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Risk Factors for Infections of Cardiac Implantable Electronic Device in Saudi Arabia

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Abstract

Background and Objectives: Cardiac implantable electronic device (CIED) infections are increasing worldwide due to the increased use of implantable cardiac devices. (CIED) infection is a serious complication that is associated with increased mortality and morbidity as well as increased healthcare costs. However, risk factors for infection of implanted devices are poorly documented in Saudi Arabia. We aimed to determine risk factors for CIED infection in our region. ***Methods and Results:*** A retrospective study was carried out in cardiology departments at different centers in Saudi Arabia. Our population consisted of all patients with device-related infections over twenty years from January 2009 to December 2020 with one control case matched to each confirmed infection of the implanted device, resulting in 137 patients with device infection. The mean age was 58±16 years, where males constituted 75.2%. Most infections occurred in patients with the first implant. (63.5%) patients had chronic kidney disease, (59.9%) of patients had diabetes mellitus, (65%) of patients had hypertension, and (43.1%) of patients had coronary artery disease. Most of the patients had a pocket infection. Preop antibiotics were obtained in all patients before implanting. The median time from the last surgical intervention involving the device to infection symptoms was 730 days. The median length of hospitalization was 27±23 days. 130 patients survived at the time of discharge, resulting in an overall mortality rate of 5.1%. Using Multivariate analysis, we identified male gender (P = 0.000), hypertension HTN (P = 0.002), diabetes DM (P = 0.006), and presence of underlying heart disease CHD (P = 0.000) Type of the device (P = 0.000) as significantly associated with a higher risk of CIED infection. ***Conclusion:*** Our data show that gender, diabetes, hypertension, and heart disease are independent risk factors for infection after cardiac device implantation. As regards device characteristics, ICD device is associated with a higher infection rate compared to other devices.

Keywords: Cardiac Implantable Electronic Device; Pacemaker; Defibrillator; CIED Infection; Risk factors; retrospective study.

1. INTRODUCTION

The use of cardiac implantable electronic devices (CIEDs) continues to grow worldwide [1-4]. The rate of device implantations is increasing with the aging of the general population, the increase in the number of patients with heart diseases, the technological advances of these devices, and expanding of clinical indications [5, 6]. Although the use of these devices enhances outcomes in patients with cardiovascular disease, it is associated with critical complications including infections [7].

Device-related infection constitutes a worrisome risk. Infections are increasing worldwide for all device types, partly related to the growing number of CIED implants due to widening indications, technological advancements of these devices, aging of the general population and increasing numbers of generator replacements [8-10].

CIED infection is a serious complication that is associated with increased mortality and morbidity as well as increased healthcare costs [11, 12]. This is due to the treatment of infections which involves potential risks including device removal and replacement, complications of long-term vascular access, adverse antibiotic reactions, healthcare-associated infection, and involvement of antimicrobial-resistant microorganisms [13, 14].

Understanding the reasons for the increased infection rate among CIED recipients as well as identifying the risk factors associated with it may allow targeted strategies to minimize infection rates. Thus, we used combined data from different centers in Saudi Arabia to determine risk factors for CIED infection.

2. METHODOLOGY

Study Population:

It is a retrospective cohort study carried out in cardiology departments at different centers in Saudi Arabia. Our population consisted of all patients with device-related infections, of both gender and all ages, over eleven years from January 2009 to December 2020. They were selected among CIED implantation procedures, both first implantation and reoperation, with one control case matched to each infection case. Controls were selected from the database of patients who underwent implantation of a cardiac device in our center. They also had to be followed up in the center for a duration at least equivalent to that of the cases.

CIED implantation procedures in Saudi Arabia are standardized through a national referral program. All centers adhere to these standards. All centers used preoperative antibiotics for patients undergoing CIED replacements or reoperations. Local guidelines determined the type and dosage of antibiotics.

The diagnosis of CIED-related infection was confirmed by clinical examinations associated with laboratory examinations. Both infection types, pocket infection and systemic infection were included. Local infection was defined as an infection limited to the pocket of the device and was clinically suspected in the presence of local signs of inflammation at the generator pocket, including erythema, warmth, pain and swelling, adherence of skin to the device, and erosion of skin with a draining sinus, as previously described [13, 15-17]. Systemic infection and infective endocarditis were defined as infection extending to the electrode leads, cardiac valve leaflets or endocardial surface and causing bloodstream infection and/or endocarditis. It was clinically confirmed by imaging valvular or lead vegetations in more than one echocardiographic plane, and positive blood and/or lead tip cultures [13, 15-17]. The modified Duke criteria [18] and the ESC 2015 criteria [19] were used as the standardized diagnostic tool for CIED endocarditis.

Both blood culture and pocket tissue culture from the generator pocket or the electrode lead samples were obtained from all infected patients. The study was approved by Biomedical Ethics Unit at King Abdulaziz University Hospital.

Data Collection:

An extensive review of the medical files of all included patients that developed infection was performed. Data were obtained from 3 centers in Saudi Arabia. The data recorded were defined and comprised of:

Clinical Data: Patient's demographics, age at implant, baseline rhythm and an indication of device implant, type of device, manufacturer, type of procedure, implant location, implant time (skin incision, to skin closure), peri-operative antibiotics, an outcome, at last, follow up, hospital stay and mortality.

Data related to devising infection: culture result, organism isolated and sensitivity profile, antibiotic treatment (type and duration), the timing of device extraction, and outcome.

We analyzed both patient-related and device-related factors that were associated with infection.

Statistical Methods:

Data are presented as mean+SD, number, percentage, or odds ratio (OR) with a 95% confidence interval (CI). Mann-Whitney tests and Chi-square tests were used to compare categorical and continuous variables. All statistical analyses were performed using IBM SPSS for windows ver.24 statistics software. P value of ≤ 0.05 was considered statistically significant.

3. RESULTS

The Characteristics of Patients:

The study included a total of 274 patients who underwent CIED implantation, of whom 62% were male patients and 37.9% were female patients. A total of 90 patients received a CRT-D system (32.8%), 84 patients received an ICD system (30.6%), 69 patients received an PPM system (25.2%), and only 31 patients received a CRT-P system (11.3%). Over half of the patients had hypertension (51.4%), one hundred twenty-eight patients had diabetes mellitus (DM) with a percentage of (46.7%), and one hundred seventy-seven patients had ischemic heart disease (IHD) (64.6%). The mean (±SD) age of all patients was 53±16 years (table 1).

Table 1: Characters of patients with and without device infections (n=274).

Parameter		Freq (%)/Mean±SD
Age, y (Mean±SD)		53±16
Gender	**Female**	104 (36.8%)
	Male	170 (63.2%)
Type of Device	**ICD**	84 (34.4%)
	CRT-D	90 (38%)
	CRT-P	31 (2.5%)
	PPM	69 (25.2%)
DM	**No**	144 (53.2%)
	Yes	128 (46.8%)
HTN	**No**	131 (48%)
	Yes	141 (52%)
CAD/IHD	**No**	95 (33.5%)
	Yes	177 (66.5%)
EF% (Mean±SD)		34.3±23.1

Infections

Of all patients, 137 participants had a device-related infection, of whom the characters are displayed in table 2. The mean age for infected patients was 58±16 years, where males constituted 75.2% and females constituted 24.8%. The majority of infections (94 cases) occurred in patients who underwent first CIED implantation with a percentage of 68.6%, whereas 43 infection cases occurred after the scheduled replacement of the cardiac device with a percentage of 31.4%. Among 137 patients with CIED infection, 87 (%63.5)patients had chronic kidney disease, 82 (59.9%) patients had diabetes mellitus, 89 (65%) patients had hypertension and 59 (43.1%) patients had coronary artery disease. The majority of the participants with infection had a pocket infection (73.7%) whereas endocarditis occurred in 68 patients (49.6%). Preop antibiotics were obtained in all patients before implanting. The median time from the last surgical intervention involving the device to the onset of infection symptoms in all operations was 730 days. The median length of hospitalization was 27±23 days. Of the 137 patients diagnosed with CIED, 130 survived at the time of discharge, resulting in an overall mortality rate of 5.1%. The comparison of baseline characteristics of the infected group is presented in table 2. Moreover, most of the patients had a positive blood culture (64.2%), and the most common isolated organism, not surprisingly, was Staphylococcus aureus, particularly, coagulase-negative Staphylococcus aureus (15.3%), and Methicillin-susceptible Staphylococcus aureus (13.9%). In 34.3% of cases, microbial data were unrevealing (negative blood cultures) (table 2 & figure 1).

Table 2: Characters of patients with device infections (n=137).

Parameter		Freq (%)/ Mean±SD
Age		58±16
Sex	**Female**	34 (24.8%)
	Male	103 (75.2%)
BMI		29.4±6.9
CKD	**Not Found**	50 (36.5%)
	Found	87 (63.5%)
DM	**Not Found**	55 (40.1%)
	Found	82 (59.9%)
HTN	**Not Found**	48 (35%)
	Found	89 (65%)
CHD	**Not Found**	78 (56.9%)
	Found	59 (43.1%)
Type of Device	**ICT**	56 (40.9%)
	CRT-D	36 (26.3%)
	CRT-P	4 (2.9%)
	PPM	41 (29.9%)
Denovo/repeated	**Denovo**	94 (68.6%)
	Repeated	43 (31.4%)
Pocket	**No**	36 (26.3%)
	Yes	101 (73.7%)

Parameter		Freq (%)/ Mean±SD
IE	**No**	69 (50.4%)
	Yes	68 (49.6%)
Received preop antibiotics	**Yes**	137 (100%)
Duration from implantation till the infection		38.2±44.1
Blood culture	**Negative**	49 (35.8%)
	Positive	88 (64.2%)
Vegetations on echo	**None**	71 (53%)
	Lead	57 (42.5%)
	Valvular	6 (4.5%)
hospital stay in Days		27±23
Mortality	**No**	130 (94.9%)
	Yes	7 (5.1%)

Risk Factors:

For identifying the risk factors that are significantly associated with CIED infection, we have used Multivariate analysis (table 3). The analysis indicates that male gender (P = 0.000), hypertension HTN (P = 0.002), diabetes DM (P = 0.006), and presence of underlying heart disease CHD (P = 0.000) were significantly associated with the occurrence of CIED infection. The type of the device was also significantly related to the presence of infection (P = 0.000) (table 3).

ICD device had a slightly higher risk of infection as compared to other devices as the percentages shown on the Scheffe test was 40.9%, whereas other systems were 29.9%, 26.2% and 3% for PPM, CRT-D and CRT-P, respectively (table 4).

Table 3: Multivariate Analysis of Infection Predictors.

Tests of Between-Subjects Effects					
Parameter	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Age	8.178	6	1.363	.348	NS
gender	1.619	6	1.270	3.759	.000
CKD	1.454	6	.242	1.040	NS
DM	1.832	6	1.305	3.277	.006
HTN	6.273	6	1.046	3.607	.002
CHD	7.545	6	1.257	4.471	.000
Denovo/repeated	1.979	6	.330	1.719	NS
Pocket	1.660	6	.277	.952	NS
Received ….	.809	6	.135	1.158	NS
Implant time till the infection	8.255	6	1.376	1.426	NS
Positive blood	.558	6	.093	.303	NS
Vegetation on echo	1.555	6	.259	.528	NS
Hospital stay	23.480	6	3.913	1.166	NS
Mortality	1.509	6	.251	1.083	NS
Type of device	191.203	6	31.867	157.953	.000

Significance level = 0.05

Table 4: Scheffe test – type of devices

Parameter	N	P		Subset 1	Subset 2
Scheffe a,b,c	**ICD**	56	40.9%	1.1429	
	CRT-D	36	26.2%	1.1944	
	PPM	41	29.9%	1.3902	1.3902
	CRT-P	4	3%		1.7500
	Sig.			.532	.202

Comparison of Outcomes between Patients with DRI after the first implant and Patients with DRI after repeated implants:

Of all CIED infections, 94 cases developed infections after the first implantation and 43 cases developed infections after replacement as shown in table 5. Importantly, the incidence of pocket infection was significantly higher in patients with repeated procedures than in patients with first implantation (p=0.027) as 86% of cases had pocket infections after repeated procedures.

However, no significant difference was observed in the median time from implantation to infection, blood cultures, vegetation on echo, the median length of hospital stay, and mortality between patients with the first implantation and patients with the repeated procedure.

Comparison of Outcomes between Patients with Early DRIs and Patients with Late DRIs:

Among all infected patients, 41 patients (29.9%) were identified as having early CIED infection (before 6 months) and 93 patients (67.9%) were identified as having late CIED infection (6 months or after) (Table 5). In particular, the incidence of pocket infection was significantly higher in patients with early CIED infections than in patients with late CIED infections (p=0.034) as the majority of early infection patients (85.4%) had pocket infections.

In addition, patients with late CIED infections were more likely to have a higher length of hospital stay (p=0.004). the median length of hospital stay was 30±25 days for patients having late CIED infections whereas it was 19±15 days for patients having early CIED infections. No significant difference was observed in blood cultures results, vegetation on echo, and mortality between patients with early CIED infections and patients with late CIED infections (table 6).

Comparison of Outcomes between Patients with Pocket CIED Infections and Patients with Infective Endocarditis

Overall, 68 patients (49.6%) were identified as having infective endocarditis and 101 patients (73.7%) were identified as having a pocket infection (Table 6). In particular, patients who had late infection exhibited a trend of higher incidence of endocarditis compared to pocket infection (p=0.046) as (70.6%) of cases had IE within 6 months of the procedure or after. In addition, a significantly higher rate of positive blood cultures was observed in patients with endocarditis (p=0.002). The results showed that (76.5%) of cases exhibited positive blood cultures. Moreover, patients with Denovo infections were more susceptible to endocarditis than pocket infections (p=0.044) as (70.6%) of endocarditis patients developed an infection after the first implant. These patients also consistently exhibited a higher rate of lead vegetation on echo (66.2%) (p=0.000).

The median length of hospital stay was significantly longer in patients with endocarditis compared to patients with pocket infections (33±26 days) (p=0.000). Mortality showed no significant difference between patients with endocarditis and patients with pocket infections (Table 7).

Table 5: Repeated infection as a determinant for the outcome and isolated organism (n=137).

Parameter		Infection		P-value
		Denovo (n=94)	Repeated (n=43)	
Pocket	**No**	30 (31.9%)	6 (14%)	**0.027**
	Yes	64 (68.1%)	37 (86%)	
IE	**No**	46 (48.9%)	23 (53.5%)	0.621
	Yes	48 (51.1%)	20 (46.5%)	
Duration from implantation till infection (months)		38.6±46	37.5±39.8	0.849
Blood culture	**Negative**	32 (34%)	17 (39.5%)	0.534
	Positive	62 (66%)	26 (60.5%)	
Vegetations on echo	**None**	45 (48.9%)	26 (61.9%)	0.139
	Lead	41 (44.6%)	16 (38.1%)	
	Valvular	6 (6.5%)	0 (0%)	
Hospital stay in Days		26±20	28±27	0.962
Mortality	**No**	89 (94.7%)	41 (95.3%)	0.869
	Yes	5 (5.3%)	2 (4.7%)	

***Mann-Whitney test was used.**

****Chi-square test was used.**

Table 6: Early infection as a determinant for the outcome and isolated organism (n=137).

Parameter		Infection		P-value
		Early (n=41)	Late (n=93)	
Pocket	**No**	6 (14.6%)	30 (32.3%)	**0.034**
	Yes	35 (85.4%)	63 (67.7%)	
IE	**No**	21 (51.2%)	45 (48.4%)	0.762
	Yes	20 (48.8%)	48 (51.6%)	
Blood culture	**Negative**	12 (29.3%)	36 (38.7%)	0.294
	Positive	29 (70.7%)	57 (61.3%)	
Denovo/repeated	**Denovo**	29 (70.7%)	64 (68.8%)	0.825
	Repeated	12 (29.3%)	29 (31.2%)	
Vegetations on echo	**None**	23 (57.5%)	45 (49.5%)	0.305
	Lead	14 (35%)	43 (47.3%)	
	Valvular	3 (7.5%)	3 (3.3%)	
Hospital stay in Days		19±15	30±25	**0.004**
Mortality	**No**	38 (92.7%)	89 (95.7%)	0.470
	Yes	3 (7.3%)	4 (4.3%)	

***Mann-Whitney test was used.**
****Chi-square test was used.**

Table 7: IE and Pocket infections as determinants for the outcome and isolated organism (n=137).

Parameter		Type of infection		P-value
		IE (n=68)	Pocket (n=101)	
Infection	**Early**	20 (29.4%)	35 (35.7%)	**0.046**
	Late	48 (70.6%)	63 (64.3%)	
Blood culture	**Negative**	16 (23.5%)	40 (39.6%)	**0.002**
	Positive	52 (76.5%)	61 (60.4%)	
Denovo/repeated	**Denovo**	48 (70.6%)	64 (63.4%)	**0.044**
	Repeated	20 (29.4%)	37 (36.6%)	
Vegetations on echo	**None**	17 (26.2%)	61 (61.6%)	**0.000**
	Lead	43 (66.2%)	34 (34.3%)	
	Valvular	5 (7.7%)	4 (4%)	
Hospital stay in Days		33±26	22±20	**0.000**
Mortality	**No**	64 (94.1%)	96 (95%)	0.960
	Yes	4 (5.9%)	5 (5%)	

***Mann-Whitney test was used.**
****Chi-square test was used.**

4. DISCUSSION

To our knowledge, our study is the first and the largest study regarding risk factors associated with CIED infections in Saudi Arabia.

In our study, we identified gender, diabetes, hypertension, heart diseases (ischemic heart disease, coronary artery disease) and type of device as being significantly associated with an increased risk of infection.

Our study showed that men were more likely to have CIED infections, as some studies have shown [20-23]. However, Birnie *et al.*, have not demonstrated male gender as a risk factor for infection [24]. The potential reasons for this are unclear, although the presence of firmer pre-pectoral subcutaneous tissue in males may result in more traumatic pocket creation.

Similar to previous studies, diabetes was a potent risk factor in our study [12, 21, 23, 25, 26]. Diabetes can be responsible for an increased risk of infection, especially in the context of surgery because it is often considered as a cause of minor immunodepression.

In addition, we found that hypertension is associated with an increased risk of CIED infection as seen in some previous studies [21], though not all [20, 25, 26]. Our study showed a correlation of heart diseases with CIED infection as found in some studies [12, 20, 25, 26].

Generally, the presence of these comorbidities indicates an underlying vulnerability resulting from medical comorbid conditions.

In terms of device-related factors, we identified that device type was associated with an

increased risk of CIED infection as the shown percentages on the Scheffe test 40.9%, 29.9%, 26.2% and 3% for ICD, PPM, CRT-D and CRT-P, respectively. whereas another study did not find this, they found that CRT device implantation was the independent predictor of device infection in the multivariate analysis (OR, 28.54; 95% CI, 3.49–233.07; P = 0.002)[27].

However, data from the Danish device registry showed that device complexity and the numbers of leads were significant predictors of infection associated with increased infection risk on multivariate analysis with an HR of 1.26, 1.67, and 2.22 for ICD, CRT-P, and CRT-D devices, respectively as compared to PMs (P<_ 0.002 for all comparisons) [22]. Hercé *et al.*, reported the use of more than one lead as an independent predictor of device-related infection in a study of 2496 patients (P = 0.016) [25]. Similar to a retrospective study, the presence of multiple defibrillation leads was a strong risk factor for the development of infectious complications [28].

The higher infection rate associated with complex devices such as ICDs, is most likely related to longer procedural times, the presence of more than one lead, and the larger generator size as these pose additional technical challenges, provide increased foreign body surface area for microbial adherence and provides an additional effect of possible abrasions, thereby potentiating infection risk [29].

In addition, several associations between clinical characteristics and different types of CIED infections were pointed out in our study. patients with recurrent infections and patients with early CIED infections were more susceptible to pocket infections than endocarditis. patients with late CIED infections tended to have higher lengths of hospital stay and were more susceptible to endocarditis than pocket infections. patients with endocarditis were more likely to have higher rates of positive cultures and higher rates of lead vegetations on echo.

Long-term mortality in CIED patients with device infection is significantly higher compared to those without device infection, for at least 3 years for all device types [30]. However, Patients who do not undergo CIED complete system extraction, mostly because they are considered too frail, have a very high mortality rate both in-hospital and over the months following discharge [31, 32]. In our study, the relationship between mortality and CIED infections did not achieve statistical significance.

5. CONCLUSION

Cardiac implantable electronic device infections constitute a worrisome risk resulting in significant burdens to healthcare systems. We identified several risk factors of device infections in our country in patients who underwent CIED procedures and found that male gender, diabetes, hypertension, heart diseases and type of device were significantly associated with an increased risk of infection. It is fundamental to take these factors into account in the prevention of infection in our country. Strategies to minimize risk include identifying higher-risk individuals using risk score systems, optimizing blood sugar level and renal function before a procedure, preoperative skin cleansing with chlorhexidine-alcohol, and shortening the procedure time.

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