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ORIGINAL ARTICLE

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Mortality outcome and predictive risk factors for death in patients with heart failure and reduced ejection fraction who declined implantable cardioverter defibrillator implantation in Singapore

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Abstract

Background: There have been conflicting data regarding the risk of sudden cardiac death (SCD) in Asian population with reduced left ventricular ejection fraction (LVEF). We aim to study mortality outcome and its risk predictors in patients with reduced LVEF who declined an implantable cardioverter defibrillator (ICD) implantation and assess whether current ICD guidelines for primary prevention are applicable to the population in Singapore.

Methods: This prospective observational study involved 240 consecutive patients who fulfilled the ACC/AHA/HRS criteria for ICD implantation for primary prevention of SCD but declined ICD implantation. Baseline characteristics and mortality outcomes through May 2017 were collected via case-note review after a mean follow-up of 44.8 ± 16.6 months.

Results: Majority of our patients were Chinese (71.3%), followed by Malays (16.2%) and Indians (10.8%). Mean age (±SD) was 61 ± 10 years, and 84% were male. Majority were in New York Heart Association (NYHA) functional classes I (46.7%) and II (46.3%). Over a mean follow-up of 44.8 ± 16.6 months, all-cause mortality rate was 34.6%. Diabetes mellitus (HR = 1.57; 95% CI, 1.01-2.44; P = 0.047) and chronic kidney disease (CKD; HR = 1.95; 95% CI, 1.17-3.23; P = 0.010) were independent predictors of mortality. Patients in NYHA classes II (HR = 2.15; 95% CI, 1.32-3.50; P = 0.002) and III (HR = 2.82; 95% CI, 1.34-5.96; P = 0.007) showed higher risk of death.

Conclusion: The mortality rate was comparable with major primary prevention trials. ICD guideline recommendations for primary prevention may thus be applicable to our local population. Patients with diabetes, CKD, and poorer NYHA status exhibited higher mortality rates.

KEYWORDS

Asian population, heart failure, implantable cardioverter defibrillator, mortality outcomes, primary prevention

1 | INTRODUCTION

Patients with reduced left ventricular ejection fraction (LVEF) due to ischemic or nonischemic cardiomyopathy (CMP) are at increased risk of sudden cardiac death (SCD). Implantable cardioverter defibrillator (ICD) implantation has been shown to reduce SCD rates in these patients.[1–4] Despite demonstrated benefits, ICD uptake rates have been low. In a tertiary care medical center in the United States, the ICD implantation rate for primary prevention was only 28%.[5] In Singapore, the number of ICD implants for primary prevention has increased 18-fold in a 10-year observational study carried out in a single local large center.[6] Despite this increase, the overall ICD implantation rate in Singapore remains low compared to other developed countries. In 2014 for example, the rate of ICD implantation in Singapore was 52.8 per million.[7] This is in contrast to the rate of ICD implantation in Australia (160 per million), Germany (290 per million), and the United States (434 per million) in the 2009 World Survey of Pacemakers and ICDs.[8]

In this prospective observational study, we report mortality rates in patients from our local Singaporean population who met current ACC/AHA/HRS criteria for ICD implantation for primary prevention[9] but declined implantation. In addition, we investigate the risk factors for mortality (specifically the presence of comorbidities such as diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease (CKD), New York Heart Association functional status, LVEF, and age) in this patient cohort to identify high-risk patients who might have benefitted from ICD implantation.

2 | METHODS

Recruitment of the 240 patients of the National Heart Centre Singapore (NHCS) with ischemic and nonischemic cardiomyopathy with reduced LVEF of ≤35% who had declined ICD implantation has been previously described.[10] The patients were recruited over a 6-month period from October 2012 to March 2013. They fulfilled the current ACC/AHA/HRS criteria for ICD implantation for primary prevention of SCD but declined ICD implantation. Inclusion criteria included age ≥21 years and patients who were able to give written informed consent. Patients meeting the criteria for secondary prevention of SCD and patients previously diagnosed with cognitive impairment or depression were excluded. The study was approved by the local institutional ethics committee and performed in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was provided by all patients.

Patients were prospectively followed up with relevant clinical information extracted from the medical records, including age, ethnicity, gender, LVEF, comorbidities, and the New York Heart Association (NYHA) functional class status as assessed by their primary cardiologist during the time of recruitment. Mortality outcomes through May 2017 were obtained from case-note review.

Continuous variable was summarized as mean and standard deviation (SD) and categorical variables as counts and percentages. A multivariable Cox proportional hazard regression model was used to analyze patient survival outcomes with adjustment for baseline risk factors. Significance test was two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

Clinical characteristics of the 240 patients are provided in Table 1. Majority of patients were Chinese (71.3%) followed by Malays (16.2%) and Indians (10.8%). A total of 202 of the patients were male (84%); mean age was 61 ± 10 years. 73% of all patients had ischemic cardiomyopathy. Majority (93%) of the patients were in New York Heart Association (NYHA) functional classes I (46.7%) and II (46.3%). Mean LVEF was 23 ± 5.9%. Majority of patients had class I indication for ICD (82.5%), and the remainder of patients (17.5%) had class IIb indication for ICD implantation. Prescription rates for heart failure medications were high with 89% of patients prescribed angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, and 92.5% prescribed beta-blockers. Slightly more than half of the patients (54.6%) were given aldosterone antagonists. There were four patients lost to follow-up as of May 2017.

Over a mean follow-up of 44.8 ± 16.6 months, all-cause mortality rate was 34.6% (83/240). Patients in NYHA class I had lower

TABLE 1 Baseline characteristics of the patients

Age (y), mean ± SD	61 ± 10
Male sex, n (%)	202 (84)
Race	
Chinese, n (%)	171 (71.3)
Malay, n (%)	39 (16.2)
Indian, n (%)	26 (10.8)
NYHA functional class, n (%)	
I	112 (46.7)
II	111 (46.3)
III	17 (7)
Left ventricular ejection fraction, mean ± SD (%)	23 ± 5.9
Ischemic etiology, n (%)	176 (73)
Diabetes, n (%)	101 (42.1)
Hypertension, n (%)	158 (65.8)
Hyperlipidemia, n (%)	188 (78.3)
Renal impairment, n (%)	40 (16.7)
Medication use at baseline, n (%)	
ACE inhibitor/ARB, n (%)	214 (89.2)
Beta-blocker, n (%)	222 (92.5)
Statin, n (%)	215 (89.6)
Aldosterone antagonist, n (%)	131 (54.6)
Antiplatelet, n (%)	190 (79.2)
Class of indication for ICD, n (%)	
I	198 (82.5)
IIb	42 (17.5)

mortality rates than patients in NYHA class II and higher ($P < 0.001$; Figure 1A). Kaplan-Meier analysis showed diabetes mellitus to be a significant risk factor for death (log-rank test, $P = 0.011$; Figure 1B). Patients who had class I indication for ICD had significantly lower survival rates compared to the patients with class IIb indication (log-rank test, $P = 0.032$; Figure 1C). In the Cox multivariable analysis, the risk of death was higher in patients with diabetes (HR = 1.57; 95% CI, 1.01-2.44; $P = 0.047$) and in those with CKD (HR = 1.95; 95% CI, 1.17-3.23; $P = 0.010$). Patients in NYHA class II (HR = 2.15; 95% CI, 1.32-3.50; $P = 0.002$) and class III (HR = 2.82; 95% CI, 1.34-5.96; $P = 0.007$) also showed higher risk of death compared to patients in NYHA class I functional status (Table 2). Gender, baseline LVEF, age, hypertension, hyperlipidemia, and stroke were not significant risk factors for all-cause death.

4 | DISCUSSION

In our study comprising patients with standard criteria for ICD implantation for primary prevention[9] but declined, the mortality rate was

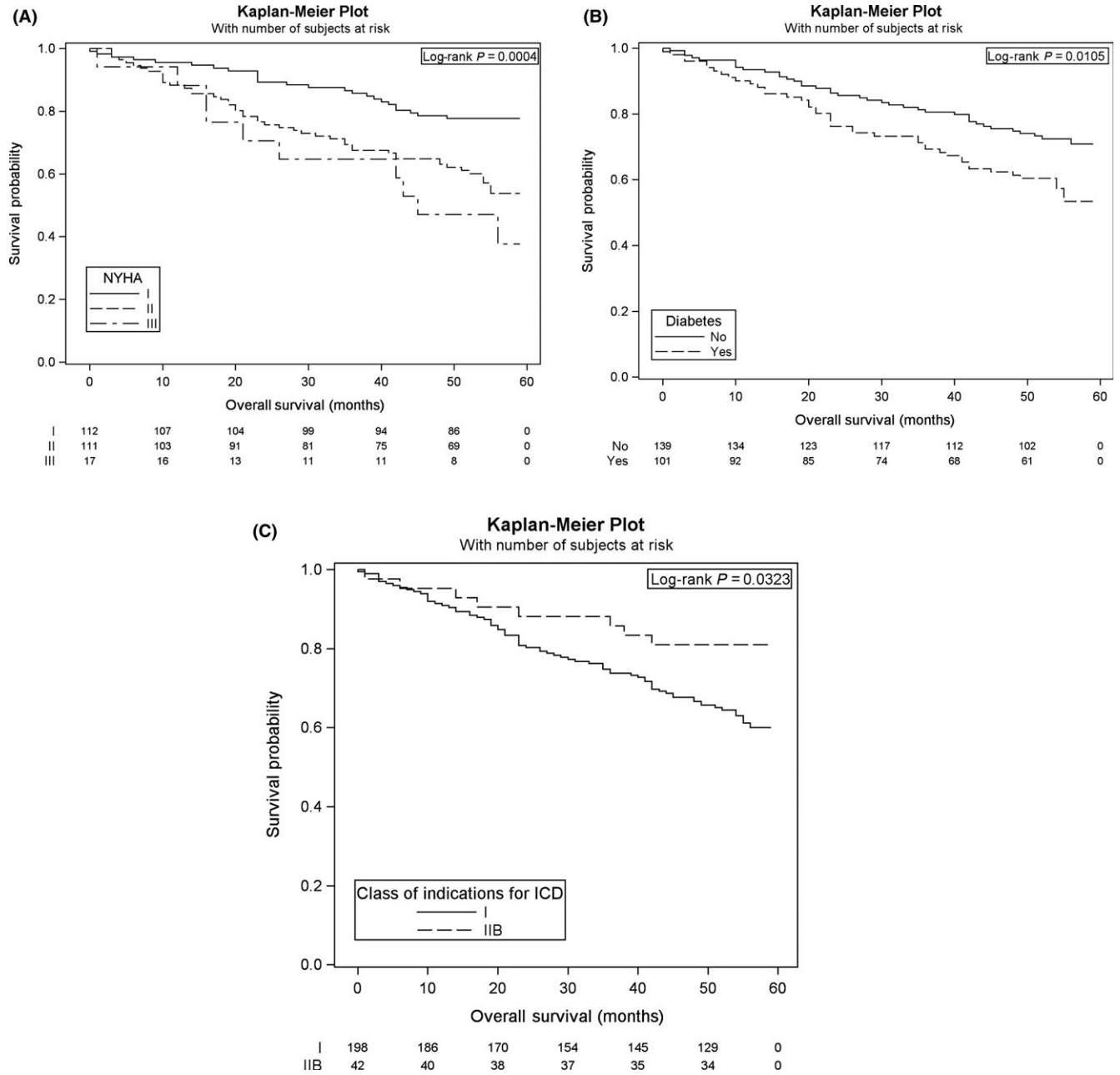

FIGURE 1 Kaplan-Meier estimates of death stratified by (A) New York Heart Association (NYHA) status showed lower mortality rates for patients in NYHA I compared to NYHA class II and higher (log-rank test, $P = 0.0004$), (B) the presence of diabetes was a significant risk factor for death for patients with depressed left ventricular ejection fraction who declined implantable cardioverter defibrillator (ICD) (log-rank test, $P = 0.0105$), and (C) patients who had class I indication for ICD had significantly lower survival rates compared to the patients with class IIb indication (log-rank test, $P = 0.032$)

TABLE 2 Cox multivariable regression analysis of all-cause mortality

	HR	CI	*P*-value
Hypertension, Yes vs No	1.27	0.70, 2.30	0.429
Hyperlipidemia, Yes vs No	0.82	0.40, 1.68	0.589
Chronic kidney disease, Yes vs No	1.85	1.02, 3.38	0.043
Stroke, Yes vs No	0.48	0.16, 1.49	0.204
NYHA			
II vs I	2.77	1.50, 5.10	0.001
III vs I	3.00	1.07, 8.04	0.036

CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association.

34.6% over a mean follow-up period of 44.8 ± 16.6 months. This is comparable to major primary prevention trials conducted in the Western population. In the MADIT II trial comprising 1232 patients with ischemic cardiomyopathy, mortality rate was 19.8% in the conventional-therapy group (490 patients) during an average follow-up of 20 months.[2] The mortality rate at 2 years was 14.1% in the standard-therapy group in the DEFINITE trial.[3] Similarly, the death rate of patients in the placebo group of the SCD-HeFT study was 29% at a median follow-up of 45.5 months.[4] Studies in Asian population patients have yielded somewhat conflicting results. In a subgroup analysis of SCD trends in the United States, rates of SCD in Asians were lower compared to their Caucasian counterparts.[11] Similarly, Tanno et al[12] reported on a group of Japanese patients who met MADIT II criteria but did not undergo ICD implantation who demonstrated lower overall risk of SCD when compared to MADIT II patients. A subsequent Chinese study showed lower all-cause death but comparable SCD rates to MADIT II population.[13] Morishima et al studied 106 patients in Japan who underwent myocardial perfusion SPECT and who had met MADIT II criteria for ICD implantation. Survival rates were similar to that of the MADIT II conventional group.[14] In a Korean study involving both ischemic and nonischemic CMP patients, the rate of SCD in the Korean patients was comparable to the MADIT II and DEFINITE cohort.[15] The mortality rate in our study was 34.6% over a mean follow-up period of 44.8 ± 16.6 months. This is comparable to mortality rates in the major primary prevention trials.[2–4]

A large proportion (93%) of our patients were assessed by their primary cardiologist to be of good functional class status, with 46.7% in NYHA class I and 46.3% in NYHA class II. Only 7% of patients were assessed to be in NYHA class III functional class status. This is in contrast to patients in conventional arm of the MADIT II trial where 39% of patients were in NYHA class I, 34% in NYHA class II, and 23% in NYHA class III.[2] Similarly, a greater proportion of patients enrolled in the SCD-HeFT had poorer functional class status, with 70% in NYHA class II and 30% in NYHA class III functional class.[4] The majority of patients receiving standard therapy recruited in the DEFINITE trial were in NYHA class II (60.7%) with 21.4% NYHA class III and 17.9% NYHA I class status.[3] Compared to the major primary prevention trials, we had a higher proportion of patients assessed by their primary cardiologist to be of good functional status (NYHA classes I and II), and yet mortality rates remained comparable.

Level of class of indication for ICD was shown to be an important factor affecting mortality, with patients who had class I indication for ICDs having higher death rates in our study. Majority of our patients had class I indication for ICD. This is likely one of contributing factors to our comparable death rates to the major primary prevention trials. This is also an important factor to be considered for physician and patient alike during the discussion for an ICD implantation.

We have shown that diabetes is an independent risk factor for death in this group of patients with depressed LVEF who declined ICD implantation for primary prevention. This finding is consistent with prior studies in diabetic patients with cardiomyopathy.[16,17] Go et al demonstrated the synergistic deleterious effect of diabetes and impaired ejection fraction. The outcome of 2121 patients with acute heart failure presenting to two centers in Singapore from 1 January 2008 to 31 December 2009, with a median follow-up of 914 (442-1190) days, was studied. Diabetic patients with impaired ejection fraction (<50%) were found to have higher mortality rates than their nondiabetic counterparts with similar ejection fraction.[16]

Chronic kidney disease was also an independent predictor of mortality in our study. In a retrospective study by Chong et al[18] on 283 patients with ICD implantation for primary or secondary prevention from 2002 to 2009 in our center, renal impairment was found to be an independent risk factor for 1-year mortality (HR 3.19). Similarly, in a retrospective analysis of the MADIT II cohort, renal impairment (HR 1.63) was found to be one of the strongest predictors of poor outcome.[19]

To our knowledge, there has been little South-East Asian data on outcomes in heart failure in patients who declined AICD. Our study provides the only reported local data demonstrating the high mortality rates in a group of patients with depressed ejection fraction and good functional status who declined ICD. Having data closer to home may better convince our patients and aid patients and physicians in making an informed decision regarding uptake of ICDs. From our previous study, the knowledge of depressed ejection fraction with its inherent increased risk of death and of ICDs reducing the risk of mortality was most predictive of patients changing their mind regarding adoption of ICDs.[10] Educational material and time spent by physicians reinforcing this knowledge in a selected group of patients may be well worth in increasing ICD uptake among this group of patients. Physician due to consideration of overall patient condition is also important in identifying suitable patients for ICD implantation.

Our study is limited by a small sample size, under-representation of female cohort, and it is a purely observational study. There was an over-representation of patients in NYHA class I functional status. There was also no control group of matched patients with ICD implantation.

5 | CONCLUSION

Death rates among patients with depressed EF remain high in our population and are comparable to patients in major ICD primary

prevention trials. Current ICD guideline recommendation for primary prevention is applicable to our local population. The presence of diabetes, CKD, and poorer NYHA status was independent risk factors for death in this group of primary prevention ICD population. Moving forward, identification of novel risk factors in addition to LVEF is of importance in identifying the individuals who may benefit most from ICD implantation.

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CONFLICT OF INTEREST

None declared.

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