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Impact of Chronic Kidney Disease on Short-Term Cardiac Implantable Electronic Device Related Infection

A Nationwide Population-Based Cohort Study

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Abstract: Chronic kidney disease (CKD) increased the incident cardiac implantable electronic device (CIED) infection, but risk factors of CIED infection in CKD patients remain unclear.

Patients who received new CIED implantation between January 1, 1997 and December 31, 2011 were selected from the Taiwan National Health Insurance Database and were divided into 3 groups: patients with normal renal function, CKD patients without dialysis, and CKD patient with dialysis. Two outcomes, CIED infection during index hospitalization and within 1 year after discharge, were evaluated.

This study included 38,354 patients, 35,060 patients in normal renal function group, 1927 patients in CKD without dialysis group, and 1367 patients in CKD with dialysis group. CKD patients without dialysis (adjusted odds ratio [aOR], 2.14, 95% confidence interval [CI], 1.32-3.46) and CKD patients with dialysis (aOR, 3.78, 95% CI, 2.37-6.02) increased incident CIED infection during index hospitalization compared to patients with normal renal function. Use of steroid (aOR: 2.74, 95% CI, 1.08-6.98) increased the risk of CIED infection in CKD patients without dialysis while chronic obstructive pulmonary disease (COPD) (aOR: 2.76, 95% CI, 1.06-7.16) increased the risk of CIED infection in CKD patient with dialysis during index hospitalization.

CKD is a risk of CIED infection during index hospitalization. Use of steroid and COPD are important risks factors for CIED infection in CKD patients.

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Abbreviations: CIED = cardiac implantable electronic device, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CRT = cardiac resynchronized therapy, ICD = implantable cardioverter-defibrillator, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Cardiac implantable electronic devices (CIEDs) are important therapeutic tools in the management of cardiac rhythm disorders and heart failure, which include pacemaker, implantable cardioverter-defibrillator (ICD) and cardiac resynchronized therapy (CRT).¹ As the population with CIEDs continues to increase annually,² the CIED-related complication evokes more and more attention from physicians. The CIED-related complications not only result in prolonged hospitalization and increased costs, but also incur worse outcomes and mortality.³ Hence, several studies have made efforts to discover the factors leading to CIED-related complications by evaluating comorbidities, procedure details, medications, and so on. Of note, the risk factors of CIED-related infection have been most frequently studied among the device-related complications, because the incidence CIED-related infection and expenses of management are highest among the CIED-related complications.³ In the literature, several risk factors of CIED-related infection were reported, which included end-stage renal disease, diabetes mellitus, temporary pacing before implantation, corticosteroid use and physician experience in CIED implantation,⁴⁻⁸ but the conclusions have been inconsistent. Baddour et al⁹ pointed out that most of such studies had a common limitation of relatively small numbers of CIED infection patients, and individual single-center study.

The population with chronic kidney disease (CKD) and even, end-stage renal disease continues to grow because patients with major risks of CKD, such as diabetes mellitus and hypertension, increased annually.^{10,11} In addition, CKD becomes a more and more important issue in the 21st century not only its increasing prevalence but also contributing comorbidities and mortality, especially in patients with cardiovascular diseases¹² and CIED implantation.¹³ In terms of CIED infection, CKD has been reported to be an important risk for CIED infection in several studies.^{4,14,15} However, the number of CKD or end-stage renal disease patients in those studies was too small to evaluate the risk factors of CIED infection in the CKD population.

In order to fill this gap of knowledge in the literature, we conducted this study using a nationwide database to investigate the incidence and potential risk factors of CIED infection in CKD patients.

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METHODS

Data Source

We conducted a nationwide population-based cohort study using data from the Taiwan National Health Insurance Research Database (NHIRD) (<http://nhird.nhri.org.tw/en/index.htm>). The NHIRD comprises healthcare data of 99.9% of the Taiwanese population, which included gender, birth date, use of medications, managements, and diagnosis based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; www.icd9-data.com/2007). Previous studies have described it in detail and validated the accuracy of the NHIRD diagnostic data.¹⁶ The insurance covers all the expenses of CIED-related procedures with appropriate indication according to the contemporary guidelines, including new implantation, replacement, revision, and removal. All CIED procedures performed between January 1, 1997 and December 31, 2011 were enrolled in this study. The CIEDs indicated pacemakers, ICD and CRT, and CIED procedures included new implantation, replacement due to any cause, revisions, or removal procedures. We used NHIRD data set for this study and obtained ethical approval from the Institutional Review Board of Chang Gung Memorial Hospital (104-5136B).

Study Designs

All patients with new CIED implantation during 14 years observation period were selected while those received only generator exchange without new implant procedure in this period were excluded. Patients were also excluded if below 20 years old, having unclassified type of lead or having CIED implantation with epicardial leads. Finally, the study group was divided into 3 groups: patients with normal renal function (normal renal function group), CKD patients without dialysis (CKD without dialysis group), and CKD patients under dialysis (CKD with dialysis group) (Figure 1). Two outcomes were specifically evaluated: CIED infection (ICD-9-CM: 99660, 99661, 99662) during index hospitalization and CIED infection after discharge but within 1 year. While evaluating patients having CIED infection within 1 year after discharge, those patients having CIED infection during index hospitalization were excluded. The study cohort was followed up until the time at any replacement procedures due to any cause, including device-related infection, death, or December 31, 2011 if the patient could not follow-up until 1 year. All admissions, including index hospitalization for new CIED implantation and after CIED procedures, were evaluated to specifically address any CIED infection. The CIED infection was defined as an infection that occurred during admission for CIED-related procedures,

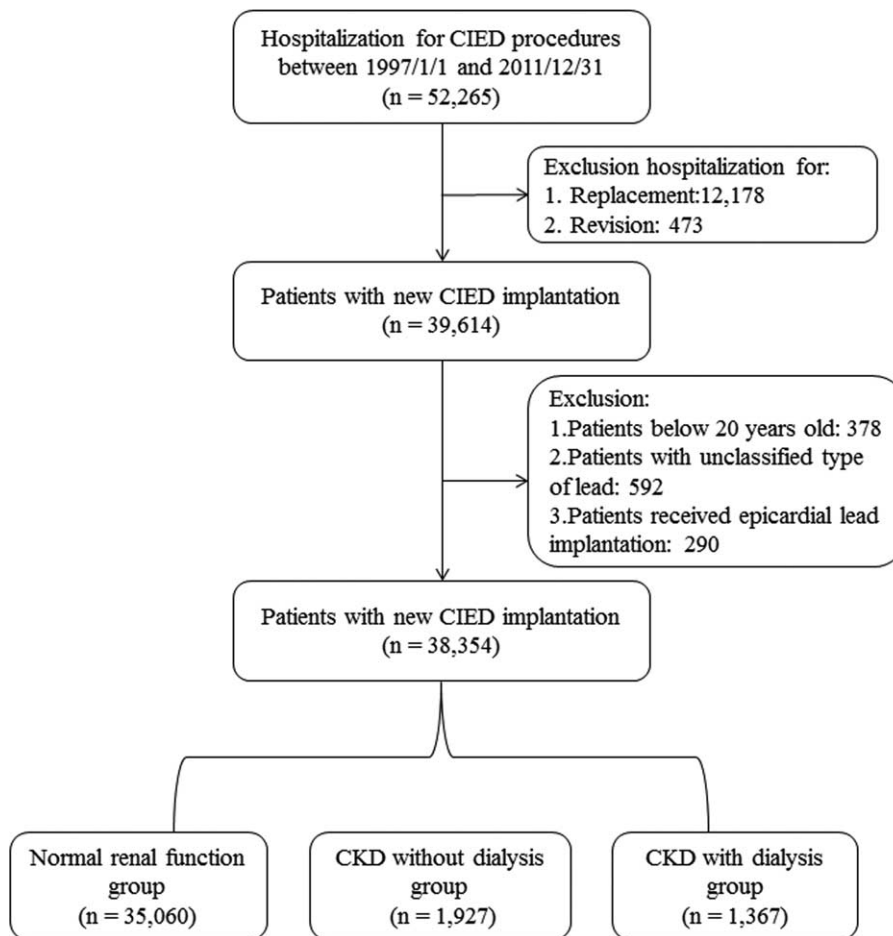


FIGURE 1. Flow chart of patient selection.

which included implantation, replacement, revision, and removal, and that required continuous intravenous antibiotics or revision.

Definition

All comorbidities were defined according to ICD-9-CM diagnosis code recorded in admission (Supplemental Table 1, <http://links.lww.com/MD/A645>). Patients were defined as having CKD based on ICD-9-CM diagnosis code (ICD-9-CM: 585), which was validated by previous study, and it had high specificity and positive predictive value when the diagnosis of \geq stage 3 of CKD was used based on ICD-9-CM.¹⁷ CKD required dialysis were identified from registrations with an end-stage renal disease catastrophic illness certificate that specifically defined dialysis patients to have long-term maintain dialysis, 24-hour urine creatinine clearance rate less than 5 ml/minute and contract kidney noted by renal echography. Therefore, patients with dialysis were defined when they were included in the Registry for Catastrophic Illness database of dialysis, which encompassed almost 100% of all CKD patients who received renal replacement therapy from 1995 to 2011 in Taiwan. Finally, those patients who did not have diagnosis of CKD in admission and were not included in the registry for catastrophic illness database of dialysis were defined as the control group.

Risk Factor Assessment

The analyzed risk factor parameters were separated into 3 components, including patient characteristics, devices, and medications. Patient factors included gender, age, and comorbidities (Table 1). Device factors referred to types of CIED and characteristics of leads. Medication factors referred to the use of antibiotics, steroid, antiplatelet, and warfarin.

Statistics

The clinical characteristics (ie, patient characteristics, devices, and medications) among the study groups were compared using 1-way analysis of variance for continuous variable or Chi-square test for categorical variable which both were followed by Bonferroni post hoc multiple comparisons. Associated factors (including study groups) related to CIED infection during the index hospitalization were identified by bivariate and multivariable logistic regression analyses. The 1-year CIED infection event-free survival rate was estimated using Kaplan–Meier method and its associated factors (including study groups) were investigated using bivariate and multivariable Cox regression analyses. The associated factors included patient's characteristics, such as gender, age groups, diabetes mellitus, liver cirrhosis, chronic obstructive pulmonary disease (COPD), CKD, heart failure, hypertension, characteristics of leads, device type, and the use of antibiotics, steroid, and combination of warfarin and antiplatelet. Data analyses were conducted by using SPSS 22 (IBM SPSS, Inc., Chicago, IL).

RESULTS

From January 1, 1997 to December 31, 2011, 38,354 eligible patients received new CIED implantation were enrolled in this study. The study population was divided into 3 groups according to renal function: 35,060 patients comprised normal renal function group, 1927 patients in CKD without dialysis group and 1367 patients in CKD with dialysis group. The baseline characteristics are listed in Table 1. The prevalence

of comorbidities was significantly higher in CKD patients compared to normal renal function group.

Impact of CKD on CIED Infection

There were 178 patients developed CIED infection during the index hospitalization, composed of 131 patients in the normal renal function group, 22 patients in the CKD without dialysis group and 25 patients in the CKD with dialysis group. After multiple adjustment for potential confounding factors, CKD patients without dialysis (adjusted odds ratio [OR], 2.14, 95% confidence interval [CI], 1.32–3.46, $P = 0.002$) and CKD patients with dialysis (adjusted OR, 3.78, 95% CI, 2.37–6.02, $P < 0.001$) had a significant higher risk for CIED infection during the index admission when compared to patients in normal renal function group (Table 2; Figure 2). Furthermore, CKD patients with dialysis had a significant higher risk for CIED infection during the index admission when compared to CKD patients without dialysis (adjusted OR, 1.92, 95% CI, 1.07–3.45, $P = 0.029$) (Figure 2).

Other than CKD, preoperative temporary pacemaker placement (OR: 3.05, 95% CI, 2.24–4.17, $P < 0.001$), and use of steroid (OR: 2.07, 95% CI, 1.44–2.97, $P < 0.001$) significantly increased the risk while use of first generation of cephalosporin (OR: 0.51, 95% CI, 0.33–0.78, $P = 0.002$) and antiplatelet (OR: 0.56, 95% CI, 0.40–0.78, $P = 0.001$) significantly reduced the risk of CIED infection during the index hospitalization in all patients after multivariable adjustment (Table 2).

Risk Factors of CIED Related Infection During Index Hospitalization in CKD Population

Among CKD patients without dialysis (Table 3), use of steroid (OR: 2.74, 95% CI, 1.08–6.98, $P = 0.035$) was an independent risk factor of CIED infection during the index hospitalization after multivariable adjustment. However, preoperative temporary pacemaker placement, use of first generation of cephalosporin and use of antiplatelet were not risk factors of CIED infection during the index hospitalization after multivariable adjustment in CKD patients without dialysis.

Among CKD patients with dialysis (Table 4), COPD (OR: 2.76, 95% CI, 1.06–7.16, $P = 0.037$) was an independent risk factor of CIED infection during the index hospitalization after multivariable adjustment while use of steroid (OR: 2.32, 95% CI, 0.91–5.91, $P = 0.077$) had a trend as a risk factor for CIED infection during the index hospitalization. However, preoperative temporary pacemaker placement, use of first generation of cephalosporin and use of antiplatelet were not risk factors of CIED infection during the index hospitalization after multivariable adjustment in CKD patients with dialysis.

Risk Factors of CIED Related Infection Within 1 Year After Discharge

In terms of CIED infection within 1 year after discharge, there were 162 patients experienced CIED related infection after discharge, composed of 150 patients in normal renal function group, 9 patients in CKD without dialysis group and 3 patients in CKD with dialysis group. Male gender, preoperative temporary pacemaker placement and passive fixation lead were independent risk factors of CIED infection within 1 year after discharge after multivariable adjustment in total population (Supplemental Table S2, <http://links.lww.com/MD/A645>). However, CKD patients with or without dialysis did not have significant risks contributing to CIED infection within

TABLE 1. Baseline Characteristics of Study Patients at CIED Implant (n = 38,354)

Variables	Normal Renal Function	Chronic Kidney Disease		P-Value
		Without Dialysis	With Dialysis	
Patient numbers	35,060	1927	1367	—
Gender--n (%)				<0.001
Male	18,159 (51.8)	1042 (54.1)	585 (42.8)*†	
Female	16,901 (48.2)	885 (45.9)	782 (57.2)	
Age (years)	73.5 ± 11.5	76.3 ± 9.9	70.8 ± 9.7	<0.001
Age group--n (%)				<0.001
20~49 years	1533 (4.4)	29 (1.5)*	29 (2.1)*	
50~59 years	2551 (7.3)	99 (5.1)*	169 (12.4)*†	
60~69 years	6550 (18.7)	291 (15.1)*	386 (28.2)*†	
70~79 years	13,860 (39.5)	778 (40.4)	545 (39.9)	
>80 years	10,566 (30.1)	730 (37.9)*	238 (17.4)*†	
Underlying disease--n (%)				
Diabetes	9329 (26.6)	1007 (52.3)*	869 (63.6)*†	<0.001
Hypertension	22,327 (63.7)	1479 (76.8)*	1204 (88.1)*†	<0.001
COPD	3020 (8.6)	319 (16.6)*	149 (10.9)*†	<0.001
Heart failure	5116 (14.6)	558 (29.0)*	195 (14.3)†	<0.001
Liver cirrhosis	866 (2.5)	110 (5.7)*	100 (7.3)*	<0.001
Warfarin or antiplatelet--n (%)				<0.001
None	18,464 (52.7)	871 (45.2)*	658 (48.1)*	
Antiplatelet only	13,840 (39.5)	895 (46.4)*	636 (46.5)*	
Warfarin only	1768 (5.0)	78 (4.0)	43 (3.1)*	
Both	988 (2.8)	83 (4.3)*	30 (2.2)†	
Steroid	3464 (9.9)	576 (29.9)*	225 (16.5)*†	<0.001
Antibiotics used at implant--n (%)				<0.001
Cephalosporin 1st generation	32,608 (93.0)	1706 (88.5)*	1204 (88.1)*	<0.001
Aminoglycoside	15,887 (45.3)	793 (41.2)*	585 (42.8)	<0.001
Device types--n (%)				<0.001
Single chamber PM	22,705 (64.8)	1348 (70.0)*	843 (61.7)†	
Dual chamber PM	10,747 (30.7)	465 (24.1)*	451 (33.0)†	
ICD	976 (2.8)	62 (3.2)	58 (4.2)*	
CRTP	609 (1.7)	52 (2.7)*	15 (1.1)†	
CRTD	23 (0.1)	0 (0.0)	0 (0.0)	
Temporary PM	10,782 (30.8)	808 (41.9)*	506 (37.0)*†	<0.001
Lead characteristics--n (%)				0.093
Active fixation	4084 (11.6)	218 (11.3)	182 (13.3)	
Passive fixation	30,093 (85.8)	1669 (86.6)	1142 (83.5)	
Mixed fixation	883 (2.5)	40 (2.1)	43 (3.1)	
Indication for device implantation--n (%)				
AV block	12,216 (34.8)	602 (31.2)*	366 (26.8)*†	<0.001
Congenital AV block	18 (0.1)	0 (0.0)	0 (0.0)	0.429
Atrial fibrillation/flutter	7366 (21.0)	317 (16.5)*	244 (17.8)*	<0.001
Sick sinus syndrome	17,110 (48.8)	831 (43.1)*	741 (54.2)*†	<0.001
Ventricular tachycardia	1142 (3.3)	79 (4.1)	75 (5.5)*	<0.001
Ventricular fibrillation	284 (0.8)	20 (1.0)	25 (1.8)*	<0.001
Ventricular flutter	42 (0.1)	4 (0.2)	2 (0.1)	0.555
Other left bundle branch block	342 (1.0)	22 (1.1)	8 (0.6)	0.258
Mean follow-up (years)	4.4 ± 3.7	2.4 ± 2.8	2.0 ± 2.1	<0.001

Data are presented as mean ± SD or number (%) of patients.

AV = atrioventricular, CIED = cardiac implantable electronic device, COPD = chronic obstructive pulmonary disease, CRTD = cardiac resynchronized therapy defibrillator, CRTP = cardiac resynchronized therapy pacemaker, ICD = implantable cardioverter-defibrillator, PM = pacemaker.

* $P < 0.05$ vs. normal renal function group.

† $P < 0.05$ vs. chronic kidney disease without dialysis group.

TABLE 2. Bivariate and Multivariable Analysis of Determinants Related to CIED Infection During the Index Admission in All Patients (n = 38,354)

Variables	CIED Infection (178 Events, 0.46%)			
	Bivariate Analysis		Multivariable Analysis	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Patient's characteristics				
Male gender	0.98 (0.73–1.32)	0.901	1.10 (0.82–1.49)	0.515
Age				
20~49 years	1 (reference)		1 (reference)	
50~59 years	0.82 (0.31–2.15)	0.683	1.21 (0.45–3.22)	0.707
60~69 years	1.38 (0.75–2.56)	0.303	1.70 (0.71–4.07)	0.234
70~79 years	1.04 (0.58–1.88)	0.890	1.33 (0.56–3.16)	0.515
>80 years	0.75 (0.40–1.41)	0.371	0.93 (0.38–2.26)	0.866
Diabetes	1.57 (1.16–2.13)	0.003	1.18 (0.85–1.64)	0.333
Hypertension	1.05 (0.77–1.43)	0.761	0.97 (0.69–1.36)	0.869
Liver cirrhosis	1.42 (0.67–3.03)	0.364	0.95 (0.44–2.05)	0.896
COPD	1.64 (1.07–2.50)	0.023	1.38 (0.89–2.14)	0.151
Heart failure	1.26 (0.86–1.84)	0.230	1.16 (0.77–1.73)	0.486
Chronic kidney disease*				
Without dialysis	3.08 (1.96–4.85)	<0.001	2.14 (1.32–3.46)	0.002
Dialysis	4.97 (3.23–7.65)	<0.001	3.78 (2.37–6.02)	<0.001
Device factors				
Device type				
Single chamber PM	1 (reference)		1 (reference)	
Dual chamber PM	0.99 (0.72–1.37)	0.969	1.12 (0.78–1.60)	0.537
ICD	1.18 (0.52–2.68)	0.700	1.23 (0.52–2.89)	0.642
CRTP/CRTD	0.61 (0.15–2.49)	0.493	0.77 (0.18–3.28)	0.721
Temporary PM	3.45 (2.55–4.67)	<0.001	3.05 (2.24–4.17)	<0.001
Lead characteristics				
Active fixation	1 (reference)		1 (reference)	
Passive fixation	1.09 (0.68–1.76)	0.722	1.25 (0.76–2.08)	0.379
Mixed fixation	1.72 (0.72–4.09)	0.224	1.72 (0.71–4.19)	0.231
Medication factors				
Cephalosporin 1st generation	0.43 (0.28–0.64)	<0.001	0.51 (0.33–0.78)	0.002
Aminoglycoside	1.20 (0.89–1.60)	0.235	1.16 (0.85–1.58)	0.340
Steroid	2.97 (2.13–4.15)	<0.001	2.07 (1.44–2.97)	<0.001
Warfarin or antiplatelet				
None	1 (reference)		1 (reference)	
Antiplatelet only	0.69 (0.50–0.96)	0.027	0.56 (0.40–0.78)	0.001
Warfarin only	1.11 (0.60–2.07)	0.744	0.96 (0.50–1.81)	0.889
Both	1.04 (0.45–2.37)	0.930	0.74 (0.32–1.71)	0.475

CI = confidence interval, CIED = cardiac implantable electronic device, COPD = chronic obstructive pulmonary disease, CRTD = cardiac resynchronized therapy defibrillator, CRTP = cardiac resynchronized therapy pacemaker, ICD = implantable cardioverter-defibrillator, OR = odds ratio, PM = pacemaker.

* Chronic kidney disease: normal renal function as the reference group.

1 year after discharge (Supplemental Tables S3 and S4, <http://links.lww.com/MD/A645>) (Figure 3).

DISCUSSION

In this nationwide cohort study, CKD with or without dialysis, is a risk of CIED infection during index hospitalization for CIED implantation but the impact of CKD on CIED infection within 1 year after discharge was limited. Furthermore, the use of steroid contributed to CIED infection in CKD patients without dialysis while COPD was a risk of CIED infection in CKD patients with dialysis.

Study Design

According to our previous study and Danish registry data,^{6,18} the major infection events occurred in the first year after new implantation. In addition, because CKD is an important factor for longevity of lifespan and mortality after device implantation,^{19,20} the follow-up period is theoretically shorter in CKD patients than that in those with normal renal function. In this study (Table 1), the mean follow-up period was 4.4 ± 3.7 years in patients with normal renal function, 2.4 ± 2.8 years in CKD patients without dialysis and 2.0 ± 2.1 years in CKD patients with dialysis. Hence, CIED infections developed during index

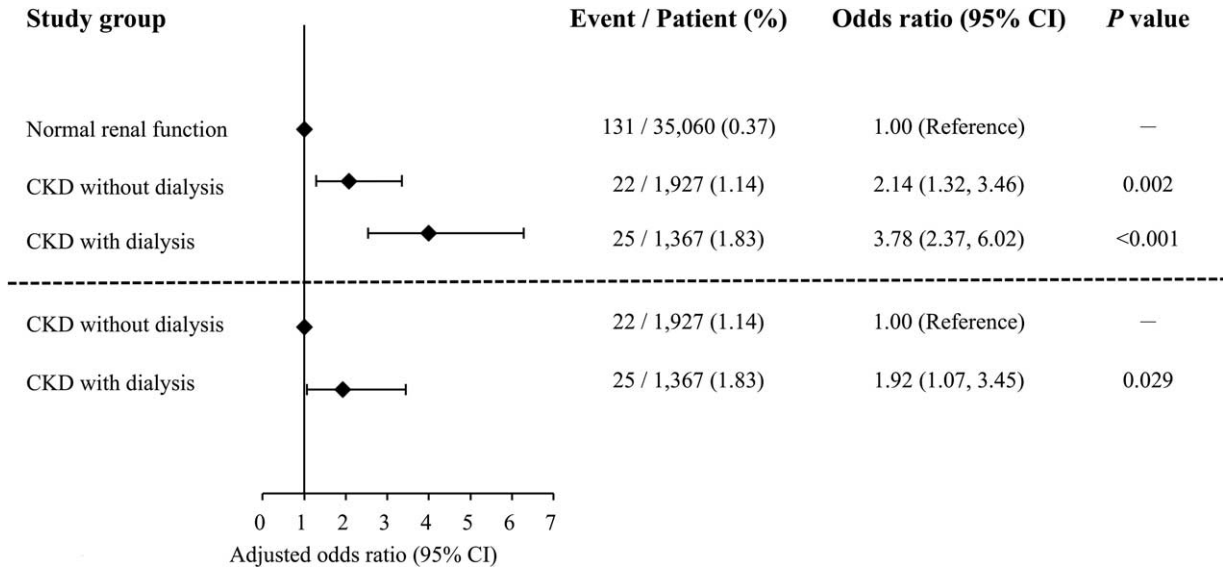


FIGURE 2. Multivariable stratified analyses of the impact of chronic kidney disease (CKD) with or without dialysis on cardiac implantable electronic device infection during index hospitalization.

hospitalization and within 1 year after index hospitalization were chosen as the outcomes. In terms of risk factors of CIED infection, more comprehensive parameters, such as baseline characteristics, the type of procedures, providers, and medications, were analyzed in our study when compared with another nation cohort study, the registry study in Danish.⁶

Impact of CKD on CIED Infection

Several risk factors of CIED infection, such as male gender, preoperation temporary pacemaker, and use of steroid, which had been mentioned in the literature, were also found to be risk factors in this study and our previous study.¹⁸

Moderate to severe kidney diseases (\geq stage 3 of CKD, especially end-stage renal disease) have been reported to be a risk of CIED infection.^{4,15} Impaired platelet function and coagulation system could contribute to postoperative hematoma, and immune dysfunction status could lead to increase susceptibility to infection and these have been proposed as the potential mechanisms responsible for the impact of CKD on CIED infection.⁴ In this study, we showed that CKD was an important risk factor of CIED infection during index hospitalization but not within 1 year after discharge. According to the results of this study, we proposed that the impaired platelet function and coagulation status of CKD patients only had impact on CIED infection during index hospitalization but not after discharge if the pacing system was stable during index hospitalization.

Factors Contributing to CIED Infection in CKD Patients

To the best of our knowledge, studies regarding risk factors of CIED infection in CKD patients were rarely reported. This study was the first study with a large number of patients to evaluate the risk factors of CIED infection in CKD patients. As mentioned above, CKD patients, especially in advanced stage of CKD (\geq stage 3), were in a status of impaired immune function and poor platelet and coagulation function. Therefore, any underlying disease or management that has further impact on the immune status should increase the risk of CIED infection in

CKD patients. In this study, we found that the use of steroid, an immunosuppressive agent, contributed to CIED infection in CKD patients without dialysis. Although subanalysis showed that patients received steroid administration had more comorbidities, such as diabetes mellitus and COPD, than those without receiving steroid administration (Supplemental Tables S5, <http://links.lww.com/MD/A645>), no specific purpose of steroid administration could be concluded. Notwithstanding, steroid administration was a risk factor of CIED infection in CKD patients without dialysis and had a trend as a risk factor of CIED infection in CKD patients with dialysis. Moreover, COPD was a risk of CIED infection in CKD patients with dialysis.

Diabetes mellitus is often considered to be in minor immune depressive status and thus could be responsible for an increased risk of infection, particularly in the context of surgery.²¹ Therefore some studies reported that diabetes mellitus was a risk of CIED infection in general population,²² but some did not.^{6,18} As shown in this study, diabetes mellitus was not a risk factor of CIED infection in CKD patient without dialysis.

COPD, which is a chronic inflammatory disease with poor nutrition status, impaired immune function^{23,24} and impaired mucociliary clearance of aspirated bacteria,²⁵ has been reported to increase postoperation mortality and morbidity, including sepsis, postoperative pneumonia, and surgical wound infection from a large registry data.²⁶ The need for repeat vascular access to permit dialysis might cause hematogenous spreading of microorganisms, and thus, the existence of COPD should further increase the risk of CIED infection in CKD patients with dialysis.

Role of Cephalosporin and Antiplatelet in CIED Infection in Pacemaker Recipients Without CKD

The use of periprocedural antibiotics reducing the risk of CIED infection has been shown in several studies.^{9,27} Bertaglia et al²⁸ reported that preoperative cefazolin was safe and effective to prevent early CIED infection but had no long-term effect. In this study, we showed that first generation of cephalosporins reduced the risk of CIED infection during index hospitalization in general population but not in CKD patients with or without

TABLE 3. Bivariate and Multivariable Analysis of Determinants Related to CIED Infection During the Index Admission in Chronic Kidney Disease Patients Without Dialysis (n = 1927)

Variables	CIED Infection (22 Events, 1.14%)			
	Bivariate Analysis		Multivariable Analysis	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Patient's characteristics				
Male gender	0.48 (0.20–1.15)	0.101	0.61 (0.25–1.52)	0.293
Age				
20 ~ 49 years	1 (reference)		1 (reference)	
50 ~ 59 years	NA	NA	NA	NA
60 ~ 69 years	NA	NA	NA	NA
70 ~ 79 years	NA	NA	NA	NA
>80 years	NA	NA	NA	NA
Diabetes	3.14 (1.15–8.55)	0.025	2.13 (0.73–6.23)	0.169
Hypertension	1.93 (0.57–6.55)	0.292	1.64 (0.44–6.09)	0.458
Liver cirrhosis	0.78 (0.10–5.89)	0.814	0.78 (0.10–6.16)	0.813
COPD	1.91 (0.74–4.91)	0.181	2.21 (0.80–6.09)	0.126
Heart failure	1.71 (0.73–4.02)	0.219	1.30 (0.52–3.28)	0.573
Device factors				
Device type				
Single chamber PM	1 (reference)		1 (reference)	
Dual chamber PM	0.85 (0.31–2.32)	0.753	1.04 (0.37–2.96)	0.940
ICD	NA	NA	NA	NA
CRTP/CRTD	NA	NA	NA	NA
Temporary PM	3.00 (1.22–7.40)	0.017	2.51 (0.97–6.47)	0.057
Lead characteristics				
Active fixation	1 (reference)		1 (reference)	
Passive fixation	2.77 (0.37–20.66)	0.322	2.37 (0.30–18.47)	0.411
Mixed fixation	NA	NA	NA	NA
Medication factors				
Antibiotics				
Cephalosporin 1st generation	0.43 (0.16–1.19)	0.105	0.44 (0.15–1.34)	0.149
Aminoglycoside	0.82 (0.34–1.95)	0.647	0.67 (0.26–1.73)	0.410
Steroid	3.44 (1.46–8.10)	0.005	2.74 (1.08–6.98)	0.035
Warfarin or antiplatelet				
None	1 (reference)		1 (reference)	
Antiplatelet only	0.87 (0.35–2.16)	0.772	0.62 (0.24–1.58)	0.316
Warfarin only	1.12 (0.14–8.85)	0.916	0.69 (0.07–6.30)	0.738
Both	2.13 (0.46–9.87)	0.336	0.97 (0.18–5.31)	0.974

CI = confidence interval, CIED = cardiac implantable electronic device, COPD = chronic obstructive pulmonary disease, CRTD = cardiac resynchronized therapy defibrillator, CRTP = cardiac resynchronized therapy pacemaker, ICD = implantable cardioverter-defibrillator, OR = odds ratio, PM = pacemaker.

dialysis probably as a result of impaired immune status in CKD patients.

Habib et al²⁹ reported that aspirin therapy before onset of CIED infection was associated with a lower likelihood of vegetation formation on CIED leads or heart valves and associated systemic manifestations of infection factors. The proposed mechanisms were aspirin's, or its metabolites', ability to reduce the expression of pivotal microbial virulence factors, including capsule production and biofilm formation and decrease vegetation growth, reduce bacterial proliferation in vegetation, and decrease hematogenous dissemination of bacteria. In this study, we showed that antiplatelet therapy reduce the risk of CIED infection during the index hospitalization in general population but not in CKD patients with or without dialysis.

Study Limitations

This cohort study had several limitations. Firstly, the details of severity of CIED infection and device procedures were not accessible in this national health insurance system because the diseases were classified by ICD-9-CM codes and reimbursement was made on the basis of procedure types. Therefore, the correlation between severity of complications and perioperative conditions, which including hematoma and procedure time, and any activity of patients could not be assessed. However, CIED infection was always related to patients' baseline characteristics and perioperative medications in the reported studies^{4,6,14,30} and these parameters were mostly included in the analysis of our study. Secondly, we could not clearly specify the stage of CKD in the group of CKD patients

TABLE 4. Bivariate and Multivariable Analysis of Determinants Related to CIED Infection During the Index Admission in Chronic Kidney Disease Patients With Dialysis (n = 1367)

Variables	CIED Infection (25 Events, 1.83%)			
	Bivariate Analysis		Multivariable Analysis	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Patient's characteristics				
Male gender	0.62 (0.27–1.46)	0.275	0.76 (0.32–1.84)	0.550
Age				
20~49 years	1 (reference)		1 (reference)	
50~59 years	NA	NA	NA	NA
60~69 years	0.76 (0.22–2.64)	0.668	NA	NA
70~79 years	0.69 (0.21–2.28)	0.545	NA	NA
>80 years	0.89 (0.23–3.35)	0.857	NA	NA
Diabetes	0.62 (0.28–1.36)	0.229	0.49 (0.21–1.15)	0.102
Hypertension	0.99 (0.29–3.35)	0.991	1.21 (0.33–4.40)	0.770
Liver cirrhosis	0.52 (0.07–3.91)	0.528	0.46 (0.06–3.51)	0.450
COPD	3.29 (1.35–8.00)	0.009	2.76 (1.06–7.16)	0.037
Heart failure	0.52 (0.12–2.21)	0.374	0.59 (0.13–2.63)	0.492
Device factors				
Device type				
Single chamber PM	1 (reference)		1 (reference)	
Dual chamber PM	0.88 (0.38–2.05)	0.763	0.83 (0.31–2.22)	0.706
ICD	NA	NA	NA	NA
CRTP/CRTD	NA	NA	NA	NA
Temporary PM	1.14 (0.51–2.55)	0.755	0.85 (0.36–2.03)	0.721
Lead characteristics				
Active fixation	1 (reference)		1 (reference)	
Passive fixation	0.75 (0.25–2.24)	0.610	0.57 (0.17–1.91)	0.364
Mixed fixation	2.17 (0.38–12.26)	0.380	2.35 (0.37–15.12)	0.367
Medication factors				
Antibiotics				
Cephalosporin 1st generation	0.42 (0.17–1.07)	0.068	0.41 (0.15–1.14)	0.089
Aminoglycoside	1.72 (0.77–3.81)	0.183	1.97 (0.83–4.67)	0.122
Steroid	2.93 (1.28–6.72)	0.011	2.32 (0.91–5.91)	0.077
Warfarin or antiplatelet				
None	1 (reference)		1 (reference)	
Antiplatelet only	0.71 (0.30–1.68)	0.438	0.85 (0.35–2.10)	0.730
Warfarin only	2.42 (0.53–11.09)	0.255	1.90 (0.38–9.48)	0.432
Both	1.71 (0.22–13.53)	0.611	1.49 (0.17–12.74)	0.718

CI = confidence interval, CIED = cardiac implantable electronic device, COPD = chronic obstructive pulmonary disease, CRTD = cardiac resynchronized therapy defibrillator, CRTP = cardiac resynchronized therapy pacemaker, ICD = implantable cardioverter-defibrillator, OR = odds ratio, PM = pacemaker.

without dialysis. The diagnosis of CKD was based on the ICD code and there was no subclassification of ICD-9-CM of 585.1~585.5 in the NHIRD. In clinical practice in Taiwan, we usually defined patients to have CKD (ICD-9-CM: 585) when a patient's creatinine clearance rate was less than 60 ml/1.73 m² for more than 3 consecutive months. Additionally, a previous study has reported the high specificity of diagnosis of stage ≥ 3 of CKD according to ICD-9-CM code and the sensitivity of ICD-9-CM code of CKD was increasing when CKD diagnostic code was used during hospitalization, especially in aged population and diabetic patients.²⁴ Of note, the design of this study was hospital-based evaluation and the characteristics of participants were aged patients with high prevalence of comorbidities. Therefore, patients with moderate to advanced kidney disease (\geq stage 3 of CKD) were the

majority in the group of CKD without dialysis. Furthermore, our study also showed that CKD was a risk of CIED infection as in other published studies.^{4,15} Finally, this national insurance database covered nearly every citizen in this country and provided a large number of CKD population and should reduce systematic bias and give better evidence in this field.

CONCLUSIONS

CKD is an important risk factor of CIED infection during index hospitalization. The use of steroid contributes to CIED infection in CKD patients without dialysis and therefore, avoiding unnecessary steroid administration or reducing dosage of steroid is important before CIED implant in CKD patients. Chronic obstructive lung disease is a risk of CIED infection in

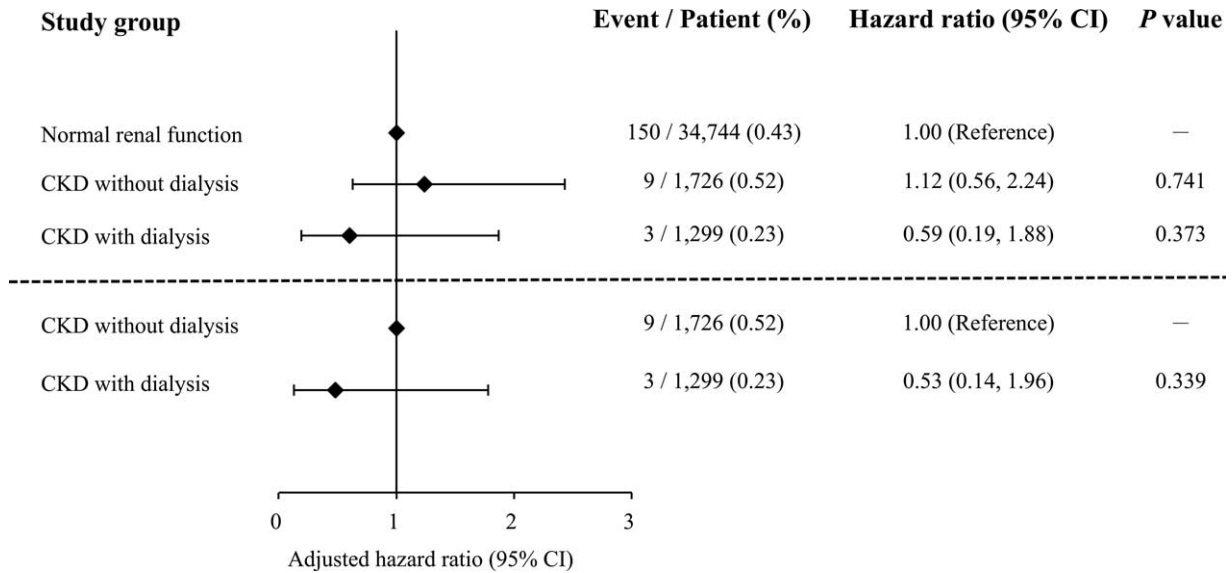


FIGURE 3. Multivariable stratified analyses of the impact of chronic kidney disease (CKD) with or without dialysis on cardiac implantable electronic device infection within 1 year after discharge.

CKD patients with dialysis and therefore, complete treatment of all infection sources and improvement of nutritional status should be implemented before CIED implant. Physicians should consider these risk factors in the integrative care for CKD patients with or without dialysis before CIED implant.

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