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Role of Remdesivir for Patients with Moderate to Severe COVID-19 Pneumonia

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Abstract

In 2019–2020 a new coronavirus named SARS-CoV-2 was identified as the causative agent of a acute respiratory infection named COVID-19, which is causing a worldwide pandemic. There are still many unresolved questions regarding the pathogenesis of this disease and especially the reasons underlying the extremely different clinical course, ranging from asymptomatic forms to severe manifestations, including the Acute Respiratory Distress Syndrome (ARDS). The objective of this study is to test the efficacy of remdesivir against moderate to severe covid infection caused by SARS-COV-2 virus. This is a retrospective cohort study at the critical care department Cairo University; one-hundred patients aged 18-79, diagnosed with covid 19 infection with moderate and severe acute respiratory syndrome who needed high oxygen support or ventilatory support that needed icu admission. We divided the patients into two groups each group 50 patients, group 1 received remdesivir in addition to standard care protocol according to the local guidelines of Egyptian ministry of health, while group 2 received only the standard care protocol. One hundred patients were admitted to the Intensive Care Unit (ICU) suffering from severe hypoxemia with moderate to severe covid pneumonia, in group (1) which received remdesivir the mean days of mechanical ventilation was 2.96 days, while in group (2) who received the standard care only was 3.48 days. The mean days of ICU stay in group 1 was 10.16, while in group was 9.2. In group (1) there were 44 patients improved (88%), while in group (2) 40 patients were improved (80%). In group (1) 6 patients died (12%), while in group (2) 10 patients died (20%). In this study there was no statistical difference in both groups of patients regarding ICU stay, days of mechanical ventilation and outcome.

Keywords: COVID-19, Pneumonia, Mechanical ventilation, Remdesivir.

Full length article **Corresponding Author*, e-mail: ptrservices2022@gmail.com

1. Introduction

Coronaviruses are important human and animal pathogens. A novel coronavirus was identified as the cause of group of pneumonia cases in Wuhan, China at the end of 2019. It spread rapidly, resulting in an epidemic throughout China, then followed by a global pandemic. In February 2020, the World Health Organization designated the disease COVID-19, which stands for corona virus disease 2019 [1]. The virus that causes COVID-19 is designated severe acute respiratory syndrome corona virus 2 (SARSCoV2); which previously referred to as 2019-nCoV. The full picture of COVID-19 is still not clear [2]. Clinical manifestations of COVID-19 are caused by replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) so the antiviral therapies are being investigated for the treatment of COVID-19. These drugs inhibit viral entry (via the angiotensin-converting enzyme 2 [ACE2] receptor and trans membrane serine protease 2 [TMPRSS2]), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNAdependent RNA polymerase. Viral replication is active early in the course of COVID-19 so antiviral therapy may have the greatest impact early before the illness progresses to the hyper inflammatory state that can characterize the later stages of disease, including critical illness [3-4]. Remdesivir is a nucleotide prodrug of an adenosine analog that is given intravenously.

Mechanism of action of Remdesivir is by binding to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription. In vitro, it has demonstrated activity against SARS-CoV-2 [5]. The Food and Drug Administration (FDA) has approved use of Remdesivir for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. Remdesivir should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital [6-8]. Remdesivir can cause elevated transaminase levels, gastrointestinal symptoms like nausea, elevation in prothrombin time, and hypersensitivity reactions. Liver function tests and prothrombin time should be obtained in all patients before remdesivir is administered and during treatment as clinically indicated. Remdesivir may need to be discontinued if alanine transaminase (ALT) levels increase to >10 times the upper limit of normal and should be discontinued if an increase in ALT level and signs or symptoms of liver inflammation are observed [9].

2. Materials and Methods

2.1. Study Design

This is a retrospective cohort study done at the critical care department Cairo University aiming at assessing the Role of Remdesivir for Patients with moderate and Severe Covid-19. Analysis of one hundred patients from March 2020 to December 2021. Inclusion criteria were patients of both sexes aged above 18 years old who had covid-19 positive tested by PCR, bilateral infiltrates in computed tomography (CT) chest and pao2/fio2<250 mmHG. Exclusion criteria patients aged below 18 years old and had mild covid-19 pneumonia. Moderate to severe form of covid -19 infection was defined by the need of high oxygen support, oxygen masks or non-rebreather mask for moderate disease and ventilatory support ((either invasive or noninvasive)) for severe. All patients were subjected to detailed history, full examinations, full laboratory profile, electrocardiogram (ECG) and chest imaging including CT.
The study was approved by the ethical committee of faculty of medicine, Cairo University. All patients provided written informed consent. Protocol number MD372021.

2.2. Procedures

All Patients received the standard care and therapeutic management including antibiotics, PPI, anticoagulation, steroids, supplement, Oxygen support and ventilatory support as needed. Patients were divided into two groups each had fifty patients, group 1 received remdesivir plus the standered carewhile group 2 received the standered care only. Group 1 received 10-days course of remdesivir, consisting of 200 mg administered intravenously on day one, followed by 100 mg daily for the remaining nine days of treatment.

2.3. Outcome

The primary outcome of the study was to evaluate the effect of remdesivir in clinical improvement and hospital mortality, need for mechanical ventilation either invasive or non-invasive, length of ICU stay and length of hospital stay.

2.4. Statistical analysis

We compared the baseline characteristics of the participants in both groups including signs and symptoms, comorbidities and inflammatory markers. We did a baseline APACHE II score for both groups to assess the risk of multiorgan failure and mortality [10]. We did standard survival analysis following up participants from the date of entry to date of discharge either with improvement or death. We compared need for mechanical ventilation either invasive of non-invasive, inflammatory markers, duration of ICU stays, duration of hospital stays and death in each group. Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi square (c2) test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered as statistically significant [11-12].

3. Results and discussion

Out of one hundred patients admitted to ICU with moderate to severe COVID-19 pneumonia, there were (74%) males and (26%) females, with mean ± SD of age 57.24 years ± 13.41 years. Out of one hundred patients, there were (42%) diabetic patients, (48%) hypertensive patients, (28%) cardiac patients, (14%) renal patients, (2%) hepatic patient, (12%) patients with chronic respiratory problems. Duration of symptoms with mean ± SD were 7.14 days ± 3.33 days. Out of one hundred patients there were (70%) with moderate symptoms and (30%) with severe symptoms according to their oxygen requirements. The mean ± SD of Oxygen saturation upon admission was 84.30% ± 8.02% and the mean ± SD of temperature upon admission was 38.82C ± 0.32C. Total leukocytic count (TLC) with mean±SD was 7.17±3.52, lymphocytes percentage with mean± SD was 16.03%±9.87%, ferritin level with mean ±SD was 477.80±356.50, lactate dehydrogenase (LDH) level with mean± SD was 693.89±296.58, C-reactive protein (CRP) level with mean± SD was 118.55±61.90, and D-dimer level with mean ± SD was 671.00µg/ml ± 1058.77µg/ml. The mean stay in ICU was 9.68±6.34 days, the minimum length of stay (LOS) was 3 days and the maximum LOS was 32 days with median 9 days, The mean stay in hospital was 13.80±6.46 days, the minimum length of stay (LOS) was 7 days and the maximum LOS was 39 days with median 12 days. Age of Remedisivir group with mean 55.84±10.79 years, while in the other group was 58.64±15.71 years. In remdesivir group out of fifty patients, thirty-six patients were males (72%) and fourteen were females (28%), While in the other group thirty-eight patients were males (76%) and twelve were females (24%) with P-value 0.747. There was no statistically significant difference between DM, HTN, cardiac, hepatic, and chronic respiratory problems in both groups of patients.

However, there was statistically significant difference between patients with renal problems with P value 0.010 as patients with chronic renal diseases didn't receive remdesivir. There was significant difference between duration of symptoms between two groups with P value 0.009 as remdesivir was given to patients with early days of symptoms. There was no statistically significant difference between TLC, lymphocytes, LDH, CRP, PCT and D-dimer. However, there was statistically significant difference between ferritin level with P-value 0.017 as ferritin level was lower in remdesivir group. There was no statistically significant difference between APACHE II score upon admission and upon discharge and expected mortality % among two groups of study. Out of fifty patients who received remdesivir eighteen patients (18%) had side effects in form of bradycardia, elevated kidney function tests (KFT), and elevated liver function tests (LFT). Out of one hundred patients, fifty-two patients (52%) received Tocilizumab (actemra) and fourty-eight patients (48%) didn't receive. Remdesivir, sold under the brand name Veklury is a broad-spectrum antiviral medication developed by Gilead Sciences, the biopharmaceutical company [13-14]. It is administration is via intravenous injection. During the COVID-19 pandemic, remdesivir was approved and authorized for use in emergency to treat COVID-19 in around 50 countries. Updated guidelines from the World Health Organization in November 2020 include a conditional recommendation against the use of remdesivir for the treatment of COVID-19 [15-16]. This is a prospective cohort study that included patients admitted to critical care medicine department, Cairo University from March 2021 to December 2021 including 100 patients, for patients diagnosed to have Covid -19 infection with moderate and severe acute respiratory syndrome who needed high oxygen support or ventilatory support that required Icu admission. Inclusion criteria were patients of both sexes aged above 18 years old who had covid-19 positive tested by PCR, bilateral infiltrates in CT chest and pao2/fio2<250 mmHG. Exclusion criteria patients aged below 18 years old and had mild covid-19 pneumonia. Moderate to severe form of covid -19 infection was defined by the need of high oxygen support, oxygen masks or non-rebreather mask for moderate disease and ventilatory support ((either invasive or non-invasive)) for severe. All patients were subjected to detailed history, full examinations, full laboratory profile and chest imaging including CT. All Patients received the standard care and therapeutic management including antibiotics, PPI, anticoagulation, steroids, supplement, Oxygen support and ventilatory support as needed. Patients were divided into two groups each had 50 patients, group 1 received remdesivir while group 2 did not. Group 1 received 10days course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. In DisCoVeRy study 832 patients were enrolled into two groups, group 1 (414 patients) received remdesivir, while group 2 (418 patients) didn't. Wang et al., studied 236 patients who were enrolled into two groups, group 1 (158 patients) received remdesivir, while group 2 (78 patients) didn't. ACTT-1 Study 1062 patients were enrolled into 2 groups, group 1 (541 patients) received remdesivir, while group 2 (521 patients) didn't [17]. The mean ± SD of age of all patients enrolled in our study was 57.24 y ± 13.41 years with range 32 – 79. This goes with ACTT-1 study as mean ± SD for age was 58.9±15.0 years. Also, in DisCoVeRy study the median age was 64 years with range (54–73) years. While in wang et al., study the median age was 65 years with range (53-73) years. The studied patients were 74 (74%) males and 26 (26%) females. this is similar to DisCoVeRy study as male participant 70% and female participant 30%. While in wang et al male patients were 60.5 % and females were 39.5%, while in ACTT-1 study male patients were 64.4% and females were 35.6%. The most common comorbidity was hypertension, (48%), then diabetes (42%), then cardiac problems (28%), followed by renal problems (14%), followed by chronic respiratory problems (12%) and finally hepatic problems (2%). This is similar with what was mentioned by Wang et al study as the most common comorbidity was hypertension (42.2%), followed by diabetes (23.7%) and finally cardiac patients, (7.2%). However, in DisCoVeRy study the most common comorbidity was obesity (34%), then cardiac patients (28%), followed by diabetes (26%), followed by chronic respiratory patients (18%) and finally HIV (<1%). While in ACTT-1 study the most common comorbidity was hypertension (50.7%), followed by obesity (45.4%) patients and finally diabetes (30.6%). The median duration of symptoms onset was 6.5 days, in contrast to DisCoVeRy study and ACTT-1 whose median duration of symptoms onset was 9 days. Also, in Wang et al study the median duration of symptoms onset was 10.5 days. Regarding the severity of symptoms according to oxygen needs upon admission there were 70 patients (70%) with disease and 30 patients (30%) with severe**.** While in DisCoVeRy study there were 504 patients (61%) with moderate symptoms and 328 patients (39%) with severe symptoms. The oxygen therapy used during our study were oxygen masks in 48 patients (48%), high flow nasal cannula or non-invasive mechanical ventilation in 92 patients (92%), invasive mechanical ventilation in 22 patients (22%). While in DisCoVeRy study 492 patients (59%) needed supplemental oxygen masks, 179 patients (22%) needed non-invasive mechanical ventilation or high flow nasal cannula, 149 patients (18%) needed invasive mechanical ventilation or ECMO. Also, in ACTT-1 study in which 435 patients (41%) needed supplemental oxygen masks, 193 patients (18.2%) needed non-invasive mechanical ventilation or high flow nasal cannula, 285 patients (26.8%) needed invasive mechanical ventilation. While in Wang et al study 194 patients (82.2%) needed supplemental oxygen masks, 17 patients (7.2%) needed non-invasive mechanical ventilation, 21 patients (8.89%) needed invasive mechanical ventilation. On studying inflammatory markers on admission for all patients, the median lymphocytic count was 0.84 10^9 cells per L, the median CRP was 136.5 mg/l. This goes with what was mentioned by DisCoVeRy study as the median lymphocytic count 0.8 10^9 cells per L, median CRP was 106 mg/l. While the median ferritin level was 399 mg/l and the median Ddimer level was 306 µg/L. This is different from what was found in DisCoVeRy study as the median ferritin level was 812 mg/l and the median D-dimer level was 930 µg/L. The higher level of inflammatory markers (ferritin and D-dimer) in DisCoveRY study may be explained by late presentation of patients denoting storming (9 days vs 6.5 days).

Days of mechanical ventilation (MV) for all patients of the study were 3.62 days ± 1.8 days. While in Wang et al study the median days of mechanical ventilation was 11.25 days. The mean stay in ICU for all patients of study was 9.68±6.34 days, the minimum length of stay (LOS) was 3 days and the maximum LOS was 32 days with median 9 days. The mean stay in hospital was 13.80±6.46 days, the minimum length of stay (LOS) was 7 days and the maximum LOS was 39 days with median 12 days. While in Wang et al., study, the median stay in hospital was 24.5 days. The longer duration of MV and ICU stay in other studies in comparison to our study may be explained by the larger number of patients and libral usage of advanced strategies in treatment like ECMO in their studies. For optimum studying of remdesivir efficacy & safety, patients were divided into two groups, each group consisted of 50 patients one received remdesivir while the other didn't. The days of mechanical ventilation were less in remdesivir group than the control group, however this was statistically non-significant, as the mean days of MV was 2.96 in remdesivir group vs 3.48 in control group. This agrees with what was mentioned in ACCT1 study as median days of mv 23 days in remdesivir group vs 26 days in control group. In our study there was no significant difference between patients who received remdesivir and control group regarding hospital and ICU stay as mean days of icu stay was 10.6 in group of remdesivir and 9.2 in control group, while mean days of hospital stay was 13.76 in remdesivir group and 13.84 in control group. This agrees with wang et al study as mean days of hospital stay in remdesivir group was 25 and was 24 in control group. In contrast to ACTT-1 study which showed significant decrease in hospital stay in remdesivir group than the control group as median days in remdesivir group was 12 days vs 17 days in non-remdesivir group. This could be explained by the different pattern of studied patients, as ACTT-1 study was a multi-center study which had larger number of patients and included patients with mild disease while our study was conducted to moderate to severe form. In our study there was no significant difference between patients who received remdesivir and control group regarding mortality rate as 6 (12%) patients died in remdesivir group vs 10 (20%) patients in control group. This agrees with DisCoVeRy study as 34 (8%) patients died in remdesivir group vs 37 (9%) patients died in control group. Also, in ACTT-1 study as 59 (10.9%) patients died in remdesivir group vs 77 (14.77%) patients in control group. On studying safety of remdesivir, the most common adverse effects of remdesivir were elevated LFT which occurred in (24%), followed by bradycardia (8%) and finally elevated KFT (4%). While in DisCoVeRy study the most common adverse effects were arrythmia (3.1%), followed by elevated KFT (3%) and finally elevated LFT (2.6%). The higher incidence of side effects in our study may be explained by higher incidence of comorbidities in our patients upon admission.

Table 1: Shows description of all patients.

	Mean	Standard Deviation	Median	Minimum	Maximum
Age	57.24	13.41	55.50	32.00	79.00
DAYS OF SYMPTOMS	7.14	3.33	6.50	2.00	15.00
O2 sat on admission %	84.30	8.02	86.50	60.00	93.00
Temperature (^{0}C)	38.82	0.32	38.80	38.20	40.00
TLC	7.17	3.52	6.50	1.60	21.00
Lymphocytes %	16.03	9.87	13.00	1.90	40.00
Ferritin	477.80	356.50	399.00	9.00	2100.00
LDH	693.98	296.58	624.00	255.00	1550.00
CRP on admission	118.55	61.90	136.50	3.00	186.00
CRP after 1 week	39.21	55.56	15.00	0.60	183.00
D-dimer	671.00	1058.77	306.00	200.00	7227.00
APACHE II Score	14.94	7.12	12.00	6.00	34.00
Expected Mortality %	21.96	17.54	15.00	4.00	75.00
Days of invasive MV	1.72	4.02	0.00	0.00	20.00
Days of non-invasive MV	1.50	3.59	0.00	0.00	18.00
ICU days	9.68	6.34	9.00	3.00	32.00
Hospital days	13.80	6.46	12.00	7.00	39.00

Table 2: Shows characteristics and comorbidities of all patients.

		Count	%
Sex	**Female**	26	26.0%
	Male	74	74.0%
HTN	**Yes**	48	48.0%
	No	52	52.0%
Diabetes	**Yes**	42	42.0%
	No	58	58.0%
Cardiac history	**AF**	2	2.0%
	IHD	26	26.0%
	No	72	72.0%
Chronic respiratory problems	**Ashtmatic**	8	8.0%
	COPD	2	2.0%
	old Pulmonary embolism	2	2.0%
	No	88	88.0%
Chronic kidney disease	**YES**	14	14.0%
	NO	86	86.0%
Chronic liver disease	**HCV**	2	2.0%
	No	98	98.0%

Table 3: Shows age distribution between two groups of study.

	Remidisivir										**Chisquare test**
	Yes					**No**					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	
Age	55.84	10.79	54.00	38.00	79.00	58.64	15.71	57.00	32.00	79.00	0.573

Table 4: Shows characteristics and comorbidities in each group of study.

		Remidisivir				P value
		Yes		No		
		Count	%	Count	%	
Sex	**Female**	14	28.0%	12	24.0%	0.747
	Male	36	72.0%	38	76.0%	
HTN	**Yes**	22	44.0%	26	52.0%	0.571
	No	28	56.0%	24	48.0%	
Diabetes	**Yes**	22	44.0%	20	40.0%	0.774
	No	28	56.0%	30	60.0%	
Cardiac history	**AF**	0	0.0%	2	4.0%	1
	IHD	14	28.0%	12	24.0%	
	No	36	72.0%	36	72.0%	
Chronic respiratory problems	**Ashtmatic**	4	8.0%	4	8.0%	1
	COPD	0	0.0%	2	4.0%	
	Old pulmonary embolism	2	4.0%	0	0.0%	
	No	44	88.0%	44	88.0%	
Chronic kidney disease	**YES**	0	0.0%	14	28.0%	0.010
	NO	50	100.0%	36	72.0%	
Chronic liver disease	**HCV**	0	0.0%	2	4.0%	1
	No	50	100.0%	48	96.0%	

Table 5: Shows duration of symptoms among two groups of study.

	Remdesivir										Chi-square test
	Yes					No					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Duration of Symptoms	5.76	2.13	6.00	2.00	10.00	8.52	3.77	8.00	3.00	15.00	0.009

Table 6: Shows APACHE II score upon admission and expected mortality %, Total days of MV, ICU stay and hospital stay among two groups of study.

	Remdesivir										Chi-square test
	Yes					No					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Apache II Score	14.56	5.85	12.00	8.00	29.00	15.32	8.30	11.00	6.00	34.00	0.807
Expected Mortality %	21.00	14.83	15.00	4.00	55.00	22.92	20.16	15.00	4.00	75.00	0.864
Total Days of MV	2.96	3.40	0.00	0.00	14.00	3.48	4.18	0.00	0.00	20.00	0.658
ICU days	10.16	6.68	8.00	3.00	32.00	9.20	6.09	9.00	3.00	32.00	0.740
Hospital days	13.76	6.95	12.00	7.00	39.00	13.84	6.09	12.00	9.00	37.00	0.922

There was no statistically significant difference between days of mechanical ventilation among two groups of study.

There was no statistically significant difference between ICU and hospital days of stay among two groups of study.

Although the hospital stay was less in group of remdesivir there was no statistically significant difference between outcome among two groups of study.

Table 7: Shows outcome among two groups of study.

		Remdesivir				**Chi-square test**
		Yes		**No**		**P value**
		Count	**%**	**Count**	**%**	
Outcome	**Improved**	44	88.0%	40	80.0%	0.702
	Died	6	12.0%	10	20.0%	

Table 8: Shows side effects of remdesivir among population of study.

		Count	%
Remdesivir	**Yes**	50	50.0%
	No	50	50.0%
Side effects	**Bradycardia**	4	8.0%
	Elevated kft	2	4.0%
	Elevated lft	12	24.0%
	No	32	64.0%

Table 9: Shows number of seven patients who received the Tocilizumab among population of study.

		Count	%
Tocilizumab	**YES**	52	52.0%
	NO	48	48.0%

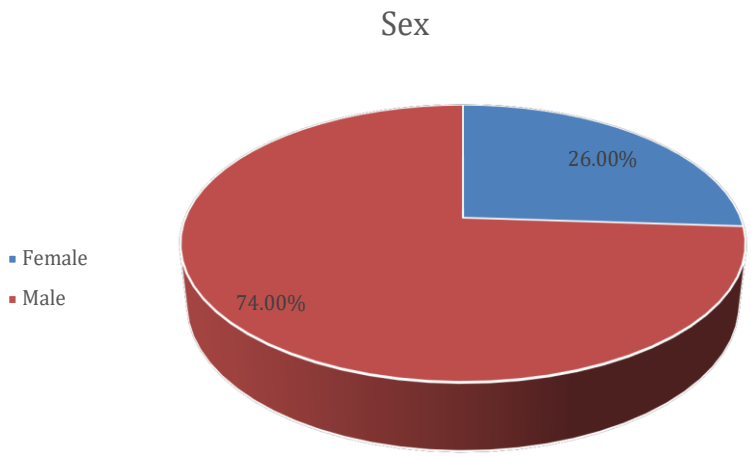

Figure 1: shows sex among groups of study.

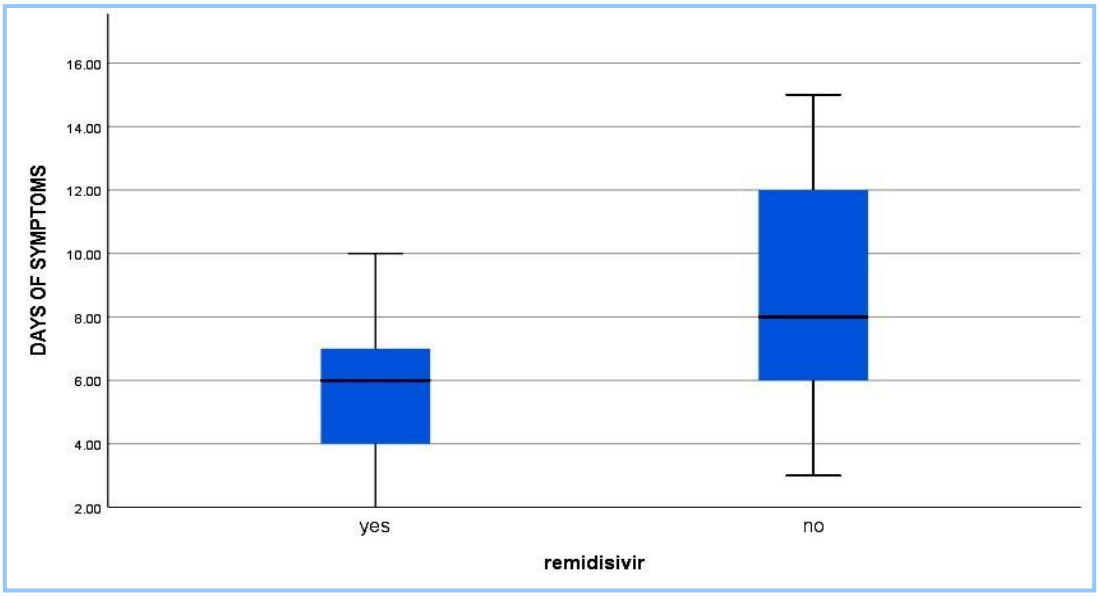

Figure 2: Shows duration of symptoms among two groups of study.

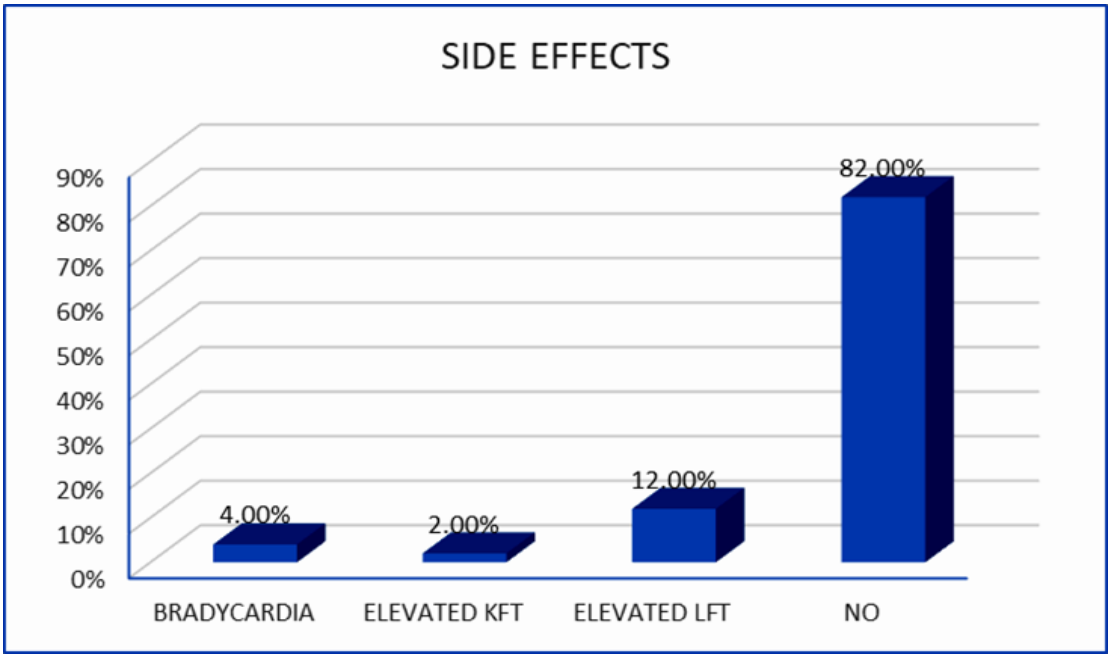

Figure 3: Shows side effects of remdesivir among population of study.

4. Conclusions

In conclusion, we found that although there is tendency to decrease mortality and hospital stay but using remdesivir did not show significant difference regarding decreasing mortality, need for mechanical ventilation (either invasive or non-invasive), duration of ICU stays and over all hospital stay in patients with moderate to severe Covid- 19 pneumonia.

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