Impact of Remdesivir in survival improvement of COVID patients; a comparative analytical study

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Abstract

Objective: To compare the survival in hospital admitted Corona patients receiving standard therapy alone and those receiving Remdesivir with standard treatment within 14 days after admission, using Kaplan Meier analysis and Cox regression analysis.

Methods: It was a quasi-experimental study conducted in the Institute of Molecular Biology and Biotechnology (IMBB) department at the University of Lahore**.** 80 COVID-19 patients of both genders were included in this study.Out of which, 40 COVID-19 patients were given standard treatment plus Remdesivir, while the remaining 40 COVID-19 patients were given standard treatment alone. Patients were followed up for 14 days during which time their survival was noted. The Kaplan-Meier-technique is used for survival analysis, Cox regression analysis was conducted toassess the relative contribution of risk factors of mortality in COVID-19 patients.

Results: The two groups were gender-matched with 82.4% males and 17.6% females in the treatment group whereas there were 83.3% males and 16.7% females in a control group respectively. Mean ages were 45.12±16.93 years, whereas, in the control group, mean ages were 60.69 years with a standard deviation of 11.13 years. The median survival in the treatment group was 9.00 days control group as well as in cases. The survival betweenthe two groups was not statistically significantly different between the two groups (p=0.69). Survival was analyzed against treatment after adjusting for age, IL-6 levels, and gender. It was found that except age (odd ratio=0.96, p value=0.05) neither treatment type (odd ratio=1.39, p value=0.50), serum level of IL-6 (Odd ratio=0.85, p value=0.11) nor gender (Odd ratio=0.90, p value=0.86) affected survival of patients.

Conclusion: We concluded from the current research that Remdesivir did not affect the survival of COVID-19 patients even after adjusting for age and gender.

Keywords: Remdesivir, Kaplan-Meier approach, cox regression analysis**.**

1.0 Introduction:

Coronavirus disease is defined as an illness caused by a novel coronavirus now called severe acute respiratory syndrome coronavirus, which was first identified among an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China. It was initially reported to the WHO on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency. On March 11, 2020, the WHO declared COVID-19 a global pandemic (Shi *et al* 2020; Aleissa *et al.,* 2021).It is a pathogenic virus that produces the symptoms of severe acute respiratory syndrome with high mortality and morbidity rate. Patients who were affected by this virus showed progressive consolidation of the lungs and pneumonia. The majority of individuals infected with the disease, i.e., eight percent (8%) of the population, had slight to mid signs. In contrast, fourteen percent (14%) of the individuals had shown severe symptoms, including breath shortness, lack of oxygen, and pulmonary damage leading to the failure of different organs (Ruan *et al.,* 2020). Severe symptoms were more frequently seen in elderly patients. Certain individuals continued with various symptoms even after recovering from the infection, and organ dysfunction was reported (Liu et al., 2020).

Increased plasma levels of cytokines (IL-2, IL-6, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon- (IFN), macrophage inflammatory protein 1 (MIP1A), and tumor necrosis factor (TNF) were seen in severe COVID-19 infected patients. The severity and prognosis of the illness are linked to increased levels in these cytokines (Lu *et al*., 2021; Sanyaolu *et al.,* 2020; Kang and Jung, 2020).

Coronaviruses belong to the order of Nidovirales, and the family of Coronaviridae. The name "Coronavirus" was given as a result of the projections that appeared to be in the form of a crown on the external layer of the viral strain. Alpha (a), beta (b), gamma (c), as well as delta (d) coronaviruses are the divisions that all belong to the family of Coronavirus (Hendaus, 2020; de groot *et al.,* 2020; Pal *et al.,* 2020).

Remdesivir is an important antiviral drug approved by the Food and Drug Administration (FDA) in the year 2019 to manage patients admitted to hospital facilities due to coronavirus infection. It is a nucleoside analog that inhibits the replication mechanism of viruses in a wide range of RNA viral groups, such as the Coronavirus. Remdesivir, a broad-spectrum antiviral first developed for the treatment of the Ebola virus, is one top option (EBOV). Despite performing well in pre-clinical investigations (Teoli *et al.,* 2021). Remdesivir seems to have a strong clinical

capacity to reduce the duration of healing in individuals with symptomatic and serious COVID-19. It also improves prognosis in patients with moderate COVID-19 (Mallah, *et al.*, 2021).

The Purpose of the study was to investigate the role of remdesivir to treated COVID patients already admitted in hospital receiving standard therapy using Kaplan Meier analysis and Cox regression analysis.

2.0 Materials and Methods:

2.1 Study Setting:

The study was conducted in the Institute of Molecular Biology and Biotechnology, The University of Lahore. Samples of all the PCR confirmed patients of Covid-19 were collected from Bahria International Hospital, Lahore.

2.2 Inclusion and Exclusion criteria:

Patients of both genders above the age of 18 years with positive PCR patients with suggestive symptoms who were admitted to COVID wards during the periods of study duration were included in this study. People with chronic inflammatory illnesses might make the clinical picture ambiguous and Patients with comorbidities like diabetes and heart disease were excluded.

2.3 Sampling Technique:

Conveinient non-probability sampling technique was employed to select the study participants.

2.4 Study Participants:

All the patients (80) were screened at the Bahria hospital Lahore. Informed consent was obtained before being included in this study. A total of 80 patients were enrolled in the study divided into remdesivir plus standard treatment and standard treatment only.

2.5 Determination of IL-6 and GP 130 by ELISA kit method:

The levels of IL-6 and GP 130 were determined by the human available diagnostic ELISA kit method according to (Mansoor *et al.*, 2022; Maqbool *et al.*, 2019). The standard was prepared from 200pg/ml and assessable concentration of interleukins and GP 130 remained at 3 pg/mL. First of all, 100µL of serum sample was added to the ELISA plate and incubated at room temperature for 120 minutes. After incubation, the plate was washed with washing buffer solution. After the removal of extra water from the ELISA plate, the plate was inverted on a paper towel. 100µl of HRP conjugate solution was added into each well and incubated at room temperature for 1 hour. The plate was washed again and dried on a paper towel for the removal of residual water.

After that, the substrate was added into each well with a concentration of 100µL and kept in dark room temperature for incubation for a period of 15 minutes. Later on, TMB was added with the amount of 100µl into each well and placed for one hour. In the last, 50µl of stop solution was added which provided the color perception during this reaction, finally, the absorbance was taken at the 460 nm wavelength by ELISA reader.

2.6 Statistical analysis:

The current study used SPSS 21 software to understand the relationship. Descriptive statistics, survival analysis using the Kaplan Meiercurve, and Cox regression tests have been applied to check the null hypothesis.

3.0 Result:

3.1 Descriptive Statistics

The total number of patients was divided into two groups based on the type of treatment received. The 80 people who took part in the study were COVID-19 positive. The first group comprised 40 patients who were given standard treatment alone. Similarly, the second group of 40 patients received standard treatment plus Remdesivir.

As seen in table 1, group-I with standard treatment alone has 83.3% male and 16.7% female participants whereas in group-II with standard treatment plus Remdesivir male members were 82.4% and female members were 17.6(p=0.95). Mean age in years in group-I was 45.12 ±16.93 years and in group-II, age in the year was 60.67 with a standarddeviation of 11.13 and their 'p'-value was 0.01 which is statistically significant.

Table: 1 Demographic characteristics of participants

Sr. no.	Characteristic	Standard treatment Alone	Standard treatment + Remdesivir	P value
1	Gender n (%)	Males 34(83.3%) Females 6(16.7%)	Males 33(82.4%) Females 7(17.6%)	0.95[a]
2	Age in years mean±SD	60.67±11.13	45.12±16.93	0.01[b]*

[a] =Chi square test; [b] = T test; *=statistical significance

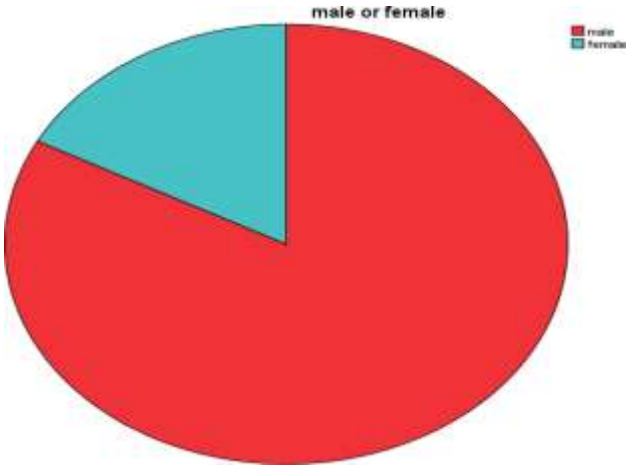

Fig: 1 Pie chart showing the distribution of genders in the cohort

3.2 Analytical Statistics

According to the table: 2, serum levels of IL-6 in group-I were 7.09±2.67 (pg/ml) whereas, in group-II, it was 7.78(pg/ml) with a standard deviation of 2.46 and the 'p' valuewas 0.49 which was not statistically significant. And the serum levels of gp130 in Group-I was 5.11(mg/ml) with a standard deviation of 2.04 and in group II the levels were 3.45(mg/ml) with a standard deviation of 1.40 at p=0.2.

Table: 2 Comparison of serum levels of IL-6 and gp130 between the treatment and control groups

Sr.no	Serum levels	Standard treatment+ Remdesivir	Standard treatmentalone	P Value*
1	Serum levels of IL-6(pg./ml)±SD	7.09±2.67	7.78±2.46	0.49

2	Serum levels of gp130(mg/ml)±SD	5.11±2.04	3.45±1.40	0.2

*calculated by Students't'-test

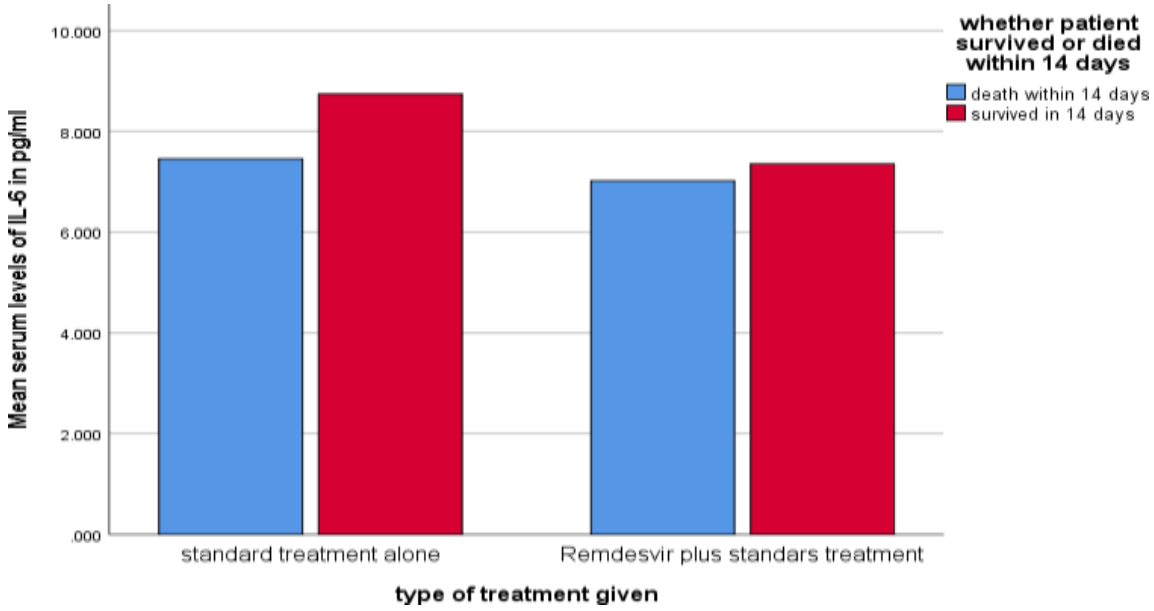

Fig: 2 Serum levels of IL-6 in treatment and control groups

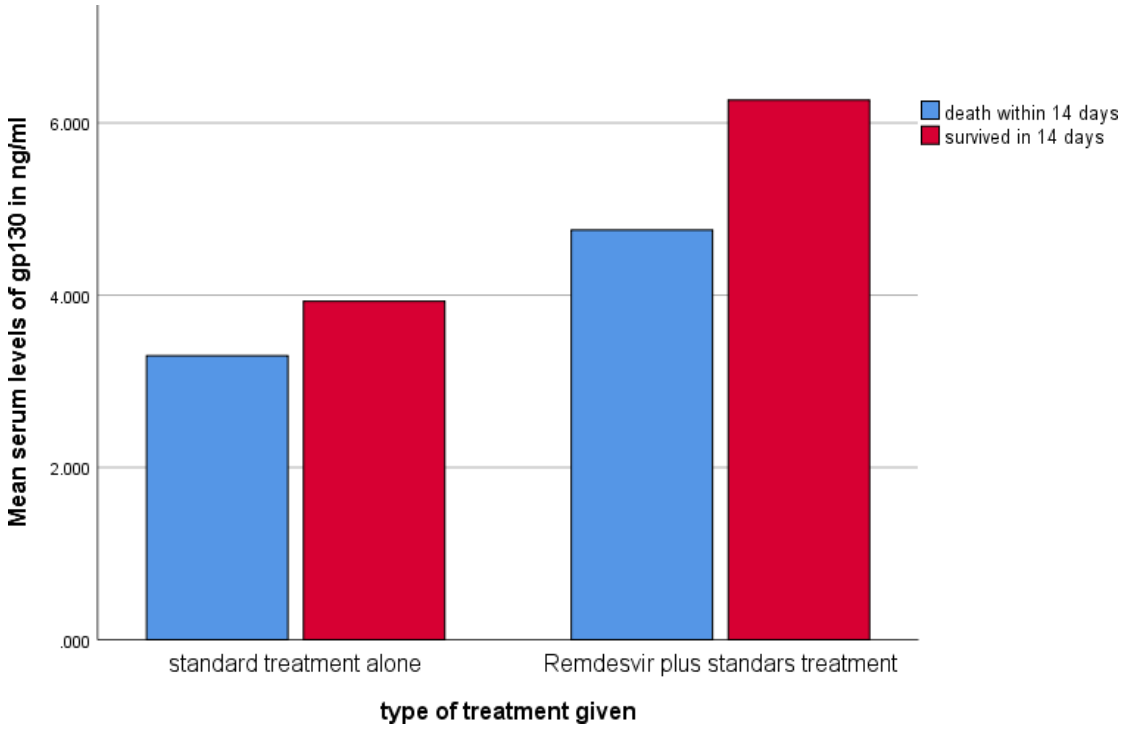

Fig: 3 Levels of gp130 according to the type of treatment given

3.3 Kaplan Meier Analysis:

As seen in table:3, Mean survival in group-I of standard treatment alone was 10.92 daysand mean survival in group II of Remdesivir with standard treatment was 10.53 days, andthe median survival in group-I of standard treatment alone was 9.00 days and median survival in group-II of Remdesivir with standard treatment was 9.00. As seen in table 4. Survival between the two groups was not statistically significantly different with the 'p'- value 0.69.

Type of treatment given	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	SEM	95% Confidence Interval	
			Lower	Upper			Lower	Upper

			Bound	**Bound**				**Bound**	**Bound**	
Standard treatmentalone	10.92	0.95	9.05		12.79	9.00	1.16		6.74	**11.26**
Remdesivir plus standard Treatment	10.53	0.99	8.58		12.48	9.00	0.68		7.67	**10.33**
Overall	10.79	0.73	9.36		12.23	9.00	0.67		7.69	**10.31**
	a. Estimation is limited to the largest survival time if it is censored.									
	Overall Comparisons									
					Chi-Square		Df		**Sig.**	
	Log Rank (Mantel-Cox)				0.16		1		**0.69**	
	Test of equality of survival distributions for the different levels of the type of treatmentgiven.									

Table: 3 Means and Medians for Survival in treatment and control groups

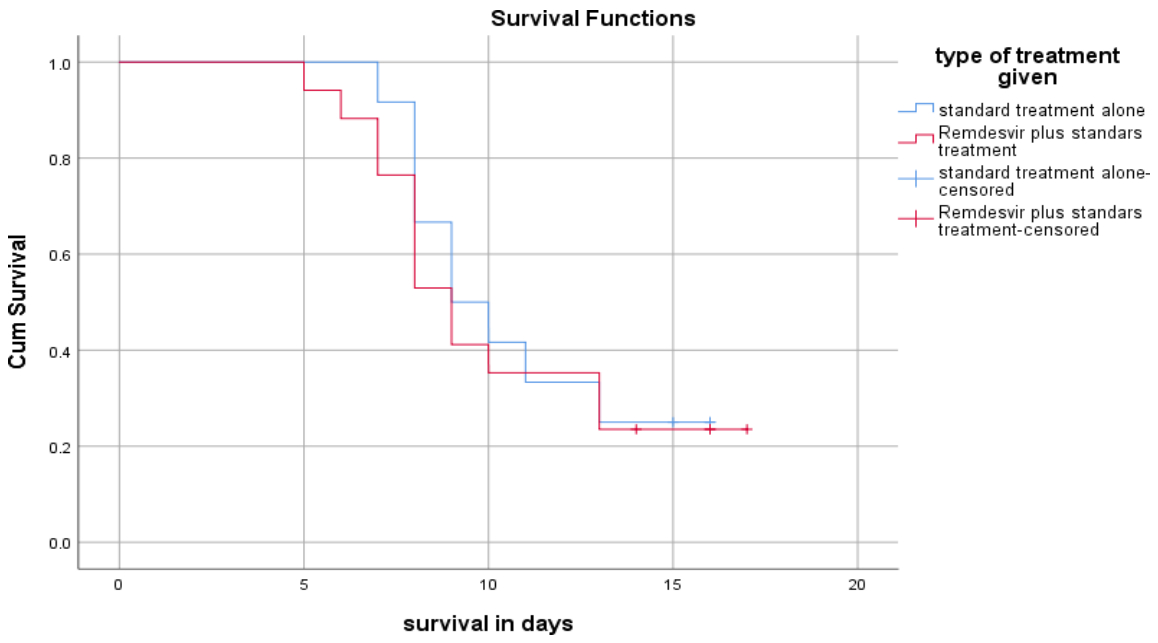

Fig:4 Comparison of Kaplan Meier survival for patients treated with Remdesiviralong with standard compared with those given standard treatments alone

Table: 4 Factor affecting survival in COVID-19 patients by Cox Regression analysis

					Lower	Upper
Type of treatment given	0.33	0.49	0.50	1.39	0.53	3.69
Serum levels of IL6 in pg ./Ml	0-.16	0.10	0.11	0.85	0.69	1.04
Age in years	-0.04	0.02	0.05	0.96	0.93	0.99
Gender	-0.10	0.58	0.86	0.90	0.29	2.81

4.0 Discussion

In the current study, we found that the median survival between patients receiving Remdesivir as compared to the control group did not differ significantly ($p<0.05$). Secondly, we found that age was the only significant factor affecting survival (beta value=-0.04, p value=0.05). Regarding the effect of Remdesivir on survival, our study is parallel with the findings of in which they studied a cohort of 568 patients who survived and 507 non-survivors from different countries and they found that the male members of age ≥70 years showed only 25% of survivors. From the onset of symptoms, the survival time was significantly less in elderly patients than that of young patients (Median: 29 versus 62 days) with the 'p' value of <0.01.

Similar findings were observed in past. For treatment of patients with severe coronavirus disease 2019 (COVID-19). No definite antiviral drug has been established evidence for treatment of patients with severe coronavirus disease 2019 (COVID-19). Remdesivir is a nucleoside analogue prodrug, that has inhibitory effects on animal and human coronaviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro, and inhibits Middle East respiratory syndrome coronavirus, SARS-CoV-1, and SARS-CoV-2 replication in animal models (Wang. *et al* 2020).

In one past research Remdesivir even showed less effective in patients with hyperglycemia. In this study, both in diabetic and nondiabetic situations, Remdesivir has been proven as a possible

therapeutic agent in the treatment of COVID-19, recovery rate was slow in diabetic patients as compared to non-diabetic patients in which the recovery rate was high.This study was conducted on a total of 850 COVID-19 patients, out of which 48% were diabetic and 52% were nondiabetics. The results indicated that nondiabetic individuals who were taking Remdesivir recovered from COVID-19 within 10 days showing a 95% confidence interval ($p < 0.01$), whereas the diabetic individuals showed slow recovery in 15 days. Remdesivir treated nondiabetic patients showed greater chances of clinical improvement at 15th day than those with diabetes. Remdesivir administration improved the levels of various biochemical parameters, such as C-reactive protein, lactate dehydrogenase, D-Dimer, and ferritin both in diabetic and nondiabetic patients. Thus, Remdesivir was not so effective in elevated blood glucose (Dande *et al.,* 2021).

Other studies did find Remdesivir to be a useful therapeutic agent (Olender, et al 2020), in a double-blind, randomized, placebo-controlled trial in which adult COVID positive hospitalized patients with respiratory tract infection were treated with intravenous Remdesivir. Patients were randomly allotted to receive either a placebo for up to 10 days or Remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days). A total of 1062 patients experienced randomization, 521 to placebo while other 541 were treated with Remdesivir. Data showed that COVID-19 hospitalized patients showed quick recovery with Remdesivir as compared to placebo and had evidence of lower respiratory tract infection. {Ansems, et al 2021}

In a study conducted by Olender, 74.4% of patients who received Remdesivir versus 59.0% in the non-Remdesivir-group attained the primary recovery at day 14, reflecting a 2-fold higher adjusted chances of recovery, which was not found in our study as we found the relation of Remdesivir not significant. Beigel in a study suggested that treatment with Remdesivir may not only reduce the disease load but may also decrease the use of limited health care resources during this pandemic, and these findings contradict our results as we didn't find any significant relation (Beigel *et al*., 2020).

According to another study, 312 and 818 patients were calculated in the Remdesivir and non-Remdesivir-cohorts, respectively. The patient who recovered in non-Remdesivir cohort on day 14 were 59.0% versus 74.4% of patients recovered in the Remdesivir-cohort. On day 14. The death percentage in non-Remdesivir cohort was 12.5% while 7.6% of patients in the Remdesivir-cohort had died. The analysis showed by day 14, that treatment of COVID patients with

Remdesivir was associated with significantly greater recovery rate versus standard-of-care treatment in patients. (Olender *et al*., 2020).

The first randomized, double-blind, placebo-controlled, multicenter clinical trial was reported on April 29, 2020. The study was conducted in China with 237 patients (158 in the Remdesivir group and 79 in the placebo control group), and the aim of the study was to assess the time in which the sign and symptoms showed improvement. The study indicated that treatment with Remdesivir did not show a significant reduction in the time taken to achieve clinical improvement. This result correlates with our findings of the study.

One report indicated that Remdesivir therapy is useful for improving the health status of patients associated with COVID; however, the study was without a control group in this study. Therefore, this information is not sufficient to confirm the efficacy of Remdesivir in treating patients with COVID-19. A recent report by Wang had shown that Remdesivir has no impact on health status, mortality rate and overall viral load (Wang et al., 2020) and these findings were matched with our findings.

The current study has several limitations. First, the sample size was limited. However, this was compulsory due to the inaccessibility of patients during the corona pandemic. Second, the study design was quasi-experimental. The ideal way to establish the efficacy of the drug is a randomized control trial but during the pandemic, it was difficult to decide treatment based on the research question, therefore treatment was given as per clinician assessment of the patient's medical need in a future study the randomized control trial is carried out better results might be obtained. The trial was implemented during a time of restricted travel, and hospitals restricted the entrance of nonessential personnel.

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