Effects of Remdesivir on in-Hospital and Late Outcomes of Patients With Confirmed or Clinically Suspected COVID-19: A Propensity Score-Matched Study

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Abstract- Remdesivir, an antiviral medication, became an early promising therapeutic candidate for coronavirus disease 2019 (COVID-19) due to its ability to inhibit the virus in vitro. Current evidence about remdesivir treatment has been very controversial, so we aim to evaluate remdesivir to improve our knowledge about COVID-19 management and its long-term effects. In this retrospective cohort study using registered data derived from the Sina Hospital COVID-19 Registry with a 9-month follow-up, we enrolled patients receiving remdesivir and then matched a "control group" which did not receive remdesivir based on age, gender, and severity using propensity score matching. We used multivariant Cox regression to evaluate the remdesivir effect on patients' 9-month and in-hospital survival. We enrolled 227 patients, 116 in remdesivir and 111 in the control group. 213(93.8%) patients developed the severe disease, 88(38.8%) died during the 9-month follow-up, and 84(37.0%) died during hospitalization. In multivariate analysis, remdesivir did not affect the 9-month all-cause mortality and in-hospital mortality. Remdesivir was associated with increased in-hospital survival only in severe patients with diabetes (HR: 0.32; 95% CI: 0.14-0.75; *P*:0.008), and there was a trend for better 9-month survival in severe patients with diabetes (HR: 0.47; 95% CI: 0.20-1.09; *P*:0.080). We concluded that remdesivir treatment did not increase the 9-month survival rate either in patients with COVID-19 or patients with severe disease and underlying diseases. On the other hand, we found that remdesivir treatment could increase in-hospital survival only in patients with severe COVID-19 and a history of diabetes mellitus.

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Keywords: Coronavirus disease 2019 (COVID-19); Cox regression; Propensity score matching; Remdesivir; Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Introduction

What started as a few pneumonia cases of unknown origin in Wuhan, China, in the last days of 2019 (1) was announced by the world health organization (WHO) as a coronavirus disease-2019 (COVID-19) pandemic in less than three months (2). The pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belongs to the same virus family which caused severe acute respiratory syndrome coronavirus (SARS-CoV)

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and middle east respiratory syndrome coronavirus (MERS-CoV) outbreaks in China and the middle east in 2002 and 2012, respectively (3). As of December 29, 2020, after one year of global struggle with this pandemic, over 113 million were diagnosed with COVID-19, and it took over 2.5 million victims (4).

Most of the infected people are asymptomatic or experience mild symptoms and recover without medical intervention. However, about 15% of adult patients show severe pneumonia symptoms, which require supplemental oxygen therapy. Unfortunately, an additional 5% become critically ill, developing hypoxemic respiratory failure, acute respiratory distress syndrome, multiorgan failure, and require obligatory ventilatory support, often for several weeks (5). Mortality among patients with mechanical ventilation support was as high as 50%, and the associated burden on healthcare systems, especially intensive care units, has been overwhelming in several affected countries (6).

Currently, no treatment is very effective in treating SARS-CoV-2 infection. However, the mainly used medications include antiviral agents, inflammation inhibitors, low-molecular-weight heparins, plasma, and hyperimmune immunoglobulins (7). Remdesivir, an inhibitor of the viral ribonucleic acid (RNA)-dependent RNA polymerase, becomes an early promising therapeutic candidate for COVID-19 because of its ability to inhibit SARS-CoV-2 Vitro and its protective effects on lung cells against MERS-CoV in primate studies (8). The effect of remdesivir in the clinical setting was controversial, and several clinical trial results were opposing. One of the latest meta-analyses showed that a 5 and 10-day regimen of remdesivir had a significantly higher clinical improvement rate based on hospital course compared to standard care alone (9).

Due to the severity of the disease as a global threat and lack of official treatment guidelines, in this study, we aim to investigate the remdesivir effect on 9-month all-cause mortality and in-hospital mortality in patients with COVID-19 and evaluate its effects in different subgroups.

Materials and Methods

This is a retrospective cohort study using registered data derived from the Sina Hospital COVID-19 Registry (SHCo-19R). SHCo-19R is an ongoing, prospective, hospital-based registry of patients with COVID-19 presenting to the emergency department of Sina Hospital, which is a primary COVID-19 referral center affiliated with Tehran University of Medical Sciences (TUMS) in south Tehran, Iran (10).

Our study was conducted under Helsinki's declaration and was approved by the COVID-19 research committee of Sina Hospital and the ethical committee of TUMS (IR.TUMS.VCR.REC.1399.338) (11). All patients signed written informed consent forms upon admission before this study. Based on WHO interim guidance and the Iranian national committee of COVID-19, we enrolled patients older than 18 with a positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test of the oropharyngeal swab or endotracheal samples or compatible chest computed tomography (CT) scan findings, including ground-glass opacity alone or ground-glass opacity accompanied by consolidation (12,13). Patients were categorized into two groups, the "remdesivir group" receiving the remdesivir regimen and the "control group," which did not receive remdesivir during admission. Remdesivir therapy is defined as a 5-day regimen with 200mg of the drug on the first day and 100mg in the next days administered intravenously by the attending physician based on the patient's condition and existing protocols.

We obtained patients' demographic, clinical, laboratory, radiological, and medical management data using SHco-19R. In terms of in-hospital outcome, acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition criteria (14), the acute cardiac injury was defined as an increased serum level of high-sensitivity cardiac troponin I (hs-cTnI) above the 99th percentile upper limit normal (15,16). Acute kidney injury (AKI) was diagnosed if serum creatinine increased by ≥0.3 mg/dL within 48 hours except for patients with known end-stage renal disease (17). Finally, we determined acute liver injury as serum transaminases ≥3×upper limit of normal (ULN) or alkaline phosphatase ≥2×ULN, or total bilirubin ≥2×ULN (18). Multiorgan damage was attributed to patients with at least two complications, including acute cardiac injury, AKI, acute liver injury, or ARDS. We also define disease severity with any of the following criteria: dyspnea, respiratory rate≥30/min, oxygen saturation ≤93%, >50% lung involvement on imaging, respiratory failure, shock, or multiorgan damage. This criterion was modified using Wu and coworkers' definition to introduce a binary outcome, severe vs. non-severe (19).

Categorical variables are presented as numbers (percentage) and compared using the Chi-square test. Numerical variables were demonstrated as mean±standard deviation or median [interquartile range] and compared using a T-test. Multivariable analysis was performed using proportional hazards regression (Cox regression). Adjusted variants were chosen based on the

statistical $P<0.1$ in binary logistic regression with in-hospital mortality as an outcome. 1:1 exact propensity score matching was performed based on the patients' age, gender, and disease severity defined before using Thoemmes techniques (20). All statistical analyses were performed using IBM SPSS® version 26.

Results

During this study using SHCo-19R, 1413 COVID-19 patients were evaluated, but 88 patients were excluded due to a lack of key information in their medical records. Among these 1325 patients, we enrolled 116 patients who received a remdesivir regimen and matched them with 111 patients based on age, gender, and disease severity using the propensity score. All patients were followed for 9 months after admission time.

The mean age was 58.6±14.3, and 99 (43.6%) were female. The overall 9-month all-cause mortality and in-hospital mortality were 88(38.8%) and 84 (37.0%), respectively. Patients in the remdesivir group had higher BMI scores, while there was no difference in comorbidities after matching. Patients in the remdesivir group received more dexamethasone and interferon β-1a treatment during hospitalization than the control group (Table 1).

Table 1. Patients' baseline characteristics.

Characteristic†		Remdesivir group (N=116)	Control Group (N=111)	*P**
Demographics				
Age		58.0±14.7	59.1±14.0	0.557
Sex	**Female**	52(44.8%)	47(42.3%)	0.706
	Male	64(55.2%)	64(57.7%)	
Body mass index (kg/m^2)		28.5±4.9	27.0±4.2	0.048
Comorbidities	**Diabetes Mellitus**	36(31.0%)	36(32.4%)	0.821
	Hypertension	57(49.1%)	50(45%)	0.537
	Cardiac disease	18(15.5%)	25(22.5%)	0.178
	Chronic lung disease	5(4.3%)	10(9.0%)	0.154
	Chronic kidney disease	3(2.6%)	9(8.1%)	0.063
	Malignancy	3(2.6%)	4(3.6%)	0.658
Treatments	**Dexamethasone**	97(83.6%)	17(15.3%)	<0.001
	Hydrocortisone	21(18.1%)	17(15.3%)	0.574
	Methylprednisolone	9(7.8%)	16(14.4%)	0.109
	Interferon β-1a	86(74.1%)	16(14.4%)	<0.001
In-hospital outcomes	**Hospital length of stay (days)**	10 [7-14]	5 [3-10]	<0.001
	In-hospital mortality	40(34.5%)	44(39.6%)	0.421
	9-month all-cause mortality	42(36.2%)	46(41.4%)	0.418
	Severity	109(94.0%)	104(93.7%)	0.932
	ICU admission	52(44.8%)	43(38.7%)	0.353
	Mechanical ventilation	38(32.8%)	45(40.5%)	0.204
	ARDS	68(58.6%)	56(50.5%)	0.216
	Acute liver injury	16(13.8%)	13(11.7%)	0.639
	AKI	30(25.9%)	33(29.7%)	0.515
	Acute cardiac injury	37(31.9%)	31(27.9%)	0.514
	Multiple organ damage	48(41.4%)	39(35.1%)	0.333

† Data are presented as mean±standard deviation, number (%), or median [interquartile range].
* Statistically significant *P* are bolded. AKI: acute kidney injury; ARDS: acute respiratory distress syndrome

During their course of hospitalization, 213(93.8%) patients developed the severe disease, 95 patients (41.9%) were admitted to the intensive care unit (ICU), and 83(36.6%) patients finally needed mechanical ventilation. Although there was no significant difference between the two groups in terms of the mortality rate and organ injuries, the remdesivir group was associated with a longer hospital course (Table 1).

Finally, we used multivariable Cox regression to investigate the remdesivir effect on 6-month all-cause mortality and in-hospital mortality after adjustment with possible confounders in different subgroups (Table 2, Figure 1). Adjusted cofounders were age, gender, history of hypertension, diabetes mellitus, receiving dexamethasone, hydrocortisone, and methylprednisolone treatment. Remdesivir significantly increased survival in unadjusted analysis (hazard ratio (HR): 0.49; 95% confidence interval (CI): 0.32-0.75; *P*:0.001). In

multivariate analysis, remdesivir did not affect the 6-month all-cause mortality (HR: 0.89; 95% CI: 0.49-1.60; *P*: 0.701) and in-hospital mortality (HR: 0.60; 95% CI: 0.34-1.03; *P*:0.066) in all patients. In subgroup analysis, remdesivir treatments were only associated with increased in-hospital survival in severe patients with diabetes (HR: 0.32; 95% CI: 0.14-0.75; *P*:0.008), and there was a trend for better 9-month survival in severe patients with diabetes (HR: 0.47; 95% CI: 0.20-1.09; *P*:0.080).

Table 2. Association of Remdesivir treatment with COVID-19 in-hospital and 9-month all-cause mortality using Cox regression

			All patients	Severe patients	Severe diabetic patients	Severe hypertensive patients
Model 1†	**HR**		0.49	0.49	0.42	0.47
	95% CI	**Lower**	0.32	0.315	0.21	0.26
		Higher	0.75	0.74	0.85	0.83
	P*		**0.001**	**0.001**	**0.016**	**0.009**
Model 2‡	**HR**		0.6	0.6	0.32	0.52
	95% CI	**Lower**	0.34	0.34	0.14	0.26
		Higher	1.03	1.03	0.75	1.02
	P*		0.066	0.063	**0.008**	0.057
Model 3	**HR**		0.89	0.9	0.47	0.82
	95% CI	**Lower**	0.49	0.5	0.2	0.4
		Higher	1.6	1.61	1.09	1.71
	P*		0.701	0.727	0.080	0.605

† Model 1: Unadjusted Cox regression
‡ Model 2: Multivariate Cox regression for in-hospital mortality adjusted with age, gender, history of diabetes mellitus, hypertension, and receiving dexamethasone, hydrocortisone, and methylprednisolone treatment
 Model 3: Multivariate Cox regression for 9-month all-cause mortality adjusted with age, gender, history of diabetes mellitus, hypertension, and receiving dexamethasone, hydrocortisone, and methylprednisolone treatment
* Statistically significant *P* are bolded

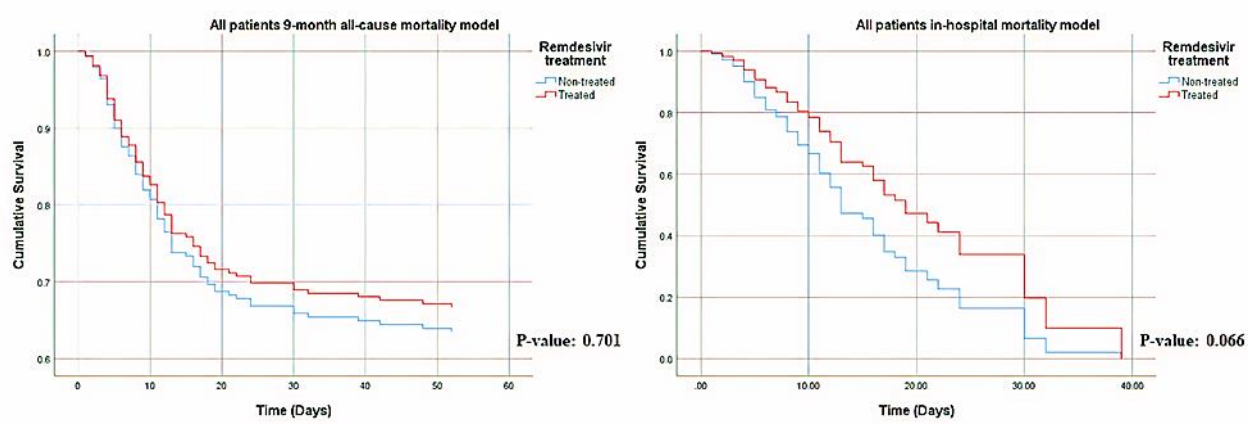

Figure 1. Survival plots comparing COVID-19 in-hospital and 9-month all-cause mortality after remdesivir treatment using multivariate Cox regression in all patients

Discussion

This study found that remdesivir treatment increased the 9-month survival neither in patients with COVID-19 nor patients with severe disease and underlying diseases. After adjustment and matching with possible confounders, we found that remdesivir treatment could increase in-hospital survival only in patients with severe COVID-19 and a history of diabetes mellitus (HR: 0.32; 95% CI: 0.14-0.75; *P*:0.008), while there was a trend for increased in-hospital survival rate in all patients (HR: 0.60; 95% CI: 0.34-1.03; *P*:0.066).

Our result was in line with Psicoya and colleagues' systematic review, which concluded that remdesivir did not significantly decrease the mortality rate and the need for assisted ventilation. The exception was a higher hospitalization length in our findings adjusted as a possible confounder during analysis (21). Another systematic review by Rochwerg and colleagues showed that although remdesivir may reduce mortality, it has no

significant effect on length of stay and the need for mechanical ventilation (22).

As for the length of stay, it is notable that remdesivir has a 5-day treatment that does not permit patient discharge less than 5 days, which means that even if the clinical symptoms are resolved, patients have to stay in the hospital to complete the drug course. For example, 50.9% of the control group were discharged in ≤5 days, but only 13.8% of the remdesivir group were discharged in ≤5 days, and no one was discharged in less than 4 days. This may contribute to this result because we documented the patient's length of hospitalization, not time to recovery. This matter was also noted by Anderson and colleagues' research about remdesivir treatment patients' length of stay (LOS) (23).

We observed that ARDS, AKI, acute cardiac injury, acute liver injury, and multiple organ damage were similar between remdesivir-treated patients and the control group. Beigel and colleagues conducted a clinical trial and concluded that the overall proportion of patients with serious adverse events (including ARDS, acute kidney injury and cardiac arrest, and multiple organ damage) tended to be lower in remdesivir recipients in comparison with the placebo group (131/532(24.6%) patients who received remdesivir vs. 163/516(31.6%) patients who received placebo) (8). In another systematic review including 35 trials, Siemieniuk RA concluded that the role of remdesivir on mortality, mechanical ventilation, and length of the hospital was not certain. However, it probably did not substantially increase adverse effects (24).

Despite the strengths of this study, including our 9-month follow-up period and using propensity score matching to minimize the selection biases for administering remdesivir, we need to mention several limitations. First, this is an observational study with possible inherent biases that raise the necessity for caution when interpreting the results, although we tend to lower these biases using propensity score matching. Most notably, we had to compare remdesivir treated patients with other treatment choices available. Second, this is a single-center study on the Iranian population, and future multicenter randomized clinical trials in different populations are warranted.

In conclusion, in this retrospective cohort study, we found that remdesivir treatment did not increase the 9-month survival rate either in patients with COVID-19 or patients with severe disease and underlying diseases. On the other hand, we found that remdesivir treatment could increase in-hospital survival only in patients with severe COVID-19 and a history of diabetes mellitus. At the same time, there was a trend for increased in-hospital survival rates in all patients. Although current evidence about remdesivir treatment is very controversial, these results are similar to some major studies. We hope that this study will help and encourage future studies to clarify the remdesivir role in COVID-19 treatment and define better treatment protocols for this global disease.

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