Journal of the American Heart Association

ORIGINAL RESEARCH

Risk Stratifying and Prognostic Analysis of Subclinical Cardiac Implantable Electronic Devices Infection: Insight From Traditional Bacterial Culture

Gaofeng Lin, MD; Tong Zou, MD, PhD; Min Dong, MD, PhD; Junpeng Liu, MD; Wen Cui, MD, PhD; Jiabin Tong, MD; Haifeng Shi, MD, PhD; Hao Chen, MD, PhD; Jia Chong, MD; You Lyu, MD; Sujuan Wu, RN; Zhilei Wang, MD; Xin Jin, MD; Xu Gao, RN; Lin Sun, RN; Yimei Qu, RN; Jiefu Yang, MD, PhD

BACKGROUND: Subclinical infection of cardiac implantable electronic devices (CIEDs) is a common condition and increases the risk of clinical infection. However, there are limited studies focused on risk stratifying and prognostic analysis of subclinical CIED infection.

METHODS AND RESULTS: Data from 418 consecutive patients undergoing CIED replacement or upgrade between January 2011 and December 2019 were used in the analysis. Among the patients included, 50 (12.0%) were detected as positive by bacterial culture of pocket tissues. The most frequently isolated bacteria were coagulase-negative staphylococci (76.9%). Compared with the noninfection group, more patients in the subclinical infection group were taking immunosuppressive agents, received electrode replacement, or received CIED upgrade and temporary pacing. Patients in the subclinical infection group had a higher PADIT (Prevention of Arrhythmia Device Infection Trial) score. Univariable and multivariable logistic regression analysis found that use of immunosuppressive agents (odds ratio [OR], 6.95 [95% CI, 1.44–33.51]; P=0.02) and electrode replacement or CIED upgrade (OR, 6.73 [95% CI, 2.23–20.38]; P=0.001) were significantly associated with subclinical CIED infection. Meanwhile, compared with the low-risk group, patients in the intermediate/high-risk group had a higher risk of subclinical CIED infection (OR, 3.43 [95% CI, 1.58–7.41]; P=0.002). After a median follow-up time of 36.5 months, the end points between the subclinical infection group and noninfection group were as follows: composite events (58.0% versus 41.8%, P=0.03), rehospitalization (54.0% versus 32.1%, P=0.002), cardiovascular rehospitalization (32.0% versus 13.9%, P=0.001), CIED infection (2.0% versus 0.5%, P=0.32), all-cause mortality (28.0% versus 21.5%, P=0.30), and cardiovascular mortality (10.0% versus 7.6%, P=0.57).

CONCLUSIONS: Subclinical CIED infection was a common phenomenon. The PADIT score had significant value for stratifying patients at high risk of subclinical CIED infection. Subclinical CIED infection was associated with increased risks of composite events, rehospitalization, and cardiovascular rehospitalization.

Key Words: bacterial culture ■ cardiac implantable electronic devices ■ prognosis ■ risk stratifying ■ subclinical infection

The use of cardiac implantable electronic devices, including permanent pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy devices has been increasing dramatically in recent years. Unfortunately, the increase of pacing therapy is associated with a high prevalence of CIED-related infection. In a cohort study that included 97 750 patients undergoing CIED implantation

Correspondence to: Jiefu Yang, MD, PhD, and Tong Zou, MD, PhD, No. 1, Dahua Road, Dongdan, Dongcheng District, Beijing 100730, China. E-mail: yangjiefu2011@126.com; zoutong2001@163.com

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022260

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- To our knowledge, this is the largest sample size and longest follow-up duration study on the topic of subclinical cardiac implantable electronic device (CIED) infection.
- In addition to prevalence and risk factors, our study evaluated a validated score, the PADIT (Prevention of Arrhythmia Device Infection Trial) score, for risk stratification of subclinical CIED infection.
- We also analyzed the prognostic importance including CIED infection, mortality, rehospitalization, and composite events of subclinical CIED infection.

What Are the Clinical Implications?

- Our findings supported that the PADIT score could be used as a routine clinical tool for stratifying high-risk patients.
- Subclinical CIED infection was associated with increased risks of composite events, rehospitalization, and cardiovascular rehospitalization, which aroused more attention for intervention of subclinical CIED infection, especially for high-risk patients.
- Our findings will also provide a foundation for further collaborative multicenter research.

Nonstandard Abbreviations and Acronyms

CoNS	coagulase-negative staphylococci
PADIT	Prevention of Arrhythmia Device Infection Trial

or reoperation, device-related infection incidence during device lifetime was 1.19% for pacemakers, 1.91% for implantable cardioverter-defibrillators, 2.18% for cardiac resynchronization therapy pacemakers, and 3.35% for cardiac resynchronization therapy defibrillators.[1] However, in many patients without apparent signs or symptoms of infection, microorganisms can be detected by using bacterial culture or 16s rRNA sequencing in pocket tissues, which is called subclinical infection or asymptomatic bacterial colonization.[2,3]

Subclinical CIED infection is insidious and hard to detect because of the implanted pacing system and long device lifetime. Device replacement or upgrade offers an ideal time to evaluate the condition of the CIED pocket. Prior studies have demonstrated that subclinical infection increased the risk of symptomatic infection, and the species of the pathogen were the same as those detected during CIED replacement or upgrade,[4,5] which implied the necessities of risk stratifying, early diagnosis, and early prevention. Nevertheless, the risk factors of subclinical CIED infection and common bacterial species have not been fully elucidated, and there is not a useful risk assessment score for stratifying high-risk patients. Moreover, in addition to clinical CIED infection, the effect of subclinical CIED infection on patients' prognosis, such as mortality and rehospitalization, has seldom been reported.

Therefore, we consecutively analyzed bacterial species by using conventional cultures from pocket tissues of the explanted devices and evaluated the use of a recently proposed risk score[6] for risk stratifying of subclinical CIED infection. The prognosis of subclinical CIED infection was analyzed during follow-up.

METHODS

According to the *Transparency and Openness Promotion Guidelines*, data and methods used in the analysis and materials used to conduct the research are available from the corresponding authors upon reasonable request.

Study Population

Four hundred eighteen consecutive patients who received CIED replacement or upgrade in Beijing Hospital were enrolled between January 2011 and December 2019. Patients who were clinically diagnosed with CIED infection, including pocket infection, bacteremia, and infective endocarditis, were excluded. This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Hospital (No. 2019BJYYEC-055-03). All patients signed medical informed consent forms.

Collection of Clinical Characteristics

The following demographic characteristics were collected: age, sex, and body mass index. Past medical history included coronary heart disease, hypertension, atrial fibrillation, diabetes, chronic kidney disease, heart failure, chronic obstructive pulmonary disease, and malignancies. Medication history was composed of immunosuppressive agents, anticoagulant drugs (warfarin and non–vitamin K oral anticoagulants), and antiplatelet drugs (aspirin, clopidogrel, or ticagrelor). Procedure-related factors (before the index procedure) were as follows: CIED indication, CIED type, implantation time, number of prior procedures, electrode replacement (referred to as the addition of a new lead but not lead extraction) or CIED upgrade, temporary pacing, perioperative fever, postoperative hematoma.

We used the PADIT (Prevention of Arrhythmia Device Infection Trial) score to assess the risk of CIED infection,[6] including: number of previous procedures (1 point for 1, 4 points for ≥2), age (1 point for age 60–69 years, 2 points for age <60 years), depressed renal function (1 point for estimated glomerular filtration rate <30 mL/min), immunocompromised (receiving therapy that suppresses resistance to infection, 3 points), and procedure type (2 points for implantable cardioverter-defibrillator, 4 points for cardiac resynchronization therapy, and 5 points for revision/upgrade). PADIT scores ranging from 0 to 15 points classified patients into low-risk (0–4), intermediate-risk (5–6), and high-risk (≥7) groups.

Collection of Specimens

Before the CIED replacement or upgrade procedure, a second- or third-generation cephalosporin (ceftriaxone, ceftizoxime, cefotaxime, or cefuroxime) was used intravenously for every patient. During the procedure, 0.5 g of the pocket tissue on the surface of the CIED was collected immediately following skin incision using a sterile scalpel. All of the specimens were reserved in sterile containers and immediately transported to the laboratory center for bacterial culture.

Bacterial Culture

The pocket tissues were subcultured onto blood agar plates (Oxoid, United Kingdom), chocolate agar plates (Oxoid), and MacConkey agar plates (Oxoid). Agar plates were incubated at 35 °C for 48 hours (the incubation time would be prolonged to 7 days for negative results). If the subculture of the samples showed bacterial growth, bacterial identification was performed by the VITEK 2 COMPACT system (bioMérieux, France). The system detects bacterial growth and metabolic changes in the microwells of thin plastic cards by using a fluorescence-based technology. The final culture results were interpreted by at least 2 microbiologists.

According to bacterial culture results, patients with positive bacterial results and not presenting any sign of CIED-related infection were defined as subclinical infection, and these patients were assigned to the subclinical infection group. Other patients with negative bacterial culture results were assigned to the noninfection group. Risk factors and PADIT scores were compared between these 2 groups.

Follow-Up

After CIED replacement, all of the patients were regularly followed up. Follow-up in these patients was performed at 1 month, 6 months, 1 year, and then once a year. The follow-up information came from outpatient follow-up review, CIED interrogation visit, or telephone follow-up. The end point for follow-up was documented CIED infection and death from cardiovascular or noncardiovascular causes. Rehospitalization, including cardiovascular rehospitalization and noncardiovascular rehospitalization was also recorded. Composite events, including CIED infection, death, and rehospitalization were also analyzed. Dates of follow-up until December 31, 2020 were recorded. Criteria of CIED infection was in accordance with the European Heart Rhythm Association criteria,[7] including superficial incisional infection, pocket infection, systemic infection, and infective endocarditis. Pocket infection was defined as an infection limited to the generator pocket, and clinical symptoms included erythema, warmth, fluctuation, wound dehiscence, decay, tenderness, and suppuration.

Statistical Analysis

Absolute numbers, percentages, mean and standard deviation, median, and upper/lower quartile were computed as appropriate. Comparison between 2 continuous variables was performed using the *t* test or Wilcoxon rank sum test. Comparison of classified variables was performed by the χ^2 test or Fisher exact test.

A refined logistic regression model was developed in 3 steps: (1) Univariable analysis: We chose factors clinically relevant with CIED infection for univariable logistic regression analysis. (2) Multivariable analysis: Factors with a $P<0.20$ in univariable analysis were selected for multivariable logistic regression analysis. (3) Model evaluation: Tolerance and variance inflation factor were used to check for multicollinearity. The Hosmer-Lemeshow test was used to assess the fit of the logistic regression model. Odds ratios (ORs) with 95% CIs and *P* values were obtained.

All *P* values were 2-tailed. A $P<0.05$ was considered statistically significant. The software used for statistical analysis was SPSS version 24.0 (IBM, Armonk, NY).

RESULTS

Microbiological Culture

Fifty patients were detected as positive in the bacterial culture. The prevalence of subclinical CIED infection was 12.0% (50/418). Forty-eight patients (96.0%) were detected with only 1 type of bacterium, and 2 patients (4.0%) were detected with 2 types of bacteria. The most frequently isolated bacteria were coagulase-negative staphylococci (CoNS) (40, 76.9%), followed by *Enterococcus* spp. (4, 7.7%) and *Micrococcus* spp. (4, 7.7%). Gram-negative bacteria accounted for 3.8% (n=2). *Streptococcus* spp. (1, 1.9%) and coagulase-positive staphylococci (1, 1.9%) were rare. The microbiological culture results are shown in Figure 1 and Table S1.

Characteristics of the Patients

Demographic and clinical characteristics of the study subjects are summarized in Table 1. The mean±SD age was 78.1±9.7 years, and 53.1% of the patients were men. Compared with the noninfection group, more patients in the subclinical infection group were taking immunosuppressive agents (6.0% versus 1.1%, *P*=0.04), and more patients received electrode replacement or CIED upgrade (16.0% versus 2.7%, *P*<0.001) and temporary pacing (16.0% versus 6.5%, *P*=0.04). Patients in the subclinical infection group had a higher PADIT score (median 2.0 versus 1.0, *P*=0.002). There were no significant differences in age, sex, body mass index, comorbidities, CIED indication, CIED types, implantation time, prior procedure, perioperative fever, postoperative hematoma, and other medications (anticoagulants and antiplatelet drugs) between the 2 groups (*P*>0.05).

Logistic Regression Analysis of Risk Factors and Risk Stratification

Univariable and multivariable logistic regression analysis were shown in Table 2. The results showed that use of immunosuppressive agents (OR, 6.95 [95% CI, 1.44–33.51]; *P*=0.02) and electrode replacement or CIED upgrade (OR, 6.73[95% CI, 2.23–20.38]; *P*=0.001) were significantly associated with subclinical CIED infection. Meanwhile, compared with the low-risk group, patients in the intermediate/high-risk group had a higher risk of subclinical CIED infection (OR, 3.43 [95% CI, 1.58–7.41]; *P*=0.002). The model evaluation test results were as follows: Hosmer-Lemeshow test indicated a good model fit (*P*=0.83); collinearity diagnostics indicated good model stability (all variance inflation factors <1.2 and tolerance >0.8).

Clinical Follow-Up

Follow-up data were available for all patients. During a median follow-up time of 36.5 months (range, 1–118 months; mean, 44.7 months), 1 patient (2.0%) in the subclinical infection group and 2 patients (0.5%) in the noninfection group developed clinical infection (*P*=0.32). Fourteen patients (28.0%) in the subclinical infection group and 79 patients (21.5%) in the noninfection group died (*P*=0.30). Among them, cardiovascular death accounted for 10.0% (5/50) and 7.6% (28/368), respectively (*P*=0.57). The rate of rehospitalization (54.0% versus 32.1%, *P*=0.002) and cardiovascular rehospitalization (32.0% versus 13.9%, *P*=0.001) in the subclinical infection group was significantly higher than that in the noninfection group. The composite events in the subclinical infection group were also higher than the noninfection group (58.0% versus 41.8%, *P*=0.03) (Figure 2). The clinical characteristics and microbiology of 3 patients with clinical infection are summarized in Table 3. All 3 patients presented with isolated pocket infection without systemic infection and infective endocarditis. In the patient in the subclinical infection group, the bacterium detected from infected pocket tissue was the same as that detected during the prior CIED replacement procedure. However, no microorganisms were identified for both patients in the noninfection group. Two patients (patients 1 and 2) experienced recurrent pocket infection and were subsequently cured with complete removal of the device. Another patient (patient 3) fully recovered after pocket debridement and empiric antibiotic therapy.

DISCUSSION

The use of CIEDs in management of cardiovascular diseases has increased with increasing life expectancy

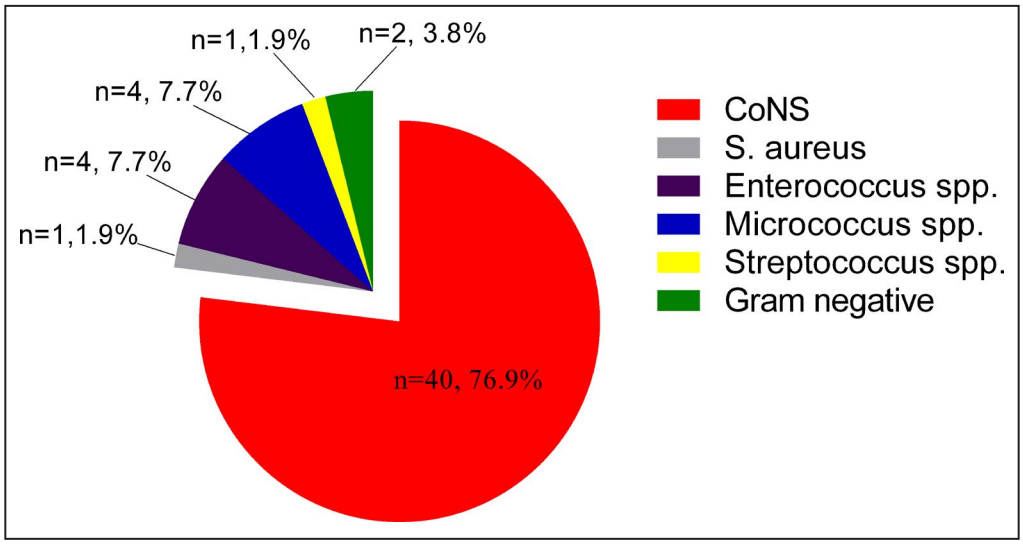

Figure 1. Microbiology of subclinical cardiac implantable electronic device infection (n=52).
CoNS indicates coagulase-negative staphylococci.

Table 1. Baseline Characteristics of 418 Patients

	Total, N=418	Subclinical infection group, n=50	Noninfection group, n=368	*P* value
Age, y	78.1±9.7	76.5±9.5	78.3±9.6	0.22
Men	222 (53.1)	33 (66.0)	189 (51.4)	0.05
BMI, kg/m^2	24.7±3.7	24.9±3.6	24.7±3.7	0.67
Comorbidities				
CKD	120 (28.7)	11 (22.0)	109 (29.6)	0.26
COPD	20 (4.8)	1 (2.0)	19 (5.2)	0.49
Hypertension	303 (72.5)	37 (74.0)	266 (72.3)	0.80
Coronary artery disease	155 (37.1)	18 (36.0)	137 (37.2)	0.87
Atrial fibrillation	169 (40.4)	20 (40.0)	149 (40.5)	0.94
Heart failure	73 (17.5)	12 (24.0)	61 (16.6)	0.20
Diabetes	128 (30.6)	17 (34.0)	111 (30.2)	0.58
Malignancies	31 (7.4)	5 (10.0)	26 (7.1)	0.40
Drugs				
Anticoagulants	34 (8.1)	6 (12.0)	28 (7.6)	0.27
Antiplatelet drugs	197 (47.1)	27 (54.0)	170 (46.2)	0.30
Immunosuppressive agents	7 (1.7)	3 (6.0)	4 (1.1)	0.04
CIED indications				0.20
SSS	252 (60.3)	29 (58.0)	223 (60.6)	
AVB	154 (36.8)	18 (36.0)	136 (37.0)	
HFrEF	8 (1.9)	3 (6.0)	5 (1.4)	
Ventricular tachycardia	4 (1.0)	0 (0)	4 (1.1)	
CIED types				0.18
Single-chamber PM	70 (16.7)	11 (22.0)	69 (18.8)	
Dual-chamber PM	321 (76.8)	35 (70.0)	286 (77.7)	
ICD	8 (1.9)	1 (2.0)	7 (1.9)	
CRT	9 (2.2)	3 (6.0)	6 (1.6)	
Implantation time, mo	125.2±58.3	127.8±58.2	124.8±58.3	0.74
No. of prior procedures	1.0 [1.0–1.0]	1.0 [1.0–2.0]	1.0 [1.0–1.0]	0.45
Electrode replacement or CIED upgrade	18 (4.3)	8 (16.0)	10 (2.7)	<0.001
Temporary pacing	31 (7.4)	8 (16.0)	24 (6.5)	0.04
Perioperative fever	18 (4.3)	4 (8.0)	14 (3.8)	0.25
Postoperative hematoma	9 (2.2)	2 (4.0)	7 (1.9)	0.29
PADIT score	1.0 [1.0–4.0]	2.0 [1.0–4.0]	1.0 [1.0–4.0]	0.002

Data are expressed as n (%), mean±SD, or median [interquartile range]. AVB indicates atrioventricular block; BMI, body mass index; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; PADIT, Prevention of Arrhythmia Device Infection Trial; PM, pacemaker; and SSS, sick sinus syndrome.

and the expansion of CIED indications. One of the most concerning and most serious complications of CIED therapy is device-related infection, which is associated with increased hospitalizations, reduced survival, and increased health care costs.[8] In previous studies, the prevalence of CIED infection ranged from 0.5% to 4.8%,[9,10] and rates varied for different studies and different CIED types.[11]

Recent research revealed that subclinical CIED infection (also called asymptomatic bacterial colonization) on CIED might be ubiquitous and is associated with symptomatic CIED infection.[2,3] To effectively control CIED infection, it is necessary to find out the risk factors for subclinical infection, to set up a useful score for stratifying high-risk patients, and to provide useful prevention strategies. Unfortunately, to date, this condition has been underrecognized and underdiagnosed because of the difficulty of obtaining pocket tissues. Therefore, previous studies have chosen patients receiving CIED replacement or upgrade as research subjects.[2–4] To the best of our knowledge, this is the largest sample size and longest follow-up duration study on the topic of subclinical CIED infection to date.

Table 2. Univariable and Multivariable Logistic Analysis of Risk Factors Associated With Subclinical CIED Infection

Risk factors	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Heart failure	1.59 (0.79–3.22)	0.20	1.03 (0.45–2.38)	0.94
COPD	0.38 (0.05–2.86)	0.34		
CKD	0.67 (0.33–1.36)	0.27		
Diabetes	1.19 (0.64–2.23)	0.58		
Malignancy	1.46 (0.53–4.00)	0.46		
Antiplatelet drugs	1.37 (0.76–2.47)	0.30		
Anticoagulants	1.66 (0.65–4.22)	0.29		
Immunosuppressive agents	5.81 (1.26–26.76)	0.02	6.95 (1.44–33.51)	0.02
CIED types*	2.38 (0.74–7.59)	0.15	1.01 (0.23–4.41)	0.99
No. of prior procedures†	1.32 (0.68–2.55)	0.42		
Electrode replacement or CIED upgrade	6.82 (2.55–18.23)	<0.001	6.73 (2.23–20.38)	0.001
Temporary pacing	2.33 (0.95–5.74)	0.07	1.19 (0.40–3.56)	0.75
Perioperative fever	2.20 (0.69–6.96)	0.18	2.29 (0.69–7.67)	0.18
Postoperative hematoma	2.15 (0.43–10.64)	0.35		
PADIT score‡	3.43 (1.58–7.41)	0.002		

CIED indicates cardiac implantable electronic devices; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; and PADIT, Prevention of Arrhythmia Device Infection Trial.

*CIED type was categorized as single-/double-chamber pacemaker and implantable cardioverter-defibrillator/cardiac resynchronization therapy.

†Number of prior procedures was categorized as 1 time and ≥2 times.

‡PADIT score was categorized as low risk and intermediate/high risk.

In the present study, the prevalence of subclinical infection in 418 patients undergoing CIED replacement or upgrade was 12.0% detected by traditional culture of CIED pocket tissues. In a previous study, in 115 episodes without clinical evidence of infection, 44 (38%) grew bacteria in the sonication fluid of the generator and/or leads.[3] Another study indicated a third of implantable cardioverter-defibrillator patients undergoing generator replacement or lead revision have an asymptomatic bacterial colonization of generator pockets.[5] Moreover, by using single strand conformation polymorphism analysis, patients carrying bacteria on their pacemakers or implantable cardioverter-defibrillators asymptomatically could be as high as 47.2%.[12]

Bacterial culture is a common and affordable method for detecting pathogens, and it has been used as a routine assay in infectious diseases for a long time. However, culture-based techniques have several limitations, which may fail to identify unculturable, fastidious, and metabolically active but unculturable bacteria.[13] In addition, culture-based methods take a long time on a routine basis (usually 2–14 days for different microorganisms) to detect the pathogen. Sonication of explanted prosthetic material has shown to be more sensitive than conventional microbiological culture in the diagnosis of foreign body infection, including prosthesis joints, breast implants, and CIEDs.[3,14,15] Recently, novel detecting methods, including 16S rRNA gene sequencing,[2] mass spectrometry,[16] and metagenomic next-generation sequencing,[17] have become more and more popular, with higher sensitivity than bacterial culture. These technologies are anticipated to be clinically applied in the near future.

The most common pathogenic microorganisms in CIED infection were gram-positive bacteria, especially CoNS and *Staphylococcus aureus*.[18,19] In our study, most of the bacteria detected were normal nonpathogenic skin commensal flora,[20] mainly CoNS, which is consistent with previous studies.[3,4] However, these bacteria can also be pathogens in skin and soft tissue infections,[21] such as a pacemaker pocket infection. CIED infections occur via different mechanisms. The most common is exogenous infection. The patient's own skin flora can be introduced into the wound at the time of implantation or replacement. Contamination may also occur via the air, the devices, or hands of the operators. After the procedure, bacteria grow on the device and form a thick, multilayered biofilm to resist antimicrobial agents and the human immune system.[22] CoNS, especially *Staphylococcus epidermidis*, are the most prevalent pathogens in nosocomial infection,[23] and biofilm formation is the main path by which *S epidermidis* colonizes and infects medical devices.[24] In the present study, 1 patient in the subclinical infection group developed pocket infection with the same organism detected during CIED revision. This observation underlines the hypothesis that primarily

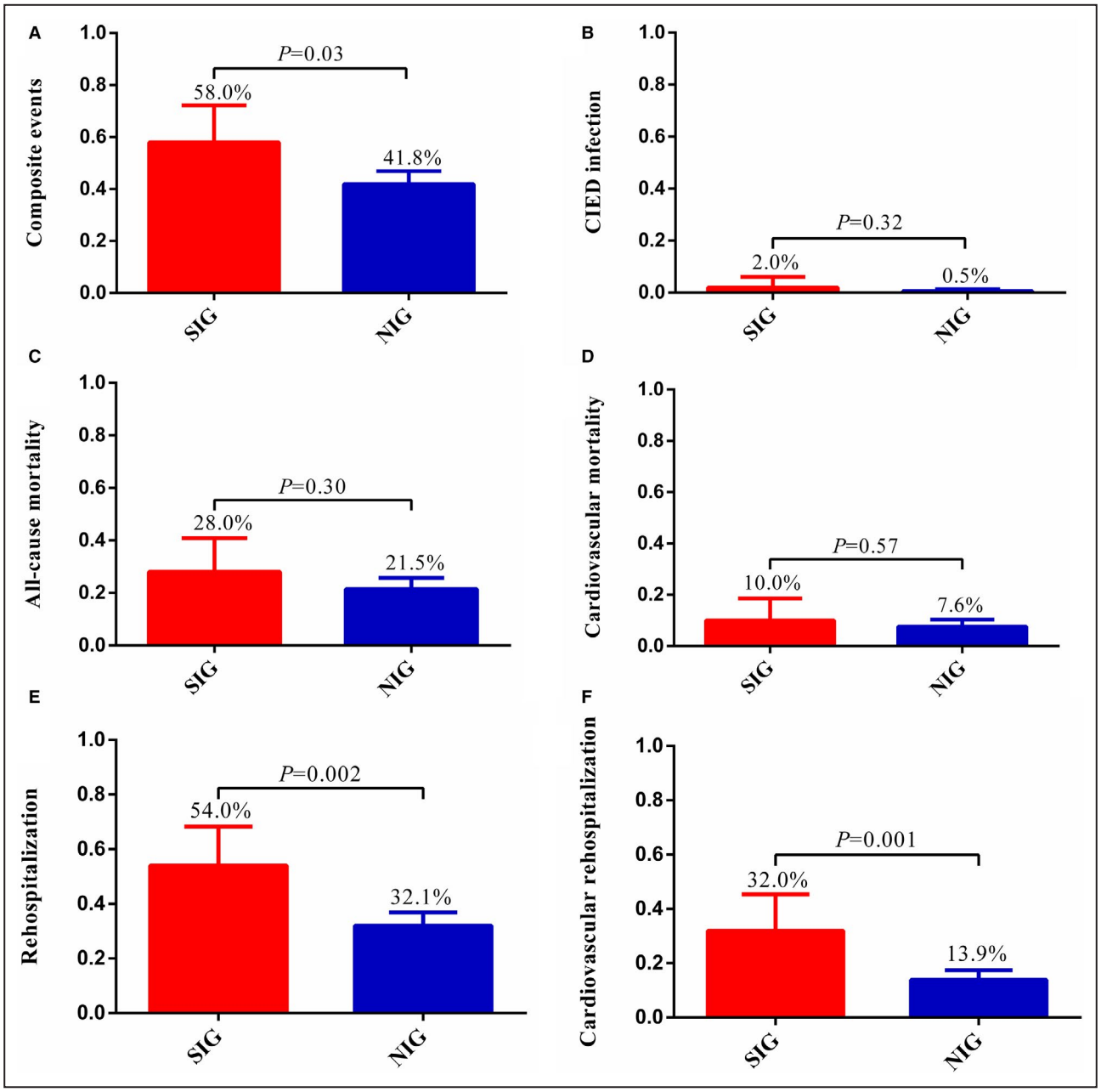

Figure 2. Follow-up of clinical events between the subclinical infection group (SIG) and noninfection group (NIG).
A, The rate of composite events. **B**, The rate of cardiac implantable electronic device (CIED) infection. **C**, The rate of all-cause mortality. **D**, The rate of cardiovascular mortality. **E**, The rate of rehospitalization. **F**, The rate of cardiovascular rehospitalization.

asymptomatic bacterial colonization can cause device infection after revision.

More than 60 studies have examined risk factors for device infection.[25] The risk factors for CIED infection also varied from study to study, including patient-related factors, procedure-related factors, and device-related factors.[7] However, there are few studies focused on risk factors of subclinical CIED infection. In the study by Chu et al, the history of bacterial infection, use of antibiotics, application of antiplatelet drugs, replacement frequency, and renal insufficiency were independent risk factors for asymptomatic bacterial colonization.[4] We found out that use of immunosuppressive agents and electrode replacement or CIED upgrade were significantly associated with subclinical CIED infection. First, long-term application of immunosuppressive agents for autoimmune diseases may cause overimmunodepression and increase the risk of opportunistic infections. Second, electrode replacement or CIED upgrade requires longer procedure time and additional electrode implantation, which is associated with higher risk of subclinical infection.

Table 3. Characteristics of 3 Patients With CIED Infection

	Patient 1	Patient 2	Patient 3
Age, y	83	72	63
Sex	Male	Male	Male
CIED types	Dual-chamber PM	CRT	Dual-chamber PM
No. of prior procedures	2	3	2
Time from last procedure, mo	41	4	49
PADIT score	4	9	5
Clinical presentation	Pocket infection	Pocket infection	Pocket infection
Culture result during CIED revision	*Staphylococcus hominis*	Negative	Negative
Culture result from infected pocket	*Staphylococcus hominis*	Negative	Negative

CIED indicates cardiac implantable electronic device; CRT, cardiac resynchronization therapy; PADIT, Prevention of Arrhythmia Device Infection Trial; and PM, pacemaker.

Several scores have been provided to assess the risk of CIED infection.[26,27] However, they are not widely used. The PADIT score is regarded as the first prospective, internally validated CIED infection risk score.[6] In our study, the results showed that patients in the subclinical group had a higher PADIT score than the noninfection group. Moreover, compared with the low-risk group, patients in the intermediate/high-risk group had a higher risk of subclinical CIED infection. Therefore, in addition to CIED infection, the PADIT score may also become a routine clinical tool for risk stratifying of subclinical CIED infection.

In the present study, the risk of subsequent clinical infection was relatively low and subclinical infection did not predict infection. The reasons for the results may be related to the short follow-up time and low sensitivity of the bacterial culture. The preoperative antibiotic dose may have impacted the ability to culture the tissues, thus increasing the false-negative rate. There were no data available about the impact of subclinical CIED infection on other clinical outcomes. We found that subclinical infection was associated with increased risks of rehospitalization, cardiovascular rehospitalization, and composite events (including CIED infection, death, and rehospitalization), which are a major economic burden on the health care system and have a negative influence on patients' quality of life. Subclinical CIED infection, as a chronic infection state, may aggravate other coexisting diseases, which is associated with higher rehospitalization rate.

A series of measures are recommended for preventing CIED infection in guidelines,[7] such as preprocedure skin preparation, preprocedure antibiotic therapy, antiseptic preparation for a sufficient time, and postprocedure wound care. However, use of postoperative antibiotic therapy was not recommended. In the PADIT, incremental antibiotic strategy did not reduce device infection rates compared with conventional antibiotic strategy, even in high-risk patients.[28] However, in the WRAP-IT (Worldwide Randomized Antibiotic Envelope Infection Prevention Trial), a 40% relative risk reduction was found using an antibacterial envelope.[29] This could also be an option for patients at higher risk when undergoing CIED replacement or upgrade. Prevention strategies, such as long-term antibiotics, were not routinely conducted for subclinical infection patients in our center. Whether prevention strategies are beneficial remains unknown, and this question has yet to be answered by prospective randomized controlled trials.

Study Limitations

There are several limitations in this study that warrant discussion. First, this is a clinical, observational study from a single center, and the sample size is relatively small, which may limit the generalizability of the findings. The results need to be confirmed by multicenter studies. Second, although bacterial cultures are widely used worldwide, the possibility of false-negative results must be considered, which may be affected by sampling error, antibiotic therapeutic regimen, culture method, and interpretation of the results. As has been mentioned above, novel detecting methods with higher sensitivity are anticipated to be applied in this field. Third, the follow-up time period is different among patients according to the time of enrollment. In patients with a short follow-up time, missed diagnosis of late CIED infection (>1 year since the last procedure) should be considered. Moreover, the time of outcome events could not be exactly collected, especially for those that happened at home or in other hospitals and for some elderly patients and their families. Time information of outcome events was not considered for analysis. Follow-up will be continued in future work.

CONCLUSIONS

Subclinical infection was a common phenomenon in patients with CIED detected by traditional bacterial culture. CoNS were the most common microorganisms. Use of immunosuppressive agents and electrode replacement

or CIED upgrade were significantly associated with subclinical CIED infection. The PADIT score had a significant value for screening patients at high risk of subclinical CIED infection. Subclinical CIED infection was associated with increased risks of composite events, rehospitalization, and cardiovascular rehospitalization. In the future, more attention should be paid to subclinical CIED infection, and intensive prevention strategies should be considered for high-risk patients.

ARTICLE INFORMATION

Received April 29, 2021; accepted October 8, 2021.

Affiliations

Department of Cardiology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine (G.L., T.Z., M.D., J.L., W.C., J.T., H.S., H.C., J.C., Y.L., S.W., Z.W., X.J., X.G., L.S., Y.Q., J.Y.) and Graduate School of Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China (G.L., T.Z., J.Y.).

Acknowledgments

The authors thank Drs Y. Hu and X. Ai (Department of Laboratory Medicine, Beijing Hospital) for their support in the bacterial culture, and Dr P. Zeng (Department of Epidemiology, Beijing Hospital) for her help with the statistical analysis. We have obtained written permission from all those named in the acknowledgments.

Sources of Funding

This study was supported by Beijing Municipal Science & Technology Commission Program (No. Z171100001017203 and No. D181100000218005).

Disclosures

None.

Supplementary Material

Table S1

REFERENCES

1. Olsen T, Jørgensen OD, Nielsen JC, Thøgersen AM, Philbert BT, Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982–2018). *Eur Heart J*. 2019;40:1862–1869. doi: 10.1093/eurheartj/ehz316
2. Zou T, Zhang Z, Zou C, Chen K, Dai Y, Tong J, Yu X, Liu J, Chen D, Xu H, et al. Subclinical infections of cardiac implantable electronic devices: insights into the host-bacteria dialog from blood and pocket tissue with pyrosequencing. *Int J Cardiol*. 2014;174:545–549. doi: 10.1016/j.ijcard.2014.04.143
3. Rohacek M, Weisser M, Kobza R, Schoenenberger AW, Pfyffer GE, Frei R, Erne P, Trampuz A. Bacterial colonization and infection of electrophysiological cardiac devices detected with sonication and swab culture. *Circulation*. 2010;121:1691–1697. doi: 10.1161/CIRCULATIONAHA.109.906461
4. Chu XM, Li B, An Y, Li XB, Guo JH. Genetic identification and risk factor analysis of asymptomatic bacterial colonization on cardiovascular implantable electronic devices. *Biomed Res Int*. 2014;2014:725163. doi: 10.1155/2014/725163
5. Kleemann T, Becker T, Strauss M, Dyck N, Weisse U, Saggau W, Burkhardt U, Seidl K. Prevalence of bacterial colonization of generator pockets in implantable cardioverter defibrillator patients without signs of infection undergoing generator replacement or lead revision. *Europace*. 2010;12:58–63. doi: 10.1093/europace/eup334
6. Birnie DH, Wang J, Alings M, Philippon F, Parkash R, Manlucu J, Angaran P, Rinne C, Coutu B, Low RA, et al. Risk factors for infections involving cardiac implanted electronic devices. *J Am Coll Cardiol*. 2019;74:2845–2854. doi: 10.1016/j.jacc.2019.09.060
7. Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG, Poole J, Boriani G, Costa R, Deharo J-C, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2020;41:2012–2032. doi: 10.1093/eurheartj/ehaa010
8. Gitenay E, Molin F, Blais S, Tremblay V, Gervais P, Plourde B, Jacques F, Steinberg C, Sarrazin J-F, Charbonneau É, et al. Cardiac implantable electronic device infection: detailed analysis of cost implications. *Can J Cardiol*. 2018;34:1026–1032. doi: 10.1016/j.cjca.2018.05.001
9. Clémenty N, Carion PL, Léotoing L, Lamarsalle L, Wilquin-Bequet F, Brown B, Verhees KJP, Fernandes J, Deharo JC. Infections and associated costs following cardiovascular implantable electronic device implantations: a nationwide cohort study. *Europace*. 2018;20:1974–1980. doi: 10.1093/europace/eux387
10. Unsworth JD, Zaidi A, Hargreaves MR. Increased late complex device infections are determined by cardiac resynchronization therapy-defibrillator infection. *Europace*. 2015;17:1708–1711. doi: 10.1093/europace/euv074
11. Rattanawong P, Kewcharoen J, Mekraksakit P, Mekritthikrai R, Prasitlumkum N, Vutthikraivit W, Putthapiban P, Dworkin J. Device infections in implantable cardioverter defibrillators versus permanent pacemakers: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol*. 2019;30:1053–1065. doi: 10.1111/jce.13932
12. Pichlmaier M, Marwitz V, Kühn C, Niehaus M, Klein G, Bara C, Haverich A, Abraham WR. High prevalence of asymptomatic bacterial colonization of rhythm management devices. *Europace*. 2008;10:1067–1072. doi: 10.1093/europace/eun191
13. Dickson RP, Erb-Downward JR, Prescott HC, Martinez FJ, Curtis JL, Lama VN, Huffnagle GB. Analysis of culture-dependent versus culture-independent techniques for identification of bacteria in clinically obtained bronchoalveolar lavage fluid. *J Clin Microbiol*. 2014;52:3605–3613. doi: 10.1128/JCM.01028-14
14. Rothenberg AC, Wilson AE, Hayes JP, O'Malley MJ, Klatt BA. Sonication of arthroplasty implants improves accuracy of periprosthetic joint infection cultures. *Clin Orthop Relat Res*. 2017;475:1827–1836. doi: 10.1007/s11999-017-5315-8
15. Rieger UM, Pierer G, Lüscher NJ, Trampuz A. Sonication of removed breast implants for improved detection of subclinical infection. *Aesthetic Plast Surg*. 2009;33:404–408. doi: 10.1007/s00266-009-9333-0
16. Oviaño M, Rodríguez-Sánchez B. MALDI-TOF mass spectrometry in the 21st century clinical microbiology laboratory. *Enferm Infecc Microbiol Clin*. 2021;39:192–200. doi: 10.1016/j.eimc.2020.02.027
17. Watts GS, Hurwitz BL. Metagenomic next-generation sequencing in clinical microbiology. *Clin Microbiol Newsl*. 2020;42:53–59. doi: 10.1016/j.clinmicnews.2020.03.004
18. Hussein AA, Baghdy Y, Wazni OM, Brunner MP, Kabbach G, Shao M, Gordon S, Saliba WI, Wilkoff BL, Tarakji KG. Microbiology of cardiac implantable electronic device infections. *JACC Clin Electrophysiol*. 2016;2:498–505. doi: 10.1016/j.jacep.2016.01.019
19. Bongiorni MG, Tascini C, Tagliaferri E, Di Cori A, Soldati E, Leonildi A, Zucchelli G, Ciullo I, Menichetti F. Microbiology of cardiac implantable electronic device infections. *Europace*. 2012;14:1334–1339. doi: 10.1093/europace/eus044
20. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. *Nat Rev Microbiol*. 2018;16:143–155. doi: 10.1038/nrmicro.2017.157
21. Natsis NE, Cohen PR. Coagulase-negative staphylococcus skin and soft tissue infections. *Am J Clin Dermatol*. 2018;19:671–677. doi: 10.1007/s40257-018-0362-9
22. Nagpal A, Baddour LM, Sohail MR. Microbiology and pathogenesis of cardiovascular implantable electronic device infections. *Circ Arrhythm Electrophysiol*. 2012;5:433–441. doi: 10.1161/CIRCEP.111.962753
23. Argemi X, Hansmann Y, Prola K, Prévost G. Coagulase-negative staphylococci pathogenomics. *Int J Mol Sci*. 2019;20:1215. doi: 10.3390/ijms20051215
24. Le KY, Park MD, Otto M. Immune evasion mechanisms of staphylococcus epidermidis biofilm infection. *Front Microbiol*. 2018;9:359. doi: 10.3389/fmicb.2018.00359
25. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace*. 2015;17:767–777. doi: 10.1093/europace/euv053

26. Mittal S, Shaw RE, Michel K, Palekar R, Arshad A, Musat D, Preminger M, Sichrovsky T, Steinberg JS. Cardiac implantable electronic device infections: incidence, risk factors, and the effect of the AigisRx antibacterial envelope. *Heart Rhythm*. 2014;11:595–601. doi: 10.1016/j.hrthm.2013.12.013
27. Shariff N, Eby E, Adelstein E, Jain S, Shalaby A, Saba S, Wang NC, Schwartzman D. Health and economic outcomes associated with use of an antimicrobial envelope as a standard of care for cardiac implantable electronic device implantation. *J Cardiovasc Electrophysiol*. 2015;26:783–789. doi: 10.1111/jce.12684
28. Krahn AD, Longtin Y, Philippon F, Birnie DH, Manlucu J, Angaran P, Rinne C, Coutu B, Low RA, Essebag V, et al. Prevention of arrhythmia device infection trial: the PADIT trial. *J Am Coll Cardiol*. 2018;72:3098–3109. doi: 10.1016/j.jacc.2018.09.068
29. Tarakji KG, Mittal S, Kennergren C, Corey R, Poole JE, Schloss E, Gallastegui J, Pickett RA, Evonich R, Philippon F, et al. WRAP-IT Investigators. Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med*. 2019;380:1895–1905. doi: 10.1056/NEJMoa1901111

Supplemental Material

Table S1. Microbiological culture results.

Bacteria	Number (%)
Coagulase-negative staphylococci (CoNS)	40 (76.9)
Staphylococcus epidermidis	14 (26.9)
CoNS(unspecified)	9 (17.3)
Staphylococcus hominis	5 (9.6)
Staphylococcus haemolyticus	4 (7.7)
Staphylococcus capitis	3 (5.8)
Staphylococcus warneri	3 (5.8)
Staphylococcus saprophyticus	1 (1.9)
Staphylococcus xylosus	1(1.9)
Coagulase-positive staphylococci (CoPS)	1(1.9)
Staphylococcus aureus	1(1.9)
Enterococcus spp.	4 (7.7)
Enterococcus faecium	2(3.8)
Enterococcus faecalis	1(1.9)
Enterococcus hirae	1(1.9)
Micrococcus spp.	4 (7.7)
Micrococcus kristinae	2(3.8)
Micrococcus luteus	1(1.9)
Micrococcus spp. (unspecified)	1(1.9)
Streptococcus spp.	1 (1.9)

Gemella morbillorum	1 (1.9)
Gram-negative bacteria	2 (3.8)
Pseudomonas stutzeri	1 (1.9)
Klebsiella pneumonia	1 (1.9)
Total	52 (100)