Clinical Outcomes of Patients with COVID-19 Infection and Cardiac Implantable Electronic Devices

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ABSTRACT

Background: Existing cardiac disease contributes to poor outcome in patients with coronavirus disease 2019 (COVID-19). Little information exists regarding COVID-19 infection in patients with a cardiac implantable electronic device (CIED).

Objectives: To assess the association between CIEDs and severity of COVID-19 infection.

Methods: We performed a retrospective analysis including 13,000 patients > 18 years old with COVID-19 infection between January and December 2020. Patients with COVID-19 who had a permanent pacemaker or defibrillator were matched 1:4 based on age and sex followed by univariate and multivariate analyses. Baseline characteristics and clinical outcomes were assessed.

Results: Forty patients with CIED and 160 patients without CIED were included in the current analysis. Mean age was 72.6 ± 13 years, and approximately 50% were females. Majority of the patients in the study arm had a pacemaker (63%), whereas only 15 patients (37%) had a defibrillator. Patients with COVID-19 and CIED presented more often with atrial fibrillation, coronary artery disease, heart failure, hypertension, diabetes, and chronic kidney disease. They were more likely to be hospitalized in the intensive care unit (ICU) and required more ventilatory support (35% vs. 18.3%). Thirty-day mortality (22.5% vs. 13.8%) and 1-year mortality (25% vs. 15%) were higher among patients with COVID-19 and CIED.

Conclusions: Patients with COVID-19 and CIED had a significantly higher prevalence of co-morbidities that were associated with increased mortality. Although, CIED by itself was not found as an independent risk factor for morbidity and mortality, it may serve as a warning for severe illness with COVID-19.

IMAJ 2023; 25: 177–181

KEY WORDS: cardiac implantable electronic device (CIED), coronavirus disease 2019 (COVID-19), defibrillator, pacemaker

The coronavirus disease 2019 (COVID-19) pandemic presented new challenges for healthcare centers and medical caregivers worldwide. Many attempts were made to identify preexisting conditions that affected morbidity and mortality in patients with COVID-19 infection. Identifying co-morbid conditions that can predict poor prognosis and adverse outcome is important and has substantial ramifications for the management of these patients [1].

Data on patients diagnosed with COVID-19 who present with co-morbidities [2-5] have suggested a correlation between cardiac risk factors and mortality risk from COVID-19 [6]. Early reports from China showed markedly elevated mortality rates in patients with hypertension, diabetes, and preexisting cardiovascular disease [7].

Although many studies have analyzed the correlation between preexisting cardiovascular disease, risk factors, and severity of COVID-19, there has been little discussion in the literature whether implantable cardiac devices constitute as a major risk marker for poor outcomes in patients with COVID-19 infection. Except for the recommendations regarding the management of cardiac electrophysiology and cardiac implantable electronic device (CIED) in patients with COVID-19 infection [8,9], to the best of our knowledge, the association between the two has not been investigated. Therefore, we examined whether patients with CIEDs were more susceptible to severe disease and adverse outcomes from COVID-19 infection.

PATIENTS AND METHODS

STUDY POPULATION

We performed a single-center retrospective study including 13,000 patients who were older than 18 years of age and tested positive for COVID-19 between January and December of 2020 in a tertiary medical center in Israel. The study group included 40 patients who tested positive for COVID-19 and had a previous implantation of CIED, including a pacemaker or defibrillator. Propensity score matching with a ratio of 1:4 was performed

based on age and sex, followed by univariate and multivariate analysis of multiple clinical variables. The control group consisted of 160 patients who tested positive for COVID-19 but had no implanted cardiac devices. All patients had the diagnosis of COVID-19 confirmed by positive results of polymerase chain reaction (PCR) testing of a nasopharyngeal swab.

DATA COLLECTION AND DEFINITIONS

Soroka University Medical Center is a high-volume tertiary medical center that serves as the only regional hospital in southern Israel. The study was approved by the institutional Helsinki committee. Demographic, baseline, laboratory, procedural, and hospitalization data including in hospital adverse events were collected from a central computerized database of Clalit Health Service system, which is the largest health care provider in southern Israel. The study population's co-morbidities data were extracted from the chronic diagnoses recorded for the patients in the documented medical file by the primary care physician from Clalit's computerized system. Hospitalization data were collected from the electronic medical records.

STATISTICAL ANALYSIS

Data of main variables are presented as mean and standard deviations for normally distributed quantitative variables, medians, and ranges for non-normally distributed quantitative variables, and distribution in percent for qualitative variables. Chi square test was used for categorical variables with Fisher's exact test when needed. Continuous variables were compared using t-test for normally distributed variables and by Mann-Whitney U test for non-normally distributed variables. Univariate analysis was mostly used for analysis initial datasets consisted of personal data records.

Multivariable analysis corresponded to the distribution of the outcome. Specifically, 30-day and one-year survival analyses were assessed by Kaplan-Meier estimates. Log rank test was

used to assess the significance of difference in survival. Logistic regression multivariate analysis was performed for evaluating the 30-day potential risk of the major exposure factor; COVID-19, and CIED with adjustment for other factors based on clinical and statistical significance (entry criteria $P < 0.05$ in univariate analysis). The results of the survival models are presented as odds ratios (OR) with 95% confidence interval (95%CI).

RESULTS

PATIENT CHARACTERISTICS

Demographic and clinical features are shown in Table 1. The study arm included 40 patients with CIEDs. The control arm included 160 patients without CIEDs. Men and Woman were represented equally, mean age was 72.6 years. Patients with cardiac devices had a significantly higher incidence of co-morbidities, including hyper-

Table 1. Clinical characteristics of the study population

Variable	CIED, N=40	No CIED, N=160	P value
Age in years, mean	72.6 ± 13.2	72.6 ± 13.1	1
Sex, male	21 (52.5%)	84 (52.5%)	1
Coronary artery disease	22 (55%)	22 (13.8%)	< 0.001
Congestive heart failure	24 (60%)	17 (10.6%)	< 0.001
Atrial fibrillation	20 (50%)	19 (11.9%)	< 0.001
Hypertension	22 (55.0%)	61 (38.1%)	0.07
Diabetes	19 (47.5%)	47 (29.4%)	0.04
Chronic renal failure	13 (32.5%)	17 (10.6%)	0.001
Smoking	14 (35.0%)	27 (16.9%)	0.02
Chronic obstructive pulmonary disease	16 (40%)	21 (13.1%)	< 0.001

CIED = cardiac implantable electronic device

Table 2. Univariate and multivariate analysis of severe COVID-19 infection including intensive care unit admission and ventilatory support. Univariate analysis of patients with COVID-19 infection who died compared to patients with COVID-19 infection who survived: 1-year follow-up

	Univariate analysis			Multivariate analysis		Univariate analysis: 1-year follow-up		
	Severe COVID (N=20)	No severe COVID (N=180)	P value	Odds ratio	95% confidence interval	Mortality (N=34)	No mortality (N=166)	P value
Sex, male	13 (65.0%)	92 (51.1%)	0.345	–	–	19 (55.9%)	86 (51.8%)	0.806
Age in years, mean	73.5 ± 13.5	72.4 ± 13.1	0.738	1.01	0.97–1.05	82.6 ± 7.31%	70.5 ± 13.1%	< 0.001
CIED	7 (35.0%)	33 (18.3%)	0.084	2.40	0.85–6.34	10 (25%)	24 (15%)	0.204
Congestive heart failure	7 (35.0%)	34 (18.9%)	0.106	2.31	0.82–6.10	15 (44.1%)	26 (15.7%)	< 0.001
Coronary artery disease	6 (30.0%)	38 (21.1%)	0.317	1.60	0.54–4.29	17 (50%)	27 (16.3%)	< 0.001
Atrial fibrillation	5 (25.0%)	34 (18.9%)	0.517	1.43	0.44–3.99	13 (38.2%)	26 (15.7%)	0.005
Smoking	2 (10.0%)	39 (21.7%)	0.233	–	–	8 (23.5%)	33 (19.9%)	0.805
Diabetes	7 (35.0%)	59 (32.8%)	0.841	–	–	18 (52.9%)	48 (28.9%)	0.012
Hypertension	9 (45.0%)	74 (41.1%)	0.742	–	–	22 (64.7%)	61 (36.7%)	0.004
Chronic renal failure	2 (10.0%)	28 (15.6%)	0.741	–	–	11 (32.4%)	19 (11.4%)	0.004

CIED = cardiac implantable electronic device

tension (55% vs. 38.1%), diabetes (47.5% vs. 29.4%), chronic renal failure (CRF) (32.5% vs. 10.6%), and chronic obstructive pulmonary disease (COPD) (40% vs. 13.1%) compared with the control group, with hypertension being the most common co-morbidity in both the study arm and control arm. Fifteen (35.0%) patients in the study arm and 27 (16.9%) in the control arm were current smokers. In addition, the incidence of coronary artery disease (CAD) (55% vs. 13.8%), congestive heart failure (CHF) (60% vs. 10.6%), and atrial fibrillation (AF) (50% vs. 11.9%) were all higher among patients with CIEDs compared to non-CIEDs patients ($P < 0.001$).

TYPE OF CIED AND MORTALITY

Of the 40 patients included in the study arm, 25 had a pacemaker with a mean ejection fraction (EF) of 50% ± 11.8 and 15 patients had implantable defibrillator with a mean EF of 29% ± 11.1. Surprisingly, seven patients with pacemakers died (28% of patients with pacemakers), whereas only two patients with cardiac defibrillator died within 30 days (13% of patients with defibrillators). In addition, ventricular pacing greater than 70% was also assessed, but we could not find a significant difference between patients who died and patients who survived: 3 of 9 (33%) patients with CIEDs who died and 11 of 31 (35%) patients who survived fulfilled this criterion. Unfortunately, due to the retrospective design of our study and given the high virulency of the virus in 2020, patients were not interrogated routinely during the admission. The date regarding ventricular arrhythmias among the patients who died during admission is lacking.

VENTILATORY SUPPORT AND MORTALITY

Data regarding in-hospital management, 30-day, and 1-year mortality are shown in Figure 1. Overall hospital admission was required in 50% of patients with cardiac devices compared to 35% of patients of the control group. Of the hospitalized patients, 15% with cardiac devices were hospitalized in the intensive care unit (ICU) versus 6.9% of those without devices. Ventilation for respiratory support was required in 12.5% of study arm versus 7.8% in control arm. Univariate and multivariate of severe COVID infection defined as ICU admissions and ventilatory support (i.e., mechanical ventilation, bi-level positive airway pressure, continuous positive airway pressure, and high flow ventilation) are presented in Table 2. Numerically, all-cause mortality was higher in the CIED group compared to patients without CIED at 30 days (22.5% vs. 13.8%) and 1 year (25% vs. 15%), although not statistically significant. Univariate analysis indicated that age, AF, diabetes, hypertension, CAD, CHF, and CRF were significantly associated with risk of 1-year mortality from COVID-19 disease [Table 2]. Kaplan-Meier survival analysis revealed higher mortality among patients with COVID-19 and CIED versus patients with no cardiac implantable device, yet the results were not statistically significant [Figure 2]. In multivariable logistics, regression

Figure 1. Distribution of hospital admissions, mortality, and in-hospital ventilation in patients with COVID-19 infection with and without CIED

BIPAP = bi-level positive airway pressure, CIED = cardiac implantable electronic device, CPAP = continuous positive airway pressure, ICU = intensive care unit
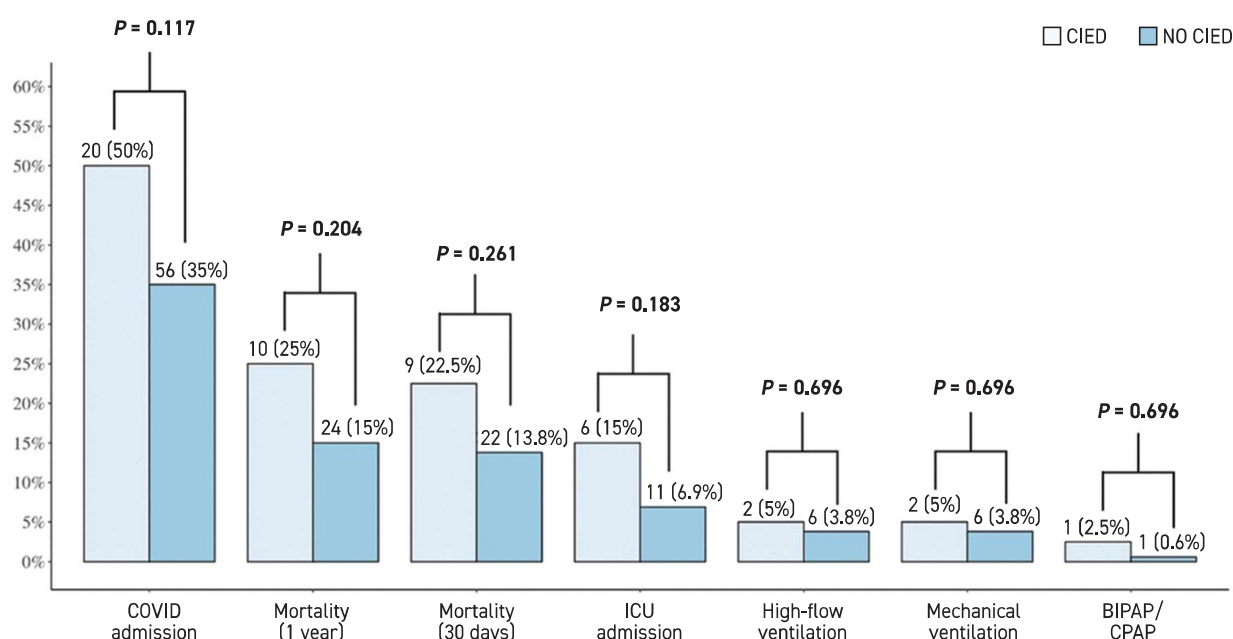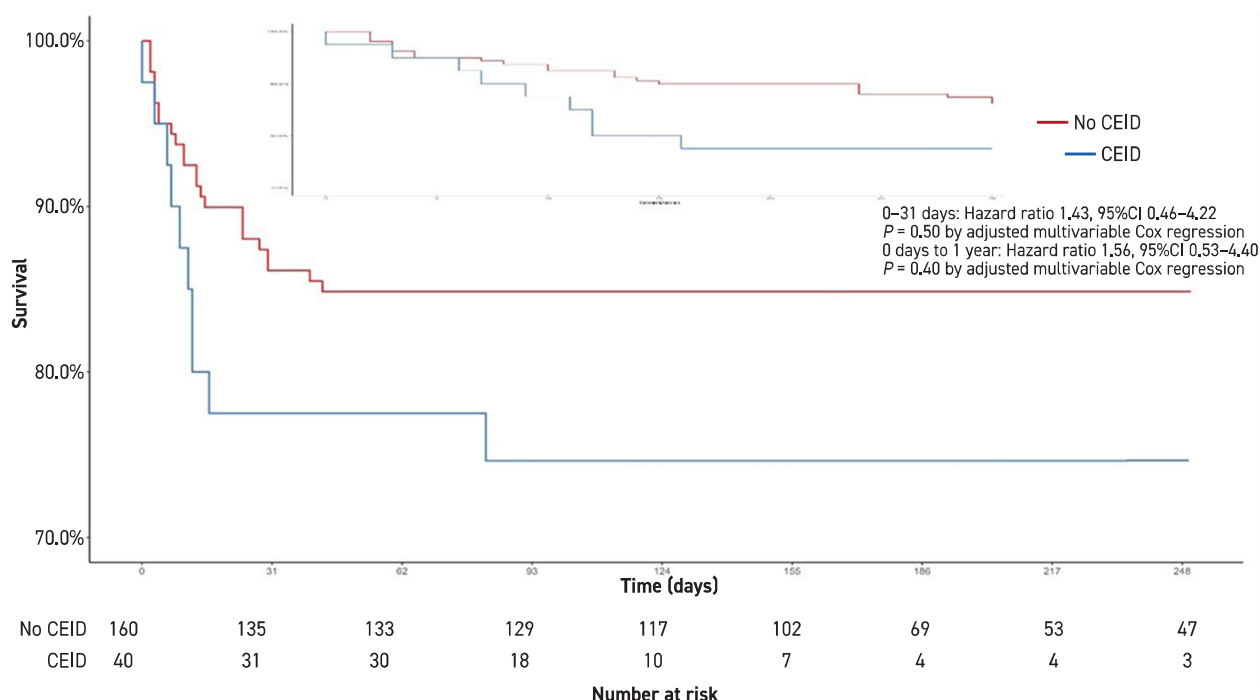
Figure 2. Kaplan-Meier curve of 1-year all-cause mortality in patients with COVID-19 infection with and without CIED
CIED = cardiac implantable electronic device

analysis including CIED, age, AF, CRF, and hypertension. Only age was found to be an independent predictor for 1-year mortality from COVID-19 disease (OR 1.11, 95%CI 1.05–1.18, $P < 0.001$).

DISCUSSION

Many risk factors have been identified as impacting the progression of COVID-19 to more severe and critical illness, including old age [10-13]; underlying co-morbidities such as hypertension, diabetes, obesity, chronic lung diseases [14-16]; and lifestyle habits such as smoking [17]. In addition, previous studies have reported CAD and AF as important independent predictors of mortality from COVID-19 [2-5]. To the best of our knowledge, this is the first study to assess the association between cardiac implantable electronic devices and outcomes in patient with COVID-19 infection. The present study confirms that cardiovascular risk factors, particularly older age, are associated with adverse outcomes in patients with COVID-19 infection. Notably, CIED by itself was not an independent risk factor of morbidity and mortality in patients with COVID-19 disease, but rather was a marker of an older and more co-morbid population.

Of the 40 patients who constituted the study arm, 25 had a permanent pacemaker for common indications including sinus node dysfunction and atrioventricular block. Of these patients, the mean EF was 50% ± 11.8, and the number of deaths was 7 (28%). Fifteen patients in the study arm had an implantable car-

diac defibrillator for primary and secondary prevention of sudden cardiac death. As expected, the mean EF (29% ± 11) was substantially lower in the latter group. The number of deaths, however, was lower than expected as only two patients with implantable defibrillator died during the study period, indicating that EF by itself was not a marker of mortality in patients with CIEDs.

The increased morbidity and mortality in the cardiac devices group was not statistically significant, yet the numerical difference between the cardiac devices group and the control arm in terms of ICU admission, need for ventilatory support, and mortality at 30 days and 1 year was substantial. The adjusted Kaplan-Meier curve of 30-day and 1-year mortality displays a remarkable difference in mortality as early as day 6 from admission [Figure 2], which cannot be disregarded.

The main limitations of the present study are its retrospective design and the small sample size. In addition, due to the relatively small number of patients with defibrillators vs. pacemakers, a separate analysis of these two populations could not be performed.

Last, our study was conducted in 2020, during the outbreak of the first SARS-CoV-2 variant; thus, it is unclear what are the ramifications of the new SARS-CoV-2 strains (i.e., Alpha, Beta, Gamma, Delta, and Omicron) on the morbidity and mortality of patients with CIEDs. As such, and given our relatively limited study sample, a larger and more contemporary studies are required to assess whether our hypothesis is still relevant to the emerging SARS-CoV-2 mutations.

CONCLUSIONS

Patients with COVID-19 and previous pacemaker or defibrillator implantation had a significantly higher prevalence of co-morbidities and numerically higher rate of ICU admissions, ventilatory support, and overall mortality, although not statistically significant. Several co-morbidities were associated with increased mortality, whereas only age was found as an independent marker of mortality. Although CIED by itself was not found as an independent risk factor for morbidity and mortality, it may serve as a warning flag for severe illness in COVID-19 patients. We believe that patients with CIED and COVID-19 infection should be regarded as a high-risk population and managed with the utmost of caution, including preventive vaccination and early admission to the ICU.

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Capsule

Autoimmunity in Down syndrome via cytokines, CD4 T cells and CD11c+ B cells

Down syndrome (DS) presents with a constellation of cardiac, neurocognitive, and growth impairments. Individuals with DS are also prone to severe infections and autoimmunity including thyroiditis, type 1 diabetes, coeliac disease, and alopecia areata. **Malle** and colleagues investigated the mechanisms underlying autoimmune susceptibility, by mapping the soluble and cellular immune landscape of individuals with DS. They found a persistent elevation of up to 22 cytokines at steady state (at levels often exceeding those in patients with acute infection) and detected basal cellular activation: chronic IL-6 signalling in CD4 T cells and a high proportion of plasmablasts and CD11c+TbethighCD21low B cells (Tbet is also known as TBX21). This subset is known to be autoimmune-prone and displayed even greater autoreactive features in DS, including receptors with fewer non-reference nucleotides and higher *IGHV4-34* utilization. In vitro, incubation of naive B cells in the plasma of individuals with DS or with IL-6-activated T cells resulted in increased plasmablast differentiation compared with control plasma or unstimulated T cells, respectively. Last, the authors detected 365 autoantibodies in the plasma of individuals with DS, which targeted the gastrointestinal tract, the pancreas, the thyroid, the central nervous system, and the immune system itself. Together, these data point to an autoimmunity-prone state in DS, in which a steady-state cytokinopathy, hyperactivated CD4 T cells, and ongoing B cell activation all contribute to a breach in immune tolerance. These findings also open therapeutic paths, as the demonstrate that T cell activation is resolved not only with broad immunosuppressyants such as Jak inhibitors, but also with the more tailored approach of IL-6 inhibition.

Nature 2023; 615: 305

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