


## REVIEW

# Characteristics of bradyarrhythmia in patients with COVID-19: Systematic scoping review

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## Abstract

COVID-19 has recently been associated with the development of bradyarrhythmias, although its mechanism is still unclear. We aim to summarize the existing evidence regarding bradyarrhythmia in COVID-19 and provide future directions for research. Following the PRISMA Extension for Scoping Reviews, we searched MEDLINE and EMBASE for all peer-reviewed articles using keywords including “Bradycardia,” “atrioventricular block,” and “COVID-19” from their inception to October 13, 2021. Forty-three articles, including 11 observational studies and 59 cases from case reports and series, were included in the systematic review. Although some observational studies reported increased mortality in those with bradyarrhythmia and COVID-19, the lack of comparative groups and small sample sizes hinder the ability to draw definitive conclusions. Among 59 COVID-19 patients with bradycardia from case reports and series, bradycardia most often occurred in those with severe or critical COVID-19, and complete heart block occurred in the majority of cases despite preserved LVEF (55.9%). Pacemaker insertion was required in 76.3% of the patients, most of which were permanent implants (45.8%). This systematic review summarizes the current evidence and characteristics of bradyarrhythmia in patients with COVID-19. Further studies are critical to assess the reversibility of bradyarrhythmia in COVID-19 patients and to clarify potential therapeutic targets including the need for permanent pacing.

## KEYWORDS

atrioventricular block, bradyarrhythmia, COVID-19, scoping review, sick sinus syndrome, systematic review

## 1 | INTRODUCTION

SARS-CoV2, the well-known coronavirus responsible for the COVID-19 pandemic, continues to be relevant worldwide. Alongside the disease's effect on the respiratory system, COVID-19's cardiac manifestations have been frequently documented. In addition to other reported cardiac dysfunctions, arrhythmias have been widely prevalent in hospitalized COVID-19 patients.<sup>1</sup> Tachyarrhythmias are the most frequent dysrhythmias commonly presenting as sinus

tachycardia or atrial tachyarrhythmias.<sup>1-3</sup> On the contrary, bradyarrhythmias present as sinus bradycardia or arrhythmias involving AV node dysfunction such as complete heart block.<sup>1</sup> Reports of bradyarrhythmia are less frequent than tachyarrhythmias, but notably have been speculated to be associated with a worse prognosis.

Despite this, the management of bradyarrhythmia in patients with COVID particularly in regards to the need for permanent pacing is not well established. SARS-CoV2 has been thought to directly affect the sinoatrial node and myocardium, leading to bradyarrhythmia.<sup>4,5</sup> It is

thought that cardiac involvement, especially in the case of bradycardia in SARS-CoV2, involves direct infiltration of the myocardial cells aggravating preexisting conduction disease, resulting in bradyarrhythmia.<sup>6</sup> This is supported by the fact that SARS-CoV2 has been shown to activate angiotensin converting enzyme 2 (ACE2) receptors, known to be present in sinoatrial nodal cells.<sup>7</sup> Another area of consideration is cardiac damage as a secondary manifestation. A suggested mechanism for cardiac damage is secondary to hypoxemia due to COVID-19, which can also aggravate pre-existing arrhythmic conditions.<sup>6</sup> Similarly, cytokine storm, triggered by an imbalance in the response of types 1 and 2 helper cells, has also been linked to cardiac myocyte injury which could indiscriminately aggravate cardiovascular diseases.<sup>8</sup>

There has been a large area of focus related to cardiac injury as authors have attempted to establish a correlation with severity of illness, mortality, and long-term prognostication, with little emphasis specifically on bradyarrhythmia.<sup>6</sup> In this systemic scoping review, we aimed to analyze bradyarrhythmia in COVID-19 patients to further characterize this specific cardiac manifestation better to help suggest future studies and ideas for management and therapy.

## 2 | METHODS

### 2.1 | Study design

This is a systematic scoping review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews (PRISMA-ScR).<sup>9-10</sup> See Appendix S1 for PRISMA-ScR Checklist of the present study.

### 2.2 | Search strategy

We searched MEDLINE and EMBASE for all peer-reviewed articles from inception to October 13th, 2021. No filters for study design and language were used. A manual screening for additional pertinent articles was done using the reference lists of all articles that met the eligibility criteria. The search strategy involved relevant keywords, including "Bradycardia," "AV block," "atrioventricular block," and "COVID-19." The search was conducted by two authors (TN and YN) independently. See Appendix S2 for detailed search terms.

### 2.3 | Eligibility criteria

The criteria for the inclusion of articles are the following:

1. Peer-reviewed articles evaluating the characteristics of bradyarrhythmia in patients with COVID-19, or reporting cases of bradyarrhythmia in patients with laboratory-confirmed COVID-19.
2. Randomized controlled trials (RCTs), case-control studies, cohort studies (prospective or retrospective), cross-sectional studies, case series, and case reports in adult patients.

The exclusion criteria included the following:

1. Qualitative studies, review articles, and commentaries.
2. Conference abstracts.
3. Studies involving pediatric patients.
4. Diagnosis of COVID-19 made without confirmatory polymerase chain reaction (PCR) testing.
5. Details of bradycardia not described

## 2.4 | Study selection

Articles selected for full-text assessment were assessed independently by TN and YN using EndNote 20 reference management software. Articles considered eligible were then evaluated in full length with the inclusion and exclusion criteria.

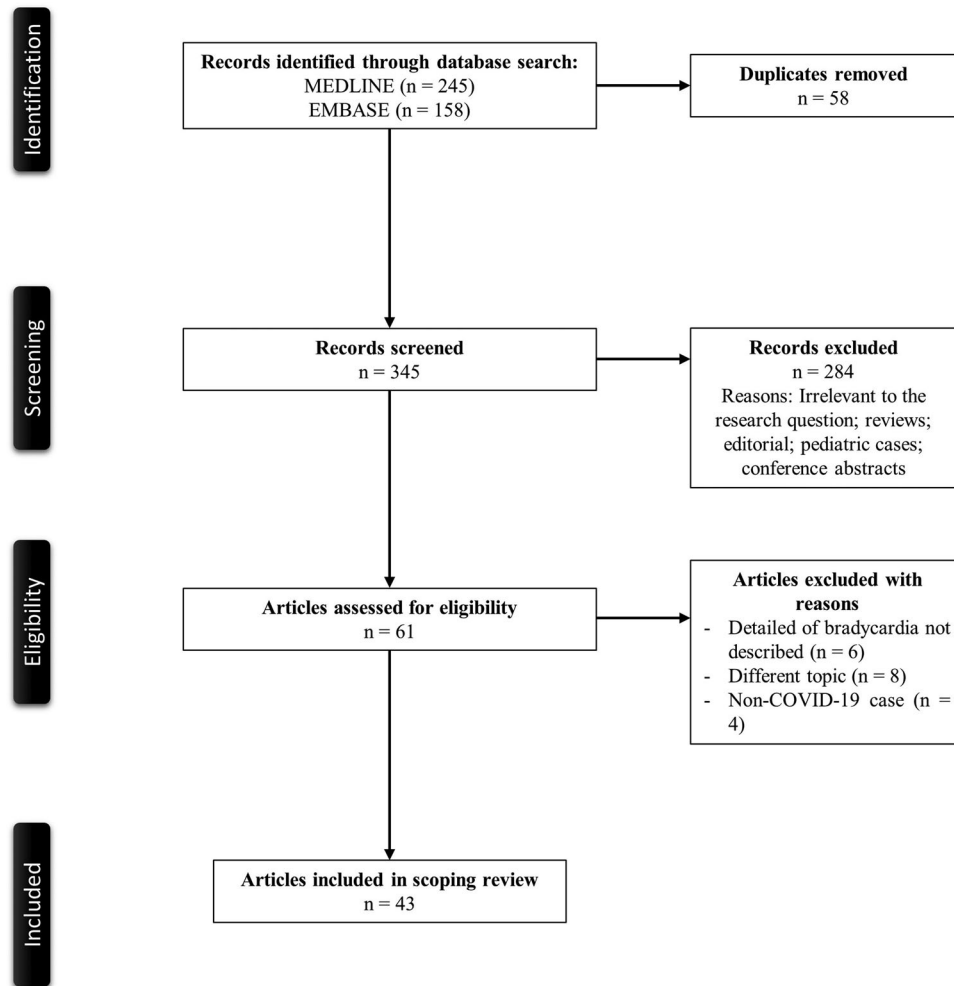
## 2.5 | Data extraction and definition

A standardized data collection form that followed the PRISMA and Cochrane Collaboration guidelines for systematic reviews was used to obtain the following information from each study: title, name of authors, year of publication, country of origin, study characteristics, target outcome, aims, study and comparative groups, key findings, and limitations. We also statistically analyzed data from existing case reports and case series to identify clinical characteristics of Bradycardia in COVID-19. For the severity of COVID-19, we employed the definition proposed by the United States National Institute of Health. In brief, patients are categorized as a moderate illness if there is evidence of lower respiratory disease with oxygen saturation (SpO<sub>2</sub>) ≥ 94% on room air. Severe illness is defined as a condition with SpO<sub>2</sub> < 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen < 300 mmHg, respiratory rate > 30/min, or lung infiltrates > 50%. Patients are categorized as having critical illness when they have respiratory failure, septic shock, or multiple organ dysfunction.

## 3 | RESULTS

### 3.1 | Search results and study selection

Figure 1 demonstrates a PRISMA flow diagram summarizing the identification, screening, eligibility, and inclusion and exclusion processes of the studies involved. The initial review of MEDLINE and EMBASE databases yielded 245 and 158 articles, respectively. A total 58 duplicate studies were removed. Total 345 articles were screened based on their relevance and type of article. Two hundred and eighty-four articles that were either review articles, editorials, pediatric cases, conference abstracts, or focused on matters irrelevant to the research question were excluded from the study. Sixty-one articles were then evaluated for full-text review for study inclusion per our eligibility



**FIGURE 1** PRISMA flowchart of the search strategy

criteria. Articles that omitted details of the bradycardia, studied non-COVID-19 cases, or addressed an unrelated topic, were excluded. Forty-three articles, including 11 observational studies and 59 cases from case reports and series were included in the scoping review (Appendix S3).

### 3.2 | Description of included studies

Table 1 describes the main characteristics of the 11 observational studies from the scoping review.<sup>11–20</sup> Seven studies (Antwi-Amoabeng et al., Chen et al., Han et al., Kunal et al., Ray-Acha et al., Wang et al., and Yang et al.) aimed to characterize electrocardiogram (EKG) findings among COVID-19 patients without a particular focus on bradycardia. Antwi-Amoabeng et al. found that atrioventricular block (AVB) was significantly more common in those who expired (25% vs. 9.1%;  $p = .02$ ) in their cohort ( $n = 186$ ). Chen et al. noted that there was no significant difference regarding the incidence of bradyarrhythmia between severe or critical illness COVID-19 patients, although their sample size was small ( $n = 54$ ). Han et al. compared COVID-19 and bacterial pneumonia patients retrospectively to compare the incidence

of conduction abnormalities, although no differences in the incidence of AVB was found between the two groups. Ray-Acha et al. stratified COVID-19 patients into those with or without arrhythmia, and found that the prevalence of arrhythmias increased with disease severity. Kunal et al., Wang et al., and Yang et al., only found that the incidence of sinus bradycardia was low in their cohorts (0.9%, 4.1%, and 4.0%, respectively).

Three studies specifically described COVID-19 patients with bradycardia without comparative groups. Among 78 patients with mild to moderate COVID-19 pneumonia, Abid et al. found the prevalence of sinus bradycardia to be 15% in their French patient cohort, although the development of sinus bradycardia was not associated with a poorer clinical prognosis. Chinitz et al. detailed seven patients with bradyarrhythmia with COVID-19, in which 43% had high degree AVB on admission, while the remaining 57% developed sinus arrest between 4 and 30 days into their hospitalization. The development of these bradycardias was associated with high inflammatory markers, even in the absence of cardiomyopathy. Despite all patients receiving either a temporary or permanent pacemaker, 71% would succumb to their infection and expire. The authors concluded that acute bradycardia in the presence of COVID-19 was associated with high mortality.

**TABLE 1** Main characteristics of the included observational studies in the scoping reviews

Author	Year	Country	Study Type	Aim	Outcome	Population	Comparative Groups	Detail of bradycardia	Key Findings	Limitations
Abid et al.	2020	France	Observational	To determine the frequency and describe the clinical features of COVID-19 patients with sinus bradycardia	Mechanical ventilation or death	Mild-moderate COVID-19 (n = 12)	N/A	Sinus Bradycardia All other types of bradycardia were excluded	Sinus bradycardia was frequently detected in those with moderate COVID-19 pneumonia, but not associated with poor prognosis	Small sample size without a control group Only included mild to moderate COVID-19 pneumonia Those with severe disease or critical illness were excluded Patients with known factors for bradycardia were excluded, and these factors were not listed.
Antwi-Amoabeng et al.	2021	USA	CC	To characterize EKG abnormalities in patients with COVID-19 and determine which arrhythmias are associated with increased risk of mortality.	All-cause mortality	COVID-19 patients who recovered (n = 154)	COVID-19 patients who expired (n = 32)	Sinus bradycardia/AVB	Sinus bradycardia was more frequently detected in those who recovered (8.4%) vs. expired (3.1%) without statistical difference. AVB were significantly more common in those who expired (25% vs. 9.1%; p = .02)	Only focused on EKG analysis, no telemetry details. Overall small sample of bradycardia patients No mention in details about sinus bradycardia and AVB
Attina et al.	2021	Italy	PC	To evaluate the incidence and clinical impact of arrhythmic events in hospitalized patients receiving Remdesivir for COVID-19	ICU admission or in hospital mortality	Those who had bradycardia after Remdesivir (n = 21)	Those without bradycardia after Remdesivir (n = 79)	Sinus bradycardia defined as < 60 BPM and 4 patients experience "extreme bradycardia" as defined by the authors as < 50 BPM	In all cases Sinus bradycardia was reversible after Remdesivir discontinuation No significant difference in ICU admission rate or increased mortality between the two groups	Small sample size Severity of COVID 19 unspecified Patients who are baseline bradycardic are contraindicated for Remdesivir therapy and were not included in study

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Study Type	Aim	Outcome	Population	Comparative Groups	Detail of bradycardia	Key Findings	Limitations
Chen et al.	2020	China	CC	To explore how COVID-19 affects Cardiovascular system and to identify potential risk factors predicting the severity of COVID-19	Cardiac injury, Hypertension, hypotension, Echocardiographic findings, cardiac arrhythmias	Severe COVID-19 (n = 39)	Critical illness COVID-19 (n = 15)	Sinus Bradycardia defined as < 50 BPM	No significant difference between critical and severe groups in developing bradycardia (5.1% in severe vs. 6.7% in critical illness; $p = .825$ )	Small sample size Study only included severe or critically ill patients No mention of interventions/therapies across groups
Chinitz et al.	2020	USA	Observational	To elucidate features of bradyarrhythmias in COVID-19 and their clinical implications	In hospital mortality	COVID-19 with Severe bradycardia requiring acute intervention (n = 7)	N/A	3/7 (43%) had high degree AVB on admission 4/7 (57%) developed sinus arrest or paroxysmal high degree AVB lasting 10-37 seconds	5/7 (71%) died within three months following admission All patients received either temporary or permanent PM Acute bradycardia events associated with elevation in inflammatory markers	Small sample size Selected only patient with severe life-threatening bradycardia 5/7 were on hydroxychloroquine, which can be a confounder No control group
Han et al.	2021	China	CC	To elucidate and describe conduction abnormalities in COVID 19 patients	Prevalence of arrhythmia and mortality	COVID-19 patients (n = 84)	Patients with bacterial pneumonia (n = 84)	3/84 (3.6%) of COVID-19 patients vs. none of bacterial pneumonia patients had AVB	Higher total means and minimum heart rates in the COVID-19 group No significant difference in development of NSAT, PVC, NSVT, or AVB between severe and non-severe COVID 19 groups.	Patients in the control group were recruited from a different hospital. Results possibly confounded by concurrent sepsis in COVID-19 patients
Kunal et al.	2020	India	Observational	To determine the cardiovascular complications in symptomatic COVID 19 patients and its impact on disease outcomes	COVID-19 related death, prevalence of arrhythmia	Symptomatic COVID-19 (n = 108)	N/A	5/108 (4.6%) had 1 <sup>st</sup> degree AVB, 1/108 (0.9%) had sinus bradycardia	The prevalence only briefly mentioned in discussion; no details noted	Small sample size

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Study Type	Aim	Outcome	Population	Comparative Groups	Detail of bradycardia	Key Findings	Limitations
Rav-Acha et al. 2021		Israel	CC	To characterize arrhythmias in hospitalized COVID-19 patients	Any arrhythmia documented during hospitalization	COVID 19 with any arrhythmia (n = 28)	COVID-19 without arrhythmia (n = 362)	3/28 (10.7%) had CHB First patient with CHB associated with prolonged QTc 550 ms Second patient had 2:1 AVB with LBBB; developed CHB hours after admission Third patient had transient sinus bradycardia with slow ventricular escape; resolved within a few hours	Higher arrhythmia prevalence with increasing disease severity (9.5% in moderate, 13.5% in severe, 23.5% in critical illness) Significant higher mortality among the patients with new arrhythmia, all types (32.1%) vs. none (5.5%) Not all patients were monitored on 24-hour Holter or telemetry; transient arrhythmias may have been missed. No post-discharge follow-up data	Single center study Not all hospitalized patients underwent blood tests for cardiac biomarkers causing selection bias Not all patients were monitored on 24-hour Holter or telemetry; transient arrhythmias may have been missed. No post-discharge follow-up data
Shrivastava et al. 2021		India	Observational	To characterize symptomatic bradyarrhythmia in COVID-19 patients.	All-cause mortality Reversal of CHB/high-grade AVB Placement of permanent PM.	COVID 19 with symptomatic CHB or high degree AV block requiring temporary PM insertion (n = 15)	N/A	Patients with CHB (n = 14) Patient with 2:1 AV block (n = 1) who later developed CHB during hospitalization	High short-term inpatient mortality (33.3%) No significant difference in inflammatory markers among patients who survived vs expired. Patients that presented with narrow complex escape rhythm had better survival than those with wide complex escape rhythm (87.4% vs. 42.9%) 3/7 patients with narrow complex escape rhythm reverted to sinus; none in the wide complex escape rhythm group	No control group with small sample size Only 3 patients had severe COVID 19 illness requiring ICU level of care

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Study Type	Aim	Outcome	Population	Comparative Groups	Detail of bradycardia	Key Findings	Limitations
Wang et al.	2020	China	CC	To characterize differences in EKG findings between non-critical and critical COVID-19 patients	EKG findings	Critically ill COVID-19 patients (n = 97)	Severe COVID-19 patients (n = 222)	No significant difference in the prevalence of sinus bradycardia (4.1% vs. 6.8% in critically ill and severe group, respectively	Sinus bradycardia was not related to the prevalence of ventilator use or in-hospital mortality	Small sample size No EKG data prior to hospitalization, unclear if these EKG findings were a result of COVID-19 or pre-existing EKG changes Specific therapies were not alluded to in inclusion criteria Failed to mention the definitions of "critically ill" and "severe" COVID-19
Yang et al.	2021	China	CC	To describe the EKG characteristics of COVID-19 non-survivors and survivors	Prevalence of arrhythmia	Non-survivors (n = 30)	Survivors (n = 27)	Sinus bradycardia only noted in 10/276 (4.0%) of survivors 1/30 (3.3%) of non-survivors had sinus arrest	N/A	Small sample size No baseline EKG data described

Abbreviations: A-fib, atrial fibrillation; AV, atrioventricular; AVB, atrioventricular block; BPM, beats per minute; CC, case control; CHB, complete heart block; COVID-19, coronavirus disease 2019; EKG, electrocardiogram; HR, heart rate; ICU, intensive care unit; LAD, left axis deviation; LBBB, left bundle branch block; PC, prospective cohort; PM, pacemaker; QTc, calculated QT adjusted for heart rate.

Sharivastava et al. also observed 15 COVID-19 patients with either high grade or complete AVB requiring temporary or permanent pacemaker implantation. Those initially presenting with a narrow complex escape rhythm demonstrated an 87.4% survival rate, compared to 42.9% among those with a wide complex escape rhythm. Additionally, 43% of those with a narrow complex escape rhythm converted back to sinus, while none with a wide complex did.

Attena et al. compared the prevalence of bradycardia in COVID-19 patients treated with Remdesivir. Among 21 patients with bradycardia on Remdesivir, bradycardia resolved with cessation of the drug. Compared with 79 patients on Remdesivir without bradycardia, no differences in intensive care admission rate or increased mortality were noted.

Table 2 presents the baseline demographics, diagnostic findings, and chief features of COVID-19 patients who developed bradycardia from the individual cases compiled ( $n = 59$ ).<sup>21–52</sup> Bradycardia predominated in male patients ( $n = 37$ ) with a median age of 58.0 years old (IQR 48.0–71.0). Bradycardia was most often observed in patients classified as having severe or critical illness COVID-19 (35.6% and 32.2%, respectively). Death occurred in 6.8% of the population. Azithromycin was the most commonly prescribed drug during admission (33.9%), with Remdesivir being the least (8.5%). Of those with reported bradycardia, complete AVB was the most common rhythm, occurring in the majority of cases (55.9%), followed by sinus bradycardia (15.3%). Pacemaker insertion was required in most patients (76.3%), most of which were permanent implants (45.8%). The median LVEF was 55% and was assessed in almost half of the cases (45.8%). BNP levels tended to be elevated, with a median of 677 pg/mL (IQR 55.3–3814), and troponin assays only mildly elevated (hs-troponin T median of 7.0 ng/L, Troponin I median of 0.027 ng/ml). D-dimer, Ferritin, LDH, and CRP showed only modest increases.

## 4 | DISCUSSION

In this scoping review, we identified 11 observational studies that included patients with bradyarrhythmia and COVID-19 and 59 patients with bradyarrhythmia in COVID-19 from case reports and series. Our results showed that patients with severe or critical COVID-19 may be more likely to have bradyarrhythmia, although there are no observational studies with comparative groups that exclusively looked into bradycardia in COVID-19 to date. Interestingly, more than half of the patients included in our studies had complete AVB requiring either permanent and/or temporary pacemakers, with most of whom had preserved LVEF. Further prospective studies are warranted to assess the need for permanent pacing in these patients.

Bradycardia has been reported as a potential rare complication of SARS-CoV infection, although its mechanism is unclear.<sup>53,54</sup> Multiple hypotheses have been proposed including hypoxia, direct myocardial injury through viral invasion to cells via ACE2 receptor, and hypercytokinemia, as summarized in Figure 2.<sup>55–57</sup> Hypoxia associated with severe COVID-19 may lead to a complex interaction of carotid body

**TABLE 2** Baseline demographics, laboratory findings, and chief features of the 59 patients from case reports and case series

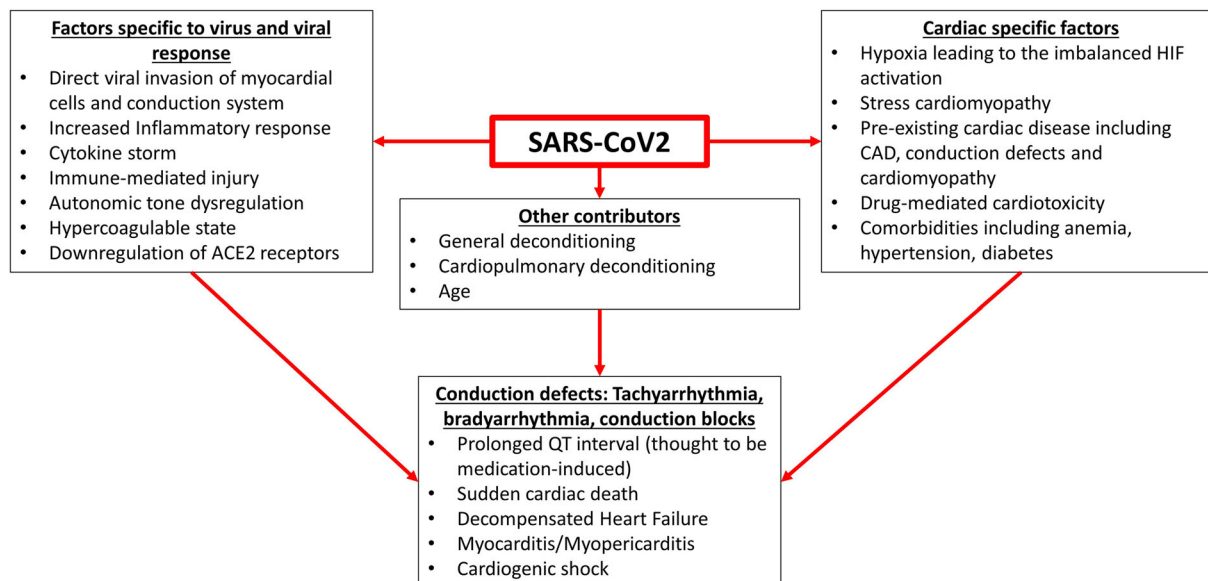
	Prevalence (%) <sup>a</sup>	Median (IQR)
Age (years)		58.0 (48.0–71.0)
Sex		
Male	37/59 (62.7)	
Female	22/59 (37.3)	
COVID-19 Severity		
Mild	7/59 (11.9)	
Moderate	12/59 (20.3)	
Severe	21/52 (35.6)	
Critical illness	19/52 (32.2)	
Death	4/59 (6.8)	
Medications		
Azithromycin	20/59 (33.9)	
Remdesivir	5/59 (8.5)	
Hydroxychloroquine	12/59 (20.3)	
Type of Bradycardia		
Wenckebach AVB	1/59 (1.7)	
Mobitz type II AVB	7/59 (11.9)	
Complete AVB	33/59 (55.9)	
Sick sinus syndrome (unspecified)	6/59 (10.2)	
Sinus arrest	3/59 (5.1)	
Sinus bradycardia	9/59 (15.3)	
Minimum HR (s)	31/59 (52.5)	37.0 (31.0–40.0)
Pacemaker insertion		
Permanent	27/59 (45.8)	
Temporary	18/59 (30.5)	
LVEF (%)	29/59 (49.2)	55.0 (55.0–60.0)
Laboratory Findings		
WBC ( $10^3/\mu\text{L}$ )	22/59 (37.3)	10.0 (7.0–13.2)
NT-proBNP (pg/ml)	11/59 (18.6)	677 (55.3–3814)
hs-troponin T (ng/L)	15/59 (25.4)	7.0 (0.029–94.4)
Troponin I (ng/ml)	14/59 (23.7)	0.027 (0.016–0.12)
D-dimer (ng/ml)	21/59 (35.6)	2374 (1008–4549)
Ferritin (ng/ml)	18/59 (30.5)	757 (427–1245)
LDH (U/L)	11/59 (18.6)	598 (336–726)
CRP (mg/L)	40/59 (67.8)	46.0 (22.2–88.5)

Abbreviations: AVB, atrioventricular block; BNP, B-type natriuretic peptide; CK-MB, creatine kinase-MB isozyme; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HR, heart rate; hs, high sensitivity; IQR, interquartile range; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; TCM, Takotsubo cardiomyopathy; WBC, white blood cell.

<sup>a</sup>Prevalence here is defined as the number of cases reported the variable divided by the number of the total cases.

\*\*Of the 59 cases, the following number of cases had normal values of the variable without specific data; WBC, 2 cases; BNP, 1 case; NT-proBNP, 2 cases; Troponin, 20 cases; LVEF, 14 cases.





**FIGURE 2** Possible pathophysiology of bradyarrhythmia in COVID-19. Factors associated with bradyarrhythmia are summarized from existing literature. ACE2, angiotensin converting enzyme 2; HIF, hypoxia-inducible factors [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

stimulation and activation of hypoxia-inducible factors (HIF).<sup>58,59</sup> HIF is a fascinating transcription factor attracting attention in various areas of medicine as a potential therapeutic target for ischemic heart disease, heart failure, and anemia of chronic kidney disease.<sup>60,61</sup> In particular, the imbalance of HIF-1 $\alpha$ , which increases reactive oxygen species (ROS) production causing sympathetic nerve activation, and HIF-2 $\alpha$ , which suppresses ROS through superoxide dismutase, may contribute to the development of arrhythmias.<sup>62</sup> Future studies are warranted to investigate HIF activity in patients with COVID-19 and bradycardia to evaluate whether HIF could be a potential therapeutic target. Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factors (TNFs) are also known to cause bradycardia via a direct pathogenic effect on the sinoatrial node. However, only a few case reports have described patients' serum IL-6 levels, which makes it challenging to draw conclusions at this time. Like HIF activity, serum IL-6 levels in COVID-19 patients and any correlation with their heart rates needs to be clarified in future observational studies.

Other factors have been brought into consideration, such as level of sedation and adverse drug reactions, specifically Remdesivir, hydroxychloroquine/chloroquine, and azithromycin.<sup>63-65</sup> Remdesivir, in particular, is a known iatrogenic precipitant of bradycardia by which the mechanism is not well understood. Currently, two suggested mechanisms of Remdesivir induced bradycardia stems from either 1) cardiac myocyte cytotoxic effect from binding human mitochondrial RNA polymerase<sup>66</sup> and/or 2) Remdesivir is a nucleoside adenosine analog which, in theory, resembles adenosine triphosphate and binds the A1 receptor in cardiac cells much like endogenous adenosine, inhibiting the atrioventricular node.<sup>67</sup> Although only 8.5% of patients were on Remdesivir in the included patients with bradycardia, clinicians may need to avoid Remdesivir in patients with underlying cardiac diseases or known arrhythmia.

Several limitations in this study should be noted. First, due to the time constraints, we were unable to contact authors to obtain data not mentioned in the literature, leading to reporting bias. Second, we included only peer-reviewed articles in the systematic review, excluding conference abstracts or preprints, which may cause selection bias. In addition, cases with transient nonsevere bradycardia in COVID-19 patients might not have been reported, which could lead to publication bias. However, this is the first systematic review to investigate the characteristics of bradyarrhythmia in COVID-19 patients. The data presented may be used by frontline clinicians to determine treatment planning for similar patients, including in decisions whether to proceed with a permanent or temporary pacemaker.

In conclusion, this systematic review summarizes the current body of evidence and characteristics of bradyarrhythmia in patients with COVID-19. While it remains hypothetical, pathophysiology may be multifactorial with potential direct myocardial injury, iatrogenicity of medications, cytokine-related effects, and/or hypoxia as contributing factors. Further studies are critical to assess the reversibility of bradyarrhythmia in COVID-19 patients as well as to clarify potential therapeutic targets, including HIF or pro-inflammatory cytokines.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest in association with the present study.

## AUTHOR CONTRIBUTIONS

Todd Nagamine conceived the study, searched the literature and drafted the manuscript. Sandeep Randhawa conceived the study. Yoshito Nishimura searched the literature, assessed the quality of the studies, drafted and revised the manuscript, and supervised the process. Ricky Huang, Thiratest Leesutipornchai, Kevin Benavente,

Stephanie Yoshimura, James Zhang, and Chanavuth Kanitsorphan revised the manuscript.

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## REFERENCES

- Gopinathannair R, Merchant FM, Lakkireddy DR, et al. COVID-19 and cardiac arrhythmias: a global perspective on arrhythmia characteristics and management strategies. *J Interv Card Electrophysiol*. 2020; 59: 329-336.
- Chen Q, Xu L, Dai Y, et al. Cardiovascular manifestations in severe and critical patients with COVID-19. *Clin Cardiol*. 2020; 43: 796-802.
- Long B, Brady WJ, Bridwell RE, et al. Electrocardiographic manifestations of COVID-19. *Am J Emerg Med*. 2021; 41: 96-103.
- Babapoor-Farrokhran Savalan, Batnyam Uyanga, Wiener Philip C., et al. Atrioventricular and Sinus Node Dysfunction in Stable COVID-19 Patients. *SN Compr Clin Med*. 2020;2(11):1955-1958. <http://doi.org/10.1007/s42399-020-00497-5>
- Hu L, Gong L, Jiang Z, Wang Q, Zou Y, Zhu L. Clinical analysis of sinus bradycardia in patients with severe COVID-19 pneumonia. *Crit Care*. 2020; 24: 257.
- Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. *J Cardiovasc Electrophysiol*. 2020; 31: 1003-1008.
- Ferreira AJ, Moraes PL, Foureaux G, Andrade AB, Santos RA, Almeida AP. The angiotensin-(1-7)/Mas receptor axis is expressed in sinoatrial node cells of rats. *J Histochem Cytochem*. 2011; 59: 761-768.
- Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol*. 2004; 136: 95-103.
- McGowan J, Straus S, Moher D, et al. Reporting scoping reviews-PRISMA ScR extension. *J Clin Epidemiol*. 2020; 123: 177-179.
- Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018; 169: 467-473.
- Abid M, Ben Abdesslem MA, Elmenif K, et al. Sinus bradycardia: an unusual manifestation of mild to moderate COVID-19 pneumonia. *Tunis Med*. 2020; 98: 886-887.
- Antwi-Amoabeng D, Beutler BD, Singh S, et al. Association between electrocardiographic features and mortality in COVID-19 patients. *Ann Noninvasive Electrocardiol*. 2021; 26: e12833.
- Attena E, Albani S, Maraolo AE, et al. Remdesivir-induced bradycardia in COVID-19: a single center prospective study. *Circ Arrhythm Electrophysiol*. 2021; 14: e009811.
- Chinitz JS, Goyal R, Harding M, et al. Bradyarrhythmias in patients with COVID-19: marker of poor prognosis? *Pacing Clin Electrophysiol*. 2020; 43: 1199-1204.
- Han Kai-Yue, Qiao Qi, Zhu Ye-Qian, et al. Atrial Arrhythmias in Patients with Severe COVID-19. *Cardiol Res Pract*. 2021;2021:1-7. <http://doi.org/10.1155/2021/8874450>
- Kunal S, Sharma SM, Sharma SK, et al. Cardiovascular complications and its impact on outcomes in COVID-19. *Indian Heart J*. 2020; 72: 593-598.
- Rav-Acha Moshe, Orlev Amir, Itzhaki Itay, et al. Cardiac arrhythmias amongst hospitalised Coronavirus 2019 (COVID-19) patients: Prevalence, characterisation, and clinical algorithm to classify arrhythmic risk. *Int J Clin Pract*. 2021;75(4):<http://doi.org/10.1111/ijcp.13788>
- Shrivastava A, Pandit BN, Thakur AK, Nath RK, Aggarwal P. Epidemiological, demographic, laboratory, clinical management, and outcome data of symptomatic bradyarrhythmia in COVID-19 patients. *Cirugia Cardiovascular*. 2021; 28: 144-150.
- Wang Yina, Chen Lie, Wang Jingyi, et al. Electrocardiogram analysis of patients with different types of COVID-19. *Ann Noninvasive Electrocardiol*. 2020;25:<http://doi.org/10.1111/anec.12806>
- Yang Deyan, Li Jing, Gao Peng, et al. The prognostic significance of electrocardiography findings in patients with coronavirus disease 2019: A retrospective study. *Clin Cardiol*. 2021;<http://doi.org/10.1002/clc.23628>
- Abdelmajid A, Osman W, Musa H, et al. Remdesivir therapy causing bradycardia in COVID-19 patients: two case reports. *IDCases*. 2021; 26: e01254.
- Abe M, Chiba S, Kataoka S, et al. Paroxysmal atrioventricular block in a relatively young patient with covid-19. *Intern Med*. 2021; 60: 2623-2626.
- Akhtar Z, Leung LWM, Kontogiannis C, et al. Prevalence of bradyarrhythmias needing pacing in COVID-19. *Pacing Clin Electrophysiol*. 2021; 44: 1340-1346.
- Al-assaf O, Mirza M, Musa A. Atypical presentation of COVID-19 as subclinical myocarditis with persistent high-degree atrioventricular block treated with pacemaker implant. *HeartRhythm Case Reports*. 2020; 6: 884-887.
- Alabdulgader AA Sr., Alabdulgader A, Sungur M, Essa H. Novel behavior of the 2019 Novel Coronavirus with invasion of the cardiac conduction system in the young. *Cureus*. 2020; 12: e11115.
- Ali M, Awadelkarim A, Bishop P, et al. severe sinus bradycardia: an unusual cardiac manifestation of COVID-19. *J Investig Med High Impact Case Rep*. 2021; 9: 23247096211013185.
- Amir M, Renata A, Ratana LT. Symptomatic sinus bradycardia due to electrolyte imbalances in syndrome of inappropriate antidiuretic hormone (SIADH) related covid-19: a case report. *BMC Infect Dis*. 2021; 21: 465.
- Amir M, Yoseph H, Farisi ATA, Phie JKP, Adam ATS. Symptomatic Bradycardia in Covid-19 hospitalized patients: a case series. *Int J Infect Dis*. 2021; 111: 1-4.
- Ashok V, Loke WI, Dinov B, et al. Case report: high-grade atrioventricular block in suspected COVID-19 myocarditis. *Eur Heart J Case Rep*. 2020; 4: 1-6.
- Bhasin Varun, Carrillo MaryKate, Ghosh Bobby, Moin Danyaal, Maglione Theodore J., Kassotis John. Reversible complete heart block in a patient with coronavirus disease 2019. *Pacing Clin Electrophysiol*. 2021;44(11):1939-1943. <http://doi.org/10.1111/pace.14321>
- Cakulev I, Sahadevan J, Osman MN, et al. A case report of unusually long episodes of asystole in a severe COVID-19 patient treated with a leadless pacemaker. *Eur Heart J Case Rep*. 2020; 4: 1-6.
- Chachar TS, Slais SK, Almadani A, Hamad AK. Unusual cardiac presentation of COVID-19 with significant sinus pauses. *J Saudi Heart Assoc*. 2020; 32: 450-453.
- Dagher L, Wanna B, Mikdadi G, Young M, Sohns C, Marrouche NF. High-degree atrioventricular block in COVID-19 hospitalized patients. *Europace*. 2021; 23: 451-455.
- Egas Diego, Guadalupe Juan José, Prado-Vivar Belén, et al. SARS-CoV-2 detection and sequencing in heart tissue associated with myocarditis and persistent arrhythmia: A case report. *IDCases*. 2021;25:e01187. <http://doi.org/10.1016/j.idcr.2021.e01187>
- Eneizat Mahdawi T, Wang H, Haddadin FI, Al-Qaysi D, Wylie JV. Heart block in patients with coronavirus disease 2019: a case series of 3 patients infected with SARS-CoV-2. *HeartRhythm Case Reports*. 2020; 6: 652-656.
- Firouzabadi MD, Goudarzi S, Firouzabadi FD, Moosaie F. Complete heart block and itchy rash in a patient with COVID-19. *Caspian J Intern Med*. 2020; 11: S569-S71.
- Gupta MD, Qamar A, Mp G, et al. Bradyarrhythmias in patients with COVID-19: a case series. *Indian Pacing Electrophysiol J*. 2020; 20: 211-212.
- Gyawali Bindu, Baral Bikash, Shah Sangam, Yadav Sutap, Poudel Chandra Mani. A Patient Infected with SARS-CoV-2 Presenting with

- Complete Heart Block. *Case Rep Cardiol.* 2021;2021:1-4. <http://doi.org/10.1155/2021/5011294>
39. Haddadin FI, Mahdawi TE, Hattar L, Beydoun H, Fram F, Homoud M. A case of complete heart block in a COVID-19 infected patient. *J Cardiol Cases.* 2021; 23: 27-30.
  40. He J, Wu B, Chen Y, et al. Characteristic electrocardiographic manifestations in patients with COVID-19. *Can J Cardiol.* 2020; 36: 966.e1-e4.
  41. Hosseini Z, Ghodsi S, Hejazi SF. Persistent complete heart block in a patient with COVID-19 infection: a case report. *SN Compr Clin Med.* 2021; 3: 259-262.
  42. Ignatiuk B, Baratto F, Monticelli J, Bacchion F, Marchese GM, Pasquetto G. Pacemaker implantation in a COVID-19 patient. Balancing the patient's needs and the team's risk of exposure. *J Arrhythm.* 2021; 37:261-263.
  43. Kang Y, Wang H, Chen H, et al. Suspected hydroxychloroquine-induced sinus bradycardia and qtc prolongation in a patient with COVID-19. *Int Heart J.* 2020; 61: 1056-1058.
  44. Kir D, Mohan C, Sancassani R. Heart Brake: an unusual cardiac manifestation of COVID-19. *JACC: Case Rep.* 2020; 2: 1252-1255.
  45. Malekrah Alireza, Fatahian Alireza. A case report of a rare cardiac complication in novel coronavirus disease. *Eur Heart J Case Rep.* 2020;4;(6):1. -4. <http://doi.org/10.1093/ehjcr/ytaa323>
  46. Pecora D, la Greca C, Pezzotti E, Botti P, Campana M, Cuccia C. An unusual presentation of cardiac involvement during the COVID-19 pandemic. *G Ital Cardiol.* 2020; 21: 594-597.
  47. Peigh G, Leya MV, Baman JR, Cantey EP, Knight BP, Flaherty JD. Novel coronavirus 19 (COVID-19) associated sinus node dysfunction: a case series. *Eur Heart J Case Rep.* 2020; 4: 1-6.
  48. Rivetti Luigi, Mantovan Roberto, Sitta Nadir, et al. Management of Pacemaker Implantation during COVID-19 Infection. *Case Rep Cardiol.* 2020;2020:1. -4. <http://doi.org/10.1155/2020/8833660>
  49. Salamanca J, Díez-Villanueva P, Martínez P, et al. COVID-19 "Fulminant Myocarditis" successfully treated with temporary mechanical circulatory support. *JACC Cardiovasc Interv.* 2020; 13: 2457-2459.
  50. Selvaraj Vijairam, Bavishi Chirag, Patel Simaben, Dapaah-Afriyie Kwame. Complete heart block associated with Remdesivir in COVID-19: a case report. *Eur Heart J Case Rep.* 2021;5(7):<http://doi.org/10.1093/ehjcr/ytab200>
  51. Sharif Muhammad Hammad, Khan Abdul Wali, Khaleeqe Madeeha, et al. Complete heart block in patients infected with SARS-CoV-2: A case series from a developing country. *Ann Med Surg.* 2021;69:102828. <http://doi.org/10.1016/j.amsu.2021.102828>
  52. Muller MP, Dresser L, Raboud J, et al. Adverse events associated with high-dose ribavirin: evidence from the Toronto outbreak of severe acute respiratory syndrome. *Pharmacotherapy.* 2007; 27:494-503.
  53. Yu CM, Wong RS, Wu EB, et al. Cardiovascular complications of severe acute respiratory syndrome. *Postgrad Med J.* 2006; 82: 140-144.
  54. Gatto Maria Chiara, Persi Alessandro, Tung Marzia, Masi Rosa, Canitano Stefano, Kol Amir. Bradyarrhythmias in patients with SARS-CoV-2 infection: A narrative review and a clinical report. *Pacing Clin Electrophysiol.* 2021;44(9):1607-1615. <http://doi.org/10.1111/pace.14308>
  55. Manolis AS, Manolis AA, Manolis TA, Apostolopoulos EJ, Papatheou D, Melita H. COVID-19 infection and cardiac arrhythmias. *Trends Cardiovasc Med.* 2020; 30: 451-460.
  56. Wang Y, Wang Z, Tse G, et al. Cardiac arrhythmias in patients with COVID-19. *J Arrhythm.* 2020; 36: 827-836.
  57. Cowburn Andrew S, Macias David, Summers Charlotte, Chilvers Edwin R, Johnson Randall S. Cardiovascular adaptation to hypoxia and the role of peripheral resistance. *eLife.* 2017;6:<http://doi.org/10.7554/elife.28755>
  58. Kato H, Menon AS, Slutsky AS. Mechanisms mediating the heart rate response to hypoxemia. *Circulation.* 1988; 77: 407-414.
  59. Prabhakar NR, Peng Y-J, Nanduri J. Hypoxia-inducible factors and obstructive sleep apnea. *J Clin Invest.* 2020; 130: 5042-5051.
  60. Semenza GL. Hypoxia-inducible factor 1 and cardiovascular disease. *Annu Rev Physiol.* 2014; 76: 39-56.
  61. Semenza Gregg L. Hypoxia-inducible factors in physiology and medicine. *Cell.* 2012; 148: 399-408.
  62. Gubitosa JC, Kakar P, Gerula C, et al. Marked sinus bradycardia associated with remdesivir in COVID-19: a case and literature review. *JACC Case Rep.* 2020; 2: 2260-2264.
  63. Pallotto C, Blanc P, Esperti S, et al. Remdesivir treatment and transient bradycardia in patients with coronavirus diseases 2019 (COVID-19). *J Infect.* 2021; 83: 237-279.
  64. Romani S, Gérard A, Fresse A, et al. Insights on the evidence of cardiotoxicity of hydroxychloroquine prior and during COVID-19 epidemic. *Clin Transl Sci.* 2021; 14: 163-169.
  65. Tchesnokov Egor, Feng Joy, Porter Danielle, Götte Matthias. Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir. *Viruses.* 2019;11(4):326. <http://doi.org/10.3390/v11040326>
  66. Choi SW, Shin JS, Park SJ, et al. Antiviral activity and safety of remdesivir against SARS-CoV-2 infection in human pluripotent stem cell-derived cardiomyocytes. *Antiviral Res.* 2020; 184: 104955.

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Nagamine T, Randhawa S, Nishimura Y, et al. Characteristics of bradyarrhythmia in patients with COVID-19: systematic scoping review. *Pacing Clin Electrophysiol.* 2022;45:556–566. <https://doi.org/10.1111/pace.14466>