Original Article

Clinical course and disease outcome in patients with severe COVID-19 receiving remdesivir

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Abstract

Background and aims: COVID-19 is a pandemic and infectious disease with high morbidity and mortality rates as well as a global spread. This study aimed to investigate the clinical outcomes for patients afflicted with COVID-19 and treated with remdesivir.

Methods: In this clinical trial study, patients with severe COVID-19 confirmed by molecular testing and hospitalized at Hajar Hospital of Shahrekord in Iran were divided into standard care group (including 52 patients) and standard + remdesivir group (including 51 patients). The patients were examined for clinical symptoms, laboratory data, as well as mortality and recovery rates during the treatment period. Then the data were analyzed by SPSS version 23 using chi-square, independent t-test and repeated-measures ANOVA.

Result: Clinical and laboratory monitoring on days 5, 10, and 14 showed that there was no significant difference between two groups ($P > 0.05$). In addition, there was no significant difference between the two groups in terms of hospitalization duration and ICU rate (58.8% versus 51.9%, $P = 0.48$). The trend of Lymph count and platelet decreased significantly in the standard group ($P = 0.003$, $P = 0.04$, and $P = 0.03$, respectively).

Conclusion: Patients with severe COVID-19 were investigated and it was concluded that remdesivir produced no improvement in the remdesivir group compared to the standard group.

Keywords: COVID-19, Treatment, Hospitalization

Introduction

COVID-19 is a pandemic and infectious disease that is caused by a virus from the *Coronaviridae* family. Coronavirus is a single-stranded, RNA-carrying virus and the seventh member of the given family, which often affects animals – including birds and mammals – and causes mild respiratory infections like a common cold in humans; however, human coronaviruses can lead to deadly endemics (1). COVID-19 infection symptoms range from asymptomatic to septic shock. The most common clinical findings are fever, fatigue, dry cough, sore throat, and diarrhea. The infection is classified into mild, moderate, severe, and vital. The mild group includes patients with mild upper respiratory tract infections symptoms like dry cough, mild fever, sore throat, headache, and myalgia without symptoms like dyspnea and radiological manifestations. The moderate group generally presents as respiratory symptoms like cough, dyspnea, and tachycardia with radiological manifestations (2,3). The severe group exhibits at least one of the three symptoms: 1. dyspnea and respiratory rate > 30 breaths per minute (RR > 30 times/min); 2. arterial blood oxygen to fraction of inspired oxygen ratio less than 300 (Pao2 / Fio2 <300); and 3. blood oxygen saturation levels less than 90% (Spo2 <93%). Finally, the vital condition group manifests itself in at least one of the three symptoms:

respiratory failure, septic shock requiring mechanical ventilation, or along with other organ failure, requiring admission to intensive care unit Multiple organ failure (4). Misra et al have shown that the mortality risk of infection varies in different people. The risk is higher in people with underlying diseases. Hypertension, cardiovascular disease, diabetes mellitus, and respiratory diseases are the most important comorbidities of COVID-19 (5). Madsen et al have reported that remdesivir can shorten the recovery time in patients with COVID-19, and presented evidence for lower respiratory tract infection (6).

Remdesivir is a monophosphate prodrug whose active metabolism is an analog of adenosine triphosphate. The active drug inhibits RNA-dependent RNA polymerase (RdPp) in Coronaviridae and Flaviviridae families. Infusion of up to 225 mg of the drug is tolerated well. It does not require renal or hepatic dose adjustment, but is not recommended in patients with a glomerular filtration rate lower than 30 mL/min (glomerular filtration rate <30 mL/min) (7). Despite the numerous studies concerning the effect of this drug on COVID-19 disease, as well as due to the differences found in people regarding genetic/epigenetic properties and in health care systems, this study aimed to examine the remdesivir in hospitalized COVID-19 patients in Shahrekord, Chaharmahal Bakhtiari province, south west Iran.

Materials and Methods

Patients

Inclusion criteria for the present study were: hospitalized patients aged 18 years or over with the SARS-CoV-2 infection confirmed by molecular test; those having blood oxygen saturation ≤93% in room air or needing supportive oxygen/ventilation; those with pulmonary infiltration detected by radiological studies.

Patients with alanine aminotransferase and aspartate aminotransferase rising five times higher than the upper limit of normal rate and those with Glomerular filtration rate less than 30 mL/min (according to Cockroft-Gault formula) based on hospital protocol were excluded from the study.

Study design

In this clinical trial study, 100 patients hospitalized in Hajar Hospital, Shahrekord, Iran were divided into standard and remdesivir groups in a ratio of 1:1. The study sampling was nonequivalence and non-randomized.

Due to the limited access to remdesivir and in order to comply with ethical principles, patients hospitalized in drug availability courses were eligible to receive remdesivir, but patients admitted in other courses only received standard treatments based on the national protocol (8). Patients in the remdesivir group received remdesivir 200 mg intravenous (BDREM-100 Company, India) on the first day and, then, received 100 mg intravenous infusion in 15-30 minutes for the following four days. Remdesivir prescription was stopped for patient meeting the exclusion criteria. All patients were assessed on the 1st, 5th, 10th, and 14th days. In addition, patients' examination period lasted for three months.

Clinical and laboratory monitoring

Patients' assessment included clinical sign blood oxygen saturation, oxygen supplementary device, body temperature, cough, dyspnea, gastrointestinal symptoms (e.g., nausea and vomiting, diarrhea, abdominal pain), headache, and myalgia. On days 1, 5, 10, and 14, blood samples were collected for measuring the blood cell count, liver enzymes (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP]), total bilirubin, prothrombin time, partial thromboplastin time, international normalized ratio (INR), and inflammatory factors (lactate dehydrogenase, erythrocyte sedimentation ratio) and creatinine.

Outcome

The first endpoint of the study was the discharge of hospital or death of patients, and the secondary endpoint was adverse effect for patients throughout the duration of study. Patients hospitalized up to day 14 or those remained hospitalized after this period until final status determination (i.e., death or discharge) were all under observation. The study's important outcomes included hospitalization duration, ICU admission, mortality, the interval between onset of symptom, and the start of therapy with remdesivir and recovery. Recovery was defined as getting discharged in two weeks (14 days) or hospitalization without oxygen supplementary on day 14.

Statistical analysis

The data were analyzed by using SPSS software (version 23) and performing chi square test, independent t-test and repeated-measures ANOVA. In all tests, a P value less than 0.05 was considered statistically significant.

Results

Out of 103 patients meeting inclusion criteria, 52 ones received only standard treatment and 51 ones received remdesivir. Patients hospitalized during the period when remdesivir was available received this drug in addition to standard treatment, while other patients only received the standard care. Patients' demographic information and the information on their underlying disease were recorded at the beginning of the study.

The mean age for remdesivir group was 62.2 ± 16.7 while it was 51.7 ± 11.7 for control group, which was significantly different ($P < 0.001$). The proportion of females was 55.8% versus males 44.2% ($P = 0.02$).

Hypertension (HTN), diabetes, and cardiovascular disease were the most common underlying diseases found in both groups; however, no difference was detected between the two groups in this regard ($P > 0.05$). The number of chronic respiratory and neurological diseases observed in the standard group was significantly higher than that in the remdesivir group (Table 1).

Clinical symptoms like fever, cough, dyspnea, gastrointestinal symptoms, and other symptoms were monitored during hospitalization. Clinical and laboratory monitoring on days 5, 10, and 14 revealed that there was no significant difference between the two groups regarding the given symptoms (Tables 2 and 3).

The highest rate of fever was recorded on the 1st day and the least one was observed on the 10th day (0%) of the study in both groups. The highest prevalence of cough and dyspnea in both groups was recorded on the 1st day while the least one was observed on the 10th and 14th days in standard and remdesivir groups, respectively.

Gastrointestinal symptoms and other symptoms prevalence were most common on the 1st and 4th days in the standard and remdesivir groups, whereas the lowest prevalence of the given symptoms was observed on the 14th and 10th days in the standard and remdesivir groups, respectively.

White blood cell count increased until day 14 in the remdesivir group but it increased until day 10 in the standard group, compared to its minimum count on the 1st day; however, no significant difference was found between the two groups in this regard.

Platelet counts in the standard group significantly changed during the hospitalization period and the highest platelet count in this group was observed on the 10th day.

Table 1. Comparison of demographic/disease variables in standard and remdesivir groups

Variable	Subgroup	Standard	Remdesivir	P value[a]
Gender	Male	23 (44.20)	34 (66.7)	0.02*
	Female	29 (55.8)	23 (44.2)	
Cardiovascular disease	Positive	8 (15.40)	6 (11.80)	0.59
	Negative	44 (84.60)	45 (88.20)	
Chronic respiratory disease	Positive	9 (17.30)	2 (3.90)	0.03*
	Negative	43 (82.70)	29 (96.10)	
Chronic renal disease	Positive	2 (3.80)	0 (0)	0.50
	Negative	50 (96.20)	51 (100)	
Diabetes mellitus	Positive	14 (27.50)	11 (21.60)	0.49
	Negative	37 (72.50)	40 (78.40)	
Hypertension	Positive	22 (42.30)	15 (29.40)	0.17
	Negative	30 (57.70)	36 (70.60)	
Liver disease chronic	Positive	1 (1.90)	0 (0)	0.99
	Negative	51 (98.10)	51 (100)	
Immunocompromised	Positive	1 (1.90)	0 (0)	0.99
	Negative	51 (98.10)	51 (100)	
Neural disease	Positive	8 (15.70)	2 (3.90)	0.04*
	Negative	43 (84.30)	49 (96.10)	
Other diseases	Positive	18 (34.60)	10 (19.60)	0.09
	Negative	34 (65.40)	41 (80.40)	

[a] Chi-square test; *Significant at $P < 0.05$.

The changes were not significant in the remdesivir group.

Measurement analysis showed that the trend of Lymph and Platelet counts decreased significantly in the standard group ($P = 0.003$, $P = 0.04$, and $P = 0.03$, respectively).

Patients' respiratory status in terms of using the respiratory devices during the studies period is present in Figure 1.

As for the standard group, the most commonly-used device was a reserve bag on days 1, 5, and 10, but the patients' status changed into the discharged status on day 14. As for the remdesivir group, most patients used reserve bags on days 1 and 5, but the discharged status was the most common status observed on days 10 and 14.

Patients receiving remdesivir were divided into two groups ≤10 and >10 based on the interval between the onset of symptoms and the start of treatment with remdesivir. This factor caused no difference in mortality rate as well as in gastrointestinal or other symptoms in the recipients of the remdesivir (Figure 2).

No significant difference was detected between the standard group and remdesivir one regarding the rate of mortality and discharge for patients with HTN, diabetes, and cardiovascular disease as the most common underlying diseases (Figure 3).

Hospitalization duration were 12.8 ± 8.5 and 12.75 ± 7.5 for the remdesivir group and control group, respectively, which were not significant ($P = 0.98$).

ICU admission rate for the two groups was not statistically different (Table 4).

Recovery was defined in terms of discharge or respiration

without the need for respiratory assistance device on day 14, whereby the difference was not significant.(80.4 versus 69.2; $P = 0.19$).

Discussion
Remdesivir had no significant effect on mortality rate, hospitalization duration, and ICU admission; and they were not even affected by sex, comorbidities, and interval

Table 2. Comparison of clinical symptoms in standard and remdesivir groups

Variable	Subgroup	Standard	Remdesivir	P value
Fever day 1	Positive	17 (32.70)	6 (12.50)	0.02*
	Negative	35 (67.30)	42 (87.50)	
Fever day5	Positive	1 (2.00)	2 (4.80)	0.59
	Negative	48 (98.00)	40 (95.20)	
Fever day 10	Positive	0 (0)	0 (0)	-
	Negative	29 (100)	21 (100)	
Fever day 14	Positive	1 (5.30)	0 (0)	0.99
	Negative	18 (94.70)	13 (100)	
Cough day 1	Positive	32 (61.50)	34 (68.00)	0.54
	Negative	20 (38.50)	16 (32.00)	
Cough day 5	Positive	22 (50.00)	14 (36.80)	0.23
	Negative	22 (50.00)	24 (63.20)	
Cough day 10	Positive	6 (23.10)	7 (41.20)	0.21
	Negative	20 (76.90)	10 (58.80)	
Cough day 14	Positive	9 (40.00)	9 (25.00)	0.68
	Negative	15 (60.00)	12 (75.00)	
Dyspnea day 1	Positive	39 (75.00)	32 (64.00)	0.23
	Negative	13 (25.00)	18 (36.00)	
Dyspnea day 5	Positive	18 (40.90)	10 (26.30)	0.17
	Negative	26 (59.10)	28 (73.70)	
Dyspnea day 10	Positive	5(19.20)	6 (35.30)	0.30
	Negative	21 (80.80)	17 (64.70)	
Dyspnea day 14	Positive	4 (28.60)	2 (16.70)	0.65
	Negative	10 (71.40)	10 (83.30)	
Gastrointestinal sign day 1	Positive	21 (40.40)	14 (28.00)	0.19
	Negative	31 (59.60)	36 (72.00)	
Gastrointestinal sign day 5	Positive	6 (13.30)	2 (5.30)	0.28
	Negative	39 (86.70)	36 (94.70)	
Gastrointestinal sign day 10	Positive	2 (7.70)	0 (0)	0.51
	Negative	24 (92.30)	17 (100)	
Gastrointestinal sign day 15	Positive	0 (0)	1 (8.30)	0.48
	Negative	13 (100)	11 (91.70)	
Other symptoms day 1	Positive	31 (59.60)	17 (34.00)	0.01*
	Negative	21 (40.40)	33 (66.00)	
Other symptoms day 5	Positive	5 (13.30)	3 (7.90)	0.50
	Negative	39 (86.70)	35 (92.10)	
Other symptoms day 10	Positive	1 (3.80)	0(0.0)	0.99
	Negative	25 (96.20)	17 (100)	
Other symptoms day 14	Positive	0(0)	1(8.30)	0.48
	Negative	13(100)	11(91.70)	

[a] Chi-square test; *Significant at $P < 0.05$.

Table 3. Comparison of the average scores of of laboratory data in standard and remdesivir groups

Variable	Remdesivir		Standard		P value[a]
	SD	Mean	SD	Mean	
WBC day 1	8787.73	3799.37	330.59	7193.88	0.04*
WBC day 5	12002.23	11041.03	2903.30	8128.57	0.48
WBC day 10	4492.49	11104.76	353.31	11065.00	0.72
WBC day 14	20009.89	16069.23	3397.98	9268.75	0.45
P value intra group		0.21		0.04	
Lymph count day 1	614.12	935.78	1441.96	1345.11	0.08
Lymph count day 5	896.30	1024.20	884.29	928.26	0.65
Lymph count day 10	332.09	836.49	564.29	764.92	0.62
Lymph count day 14	2321.59	1461.90	362.34	449.86	0.10
P-value intra group		0.25		0.04	
Platelet day 1	80.36	207.34	81.27	189.76	0.30
Platelet day 5	116.44	249.15	99.99	216.06	0.97
Platelet day 10	96.00	198.95	104.46	226.95	0.13
Platelet day 14	73.87	161.38	66.01	146.81	0.98
P value intra group		0.23		0.03	
AST day1	32.78	52.20	27.64	46.60	0.38
AST day 5	21.90	46.30	25.87	46.56	0.77
AST day 10	50.28	45.73	21.60	47.25	0.99
AST day 14	89.58	63.36	570.51	243.07	0.21
P value intra group		0.60		0.19	
ALT day 1	34.35	50.38	24.07	36.98	0.04*
ALT day 5	54.23	76.98	185.70	80.65	0.08
ALT day 10	165.42	101.00	40.34	65.45	0.37
ALT day 14	55.28	63.91	431.42	196.73	0.24
P value intra group		0.86		0.19	
ALP day 1	116.10	127.38	49.18	115.00	0.56
ALP day 5	136.16	14.93	44.61	116.96	0.78
ALP day 10	72.14	128.09	47.30	126.68	0.47
ALP day 14	53.98	115.70	32.94	112.85	0.43
P-value intra group		0.59		0.82	
PT day 1	9.61	14.30	2.36	13.17	0.45
PT day 5	7.85	15.53	8.78	17.58	0.55
PT day 10	6.36	15.89	4.69	15.55	0.81
PT day 14	10.36	19.55	9.19	19.11	0.26
P value intra group		0.20		0.29	
PTT day 1	3.26	29.56	13.86	30.92	0.63
PTT day 5	22.65	39.91	4.55	31.24	0.15
PTT day 10	19.91	38.71	2.26	29.25	0.08
PTT day 14	9.43	38.77	12.55	35.93	0.44
P value intra group		0.11		0.69	
INR day 1	0.11	1.05	0.24	1.12	0.17
INR day 5	0.97	1.44	0.940	1.46	0.28
INR day 10	1.34	1.65	0.54	1.37	0.25
INR day 14	0.98	1.49	0.73	1.49	0.28
P value intra group		0.39		0.07	
ESR day 1	30.74	39.90	25.95	35.05	0.60
ESR day 5	18.38	61.00	10.65	21.25	0.87

Table 3. Continued

Variable	Remdesivir		Standard		P value[a]
	SD	Mean	SD	Mean	
ESR day 10	00.00	57.00	8.73	13.67	---
ESR day 14	10.60	16.50	---	---	---
P value intra group	---		0.60		
LDH day 1	301.11	622.85	203.53	448.64	0.006*
LDH day 5	538.47	682.59	414.49	620.53	0.87
LDH day 10	401.64	787.69	342.38	597.85	0.77
LDH day 14	401.95	557.13	253.86	537.63	0.87
P value intra group	0.32		0.28		
Creatinine day 1	0.20	0.81	0.30	0.91	0.06
Creatinine day 5	0.23	0.78	0.24	0.79	0.16
Creatinine day 10	0.53	0.89	0.32	0.80	0.07
Creatinine day 14	4.87	2.27	0.53	0.81	0.42
P value intra group	0.26		0.36		
Direct bilirubin day 1	0.21	0.26	0.12	0.21	0.14
Direct bilirubin day 5	0.29	0.27	0.17	0.25	0.66
Direct bilirubin day 10	0.24	0.30	1.02	0.25	0.42
Direct bilirubin day 14	1.04	0.68	0.15	0.30	0.99
P value intra group	0.91		0.14		

[a] Intergroup Independent t-test results; *Significant at $P < 0.05$.

Table 4. Comparison of hospitalization and ICU admission in standard and remdesivir groups

Variable		Remdesivir	Standard	P value (Chi-square test)
Hospitalized duration		12.8 ± 8.5	12.82 ± 7.5	0.98
ICU	No	30 (58.8)	27 (51.9)	0.48
	Yes	21 (41.2)	25 (48.1)	

between symptom onset and remdesivir prescription. In a study by Wang et al in Wuhan, it was determined that remdesivir had no impact on mortality rate and clinical recovery time (3); while in the study by Olender et al, it was shown that remdesivir significantly reduced the mortality rate compared to the standard group. Also, Tomashek et al found that hospitalization duration and mortality rate in the remdesivir group on days 5 and 29 were less than those observed in the standard group (6, 9).

Goldman and colleagues' study found no significant difference among remdesivir treated groups in terms of mortality rate and hospitalization duration between days 5 to 10, although the discharge rate was higher in remdesivir treated group on the 5th day (10). Taking into account Goldman and colleagues' results concerning the insignificant difference in mortality and hospitalization period after using remdesivir for 5 days, it seemed that using remdesivir for 5 days in our study could not have also been an important factor in remdesivir efficacy.

In another study by Grein et al, no difference was observed among patients receiving remdesivir with invasive or non-invasive oxygen supplementary (11). In this study, the most common underlying diseases among

patients in both groups were HTN and diabetes mellitus. The most common comorbidities were the same ones found in Wang's study, while cardiovascular diseases, HTN, and diabetes mellitus were the most common comorbidities detected in several studies (12, 13). According to the results of this study, mortality hospitalization and ICU admission were not significantly influenced by remdesivir, which were in line with the results from the study by Mahajan et al where remdesivir therapy was discovered to have caused no improvement in clinical outcomes in moderate to severe COVID-19 patients (14). In another study, a group of patients received remdesivir plus corticosteroids while another group only received remdesivir. In contrast, the results of this study showed that remdesivir was associated with prompt clinical improvement in a cohort of predominantly non-White cases. remdesivir plus corticosteroid administration did not delay the death (15). This difference may have been due to the differences in genetic properties of the study population, which could have also affected the results of the study. However, there were some studies showing that the effects of remdesivir in reducing mortality and clinical symptoms of patients were unreliable (13). The trend of clinical symptoms, including gastrointestinal and other symptoms, was not significantly different between the standard and remdesivir groups; however, the prevalence of the symptoms was decreased numerically and constantly in the standard group, while the symptoms in the remdesivir group were initially decreased but later increased again. This later increase in the rate of symptoms may have been due to the side effects of remdesivir.
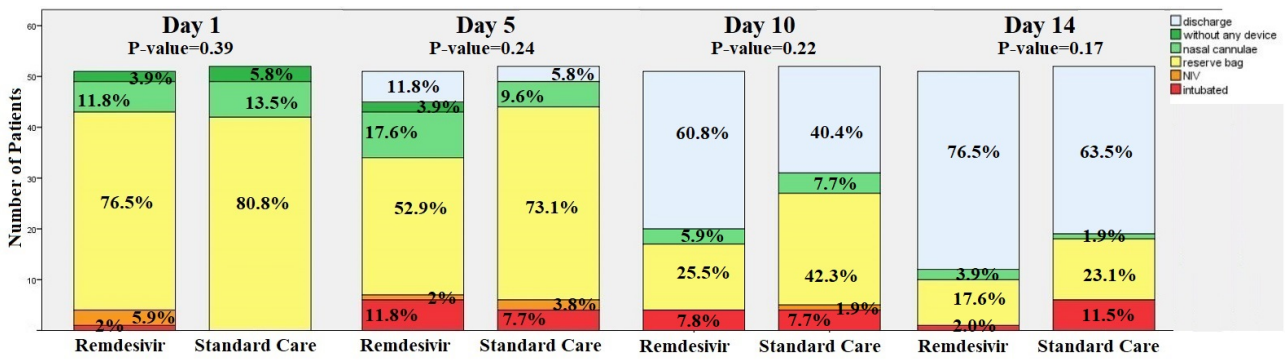
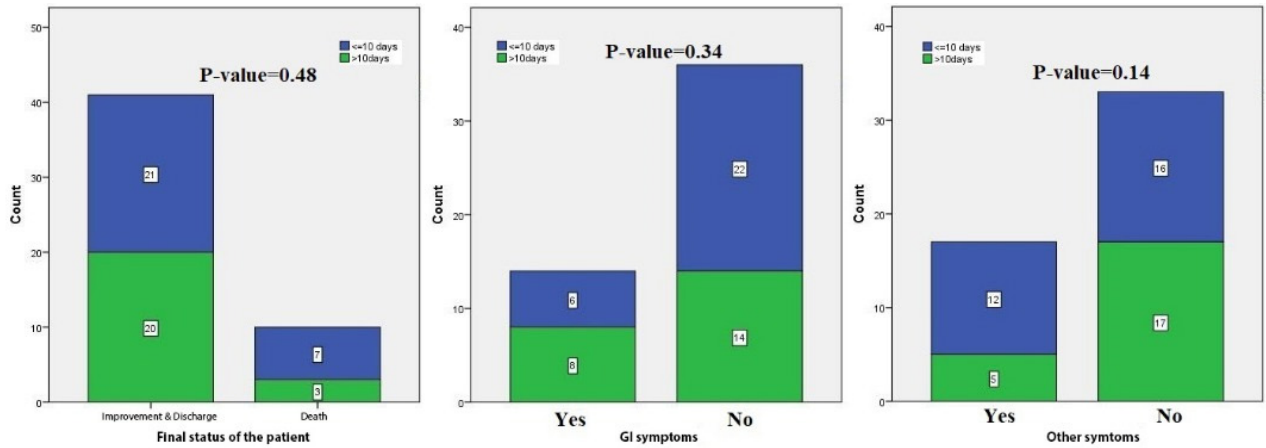**Figure 1.** Respiratory status in standard and remdesivir groups.

Figure 2. Mortality/discharge and gastrointestinal/other symptoms in terms of symptom onset to remdesivir treatment interval.
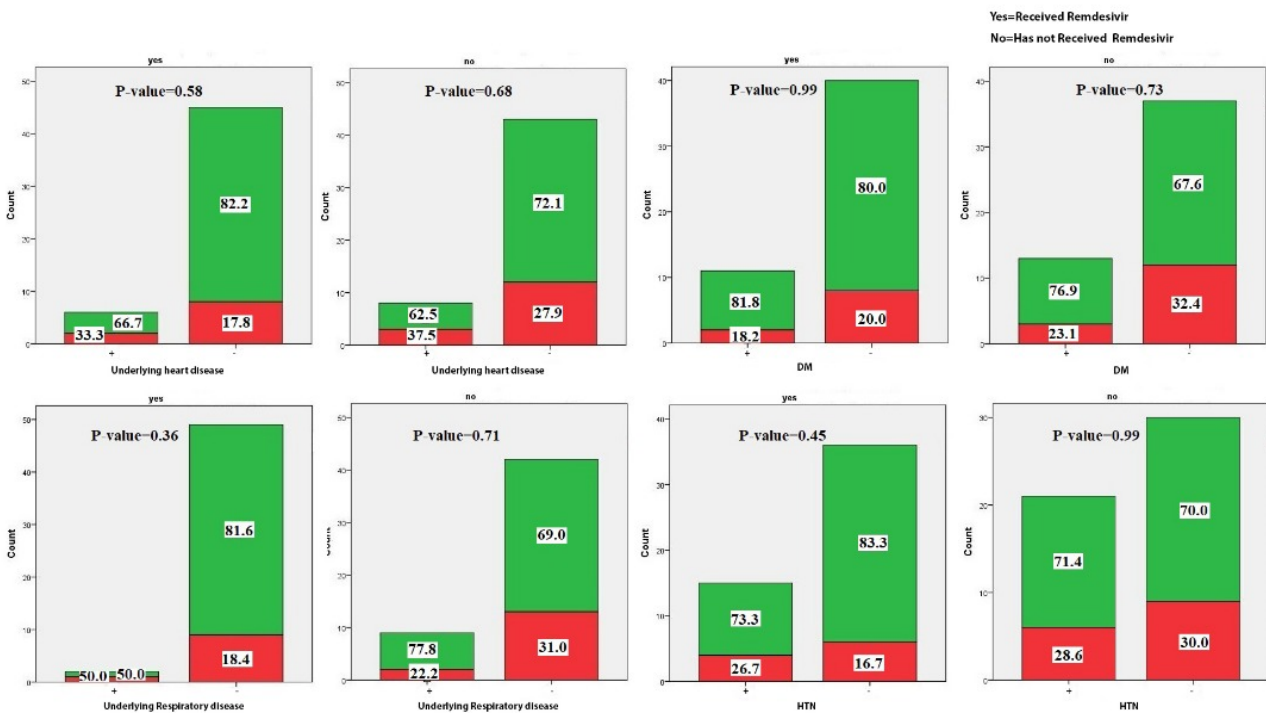

Figure 3. Mortality and discharge in term of underlying disease.

Remdesivir produced neither a significant improvement nor a decrease in lymphocyte count in the remdesivir group comparing to the standard group ($P = 0.04$). Compared to the count observed on the 1st day, platelet count in both groups initially increased but later decreased;

and these changes were only significant in the standard group. Different factors were likely responsible for the fluctuation in platelet count, specially the one concerning the application of various given drugs.

In this study, it was detected that remdesivir neither

increased liver enzymes nor contributed to abnormal coagulation factors; according to the findings from Grein and colleagues' study, however, patients receiving remdesivir in the invasive oxygen supplementary group had higher levels of ALT and creatinine (11).

There was no significant difference between groups in terms of the patients' respiratory status. Following Tomashek and colleagues' study, however, the remdesivir group was treated with supportive oxygen for a shorter period and the incidence of supportive oxygen use in non-oxygenated cases was less in the remdesivir group (6).

The symptom onset to remdesivir therapy interval in patients in the remdesivir group was not shown to be different in the rate of recovery and mortality and gastrointestinal symptoms and myalgia and headache. Wang and colleagues' study also found no difference between the onset of symptoms and the start of treatment in terms of mortality. Goldman and colleagues however, found that patients who had symptoms less than 10 days prior to receiving remdesivir had significantly higher discharge rates compared to those who had symptoms more than 10 days between the onset of symptoms and the treatment. Tomashek and colleagues' study also demonstrated that early administration of remdesivir had more benefits. Grein and colleagues' study found no significant relationship between the mean duration of symptoms and symptom onset to the start of remdesivir treatment interval (6,10,11).

No significant difference was observed regarding mortality rate affected by underlying diseases like cardiovascular disease, diabetes mellitus, HTN, and chronic respiratory disease since the most common comorbidities in both groups did not increase mortality rate.

Olender and colleagues' study identified HTN as a risk factor and the recovery rate in the non-HTN group was found to be significantly higher (9). Similar to the Goldman and colleagues' study, no significant difference was detected between our study groups regarding recovery from 5-day to 10-day courses of remdesivir treatment, whereas the recovery rate on day 14 for Olender and colleagues' study participants receiving remdesivir was two to three times higher than that for the standard group members (9,10). Tomashek and colleagues' study also revealed that the remdesivir group had a shorter recovery time than the placebo group (6).

Conclusion
In this study, patients with severe COVID-19 were examined and no significant difference was found between the group receiving remdesivir and the standard care group in terms of mortality hospitalization and ICU admission. Changes in national protocols and problems regarding the lack of evidence about the confounding effects of personal variables were the limitations of the present study.

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