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Thrombocytopenia and end stage renal disease are key predictors of survival in patients with cardiac implantable electronic device infections

Florian Ernst Martin Herrmann MD | Felix Ehrenfeld MD | Petra Wellmann MD, MHBA | Christian Hagl MD | Sebastian Sadoni MD | Gerd Juchem MD

Department of Cardiac Surgery, Ludwig Maximilian University, Munich, Germany

Correspondence
Florian Ernst Martin Herrmann, MD, Department of Cardiac Surgery, Ludwig Maximilian University, Munich, Marchioninistraße 15, 81377 München, Germany.
Email: Florian.Herrmann@med.uni-muenchen.de

Abstract

Introduction: Cardiac implantable electronic device (CIED) infections are associated with a high mortality. Our aim was to identify key predictors of survival in patients with CIED infections as to be able to detect high-risk patients and possibly affect modifiable factors.

Methods and Results: In this observational study, we collected data from 277 patients with CIED infections treated in our department between 2001 and 2017; predictors of survival were evaluated. The median time since the last CIED procedure was 0.83 years (interquartile range [IQR]: 0.25-3.01), median time since initial CIED implant was 4.79 years (IQR: 0.90-11.0 years). Survival at 30 days was 94.9% (95% confidence interval [CI]: 92.3-97.5) and survival at 1 year was 80.9% (CI: 76.4-85.7). Age (odds ratio [OR]: 1.05, CI: 1.01-1.09; $P = .009$), end stage renal disease (ESRD) with dialysis (OR: 5.14, CI: 1.87-14.11; $P = .001$), positive blood cultures (OR: 2.19, CI: 1.08-4.45; $P = .030$), and thrombocytopenia (OR: 2.3, CI, 1.03-5.15; $P = .042$) were identified as predictors of death within 1 year of treatment of CIED infection.

Conclusion: Patients with CIED infection with prior ESRD with dialysis or preoperative thrombocytopenia are at an increased risk of 1-year mortality. We suggest that these patients be evaluated critically and resources be allocated to these patients more liberally. A greater understanding of the role of platelets in immunity may improve treatment of advanced infection in the future.

KEYWORDS

blood culture, cardiac implantable electronic device infection, end stage renal disease, survival, thrombocytopenia

1 | INTRODUCTION

Cardiac implantable electronic device (CIED) infections are associated with a high mortality rate[1] and high treatment costs.[2] The number of devices implanted is steadily rising as the era of transcatheter valve implantation accelerates. With CIED infections constituting the most critical complication of CIED therapy, it is key that this entity be understood to the fullest. To this end the authors of the 2018 EHRA consensus statement on lead extraction made a point of mentioning that there are several gaps in evidence and that further research is required.[3]

The high mortality rate associated with these infections was the stimulus for our group to investigate our center's experience. It was our goal to identify specific predictors which would allow us to detect patients at an increased risk of mortality and identify modifiable factors. It is an understanding of the individual patient's risk which will allow us to provide more accurate information preoperatively and a greater level of resources in the perioperative period. Ultimately in the next years it must be our objective, not only to reduce the burden of CIED infections but also to improve the mortality associated with such infections.

2 | MATERIALS AND METHODS

2.1 Study design

We performed an observational study in which demographic characteristics, procedural data, and postoperative outcomes were collected from our local operative data collection system, patient files, and routine postoperative follow-up. Our cohort included all the patients treated for CIED infections in our department from 2001 to 2017. The study was approved by the local ethics committee.

2.2. Definitions and current patient management

Based on the therapeutic distinctions made in the Heart Rhythm Society[4] consensus statement on lead extraction,[3] we defined isolated pocket infections (IPI) as infections with local signs of infection, negative blood cultures, and no evidence of a vegetation in echocardiography. Device infections with signs of local or systemic infection, positive blood cultures, and a vegetation in echocardiography (preferably transesophageal echocardiography [TEE]) were termed cardiac implantable electronic device related infective endocarditis (CIEDR-IE). Device infections with signs of local or systemic infection and either positive blood cultures or positive TEE were also termed CIEDR-IE. Patients with active left sided endocarditis, positive blood cultures, and a CIED were included in the CIEDR-IE group.

As dictated by the current guidelines, in our clinical practice IPI and CIEDR-IE are indications for complete device removal. Multiple blood cultures and swabs are collected preoperatively, preferably before beginning empirical antibiotic treatment without allowing a relevant delay of such treatment. Complete removal of the device is performed as soon as possible and performed preferably using a transvenous methodology—always with the option of performing an emergency sternotomy, should complications arise. Should a transvenous methodology not succeed, extraction of infected leads may be performed via a sternotomy access with the support of the heart-lung machine. During the extraction procedure, tissue samples from the infected pocket or infected lead are collected for microbiological evaluation. Changes of the antimicrobial regimen are based on the microbiological results.

2.3 Statistical analysis

Data analysis was performed using R Version 3.5.0[5] with the support of the additional software packages: Rcmdr,[6] survival,[7] ggplot2,[8] and survminer.[9] Pearson's χ^2 test and Fisher's exact test were used for the analysis of dichotomous nominal and categorical data. Pretesting with the Shapiro-Wilk test was performed to determine whether scale data was normally distributed; parametric data was tested using Student's independent sample *t* test; nonparametric data was tested using the Wilcoxon test. Scale data are presented as medians with the interquartile range (IQR). Select variables found to be significant in univariable testing were evaluated using a binary multivariable logistic regression. Values of $P < .05$ are considered to be statistically significant. Figures 2-4 represent Kaplan-Meier graphs displaying survival up to 1 year, using the date of surgical treatment of the CIED infection as the start date. The median follow-up time was calculated using the reverse Kaplan-Meier method.

3 | RESULTS

3.1. Study cohort and patient presentation

Our cohort consists of 277 patients with CIED infections; 148 patients (53.4%) with CIEDR-IE and 129 (46.6%) with IPI. The median patient age was 73.8 years (IQR: 65.7-80.4); 79 patients were female (28.5%). The infected device was a pacemaker in 172 (62.1%), an implantable cardioverter defibrillator in 44 (16%) and a cardiac resynchronization therapy device with or without defibrillation (CRT-D/CRT-P) in 61 (22.0%) cases.

The patients presented with local symptoms at the generator pocket in 165 cases (59.6%). In the IPI group 126 patients (97.7%) and in the CIEDR-IE group 39 patients (26.4%) presented with local symptoms. In the CIEDR-IE group 87 patients (58.8%) and in the IPI group 6 patients (4.7%) presented with fever (For more information on presenting symptoms see Tables S1 and S2).

3.2 Time point of infection

The median time since the last CIED procedure was 0.83 years, IQR: 0.25–3.01 years (ie, 304 days, IQR: 93-1100 days); the median time since initial CIED implant was 4.79 years, IQR: 0.90-11.0 years (ie, 1748 days; IQR: 325-4015) (see Figure 1).

3.3 Procedural goals and procedural success

In 230 cases (83.0%) the goal of the procedure was removal of the CIED and leads. In eight cases (2.9%) the patient was referred to our tertiary care center for lead removal after failed lead removal in a secondary care center. Patient characteristics or the patient's wish dictated that the generator be removed but the leads remain in place in 28 cases (10.1%) and that local wound debridement or wound revision be performed in 11 cases (4.0%). Complete procedural success[3] of lead extraction could be achieved in 207 (87.0%) and

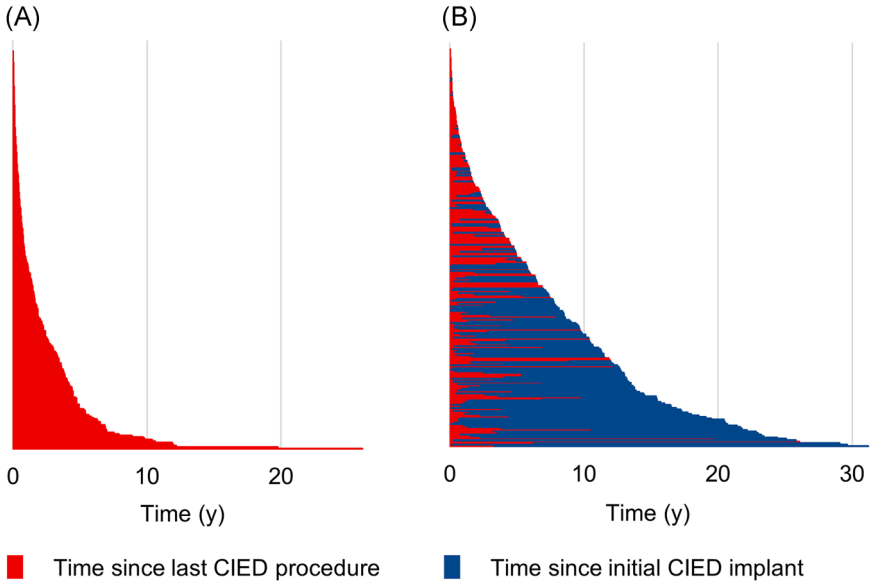

FIGURE 1 Time since last cardiac implantable electronic device (CIED) procedure (A) and time since initial CIED implant (B) in patients with CIED infection. In both graphs the time since the last CIED procedure is featured in red with blue depicting the time from the last to the initial procedure in B

TABLE 1 Microbiological results in patients with cardiac implantable electronic device infection depending on the source of the materials cultured, ie, blood culture or culture of swabs/intraoperative material (generator pocket swab, generator pocket tissue, lead or valve tissue)

Microbiological results	Blood culture	Intraoperative material
Staphylococcus spp.	83 (72.8%)	124 (67.8%)
Coagulase negative staphylococci	30 (26.3%)	86 (47.0%)
Staphylococcus aureus	53 (46.5%)	38 (20.8%)
Streptococcus spp.	6 (5.3%)	4 (2.2%)
Enterococcus spp.	9 (7.9%)	6 (3.3%)
Gram negative	4 (3.5%)	4 (2.2%)
Other	2 (1.8%)	11 (6.0%)
Polymicrobial	10 (8.8%)	34 (18.6%)
Total	114 (100.0%)	183 (100.0%)
Total cases with positive microbiological isolates	114 (41.2%)	183 (66.1%)
Total cases without positive microbiological isolates	163 (58.8%)	94 (33.9%)

clinical procedural success[3] of lead extraction could be achieved in 226 cases (95.0%).

3.4 Microbiological features of infection

The bacterial species encountered in our patients can be found in Table 1. (See Table S3 for the source of bacterial isolates in the patients with bacteria discovered in intraoperative material and Table S4 for the microbiological results of polymicrobial infections).

3.5 Survival

In the complete cohort the survival rate at 30 days was 94.9% (CI: 92.3-97.5), at 6 month: 86.5% (CI: 82.5-90.6), at 1 year: 80.9% (CI: 76.4-85.7), at 5 years: 56.3% (CI: 50.2-63.2) and at 10 years: 41.9% (CI: 35.0-50.2). Figure 2A depicts the survival in the complete cohort. The median follow-up time of the study was 77.64 months; CI: 71.28-94.44 (6.47 years; CI: 5.94-7.87). Tables S5-S8 present the causes of death and the relation of these to infection.

3.6 Predictors of 30-day and 1-year survival

Tables 2 and 3 show the results of univariable analysis of predictors of 30-day and 1-year survival. Figures 2B-E and 3A-D are Kaplan-Meier graphs of survival depicting survival depending on disease related variables/preoperative laboratory parameters. Figure 4 displays the survival depending on the bacterial species found in blood culture positive patients. Table 4 presents the results of multivariable analysis of predictors of death within 1 year of treatment of CIED infection.

3.7 Complications and recurrent infections

Three major complications occurred in our cohort. One patient was reanimated intraoperatively after developing sinus arrest, one patient required operative treatment of hemopericardium and one patient required operative treatment for a laceration of the brachiocephalic-caval junction. Eight patients in our cohort developed a recurrent IPI of the newly implanted pacemaker. Three further patients developed a CIEDR-IE of the new CIED after complete removal of the initial device.

TABLE 2 Demographic characteristics of patients with cardiac implantable electronic device infection with statistical analysis regarding 30-day and 1-year mortality

		30-Day mortality			1-Year mortality		
	All (%/IQR)	Survival over 30 days (%/IQR)	Death within 30 days (%/IQR)	*P*	Survival over 1 year (%/IQR)	Death within 1 year (%/IQR)	*P*
Total	277 (100)	261 (94.2)	14 (5.1)		214 (77.3)	52 (18.8)	
Female gender	79 (28.5)	73 (28.0)	4 (28.6)	1.000	57 (26.6)	12 (23.1)	.725
Age, y	73.8 (65.7-80.4)	73.2 (65.1-80.2)	78.6 (71.8-81.1)	.098	71.8 (64.5-79.7)	78.3 (73.0-82.7)	**.000**
Body mass index, kg/m^2	26.1 (23.8-29.4)	26.0 (23.8-29.3)	28.1 (25.7-32.5)	.052	26.0 (23.7-30.2)	25.9 (24.4-30.2)	.479
Coronary heart disease	128 (46.2)	119 (45.6)	9 (64.3)	.172	90 (42.1)	32 (61.5)	**.011**
Congestive heart disease	130 (47.1)	118 (45.4)	10 (71.4)	.096	96 (45.1)	31 (59.6)	.065
Severely reduced LVEF	70 (25.5)	63 (24.3)	6 (42.9)	.126	55 (25.9)	13 (25.0)	.889
Previous cardiac valve surgery	41 (14.8)	41 (15.7)	0 (0.0)	.237	29 (13.6)	10 (19.2)	.299
COPD	41 (14.8)	37 (14.2)	4 (28.6)	.139	30 (14.0)	10 (19.2)	.346
Peripheral arterial occlusive disease	30 (10.8)	29 (11.1)	1 (7.1)	1.000	22 (10.3)	6 (11.5)	.791
Malignancy	49 (17.7)	46 (17.6)	3 (21.4)	.721	35 (16.4)	12 (23.1)	.254
Diabetes mellitus	93 (33.7)	86 (33.1)	7 (50.0)	.247	72 (33.8)	20 (38.5)	.527
Inhalative corticosteroid	24 (8.7)	21 (8.0)	3 (21.4)	.112	15 (7.0)	8 (15.4)	.093
Oral corticosteroid	21 (7.6)	18 (6.9)	3 (21.4)	.082	13 (6.1)	8 (15.4)	**.041**
Immunosuppressive medication	17 (6.1)	17 (6.5)	0 (0.0)	1.000	9 (4.2)	7 (13.5)	**.020**
Preoperative creatinine, mg/dL	1.2 (1.0-1.6)	1.2 (1.0-1.6)	1.6 (1.2-3.1)	**.028**	1.2 (1.0-1.5)	1.5 (1.1-2.4)	**.002**
GFR, mL/min	56 (38-72)	57 (38-74)	43 (18-52)	**.018**	58 (39-75)	44 (24-61)	**.001**
GFR under 60 mL/min	154 (56.4)	143 (55.4)	10 (71.4)	.127	110 (51.9)	36 (72.0)	**.010**
End stage renal disease (with dialysis)	23 (8.6)	20 (7.9)	3 (23.1)	.092	11 (5.3)	12 (25.0)	**.000**
History of endocarditis	10 (3.6)	9 (3.4)	1 (7.1)	.412	7 (3.3)	3 (5.8)	.416
History of pocket infection	14 (5.1)	14 (5.4)	0 (0.0)	1.000	11 (5.1)	2 (3.8)	1.000

Note that patients censored prior to the time investigated (ie 30 days and 1 year) were not included in the death or survival group for each statistical analysis such that the total patients analysed does not add up to 277 patients.

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction.

Values of $P < .05$ are shown in bold.

TABLE 3 Device related and procedural characteristics of patients with cardiac implantable electronic device infection with statistical analysis regarding 30-day and 1-year mortality

		30-Day mortality			1-Year mortality		
	All (%/IQR)	Survival over 30 days (%/IQR)	Death within 30 days (%/IQR)	*P*	Survival over 1 year (%/IQR)	Death within 1 year (%/IQR)	*P*
Total	277 (100)	261 (94.2)	14 (5.1)		214 (77.3)	52 (18.8)	
Device type				.074			.234
Pacemaker	172 (62.1)	165 (63.2)	6 (42.9)		133 (62.7)	31 (59.6)	
ICD	44 (15.9)	40 (15.3)	4 (28.6)		30 (14.0)	12 (23.1)	
CRT-Pacemaker	4 (1.4)	2 (0.8)	1 (7.1)		2 (0.9)	1 (1.9)	
CRT-Defibrillator	57 (20.6)	54 (20.7)	3 (21.4)		49 (22.9)	8 (15.4)	
ICD lead present	92 (33.2)	85 (32.6)	7 (50.0)	.243	71 (33.2)	19 (36.5)	.664
Dual coil ICD lead present	42 (15.2)	40 (15.3)	2 (14.3)	1.000	34 (15.9)	7 (13.5)	.832
Time between last procedure and extraction, d	304 (93-1100)	314 (94-1153)	242 (90-570)	.391	295 (78-1002)	304 (142-1163)	.527
Time between initial implant and extraction, d	1748 (325-4015)	1814 (366-4094)	506 (240-986)	**.016**	1819 (404-4117)	1166 (231-3854)	.456
Device procedures before last procedure	2 (1-3)	2 (1-3)	1 (1-3)	.244	2 (1-3)	1 (1-3)	.161
CIED related infective endocarditis	148 (53.4)	134 (51.3)	14 (100)	**.000**	108 (50.5)	37 (71.2)	**.007**
Duke score 2	74 (26.7)	67 (25.7)	7 (50.0)	.062	51 (23.8)	23 (44.2)	**.003**
Blood culture positive	114 (41.2)	103 (39.5)	11 (78.6)	**.004**	80 (37.4)	32 (61.5)	**.002**
TEE performed	151 (55.1)	137 (53.1)	13 (92.9)	**.004**	108 (50.9)	38 (74.5)	**.002**
Vegetation detected (when echocardiography performed)	111 (73.0)	101 (73.2)	10 (76.9)	1.000	81 (74.3)	27 (71.1)	.695
Vegetation size >1 cm	90 (32.5)	81 (31.0)	9 (64.3)	**.016**	68 (31.8)	21 (40.4)	.238
Concurrent valve endocarditis	30 (10.8)	28 (10.7)	2 (14.3)	.655	21 (9.8)	9 (17.3)	.143
Concomitant valve procedure	16 (5.8)	16 (6.1)	0 (0.0)	1.000	13 (6.1)	3 (5.8)	1.000
Complications of infection	190 (68.8)	176 (67.2)	14 (100)	**.006**	137 (64.3)	45 (86.5)	**.002**
Local complication	101 (36.6)	95 (36.5)	4 (28.6)	.776	76 (35.7)	18 (34.6)	.886
Systemic complication	121 (43.7)	107 (41.0)	14 (100)	**.000**	78 (36.4)	40 (76.9)	**.000**
Total	277 (100)	261 (94.2)	14 (5.1)		214 (77.3)	52 (18.8)	
Duration of extraction procedure, min	58 (35-90)	58 (35-90)	30 (26-70)	**.026**	58 (35-90)	54 (30-81)	.350

(Continues)

TABLE 3 (Continued)

	All (%/IQR)	30-Day mortality			1-Year mortality		
		Survival over 30 days (%/IQR)	Death within 30 days (%/IQR)	*P*	Survival over 1 year (%/IQR)	Death within 1 year (%/IQR)	*P*
Tools required for extraction	106 (45.3)	101 (46.1)	4 (30.8)	.280	79 (44.6)	21 (45.7)	.901
Heart-lung machine standby	73 (26.4)	72 (27.6)	1 (7.1)	.123	61 (28.5)	11 (21.2)	.285
Heart-lung machine used for extraction	21 (7.6)	21 (8.0)	0 (0.0)	.610	18 (8.4)	3 (5.8)	.775
Incomplete lead removal (vascular or extravascular) with initial procedure	80 (28.9)	77 (29.5)	2 (14.3)	.529	64 (29.9)	14 (26.9)	.672
Incomplete lead removal (vascular or extravascular) with all extraction procedures	68 (24.6)	65 (24.9)	2 (14.3)	.529	53 (24.8)	14 (26.9)	0.748
Any procedural complications	30 (10.8)	29 (11.1)	1 (7.1)	1.000	22 (10.3)	7 (13.5)	.509
Major procedural complications	3 (1.2)	3 (1.3)	0 (0.0)	1.000	3 (1.6)	0 (0.0)	1.000
Minor procedural complications	19 (7.8)	18 (7.9)	1 (7.1)	1.000	12 (6.5)	6 (12.5)	.219
Preoperative antibiotic therapy, d	7 (2-13)	7 (2-13)	10 (7-13)	.070	7 (2-13)	8 (3-13)	.240
Complete duration of antibiotic therapy, d	30 (14-45)	30 (14-47)	27 (22-34)	.478	28 (14-47)	36 (28-42)	.055
Reimplantation of a CIED	185 (66.8)	183 (70.1)	2 (14.3)	**.000**	158 (73.8)	23 (44.2)	**.000**
Time between extraction and reimplantation, d	17 (3-49)	17 (4-50)	6 (3-8)	.248	18 (4-50)	14 (1-50)	.751
Hospital stay tertiary center, d	10 (5-20)	10 (5-20)	12 (5-19)	.973	10 (6-20)	7 (5-16)	**.083**
Preoperative C-reactive protein, mg/dL	2.4 (0.6-8.3)	2.1 (0.6-7.4)	11.2 (9.0-12.2)	**.000**	2.1 (0.6-7.5)	7.0 (1.4-11.1)	**.005**
Preoperative leukocyte count, $x10^9$/L	7.9 (6.3-10.4)	7.9 (6.2-10.0)	11 (6.9-12.8)	.224	7.8 (6.2-9.7)	9.5 (6.4-12.5)	**.046**
Preoperative platelet count, $x10^9$/L	223 (167-284)	224 (171-287)	153 (116-259)	.054	230 (174-292)	190 (124-249)	**.000**
Preoperative hemoglobin level, g/dL	11.8 (10.2-13.6)	12.0 (10.3-13.7)	10.3 (8.6-11.2)	**.001**	12.3 (10.6-13.9)	10.4 (9.6-11.7)	**.000**

Note that patients censored prior to the time investigated (ie 30 days and 1 year) were not included in the death or survival group for each statistical analysis such that the total patients analysed does not add up to 277 patients.

Abbreviations: CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LLD, lead locking device; TEE, transesophageal echocardiography.

Values of $P < .05$ are shown in bold.

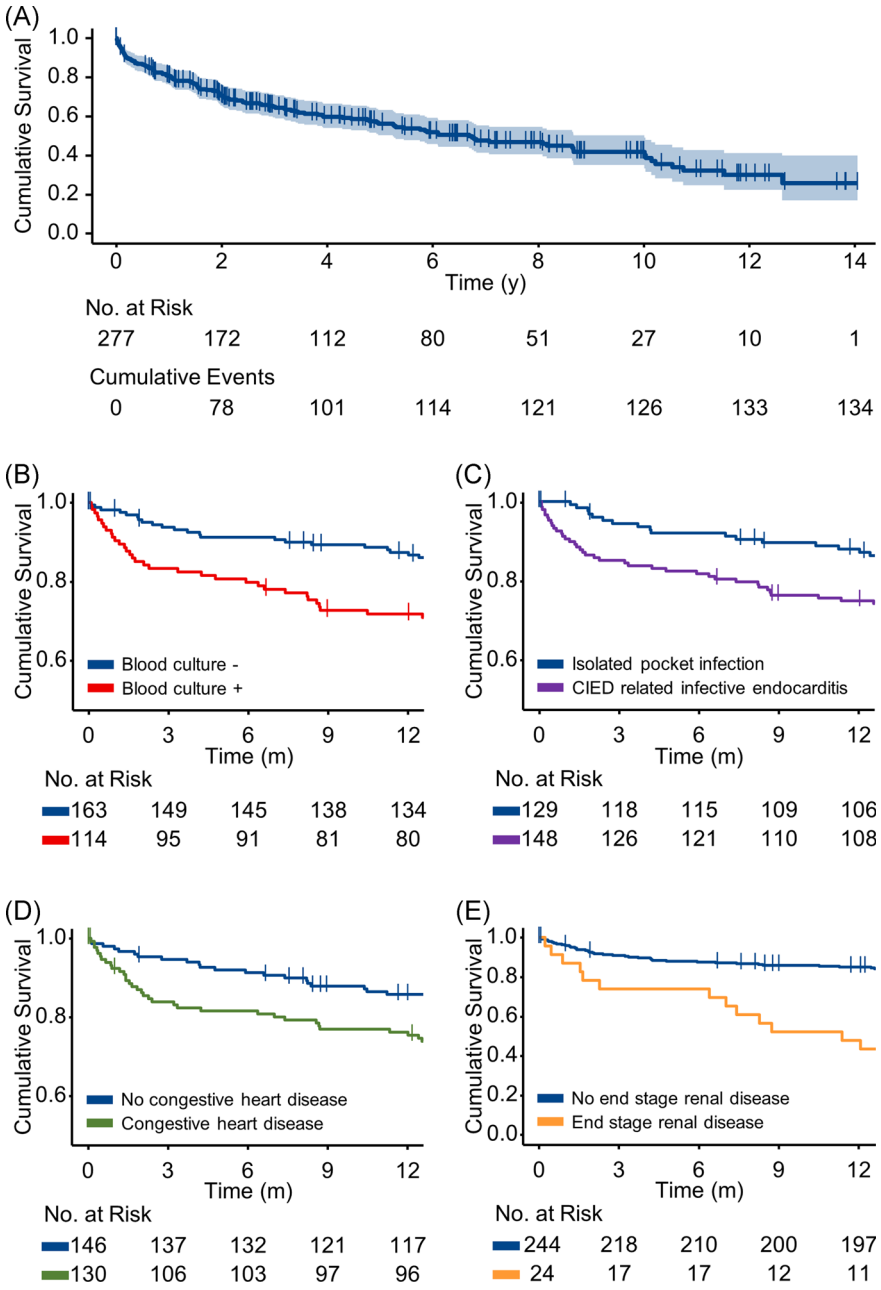

FIGURE 2 Kaplan-Meier graphs of survival after treatment of cardiac implantable electronic device (CIED) infection. A, Survival data of the complete cohort with a band indicating the confidence interval for survival estimates. B, Comparison of survival in patients with (red) and without (blue) positive blood cultures. C, Comparison of survival in patients with CIED related infective endocarditis (purple) and isolated pocket infection (blue). D, Comparison of survival in patients with (green) and without (blue) congestive heart disease preoperatively. E, Comparison of survival in patients with (orange) and without (blue) end stage renal disease with dialysis preoperatively. Note that in panel E the scale of y axis differs to those in panels B-D

4 | DISCUSSION

With a 94.9% 30-day survival rate and an 80.9% 1-year survival rate, we report similar rates as previous investigators.[10] One-year mortality rates as high as 25.3% have been reported for CIED infections.[11] In our cohort within the first 30 days 10 patients died of sepsis, two died of arrhythmia, and two of cardiogenic shock. Gould et al[12] similarly report that most early mortality is related to sepsis. Patients which died within the first 30 days after treatment all suffered from CIEDR-IE making CIEDR-IE a significant predictor of 30-day mortality.

Patients which died within 1 year of the extraction procedure also mainly died of sepsis, cardiogenic shock, and arrhythmia (see Table S7). In univariable analysis all baseline cardiovascular profile variables except coronary heart disease were found not to have a significant impact on 1-year survival. Patients which died within 1 year of surgery were found to suffer from coronary heart disease statistically more frequently. Multivariable analysis of predictors of 1-year mortality suggests that patient age, end state renal disease (ESRD) with dialysis, positive blood cultures, and thrombocytopenia are key predictors. In a recent meta-analysis Polyzos et al[13] were able to demonstrate that ESRD is associated with an odds ratio of 8.73 for the development of a CIED infection. Further reports have demonstrated the negative effect of ESRD on survival after lead extraction for lead related infective endocarditis.[14,15] In our subgroup of patients with death within 1 year we found 25% to suffer from ESRD. The high mortality rate in ESRD patients is most likely associated with the fact that these patients are multimorbid, have a

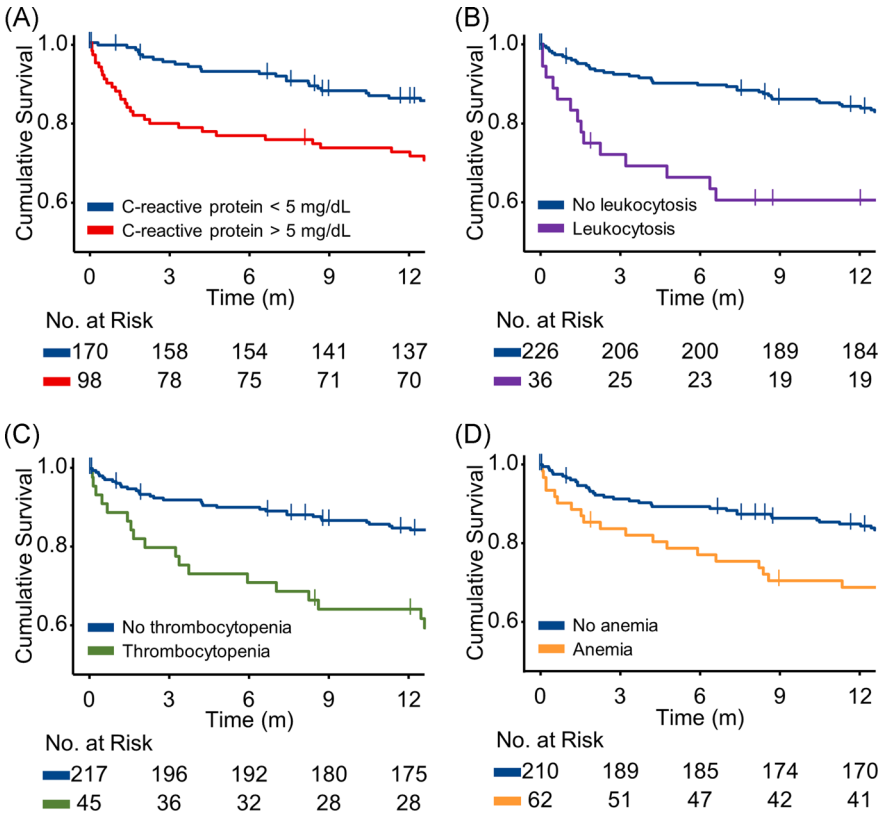

FIGURE 3 Kaplan-Meier graphs of survival after treatment of cardiac implantable electronic device infection. A, Comparison of survival in patients with a preoperative C-reactive protein value greater than (red) with patients with one lower than 5 mg/dL (blue). B, Comparison of survival in patients with a preoperative leukocyte count greater than (purple) with patients with one lower than 12×10^9/L (blue). C, Comparison of survival in patients with a preoperative platelet count lower than (green) with patients with one greater than 150×10^9/L (blue). D, Comparison of survival in patients with a preoperative hemoglobin value lower than (orange) with patients with one greater than 10 g/dL (blue)

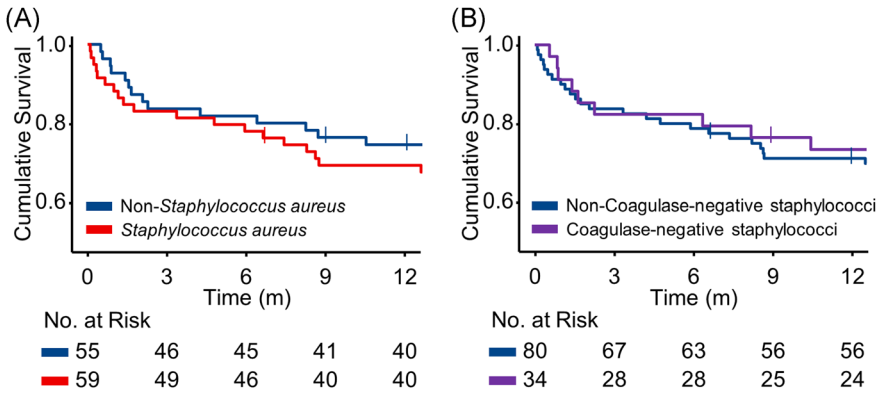

FIGURE 4 Kaplan-Meier graphs of survival after treatment of cardiac implantable electronic device infection in blood culture positive patients. A, Comparison of survival in patients with infection caused by *Staphylococcus aureus* (red) and any other bacterial species (blue). B, Comparison of survival in patients with infection caused by coagulase negative staphylococci (purple) and any other bacterial species (blue)

TABLE 4 Multivariable analysis of predictors of death within 1 year of treatment of cardiac implantable electronic device infection

Variable	Odds ratio	95% CI	*P*
Age, y	1.05	(1.01-1.09)	.009
Dialysis	5.14	(1.87-14.11)	.001
Bacterial isolates in blood culture	2.19	(1.08-4.45)	.030
Preoperative thrombocytopenia[a]	2.30	(1.03-5.15)	.042

Abbreviation: CI: confidence interval.
[a]Thrombocytopenia was defined as a platelet count under 150×10^9/L.

higher risk of cardiovascular disease, but may also be associated with the frequent transient bacteremia found in hemodialysis patients (which subsequently makes infection the second leading cause of death in hemodialysis patients).[16] We did not find an increased presence of dialysis catheters as a source of infection in this specific patient subgroup.

Distinguishing between CIED-IE and IPI is critical when evaluating patient mortality related to CIED infections. Via univariable analysis we were able to demonstrate that CIED-IE was associated with a significantly higher 30-day and 1-year mortality. The role of positive blood cultures in evaluating the risk of mortality in patients with infections is well established. It is not surprising that we identified this variable as a significant predictor of survival. As expected most patients with positive blood cultures were infected with staphylococcal species, *Staphylococcus aureus* constituting 46.5% and coagulase negative staphylococci (CoNS) constituting 26.3% of positive blood cultures. The virulence of *S. aureus* is frequently cited and *S. aureus* has

previously been identified as a predictor of early mortality in infective endocarditis.[17] Unexpectedly we did not find a significant difference between survival in patients with *S. aureus*, CoNS, and other bacterial species. Polewczyk et al[14] similarly did not find *S. aureus* to be predictive of a worse outcome in their cohort. We thus suggest that once blood cultures are positive survival is significantly impaired irrespective of which bacterial species is the causative agent. Patients which died within the first 30 days of operative treatment were found to have received antibiotic therapy for a longer period of time preoperatively than patients which survived after 30 days. Preoperative antibiotic therapy duration may be seen as a surrogate of time from diagnosis to extraction. One can thus suggest that these results support the dogma that extraction should be performed as swiftly as possible after a CIED infection has been confirmed.[11,18]

With the aim of identifying factors which could allow a stratification of mortality risk we also investigated preoperative laboratory parameters in our cohort. We found that the preoperative presence of anemia predicts a reduced survival in patients with CIED infections in univariable analysis. In inflammatory disease the activation of immune effector mechanisms can lead to a decrease in iron availability to erythroid cells via multiple pathways.[19] Iron is essential for microbial proliferation such that this process may be seen as a defense mechanism. One could subsequently interpret the increased presence of anemia in patients with death within 1 year as an indicator of pronounced infection rather than as the result of a causal relationship. Anemia has also been associated with frailty[20,21] such that a further possible explanation is that anemia is a confounder and patient frailty is the cause for an increased mortality in the anemic subgroup.

Analogously we found a lower platelet count in patients with survival under 1 year. Patients with a platelet level under 150×10^9/L had an odds ratio of 2.3 for death within 1 year after treatment. Platelets have been identified as "integral players in inflammatory processes and immunity"[22] in the past two decades such that thrombocytopenia could be a motor of reduced survival rather than just a surrogate marker. Sullam et al[23] were able to show that induction of thrombocytopenia in rabbits with endocarditis resulted in higher bacterial densities in vegetations suggesting that a reduced platelet count may have an impact on infection severity.

While some studies suggest a relationship between thrombocytopenia and infection severity this has not been understood fully as of yet. Further research is required to better understand the pathophysiological relationship between platelets and infection. Until we have a better understanding of this issue we can still be satisfied to use the insights from our data for risk evaluation in clinical practice. The predictors established herein can be used to identify high-risk patients. Subsequently in the treatment of high-risk patients a lower threshold for intensive care admission and escalation of antimicrobial therapy can be adopted.

Limitations of our study are the study format and the time frame of the study. As patients from over a decade of clinical practice were included in our cohort treatment strategies vary depending on the time when treatment took place; treatment strategies have relevantly been adapted according to results and guidelines published in this field.

5 | CONCLUSION

In this investigation of our 17-year experience with the treatment of CIED infections we were able to underline the previously known high mortality associated with this condition. We identified key predictors of 1-year mortality. We recommend a critical evaluation of patient history and preoperative laboratory parameters in patients with CIED infection. Patients with ESRD and patients with thrombocytopenia may be viewed as high-risk patients and should be treated with caution. The role of platelets in the immune response warrants further preclinical as well as clinical research as their role in immunity could have an impact of future therapeutic approaches.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

Florian Ernst Martin Herrmann http://orcid.org/0000-0002-3820-1655

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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