

Prediction Efficiency of MADIT-ICD Benefit Score for Outcome in Asian Patients with Implantable Cardioverter-Defibrillator

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Background: Not all patients with heart failure derive consistent benefit from prophylactic implantable cardioverter-defibrillator (ICD). We aimed to evaluate the role of MADIT-ICD benefit score in risk-stratifying in Asian patients with left ventricular ejection fraction (LVEF) $\leq 35\%$.

Methods: In this two-center, retrospective study, a total of 136 patients with LVEF $\leq 35\%$ who received an ICD for primary prevention were enrolled. The endpoints were defined as the ventricular tachycardia ≥ 200 bpm (VT) or ventricular fibrillation (VF) and non-arrhythmic death. Based on the MADIT-ICD benefit score system, all patients were categorized into three groups: highest benefit group (n = 41), intermediate benefit group (n = 80), and lowest benefit group (n = 15).

Results: Forty patients experienced VT/VF and seven died of non-arrhythmic causes during a median follow-up of 44.8 ± 28.9 months. Kaplan–Meier curves showed that patients in highest benefit group had a worse VT/VF occurrence compared to those in other groups. In the highest benefit group, the predicted risk of VT/VF was 17-fold higher than the risk of non-arrhythmic mortality (41.5% vs 2.4%, $P < 0.001$). In the intermediate benefit group, the predicted risk of VT/VF was 4.2-fold higher than the risk of non-arrhythmic mortality (26.3% vs 6.3%, $P = 0.001$). In the lowest benefit group, however, the difference in the corresponding predicted risks was attenuated without statistically significant (13.3% vs 5.1%, $P = 0.56$).

Conclusion: We demonstrate that MADIT-ICD benefit score can be used for the assessment of ICD primary prevention benefits in Asian patients with LVEF $\leq 35\%$.

Keywords: implantable cardioverter-defibrillator, primary prevention, risk score, risk stratification, heart failure with reduced ejection fraction

Introduction

Randomized trials have demonstrated that implantable cardioverter-defibrillator (ICD) reduces mortality in patients with low left ventricular ejection fraction (LVEF).^{1,2} Current guidelines recommend the device in the management of such patients, both for primary and secondary prevention of sudden cardiac death (SCD).³ However, not all patients with a reduced LVEF derive consistent benefit from prophylactic ICD.^{4,5} The selection of most suitable patients at high risk of SCD is warranted, aimed at closing the gap between scientific evidence and the limited resources of healthcare, especially in developing countries.⁶

Recently, a novel risk score system that predicts the likelihood of prophylactic ICD benefit through personalized assessment of the risk of life-threatening ventricular tachycardia (VT)/ ventricular fibrillation (VF) weighed against the risk of non-arrhythmic mortality has been evaluated.⁷ The study showed two scores being used to stratify patients into three MADIT-ICD benefit groups. However, this study was based on the MADIT trials, and the results may not be applicable to

elderly (age >80 years), Asian patients or those with advanced renal dysfunction. Besides, previous studies focusing on risk stratification score for VT/VF prediction in Asian patients were limited.⁸ Hence, the aim of our study was designed to evaluate this MADIT-ICD benefit score for the assessment of primary prevention benefits in Asian patients with ICD.

Methods

Study Population and Design

We reviewed 136 patients with LVEF \leq 35% who successfully underwent first ICD implantation for the primary prevention of SCD from April 2010 to November 2017. The enrolled patients from two centers [Fuwai Hospital (Beijing, China) and Tiantan hospital (Beijing, China)] had continuous records of outpatient clinic follow-up, data of ICD interrogation or remote monitoring. The study was performed with written informed consent from all patients and approval from the ethics committee of Fuwai/Tiantan Hospital and in accordance with the Declaration of Helsinki.

MADIT-ICD Benefit Score and Definitions

Our study employs a recently reported MADIT-ICD benefit score.⁷ This score system was constructed as a count of risk factors identified in each patient, which including two dichotomized competing risk scores: (1) VT/VF score, following eight risk factors: LVEF \leq 25% (+1 point), atrial arrhythmia (+1 point), heart rate >75bpm (+1 point), systolic blood pressure <140mmHg (+2 point), myocardial infarction (+2 point), age <75 years (+2 point), male (+2 point) and prior non-sustained ventricular tachycardia (+2 point); (2) Non-arrhythmic Mortality Score, following seven risk factors: Cardiac resynchronization therapy-defibrillator (-1 point), New York Heart Association class \geq II (+1 point), Diabetes (+1 point), Body mass index <23kg/m² (+2 point), Atrial Arrhythmia (+2 point), LVEF \leq 25% (+2 point) and Age \geq 75 years (+2 point). Based on the two dichotomized competing risk scores mentioned above, the 136 patients in our study were categorized into three MADIT-ICD benefit groups: (1) highest benefit group (high VT/VF score and low non-arrhythmic mortality score) (n=41); (2) intermediate benefit group (low VT/VF score and low non-arrhythmic score, or high VT/VF score and high non-arrhythmic mortality score) (n=80), and (3) lowest benefit group (low VT/VF score and high non-arrhythmic mortality score) (n=15) (Figure 1).

The occurrence of life-threatening VT/VF defined as ICD-recorded, treated, or monitored sustained VT \geq 200bpm or VF.⁷ VT was defined as the regular (monomorphic) or irregular (polymorphic) ventricular arrhythmia with a mean cycle length of more than 240ms. VF or ventricular flutter was defined as ventricular arrhythmia, with a mean cycle length of 240 ms or less, which was considered potentially fatal in the absence of an ICD. Non-arrhythmic mortality was defined as death without

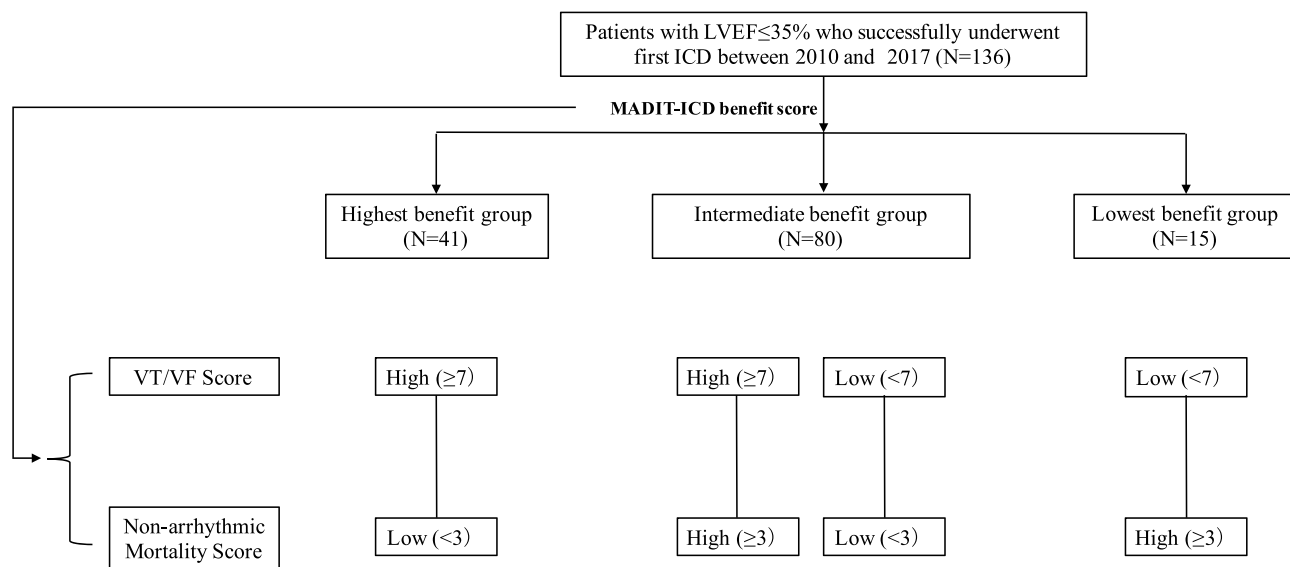


Figure 1 Flow diagram of included subjects.

Abbreviations: ICD, implantable cardioverter-defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation.

experiencing sustained VT/VF at any time during follow-up. Non-sustained ventricular tachycardia (NSVT) was defined as 3 or more consecutive ventricular premature beats lasting <30 seconds without hemodynamic compromise.

ICD Implantation and Programming

The ICD implantation procedures were routine in two centers. The lead was implanted transvenously. The active fixation ventricular lead was screwed into the septum and the passive atrial lead was located at the right auricle (if dual-chamber). Basic pacing rate, parameters used for detection and therapy, and other auxiliary functions were programmed individually by the patients' attending physicians based upon their clinical histories and complications.

Data Collection and Follow-Up

Baseline clinical data during hospitalization, including demographic characteristics, comorbidities, medications, were obtained from Fuwai and Tiantan Electronic Medical Record System. The patients were continually given the recommended anti-arrhythmia drugs when discharged. After that, patients were required for examination at our hospital, typically at 6/12-month interval or in case of ICD discharges. Besides, we made a telephone to patients or their family members at regular intervals, to remind them of next visit or to find endpoints. At each visit, devices were interrogated. Classification of the arrhythmia stored by an ICD was confirmed by at least two experienced electrophysiologists. When detailed ICD tracings were incomplete, we relied on the previous interpretations made by the outpatient clinic electrophysiologists. All enrolled patients were followed up to December 2019 and the data from two centers were finally sent to the Fuwai Hospital for analysis.

Statistical Analysis

We performed statistical analysis with SPSS version 22.0 (SPSS, Inc, IBM, Armonk, New York) and R package survminer version 0.4.9. Continuous variables were expressed as mean \pm SD, and categorical variables as numbers and percentage. Group comparisons were carried out through the one-way ANOVA test. Multivariate Cox proportional hazards regression analysis with Forward LR method was used to assess for associations with the endpoints across the score groups at follow-up. Kaplan–Meier analyses with a Log rank test was used to assess life-threatening VT/VF or non-arrhythmic death across the score group. All tests were 2-tailed, and a P-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

The baseline characteristics of study patients by score system are shown in [Table 1](#). Mean age of all patients was 59.4 ± 11.7 years and 77.9% were males. The mean LVEF was $29.1 \pm 4.8\%$. As expected, patients in the highest and intermediate subgroups were younger and had higher proportion of male as compared with the lowest subgroup. In addition, patients in the highest subgroup as compared with the intermediate and lowest subgroups exhibited a lower prevalence of non-ischemic cardiomyopathy and New York Heart Association (NYHA) II–IV. They had higher LVEF and higher rate of smoking.

Observed Risk of VT/VF and Non-Arrhythmic Mortality by the MADIT-ICD Benefit Groups

In our study population, 40 patients experienced life-threatening VT/VF and 7 died of non-arrhythmic causes during a median follow-up of 44.8 ± 28.9 months. Specifically, the VT/VF occurred in 17 patients (41.5%) in the highest benefit group, 21 patients (26.3%) in the intermediate benefit group and 2 patients (13.3%) in the lowest benefit group. The non-arrhythmic death occurred in 1 patients (2.4%) in the highest benefit group, 5 patients (6.3%) in the intermediate benefit group and 1 patients (5.1%) in the lowest benefit group. [Figures 2](#) and [3](#) shows Kaplan–Meier estimates of life-threatening VT/VF occurrence and non-arrhythmic death for the three groups stratified by MADIT-ICD score system, separately. After adjustment for multiple comorbidities (ages, sex, prior NSVT, myocardial

Table 1 Patient Characteristics by MADIT-ICD Benefit Score

| | All (n=136) | Highest (n=41) | Intermediate (n=80) | Lowest (n=15) | P-value |
|--------------------------------------|--------------|----------------|---------------------|---------------|---------|
| Age, yrs | 59.4 ± 11.7 | 57.9 ± 12.2 | 58.4 ± 9.8 | 69.3 ± 15.2 | 0.002 |
| Male, n (%) | 106 (77.9) | 34 (82.9) | 66 (82.5) | 6 (40.0) | 0.003 |
| BMI, kg/m ² | 24.5 ± 3.8 | 25.3 ± 3.6 | 24.5 ± 3.6 | 22.2 ± 4.3 | 0.025 |
| Smoking, n (%) | 80 (58.8) | 31 (75.6) | 44 (55.0) | 5 (33.3) | 0.010 |
| SBP, mmHg | 116.7 ± 14.8 | 113.6 ± 10.9 | 117.6 ± 16.0 | 120.3 ± 16.1 | 0.226 |
| Heart Rate, bpm | 70.0 ± 17.0 | 73.8 ± 14.5 | 68.2 ± 18.5 | 68.8 ± 13.7 | 0.223 |
| Single-chamber ICD, n (%) | 107 (78.7) | 31 (75.6) | 65 (81.3) | 11 (73.3) | 0.674 |
| Non-ischemic Cardiomyopathy, n (%) | 78 (57.3) | 16 (39.0) | 53 (66.3) | 9 (60.0) | 0.016 |
| Myocardial Infarction, n (%) | 42 (30.9) | 19 (46.3) | 17 (21.3) | 6 (40.0) | 0.014 |
| NYHA II–IV, n (%) | 115 (84.6) | 32 (78.0) | 69 (86.2) | 14 (93.3) | 0.636 |
| Atrial arrhythmias, n (%) | 20 (14.7) | 5 (12.2) | 12 (15.0) | 3 (20.0) | 0.768 |
| Prior NSVT, n (%) | 13 (9.5) | 7 (17.1) | 6 (7.5) | 0 (0.0) | 0.059 |
| Hypertension, n (%) | 53 (38.9) | 15 (36.6) | 31 (38.8) | 7 (46.7) | 0.789 |
| Diabetes, n (%) | 42 (30.9) | 18 (43.9) | 19 (23.8) | 5 (33.3) | 0.078 |
| eGFR, mL/min per 1.73 m ² | 92.5 ± 28.0 | 94.4 ± 29.7 | 94.9 ± 25.0 | 74.4 ± 33.3 | 0.028 |
| LVEF, % | 29.1 ± 4.8 | 31.1 ± 3.4 | 28.4 ± 5.0 | 27.6 ± 5.2 | 0.006 |
| ACEI/ARB, n (%) | 90 (66.2) | 28 (68.3) | 55 (68.8) | 7 (46.7) | 0.238 |
| Beta-blocker, n (%) | 97 (71.3) | 33 (80.5) | 50 (62.5) | 14 (93.3) | 0.009 |
| Aldosterone, n (%) | 106 (77.9) | 34 (82.9) | 62 (77.5) | 10 (66.7) | 0.440 |
| Amiodarone, n (%) | 73 (53.7) | 17 (41.5) | 47 (58.8) | 9 (60.0) | 0.171 |

Note: Data are presented as mean ± SD or percentage.

Abbreviations: ICD, implantable cardioverter-defibrillator; BMI, body mass index; SBP, systolic blood pressure; NYHA, New York Heart Association class; NSVT, non-sustained ventricular tachyarrhythmia; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

infarction, SBP, HR, atrial arrhythmia and LVEF), the highest and intermediate score group were shown to have respective 1.81-fold ($P=0.484$) and 1.50-fold increases in the risk of life-threatening VT/VF occurrence as compared with the lowest score group. Also after adjustment for multiple comorbidities (age, sex, NYHA, diabetes, BMI, atrial arrhythmia and LVEF), patients in highest and intermediate score group were shown to have 0.75-fold ($P=0.441$) and 0.52-fold ($P=0.585$) reduces in the risk of non-arrhythmic death compared to patients in lowest score group, respectively (Table 2).

Predicted Risk of VT/VF and Non-Arrhythmic Mortality by the MADIT-ICD Benefit Groups

The predicted risk estimate graphs among the three MADIT-ICD benefit score groups for the end points of VT/VF and non-arrhythmic mortality are shown in the Figure 4. In the highest benefit group, the predicted risk of VT/VF was 17-fold higher than the risk of non-arrhythmic mortality (41.5% vs 2.4%, $P < 0.001$). In the intermediate benefit group, the predicted risk of VT/VF was 4.2-fold higher than the risk of non-arrhythmic mortality (26.3% vs 6.3%, $P = 0.001$). In the lowest benefit group, however, the difference in the corresponding predicted risks was attenuated without statistically significant (13.3% vs 5.1%, $P = 0.56$).

Discussion

In this study, we firstly used a recently reported MADIT-ICD benefit score among Asian patients from two centers to demonstrate its efficacy in predicts the likelihood of prophylactic ICD benefit. Our findings were as follows: (1) MADIT-ICD benefit score for the assessment of primary prevention benefits in Asian patients with ICD was feasible and effective; (2) this score system can be applied for improved risk stratification by identifying Asian patients for primary ICD implantation with a greater potential for survival benefit, in whom the predicted risk of life-threatening VT/VF is a higher than the competing risk of non-arrhythmic mortality; (3) Among Asian patients in the highest benefit group, the

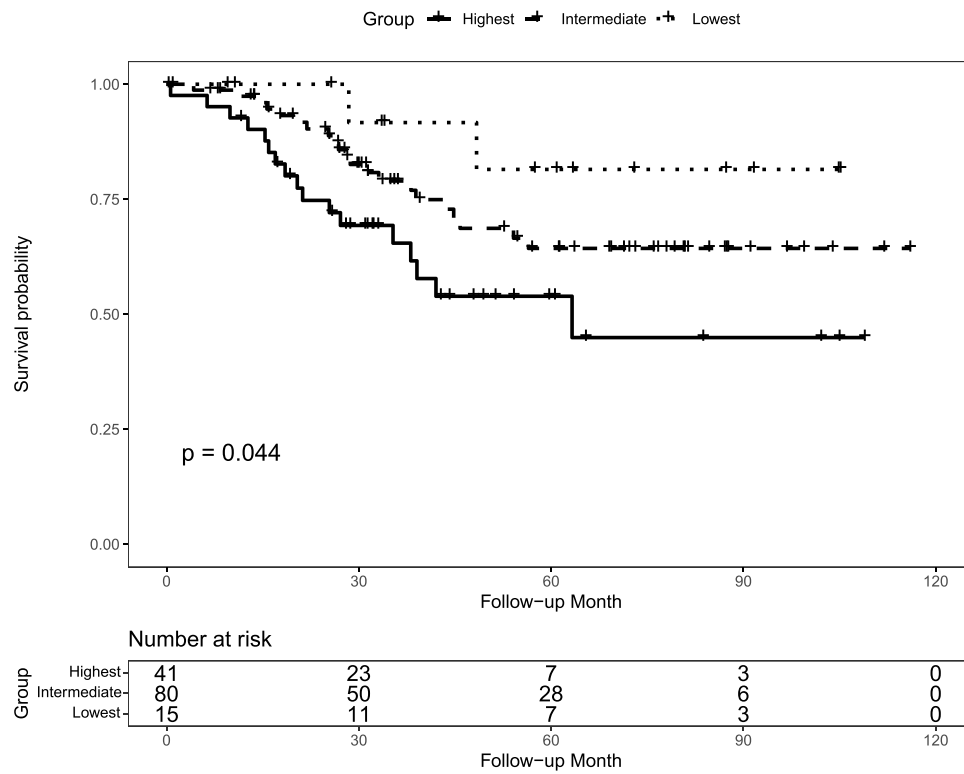


Figure 2 Kaplan–Meier estimates of life-threatening VT/VF occurrence for the three groups stratified by MADIT-ICD score system. **Abbreviations:** VT, ventricular tachycardia; VF, ventricular fibrillation.

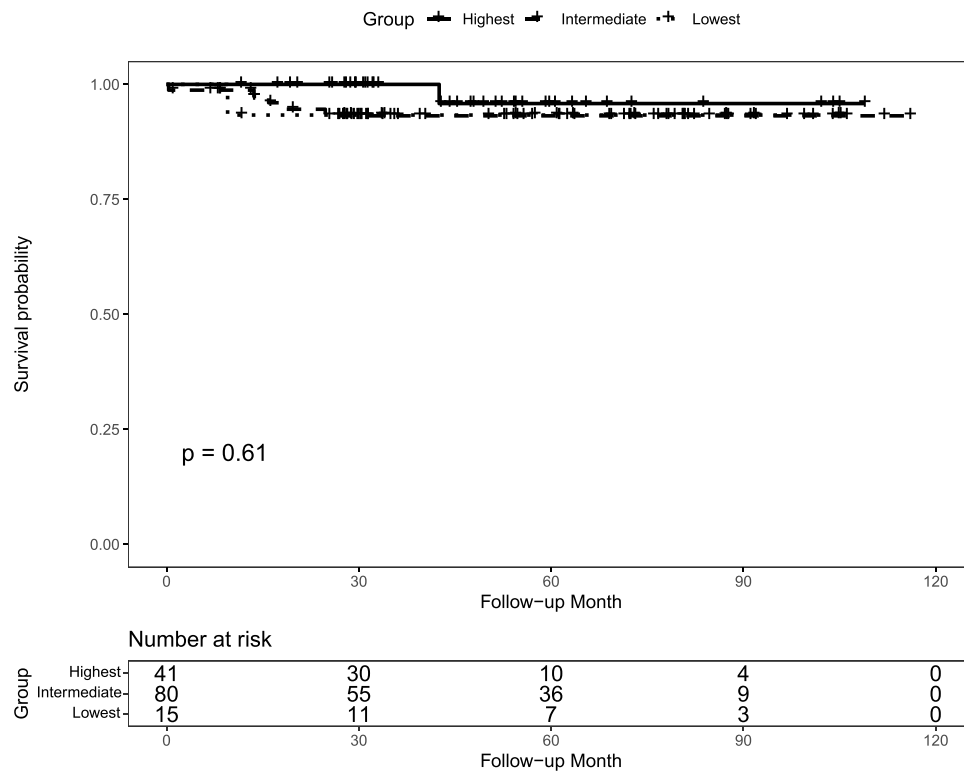


Figure 3 Kaplan–Meier estimates of non-arrhythmic death for the three groups stratified by MADIT-ICD score system.

Table 2 Cox Proportional Hazards Regression Analysis of Score Categories of Endpoint

| Endpoint and Score | No. of Patients | No. of Patients with Events (%) | Adjusted HR | 95% CI | P value |
|---|-----------------|---------------------------------|-------------|--------------|-----------|
| VT (≥ 200bpm)/VF | | | | | |
| Lowest score group | 15 | 2 (13.3) | 1.00 | Reference | Reference |
| Intermediate score group | 80 | 21 (26.3) | 1.50 | 0.32 to 7.08 | 0.609 |
| Highest score group | 41 | 17 (41.5) | 1.81 | 0.35 to 9.49 | 0.484 |
| Non-arrhythmic mortality | | | | | |
| Lowest score group | 15 | 1 (6.7) | 1.00 | Reference | Reference |
| Intermediate score group | 80 | 5 (6.2) | 0.48 | 0.04 to 6.58 | 0.585 |
| Highest score group | 41 | 1 (2.4) | 0.25 | 0.01 to 8.54 | 0.441 |

Abbreviations: VT/VF, ventricular tachycardia/ventricular fibrillation; HR, hazard ratio; CI, confidence interval.

predicted risk of life-threatening VT/VF was 17-fold higher than the risk of non-arrhythmic mortality. In the intermediate benefit group, in contrast, the predicted risk of VT/VF was 4.2-fold higher than the risk of non-arrhythmic mortality.

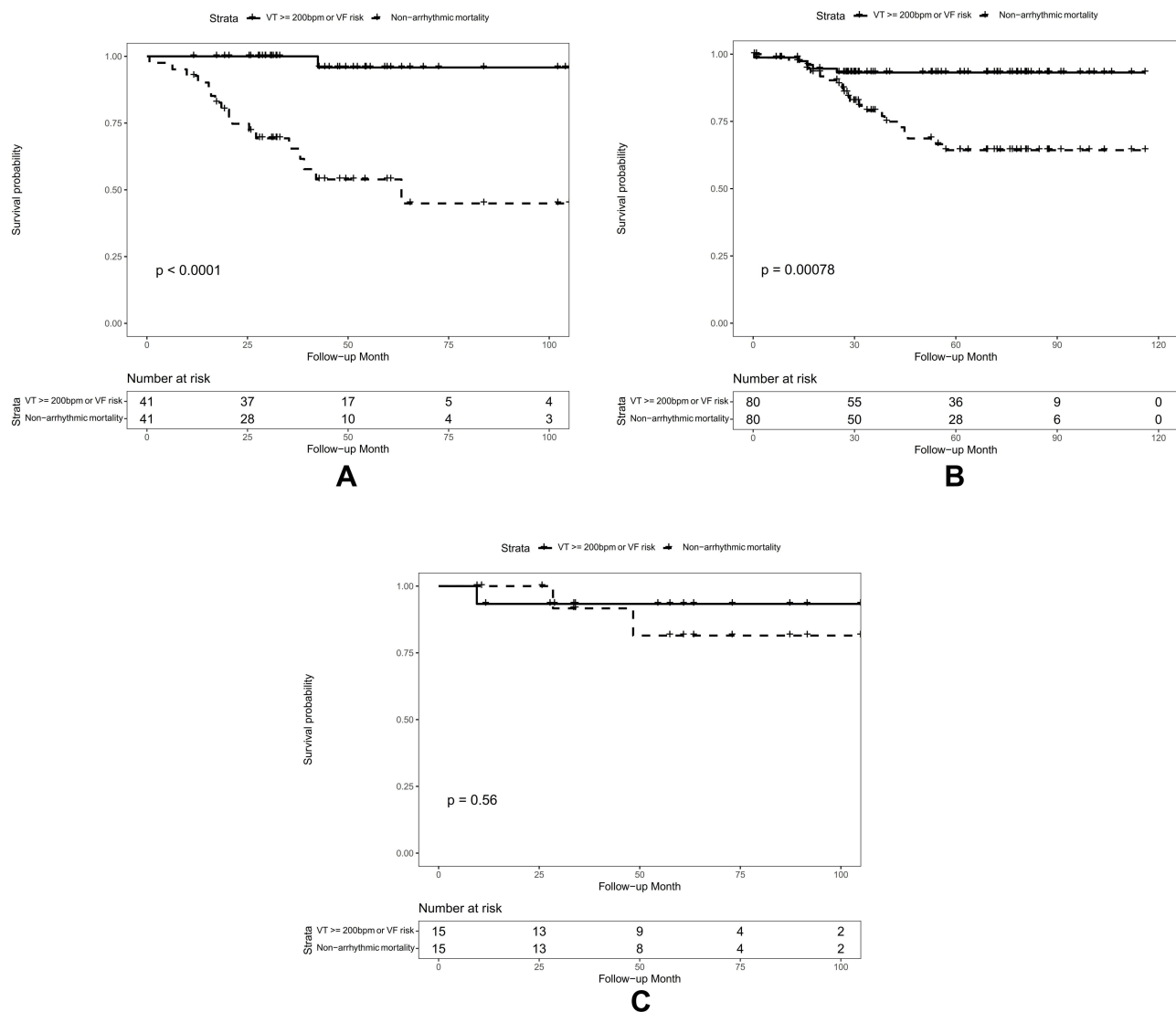


Figure 4 Kaplan–Meier curve for ventricular tachyarrhythmia (VT ≥ 200 b.p.m., or VF) and for the competing risk of non-arrhythmic mortality by MADIT-ICD benefit groups. (A) Highest benefit group; (B) intermediate benefit group; and (C) lowest benefit group. **Abbreviations:** VT, ventricular tachycardia; VF, ventricular fibrillation.

Prophylactic implantation of an ICD is recommended by guidelines for patients with LVEF $\leq 35\%$.³ However, previous studies have demonstrated that ICD therapy failed to show a significant mortality benefit for primary prevention of SCD in patients with reduced LVEF.^{4,9} It is possible that the absolute benefit of ICD in a typical and well-treated population with LVEF $\leq 35\%$ might be small.¹⁰ Besides, ICDs are costly devices, especially for developing countries in Asia. A study in China found that in 497 patients meeting Class I indications for an ICD, only 112 (22.5%) accepted an ICD implant. The remaining 385 refused due to economic reasons or other reasons.¹¹ It is, therefore, desirable to avoid their use in patients who are unlikely to obtain a worthwhile benefit. These considerations highlight the need to develop a personalized risk score system to improve the cost-efficiency of primary prevention ICD implants.

Several risk scores have been developed to predict SCD and/or mortality in patients with LVEF $\leq 35\%$. However, these studies focusing on creating risk scores were limited.

The Seattle Heart Failure Score was developed to predict the survival benefit with ICDs in patients with heart failure.¹² The patients in the study were enrolled before 2005 when ICDs were not widely available for primary prevention. Shadman et al confirmed the Seattle Proportional Risk Model that younger age, male sex, and higher body mass index were independently associated with a greater proportional risk of sudden death in patients with cardiomyopathy.¹³ While this score system was not focus on primary prevention of SCD. Li et al created a quantitative late gadolinium enhancement based score (ESTIMATED) for prediction of 3-year SCD risk in Chinese patients.⁸ The results demonstrated that ESTIMATED score might be a powerful tool to identify high-risk patients who could benefit most from ICDs, but the observed candidates in this study were only patients with non-ischemic dilated cardiomyopathy. Barsheshet et al used a simple risk stratification score in patients receiving ICD for primary prevention.¹⁴ This risk score, including 5 clinical factors (NYHA class $>II$, age >70 years, blood urea nitrogen >26 mg/dl, QRS duration >0.12 s, and atrial fibrillation), had ability to identify high-risk patients who did not derive long-term benefit from device therapy. In respect to MADIT-ICD benefit score, the variables are associated with the simple, common baseline clinical indicators and could be easily calculated by physicians.⁷ It integrates the competing risks of VT/VF and non-arrhythmic mortality into a score that provides the expected benefit of the defibrillator in the primary prevention population.

In the present study, we have also shown a significant benefit with an ICD among Asian patients with highest benefit score, of whom the predicted risk of life-threatening VT/VF was 17-fold higher than the risk of non-arrhythmic mortality. In the intermediate benefit group, the predicted risk of VT/VF was 4.2-fold higher than the risk of non-arrhythmic mortality. In MADIT-ICD study, however, the predicted risk in the highest and intermediate benefit group was attenuated to 3.0- and 1.6-fold higher, respectively. The reason why these results differing from us may possibly due to differences in samples (more large number of patients and non-Asian population) and longer follow-up intervals.⁷ Nevertheless, our study for the first time employs the MADIT-ICD benefit score for the assessment of primary prevention benefits in Asian patients, and demonstrates the feasibility and effectivity of this novel score system. The findings imply that Asian patients with LVEF $\leq 35\%$ with highest or intermediate benefit scores deserve more attention from physicians for ICD primary prevention, with potentials for further improvement of this score system.

Limitations

There are several limitations in our study. Firstly, it was based on the retrospective, two-center experience and limited number of patients. Primary prevention ICD utilization still remains low in Asian regions and varies greatly, leading to lacking of related evidence-based populations and studies.¹⁵ To generally utilize MADIT-ICD benefit score in Chinese patients in clinical practice, large and multi-center studies were needed in the future. Secondly, a small proportion of the enrolled patients receiving ICD with home monitoring functions mainly due to economic reasons. After the emergency of epidemic Covid-19 in China, many patients were restricted in the local hometown. Many of them could not finish ICD devices interrogation in the year of 2020, leading to relatively short follow-up intervals in our study.

Conclusions

We have demonstrated that MADIT-ICD benefit score can be used for the assessment of ICD primary prevention benefits in Asian patients with LVEF $\leq 35\%$. The score system can be applied for improved risk stratification by identifying Asian patients for primary ICD implantation with a greater potential for survival benefit, in whom the predicted risk of life-threatening VT/VF is a higher than the competing risk of non-arrhythmic mortality.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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