M.R. Badykov, I.A. Lakman, E.A. Badykova, V.V. Plechev, I.N. Usmanova, I.D. Ushnitsky, N.Sh. Zagidullin

DOI 10.25789/YMJ.2024.87.16

UDC 616.12-089:124.7

IMPACT OF COVID-19 ON REMOTE CARDIOVASCULAR ENDPOINTS IN PATIENTS WITH SICK SINUS SYNDROME AND IMPLANTED PACEMAKER

SARS-CoV2, responsible for the COVID-19 pandemic, is still relevant for the medical system throughout the world. In addition to the effect on the respiratory system, cardiac manifestations of COVID-19 are also known in the acute and post-COVID-19 period, including known coronary heart disease, proarrhythmogenic effects including impact on sick sinus syndrome (SSS). Cardiovascular diseases including myocarditis, heart failure, tachyarrhythmias and myocardial infarction, where arrhythmias are widespread were detected among hospitalized patients with COVID-19.

Objective: To investigate the impact of COVID-19 incidence on long-term cardiovascular endpoints in patients with SSS with implanted pacemaker. Methods. In a retrospective, non-randomized, uncontrolled study, 447 patients with SSS were examined, of which 205 patients experienced and 242 - did not have COVID-19. The follow-up period was 30 months and the endpoints were cardiovascular death, myocardial infarction, stroke and cardiovascular hospitalization. Adverse cardiovascular events were monitored using the "Promed" electronic medical record system, as well as during follow-up examinations at the consultative and diagnostic clinic. **Results.** Comparison of the incidence of adverse cardiovascular endpoints in the COVID-19 and control groups showed no differences in all endpoints according to the Chi-square test ($p>0.1$), with the exception of frequency of myocardial infarction in the "COVID-19" ($p=0.040$). The close relationship between tachy-bradicardia, microvascular dysfunction and coronary artery disease, and at the same time the impossibility of modulating the heart rhythm in the presence of vegetative dysfunction and an established pacemaker assumed that autonomic dysfunction in post-COVID patients caused myocardial ischemia and, as a result, an increase of myocardial infarction rate. Conclusion. During long-term follow-up, COVID-19 in patients with SSS increased the risk of myocardial infarction.

Keywords: sinus node weakness syndrome, COVID-19, pacemaker, coronary artery disease, cardiovascular endpoints.

Introduction. SARS-CoV2, the well-known coronavirus responsible for the COVID-19 pandemic, continues to be relevant worldwide. Along with the impact of the disease on the respiratory system, there are also known cardiac manifestations of COVID-19. In addition to other cardiovascular diseases, including myocarditis, heart failure, tachyarrhythmias, and myocardial infarction (MI) [3,13], arrhythmias are widespread among hospitalized patients with COVID-19 [8]. Tachyarrhythmias are the most common rhythm disorders. Scientific publications about bradyarrhythmia, including sinus and atrioventricular node dysfunctions are much less common, despite the fact that they are associated with a worser prognosis. Several observational studies and clinical cases have been published that do not provide data on the long-term prognosis of bradyarrhythmia and sinus node dysfunction in COVID-19 [3]. Recently published reports indicate the involvement of COVID-19 in heart's conduction system damage, especially in the sinoatrial node and atrioventricular node. Although the exact mechanism remains unclear, it is thought to be the result of hypoxemia, inflammation, or direct viral infiltration leading to impaired myocardial function [1-11]. Methods for treating bradyarrhythmia in patients with COVID, especially with regard to the reversibility of the process and the need for constant pacing, are not properly investigated. Despite implantation of pacemaker, mortality in patients with SSS remains high [6]. The clinical consequences of first-time bradyarrhythmia in patients with COVID-19 are unknown, and the treatment approach is controversial without understanding the short-and long-term outcomes [3].

Sinus sick syndrome syndrome (also known as sinus node dysfunction) is a medical condition characterized by a malfunction of the sinus node. This dysfunction can lead to heart failure and bradycardia. Sinus node weakness syndrome most often affects the elderly, but can affect all age groups. Causal factors can be divided into internal and external. Internal factors include idiopathic degenerative fibrosis, cardiomyopathy, and ischemia. External factors include medications, hypothyroidism, autonomic dysfunction, and electrolyte disturbances. Patients usually experience fainting or pre-fainting states, palpitations, dizziness, and fatigue. Treatment consists of eliminating the underlying causes and installing a pacemaker [1].

The aim of the study was to identify the impact COVID of COVID-19 morbidity on long-term cardiovascular endpoints in patients with sick sinus syndrome and an implanted pacemaker.

Materials and methods. In a retrospective longterm controlled study, a comparison of longterm cardiovascular endpoints was performed in patients with SSS and implanted pacemaker in the period from April 2020 по to December 2020. Implantation of the pacemaker was performed in the Department of Arrythmology in the Republic Cardiological Center (Ufa).

Inclusion criteria: established diagnosis of SSS, no indications for permanent

FSBEI HE Bashkir State Medical University Ministry of Health Russian Federation, Ufa: **BADYKOV Marat Rifkatovich** – PhD, associate professor, ORCID: 0000-0002-9397-6250, cvsurgery@mail.ru; **LAKMAN Irina Alexandrovna** – candidate of technical sciences, head of the lab. FSBEI HE Ufa University of Science and Technology, ORCID: 0000-0001-9876-9202, Lackmania@mail.ru; **BADYKOVA Elena Albertovna** – PhD, associate professor, ORCID: 0000-0002-8167-4271, lnurova@mail.ru; **PLECHEV Vladimir Vyacheslavjvich** – MD, head of the Department, ORCID: 0000-0002-6716-4048, cvsurgery@mail.ru; **ZAGIDULLIN Naufal Shamilevich** – MD, professor and head of the Department, ORCID: 0000-0003-2386-6707, znaufal@mail.ru; **USMANOVA Irina Nikolayevna** – MD, ORCID ID: 0000-0002-1781-0291, Scopus Author ID: 57197718385, SPIN-код:1978-9470, irinausma@mail.ru; **USHNITSKY Innokentiy Dmitrievich** – MD, professor, head of the Department of Medical Institute FSAEI HE M.K. Ammosov Northeastern Federal University, ORSID 0000-0002-4044-3004, Scopus Author ID: 56943434600, SPIN-code: 9424-3807, incadim @mail.ru.

pacemaker implantation, according to the Clinical Recommendations of Bradiarrhythmias and Conduction Disorders (2020) [2], voluntary informed consent, age 40-85 years old, absence of decompensation. Non-inclusion criteria: unstable coronary heart disease (CHD), MI for 3 months, and stroke for 3 months, chronic heart failure of the IV degree according to the NYHA classification, ejection fraction <35%, severe chronic concomitant diseases, and the presence of a malignant tumor for 5 years. The criterion for exclusion from the study was the patient's refusal to participate in the study.

A total of 607 patients were selected who were admitted during the COVID-19 pandemic and developed severe bradiarrhythmias requiring pacemaker implantation. For the analysis, two groups of patients with SSS were identified: the "COVID-19" group (*n*=205) and the "Control" group (*n*=242), which included patients who did not tolerate COVID-19 during the follow-up period. 160 patients were later completely excluded from the study with a diagnosis of acute respiratory viral infections, without confirmed COVID-19.

The diagnosis of COVID-19 was established based on the presence of detected SARS-CoV-2 RNA using nucleic acid amplification methods and / or detected SARS-CoV-2 class M and G immunoglobulins, in accordance with the current recommendations on COVID-19 of the Ministry of Health of the Russian Federation at the time of the study.

The following unfavorable events were selected as endpoints: MI, stroke, pulmonary embolism (PE), death, and cardiovascular hospitalization. Adverse cardiovascular events were monitored using the “Promed” electronic medical record system, as well as during follow-up examinations in the consultative and diagnostic polyclinic of the Republic Cardiologic Center for the period of 30 months from April 2020 to June 2024.

To analyze the main clinical and demographic characteristics of SSS patients, continuous numerical features were presented in the form of median *Me* and interquartile range (Q1-Q3), for nominal features in the form of absolute and relative frequency (%). Frequency differences were evaluated using nonparametric criteria: for continuous numerical features – the Mann-Whitney criterion, for categorical features – the "Chi-square" criterion with the Yates correction for the rarity of events (if necessary). Differences were considered statistically significant if the significance level of rejecting the null hypothesis of no differences in

Table 1

Clinical and instrumental characteristics of patients with SSS

Sign	of COVID-19 (*n*=205)	Control (*n*=242)	*p*-level of differences
Representation of continuous features: median and interquartile range interquartile			
range of LV EF	62 (58. 64)	62 (58. 64)	0.637
LA	39 (37. 42)	39 (37. 42)	0.879
RV	23 (22. 25)	24 (22. 25)	0.878
BMI	28.2 (25.1 – 32.1)	27.7 (24.7 -30.6)	0.176
Representation of categorical features: absolute frequency and relative frequency (%)			
AH	193 (94.2)	230 (95)	0.988
AF	87 (42.4)	93 (38.4)	0.390
DM	37 (18.1)	38 (15.7)	0.509
CKD	32 (15.6)	35 (14.5)	0.735
IHD	199 (96.6)	238 (98.3)	0.558†
PMIC	40 (19.5)	47 (19.4)	0.981
CHF	198 (96.6)	234 (96.7)	0.842†
stroke in history	19 (9.3)	25 (10.3)	0.708
COPD+ Bronchial Asthma	10 (4.9)	7 (2.9)	0.275
stenting	53 (25.8)	47 (19.4)	0.104

Note: AH – arterial hypertension, CHD – coronary heart disease, BMI – body mass index, LA – anterior-posterior size of the left atrium, - acute cerebrovascular мозгового accident, RV-basal diameter of the right ventricle, PMIC - postmyocardial infarction cardiosclerosis, DM - diabetes mellitus, LV EF-left ventricular ejection fraction, AF – atrial fibrillation, CKD - chronic kidney disease, COPD-chronic obstructive pulmonary disease, CHF-chronic heart failure; † - the "chi-square" test was performed with the Yates correction.

Table 2

Comparison of end point frequencies in patients in the study groups

End point	COVID-19 endpoint (n=205), %	Control (n=242), %	p
Death All-cause death	26 (12.7)	27 (11.2)	0.620
CV death	15 (7.3)	19 (7.9)	0.832
CV hospitalization	71 (34.6)	94 (38.8)	0.359
MI	**24 (11.7)**	**15 (6.2)**	**0.040***
Stroke	14 (6.8)	18 (7.4)	0.804
AF	34 (16.6)	38 (15.7)	0.801
PE	0 (0)	1 (0.4)	0.934†

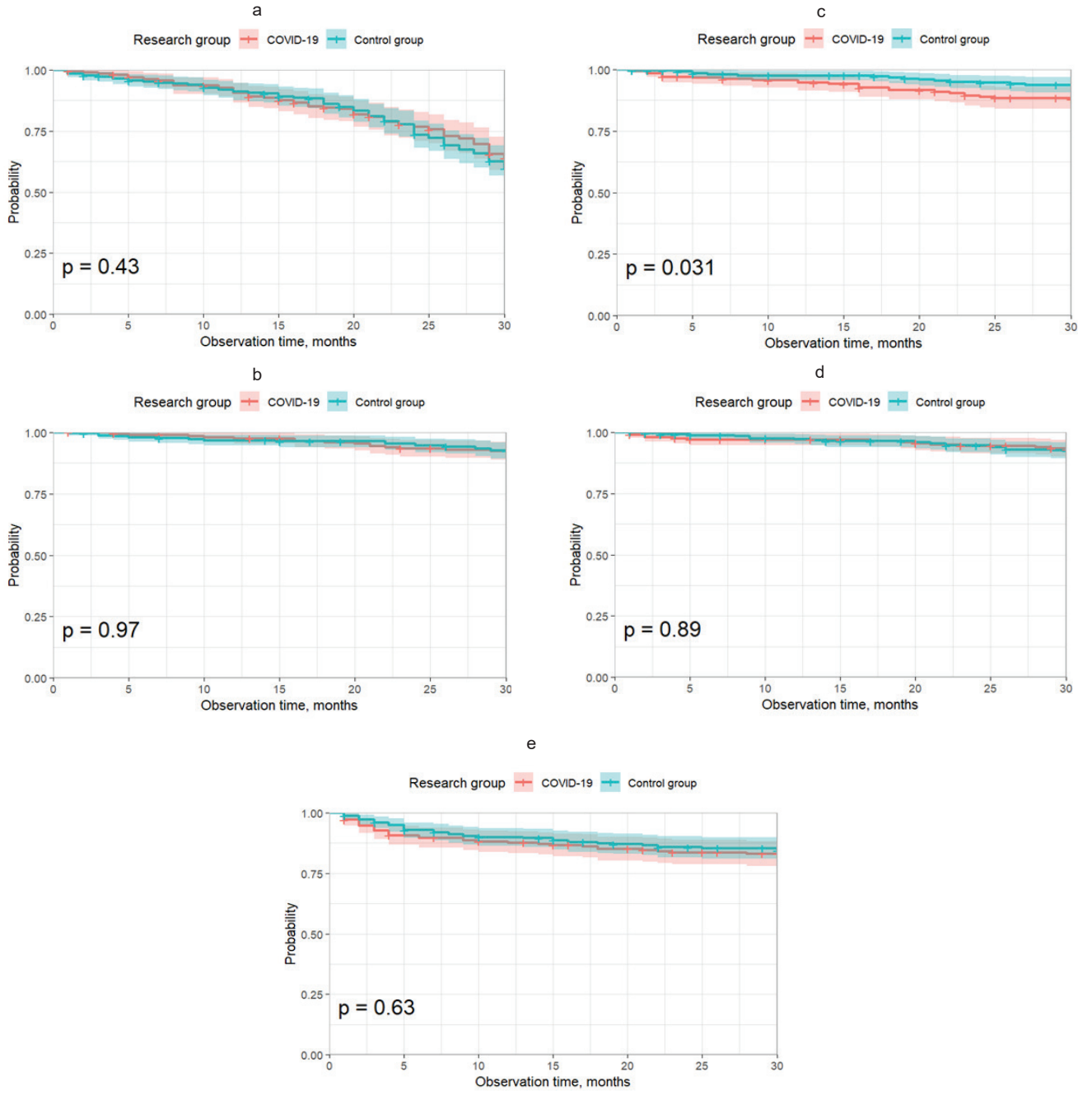
Note: MI – myocardial infarction, PE – pulmonary embolism, AF- new-onset atrial fibrillation, CV hospitalization – cardiovascular hospitalization, CV death – cardiovascular death;† - the chi-square test was performed with the Yates correction. * - differences are statistically significant at p<0.05

Table 3

Results of the Gehan-Wilcoxon test comparing the duration of the period before the end point in patients in the study groups

Endpoint	Number of censored observations		*p*-level
	of COVID-19 differences (*n*=205)	Control (*n*=242)	
CV death	11	8	0.431
CV hospitalization	17	20	0.968
MI	**9**	**10**	**0.031***
Stroke	11	11	0.890
AF	6	8	0.627

Note: MI – myocardial infarction, AF-new-onset atrial fibrillation, CV hospitalization – cardiovascular hospitalization, CV death – cardiovascular death; * - differences are statistically significant at p<0.05.



Kaplan-Meier curves with confidence intervals according to the Greenwood form for end points: a - cardiovascular hospitalization; b - death due to cardiovascular causes; c - myocardial infarction; g - stroke; e - newly diagnosed atrial fibrillation for patients with CVS in the COVID-19 group and the control group during an observation period of 30 months

the study groups was $p<0.05$. The study of differences in the duration of the period before the onset of adverse cardiovascular endpoints in patients with SSS, depending on the presence of a history of COVID-19, was carried out using a survival analysis. In particular, we used Kaplan-Meier multiplication scores with an estimate of the confidence interval for them using the Greenwood formula, and also performed the Gehan-Wilcoxon test for differences in survival. When finding Kaplan-Meier estimates for the endpoints of cardiovascular hospitalization, MI, stroke, atrial fibrillation, censored events were the patient's death before the follow-up period (30 months), for cardiovascular mortality, censored events were deaths from other causes before the end of the follow-up period.

The study was conducted in accordance with the standards of Good Clinical Practice and the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the Bashkir State Medical University of the Ministry of Health of the Russian Federation, Meeting No. 9 of 17.12.2021. Prior to inclusion in the study, all participants received written voluntary informed consent.

Results. Table 1 shows the results of the analysis of clinical and demographic characteristics of patients with SSS in the "COVID-19" (n=205) and "Control" (n=242) groups. As can be seen, the groups did not differ in gender and age composition, the age of patients in the COVID-19 group was 73 (66, 80) years, and in the Control group - 73 (67, 81), according to the main indicators of the structure and functions of the heart

chambers, and the frequency of concomitant diseases (p>0.1).

Comparison of the frequency of occurrence of unfavorable cardiovascular endpoints in the COVID-19 and control groups in patients with SSS over the 30-month follow-up period showed no differences in all endpoints according to the "Chi – square" criterion (p>0.1), with the exception of MI in the "COVID-19" group, it occurred more often (p=0.040), Table 2.

Table 3 shows the results of the Gehan-Wilcoxon test comparing the duration of the period before the onset of various adverse cardiovascular endpoints in the COVID-19 and control groups in patients with SSS over a 30-month follow-up period. The table shows how many observations were censored in each group during the survival analysis for different endpoints. That is, for example, in the group of patients with SSS who experienced COVID-19, 9 persons died before the end of the 30-month follow-up period, while they did not have MI during the follow-up period before death. As can be seen from the test results, significant differences in the duration of the period before the onset of unfavorable endpoints were observed only for MI (p=0.031). For the pulmonary embolism (PE), the Gehan-Wilkoskon test was not performed, as COVID was not observed in the COVID-19 group of patients.

Figures 1-5 show Kaplan-Meier curves with confidence intervals for the endpoints of cardiovascular hospitalization, cardiovascular death, MI, stroke, and new-onset atrial fibrillation, respectively, for patients with SSS in the «COVID-19» and «Control» groups during the 30-month follow-up period. Censored observations were marked with a " + " sign on the graphs, and the confidence intervals of Greenwood-shaped survival curves at 95% confidence are highlighted with a blurred shadow of the corresponding color curve.

Discussion. More than 6 billion patients were infected during the COVID-19 pandemic, including those with atrial arrhythmias, the presence of SSS with an implanted pacemaker [12]. A number of studies have shown clinical cases of a combination of SSS and COVID-19 [3, 8, 11].

Comparison of the frequency of occurrence of adverse cardiovascular endpoints in the COVID-19 and control groups in patients with SSS 30 months of follow-up showed no differences in all endpoints according to the "chi-square" criterion (p>0.1), with the exception of MI – in the "COVID-19" group-it occurred significantly more often (p<0.05). Patients with SSS and COVID-19, the frequency of MI was higher than in the group without COVID-19, despite the correction of bradycardia by pacing. This is consistent with the results of a large study by Yan Xie et al. (2022), which included 153153,760 persons with COVID-19 and showed that patients with COVID-19 in 12 months long-term follow-up had an increased risk of cardiovascular diseases, including CHD and MI [10]. Cardiovascular symptoms such as tachycardia, arterial hypertension, and cardialgia are important component of post-COVID-19 syndrome and can affect up to a third of patients with COVID-19 [4]. Currently, post-COVID syndrome, which is observed in 20% of the population, is largely associated with symptoms of cardiovascular autonomic dysfunction (CVAD) [5]. The consequences of CVAD are usually manifested in the form of microvascular dysfunction, which can lead to type 2 MI. CVAD can also manifest with arterial hypotension, such as orthostatic or postprandial hypotension, and recurrent reflex syncope [5]. Asarcikli L. D. et al. [9] when examining COVID-19 convalescents, showed significantly higher values of RMSSD, pNN50 and HF indicators of heart rate variability in regard to CVAD in the group with COVID-19 compared to the control in the period up to 3 months after viral infection [7].

Conclusion. Early-onset of COVID-19 in patients with SSS increases the risk of MI during long-term follow-up, which is probably associated with cardiovascular autonomic dysfunction. Given the close relationship between CVAD, microvascular dysfunction, and CHD [5], and at the same time, the inability to modulate the heart rate in the presence of SSS and an established pacemaker, it can be assumed that autonomic dysfunction in post-COVID patients with SSS and implanted pacemaker causes myocardial ischemia and, as a consequence, an increase in the probability of MI. There is currently no available literature data on the long-term impact of COVID-19 on adverse cardiovascular events in patients with SSS.

The authors stated that there was no conflict of interest. This work was supported by a grant from the Russian Science Foundation (No. 22-18-20123).

References

1. Badykov MR, Plechev VV, Sagitov IS, Lakman IA, Zagidullin NS. Analiz otdalyonnyh serdechno-sosudistyh sobytij u pacientov s disfunkciej sinusovogo uzla i implantirovannym elektrokardiostimulyatorom [Cardiovascular events follow-up analysis in patients with sinus node dysfunction and implanted pacemaker]. Rossijskij kardiologicheskij zhurnal [Russian Journal of Cardiology. 2019;(2):53-57 (In Russ.).] doi: 10.15829/1560-4071-2019-2-53-57.

2. Revishvili ASh, et al. Bradiaritmii i narusheniya provodimosti [Clinical practice guidelines for Bradyarrhythmias and conduction disorders]. Rossijskij kardiologicheskij zhurnal [Russian Journal of Cardiology. 2021;(4):203-24 (In Russ).] doi: 10.15829/1560-4071--2021-4448.

3. Chinitz, JS, et al. Bradyarrhythmias in patients with COVID-19: marker of poor prognosis? Pacing Clin Electrophysiol. 2020;43:1199–1204. doi:10.1111/pace.14042.

4. Brogi E, et al. Cardiac complications in patients with COVID-19: A systematic review. J Anesth Analg Cri. Care. 2022;2:18. doi:10.1186/s44158-022-00046-7

5. Fedorowski A, et al. Cardiovascular autonomic dysfunction in post-COVID-19 syndrome: a major health-care burden. Nat Rev Cardiol. 2024 Jun;21(6):379-395. doi: 10.1038/s41569-023-00962-3.

6. Nagamine T, et al. Characteristics of bradyarrhythmia in patients with COVID-19: Systematic scoping review. Pacing Clin Electrophysiol. 2022;45(4):556-566. doi: 10.1111/pace.14466.

7. Kaliyaperumal D, et al. Characterization of Cardiac Autonomic Function in COVID-19 Using Heart Rate Variability: A Hospital Based Preliminary Observational Study. J Basic Clin Physiol Pharmacol. 2021;32:247–253. doi: 10.1515/jbcpp-2020-0378.

8. Gopinathannair R, et al. COVID-19 and cardiac arrhythmias: a global perspective on arrhythmia characteristics and management strategies. J Interv Card Electrophysiol. 2020; 59: 329-336. doi: 10.1007/s10840-020-00789-9.

9. Asarcikli LD, et al. Heart Rate Variability and Cardiac Autonomic Functions in Post-COVID. Period J Interv Card Electrophysiol. 2022;63:715-721. doi: 10.1007/s10840-022-01138-8.

10. Xie Y, et al. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28(3):583-590. doi: 10.1038/s41591-022-01689-3.

11. Gm Peigh, et al. Novel coronavirus 19 (COVID-19) associated sinus node dysfunction: a case series. 2020 May 8;4(FI1):1-6. doi: 10.1093/ehjcr/ytaa132.

12. Sundaram Ch, et al. Reversible sinus node dysfunction in novel COVID-19 infection: two years of follow-up. IHJ Cardiovascular Case Reports (CVCR). 2023;7(3-4):89-91. doi:10.1016/j.ihjccr.2023.11.001.

13. Fried JA, et. al. The variety of cardiovascular presentations of COVID-19. Circulation. 2020;141(23):1930–1936. doi: 10.1161/ CIRCULATIONAHA.120.047164.