Clinical Drug Investigation (2022) 42:763–774
https://doi.org/10.1007/s40261-022-01187-x

ORIGINAL RESEARCH ARTICLE

Clinical Characteristics and Implications of Bradycardia in COVID-19 Patients Treated with Remdesivir: A Single-Center Retrospective Cohort Study

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Accepted: 26 July 2022 / Published online: 17 August 2022

Abstract

Background and Objectives Remdesivir is an antiviral drug used to treat coronavirus disease 2019 (COVID-19) with a relatively obscure cardiac effect profile. Previous studies have reported bradycardia associated with remdesivir, but few have examined its clinical characteristics. The objective of this study was to investigate remdesivir associated bradycardia and its associated clinical characteristics and outcomes.

Methods This is a single-institution retrospective study that investigated bradycardia in 600 patients who received remdesivir for treatment of COVID-19. A total of 375 patients were included in the study after screening for other known causes of bradycardia (atrioventricular [AV] nodal blockers). All patients were analyzed for episodes of bradycardia from when remdesivir was initiated up to 5 days after completion, a time frame based on the drug's putative elimination half-life. Univariate and multivariate statistical tests were conducted to analyze the data.

Results The mean age of the sample was 56.63 ± 13.23 years. Of patients who met inclusion criteria, 49% were found to have bradycardia within 5 days of remdesivir administration. Compared to the cohort without a documented bradycardic episode, patients with bradycardia were significantly more likely to experience inpatient mortality (22% vs 12%, $p = 0.01$). The patients with bradycardia were found to have marginally higher serum D-dimer levels (5.2 vs 3.4 µg/mL, $p = 0.05$) and were more likely to undergo endotracheal intubation (28% vs 14%, $p = 0.008$). Male sex, hyperlipidemia, and bradycardia within 5 days of completing remdesivir were significant predictors of inpatient mortality. No significant differences in length of stay were found.

Conclusions Bradycardia that occurs during or shortly after remdesivir treatment in COVID-19 patients may be associated with an increased rate of in-hospital mortality. However, COVID-19 and its cardiac complications cannot be excluded as potential contributors of bradycardia in the present study. Future studies are needed to further delineate the cardiac characteristics of COVID-19 and remdesivir.

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Key Points

Despite being a common treatment for severe coronavirus disease 2019 (COVID-19), the cardiac profile of remdesivir and its associated clinical outcomes are not well characterized.

This retrospective study reviewed remdesivir-associated bradycardia based on the drug's elimination half-life and found an increased risk of in-hospital mortality.

The results highlight the need to evaluate the cardiac-related adverse events of remdesivir treatment.

1 Background

Remdesivir is an antiviral prodrug of a nucleotide analog and currently a mainstay therapy in the treatment of coronavirus disease 2019 (COVID-19) [1]. Although the drug has been studied extensively in clinical trials, the cardiac side effect profile of remdesivir is not well studied [2]. One such phenomenon is remdesivir-associated bradycardia (RAB). Touafchia et al. [3] found an increased risk of reporting bradycardia following the use of remdesivir compared to other drugs, a finding consistent with a number of case reports and observational studies [3–7]. RAB is fairly common, with a reported incidence of 21–60% [3, 4, 7]. One proposed mechanism of RAB refers to remdesivir's active metabolite, GS-441524, a nucleotide triphosphate derivative similar in structure to adenosine [8]. Adenosine is known to exert a negative chronotropic and dromotropic effect by slowing sinoatrial automaticity [9]; GS-441524 may lead to RAB via a similar mechanism to adenosine. Remdesivir antiviral therapy has offered a potential decrease in recovery time for COVID-19 patients, with an acceptable side effect profile [14]. However, despite its wide utilization, there remains a paucity of data regarding the cardiac-related clinical outcomes of remdesivir. RAB appears to occur at a disproportionate rate when compared to other pharmaceuticals administered to patients with COVID-19 [3], but only a few studies have appreciated the clinically relevant outcomes that result from the bradycardia [4, 7].

Likewise, the association between COVID-19 and sinus bradycardia is well documented in the literature [10, 11]. Bradycardia in the context of COVID-19 may be associated with increased rates of mortality [12]. Furthermore, patients with severe disease may be more prone to incident bradycardia [12, 13]. The potential etiology for COVID-19 arrhythmogenicity is manifold and includes myocardial insults (infarction, myocarditis), hypoxic injury, a systemic inflammatory response, autonomic disturbance, and electrolyte abnormalities [10]. It is not entirely clear whether drugs used in the treatment of COVID-19 that have QT interval-prolonging properties or certain drug–drug interactions also induce bradycardia [10].

Given the current widespread use of remdesivir and the comparatively modest attention placed on its potential cardiac pharmacodynamic properties, a better understanding of the clinical implications of RAB is warranted. The overarching goal of this study was to investigate RAB and its associated clinical characteristics and outcomes.

2 Methods

2.1 Patient Selection Criteria

Following University Medical Center of Southern Nevada institutional review board approval, a retrospective audit was performed on 600 consecutive patients at a single institution who were evaluated at hospital admission for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as defined by the COVID-19 treatment guidelines panel of the National Institute of Health, identified via polymerase chain reaction (PCR) between March 1, 2020 and March 31, 2021. Exclusion criteria included patients who tested negative for SARS-CoV-2, were less than 18 years old, were found to be pregnant, had less than 2 days length of stay (LOS), had severe hepatic dysfunction (AST or ALT > 5 times the upper limit of normal), or had evidence of renal impairment (glomerular filtration rate < 30 mL/min) (see the electronic supplementary material, Supplementary Material A) [15]. Patients who received atrioventricular (AV) nodal agents, a known cause of bradycardia, on admission or within 5 days of completing remdesivir treatment were also excluded [16]. Only patients who received a full 5-day course of remdesivir (200-mg intravenous [IV] loading dose, 100-mg IV daily maintenance dose for 4 days) were included in the present analysis [15].

Remdesivir's active form, GS-441524, has a half-life of 20–27 h [1]. Over 95% elimination of the active metabolite would be expected approximately 5 days following completion of IV infusion of the drug [1, 17]. This study utilized a therapeutic window based on the drug's elimination half-life, which was defined as when remdesivir was initiated up to 5 days after completion of a full course [15]. Bradycardia that was recorded during this window was considered RAB+, while bradycardia that occurred outside of this window was determined as RAB−. Two physician reviewers independently verified all inclusion and exclusion criteria (Online Resource 1, see the electronic supplementary material).

2.2 Definition of Bradycardia

For the purposes of this study, an episode of bradycardia (EB) was defined as two consecutive episodes of sustained heart rate (HR) less than 60 bpm at least 4 h apart throughout a patient's admission. EBs were then classified based on whether they presented as single (i.e., one isolated instance of EB as defined above) or multiple events. Multi-event EBs were further defined as episodic (two episodes of EB separated by a normal HR), continuous (at least three consecutive episodes of sustained HR < 60 bpm), or both. An EB was determined to meet "symptomatic bradycardia" if systolic blood pressure (BP) was < 90 mmHg, diastolic BP was < 60 mmHg, or if patients showed clinical symptoms related to bradycardia as identified in their chart. Patients who experienced an EB during the drug effect window (DEW) were stratified into RAB+ (documented EB within DEW) and RAB− (no EB within DEW), which

were verified by two separate reviewers using a Microsoft Excel macro [18].

2.3 Data Collection

Clinical data for all included patients was abstracted by a team of physician reviewers and medical trainees using both physician-facing medical record export (when available) and manual collection. Variables included demographics (age, race/ethnicity, sex, body mass index); LOS; mortality; baseline vitals from admission (HR, temperature, oxygen saturation); inflammatory biochemical markers (white blood cell count, ferritin, C-reactive protein [CRP], D-dimer) and highest level of oxygenation (i.e., bilevel positive airway pressure [BiPAP], endotracheal intubation) between admission and 5 days after completing remdesivir; past medical history (including prior arrhythmia, thyroid disease, and sleep apnea); tobacco use; electrocardiographic (ECG) data; and cardiac studies (echocardiogram, wire pacing, and cardiac catheterization). Data cleaning was performed to eliminate errors of transcription and implausible values.

2.4 Sample Size Justification

Due to the lack of existing literature on this topic area, we relied on the conventional method of power analysis. G power software (version 3.1) was used to perform a priori power analysis [19–21]. The a priori power analysis was conducted to ascertain the required sample size for a test with a predetermined alpha and beta (power) level. Power was ascertained separately for *t*, chi-square, and multiple logistic regression by using Cohen's effect size conventions (effect size = 0.5 for *t* tests; effect size = 0.3 for chi-square test) [22]. For the logistic regression analysis, we used the formula proposed by Green (223, $N \geq 50 + 8m$, where m corresponds to the number of predictors) [23]. The total number of predictors was 11, according to which, $N = 138$ was deemed appropriate. The total sample size estimated with a power of 0.95 was 210 and 220 for *t* test and chi-square test, respectively. The sample size with the greatest value ($N = 220$) was considered appropriate since it satisfies the minimum requirement of all the statistical tests used. The sample used in this study was relatively larger to allow subgroup comparisons.

2.5 Data Analysis

The primary outcomes of the study were rates of inpatient mortality and hospital LOS. Patients who underwent inpatient mortality were not included in the LOS analysis. Data were first cleaned and re-coded for running analytical operations. All statistical assumptions, including the normality, homogeneity of variance, and multicollinearity were accessed. Box plots were visually inspected to identify outliers in the data. Depending on their distribution (normal or not), quantitative variables were expressed as means ± standard deviations (SDs), and then compared with an independent samples *t* test/Welch two-sample *t* test or as medians (25th–75th percentiles) and then compared with a Mann-Whitney U test. Kruskal-Wallis test was used to compare medians of more than two groups. Qualitative variables were expressed as counts (percentages) and then compared with the chi-square analysis. Adjusted standardized residuals greater than 2 were considered significant cells for contingency tables larger than 2×2 chi-square analysis. In univariate statistics, 95% confidence intervals (CIs) of proportions were calculated using normal approximation to the binomial distribution. Two multivariate logistic regression models were fit to generate adjusted odds ratios for inpatient mortality and intubation as outcomes. Estimates of parameters were obtained through the maximum likelihood estimation method with 95% Wald's confidence limits for the logistic model. The final model was selected based upon the Akaike information criterion (AIC) and the Schwarz criterion (SC) [24]. For regression analyses, polytomous categorical variables were dummy coded to calculate accurate parameters. All tests were two-sided, and a p value of < 0.05 was considered significant. The Statistical Package for Social Sciences for Windows, version 27.0 (SPSS, Chicago, IL, USA), and Statistical Analysis System (SAS 9.4) were used to analyze the data.

3 Results

A total of 375 patients were included in the analysis. The mean age of the sample was 56.63 ± 13.23 years. Over 60% of the sample were males, with the remaining 40% being females (Table 1). The white and non-white racial groups were nearly equally split. The mean body mass index of the sample population was 32.8 ± 8.57 kg/m^2, and nearly 60% of the patients were obese. Approximately half of the sample (45.1%) had type 2 diabetes mellitus, and 42.7% had a medical history of hypertension. Hyperlipidemia was found among 31% of the cases (Table 1). As indicated in Supplementary Material B (see the electronic supplementary material), the minimum and maximum HR was 50.59 ± 12.8 and 112.91 ± 20.5 bpm, respectively. The mean levels of ferritin, CRP, low-density lipoprotein, and D-dimer were 948.64 ± 183.07 µg/L, 123.88 ± 63.5 mg/L, 492.26 ± 218.0 µL, and 5.06 ± 3.80 µg/mL, respectively. Clinical data were missing for certain variables during the retrospective abstraction process, as noted in Table 1, which did not exceed 0.5% of patients per variable.

As shown in Supplementary Material B, the RAB+ group had a lower mean minimum HR than the RAB− group, with

Table 1 Baseline demographic, behavioral, medical, clinical, and cardiac characteristics of study population at time of admission ($N = 375$)

Variable	Categories	Overall sample, *n* (%)	Patients with bradycardia within 5 days of remdesivir, *n* (%)		*P* value
			Yes 182 (48.5)	No 193 (51.5)	
Age (mean ± SD)	–	56.63 ± 13.23	56.74 ± 12.85	56.53 ± 13.62	0.8
Sex	Female	145 (38.7)	69 (37.9)	76 (39.4)	0.7
	Male	230 (61.3)	113 (62.1)	117 (60.6)	
Race/ethnicity	White	71 (18.9)	33 (18.6)	38 (20.8)	0.3
	Non-white	75 (20.0)	32 (18.1)	43 (23.5)	
	Hispanic	214 (57.1)	112 (63.3)	102 (55.7)	
Body mass index in kg/m^2 (mean ± SD)	–	32.8 ± 8.57	32.7 ± 7.57	32.8 ± 9.43	0.9
Body mass index categories	Underweight	1 (3.0)	0 (0.0)	1 (0.5)	0.6
	Normal weight	69 (18.4)	29 (15.9)	40 (20.7)	
	Overweight	86 (22.9)	46 (25.3)	40 (20.7)	
	Obesity class 1	94 (25.1)	48 (26.4)	46 (23.8)	
	Obesity class II	57 (15.2)	28 (15.4)	29 (15.0)	
	Obesity class III	68 (18.1)	31 (17.0)	37 (19.2)	
History of tobacco use	Current	16 (4.3)	7 (3.8)	9 (4.7)	0.2
	Former	41 (10.9)	25 (13.7)	16 (8.3)	
	Never	318 (84.8)	150 (82.4)	168 (87.0)	
History of drug abuse	Yes	12 (3.2)	6 (3.3)	6 (3.1)	0.9
	No	363 (96.8)	176 (96.7)	187 (96.9)	
Type 2 diabetes mellitus	Yes	169 (45.1)	82 (45.1)	87 (45.3)	0.9
	No	205 (54.7)	100 (54.9)	105 (54.7)	
Hypertension	Yes	160 (42.7)	79 (43.4)	81 (42.2)	0.8
	No	214 (57.1)	103 (56.6)	111 (57.8)	
Hyperlipidemia	Yes	115 (30.7)	60 (33.0)	50 (28.6)	0.4
	No	259 (69.1)	122 (67.0)	137 (71.4)	
Hypothyroidism	Yes	28 (7.5)	16 (8.8)	12 (6.2)	0.3
	No	347 (92.5)	166 (91.2)	181 (93.8)	
Prior arrhythmia	Yes	5 (1.3)	1 (0.5)	4 (2.1)	0.2
	No	369 (98.4)	181 (99.5)	188 (97.9)	
Coronary artery disease	Yes	14 (3.7)	7 (3.8)	7 (3.6)	0.9
	No	360 (96.0)	175 (96.2)	185 (96.4)	
Obstructive sleep apnea	Yes	17 (4.5)	9 (4.9)	8 (4.1)	0.7
	No	358 (95.5)	173 (95.1)	185 (95.9)	

Some percentages may not add up to 100% due to missing information

P values < 0.05 are considered statistically significant

a statistically significant mean difference (44.78 ± 10.66 vs 57.52 ± 9.43 bpm, $p < 0.001$). Likewise, the mean maximum HR was lower among patients with bradycardia than with patients without bradycardia (108.24 ± 22.60 vs 113.20 ± 18.47, $p = 0.02$). The mean values of minimum body temperature were also statistically different. The differences between mean values of D-dimer levels were marginally significant, with the RAB+ group having the value of 5.19 ± 5.76 µg/mL compared with 3.38 ± 2.31 µg/mL among patients without an EB ($p = 0.05$, Table 2). Patients with an EB had lower mean HR on ECG as compared to RAB− patients, with a statistically significant mean difference (70.81 ± 23.41 vs 91.49 ± 23.41, $p < 0.001$, Table 2). Among bradycardic patients, a significantly larger proportion underwent intubation as opposed to non-bradycardic patients (27.5% vs 14.0%, $p = 0.008$). Among RAB+ patients ($n = 182$), 148 (81.3%) had the multiple events of bradycardia and only 18.7% had the single event (Table 3). The mean days of bradycardia were 3.51 ± 2.28. The mean systolic and diastolic BP values of this group were 107.57 ± 17.82 mmHg and 54.12 ± 11.5 mmHg, respectively. The PR, QRS, and QTc intervals were 149.75 ± 20.8 ms, 98.19

Table 2 Comparing clinical characteristics among groups with or without bradycardia after initiation of remdesivir (N = 375)

Variable	Patients with bradycardia within 5 days of remdesivir, mean ± SD		*P* value
	Yes	No	
Number of patients, *n (%)*	182 (48.5)	193 (51.5)	–
Minimum HR (bpm)	44.78 ± 10.66	57.52 ± 9.43	**< 0.001**
Maximum HR (bpm)	108.24 ± 22.60	113.20 ± 18.47	0.02
Minimum temperature (Celsius)	35.96 ± 0.72	36.14 ± 0.36	**0.003**
Maximum temperature (Celsius)	37.85 ± 0.93	37.85 ± 0.93	0.5
Minimum SpO_2 (%)	82.31 ± 10.90	82.89 ± 12.25	0.6
Maximum SpO_2 (%)	99.27 ± 1.132	99.26 ± 1.025	0.9
WBC (cu/mm^3)	12.88 ± 0.57	13.24 ± 1.10	0.6
Ferritin (µg/L)	806.56 ± 114.91	825.98 ± 182.25	0.8
CRP (mg/L)	105.94 ± 67.01	106.36 ± 65.22	0.9
D-dimer (µg/mL)	5.19 ± 5.76	3.38 ± 2.31	0.05[a]
LDL (µL)	494.37 ± 191.21	458.92 ± 205.29	0.1
HR on ECG (bpm)	70.81 ± 23.41	91.49 ± 23.41	**< 0.001**
PR interval (ms)	149.56 ± 22.67	150.78 ± 27.61	0.7
QRS interval (ms)	97.92 ± 14.32	94.21 ± 17.47	0.1
QTc (ms)	436.55 ± 28.65	445.24 ± 30.68	0.06
Supplemental O_2 method			**0.008**
BiPAP, *n* (%)	1 (0.5)	1 (0.5)	
HFNC, *n* (%)	65 (35.7)	70 (36.3)	
Intubation, *n* (%)	50 (27.5)	27 (14.0)	
NC, *n* (%)	63 (34.6)	94 (48.7)	
None, *n* (%)	3 (1.6)	1 (0.5)	

BiPAP bilevel positive airway pressure, *CRP* C-reactive protein, *ECG* electrocardiogram, *HFNC* high-flow nasal cannula, *HR* heart rate, *LDL* low-density lipoprotein, *NC* nasal cannula, *WBC* white blood count, *SpO_2* oxygen saturation

P values < 0.05 are considered statistically significant and are bolded in the table

± 13.60 ms, and 435.16 ± 26.54 ms, respectively. Among RAB+ patients, 17.6% of patients had hypoxia (Table 3). A significantly larger proportion of the RAB+ group had inpatient mortality as compared to the RAB− group (22.0% vs 12.4%, p = 0.01). However, no significant differences in the median length of hospital stay were observed. Upon analyzing the subgroups of patients with a documented EB by characteristics of bradycardia, no significant differences were noted for inpatient mortality (Table 4). The median LOS did not differ significantly by the bradycardia characteristics (Table 5).

As shown in Fig. 1 and Table 6, the sex of the patient, hyperlipidemia, and bradycardia within 5 days of completing remdesivir treatment were significant predictors of inpatient mortality. Males had the higher odds (adjusted odds ratio = 3.39, 95% CI 1.69–6.76) of inpatient mortality compared with their female counterparts. Patients who developed bradycardia within 5 days of remdesivir were nearly two times more likely to die as opposed to those who did not develop bradycardia (adjusted odds ratio = 1.93, 95% CI 1.058–3.537). Hyperlipidemic patients had the higher odds

Table 3 ECG and bradycardia characteristics of group with remdesivir associated bradycardia (N = 182)

Variable	Value	95% CI
Single event of bradycardia, *n* (%)	34 (18.7)	13.30–25.11
Multiple events of bradycardia, *n* (%)	148 (81.3)	74.8–86.70
Diastolic BP (mmHg)	54.12 ± 11.5	51.35–56.88
Systolic BP (mmHg)	107.57 ± 17.82	103.28–111.85
Pulse pressure (mmHg)	53.45 ± 20.96	48.41–58.59
HR on ECG	66.61 ± 18.8	62.08–71.14
PR interval (ms)	149.75 ± 20.8	144.73–154.77
QRS interval (ms)	98.19 ± 13.60	94.92–101.45
QTc (ms)	435.16 ± 26.54	428.78–441.54
Hypoxia during bradycardia, *n* (%)		
Yes	32 (17.6)	12.4–23.9
No	150 (82.4)	76.10–87.65

Values are expressed as mean ± SD unless specified otherwise

BP blood pressure, *CI* confidence interval, *ECG* electrocardiogram, *HR* heart rate

Table 4 Comparing inpatient mortality among subgroups by the quality and type of bradycardia among patients who developed it within 5 days of remdesivir (N = 182)

Variable	Inpatient mortality, *n* (%)		*P* value
	Yes	No	
Single event of bradycardia	7 (17.5)	27 (19.0)	0.8
Multiple events of bradycardia	33 (82.5)	115 (81.0)	
Episodic	4 (12.1)	18 (15.7)	0.7
Continuous	6 (18.2)	15 (13.0)	
Both	23 (69.7)	82 (71.3)	
Symptomatic bradycardia			
Yes	27 (67.5)	74 (52.1)	0.08
No	13 (32.5)	68 (47.9)	

Table 5 Comparing length of hospital stay among subgroups by the quality and type of bradycardia among patients who developed it within 5 days of remdesivir (N = 182)

Variable	Category	Length of hospital stay[a]		*P* value
		Median	25th, 75th percentile	
Bradycardia frequency	Single events	8.0	5, 16	0.8
	Multiple events	10.00	8, 22	
Multi-event bradycardia characteristics	Episodic	10.00	8, 16.75	0.06
	Continuous	18.00	6, 30.00	
	Both	10.00	8, 20.25	
Symptomatic bradycardia	Yes	11.50	8, 22	0.3
Yes	No	10.00	6.25, 17	

[a]Patients who underwent inpatient mortality were not included in the length of hospital stay calculations

of inpatient mortality as compared to non-hyperlipidemic patients (adjusted odds ratio = 3.27, 95% CI 1.69–6.30; Fig. 1; Table 6).

4 Discussion

Our study focused primarily on the clinical ramifications of RAB. This study defined RAB as any bradycardic episode (i.e., EB) that occurred during the DEW, defined as the period between initiation to up to 5 days after completion of a full course of remdesivir. Twenty-two percent of RAB+ patients met in-hospital mortality, which is a 1.8-fold increase in all-cause mortality compared to RAB− patients. This is consistent with one study that observed RAB-related death in up to 17% of patients given remdesivir [3]. After adjusting for other potential causes of bradycardia, RAB+ patients experienced inpatient death nearly twice more than RAB− patients, suggesting that any documented EB during DEW predicted mortality.

Previous investigations have identified a relationship between bradycardia and COVID-19 [25, 26]. Potential mechanisms include aggravation of pre-existing heart conduction disorders during acute illness, pulmonary injury leading to hypoxia and secondary bradycardia, as well as myocardial damage resulting from inflammatory storm [27, 28]. Mol et al. [29] have proposed viewing bradycardia as a marker of COVID-19-induced inflammation. Another possible explanation is that bradycardia stems from carotid and aortic body-mediated sympathetic inhibition due to proximal aortic dilation as a result of increasing respiratory distress [29]. In this theory, COVID-driven hypoxia modulates respiratory effort and increases negative intrathoracic pressures, which transmit through the pericardial cavity and increase left ventricular afterload, which is then sensed by the carotid and aortic bodies [30].

Although previous COVID-19 studies have found associations between bradycardia and mortality [25, 26, 31, 32], the literature is conflicting. Several cases have observed RAB followed by a return to normal HR range following withdrawal of remdesivir therapy [33, 34]. One subgroup analysis in a small prospective study identified sinus bradycardia in one in five remdesivir-treated patients [7]. No differences in mortality or intensive care admission rate were found, although the limited sample size may have restricted the analysis. Another large multicenter investigation did not find a significant relationship between remdesivir and bradycardia [32]. In both studies, bradycardic episodes were measured throughout the entirety of a patient's hospital course, which may introduce a confounding effect. Randomized clinical trials have reported serious cardiac-related adverse events (e.g., myocardial infarction, arrhythmia), but bradycardia has not been noted specifically [14]. No studies to date have analyzed RAB in relation to remdesivir's elimination half-life. This study is the first to analyze RAB that occurred specifically within a predefined DEW. EBs occurring outside the DEW cannot be attributed to remdesivir given > 95% clearance of the active metabolites; bradycardia documented outside of the DEW may be related to other agents or to COVID-19 itself.

Our study also attempted to delineate EB characteristics amongst patients who experienced RAB, in order to identify markers that may correlate with poor clinical outcomes. This included EB patterns, the DEW, and sequelae attributable to a bradycardic episode (i.e., hypotension, clinical symptoms). Subgroup analysis of RAB+ cohort showed a 15% increase in death relative to the non-symptomatic counterparts, but

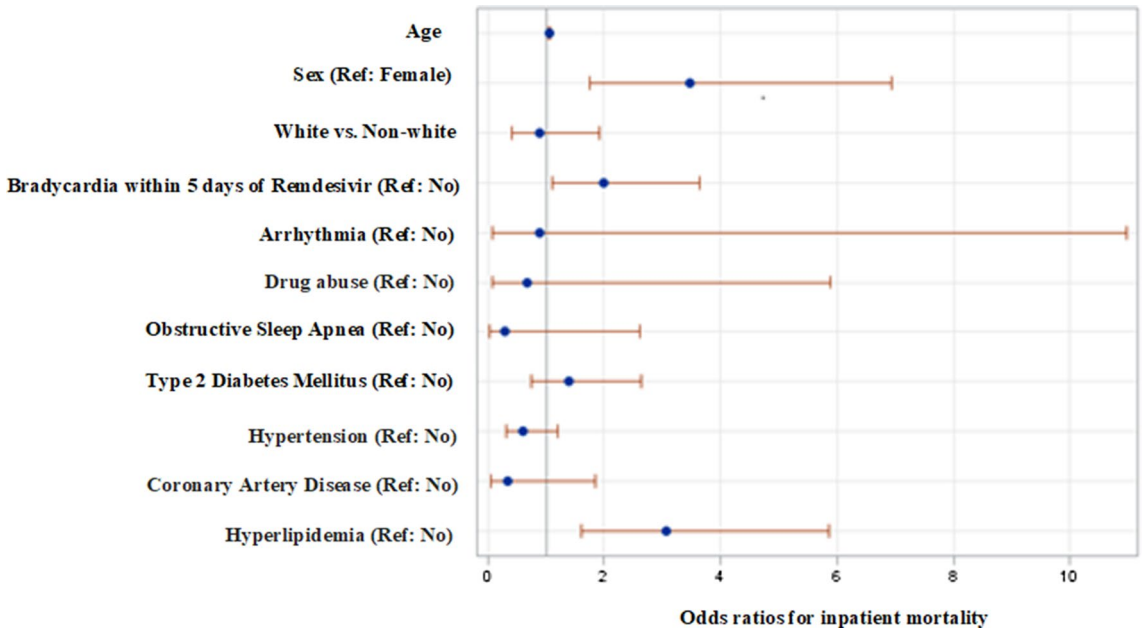

Fig. 1 Forest plot displaying odds ratios and 95% Wald confidence intervals for inpatient mortality

Table 6 Odds ratio estimates for inpatient mortality

Variable	Odds ratio	95% CI	
		LCL	UCL
Age	1.054	1.028	1.082
Sex (Ref. female)	3.470	1.739	6.925
White vs non-white	0.896	0.421	1.905
Bradycardia within 5 days of remdesivir (Ref. no)	1.997	1.096	3.641
Arrhythmia (Ref. no)	0.896	0.073	10.969
Drug abuse (Ref. no)	0.678	0.078	5.877
Obstructive sleep apnea (Ref. no)	0.297	0.034	2.613
Type 2 diabetes mellitus (Ref. no)	1.393	0.737	2.635
Hypertension (Ref. no)	0.615	0.312	1.209
Coronary artery disease (Ref. no)	0.333	0.060	1.833
Hyperlipidemia (Ref. no)	3.072	1.610	5.862

CI confidence interval, *Ref.* reference

this was not a statistically significant finding. Likewise, median LOS appeared longer in patients with a "continuous" EB pattern, but the finding was not quite significant.

Biological sex was one factor that significantly predicted mortality in this study, with males being 3.4 times more likely to experience in-hospital mortality compared to females. A substantial number of epidemiologic studies worldwide have found higher fatality rates of men over women [35–37], with males also being more likely to experience complications [35, 38–43]. This trend appears to persist in the United States even after adjusting for age, race, and comorbidities [43]. One proposed theory suggests that this dichotomy may be explained by sex-associated differences in gene expression and regulation of the angiotensin-converting enzyme 2 (ACE2) receptor and TMPRSS2, cell surface proteins that mediate the binding of SARS-CoV-2 and promote cell entry [35, 44]. More robust inflammatory and immune responses in females, as well as the potentially protective properties of estrogen in dampening the harmful effects of COVID-19, may also play a significant role in sex-specific differences [35, 44, 45]. Future studies are warranted to further elucidate the precise underlying mechanisms to account for these biological sex-related differences.

Multiple cardiovascular disease risk factors (hypertension, diabetes mellitus) and other conditions (obstructive sleep apnea, hypothyroidism) were analyzed that may have portended a greater likelihood of bradyarrhythmia [41, 46]. In our analysis, only dyslipidemia was found to have a significant association. The relationship between dyslipidemia and COVID-19 disease has been studied extensively [47, 48]. Our study found that a prior diagnosis of dyslipidemia rendered patients a 3.3-fold greater likelihood of experiencing death during hospital admission, consistent with other studies in the literature [41, 48]. A pooled cohort analysis of 28 studies by Liu and colleagues found that dyslipidemia independently predicted both a greater degree of COVID-19 disease severity along with an increased risk of mortality. One hypothesis suggests that the innate response to SARS-CoV-2 infection may directly alter serum high-density lipoprotein (HDL), which may lead to a diminished anti-inflammatory response and resultant lung inflammation in severe

COVID-19 disease [49]. Another suggested mechanism involves viral-led organ damage secondary to overactivation of the innate immune system and increased oxidized phospholipids [49]. Only 23 patients in this study were found to have abnormalities via echocardiogram; none underwent interventional cardiac studies such as temporary cardiac pacing or catheterization.

LOS was of primary interest, but no meaningful differences were appreciated. Compared to placebo, a number of randomized controlled trials have observed a reduction in LOS and increased hospital discharge rates in patients receiving remdesivir [14, 50, 51]. However, this potential benefit has been challenged in follow-up studies [52–55] under the pretense that completing the full therapeutic course may be taking precedence over earlier discharges in otherwise recovering patients [56–59]. In relation to bradycardia, one study observed extended hospital stays in COVID-19 patients with bradycardia [58], while another found similar LOS between RAB and non-RAB patients [7]. Although a subgroup analysis revealed that RAB+ patients who had more than two consecutive EBs remained more than a week longer before discharge, this finding did not reach statistical significance.

Of all the laboratory biomarkers analyzed, only D-dimer was found to be marginally significant with RAB+ patients compared to RAB− patients, a finding supported in one other study [7]. D-dimer is a degradation product formed by the breakdown of fibrin cross-links in a clot [60]. Severe disease course and mortality have been strongly associated with the thrombotic complications of COVID-19, which is theorized to result from SARS-CoV-2 endothelial cell invasion and the downstream immune and inflammatory responses [61, 62]. The relationship between mild versus severe COVID-19 cohorts and D-dimer levels has prompted investigations into D-dimer as a predictive biomarker for disease severity and survival [41, 62–65]. One multicenter laboratory analysis identified 1.5 µg/mL as an optimal cutoff when obtained at hospital admission to accurately determine an increased risk of inpatient mortality in COVID-19 patients [66]. However, recent studies have questioned the true predictive utility of D-dimer in the inpatient setting [67].

A significant percentage (28%) of RAB+ patients underwent endotracheal intubation for invasive mechanical ventilation, which is double the number of RAB− patients and appears consistent with at least one other study focused on COVID-related bradycardia [58]. Furthermore, hypoxia occurred in nearly one in five RAB+ patients during an EB. In contrast, the RAB− population was 15% more likely to utilize non-invasive measures (i.e., nasal cannula) for respiratory support. Our results suggest that patients with any documented EB receive close monitoring in anticipation of requiring more invasive modalities of respiratory support. Although prior COVID-19 studies have identified risk factors for intubation such as sex and body mass index [42, 43], this is the first study to the authors' knowledge where bradycardia may be attributable to invasive mechanical support. Given the multiple risks associated with intubation [68], future studies are warranted to investigate this finding further.

The presumed mechanism by which RAB occurs is via the adenosine moiety on remdesivir's active metabolite, GS-441524 [3, 8, 69–71]. Adenosine is an antiarrhythmic agent known to have negative chronotropic and dromotropic effects via a left ventricular vagal reflex resulting in sinus bradycardia [9, 11]. It is used in the treatment of AV nodal reentrant tachycardias, given its inhibitory effects on the AV node [9, 72]. Although plausible, our findings entertain the possibility of RAB being influenced by a combination of both severity of illness and the adenosine moiety of GS-441524. RAB+ patients were found to be associated with a greater propensity for inpatient mortality, elevated inflammatory markers such as D-dimer, and higher rates of invasive mechanical ventilation ($p = 0.008$), suggesting that EBs amongst RAB+ patients may be related to the severity of illness. Furthermore, the incidence of EBs amongst patients receiving remdesivir appeared to be higher compared to rates of bradycardia in studies of patients with COVID-19 in the literature [25, 26, 31, 32]. Further comparative studies are needed to tease out the exact etiology of RAB.

With regard to the ECG findings, all of which were obtained during remdesivir's DEW, there were no appreciable differences between patients who experienced bradycardia and those who did not. We expected the ECG effects of remdesivir to manifest uniformly amongst both the RAB+ and RAB− groups. Previous reports that observed RAB noted variations in the QTc interval, specifically in patients who experienced bradycardia [5, 6]. Although there were differences in QTc between the RAB+ and RAB− cohorts, the findings demonstrated no statistical or clinical significance ($p = 0.06$). Further studies comparing ECG results between patients who received remdesivir and those who did not may be beneficial.

There are a number of limitations to this study. The retrospective nature makes it prone to potential selection biases, and certain variables were missing clinical data, although this was never more than 0.5% per variable. All patients in this study met criteria for severe COVID-19, which has been purported to causes bradycardia in and of itself. As such, treatment with remdesivir cannot exclusively explain the incidence of bradycardia and RAB-related mortality, and a follow-up comparison study with matched controls would be of benefit. There may be a residual confounding effect secondary to variables that were left unmeasured (e.g., when bradycardia occurred in a patient's hospital course, how many experienced bradycardia after completion of

remdesivir, concomitant therapies). The study population predominantly lacked medical and cardiovascular risk factors, which weakens the formal predictors of mortality analysis. The relatively large study size and roughly equal representation of sex and ethnic backgrounds are a strength in our study and improve the generalizability of our findings. However, future prospective and randomized studies are needed to further elucidate the mechanisms of RAB and better understand its associated clinical implications.

5 Conclusions

Patients with COVID-19 who experienced bradycardia shortly after completing a course of remdesivir had higher rates of associated death, increased serum D-dimer levels, and a greater likelihood of requiring endotracheal intubation. Sex, hyperlipidemia, and any observed EB during administration of remdesivir up to 5 days after completion predicted inpatient mortality. The exact etiology of RAB and its associated clinical outcomes remains speculative, and future comparison trials are warranted.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-022-01187-x.

Acknowledgements The authors would like to acknowledge Shabada Asad, M.D. for assisting with project design and for providing crucial feedback on clinical questions.

Declarations

Author contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by AS, JB, SM, KL, NH, UP, CC, KI, and AG. Data analysis was performed by KB, AS, and JB. The first draft of the manuscript was written by ASr and JB, and all authors commented on previous versions of the manuscript. DH, JD, and CA provided supervision. All authors read and approved the final manuscript.

Ethics approval This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the institutional review board (IRB) of the University Medical Center of Southern Nevada, who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the University Medical Center of Southern Nevada.

Conflicts of interest The authors declare no conflicts of interests.

Funding This research did not receive any specific grant from funding agencies in public, commercial, or not-for-profit sectors.

Consent to participate Not applicable.

Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

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