

ORIGINAL ARTICLE

Validation of a Five-Year Prognostic Model Using ^{123}I -metaiodobenzylguanidine Scintigraphy in Patients with Heart Failure

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Abstract

Background: ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy evaluates the severity and prognosis of patients with heart failure. A prognostic model has been proposed using a multicenter study data of ^{123}I -MIBG scintigraphy. We evaluated the usefulness of the model using a database.

Methods: The study included 208 patients with noncompensated heart failure requiring hospitalization. ^{123}I -MIBG scintigraphy and echocardiography were performed predischage and 6 months postdischarge. The 5-year mortality rate was calculated by the model and classified into tertiles.

Results: In 208 patients, 56 cardiac deaths occurred within the observation period (median, 4.83 years). In the evaluation of predischage parameters, the predicted 5-year mortality was $15.5\% \pm 5.0\%$, $33.5\% \pm 3.9\%$, and $51.2\% \pm 8.2\%$, and 11 (16.2%), 18 (27.3%), and 27 (36.5%) cardiac deaths occurred in groups 1, 2, and 3, respectively. At the 6-month postdischarge evaluation, the estimated mortality was $8.2\% \pm 2.2\%$, $18.5\% \pm 4.8\%$, and $43.0\% \pm 12.1\%$, and 6 (9.4%), 21 (29.2%), and 29 (40.3%) cardiac deaths occurred, respectively. The predischage Kaplan–Meier survival analysis showed significant difference between groups 1 and 3 (P value 0.014). Moreover, the 6-month postdischarge evaluation showed significant difference between group 1 and 2, and between groups 1 and 3 (P value 0.016, <0.001, respectively). For groups 1 and 3, the 6-month postdischarge difference was more significant than the predischage difference (Chi-square 16.7 and 8.1, respectively).

Conclusions: The prognostic model using ^{123}I -MIBG scintigraphy was useful in predicting mortality risk in patients with heart failure. The estimated mortality at 6 months postdischarge was more useful than the predischage estimation for heart failure hospitalization.

Keywords: ^{123}I -metaiodobenzylguanidine, Heart failure, Prediction model, Prognosis

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The number of patients with heart failure is increasing annually in an aging society. Mortality rates in patients with chronic heart failure are decreasing because of improved treatments (1). In the management of patients with chronic heart failure, recognizing the severity of heart failure and predicting prognosis while managing heart failure are important. Scintigraphy using ^{123}I -metaiodobenzylguanidine (MIBG), an analog of norepinephrine, evaluates the activity of the sympathetic nerve system of patients with heart failure,

and the heart-to-mediastinal ratio (HMR) and washout rate (WR) have been shown to be associated with the severity and prognosis of heart failure (2, 3).

A prognostic model has been proposed using data from a Japanese multicenter study of ^{123}I -MIBG scintigraphy to predict 5-year mortality based on five factors: age, sex, New York Heart Association (NYHA) functional class, and left ventricular ejection fraction (LVEF), in addition to HMR evaluated by ^{123}I -MIBG scintigraphy (4). The predictive model

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is commercially available as software called “smart MIBG-HF software (PDRadiopharma Inc., Japan),” which can predict 5-year mortality in patients with heart failure. Although this model has been proposed as a prognostic model for patients with heart failure, to our knowledge, there are still few reports of validation using actual clinical data. Accordingly, we estimated the predicted mortality at 5 years using the 5-year MIBG risk model in our database and tested whether it correlates with actual outcomes.

Furthermore, patients with heart failure are in a constant state of flux, depending on their heart failure status or therapeutic interventions, pointing to the usefulness of repeated assessments (5). We additionally assessed patients at two time points; at the time of heart failure admission and approximately six months after discharge, using the predictive model to compare prognoses.

Materials and methods

Study patients and protocol

Patients with LVEF <45%, but without cardiac events for at least 5 months before the study, were prospectively identified according to their history of decompensated acute heart failure requiring hospitalization, as previously reported (5). In brief, unstable angina and acute myocardial infarction, liver and kidney failure, active malignancy, and severe cases requiring mechanical support (such as intra-aortic balloon pumping, left ventricular assist device, and cardiac resynchronization therapy) were excluded. After the stabilization of the acute phase of heart failure, the patients were treated with oral medications including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), β -blockers, and mineralocorticoid receptor antagonists (MRAs). No patients were taking tricyclic antidepressants or serotonin reuptake inhibitors.

¹²³I-MIBG scintigraphy and echocardiography were performed to evaluate the compensatory phase before hospital discharge. Patients who did not undergo scintigraphy or echocardiography before discharge were excluded. Other patients were excluded because they had cardiac death or heart failure hospitalization within 5 months after enrollment. We also excluded patients who had changed their basic heart failure medications up to six months after discharge. ¹²³I-MIBG scintigraphy and echocardiography were performed again approximately 6 months after hospital discharge (mean 6.4 months), and that date was considered day 0 of the observation period.

Finally, prognostic information was collected from the patients themselves, their families, and associated hospitals, and 208 patients were followed up. Of the 208 patients, 130 were men and 78 were women, with a mean age of 68.6 (range, 35–87) years. Cardiac deaths were classified as sudden

death, heart failure death, or death secondary to myocardial infarction. Unexpected deaths, such as deaths outside the hospital within 15 min of the onset of unexpected symptoms or deaths while sleeping, were considered sudden deaths. Deaths during hospitalization because of worsening congestive symptoms were considered cardiac deaths.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee of Cardiovascular Hospital of Central Japan and/or national research committee and with the Helsinki declaration, its later amendments, or comparable ethical standards. Informed consent was obtained from each study participant.

¹²³I-MIBG scintigraphy

Patients were injected intravenously with ¹²³I-MIBG (111 MBq) in the supine position. ¹²³I-MIBG was commercially available (PDRadiopharma Inc., Japan). At 15 min and 4 h after injection, static images were acquired in an anterior view using a single-head γ camera (Millenium MPR, GE Healthcare, Chicago, IL, USA) equipped with a low-energy general-purpose parallel hole collimator. Then, 128 \times 128 matrix static images with a 20% window were centered at 159 keV, which corresponds to ¹²³I photopeak, and 128-matrix static images were collected for 5 min. After the acquisition of static planar images, single-photon emission computed tomography (SPECT) images were acquired. The camera was rotated over 180° from a right anterior oblique 45° position to a left posterior oblique 45° position, with 32 views and 40 seconds per view. Scans were performed in a 64 \times 64 matrix, and images were reconstructed using the filtered back-projection method.

The HMR was obtained from anterior delayed ¹²³I-MIBG images using the method reported previously (3). WR was calculated using the following formula: $\{(early [H] - early [M]) - (delayed [H] - delayed [M])\} \div (early [H] - early [M]) \times 100 (\%)$, where early [H] and delayed [H] equal the mean count per pixel in the left ventricle in early and delayed images, respectively, and early [M] and delayed [M] equal the mean count per pixel in the upper mediastinum in early and delayed images, respectively. In this study, no correction for time decay was made when calculating WR. Each patient's delayed myocardial SPECT image was divided into 17 segments. Local tracer uptake was evaluated semiquantitatively with a 5-point scoring system (0, normal uptake; 1, mildly reduced uptake; 2, moderately reduced uptake; 3, markedly reduced uptake; 4, no uptake). The total defect score (TDS) was converted to the percentage of the total myocardium that was denervated (% denervation). Then, % denervation was calculated using the following formula: $(TDS \div 68 [highest score = 4 \times 17] \times 100)$. The normal range at our

institution is 6–18 for % denervation, 2.18–2.70 for delayed HMR, and 20%–30% for WR, as previously reported (6).

Echocardiography

Echocardiography was performed under mask using standard methods by two experienced independent echocardiographers. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF were calculated using the two-dimensional biplane method, as previously reported (5).

Five-year prognostic model using MIBG scintigraphy

A model for predicting 5-year cardiac mortality in patients with chronic heart failure was published by Nakajima et al. using data from a multicenter cohort study in Japan (4). The model estimates a patient's 5-year mortality based on five parameters: age, sex, NYHA functional classification, LVEF, and HMR. In this study, we used the predischARGE results of ¹²³I-MIBG scintigraphy and echocardiography to calculate the predicted mortality for each patient using this model. Patients were divided into tertiles according to the predicted mortality rate, and each group was compared. In addition, using the results of ¹²³I-MIBG scintigraphy and echocardiography at 6 months post-discharge, the software calculated the predicted mortality rate for each patient. Patients were also divided into tertiles, and each group was compared.

Data analysis and statistics

All statistical analyses were performed using EZR (Saitama Center, Jichi Medical University, Japan), a GUI for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Normally distributed continuous variables were expressed as mean \pm standard deviation. Categorical variables were presented as numbers and percentages. Distributions of continuous and categorical variables were compared using Kruskal–Wallis and chi-square tests, respectively. If comparisons between three groups were significant, multiple comparisons between groups were performed using Bonferroni test. Kaplan–Meier survival analysis was performed in three groups predischARGE and 6 months postdischarge, and these comparisons were made using the log-rank test. Comparisons of survival analysis were made between each group using the chi-square test. For all analyses, a P value of <0.05 was considered statistically significant.

Results

Follow-up periods

The follow-up period was 4.83 (0.78–7.48) years. In 208 patients, 56 cardiac deaths occurred (26.9%). Fatal cardiac

events occurred at a mean of 2.2 ± 0.9 (range, 0.8–5.1) years after the second evaluation. Thirty-eight (67.9%) deaths were caused by advanced heart failure, 13 (23.2%) were sudden deaths, and the remaining 5 (8.9%) were caused by myocardial infarction.

Clinical characteristics

The characteristics of the 208 patients are summarized in Table 1 by tertiles of the estimated mortality before hospital discharge. The predicted mortality rates in 5 years were $15.5\% \pm 5.0\%$, $33.5\% \pm 3.9\%$, and $51.2\% \pm 8.2\%$ for groups 1, 2, and 3, respectively. Among the three groups, those with higher predicted mortality (i.e., group 3) were significantly older and had worse NYHA functional class, worse ¹²³I-MIBG parameters (% denervation, HMR, and WR), and worse echocardiographic parameters (LVEDV, LVESV, and LVEF). No significant differences in sex, ischemic heart disease, or drugs such as ACE inhibitors, ARBs, β -blockers, or MRAs.

Patient characteristics at 6 months postdischarge are shown in Table 2. The estimated mortality rates were $8.2\% \pm 2.2\%$, $18.5\% \pm 4.8\%$, and $43.0\% \pm 12.1\%$. Regarding predischARGE clinical characteristics, the groups with higher estimated mortality rates were older and had worse NYHA functional class and worse ¹²³I-MIBG and echocardiographic parameters. Significant differences were found in the combined groups (Table 2). Sex, ischemic heart disease, and drug therapies were comparable in each group.

In the tertile at discharge and six months after discharge, 109 of the 208 patients were in the same group. The remaining 99 patients moved between Groups; 23 moved from Group 1 to 2, 8 from Group 1 to 3, 18 from Group 2 to 3, 23 from Group 3 to 2, 5 from Group 3 to 1, and 22 moved from Group 2 to 1.

Kaplan–Meier survival analysis

In the predischARGE groups, 11 (16.2%), 18 (27.3%), and 27 (36.5%) cardiac deaths occurred in groups 1, 2, and 3, respectively (Figure 1A). In the 6-month postdischarge groups, 6 (9.4%), 21 (29.2%), and 29 (40.3%) cardiac deaths occurred in groups 1, 2, and 3, respectively (Figure 1B).

The Kaplan–Meier survival curves for the three groups of estimated mortality at hospital discharge are shown in Figure 2 (A). Groups 1–3 were found to have more actual deaths, in that order. Mortality was significantly higher in groups 1 and 3, with a P value of 0.014, a chi-square coefficient of 8.1. On the contrary, the Kaplan–Meier survival curves at 6 months after hospital discharge are shown in Figure 2(B). Similarly, the number of actual deaths was higher in the order of groups 1, 2, and 3, and the apparent difference was greater than the survival curve before discharge. Significant differences were found between groups 1 and 2 and between groups 1 and 3,

Table 1 Clinical characteristics of the tertiles based on data at hospital discharge

	Group 1	Group 2	Group 3	p value (Group 1 vs 2, 1 vs 3, 2 vs 3)
Patients (N)	68	66	74	
Estimated 5-year mortality, %	15.5 ± 5.0	33.5 ± 3.9	51.2 ± 8.2	
Age	66.3 ± 12.1	66.7 ± 11.8	72.0 ± 8.9	0.969, 0.006, 0.015
Sex (male)	40 (58.8%)	40 (60.6%)	49 (66.2%)	0.675
Ischemic heart disease	33 (48.5%)	24 (36.3%)	31 (41.9%)	0.435
Pharmacotherapy				
ACE inhibitors	42 (61.8%)	44 (66.7%)	50 (67.6%)	0.665
ARBs	45 (66.2%)	39 (59.0%)	48 (64.9%)	0.827
β-blockers	27 (39.7%)	31 (47.0%)	33 (44.6%)	0.586
MRAs	31 (45.6%)	18 (27.3%)	32 (43.2%)	0.082
NYHA functional class (I/II/III/IV)	0/62/6/0	0/8/48/10	0/0/59/15	<0.001, <0.001, <0.001
MIBG scintigraphy				
% denervation	55.8 ± 12.4	59.5 ± 10.0	60.4 ± 8.4	0.959, <0.001, 0.002
HMR	1.74 ± 0.15	1.73 ± 0.18	1.52 ± 0.18	0.923, <0.001, <0.001
WR	46.1 ± 9.8	45.7 ± 10.2	53.2 ± 10.1	0.974, 0.001, <0.001
Echocardiography				
LVEDV, mL	183 ± 48.1	171 ± 25.1	193 ± 47.0	0.243, 0.267, 0.005
LVESV, mL	122 ± 40.6	114 ± 25.0	138 ± 48.7	0.431, 0.046, 0.001
LVEF, %	33.8 ± 7.15	33.9 ± 7.19	29.8 ± 9.57	0.974, 0.001, <0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; HMR, heart-to-mediastinum ratio; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MIBG, metaiodobenzylguanidine; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; WR, washout rate.

P value notes the value of each group by multiple comparisons when P value of the comparison of three groups is <0.05.

with P values of 0.016, <0.001, and chi-square coefficients of 7.7 and 16.7, respectively.

Discussion

Study findings

In this study, the three groups based on estimated mortality from the 5-year MIBG risk model confirmed that actual mortality was higher in the group with the highest estimated mortality than in the group with the lowest estimated mortality. Moreover, the estimated mortality at the second assessment at approximately 6 months postdischarge was more closely associated with actual mortality than that at the initial assessment predischARGE for heart failure.

Prediction models for patients with heart failure

Understanding the prognostic risk is important when treating patients with heart failure. Understanding the expected risks helps make optimal treatment choices, especially in patients with high-risk status. Specifically, it can help determine the need for further medications, device therapy such as cardiac resynchronization therapy, implantable cardioverter defibrillators, implantable artificial hearts, and heart transplantation. However, predicting mortalities of

patients with heart failure are sometimes more difficult than those of patients with other diseases because of rapid and sometimes abrupt changes in patients' condition (7).

Several models have been proposed as prognostic tools for heart failure. The Seattle Heart Failure Model (SHFM) is one of the most representative models, which estimates the survival rate of patients with heart failure based on multiple factors, including clinical information, blood data, and drug therapy (8). Moreover, the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) prognostic model is built from a meta-analysis of patients with chronic heart failure enrolled in randomized controlled trials or a large registry of 30 trials. MAGGIC is relatively simple compared with SHFM (9). Several other models can predict heart failure prognosis, but no one model could be clearly recommended (10).

MIBG is an analog of norepinephrine, and ¹²³I-MIBG scintigraphy can image and quantify cardiac sympathetic nerve activity (11, 12). In the case of heart failure, norepinephrine is increased from the sympathetic nerve terminals in the heart and reuptake function is impaired, resulting in reduced norepinephrine stores. Furthermore, norepinephrine in the synaptic cleft is known to spill over the bloodstream (13). Therefore, patients with heart failure have a

Table 2 Clinical characteristics of the tertiles based on data 6 months postdischarge

	Group 1	Group 2	Group 3	p value (Group 1 vs 2, 1 vs 3, 2 vs 3)
Patients (N)	64	72	72	
Estimated 5-year mortality, %	8.2 ± 2.2	18.5 ± 4.8	43.0 ± 12.1	
Age	62.6 ± 11.9	69.6 ± 10.3	72.7 ± 7.0	<0.001, <0.001, 0.177
Sex (male)	37 (57.8%)	47 (65.3%)	46 (63.9%)	0.636
Ischemic heart disease	28 (43.8%)	32 (44.4%)	29 (40.3%)	0.879
Pharmacotherapy				
ACE inhibitors	35 (54.7%)	51 (70.8%)	51 (70.8%)	0.086
ARBs	46 (71.9%)	49 (68.1%)	39 (54.2%)	0.074
β-blockers	36 (56.3%)	29 (40.3%)	27 (37.5%)	0.065
MRAs	31 (48.4%)	27 (37.5%)	24 (33.3%)	0.189
NYHA functional class (I/II/III/IV)	24/38/2/0	13/42/17/0	3/6/62/1	<0.001, <0.001, <0.001
MIBG scintigraphy				
% denervation	41.9 ± 11.9	52.3 ± 12.9	59.4 ± 13.9	<0.001, <0.001, 0.004
HMR	1.96 ± 0.18	1.73 ± 0.18	1.60 ± 0.24	<0.001, <0.001, <0.001
WR	36.8 ± 9.56	44.2 ± 11.0	53.2 ± 14.0	<0.001, <0.001, <0.001
Echocardiography				
LVEDV, mL	148 ± 40.1	174 ± 52.8	181 ± 50.0	0.005, <0.001, 0.628
LVESV, mL	85.6 ± 34.9	112 ± 50.7	125 ± 52.1	0.003, <0.001, 0.234
LVEF, %	43.5 ± 9.03	37.4 ± 9.74	32.8 ± 10.8	0.001, <0.001, 0.017

ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; HMR, heart-to-mediastinum ratio; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MIBG, metaiodobenzylguanidine; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; WR, washout rate.

P value notes the value of each group by multiple comparisons when P value of the comparison of three groups is <0.05.

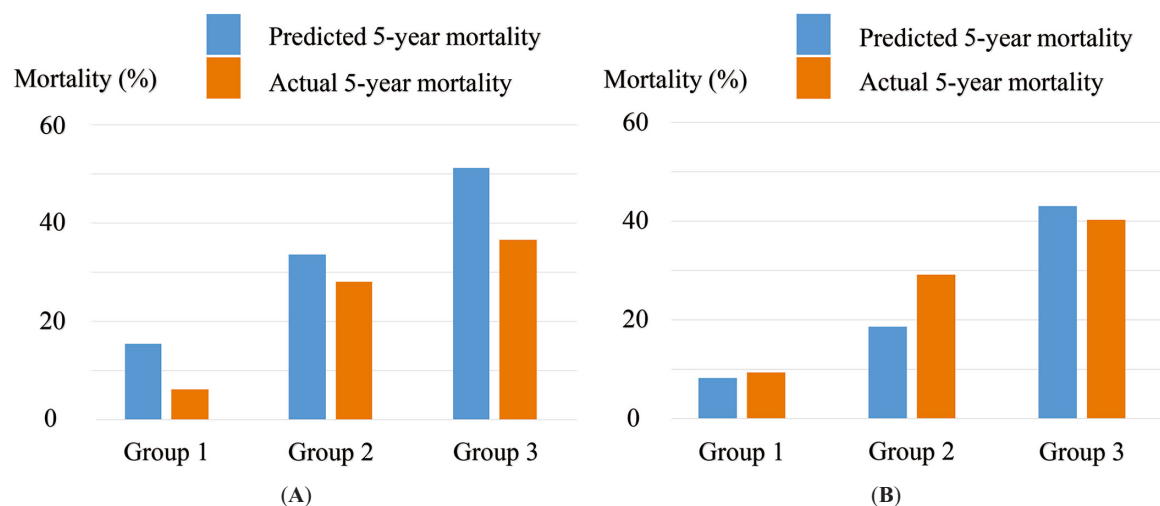


Figure 1 Predicted 5-year mortality rates and actual mortality event rates at predischage (A) and 6 months postdischarge (B).

In the evaluation of predischage parameters, the predicted 5-year mortality was 15.5% ± 5.0%, 33.5% ± 3.9%, and 51.2% ± 8.2%, and 11 (16.2%), 18 (27.3%), and 27 (36.5%) cardiac deaths occurred in groups 1, 2, and 3, respectively (A). At the 6-month postdischarge evaluation, the estimated mortality was 8.2% ± 2.2%, 18.5% ± 4.8%, and 43.0% ± 12.1%, and 6 (9.4%), 21 (29.2%), and 29 (40.3%) cardiac deaths occurred, respectively (B).

decreased HMR and increased WR. Many studies have shown that a low HMR or high WR of ¹²³I-MIBG correlate with the severity and prognosis of heart failure (2, 3, 14, 15). Moreover, a study reported that adding ¹²³I-MIBG parameters

to the SHFM improved its prognostic value (16).

The 5-year MIBG risk model is built on a database pooled from a cohort study of six Japanese institutions (4). The model is based on Cox proportional hazards analysis and logistic

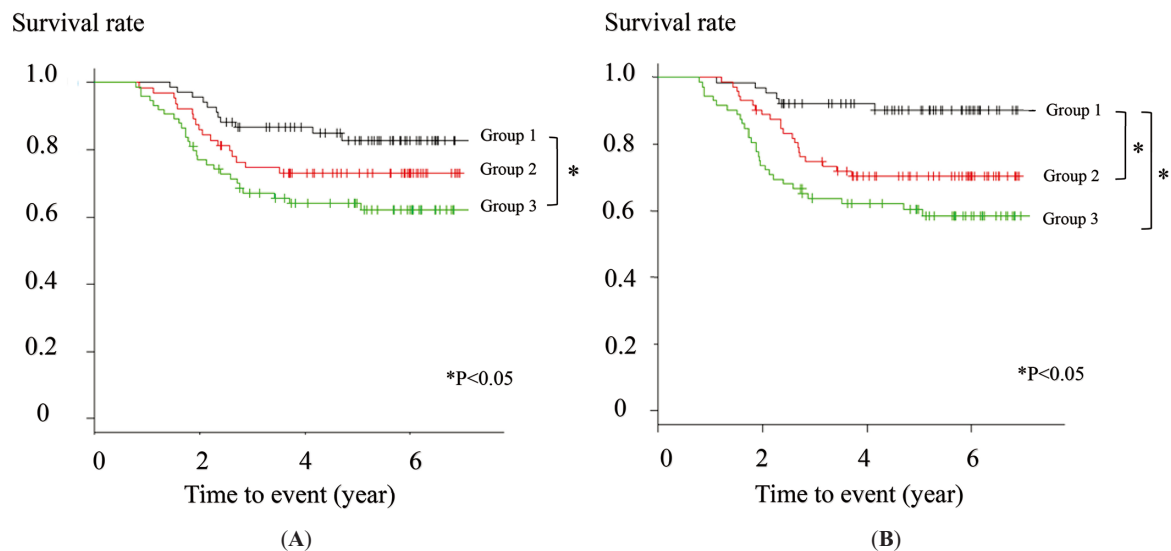


Figure 2 Kaplan–Meier survival curves for the tertiles at discharge (A) and 6-month postdischarge (B).

The following is the tertile survival curve using data at discharge (A) and 6 months postdischarge (B). In the tertiles at discharge, group 1 had significantly lower mortality than group 3. The chi-square coefficient was 8.1. In the tertiles 6 months postdischarge, group 1 had significantly lower mortality than groups 2 and 3, and the chi-square coefficients were 7.7 and 16.7, respectively.

regression analysis, which shows that adding the HMR of ¹²³I-MIBG scintigraphy to age, sex, NYHA functional class, and LVEF improves the prognostic ability and can calculate the 5-year mortality risk. The 5-year mortality risk is calculated from these five factors. This heart failure prognostic model includes ¹²³I-MIBG scintigraphy parameters that reflect the severity and prognosis of heart failure, and this model is expected to evaluate severity and prognosis with higher accuracy. Furthermore, this model is simple enough to predict prognosis with only five factors, without the need for complex clinical data input in other prediction models.

Several studies have validated this prognostic MIBG risk model, demonstrating its predictive utility for mortality at 2 years (17, 18). We validated this model for 5-year mortality risk in our database by comparing the cumulative event rates in the tertiles of mortality risk. In the tertiles divided by predicted mortality, groups 1 and 3 showed significantly different mortality rates before discharge. At 6 months postdischarge, significant differences were found between groups 1 and 2 and between groups 1 and 3. Since the actual mortality rates are also lower in the order of decreasing mortality rate, we have shown that this model can be used to stratify the mortality rates.

Importance of repeated evaluations

In the treatment of patients with heart failure, repeated evaluation of their changing conditions is important. Drug therapy such as β -blockers, ACE inhibitors, ARBs, and MRAs has been shown to improve ¹²³I-MIBG scintigraphy findings and prognosis in patients with heart failure. A study

comparing ¹²³I-MIBG scintigraphy before and after optimal medical therapy in patients with heart failure with dilated cardiomyopathy reported that the HMR after 6 months of treatment was more predictive of prognosis (19). In addition, differences in HMR and WR between patients with pre- and post-treatment heart failure were also shown to be more prognostic value in patients with heart failure (5). In the treatment of heart failure, repeated evaluations of ¹²³I-MIBG scintigraphic parameters may be important because conditions are constantly changing due to natural processes, therapeutic interventions, and other factors.

This study included evaluations of two timings, i.e., one before discharge after hospitalization for noncompensated heart failure and the other during the compensated period 6 months postdischarge. Both evaluations resulted in a stratified prognosis; however, given the visual stratification of the survival curves, combination of groups with significant differences between the tertiles, and chi-square coefficients for groups 1 and 3, we found that the stratification was more accurate 6 months postdischarge than predischage.

The pooled data, which the 5-year MIBG risk model was based on, were aggregated from several prospective cohort studies at six Japanese institutions (2, 5, 19–24). Despite the small differences, all studies performed ¹²³I-MIBG scintigraphy at the time of compensated heart failure. In this study, both the predischage and 6-month postdischarge data were obtained when the heart failure was compensated and stable, similar to the conditions in the original cohort studies.

However, given that all three groups overestimated mortality in the pre-discharge predicted mortality (Figure 1A),

this suggests that the sympathetic storm in the acute phase of heart failure, even in a compensated state, may affect MIBG uptake and washout rates before discharge. In the Kaplan-Meier curves (Figure 2), groups 2 and 3 showed similar curves before and 6 months after discharge, but group 1 had less mortality 6 months after discharge. This suggests that MIBG before discharge may overestimate mortality, especially in mild disease groups such as group 1.

Therefore, it may be more clinically useful to estimate prognosis using the prognostic model at a more stable time point, such as 6 months after discharge from the hospital.

Study limitations

First, this single-center study has a small number of cases, which may have introduced biases. Further validation in a multicenter study with a large number of cases is warranted. Second, analyses were performed by comparing outcomes across the tertiles to validate the predictive models, but models such as the receiver operating characteristic curve or concordance statistic were not tested. Further statistical validation is also needed. Third, the database is included as part of the pooled data from which the prognostic model was created. However, it is only a small portion of the data, and we believe that the analysis of this study may be useful. Finally, this study shows relatively low use of β -blockers, ACE inhibitors, ARBs, and MRAs, all of which are important in improving heart failure outcomes. Furthermore, this study includes cases without drugs such as ivabradine, angiotensin-receptor-neprilysin inhibitor, and sodium glucose co-transporter 2 inhibitors, which have been reported to improve heart failure outcomes in recent years. Therefore, the current drug therapy may have improved the prognosis compared with that in the current study.

Conclusion

The 5-year prognostic model using ¹²³I-MIBG scintigraphy is a useful tool for predicting mortality risk in patients with heart failure. Furthermore, an assessment 6 months postdischarge from heart failure hospitalization may be more useful in predicting mortality risk than an assessment predischARGE.

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Conflicts of interest

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References

1. Taylor CJ, Ordóñez-Mena JM, Roalfe AK, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *BMJ* 2019; 364: I223.
2. Nakata T, Nakajima K, Yamashina S, et al. A pooled analysis of multicenter cohort studies of ¹²³I-MIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. *JACC Cardiovasc Imaging* 2013; 6: 772-84.
3. Merlet P, Valette H, Dubois-Randé JL, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med* 1992; 33: 471-7.
4. Nakajima K, Nakata T, Yamada T, et al. A prediction model for 5-year cardiac mortality in patients with chronic heart failure using ¹²³I-metaiodobenzylguanidine imaging. *Eur J Nucl Med Mol Imaging* 2014; 41: 1673-82.
5. Kasama S, Toyama T, Sumino H, et al. Prognostic value of serial cardiac ¹²³I-MIBG imaging in patients with stabilized chronic heart failure and reduced left ventricular ejection fraction. *J Nucl Med* 2008; 49: 907-14.
6. Kasama S, Toyama T, Hatori T, et al. Evaluation of cardiac sympathetic nerve activity and left ventricular remodelling in patients with dilated cardiomyopathy on the treatment containing carvedilol. *Eur Heart J* 2007; 28: 989-95.
7. Lunney JR, Lynn J, Foley DJ, Lipson S, Guralnik JM. Patterns of functional decline at the end of life. *JAMA* 2003; 289: 2387-92.
8. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: Prediction of survival in heart failure. *Circulation* 2006; 113: 1424-33.
9. Pocock SJ, Ariti CA, McMurray JJV, et al. Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013; 34: 1404-13.
10. Alba AC, Agoritsas T, Jankowski M, et al. Risk prediction models for mortality in ambulatory patients with heart failure: A systematic review. *Circ Hear Fail* 2013; 6: 881-9.
11. Wieland DM, Wu J, Brown LE, Mangner TJ, Swanson DP, Beierwaltes WH. Radiolabeled adrenergic neuron-blocking agents: Adrenomedullary imaging with [¹³¹I]iodobenzylguanidine. *J Nucl Med* 1980; 21: 349-53.
12. Schofer J, Spielmann R, Schuchert A, Weber K, Schlüter M.

- Iodine-123 meta-iodobenzylguanidine scintigraphy: A noninvasive method to demonstrate myocardial adrenergic nervous system disintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1988; 12: 1252–8.
13. Liang CS. Cardiac sympathetic nerve terminal function in congestive heart failure. *Acta Pharmacol Sin* 2007; 28: 921–7.
 14. Jacobson AF, Senior R, Cerqueira MD, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J Am Coll Cardiol* 2010; 55: 2212–21.
 15. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BLF. Prognostic value of myocardial ¹²³I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: A systematic review. *Eur Heart J* 2008; 29: 1147–59.
 16. Kuramoto Y, Yamada T, Tamaki S, et al. Usefulness of cardiac iodine-123 meta-iodobenzylguanidine imaging to improve prognostic power of Seattle heart failure model in patients with chronic heart failure. *Am J Cardiol* 2011; 107: 1185–90.
 17. Nakajima K, Nakata T, Doi T, et al. Validation of 2-year ¹²³I-meta-iodobenzylguanidine-based cardiac mortality risk model in chronic heart failure. *Eur Heart J Cardiovasc Imaging* 2018; 19: 749–56.
 18. Tamaki S, Yamada T, Watanabe T, et al. Usefulness of the 2-year iodine-123 metaiodobenzylguanidine-based risk model for post-discharge risk stratification of patients with acute decompensated heart failure. *Eur J Nucl Med Mol Imaging* 2022; 49: 1906–17.
 19. Matsui T, Tsutamoto T, Maeda K, Kusukawa J, Kinoshita M. Prognostic value of repeated ¹²³I-metaiodobenzylguanidine imaging in patients with dilated cardiomyopathy with congestive heart failure before and after optimized treatments—Comparison with neurohumoral factors. *Circ J* 2002; 66: 537–43.
 20. Nakata T, Miyamoto K, Doi A, et al. Cardiac death prediction and impaired cardiac sympathetic innervation assessed by MIBG in patients with failing and nonfailing hearts. *J Nucl Cardiol* 1998; 5: 579–90.
 21. Wakabayashi T, Nakata T, Hashimoto A, et al. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac death. *J Nucl Med* 2001; 42: 1757–67.
 22. Yamada T, Shimonagata T, Fukunami M, et al. Comparison of the prognostic value of cardiac iodine-123 metaiodobenzylguanidine imaging and heart rate variability in patients with chronic heart failure: A prospective study. *J Am Coll Cardiol* 2003; 41: 231–8.
 23. Yamazaki J, Muto H, Kabano T, Yamashina S, Nanjo S, Inoue A. Evaluation of β -blocker therapy in patients with dilated cardiomyopathy—Clinical meaning of iodine 123-metaiodobenzylguanidine myocardial single-photon emission computed tomography. *Am Heart J* 2001; 141: 645–52.
 24. Momose M, Kobayashi H, Iguchi N, et al. Comparison of parameters of ¹²³I-MIBG scintigraphy for predicting prognosis in patients with dilated cardiomyopathy. *Nucl Med Commun* 1999; 20: 529–35.