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Bradycardia and Outcomes in COVID-19 Patients on Remdesivir: A Multicenter Retrospective Study

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Abstract

Background: Antiviral agents, such as remdesivir, have shown promising results in helping reduce the morbidity and healthcare burden of coronavirus disease 2019 (COVID-19) in hospitalized patients. However, many studies have reported a relationship between remdesivir and bradycardia. Therefore, this study aimed to analyze the relationship between bradycardia and outcomes in patients on remdesivir.

Methods: We conducted a retrospective study of 2,935 consecutive COVID-19 patients admitted to seven hospitals in Southern California in the United States between January 2020 and August 2021. First, we did a backward logistic regression to analyze the relationship between remdesivir use and other independent variables. Finally, we did a backward selection Cox multivariate regression analysis on the subgroup of patients who received remdesivir to evaluate the mortality risk in bradycardic patients on remdesivir.

Results: The mean age of the study population was 61.5 years; 56% were males, 44% received remdesivir, and 52% developed bradycardia. Our analysis showed that remdesivir was associated with increased odds of bradycardia (odds ratio (OR): 1.9, $P < 0.001$). Patients that were on remdesivir in our study were sicker patients with increased odds of having elevated C-reactive protein (CRP) (OR: 1.03, $P < 0.001$), elevated white blood cell (WBC) on admission (OR: 1.06, $P < 0.001$), and increased length of hospital stay (OR: 1.02, $P = 0.002$). However, remdesivir was associated with decreased odds of mechanical ventilation (OR: 0.53, $P < 0.001$). In the sub-group analysis of patients that received remdesivir, bradycardia was associated with reduced mortality risk (hazard ratio (HR): 0.69, $P = 0.002$).

Conclusions: Our study showed that remdesivir was associated with bradycardia in COVID-19 patients. However, it decreased the odds of being on a ventilator, even in patients with increased inflammatory markers on admission. Furthermore, patients on remdesivir that developed bradycardia had no increased risk of death. Clinicians should not withhold remdesivir from patients at risk of developing bradycardia because bradycardia in such patients was not found to worsen the clinical outcome.

Keywords: Remdesivir; Bradycardia; COVID-19; Mortality; Mechanical ventilation

Introduction

One of the most challenging crises in the history of global health emerged due to the coronavirus disease 2019 (COVID-19) pandemic. As of March 2023, over 750 million confirmed cases of COVID-19, including over 6.8 million deaths, were reported globally [1]. During this time, numerous medications were studied for the treatment of COVID-19. Among those, remdesivir was the first approved medication by the US Food and Drug Administration (FDA) for the treatment of COVID-19 infection [2].

Remdesivir is a nucleoside analog antiviral that inhibits viral RNA polymerases and is found to have inhibitory effects on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication by interfering with the RNA replication process [3]. It was initially created to treat hepatitis C and respiratory syncytial virus (RSV) infection [4]. However, remdesivir later demonstrated antiviral effects against several virus families, such as filoviruses (Ebola) and coronaviruses (Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome) [5].

Several studies on COVID-19 patients reported remdesivir's association with an increased early clinical recovery rate, decreased mortality, and a lower probability of requiring high-flow supplemental oxygen and invasive mechanical ventilation. Patients on remdesivir also reported having fewer side effects than those receiving a placebo [6]. On the other hand, some studies proposed that remdesivir showed no mortality benefit or cost-benefit in the treatment of COVID-19. They suggested the administration of remdesivir should be based on individual characteristics, particularly in low- and middle-income countries [7].

Current literature supports the use of remdesivir in patients needing supplemental oxygen and who are within 10 days of their illness and are at higher risk for hyperinflammation as it could accelerate recovery and lowers the risk of

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Table 1. Descriptive Statistics of Continuous Variables

	N	Minimum	Maximum	Mean	Standard deviation
Length of stay	2,935	1	117.0	10.62	11.26
Age	2,935	19	110.0	61.46	18.36
White blood cell count	2,873	1.8	80.7	14.58	8.52
Potassium	2,266	2.70	10.5	4.66	0.85
Platelet	2,877	21	1,176.0	329.84	142.79
Creatinine phosphokinase	1,184	0.04	88,961.0	715.52	4,262.21
Troponin	1,788	0.01	32.8	0.49	2.41
Ferritin	1,836	5.1	47,560.8	916.14	1,861.28
Lactate dehydrogenase	1,967	55	8,180.0	447.40	464.92
C-reactive protein	2,375	0.04	54.4	13.80	9.55
BMI	2,814	13.98	83.1	30.05	8.37

BMI: body mass index.

advancement. However, the administration of remdesivir is not recommended in patients with mild to moderate infection who do not need respiratory support as it was not associated with a substantial change in the clinical outcome [8].

As with any new medication, assessment of the drug's efficacy in relation to mortality, length of hospital stay, and the side effect profile is essential. Though few cases of hypotension, atrial fibrillation, and cardiac arrest have been reported, little is known about remdesivir's adverse cardiovascular events [9]. The most frequent adverse events are liver enzyme elevation, nausea, vomiting, diarrhea, constipation, and acute kidney injury [10-12]. As remdesivir is used more, bradycardia is increasingly recognized as an adverse event. Therefore, the primary aim of our study was to evaluate the effects of remdesivir-associated bradycardia on mortality in COVID-19 patients. The secondary objective of our study is to assess the impact of remdesivir on patients' outcomes, such as length of hospital stay and mechanical ventilation.

Materials and Methods

The study enrolled 2,935 consecutive COVID-19 patients admitted to seven hospitals in Southern California between March 2020 and August 2021 and confirmed to have COVID-19 infection through a positive polymerase chain reaction (PCR) nasopharyngeal swab. We extracted relevant deidentified patient data from the electronic medical record, including age, gender, race, comorbidities, laboratory results on admission, date of hospital admission, date of discharge, medications they received while on admission, heart rate, and disposition at discharge. Our primary outcome of interest was the association of mortality with bradycardia in COVID-19 patients who received remdesivir. Our secondary outcome of interest was the factors associated with remdesivir use in COVID-19 patients. We defined bradycardia as a heart rate of less than 60 beats per minute on two separate occasions, a minimum of 4 h apart during the hospitalization. End-of-life bradycardia was excluded from the study.

First, we performed a univariate analysis of the independent variables, including patients' age, gender, race, marital status, comorbidities, medication received in the hospital, and laboratory results using means and percentages. Furthermore, we performed a bivariate analysis of the relationship between remdesivir use and different study variables using Chi-square and *t*-test, with a P value of 0.05 considered significant. Then, we did a backward selection logistic regression to determine the factors associated with remdesivir use. Finally, we did a Cox regression analysis to determine the predictors of mortality in the subset of patients who received remdesivir. In the backward selection logistic and Cox regression analysis, we initially included biologically plausible or statistically significant variables from the bivariate analysis, such as patients' age, sex, body mass index (BMI), comorbidities, intensive care unit (ICU) admission, and mechanical ventilation, as independent variables in the multivariate model. The effect size was expressed as the odds and hazards ratio for the logistic and Cox regression, respectively. The hypothesis was tested using a two-sided test, and an alpha value of 0.05 was considered statistically significant. Statistical analysis was done using IBM SPSS version 27. The WIRB-Copernicus Group (WCG) Institutional Review Board (IRB) approved the study. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

There were 2,935 patients in the study with a mean age of 61.5, and 56.4% were males. The mean length of stay was 10.6 days, and the mean BMI was 30.1. About 18% were admitted to ICU and placed on the ventilator, and 22% expired. The patients had comorbidities, including diabetes (19%), hypertension (41%), chronic kidney disease (CKD) (20%), congestive heart failure (CHF) (13.8%), and chronic obstructive pulmonary disease (COPD) (5%). Dexamethasone was given to 63%, and 44% received remdesivir. Fifty-two percent of the study population had bradycardia (Tables 1, 2).

Table 2. Descriptive Analysis of Categorical Variable

	Frequency	Percent
Gender		
Female	1,279	43.6%
Male	1,656	56.4%
Race		
Asian	165	5.6%
Black	108	3.7%
White	1,676	57.1%
Others	985	33.6%
Expired		
No	2,282	77.8%
Yes	653	22.2%
Ventilator use		
No	2,399	81.7%
Yes	536	18.3%
Intensive care unit admission		
No	2,392	81.5%
Yes	542	18.5%
Remdesivir use		
No	1,606	56.2%
Yes	1254	43.8%
Dexamethasone use		
No	1,107	37.7%
Yes	1,828	63.3%
Diabetes mellitus		
No	2,373	80.9%
Yes	562	19.1%
Hypertension		
No	1,743	59.4%
Yes	1,192	40.6%
Chronic kidney disease		
No	2,348	80.2%
Yes	579	19.8%
Acute kidney injury		
No	2,678	91.2%
Yes	257	8.8%
Congestive heart failure		
No	2,530	86.2%
Yes	405	13.8%
Chronic obstructive pulmonary disease		
No	2,789	95.0%
Yes	146	5.0%
Bradycardia		
No	1,367	47.8%
Yes	1,493	52.2%

In the *t*-test bivariate analysis of continuous variables, age ($P < 0.001$), length of hospital stay ($P < 0.001$), BMI ($P < 0.001$), C-reactive protein (CRP) ($P < 0.001$), lactate dehydrogenase (LDH) ($P < 0.001$) platelet count ($P < 0.001$), white blood cell (WBC) count ($P < 0.001$) and potassium ($P < 0.001$) were significantly associated with remdesivir use. Patients that received remdesivir were older and had increased inflammatory markers such as CRP and LDH. Furthermore, those who received remdesivir had lower average minimum heart rate (53 vs. 60, $P < 0.001$). Additionally, the patients that received remdesivir had higher BMI and stayed longer in the hospital (Table 3). In the Chi-square bivariate analysis of categorical variables, gender ($P < 0.001$), race ($P < 0.001$), death ($P < 0.001$), ICU admission ($P < 0.001$), mechanical ventilation ($P < 0.001$), hypertension ($P = 0.01$), COPD ($P = 0.006$), and bradycardia ($P < 0.001$) were significantly associated with remdesivir use (Table 4). In the subset of patients who received remdesivir, COPD ($P = 0.001$), CHF ($P = 0.038$) (Table 5), CRP ($P < 0.001$), and length of hospital stay ($P = 0.001$) were associated with bradycardia.

In the backward selection logistic regression multivariate analysis, the use of remdesivir was independently associated with increased length of hospital stay (OR: 1.02, $P = 0.002$), CRP (OR: 1.03, $P < 0.001$), WBC (OR: 1.06, $P < 0.001$), and bradycardia (OR: 1.9, $P < 0.001$). Additionally, remdesivir use was associated with decreased odds of ventilator use (OR: 0.53, $P < 0.001$) (Table 6).

In the multivariate Cox regression of only patients who received remdesivir, age (hazard ratio (HR): 1.03, $P < 0.001$) and ICU admission (HR: 4.65, $P < 0.001$) were associated with increased mortality. However, bradycardia (HR: 0.69, $P = 0.002$) was associated with decreased odds of mortality (Table 7).

Discussion

In our study, remdesivir was associated with an increased length of hospital stay but decreased odds of mechanical ventilation. Although some studies and meta-analyses suggested that remdesivir did not reduce all-cause mortality and the need for invasive mechanical ventilation [13-15], others, similar to our findings, showed that remdesivir was associated with a significantly reduced need for invasive mechanical ventilation or extracorporeal membrane oxygenation in COVID-19 patients [16-18]. Many studies agree that the use of remdesivir was associated with improved time to recovery and recovery rate, especially in non-mechanically ventilated patients [19-21]. However, similar to our study, other studies have found a more prolonged hospital stay in patients on remdesivir [22, 23]. The reasons for the more extended hospital stay in those on remdesivir are unclear since remdesivir has been shown in some studies to improve the time to recovery. One reason will be that patients were kept longer in the hospital to complete the 5-day course of intravenous remdesivir. Although the treatment guidelines recommend using remdesivir for 5 days or until hospital discharge, whichever comes first [4], anecdotally, that has not been the case, as some pa-

Table 3. Bivariate Analysis (*t*-Test) of the Relationship Between Continuous Variables and Remdesivir Use in All Patients

	Remdesivir	N	Mean	Std	P value
Length of stay	No	1,606	8.31	10.41	< 0.001
	Yes	1,254	13.71	11.72	
Age	No	1,606	60.09	19.79	< 0.001
	Yes	1,254	62.96	16.09	
BMI	No	1,515	29.32	8.13	< 0.001
	Yes	1,225	30.99	8.59	
C-reactive protein	No	1,128	11.81	9.57	< 0.001
	Yes	1,180	15.89	9.24	
Lactate dehydrogenase	No	908	391.97	472.65	< 0.001
	Yes	1,007	499.76	461.49	
Ferritin	No	910	866.36	1,764.42	0.45
	Yes	901	931.70	1,877.01	
Troponin	No	853	0.44	2.17	0.42
	Yes	883	0.53	2.61	
Creatinine phosphokinase	No	614	776.99	4,246.95	0.74
	Yes	511	689.08	4,510.65	
Platelet	No	1,565	300.47	138.12	< 0.001
	Yes	1,249	367.57	138.40	
White blood cell count	No	1,566	12.52	7.42	< 0.001
	Yes	1,249	17.10	8.88	
Potassium	No	1,228	4.55	0.81	< 0.001
	Yes	972	4.79	0.83	
Total bilirubin	No	1,463	0.90	1.27	0.08
	Yes	1,238	0.97	0.97	
Minimum heart rate during hospitalization	No	1,461	60.10	13.77	< 0.001
	Yes	1,113	52.87	12.62	

BMI: body mass index; Std: standard deviation.

tients who have significantly improved are kept in the hospital to complete the dose.

Furthermore, our study found that remdesivir use was independently associated with increased odds of bradycardia. Bradycardia in COVID-19 patients on remdesivir has been reported in previous studies [24-26]. The mechanism through which remdesivir causes bradycardia is unknown [25]. One possible mechanism through which remdesivir causes bradycardia is its triphosphorylated form binding to the A1 receptor in the cardiac cells. Remdesivir, a nucleoside analog prodrug, changes into its triphosphorylated metabolite in the body, which resembles adenosine triphosphate. Adenosine has been used as an atrioventricular nodal blocker in treating supraventricular tachycardia. It is postulated that the triphosphorylated metabolite in the body binds to the same A1 receptors as adenosine resulting in bradycardia [26, 27]. A study of the VigiBase®, the World Health Organization Global Individual Case Safety Reports database, showed that bradycardia comprised 3.6% of all remdesivir adverse drug reactions reported in COVID-19 patients and 31% of the cardiac adverse reactions reported [25]. In a study of COVID-19 patients, those who received remdesivir had a higher incidence of sinus bradycardia than the control group (21% versus 3.0%; P = 0.001), and the bradycardia resolved after stopping remdesivir [24].

Our study found that in the subset of COVID-19 patients on remdesivir, bradycardia was associated with decreased odds of mortality. According to a prior study, remdesivir-associated bradycardia did not increase the mortality rate in COVID-19 patients, and sudden cardiac death was not reported in the studied patients [28]. Similar to our study, another study found that bradycardia in COVID-19 patients treated with remdesivir was significantly associated with lower odds for in-hospital mortality (OR: 0.3 (95% confidence interval (CI): 0.14 to 0.79); P = 0.014). The reason for the lower mortality in bradycardic COVID-19 patients that received remdesivir is unknown. One possible explanation is that COVID-19 patients with cytokine storms might be less responsive

Table 4. Chi-Square Bivariate Analysis of the Relationship Between Categorical Variables and Use of Remdesivir for All Patients

Variable	Remdesivir		P value
	No	Yes	
Gender			
Male	857 (53.1%)	758 (46.9%)	< 0.001
Female	749 (60.2%)	496 (39.8%)	
Race			
Asia	78 (47.9%)	85 (52.1%)	< 0.001
Black	74 (71.8%)	29 (28.2%)	
White	933 (57.7%)	683 (42.3%)	
Others	521 (53.3%)	457 (46.7%)	
Expired			
Yes	277 (43.1%)	365 (56.9%)	< 0.001
No	1,329 (59.9%)	889 (40.1%)	
Ventilator use			
Yes	231 (43.9%)	295 (56.1%)	< 0.001
No	1375 (58.9%)	959 (41.1%)	
Intensive care unit admission			
Yes	214 (40.9%)	309 (59.1%)	< 0.001
No	1,391 (59.5%)	945 (40.5%)	
Diabetes mellitus			
Yes	285 (52.9%)	254 (47.1%)	0.09
No	1,321 (56.9%)	1,000 (43.1%)	
Hypertension			
Yes	606 (53.2%)	533 (46.8%)	0.01
No	1,000 (58.1%)	721 (41.9%)	
Chronic kidney disease			
Yes	339 (59.2%)	234 (40.8%)	0.1
No	1,262 (55.4%)	1,017 (44.6%)	
Acute kidney injury			
Yes	138 (59.2%)	95 (40.8%)	0.32
No	1,468 (55.9%)	1,159 (44.1%)	
Congestive heart failure			
Yes	237 (60.3%)	156 (39.7%)	0.07
No	1,369 (55.5%)	1,098 (44.5%)	
Chronic obstructive pulmonary disease			
Yes	67 (69.8%)	29 (30.2%)	0.006
No	1,539 (55.7%)	1,225 (44.3%)	
Bradycardia			
Yes	692 (46.3%)	801 (53.7%)	< 0.001
No	914 (66.9%)	453 (33.1%)	

to the bradycardia effect of remdesivir due to their intense sympathetic-adrenergic stimulation and are more likely to have worse outcomes [29]. However, this does not appear to be the case in our study because the patients on remdesivir who developed bradycardia, on average, had more elevated inflammatory markers (CRP and LDH) than those without bradycardia. Another possible explanation is that remdesivir might have anti-arrhythmogenic properties through the same

Table 5. Chi-Square Bivariate Analysis of the Relationship Between Categorical Variables and Bradycardia in Patients That Received Remdesivir

Variable	Bradycardia		P value
	No	Yes	
Gender			
Male	261 (34.4%)	497 (65.6%)	0.123
Female	192 (38.7%)	304 (61.3%)	
Expired			
Yes	133 (36.4%)	232 (63.6%)	0.882
No	320 (36.0%)	569 (64.0%)	
Ventilator			
Yes	97 (32.9%)	198 (67.1%)	0.185
No	356 (37.1%)	603 (62.9%)	
Intensive care unit admission			
Yes	105 (34.0%)	204 (66.0%)	0.366
No	348 (36.8%)	597 (63.2%)	
Dexamethasone use			
Yes	403 (35.4%)	739 (64.6%)	0.085
No	50 (43.5%)	65 (56.5%)	
Chronic kidney disease			
Yes	73 (31.2%)	161 (68.8%)	0.081
No	379 (37.3%)	638 (62.7%)	
Congestive heart failure			
Yes	68 (43.6%)	88 (56.4%)	0.038
No	385 (35.1%)	713 (64.9%)	
Chronic obstructive pulmonary disease			
Yes	19 (65.5%)	10 (34.5%)	0.001
No	434 (35.4%)	791 (64.6%)	

mechanism through which it causes bradycardia that reduces death in COVID-19 patients.

Limitations of the study

The study has some limitations. Firstly, the retrospective design makes the study prone to confounding bias from unmeasured variables, which might have affected the outcome. In addition, other therapies, such as beta-blockers that might have resulted in bradycardia, were not adjusted for in the analysis, which might have affected the study outcome. Furthermore, we do not have data on the onset of bradycardia in relation to remdesivir use. Therefore, it is possible that some of the brady-

Table 6. Logistic Regression on Remdesivir Use

	B	SE	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
Length of stay	0.017	0.005	9.567	1	0.002	1.017	1.006	1.028
Ventilator	-0.637	0.160	15.917	1	0.000	0.529	0.387	0.723
C-reactive protein	0.029	0.006	21.663	1	0.000	1.029	1.017	1.042
Lactate dehydrogenase	0.000	0.000	3.188	1	0.074	1.000	1.000	1.001
White blood cell count	0.055	0.008	45.407	1	0.000	1.056	1.040	1.073
Bradycardia	0.639	0.101	40.390	1	0.000	1.895	1.556	2.309

CI: confidence interval; SE: standard error.

Table 7. Cox Regression for Only Patients on Remdesivir

	B	SE	Wald	df	Sig.	Exp(B)	950% CI for Exp(B)	
							Lower	Upper
Age	0.027	0.005	31.906	1	0.000	1.027	1.018	1.037
ICU	1.536	0.180	73.230	1	0.000	4.647	3.269	6.607
Bradycardia	-0.376	0.120	9.724	1	0.002	0.687	0.542	0.870
Lactate dehydrogenase	0.000	0.000	3.507	1	0.061	1.000	1.000	1.000

CI: confidence interval; ICU: intensive care unit; SE: standard error.

cardia was unrelated to remdesivir use. On the other hand, the strength of our study includes its large sample size and data collection from multiple hospitals in Southern California.

Suggestions for future research

Bradycardia in COVID-19 patients is not always suggestive of a favorable prognosis. While some studies suggest that bradycardia in COVID-19 patients is a sign of worse clinical outcomes [9, 30], others have not found any worse outcomes with remdesivir [31]. Further studies are required to identify mortality rate differences between remdesivir-induced bradycardia and bradycardia caused by other reasons.

Additionally, we are unclear why bradycardia causes reduced mortality in COVID-19 patients on remdesivir. One mechanism we have proposed is that remdesivir may lead to decreased arrhythmias in these patients, reducing mortality. Further studies are needed to investigate the possible causes of reduced mortality in these patients and the incidence of cardiac arrhythmias in this patient population compared to those without bradycardia.

Conclusions and clinical implications

Our study showed that remdesivir was associated with bradycardia in COVID-19 patients. Physicians should be aware of this side effect and monitor heart rate during the administration of remdesivir. However, it decreased the odds of being on a ventilator, even in patients with increased inflammatory markers on admission. Furthermore, patients on remdesivir that developed bradycardia had no increased risk of death. Bradycardia in patients on remdesivir appears to be a good prognostic sign. Physicians should continue remdesivir in patients that develop bradycardia, with appropriate surveillance in the general population and patients with significant cardiovascular risk factors.

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None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

All authors conceptualized and revised the study design. CA Umeh analyzed the data. CA Umeh, S. Maguwudze, H. Kaur, O. Dimowo, N. Naderi, and A. Safdarpour wrote the first draft of the paper. R. Gupta, T. Hussein, and CA Umeh reviewed and revised the paper. S. Maguwudze and H. Kaur led and coordinated the research and writing of the manuscript. T. Hussein, R. Gupta and CA Umeh supervised the project. All authors have read and approved the final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

BMI: body mass index; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; CPK: creatinine phosphokinase; CRP: C-reactive protein; FDA: United States Food and Drug Administration; HR: hazard ratio; ICU: intensive care unit; LDH: lactate dehydrogenase; OR: odds ratio; PCR: polymerase chain reaction; RSV: respiratory syncytial virus; WBC: white blood cell; WCG: WIRB-Copernicus Group

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