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Validation of 2-year ^{123}I-*meta*-iodobenzylguanidine-based cardiac mortality risk model in chronic heart failure

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Aims The aim of this study was to validate a four-parameter risk model including ^{123}I-*meta*-iodobenzylguanidine (MIBG) imaging, which was previously developed for predicting cardiac mortality, in a new cohort of patients with chronic heart failure (CHF).

Methods and results Clinical and outcome data were retrospectively obtained from 546 patients (age 66 ± 14 years) who had undergone ^{123}I-MIBG imaging with a heart-to-mediastinum ratio (HMR). The mean follow-up time was 30 ± 20 months, and the endpoint was cardiac death. The mortality outcome predicted by the model was compared with actual 2-year event rates in pre-specified risk categories of three or four risk groups using Kaplan–Meier survival analysis for cardiac death and receiver-operating characteristic (ROC) analysis. Cardiac death occurred in 137 patients, including 105 (68%) patients due to heart-failure death. With a 2-year mortality risk from the model divided into three categories of low- (<4%), intermediate- (4–12%), and high-risk (>12%), 2-year cardiac mortality was 1.1%, 7.9%, and 54.7%, respectively in the validation population ($P < 0.0001$). In a quartile analysis, although the predicted numbers of cardiac death was comparable with actual number of cardiac death for low- to intermediate-risk groups with a mortality risk <13.8%, it was underestimated in the high-risk group with a mortality risk ≥13.8%. The ROC analysis showed that the 2-year risk model had better ($P < 0.0001$) diagnostic ability for predicting heart failure death than left ventricular ejection fraction, natriuretic peptides or HMR alone.

Conclusion The 2-year risk model was successfully validated particularly in CHF patients at a low to intermediate cardiac mortality risk.

Keywords cardiac sympathetic function • neuroimaging • cardiac death • heart failure • risk prediction model

Introduction

Chronic heart failure (CHF) is a life-threatening condition affecting approximately 26 million people worldwide, and heart failure carries substantial risk of morbidity and mortality.[1] Recent advances in non-pharmacological treatment, including device therapy, can improve quality of life and survival in CHF patients. Ineffective or less appropriate use of aggressive therapeutic approaches, however, has been reported not only in high-risk patients with advanced systolic dysfunction or end-stage heart failure but also those at a low risk for

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lethal outcomes.[2] From a medico-economical point of view, there is a clear need for more precise risk-stratification in order to achieve more effective management of CHF.

With respect to risk assessment for cardiac mortality, conventional functional evaluations, and diagnostic biomarkers, such as heart failure symptoms, circulating hormones and peptides, and left ventricular functional parameters, have non-negligible limitations in the discrimination of low-, intermediate-, and high-risk as a basis for short- or long-term clinical management. To enhance the utility of individual risk markers, a large number of multivariate risk models have been developed in the past 2 decades.[3–5] However, use of these models in clinical practice remains limited.[6,7]

Sympathetic nerve function plays a crucial role in CHF outcomes. In the early stages of CHF, sympathetic nerve function is increased to compensate for symptomatic and cardiac functional deteriorations. With a CHF progression, however, sympathetic outflow and circulating neurohormones become further augmented and long-lasting sympathetic hyperactivity induces a loss of both presynaptic neurons and post-synaptic receptors,[8,9] resulting in compensatory mechanisms being blunted and in unfavourable outcomes. In the clinical assessment of CHF condition, neuroimaging with ^{123}I-meta-iodobenzylguanidine (MIBG) is a unique diagnostic method to evaluate the integrity of cardiac sympathetic activity and innervation.[9] Furthermore, a number of studies have demonstrated the potent prognostic values of cardiac ^{123}I-MIBG activity,[10–15] which is quantified as a heart-to-mediastinum ratio (HMR), in a single- and multi-centre studies.[16–19] Recently, a CHF mortality risk model using a cardiac ^{123}I-MIBG parameter together with clinical information was developed using a Japanese CHF database consisting of 1322 patients, which was shown effective for the prediction of 2- and 5-year cardiac mortality risks.[20,21]

The present study was designed to validate the predictability of the 2-year mortality risk model using a new cohort of CHF patients derived from multiple clinical centres in Japan.

Methods

Patients

A total of 546 patients diagnosed with CHF who had undergone ^{123}I-MIBG study during clinically stable condition, and had been followed up for at least 1 year in four medical centres were retrospectively included in this study (*Table 1*). Cardiac ^{123}I-MIBG studies were performed between 2005 and 2016. An average follow-up period was 30 ± 20 months (range 0.1–108 months) and left ventricular ejection fraction (LVEF) either by echocardiography or gated single-photon emission computed tomography was 39 ± 14%. New York Heart Association (NYHA) functional class was 77% in class I/II and 23% in III/IV. CHF aetiology was ischemic in 36% of the patients. Standard optimal medical care for CHF was continued in each university and community hospital after MIBG imaging. Seventy-three (13%) patients underwent haemodialysis due to chronic renal failure.

Table 1 Demographics of patients (n = 546)

	n (%), mean ± SD
Age (years)	66 ± 14
Gender (male)	392 (72)
Follow-up (months)	30 ± 20
NYHA functional class	
I	284 (52)
II	136 (25)
III	101 (18)
IV	25 (5)
Ischaemic aetiology (%)	36
Left ventricular ejection fraction (%)	39 ± 14
BNP (pg/mL)	475 ± 54
Log BNP	2.38 ± 0.57
NT-ProBNP (pg/mL)	10852 ± 37 998
Log NT-proBNP	3.44 ± 0.69
^{123}I-MIBG parameters	
Early HMR	
Standardized to ME collimator[a]	1.91 ± 0.44
LE collimator equivalent[b]	1.62 ± 0.30
Late HMR	
Standardized to ME collimator[a]	1.74 ± 0.43
LE collimator equivalent[b]	1.51 ± 0.29
Washout rate (%)	30 ± 12
Complications	
Hypertension (%)	52
Diabetes (%)	39
Dyslipidaemia (%)	34
Medications	
Beta-blocker (%)	84
ARB, ACE inhibitor (%)	70
Diuretics (%)	77
Aldosterone antagonist (%)	32

ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; BNP, b-type natriuretic peptide; HMR, heart-to-mediastinum ratio; LE, low energy; ME, medium energy; MIBG, meta-iodobenzylguanidine; NYHA, New York Heart Association; NT-ProBNP, N-terminal Pro BNP.
[a]Conversion coefficient = 0.88.
[b]Conversion coefficient = 0.60.

Cardiac ^{123}I-MIBG imaging

Planar anterior images of the thorax were obtained at 15–20 min (early) and 3–4 h (late) after intravenous injection of ^{123}I-MIBG (111 MBq, FUJIFILM RI Pharma Co. Ltd., Tokyo, Japan). Image processing was performed locally at each institution. Regions of interest were set over the heart and upper mediastinum to calculate an HMR. Since collimators used in the four hospitals were low-energy (LE) high-resolution, LE general purpose, and low-medium energy general-purpose collimators, all the HMR values were converted to medium-energy (ME) general-purpose collimator-equivalent HMR [conversion coefficient (CC) of 0.88 by phantom experiments] by using the standardization method developed previously.[22,23] Since HMR used for creating the 2-year risk model was based on LE collimators, the model was adjusted to HMR values for the LE collimators with an average CC of 0.60.

Biomarkers

Blood b-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-ProBNP) was measured in each hospital, and the data obtained at a stable clinical condition around the time of MIBG imaging were used for the analysis.

Definitions of events

A primary endpoint in this study was cardiac death; end-stage heart failure death (death due to pump failure), arrhythmic/sudden cardiac death and fatal acute myocardial infarction. The following non-fatal arrhythmic events were also documented; appropriate anti-arrhythmia pacing against lethal arrhythmias, and appropriate discharge by implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy with defibrillator (CRTD).

2-year mortality risk model

The 2-year risk model was developed based on a database consisting of 1280 subjects who underwent MIBG imaging from 1990 to 2009 in Japan.[21] In that study, the multivariate logistic model selected four significant independent variables: age, LVEF, NYHA functional class (I–II vs. III–IV), and MIBG HMR. The risk model provides a 2-year probability of cardiac death (unit %/2 years) due to pump failure, sudden cardiac death, lethal arrhythmia, and/or acute myocardial infarction.

Statistical analysis

All the values were expressed as mean ± standard deviations (SDs). Mean values among groups were compared using analysis of variance with T- and F-tests and comparison of all pairs by Tukey–Kramer (honestly significant difference) statistics. Kaplan–Meier survival analysis was performed among three groups classified by thresholds of LVEF, a predicted 2-year mortality risk and BNP/NT-ProBNP as follows. LVEF groups were <35%, 35–50%, and >50%: 2-year mortality risk groups were <4%, 4–12%, and >12%: BNP and NT-ProBNP groups were <100, 100–200, >200 pg/mL, and <400, 400–900, and >900 pg/mL, respectively.[24,25] Predicted mortality by the risk model was compared with actual outcomes observed during the follow-up period in patients in whom 2-year follow-up data were available. Receiver-operating characteristics (ROCs) analysis with area under curve (AUC) was used to compare the risk model and individual variables. A *P*-value <0.05 was considered significant. All analyses were performed using the SAS statistical program package (JMP version 12, SAS, Cary, NC, USA).

Results

Number of events

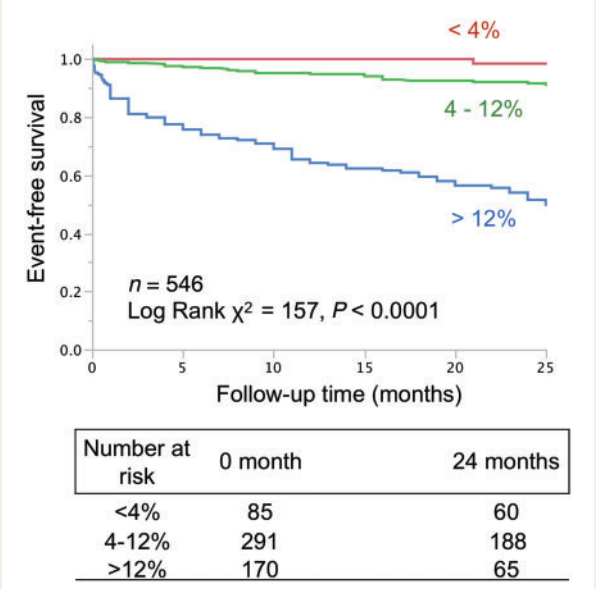
Fatal events occurred in 137 (25%) patients; 105 (68%) patients due to pump failure and the remaining 32 patients due to arrhythmic or sudden death. Non-fatal arrhythmic events were observed in 17 patients; resuscitated cardiac arrest in 5 and appropriate ICD shocks in 12 (29%) of 41 patients undergoing ICD/CRTD therapy. The total number of events was 154 (28%).

Survival analysis

The actually documented 2-year mortality rates of 3 predicted risk groups (<4%, 4–12%, and >12%) were 1.6, 8.4, and 48.5% ($P < 0.0001$), respectively (*Figure 1*). For further comparisons of survival curves, thresholds of LVEF and BNP/NT-ProBNP were combined with the predicted 2-year mortality risks. The survival rates in the three LVEF subgroups (<30%, 30–35%, and >35%) were significantly discriminated by the risk model ($P < 0.0001$ for all) (*Figure 2*). Likewise, the survival rates in the three BNP/NT-ProBNP subgroups were significantly ($P = 0.003$ to $P < 0.0001$) discriminated (*Figure 3*).

Comparison of predicted and actual mortality

The average 2-year mortality rate predicted by the risk model was 12.1 ± 10.9% (range 0.0–52.1%, median 8.3%). Based upon predicted risks, patients were classified into quartiles; <5.1% for Q1, 5.1–8.2% for Q2, 8.3–13.7% for Q3, and ≥13.8% for Q4. With respect to clinical backgrounds, Q3 and Q4 groups showed greater abnormalities of MIBG HMR, BNP/NT-ProBNP levels, estimated glomerular filtration rate (eGFR), and LVEF than did Q1 and Q2 groups (*Table 2*). The 2-year mortality rates predicted by the risk model were nearly identical to those actually documented in Q1–Q3; 3% vs. 4% for Q1; 7% vs. 8% for Q2; and 11% vs. 15% for Q3, respectively. The risk model, underestimated the mortality rate in Q4: 28% vs. 54% (*Figure 4*).



Number at risk	0 month	24 months
<4%	85	60
4-12%	291	188
>12%	170	65

Figure 1 Survival analysis of three 2-year risk groups (<4%, 4–12%, and >12%) for cardiac death.

Prediction of heart failure death

Because most frequent deaths observed in the study were due to progressive heart failure, the predictability of this event was compared among the 2-year risk model, MIBG HMR, BNP/NT-ProBNP, eGFR, and LVEF by ROC analysis (*Figure 5*). For this analysis, additional thresholds of natriuretic peptide levels were determined by ROC analysis as follows; 560 pg/mL for BNP and 4800 pg/mL for NT-ProBNP. The 2-year risk model had the significantly greater ($\chi^2 = 58$, $P < 0.0001$) ROC AUC of 0.84 with a 95% confidence interval (CI) of 0.79–0.88 when compared with other individual variables: ROC AUC 0.76 (CI 0.71–0.80; $\chi^2 = 12$, $P = 0.0004$) for MIBG HMR, ROC AUC 0.70 (CI 0.65–0.75; $\chi^2 = 22$, $P < 0.0001$) for BNP/NT-ProBNP, ROC AUC 0.63 (CI 0.56–0.69; $\chi^2 = 41$, $P < 0.0001$) for LVEF, and ROC AUC 0.67 (CI 0.61–0.73; $\chi^2 = 19$, $P < 0.0001$) for eGFR (*Figure 5*).

Arrhythmic death and appropriate cardiac device therapy

When arrhythmic/sudden cardiac death and non-fatal arrhythmic events with appropriate treatment of ICD and CRTD ($n = 26$) were combined, the observed event rates were 3.7%, 2.9%, 4.4%, and 8.1% for Q1, Q2, Q3, and Q4, respectively ($P = 0.0359$ for trend). However, when HMR quartiles of < 1.43 ($n = 137$), 1.43–1.66

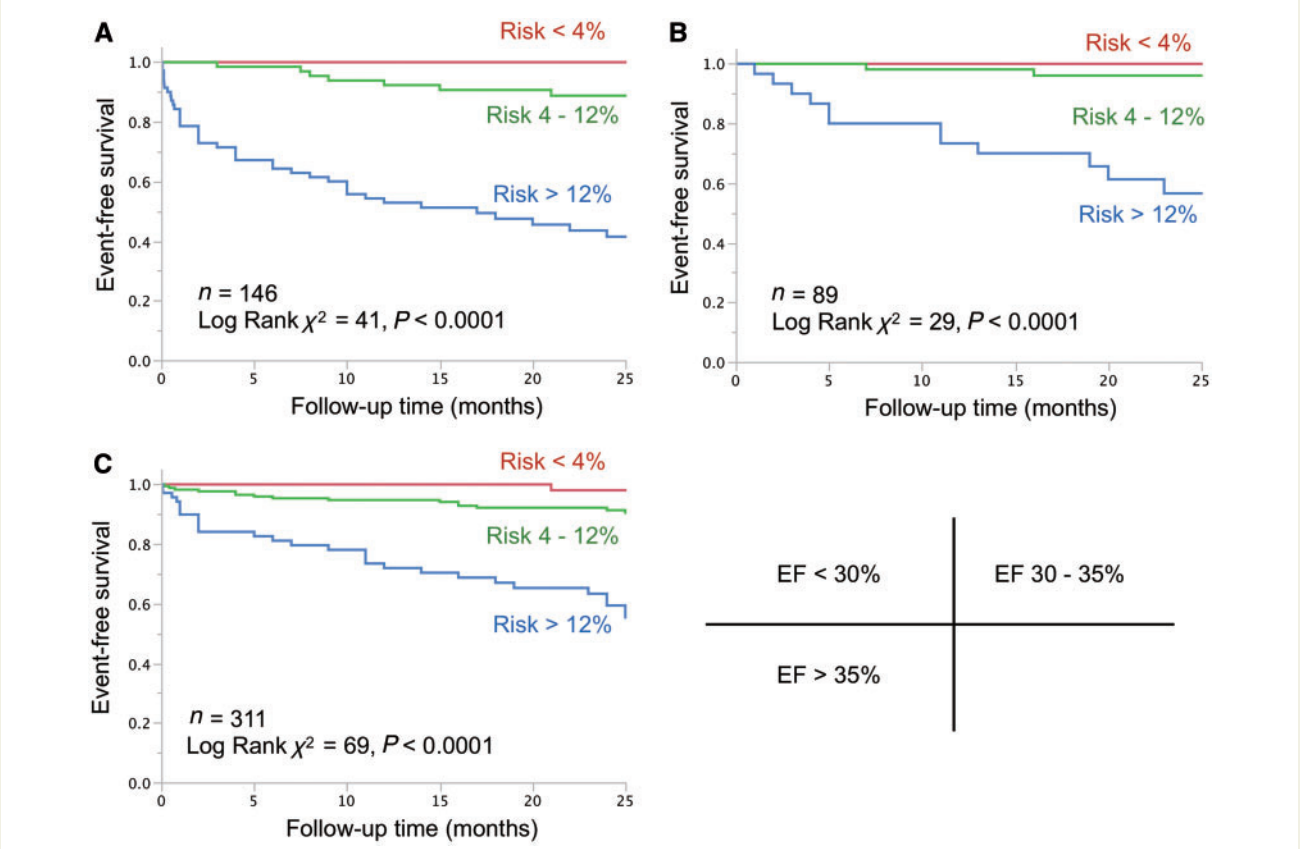


Figure 2 Survival analysis of three 2-year risk groups (<4%, 4–12%, and >12%) for three left ventricular ejection fraction (EF) ranges with <30% (*A*), 30–35% (*B*), and >35% (*C*).

(*n* = 132), 1.67–1.92 (*n* = 141), and >1.92 (*n* = 136) were analysed, the observed event rates were 5.1%, 8.3%, 3.6%, and 2.2%, respectively (*P* = 0.10).

Discussion

The presented findings validated the reliability of the 2-year risk model developed by combining cardiac ^{123}I-MIBG HMR with clinical information. The prediction of the 2-year risk model was superior to that of individual variables such as LVEF, BNP/NT-ProBNP, or MIBG HMR. It is particularly noted that, irrespective of LVEF and BNP/NT-proBNP levels, the risk model discriminated CHF patients at low to intermediate risks. The high-risk population was well discriminated from others, but the actual event rate observed was underestimated by this model.

Utility of ^{123}I-MIBG and classical prognostic biomarkers

Cardiac sympathetic innervation assessed by ^{123}I-MIBG activity has potent prognostic value in patients with CHF independently of and synergistically with known variables such as age, symptoms or NYHA functional class, LV function, and circulating biomarkers. [10–13,26–28] Recent multicentre CHF prognosis cohort studies demonstrated that ^{123}I-MIBG HMR is a powerful measurement for predicting progression and fatal outcomes of CHF, including lethal arrhythmias and sudden cardiac death.[16–19] The present findings further support the clinical utilities of a 2-year risk model for predicting the probability of lethal cardiac events. BNP and NT-ProBNP are routinely used at a clinical practice as biomarkers for initial diagnosis and for monitoring therapeutic effects in CHF. During a relatively long-term entry interval, both BNP and NT-ProBNP data were collected for this study. BNP and NT-ProBNP have different physiological properties, and are affected by age and renal function. Because of a difficulty in a simple conversion, these parameters were treated as categorical variables for statistical analysis based on the recommendations of Japanese Heart Failure Society and European Society of Cardiology.[24,25] Irrespective of LVEF and BNP/NT-ProBNP categories, a high-risk population with a 2-year cardiac mortality risk more than 12% was clearly identified and discriminated from other populations at low-to-intermediate risks.

Accuracy for prediction of cardiac death

The 2-year risk model demonstrated satisfactory diagnostic accuracy in low- to intermediate-risk patients who had 2-year mortality risk less than 14%. In high-risk patients who were predicted to have a mortality risk of more than 14%, however, the actual cardiac death rate was nearly two times greater than predicted. There are several

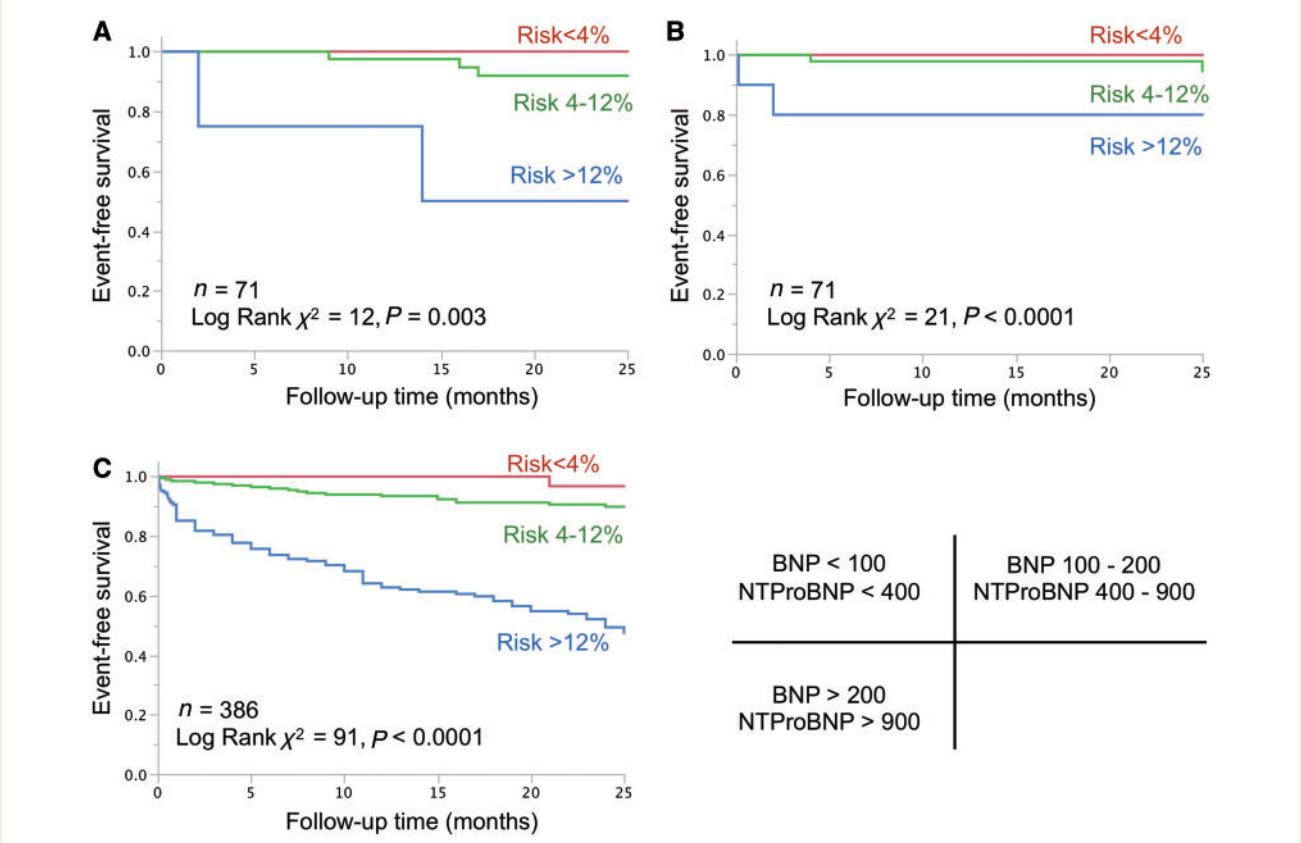


Figure 3 Survival analysis of three 2-year risk groups (<4%, 4–12%, and >12%) for three BNP/NT-ProBNP ranges of BNP <100 pg/mL or NT-ProBNP <400 pg/mL (*A*), BNP 100–200 pg/mL or NT-ProBNP 400–900 pg/mL (*B*), and BNP >200 pg/mL or NT-ProBNP >900 pg/mL (*C*).

Table 2 Quartiles of the 2-year mortality risk

	Q1	Q2	Q3	Q4	*P*-value
n	136	137	137	136	
Range (%)	<5.1	5.1–8.2	8.3–13.7	≥13.8	
2-year mortality risk (%), mean ± SD	3.2 ± 1.3	6.7 ± 0.9	10.7 ± 1.7	27.9 ± 10.5	<0.0001
Age (years), mean ± SD	57 ± 15	64 ± 12	70 ± 11	73 ± 11	<0.0001
LVEF (%), mean ± SD	47 ± 16	38 ± 11	36 ± 12	33 ± 13	<0.0001
^{123}I-MIBG HMR (standardized ME collimator[a]), mean ± SD	2.22 ± 0.41	1.74 ± 0.22	1.54 ± 0.30	1.46 ± 0.28	<0.0001
^{123}I-MIBG HMR (LE collimator-equivalent[b]), mean ± SD	1.83 ± 0.28	1.51 ± 0.16	1.37 ± 0.20	1.31 ± 0.19	<0.0001
BNP >200 pg/mL	41%	40%	83%	91%	<0.0001
NT-ProBNP >900 pg/mL	60%	67%	86%	94%	<0.0001
eGFR (mL/min), mean ± SD	69 ± 22	69 ± 24	55 ± 29	49 ± 25	0.0002

BNP, b-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HMR, heart-to-mediastinum ration; LE, low energy; LVEF, left ventricular ejection fraction; ME, medium energy; MIBG, meta-iodobenzylguanidine; NT-ProBNP, N-terminal Pro-BNP.
[a]Conversion coefficient = 0.88.
[b]Conversion coefficient = 0.60.

possible reasons for this discrepancy. The risk model was developed using multiple cohorts dating as far back as 1990, including many early research studies into the potential utility of ^{123}I-MIBG imaging in CHF.[12–14,29,30] As these studies tended to include larger proportions of patients with less severe CHF being closely followed, it is likely the derivation population experienced fewer adverse outcomes compared with an unselected cohort of clinical HF patients. This is borne out by the overall relatively low 2-year cardiac death rate in the total derivation population (9.8%) as well as in NYHA classes III and IV patients (18% and 30%, respectively). The greater disease severity in

the validation population is also observed in eGFR results [65 ± 23 and 50 ± 29 mL/min/1.73 m^2 for the derivation (n = 324 available) and validation datasets, respectively; $P < 0.0001$] and BNP levels [mean BNP 373 (range 5–2996) pg/mL and 475 (range 3–4370) pg/mL, respectively; $P = 0.019$]. The lower eGFR results in the present study reflected inclusion of many high-risk patients with chronic renal dysfunction and haemodialysis.[31,32]

Given the known adverse prognostic significance of high BNP/NT-ProBNP and low eGFR in CHF patients, absence of these variables in the risk model is probably the primary reason why the predicted mortality rate was underestimated in the highest risk patients in the validation cohort. Such high-risk patients were more likely to undergo ^{123}I-MIBG imaging in Japan in the 2000s since clinical use of the technique expanded to patients with more severe CHF and those with comorbidities such as diabetes and renal failure. An additional supplementary model including BNP/NT-ProBNP and eGFR may improve the predictive accuracy for identifying exceptionally high-risk patients.

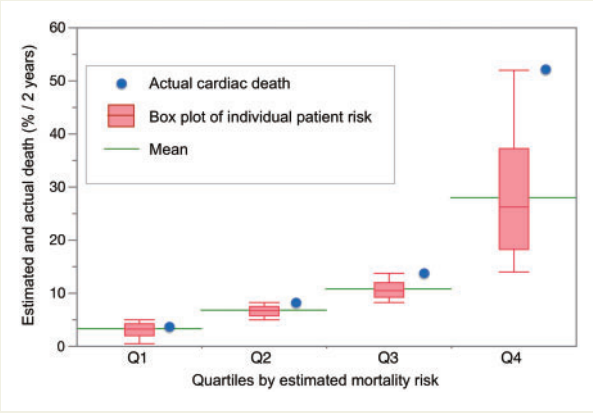


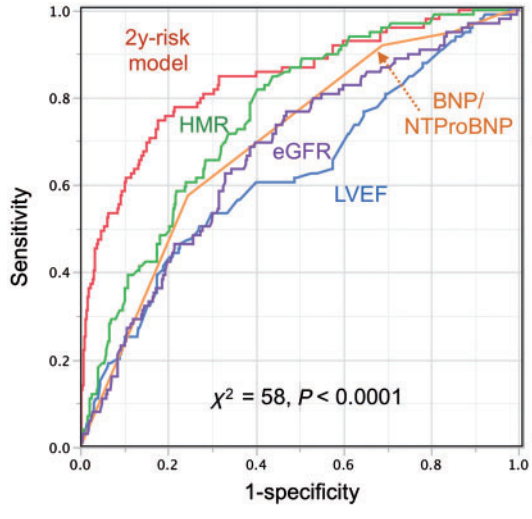
Figure 4 2-year mortality risk estimated by the model (box plots) and actual cardiac death (blue dots). Quartile ranges for Q1–Q4 were <5.1%, 5.1–8.2%, 8.3–13.7%, and ≥13.8%, respectively. The box plot denotes median and first and third quartiles, and whiskers for value ranges.

Discrimination of low- to intermediate- and high-risk patients

Irrespective of LVEF and BNP/NT-ProBNP levels, a low risk prediction by the model was validated; no patients died when the 2-year mortality risk was <2% and the observed cardiac mortality was 1.6% when the predicted risk was <4%. Likewise, a high-risk population with a 2-year cardiac mortality risk more than 12% was clearly discriminated from the populations at low- to intermediate-risks. Thus, the presented risk-stratification concept incorporating cardiac sympathetic functional parameters can address some limitations of conventional prognostic biomarkers recommended by the current guidelines[6,7] and help select more appropriate therapeutic strategies. For example, patients with LVEF ≥35% but at a high risk in this model (i.e. a 2-year cardiac mortality risk >12%) could benefit from more aggressive medical and device treatments. On the other hand, patients who have LVEF <35% but are at a low risk in this model (i.e. 2-year cardiac mortality risk <4%) may be able to undergo less aggressive treatment than that recommended by current guidelines.

Prediction of heart failure death and lethal arrhythmic events

With respect to pump-failure death, the 2-year risk model had definitively better predictive capability compared with each conventional variable such as LVEF, BNP/NT-ProBNP, renal function, and HMR. Concerning arrhythmia/sudden death events including appropriate ICD/CRTD shocks, however, the presented results are more



	AUC	SE	Lower 95%	Upper 95%	P vs. 2y-risk model
2y-risk model	0.84	0.02	0.79	0.88	-
Late HMR	0.76	0.02	0.71	0.80	0.0004
BNP/NT-ProBNP	0.70	0.03	0.65	0.75	< 0.0001
eGFR	0.67	0.03	0.61	0.73	< 0.0001
LVEF	0.63	0.03	0.56	0.69	< 0.0001

Figure 5 Receiver-operating characteristic analysis for the 2-year risk model (red), MIBG HMR (green), BNP/NT-ProBNP (orange), LVEF (blue), and eGFR (purple) to predict heart failure death. ROC AUC (0.84) of the 2-year risk model was significantly greater than other four individual variables.

complicated for interpretation of clinical implications. A bell-shaped mortality rate in association with impairment of cardiac sympathetic function was also observed in the sub-analysis of ADMIRE-HF study[33] and the more recent ^{123}I-MIBG multicentre study in patients with ICD.[34] Perfusion-innervation imbalance or denervated but viable myocardium assessed by cardiac MIBG imaging is likely to be responsible for arrhythmogenecity[35–37] probably because impaired cardiac sympathetic innervation and residual myocardial viability is synergistically related to arrhythmogenic substrate, inhomogeneous refractory period, and denervated supersensitivity to adrenoceptor function of myocytes.[38,39]

Standardized HMR for the risk model

As HMR calculated in ME- and LE-collimator conditions differed significantly (*Table 1*), importance of adjusting HMR among institutions was recognized. The CC of 0.60 was used for internal calculation even after standardization to the ME collimator condition (CC of 0.88).[21,22] The use of HMR standardization enabled inter-institutional comparison and allowed inclusion of more patients for this validation study than would have been available if only images acquired using LE collimation (as per the derivation study) were accepted. The linear HMR conversion enhanced the current validation study by increasing the sample size and the robustness of the statistical analyses.

Limitations

Because of a retrospective and non-interventional nature, patients were studied over a long-term interval (2005–16). The 2-year risk model was developed by the database of patient data collected between 1990 and 2009 during which cardiac device treatment was not widely available at cardiac practice. In this context, advances in therapeutic strategies and revised guidelines for CHF might have affected outcomes and current cardiac prognosis of CHF patients modifiable by recent devices and pharmacotherapy. Such modifications by the treatments cannot be necessarily predicted precisely by the presented risk model. Nevertheless, the good agreement between the predicted risk and the observed outcomes in this study using the relatively recent cohort indicates that the limitation is less important particularly in patients at a low- to intermediate-mortality risk. For example, improved therapeutics would be less likely to have a dramatic effect on prognosis in a derivation cohort patient with low-risk characteristics than in one with a high-risk profile, an expectation consistent with the results shown in this validation study. On the other hand, patients at high-risk despite use of modern therapeutics such as implanted devices could be the subset that resulted in underestimation of risk by the model. A further study in patients eligible for and receiving devices is required to more appropriately identify high-risk patients who could benefit most from current indications of ICD/CRT/CRTD.

Conclusion

The 2-year risk model with age, NYHA functional class, MIBG HMR, and LVEF was successfully validated by the good agreement between predicted and observed cardiac mortality rates and by showing the better predictive accuracy of heart failure death compared with LVEF, BNP/NT-Pro BNP, or HMR alone. The prognostic value is evident particularly when CHF patients at a low to intermediate cardiac mortality risk.

Ethics

All procedures involving human participants complied with the ethical standards enshrined in the Declaration of Helsinki (1964), and its later amendments or comparable ethical standards. The institutional ethics committee at Kanazawa University approved this study as the core laboratory, and institutional review boards or ethics committees at all involved hospitals approved participation in this study.

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Conflict of interest: K.N. has collaborative research works of FUJIFILM RI Pharma, Co, Ltd, Tokyo, Japan, a supplier of ^{123}I-MIBG in Japan. Other co-authors have nothing to disclose.

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