ORIGINAL ARTICLE

Risk of Subclinical Atrial Fibrillation in Patients with Cardiac Implantable Electronic Devices after COVID-19 Infection: A Single-Center Study

Komsing Methavigul, MD[1], Ratikorn Methavigul, MD[1]

[1] Department of Cardiology, Central Chest Institute of Thailand, Nonthaburi, Thailand

Objective: To evaluate the risk of subclinical atrial fibrillation (SCAF) in patients with cardiac implantable electronic devices (CIEDs) after COVID-19 infection.

Materials and Methods: The authors retrospectively enrolled patients receiving CIEDs with atrial leads at the device clinic between January 2022 and September 2023. Patients with 12-lead ECG documented atrial fibrillation, atrial flutter, or atrial tachycardia were excluded. The authors classified these patients as COVID-19 and non-COVID-19 groups. The outcome was the new onset and/or 20% increased episodes of the longest SCAF duration. The authors compared the outcome using a chi-square or Fisher's exact test between both groups.

Results: One hundred thirty-two patients were enrolled. Of the 132 patients, 44 patients were in COVID-19 group and 88 patients were in non-COVID-19 group. The average age was 67.6 years. About one-third of these patients were males. Most of these patients had hypertension and dyslipidemia. The average follow-up time was 9.3 months. Eighteen patients (40.9%) had the longest SCAF duration in the COVID-19 group, while 23 patients (26.1%) had the longest SCAF duration in the non-COVID-19 group. More patients in the COVID-19 group had the longest SCAF duration than those in non-COVID-19 group with no statistical significance (odds ratio 1.96, 95% confidence interval 0.91 to 4.21, p=0.13).

Conclusion: Patients with a history of previous COVID-19 infection receiving CIEDs had no significantly increased risk of SCAF.

Keywords: COVID-19; CIEDs; Subclinical atrial fibrillation; AHRE burden; Atrial high-rate episode

Received 11 January 2024 | Revised 22 February 2024 | Accepted 24 February 2024

J Med Assoc Thai 2024;107(3):200-5

Website: http://www.jmatonline.com

The coronavirus disease 2019 (COVID-19) has been the most contagious and infectious disease leading to global pandemic. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped virus in the *Coronaviridae* family using the angiotensin-converting enzyme 2 (ACE2) protein for cell entry. COVID-19-associated cardiovascular sequelae have been reported[1]. Pulmonary embolism, acute coronary syndromes, heart failure (HF), and cardiac arrhythmias are the cardiovascular involvement in patients with COVID-19[2]. Previous trial showed that acute ischemic heart disease and acute HF were the most frequent cardiac events during COVID-19-associated hospitalized patients and one or more cardiac event had the increased risk of intensive care unit admission and in-hospital death[3]. Moreover, previous trial showed that hospitalized patients with COVID-19 also had increased risk of atrial fibrillation (AF)[4]. Studies demonstrated that AF was associated with the increased risk of unfavorable outcomes in patients with COVID-19[5-7].

Based on the authors' knowledge, previous trials have demonstrated that subclinical atrial fibrillation (SCAF) has been associated with the increased risk of ischemic stroke or systemic embolism[8-10]. Data from the United States of America (USA) during the COVID-19 pandemic showed that there was an increase in AF episodes in patients with cardiac implantable electronic devices (CIEDs) in high COVID-19 prevalence states[11].

To date, cardiovascular sequelae after COVID-19 infection have been reported[12,13]. The terms "long COVID", "post-acute COVID-19 syndrome", "post-acute sequelae of SARS-CoV-2 infection (PASC)",

Correspondence to:

Methavigul K.

Department of Cardiology, Central Chest Institute of Thailand, Nonthaburi 11000, Thailand.

Phone: +66-2-5470920, **Fax:** +66-2-5470990

Email: methavigul.k@gmail.com

How to cite this article:

Methavigul K, Methavigul R. Risk of Subclinical Atrial Fibrillation in Patients with Cardiac Implantable Electronic Devices after COVID-19 Infection: A Single-Center Study. J Med Assoc Thai 2024;107:200-5.

DOI: 10.35755/jmedassocthai.2024.3.13958

or "post COVID-19 condition" were used to describe persistent symptoms of the patients after COVID-19 infection[14-16]. However, data about the risk of SCAF in patients after COVID-19 infection are lacking. The present study aimed to evaluate the risk of SCAF in patients with CIEDs after COVID-19 infection.

Materials and Methods

Study population

The authors retrospectively enrolled patients aged 18 years or older receiving CIEDs with atrial leads at the device clinic, Central Chest Institute of Thailand between January 2022 and September 2023. Patients with 12-lead ECG documented AF, atrial flutter, or atrial tachycardia, a history of previous cardiac surgery, thyrotoxicosis, sepsis, electrolyte disturbances from hypokalemia or hypomagnesemia, end-stage renal disease (ESRD) with or without renal replacement therapy, pregnancy, or concealed study participation were excluded.

The present study protocol was approved by the Human Research Ethics Committee of Central Chest Institute of Thailand (No. 032/2566). The authors conducted the present study in accordance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice Guidelines. The present trial was registered on Thai Clinical Trials Registry (TCTR20230324004).

Data collection

The authors retrieved demographic and clinical data of the present study patients from the electronic medical record and classified them into two groups according to a history of previous COVID-19 infection. Patients with previous COVID-19 infection, which are the COVID-19 group, were recruited three months after the onset of COVID-19 infection. Those without previous COVID-19 infection, which are the non-COVID-19 group, were recruited at follow-up time in the device clinic. The authors collected the baseline demographic data such as age, sex, medical history, indication of CIEDs implantation, type of CIEDs, renal function, and left ventricular (LV) function. The patients' data during device interrogation at the device clinic follow-up visit were recorded for at least six months after recruitment.

Clinical outcome

The outcome of the present study was the new onset and/or 20% increased episodes of the longest SCAF duration during follow-up visit. SCAF was defined following 2020 European Society of Cardiology (ESC) guidelines for the diagnosis and management of AF[17]. The electrograms of SCAF during events were reviewed by a cardiac electrophysiologist.

Statistical analysis

The authors specified 0.05 for type I error and 0.20 for type II error with 80% power and estimated 0.1 and 0.3 for SCAF events in non-COVID-19 and COVID-19 groups, respectively[4,9]. The ratio between patients in non-COVID-19 and COVID-19 groups was 2. By comparing two independent proportions in the present study using a chi-square test and a sample size of 132 patients was estimated.

The authors used descriptive statistics for analysis of baseline demographic and clinical data. The categorical data were analyzed using a chi-square test and the continuous data were analyzed using an independent t-test. The categorical data are presented as numbers and percentage and the continuous data are presented as mean and standard deviation (SD). The authors compared the outcome using a chi-square or Fisher's exact test between COVID-19 and non-COVID-19 groups. A p-value less than 0.05 was considered statistical significance.

Results

One hundred thirty-two patients were enrolled in the present study at the device clinic, Central Chest Institute of Thailand between January 2022 and September 2023. The average age was 67.6 years. About one-third of these patients were males. Most of these patients had hypertension and dyslipidemia. About one-fifth of these patients had chronic kidney disease. Most of these patients were implanted with pacemakers because of sick sinus syndrome (SSS) and atrioventricular (AV) block. The average left ventricular ejection fraction (LVEF) was 50.6%. The average follow-up time was 9.3 months.

Of the 132 patients, 44 patients had a history of previous COVID-19 infection, and 88 patients had no history of COVID-19 infection (Figure 1). Patients in the non-COVID-19 group were older and had more hypertension, dyslipidemia, and coronary artery disease (CAD) than those in the COVID-19 group. Baseline characteristics are shown in Table 1.

The distribution of the SCAF duration in patients with and without a history of previous COVID-19 infection

Of the 44 patients with a history of previous

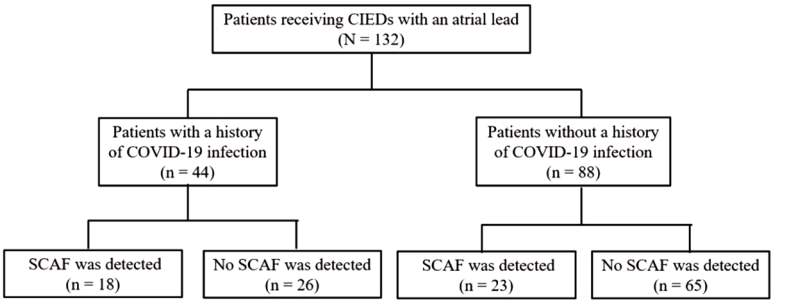

Figure 1. Flow diagram of study patients.

CIEDs=cardiac implantable electronic devices; SCAF=subclinical atrial fibrillation

Table 1. Baseline characteristics of the patients

Demographic data	Total (n=132)	COVID-19 (n=44)	Non-COVID-19 (n=88)	p-value
Age (years); mean±SD	67.6±14.5	62.4±16.5	70.1±12.7	0.01*
Male sex; n (%)	48 (36.4)	11 (25.0)	37 (42.0)	0.08
Medical history; n (%)				
Diabetes	28 (21.2)	6 (13.6)	22 (25.0)	0.20
Hypertension	86 (65.2)	23 (52.3)	63 (71.6)	0.045*
Dyslipidemia	83 (62.9)	19 (43.2)	64 (72.7)	<0.01*
CAD	19 (14.4)	2 (4.5)	17 (19.3)	0.04*
PAD	0 (0.0)	0 (0.0)	0 (0.0)	-
Previous stroke/TIA	3 (2.3)	2 (4.5)	1 (1.1)	0.54
History of HF	11 (8.3)	4 (9.1)	7 (8.0)	>0.99
Valvular heart disease	8 (6.1)	2 (4.5)	6 (6.8)	0.90
CKD	30 (22.7)	11 (25)	19 (21.6)	0.83
Liver disease	0 (0.0)	0 (0.0)	0 (0.0)	-
Pulmonary disease	4 (3.0)	1 (2.3)	3 (3.4)	>0.99
Indication of CIEDs implantation; n (%)				0.49
Sick sinus syndrome	50 (37.9)	13 (29.5)	37 (42.0)	
AV block	67 (50.8)	26 (59.1)	41 (46.6)	
ICM	2 (1.5)	1 (2.3)	1 (1.1)	
Non-ICM	13 (9.8)	4 (9.1)	9 (10.2)	
Type of CIEDs; n (%)				0.75
Pacemaker	115 (87.1)	39 (88.6)	76 (86.4)	
ICD	2 (1.5)	1 (2.3)	1 (1.1)	
CRT	15 (11.4)	4 (9.1)	11 (12.5)	
Serum creatinine (mg/dL); mean±SD	0.9±0.3	0.9±0.2	0.9±0.4	0.69
eGFR (mL/minute/1.73 m^2); mean±SD	76.2±23.5	79.2±24.1	74.6±23.1	0.29
LVEF (%); mean±SD	50.6±27.3	49.9±28.5	51.0±26.8	0.82

SD=standard deviation; CAD=coronary artery disease; PAD=peripheral artery disease; TIA=transient ischemic attack; HF=heart failure; CKD=chronic kidney disease; AV=atrioventricular; ICM=ischemic cardiomyopathy; CIEDs=cardiac implantable electronic devices; ICD=implantable cardioverter defibrillator; CRT=cardiac resynchronization therapy; eGFR=estimated glomerular filtration rate; LVEF=left ventricular ejection fraction

* $p<0.05$ indicates statistical significance

COVID-19 infection, 27.3% and 13.6% had the longest SCAF duration of six minutes or less and more than six minutes up to six hours, respectively, while no patients had SCAF duration of more than six hours up to 24 hours and more than 24 hours. Of the 88 patients with no history of COVID-19 infection, 15.9%, 9.1%, and 1.1% had the longest SCAF duration of six minutes or less, more than six minutes up to six hours, and more than six hours up to 24 hours, respectively while no patients had SCAF duration of more than 24 hours. Most of patients in both groups had the longest SCAF duration of six

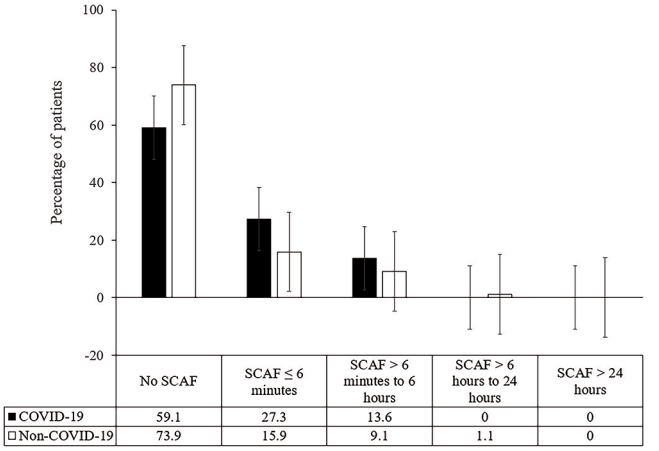

Figure 2. The distribution of the longest SCAF duration in patients with and without a history of COVID-19 infection.

SCAF=subclinical atrial fibrillation

Table 2. Risk of SCAF in patients with CIEDs after COVID-19 infection

Outcomes	COVID-19 (n=44); n (%)	Non-COVID-19 (n=88); n (%)	OR (95% CI)	p-value
The longest SCAF duration (overall)	18 (40.9)	23 (26.1)	1.96 (0.91 to 4.21)	0.13
The longest SCAF duration >6 minutes	6 (13.6)	9 (10.2)	1.39 (0.46 to 4.18)	0.77

SCAF=subclinical atrial fibrillation; CIEDs=cardiac implantable electronic devices; OR=odds ratio; CI=confidence interval

* $p<0.05$ indicates statistical significance

minutes or less. The distribution of the longest SCAF duration in COVID-19 and non-COVID-19 groups is shown in Figure 2.

The risk of SCAF based on a history of previous COVID-19 infection

Eighteen patients (40.9%) had the longest SCAF duration in COVID-19 group, while 23 patients (26.1%) had the longest SCAF duration in non-COVID-19 group. More patients in COVID-19 group had the longest SCAF duration than those in non-COVID-19 group with no statistical significance (odds ratio [OR] 1.96, 95% confidence interval [CI] 0.91 to 4.21, p=0.13). After analyzing only patients with the longest SCAF duration of more than six minutes, there was no significantly increased risk of the longest SCAF duration in patients between the two groups (OR 1.39, 95% CI 0.46 to 4.18, p=0.77) (Table 2).

Discussion

The present study was the first trial showing the risk of SCAF did not significantly increase in patients receiving CIEDs with a history of previous COVID-19 infection. Most of the patients with the longest SCAF duration in the COVID-19 group had shorter duration than expected.

Despite previous studies that showed that patients with COVID-19 had significantly increased risk of AF[4], the present study showed the disparate results. However, there were different baseline characteristics between those and the present patients. Those studies collected data in hospitalized patients during COVID-19 positive. There might be precipitating factors of AF during hospital admission such as electrolyte disturbance, concomitant infection, and medication during hospitalization leading to increased risk of AF. The present study collected ambulatory patients at the device clinic, so the patients had lower precipitating factors of AF compared to hospitalized patients. Additionally, the present study evaluated the SCAF after three months from the onset of COVID-19 infection having the lower rate of AF compared to acute phase of COVID-19 infection. Previous USA trial revealing that an increased AF episodes in patients with CIEDs in high COVID-19 prevalence states during COVID-19 pandemic could be also used to support the authors explanation[11]. Nevertheless, recent trial reported the increased risk for major arrhythmic risks including AF following severe COVID-19 infection after adjusting cardiovascular risk factors

and for socio-economic factors[18]. The present study had lower rate of SCAF in patients with a history of COVID-19 infection because of lower severity of COVID-19 infection. Most COVID-19 patients in the present study were treated by the method of home isolation supporting the less severe form. Additionally, the patients in non-COVID-19 group were older and had more hypertension, dyslipidemia, and CAD than those in the COVID-19 group. Those are risk factors for AF as well[19]. The risk of SCAF may increase in non-COVID-19 group leading to no significant difference between the COVID-19 and the non-COVID-19 groups. A larger prospective study will need to be conducted in the future. Lastly, the authors enrolled patients during Omicron pandemic having lower severity than the previous COVID-19 strain. Those may be the explanation of lower SCAF episodes.

There are limitations in the present study. First, the study was a retrospective chart review. There may be missing data in the study patients. Lower rate of antigen test kit led to lower detection rate of COVID-19 infection and misclassified to non-COVID-19 group. Recall and interviewing bias could not be excluded. Second, there were a small number of patients in the present study leading to lower event rate than expected and could not achieve statistical significance due to wide 95% CI. However, when the authors compared only the longest SCAF duration of more than six minutes, it had more clinical significance, but it still did not reach a significant result. Nevertheless, the present study was the first study demonstrating the risk of SCAF three months after a COVID-19 infection. Third, the short follow-up time in the present study was another limitation. Patients in the present study infrequently visited for CIEDs interrogation. However, the CIEDs were responsible for the continuous recorder during follow-up period. The SCAF events were recorded and collected when those patients visited for CIEDs interrogation. Finally, the present study collected data in only Thai patients leading to limit generalizability. In addition, no previous other Asian trials has revealed the risk of SCAF in patients three months after COVID-19. Further larger multinational study will be required.

Conclusion

Patients with a history of previous COVID-19 infection three months after receiving CIEDs had no significantly increased risk of SCAF.

What is already known on this topic?

Previous trial showed that hospitalized patients with COVID-19 had increased risk of AF.

What does this study add?

This study showed that patients that received CIEDs had no significant increase in risk of SCAF three months after a COVID-19 infection.

Acknowledgement

The authors gratefully acknowledge all patients participating in the present study, cardiac electrophysiology staffs, cardiology fellows, cardiovascular nurses, and other medical personnel at the device clinic, Department of Cardiology, Central Chest Institute of Thailand.

Conflicts of interest

The authors declare no conflict of interests.

References

1. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol 2020;75:2352-71.
2. Baigent C, Windecker S, Andreini D, Arbelo E, Barbato E, Bartorelli AL, et al. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1-epidemiology, pathophysiology, and diagnosis. Eur Heart J 2022;43:1033-58.
3. Woodruff RC, Garg S, George MG, Patel K, Jackson SL, Loustalot F, et al. Acute cardiac events during COVID-19-associated hospitalizations. J Am Coll Cardiol 2023;81:557-69.
4. Wollborn J, Karamnov S, Fields KG, Yeh T, Muehlschlegel JD. COVID-19 increases the risk for the onset of atrial fibrillation in hospitalized patients. Sci Rep 2022;12:12014.
5. Mulia EPB, Maghfirah I, Rachmi DA, Julario R. Atrial arrhythmia and its association with COVID-19 outcome: a pooled analysis. Diagnosis (Berl) 2021;8:532-5.
6. Yang H, Liang X, Xu J, Hou H, Wang Y. Meta-analysis of atrial fibrillation in patients with COVID-19. Am J Cardiol 2021;144:152-6.
7. Zuin M, Bilato C. Increase in atrial fibrillation-related mortality in the United States during the COVID-19 pandemic. Heart Rhythm 2023;20:163-4.
8. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol

2009;2:474-80.
9. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366:120-9.
10. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). Eur Heart J 2014;35:508-16.
11. O'Shea CJ, Middeldorp ME, Thomas G, Harper C, Elliott AD, Ray N, et al. Atrial fibrillation burden during the coronavirus disease 2019 pandemic. Europace 2021;23:1493-501.
12. Cenko E, Badimon L, Bugiardini R, Claeys MJ, De Luca G, de Wit C, et al. Cardiovascular disease and COVID-19: a consensus paper from the ESC Working Group on Coronary Pathophysiology & Microcirculation, ESC Working Group on Thrombosis and the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Heart Rhythm Association (EHRA). Cardiovasc Res 2021;117:2705-29.
13. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27:601-15.
14. Gluckman TJ, Bhave NM, Allen LA, Chung EH, Spatz ES, Ammirati E, et al. 2022 ACC expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults: Myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: A report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2022;79:1717-56.
15. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022;22:e102-7.
16. National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE Guideline, No. 188. London: NICE (UK); 2020.
17. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373-498.
18. Liliequist A, Svensson P, Hoffmann R, Habel H, Nordberg P, Stahlberg M. Surviving critical COVID-19 requiring mechanical ventilation is associated with a high long-term risk of de novo arrhythmic events. Europace 2023;25 Suppl 1:euad122.040.
19. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: Time for a new model. Stroke 2016;47:895-900.