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RESEARCH ARTICLE

Role of Remdesivir in Covid-19 Patients: A Study from the Capital City of Pakistan

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ABSTRACT

Background: Coronavirus disease 2019, caused by SARS-COVID-19 has emerged as a pandemic. It usually causes severe respiratory disease. Characteristically it undergoes genetic variability and newer strains emerge as a result of genetic mutations or environmental factors. It makes it difficult to be treated. We used remdesivir in our hospital to treat covid-19 patients. The aim of our study was to evaluate the role of remdesivir in COVID-19 patients.

Patients and Methods: We conducted a descriptive cross-sectional study on the patients admitted in the department of Medicine, Capital hospital, Islamabad, Pakistan from November 2020 to October 2021. All patients aged 14 years and above were included. Both SARS-CoV-2 positive patients by molecular biology and COVID suspected cases, selected on the basis of low oxygen saturation, deranged inflammatory markers, positive contact history and radiological findings with negative COVID19 PCR testing were included in the study. The data was compiled using Microsoft Excel and later was analyzed on SPSS version 24.

Results: Among 669 patients, 375 (56.1 %) were males and 294 (43.9%) were females. Median age of patients was 58.2 years. 349 (52.2%) were COVID PCR positive and 320 (47.8%) were PCR negative. Out of 669 patients 573 (85.7%) were discharged and 96 (14.3%) expired. Inflammatory markers before and after the treatment were measured with overall significant decrease (P-value 0.000) after treatment. Patients were divided into two groups, remdesivir given (n=436) and remdesivir not given (n=233). Hospital stay was of shorter duration among 249(57.6%) in remdesivir given group than in remdesivir not given group 183(42.4%). While evaluating outcome 370(64.6%) patients were discharged and 66(68.7%) expired in remdesivir given group and 203 (35.4%) patients were discharged and 30 (31.3%) expired in second group. Lactic dehydrogenase (LDH) level was raised (>480 U/L) in 378(68.5%) patients before taking remdesivir and was raised only in 209(47.9%) patients after taking remdesivir (P-0.027).

Conclusion: Our study revealed that Hospital stay was shorter (P-value 0.000) in remdesivir given group. There was no significant effect of remdesivir on patient's outcome and mortality (P-value 0.250). Only Lactic dehydrogenase was significantly decreased (p-value 0.027) in remdesivir given group.

Keywords: COVID-19, Remdesivir, outcome, Inflammatory markers

Introduction

Coronavirus causes corona virus disease, characterized by severe acute respiratory syndrome. It was first identified in an outbreak in the Wuhan city of China. The World Health Organization (WHO) termed the disease COVID-19. The coronavirus study group issued a name of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2)[1] because of its homology to SARS-CoV which caused severe respiratory infection in 2002-2003.[2]

As per WHO epidemiological update on COVID-19, dated 28 December 2021, over 278 million cases were reported globally and just under 5.4 million deaths worldwide[3]. In Pakistan, the December 2021 statistics revealed 1,430,366 confirmed cases with 29,301 deaths. Most confirmed cases were reported in Sindh (568,635) and most number of deaths 13,504 reported in Punjab.[4]

Coronaviruses are enveloped single stranded DNA viruses. SARS-CoV and MERS -CoV are beta corona viruses. They attach to host cells, penetrate and then replicate viral RNA in the nuclei of host cells. Viral proteins (spike, membrane, envelop and nucleocapsid) are formed via mRNA. ACE2 is identified as a fundamental receptor for SARS CoV. These receptors are high in heart, ileum, kidney, bladder and lungs (especially apical surface of alveolar epithelial cells). It may be a reason that early lung injury is seen in the distil parts of lung.[5]

CD4 T cells activation leads to antibody formation via B lymphocytes while CD8 T lymphocytes kill viral infected cells. Patients with severe COVID disease develop lymphopenia. Proinflammatory cytokines are released like IL-6, IL-10, granulocyte colony stimulatory factor, tumor necrotic factor alpha[6]. Severe COVID infection leads to higher IL-6 levels resulting in cytokine storm. Endothelial cell injury also leads to higher capillary leak and hypercoagubility. Endothelial cells also exhibit ACE-2 receptors.

Incubation period is three to five days on average but it may be upto 14 days. The clinical presentation of COVID-19 infection ranges from asymptomatic and mild disease to critical or fatal disease. A case surveillance in United States has shown that elderly and underline health conditions were associated with high risk for severe outcomes in the form of higher rates of hospitalization and deaths.[7]

It is the nature of virus to acquire new forms with time through mutations. For COVID-19 the variants of concern by WHO are Alpha, Beta, Gamma, Delta and Omicron. These variants may result in more severe disease, diagnostic difficulties and reduced effectiveness of treatment and vaccination. The variants of interest are Lambda, Mu.[8]

A nucleotide analog prodrug Remdesivir was the first drug which was approved by FDA of United States in May, 2020 for the treatment of COVID-19 infection. It is used in adult population more than 12 years of age[9], who weigh more than 40 kg. Side effects are gastrointestinal symptoms, raised transaminases levels, an increase in prothrombin time and hypersensitivity.

Baricitinib and Sotrovimab are new drugs suggested by World Health Organization for treatment of patients with COVID-19. Baricitinib, a selective inhibitor of Janus Kinase 1 and 2, is administered orally. It inhibits the cytokine pathway and is prescribed for severe cases. Whereas, Sotrovimab is a monoclonal antibody given intravenously authorized for treating mild to moderate COVID-19 patients who are not hospitalized yet and do not require oxygen therapy. [10]

In this study we tried to evaluate the charecteristics and laboratory parameters of COVID patients. Remdesivir, corticosteroids, anticoagulants and Tocilizumab were among the main treatment modalities. The study of 436 patients who were given Remdesivir and its comparison to 233 patients who did not take it may be helpful in the management plan of COVID patients in future.

Patient and Methodology

This was a hospital based descriptive cross-sectional study. Patients included in the study were admitted in the Medical Department of Capital Hospital, Islamabad, Pakistan from 1st November, 2021 to 31st October, 2021. The study was conducted after approval from the hospital administration. The purpose of the study was explained to all the patients and consent was obtained.

Patients were of either gender and of age 14 years and above. Total 669 patients were included in this study. The sampling technique was non-probability consecutive sampling. Patients both Covid Real-time polymerase chain reaction (RT-PCR) positive and negative were included. In PCR negative COVID suspected patients clinical features, oxygen saturation, radiological findings,

contact history and raised inflammatory markers were used to detect the Covid-19 infection. The patients less than 14 years of age and Covid PCR negative patients with normal oxygen saturation, normal radiographs and inflammatory markers were excluded from this study.

Blood Complete Picture (CP), serum ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-Dimers and Interleukin-6 (IL-6) levels were noted. Reference normal range for Blood CP: WBC count of 4500-10000 per micro liter, lymphocyte count 20-45%, serum LDH less than 480 U/l, CRP <10 mg/dl, D-dimers <500 ng/ml and serum ferritin < 250 ng/ml were considered normal. Chest x-ray and high resolution computed tomography (where technically feasible) were performed too.

We categorized the study group in remdesivr given and not given groups. Remdesivir was prescribed to admitted patients with moderate to severe disease where not contraindicated. In mild cases it was prescribed only for patients with co-morbids, relatively older age group and deranged inflammatory markers. Few patients who may not need remdesivir were given on request.

Remdesivir not given patients were the patients who either refused to take it, could not afford or it was contraindicated. Patients either presented late in the hospital or presented in critical state and expired. At times remdesivir was not available in the market.

Remdesivir was given in a bolus dose of 200 mg on day 1, then 100 mg daily for next 4, 6 or 9 days. Duration of treatment was according to patient's response. Mild and moderate cases were mostly given five days treatment. If general condition of patient, oxygen saturation and inflammatory markers did not improve then we continued treatment for seven or ten days.

Disease was clinically classified as mild, moderate and severe according to National Institute of Health, Pakistan guidelines as follow:

Mild Disease: No hemodynamic compromise, oxygen saturation above 94%, no chest infiltrates.

Moderate Disease: Oxygen saturation 90-94%, Chest x-ray with infiltrates involving lung fields.

Severe/ critical Disease: Clinical signs of pneumonia (fever, cough + any of the following), Respiratory rate > 30/min, SPO2 <90% on room air, chest X-ray involving >50% of lung fields or multiple organ failure

The data about the age, gender, disease severity, oxygen saturation and inflammatory markers was entered into a proforma for collection and analysis. Data was analyzed using SPSS version 24. Mean value +/- S.D was determined for quantitative data (i.e. C-reactive protein, ferritin, d-dimers, LDH). Frequencies (%) were determined for qualitative data (i.e. age, gender, PCR status, covid severity, presence or absence of lymphopenia).

Chi-square test was applied as a test of significance to study association of remdesivir with age, gender, lymphopenia, derangement of inflammatory markers, stay in the hospital and outcome. P-value <0.05 was taken as statistically significant. Data was presented in the form of tables, bar graphs and pie charts. Paired T test was also applied for the values of LDH, D.Dimers, ferritin, CRP, oxygen saturation at the time of comparing their values before and after the treatment (table 2).

Results

Table 1: Presenting the demographic features of COVID cases

Variable	Frequency/percentage
Age	
• **< 45 years**	115(17.2%)
• **> 45 years**	554(82.8%)
Gender	
• **Males**	375(56.1%)
• **Females**	294(43.9%)
PCR status	
• **Positive**	349(52.2%)
• **Negative**	320(47.8%)

Severity	
• **Mild**	253(37.8%)
• **Moderate**	189(28.3%)
• **Severe**	227(33.9%)
Lymphocyte count	
• **<20 %**	482(72%)
• **>20%**	187(28 %)
Outcome	
• **Discharged**	573(85.7%)
• **Expired**	96(14.3%)
Remdesivir	
• **Given**	436(65.2%)
• **Not given**	233(34.8%)

The study included 669 patients. The mean age of patients in the study was 58.2 years, with a range of 14-95 years. 115(17.2 %) patients were less than 45 years of age and 554 (82.8%) patients were >more than 45 years old. There were 375 (56.1%) males and 294 (43.9%) females. Regarding severity index of COVID-19 253 (37.8%) cases had mild, 189(28.3%) cases had moderate and 227 (33.9%) cases had severe covid-19 infection. 349 (52.2 %) cases were covid-19 PCR positive and 320 (47.8 %) cases were PCR negative.

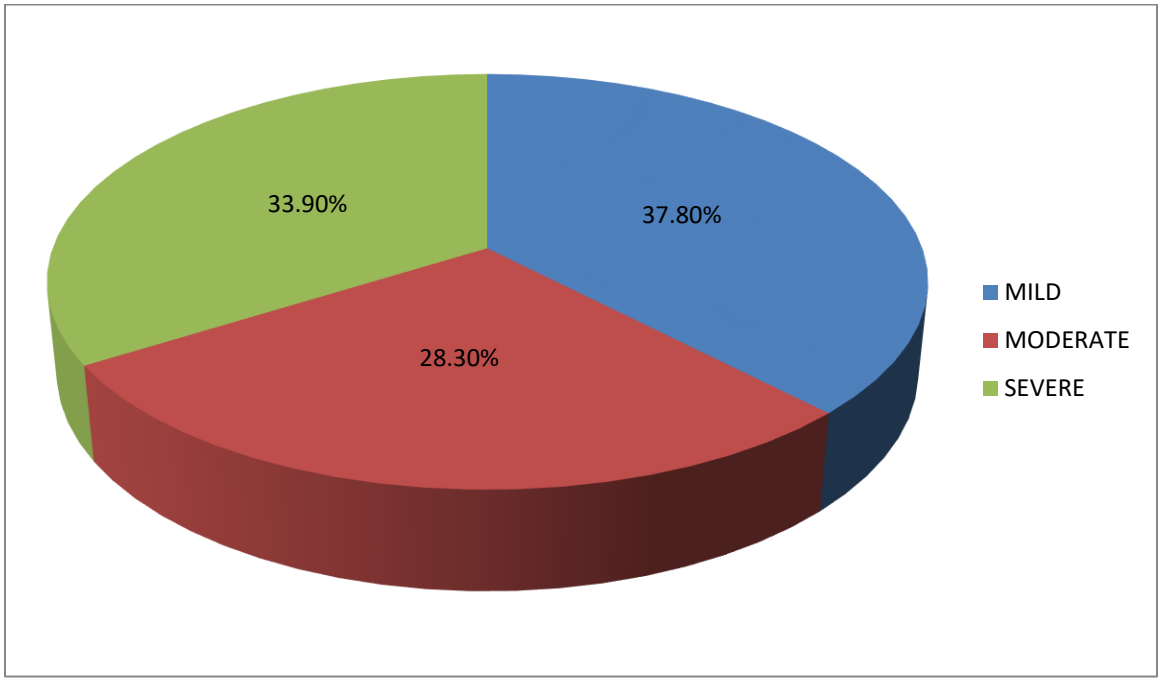

Figure 1: Severity of COVID-19 disease

We measured different variables before and after the treatment. Mean Oxygen saturation before treatment was 90.54 and after treatment was 92.77 with significance of 0.000. Mean CRP before treatment was 48.25 and after treatment was 19.20 mg/dl with significance of 0.000. Mean LDH value was 693.61 before treatment and 617.35 U/L after treatment with significance of 0.001. Mean D. Dimers value was 1951.06 and after treatment value of 1273.45 ng/ml with significance

of 0.00. Mean serum ferritin level was 531.95 and after treatment value was 404.22 ng/ml with significance of 0.000.

Table 2: Presenting the variables before and after the treatment (n=669)

Variable	Before treatment	After treatment	P-value
Oxygen saturation			
Mean±SD	90.545±8.62	92.779±9.98	0.000
CRP			
> 10 mg/dl	498(74.4%)	64(9.6%)	0.000
< 10 mg/dl	171(25.0%)	604(90.3%)	
Mean±SD	48.25±52.08	19.20±28.20	
D. Dimers			
>500 ng/ml	348(52.0%)	190(28.4%)	0.000
<500 ng/ml	321(48.0%)	479(71.6%)	
Mean±SD	1951.06±2709.99	1273.45±2041.21	
LDH			
>480 U/L	552(82.5%)	301(45.0%)	0.001
<480 U/L	117(17.5%)	366(54.7%)	
Mean±SD	693.61±441.95	617.35±440.92	
Ferritin			
>250ng/ml	313(46.8%)	187(28.0%)	0.000
<280 ng/ml	356(53.2%)	482(72.0%)	
Mean±SD	531.95±644.98	404.22±426.06	

We divided the main study group into group one "Remdesivir given" and group two "Remdesivir not given". In the first group 248(66.1%) cases were male and 188(63.9%) cases were female. In the second group 127(33.9%) cases were male and 106(36.1%) were female. (P-0.306). In the first group 273(78.2%) cases were COVID PCR positive and 163(50.9%) cases were PCR negative. In second group 76(21.8%) cases were PCR positive and 157(49.1%) negative (P- value 0.000).

In Remdesivir given group 66(68.7%) patients expired and 370(64.6%) were discharged while in second group 30 (31.3%) patients expired and 203(35.4%) were discharged (P- value 0.250). 66.8% of remdesivir given patients were lymphopenic as compared to 33.2 % of remdesivir not given group. In remdesivir given group 249 (57.6%) cases stayed <10 days in hospital as compared to 183 (42.4%) patients in remdesivir not given group had shorter stay. We also compared values of oxygen saturation and inflammatory markers between group 1 and 2, both before and after treatment.

Table 3: Comparing the COVID data in Remdesivir given and Remdesivir not given groups

Variable	Remdesivir given	Remdesivir not given	p-value
Age			
<45 years	68(59.1%)	47(40.9%)	0.090
>45 years	368(66.4%)	186(33.6%)	
Gender			
Male	248(66.1%)	127(33.9%)	0.306
female	188(63.9%)	106(36.1%)	
PCR status			

Positive	273(78.2%)	76(21.8%)	0.000
Negative	163(50.9%)	157(49.1%)	
Severity of disease			
Mild	137(54.2%)	116(45.8%)	0.000
Moderate	119(63.0%)	70(37.0%)	
Severe	180(79.3%)	47(20.7%)	
Lymphocyte count			
>20%	114(61.0%)	73(39%)	0.092
<20%	322(66.8%)	160(33.2%)	
Hospital stay			
Short <10 days	249(57.6%)	183(42.2%)	0.000
Long >10 days	183(79.9%)	46(20.1%)	
Outcome			
Discharged	370(64.6%)	203(35.4%)	0.250
expired	66(68.8%)	30(31.31%)	
Oxygen saturation			
>94%	329(63.0%)	193(37.0%)	0.097
90-94%	45(73.8%)	16(26.2%)	
<90%	61(71.8%)	24(28.2%)	
CRP			
Before treatment			
<10	106(62%)	65(38.0%)	0.179
>10	330(66.3%)	168(33.7%)	
After treatment			
< 10	368(64.2%)	216(35.8%)	0.090
>10	48(75.0%)	16(25.0%)	
D. Dimers			
Before treatment			
>500	215(67.0%)	106(33.0%)	0.195
<500	221(63.5%)	127(36.6%)	
After treatment			
>500	300(62.6%)	179(37.4%)	0.017
<500	136(71.9%)	54(28.4%)	
LDH			
Before treatment			
< 480	58(49.6%)	59(50.4%)	0.000
>480	378(68.5%)	174(31.5%)	
After treatment			
<480	227(52.1%)	139(60.2)	0.027
>480	209(47.9%)	92(39.8%)	
Ferritin			
Before treatment			
< 250	211(59.3%)	145(40.7%)	0.000
>250	225(71.9%)	88(28.1%)	
After treatment			
< 250	295(61.2%)	157(38.8%)	0.000
>250	141(75.4%)	46(24.6%)	

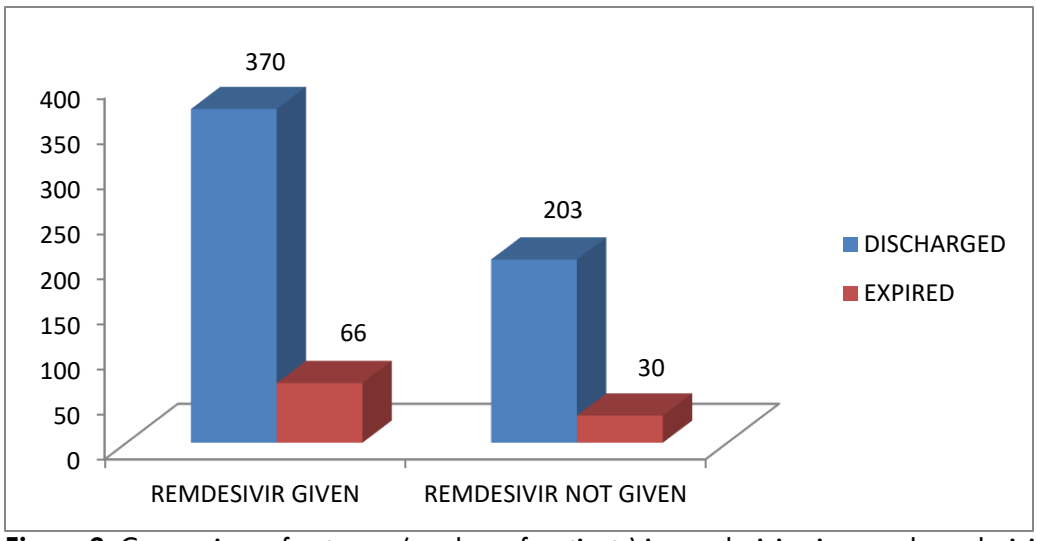

Figure 2: Comparison of outcome (number of patients) in remdesivir given and remdesivir not given groups

Discussion:

Remdesivir was used in our hospital to treat COVID-19 patients during the pandemic when no other effective treatment for COVID was available. The aim of our study was to assess the effectiveness of this drug. Majority of patients who were hospitalized fell in older age group and there was male predominance. Many studies have noted that COVID-19 affects male gender more than the females. Multinational data of COVID-19 patients from United States and other countries has shown that all-cause mortality remained significantly higher in men than in women (8.13% vs 4.60%; odds ratio, 1.81; 95% CI, 1.55 to 2.11; P < 0.001).[11]

There may be differences in hormonal, inflammatory or immune responses to infection between males and females. Estrogen is associated with decrease expression of ACE2 receptors and better innate and adaptive immune responses[12] whiles testosterone has suppressive effect on immune system. Reduced testosterone level with aging is shown to be associated with increase in the proinflammatory markers resulting in higher incidence of cytokine release syndrome.[13]

Studies have reported that the median age of the hospitalized patients ranged from 49 to 56 years.[14] In our study 82 % of patients were >45 years of age with median age of 58 years. Another study on Pakistani population has shown that increasing age is a risk factor for adverse COVID-19 outcome.[15]

COVID 19 is associated with significant mortality and morbidity. In our study 14.3 % patients who were admitted in the hospital, expired. Another study from Pakistan has shown that 21.9 % patients who were admitted in various hospital passed away.[16] Temporal variations of in hospital mortality from COVID-19 are largely unknown. Another observational study from Germany noticed mortality rate of 19 % (890/4704).[17]

Inflammatory markers and oxygen saturation improved significantly after treatment (P-value 0.000) when we studied Serum ferritin, CRP, LDH and. Dimers before and after the treatment (table-1). Hospitalized patients were treated with oxygen, anticoagulant and steroids where indicated and remdesivir in selected patients with reduced oxygen saturation and raised inflammatory markers. A study recorded about 50 % reduction in CRP within 72 hours of initiating corticosteroid therapy potentially predicts inpatient mortality[18]. So CRP may be used as a biomarker of response to treatment in covid-19 patients.

In a study serum LDH was found potentially useful not only in predicting severity but also monitoring treatment response in COVID-19 pneumonia. Increase or decrease of LDH was associated with a radiographic progress or improvement. Normalization of serum LDH titer was also accurate in predicting treatment success in the patients[19]. A trial analyzing use of remdesivir in COVID-19 patients on hemodialysis has shown improvement in CRP levels (P-<0.001) after treatment with remdesivir. Oxygen requirement also improved in two thirds of patients (68.57%).[20]

In our study patients were divided in two groups one who received remdesivir and one who did not.

We assessed the effect of age and gender in both groups which was not significant both for age (P-value 0.090) and gender (P-value 0.306). A study from Europe has also measured the effects of age and gender on incidence and case fatality of COVID 19 infection and also emphasized to include sex and gender analysis in the prophylactic and therapeutic treatment studies on COVID.[21]

We studied the severity of disease in both groups. Remdesivir was given to significant number of moderate and severe disease patients and study showed significant P-value (0.000) while comparing severity of disease in non-remdesiver given group. Effect of remdesivir on severity needs to be studied. A clinical trial performed on non-hospitalized patients of covid-19 with mild to moderate disease revealed that early administration of remdesivir to those at high risk of disease progression resulted in lower risk of hospitalization and death when compared with placebo.[22]

In our study, hospital stay was shorter (less than 10 days) in more patients in remdesivir given group (P-value 0.000) than remdesivir not given group. This was a significant finding. Clinical trials in hospitalized patients with Covid-19 show that those patients who were given Remdesivir early in disease course, recovered quickly as compared to those on placebo. Remdesevir was overall well tolerated and in 84% of cases, patient's condition improved. Higher improvement was noted in less than 60 years age group and on standard low flow oxygen.[23]

Effect of remdesivir on mortality from COVID-19 is being studied. WHO solidarity study has shown that remdesivir has no or little effect on 28 day mortality, the need for mechanical ventilation or duration of hospital stay.[24] In our study there was also no improvement (P-0.250) in respect of outcome. Remdesivir given patients did not show improvement in survival as compared to another group. COVID PCR positive and patients with severe/critical disease were more in number in remdesivir given group.

A study indicated that there was no difference in tolerability and reduction of mortality, between 10 days or 5 days course of remdesivir.[25] We gave remdesivir for 5, 7 or 10 days to our patients. Our patients tolerated remdesivir well. 5 cases reported mild macroscopic hematuria which settled after stopping treatment. There was no grade 4 adverse drug reaction. A study reported serious adverse effects with remdesivir in 131/532 patients (24.6%) and in 163/516 patients who received placebo (31.6%). Estimates of mortality were 6.7% with remdesivir and 15.2 % with placebo by day 29. Remdesivir was superior to placebo in shortening the time to recovery.[26]

A study in Norway showed no difference in mortality during hospital and on viral clearance with remdesivir . No significant remdesivir effect on baseline CRP and ferritin levels below median levels was observed. We studied inflammatory markers before and after giving remdesivir. Our study showed reasonable remdesivir effect on LDH levels only.[27]

Our study has real time data of significant number of patients and our results may be generalized to similar patient population. One limitation of study is that it is not placebo controlled although we tried to compare the COVID-19 patients who were given remdesivir with those who were not given. Other limitations were financial constraints and all data was not available from all patients. Despite these limitations we hope that this study will serve as a useful reference on COVID-19 situation in our area and it will help in the evaluation of disease management in future.

Conclusion

In our study, COVID-19 infection was more common in males and affacted older age group predominantly. There was overall improvement in inflammatory makers and oxygen saturation after the treatment of COVID-19 infection. Improvement in the inflammatory markers was not significant, except LDH levels, when remdesivir given patients were compared with remdesivir not given patients. Remdesivir shortened the duration of stay in hospitalized patients but it had no significant effect on mortality in the hospitalized patients. The lack of effect on mortality may be due to higher number of moderate and severe COVID-19 patients in remdesivir treated group than in other group. More comparative, placebo controlled and double blind studies are needed to evaluate the role of various antiviral treatments in COVID-19 disease.

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