	0.605	1.1 ±1.3	0.733
SGOT	45.6 ±58.6	31.6 ±23.6	0.026	41.6±48.4	0.451	75.9 ±102.7	0.002
SGPT	41.5 ±33.7	32.8 ±22.8	0.010	35 ±22.1	0.992	55.8 ±43.7	0.001
ALK Phos	100.2 ± 36.1	64.4 ±54.6	0.197	88.7±46.8	0.586	120 ±30.5	0.499
CRP	12.9 ±11.7	7.5 ±8.3	0.002	12.6±13.5	0.169	14.7 ±15.4	0.12
IL 6	103.7±80.0	-	-	-	-	-	-
Ferritin	891.9±1782.5	-	-	-	-	-	-
DDIMER	964 ± 1781.5	-	-	-	-	-	-
LDH	381.5 ±290.4	-	-	-	-	-	-

In the control group, the mean change in NL ratio from baseline to day 1, day 3 and the date of discharge or death was significantly different. The total leukocyte Count (TLC) values also showed statistically significant difference from baseline and at the follow-ups. The BUN values also showed significant difference at day 3 and day of discharge or death from baseline. SGOT, SGPT, and CRP values showed statistical difference at day 1 and last day of follow up from baseline. Mean levels of IL6 were found to be higher among remdesivir group (103.7± 80.0 vs 73.4 ± 69.73 control group, p=0.019) indicating significantly higher concentrations of IL-6 in remdesivir group, whereas Ferritin, D-DIMER and LDH had no statistically significant difference across the study groups (Table 7).

Table 7: Change in clinical biomarkers for controlled group patients

Biomarkers- Control	Baseline	day 1		Day 3		Date of Discharge/Death	
Parameter	**Mean ± SD**	**Mean ± SD**	**P-Value**	**Mean ± SD**	**P-Value**	**Mean ± SD**	**P-Value**
CBC							
NL ratio	10 ±6.9	17.6 ±15	0.015	29.2±27.6	0.000	23.1 ± 17.9	<0.001
Hb	14.1 ±1.5	12.9 ±1.6	0.315	12.3 ±1.8	0.265	12.3 ± 1.9	0.338
TLC	9268.5 ±4851.4	10914.2 ±5709.5	0.002	15417.1 ±7002.1	0.000	14107.9 ± 8862.2	0.000
Platelet count	189065.5 ±130810.3	205474.1 ±112963.2	0.627	365511.8 ±717920.9	0.257	212081± 86015.3	0.596
RFT							
BUN	23.5 ±15	23.8 ±12.3	0.851	25.3±15.5	0.071	29.4 ±26	<0.001
Creatinine	1.3 ±1.4	1.3 ±1.6	0.749	2 ±4.5	0.321	1.2 ±0.8	0.580
LFT							
Bilirubin	0.6 ±0.4	1.8 ±9.8	0.282	0.7 ±0.7	0.321	0.8 ±0.9	0.001
SGOT	46.2 ±49.8	36.3 ±24.5	0.023	42.3±64.9	0.597	51.1 ±82.6	0.087
SGPT	66.9 ±208.1	37.8 ±28.8	0.225	36.7±26.5	0.214	51.8 ±109.5	0.144
ALK Phos	72.5 ±39.4	95.1 ±38.5	0.038	62.8±34.6	0.349	82.1 ±29.6	0.520
CRP	10.1 ±10.5	5.6 ±7.8	0.003	11.2±11.9	0.674	8.6 ±12.7	0.300
IL 6	73.4±69.73	-	-	-	-	-	-
Ferritin	720.2±1074.6	-	-	-	-	-	-
DDIMER	1211.8± 2146	-	-	-	-	-	-
LDH	431.5 ± 310.7	-	-	-	-	-	-

DISCUSSION

This study evaluated the treatment effect of remdesivir in patients with moderate-to-severe COVID-19 and its association on in-hospital overall mortality, Length of hospital stay (LOHS) and safety outcomes. Results of this study revealed that the mean duration of hospitalization from onset of COVID 19 symptoms is significantly higher in remdesivir group, though there is no significant difference in overall mortality at 28 days. A simple study executed in different countries with more than 11,000 patients enrolled for the period of six months, showed no mortality benefit with the administration of Remdesivir, similar to results of our study [11]. Likewise results were reported by the study using Remdesivir on COVID-19 patients with shortening the recovery and hospitalization time but again no benefit was noticed in relation to mortality status of COVID-19 patients [4]. A meta-analysis reported the final outcomes of several studies done to evaluate the role of Remdesivir in COVID-19 patients and all of them reported no significant depletion in overall mortality when compared to control group [12]. A sequential analysis of randomized controlled trials showed that the remdesivir had no significance in curbing all-cause mortality in COVID-19 patients (RR 1.48, 95% CI 0.25–8.78; 1 RCT; 384 patients) [13].

LOHS was lower in Remdesivir group and which is significant in the female sub-group as compared to control arm in in the present study. A brief report of rapid review on COVID-19 by South African department of health presented the conclusions of the studies stating no significant difference in hospital stay between Remdesivir and control group [14]. An original research on Remdesivir effect showed a longer hospital stay in Remdesivir group but no effect on survival rate. Reason for longer stay was discussed with the conclusion that the longer stay may be attributed to decision of the physician for the completion of the Remdesivir course which is 5 days or 10 days, with no relation to clinical condition of the patient [15]. However, in the present study, females in the remdesivir group were found to have a reduced LOHS compared to the males, which is not supported by the real-world evidence as per the various publications and needs to be re-evaluated in upcoming studies to get a realistic and an authentic explanation.

In our study, no adverse events were reported to be occurred in the remdesivir group. The safety profile of remdesivir has already been evaluated in several studies. A retrospective review of medical records was conducted which reported no adverse events in Remdesivir receiving group that coincides with the results of our study [16]. A review conducted on effect of Remdesivir data reported it to be favourable over-all as per results of several clinical trials which supports the outcome of this study [17]. A multicenter open-label trial was conducted to evaluate the efficacy of Remdesivir in COVID-19 patients and the results were again backing the results of this study by showing no adverse events in remdesivir receiving patients [18].

A systematic review reinforce the results of our study by concluding that the serious adverse events were significantly less in Remdesivir group with the absolute risk difference of 6% (RD −0.06; 95% CI −0.09 to −0.03) as compared to the control group [19]. Decreased rate of adverse events with both short-term (5-day) and long-term (10-day course) course of remdesivir compared with standard care were reported in a systematic review [20]. A review literature evaluating the efficacy of Remdesivir in COVID-19 patients reported lesser adverse events in remdesivir group than placebo, backing up for the results of present study [21].

Hypertension, followed by diabetes mellitus, has been found to be the most common pre-existing comorbidity that is associated with COVID-19 [22]. A retrospective study concluded hypertension to be an independent risk factor in relation to COVID-19 severity and death [23].

Hypertension was found to be associated with COVID-19 mortality and severity in a multicentre study conducted in China [24]. This study spotted the same results in relation to hypertension in COVID-19 and showed it to be statistically significant ($p<0.05$) and to be associated with the most number of deaths in Remdesivir group.

In this study the invasive mechanical ventilation days were significantly higher in control group as compared to remdesivir group. ACTT-1 Study Group (Adaptive Covid-19 Treatment Trial) also showed the same as patients who were not requiring any non-invasive ventilation, high-flow oxygen, invasive ventilation, or ECMO (extracorporeal membrane oxygenation) at baseline, the occurrence of new non-invasive ventilation and high-flow oxygen requirement was lesser in Remdesivir group than in placebo group (17% [95% CI, 13 to 22] vs. 24% [95% CI, 19 to 30]). Patients who were enrolled on mechanical ventilation or ECMO required them for lesser number of days as compared to patients in control group (median, 17 days vs. 20 days). Also, patients who were not enrolled on mechanical ventilation or ECMO required these measures lesser in number in during the treatment in remdesivir group than in control group (13% [95% CI, 10 to 17] vs. 23% [95% CI, 19 to 27]) [4].

A review evaluating the role of biomarkers in COVID-19 tabulated the results of several studies which showed that CRP level was an important factor in evaluating the disease severity and prognosis during the treatment expect for Luo et al. who did not find any association of CRP levels to severity or prognosis of COVID-19 infection. Also, the cytokine IL-6 was found to be strongly associated with the disease severity and its higher values have shown a correlation to requirement of mechanical ventilation, lung damage on CT scan and other inflammatory markers [25].

In the present study, IL-6 was also found to be significantly high (103.7±80.0) in remdesivir group as compared to the control (73.4±69.73). IL-6 appears to be highly effective in discriminating and predicting the severity of COVID-19 infection in patients, thereby evaluating the outcomes [26]. An increase in IL-6 levels is thought to imply a possible mechanism of cytokine-mediated lung damage caused by COVID-9 infection [27]. Evidence from a multi-center retrospective study confirmed a significant increase in the levels of IL-6 in non-survivors of COVID-19 suggesting a strong association of IL6 with prediction, treatment response and outcome to the severity of COVID-19 [28,29]. In our work, despite the high serum levels of IL-6 were found among patients in the Remdesivir group, the all-cause mortality at 28 days among Remdesivir treated did not show any significant difference compared to the control group.

Present study also showed that the biomarkers have significant role in COVID-19 population presenting a benefit of evaluating the risk related to the infection. A review states the same by stating that the early evaluation of biomarkers in COVID-19 can be helpful in ruling out the disease severity and thereby reducing the risks associated with it. Lymphocytes generate inflammatory response in our body to counteract the virus present. In COVID-19 the levels of lymphocytes become lower indicating poor outcomes of the disease. The SGPT and SGOT are released in case of abnormal liver functioning which in COVID-19 is related to inflammation rather than COVID-19 as a disease itself [30].

Our study has the limitation of being a single centred study, and the number of patients enrolled were also very less to generalise the results to the global population. Thus, more studies on lager scale with larger number of patients are required to be done to substantiate the results of the present study.

CONCLUSION

The randomized controlled trial showed that antiviral drug remdesivir was adequately tolerated, but did not show significant clinical effects on all-cause mortality status at 28 days in patients with moderate to severe COVID-19 as compared to control arm. Despite the high level of IL-6, a marker of inflammation and late hospitalization, remdesivir group showed similar clinical outcome to control group in terms of all-cause mortality. However, Remdesivir group has shown reduction in length of hospital stay which is significant in female sub-group and the invasive ventilation support is significantly lower in remdesivir arm. Among all the pre-existing comorbidities, hypertension followed by diabetes mellitus, was found to be the most common comorbidity in overall study population. Biomarker values were found to be an indispensable tool in detecting severity and prognosis of the infection, providing a substantial clinical applicability and assistance to the healthcare workers in treating the life-threatening disease. More rigorous studies with larger sample sizes are needed to continue to understand the effects of remdesivir on a generalized scale in patients with severe form of COVID-19.

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