Clinical Investigation

Validation and Recalibration of Seattle Heart Failure Model in Japanese Acute Heart Failure Patients

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ABSTRACT

Background: Precise risk stratification in heart failure (HF) patients enables clinicians to tailor the intensity of their management. The Seattle Heart Failure Model (SHFM), which uses conventional clinical variables for its prediction, is widely used. We aimed to externally validate SHFM in Japanese HF patients with a recent episode of acute decompensation requiring hospital admission.

Methods and Results: SHFM was applied to 2470 HF patients registered in the West Tokyo Heart Failure and National Cerebral And Cardiovascular Center Acute Decompensated Heart Failure databases from 2006 to 2016. Discrimination and calibration were assessed with the use of the c-statistic and calibration plots, respectively, in HF patients with reduced ejection fraction (HFrEF; <40%) and preserved ejection fraction (HFpEF; ≥40%). In a perfectly calibrated model, the slope and intercept would be 1.0 and 0.0, respectively. The method of intercept recalibration was used to update the model. The registered patients (mean age 74 ± 13 y) were predominantly men (62%). Overall, 572 patients (23.2%) died during a mean follow-up of 2.1 years. Among HFrEF patients, SHFM showed good discrimination (c-statistic = 0.75) but miscalibration, tending to overestimate 1-year survival (slope = 0.78; intercept = −0.22). Among HFpEF patients, SHFM showed modest discrimination (c-statistic = 0.69) and calibration, tending to underestimate 1-year survival (slope = 1.18; intercept = 0.16). Intercept recalibration (replacing the baseline survival function) successfully updated the model for HFrEF (slope = 1.03; intercept = −0.04) but not for HFpEF patients.

Conclusions: In Japanese acute HF patients, SHFM showed adequate performance after recalibration among HFrEF patients. Using prediction models to tailor the care for HF patients may improve the allocation of medical resources. (*J Cardiac Fail 2019;25:561−567*)

Key Words: Seattle Heart Failure Model, heart failure, risk model, validation, recalibration.

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Cardiovascular disease is the leading cause of death throughout the world. In Asian countries, it is estimated that 4.2 million individuals have heart failure (HF).[1,2] Moreover, the number of HF patients is predicted to increase worldwide. In Japan, it has been estimated that the number of HF patients will increase from 1 million in 2005 to 1.3 million by 2030.[3] In addition, in most non-Western countries, heart transplantation is a limited option owing to the shortage of donors.[4] For example, only 30−40 cases are performed annually in Japan, largely because of religious reasons and delays in the legal system.[5]

Risk stratification is a key element of clinical practice to facilitate the discrimination between high- and low-risk patients to tailor the management for HF and improve patient prognosis. However, before applying risk models in clinical practice, it is crucial to externally validate any models with the use of data collected over time and/or in different locations or hospitals. The Seattle Heart Failure Model (SHFM) uses conventional clinical variables to predict long-term survival and tailor the management of ambulatory HF outpatients, and is available online (https://SeattleHeartFailureModel.org).[6] It has been validated in various populations, mostly in Western countries.[7−9] Although the model has been applied most stringently in evaluating candidates for ventricular assist devices (VADs) and heart transplantation,[10−12] it has other possibilities for improving care, such as shared decision making.[13] Importantly, SHFM was derived from a trial dataset of ambulatory HF outpatients with reduced ejection fraction (HFrEF). Its validity remains uncertain among HF patients with preserved ejection fraction (HFpEF).

The present study aimed to validate SHFM in a large number of acute HF (AHF) patients and compare the model performance between HFrEF and HFpEF patients. Determining the generalizability of SHFM could support the timely referral of eligible patients for advanced HF clinics and aid the effective utilization of limited medical resources such as VAD or heart transplantation.

Methods

Study Design and Sample

The present study was based on data from 2 Japanese AHF registries: the West Tokyo Heart Failure (WET-HF) and National Cerebral And Cardiovascular Center Acute Decompensated Heart Failure (NaDEF) registries. The design of the WET-HF and NaDEF registries has been reported previously.[14,15] Briefly, the WET-HF registry is a large, ongoing, prospective, multicenter cohort registry designed to collect data on clinical backgrounds and outcomes of patients hospitalized for AHF.[14] From 2006 to 2016, AHF patients were consecutively registered from 5 tertiary care hospitals in the WET-HF registry. The NaDEF registry is a single-center, ongoing, prospective cohort registry that includes consecutive patients requiring hospitalization for AHF from 2013 to 2015.[15] In both registries, AHF is defined as rapid-onset HF or a change in the signs and symptoms of HF requiring urgent therapy and hospitalization, based on the Framingham criteria.[16] The clinical diagnosis of AHF was made by experienced cardiologists at each participating institution.

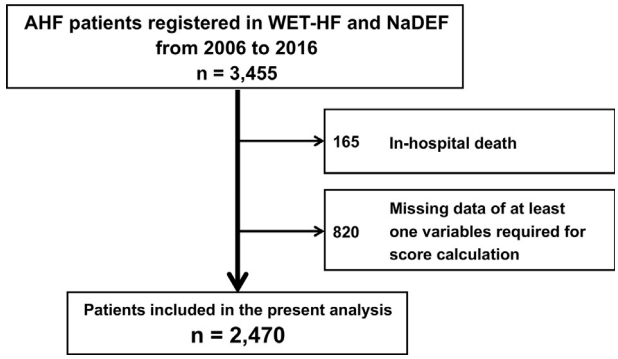

Fig. 1. Patient flow chart. WET-HF, West Tokyo Heart Failure; MaDEF, National Cerebral And Cardiovascular Center Acute Decompensated Heart Failure.

Both the WET and NaDEF databases are clinical datasets that contain similar data elements with standardized data definitions. The variables were recorded at hospital discharge, at which time the patients are usually stable owing to the much longer hospital stays (median 14 [interquartile range (IQR) 9−22] days in this cohort) in Japan.[17] In total, 3290 patients were registered in the 2 databases during the study period. Missing data regarding variables required for SHFM score calculation were rare (<3%), with the exception of total cholesterol (9.9%), lymphocytes (6.4%), and left ventricular ejection fraction (LVEF) (3.3%), leaving 2470 eligible patients (75.1%) for the present analysis (Fig. 1).

The study protocol was approved by the Institutional Review Boards at each site, and the research was conducted in accordance with the Declaration of Helsinki. Written or oral informed consent was obtained from each subject before the study.

SHFM Score Calculation

The SHFM score was calculated as previously described.[6] The following conversion was used for diuretics dose: furosemide 20 mg = azosemide 30 mg = torasemide 10 mg. Survival at time (t) for the score was calculated using the following equation ($\lambda = -0.0405$):

$$Survival(t) = e^{(\lambda \times t)e(SHFM\ score)}$$

Definitions of Outcomes and Variables

The combined end point of 1-year postdischarge mortality and VAD implantation was used for all analyses. None of the patients in this cohort underwent heart transplantation within 1 year after discharge. The New York Heart Association (NYHA) functional class also was evaluated at discharge by the treating cardiologists at each institution.

Table 1. Differences in Baseline Characteristics of Patients With Heart Failure in the Derivation and Validation Cohorts

Variable	Derivation Cohort: PRAISE Trial All Patients: n = 1,153	Validation Cohort: Japan		
		All Patients: n = 2,470	HFrEF Patients: n = 1,129	HFpEF Patients: n = 1,341
Age, y	65 ± 11	74 ± 13†	71 ± 14‡,§	76 ± 12§
Male, %	76	62†	71‡	54§
NYHA functional class, mean	3.6	2.2†	2.1§	2.2§
SBP, mm Hg	118 ± 18	112 ± 18†	107 ± 17‡,§	116 ± 18
Ejection fraction, %	21 ± 6	43 ± 16†	29 ± 7‡,§	56 ± 9§
Ejection fraction <40%, %	100	46	100	0
Ischemic etiology, %	64	29†	37‡,§	22§
Comorbidities				
Previous admissions for HF, %	N/A	33	39‡	28
Hypertension, %	N/A	71	67‡	74
Dyslipidemia, %	N/A	43	45	41
Diabetes, %	37	38	40	36
AF or AFL, %	N/A	47	41‡	52
Stroke, %	N/A	15	15	14
COPD, %	N/A	5	5	6
Laboratory findings				
Hemoglobin, mg/dL	13.9 ± 1.7	12.1 ± 2.2†	12.6 ± 2.2‡,§	11.7 ± 2.0§
Serum creatinine, mg/dL	1.37 ± 0.48	1.44 ± 1.05	1.43 ± 1.23	1.45 ± 1.53
BUN, mg/dL	26 ± 15	28 ± 16	27 ± 16	28 ± 17
Sodium, mEq/L	139 ± 4	139 ± 4	138 ± 3	139 ± 4
Uric acid, mg/dL	8.9 ± 2.6	7.0 ± 2.0†	7.1 ± 2.1§	6.9 ± 2.2§
Total cholesterol, mg/dL	202 ± 50	160 ± 39†	162 ± 40§	158 ± 37§
WBC count, $\times 10^3$	7.7 ± 2.3	7.5 ± 4.0	7.6 ± 3.4	7.5 ± 4.4
Lymphocytes, %	26 ± 9	23 ± 10†	24 ± 10‡	22 ± 10§
Albumin, mg/dL	4.1 ± 0.4	3.5 ± 0.5†	3.6 ± 0.5§	3.5 ± 0.5§
BNP, pg/mL*	N/A	244 (117−481)	289 (148−567)‡	204 (100−419)
Medical therapy				
ACEI, %	99	32†	40‡,§	25§
ARB, %	0	36	34	38
Beta-blocker, %	0	78	89‡	70
Aldosterone antagonist, %	3	39†	49‡,§	31§
Diuretics dose, mg/kg	1.45 ± 1.33	0.61 ± 0.49†	0.62 ± 0.51§	0.61 ± 0.47§
Statin, %	8	38†	42‡,§	35§
Allopurinol	10	26†	28§	23§
Device therapy				
ICD, %	0	7	13‡	2
CRT, %	0	4	7‡	1

Abbreviations: HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; EF, ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; HR, heart rate; HF, heart failure; AF, atrial fibrillation; AFL, atrial flutter; COPD, chronic obstructive pulmonary disease; BUN, blood urea nitrogen; WBC, white blood cell; BNP, B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy.

*The data of 1,293 patients in Japan were available.

†$P < .001$ between all patients of the derivation and validation cohorts.

‡$P < .001$ between HFrEF (<40%) and HFpEF (≥40%) patients in the validation cohort.

§$P < .001$ between the patients of the derivation cohort versus HFrEF and HFpEF patients in the validation cohort, respectively.

Statistical Analysis

Patients were divided into 2 groups based on left ventricular ejection fraction (LVEF; <40% and ≥40%), and their baseline characteristics were compared with the use of the unpaired *t* test or Mann-Whitney *U* test for continuous variables and the Pearson chi-square test for categoric variables.

The discrimination of the SHFM score was evaluated with the use of Cox regression models and the calculation of c-statistics. The calibration of the model's performance was assessed with the use of calibration plots where the predicted survival, divided into deciles based on the SHFM score, was plotted against the observed event-free survival at 1 year. The evaluation of model discrimination and calibration was also performed separately among patients with HFrEF (LVEF <40%) and HFpEF (LVEF ≥40%). Calibration is known to be strongly influenced by the incidence of the outcome in the validation population. Therefore, to reduce the source of miscalibration, we updated SHFM by implementing a simple recalibration method (intercept calibration), which replaces the original baseline survival function with the updated baseline survival function derived from the present Japanese cohort.[18,19]

All probability values were 2 tailed, and *P* values of <.05 were considered to indicate statistical significance. All statistical analyses were performed with the use of SPSS version 24.0 (SPSS, Chicago, Illinois).

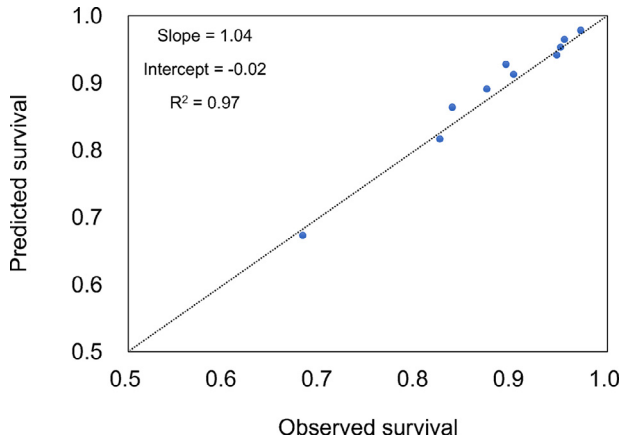

Fig. 2. Calibration plot for the entire cohort. The Seattle Heart Failure Model demonstrated good discrimination (c-statistic = 0.72) and calibration in the entire cohort.

Results

Patient Characteristics

Initially, the data of the SHFM derivation cohort were extracted from an earlier trial, the Prospective Randomized Amlodipine Survival Evaluation (PRAISE), in which the patients were registered from 1992 to 1994 in the United States and Canada.[20] All patients had dyspnea or fatigue at rest or on minimal exertion (NYHA functional class IIIB or IV) and reduced LVEF despite treatment with angiotensin-converting enzyme (ACE) inhibitors but not beta-blockers.

Compared with the SHFM-derivation cohort (Table 1), the patients in the Japanese cohort were more likely to be older and female and to have less ischemic etiology. Although the Japanese cohort tended to have lower systolic blood pressure (SBP) and NYHA functional class, higher levels of hemoglobin, uric acid, and total cholesterol were observed in the SHFM-derivation cohort. In addition, differences in medical and device therapies were noted between the cohorts.

Among our 2470 patients, 1129 (45.7%) were HFrEF patients and 1341 (54.3%) were HFpEF patients. The HFrEF patients tended to be younger and male, with a higher frequency of ischemic etiology and previous admissions for HF, lower SBP, and higher B-type natriuretic peptide levels. The HFpEF patients tended to be older, female, to have more valvular disease, hypertension, and atrial arrhythmias, and to have lower hemoglobin levels. The discharge prescription rates of ACE inhibitors, beta-blockers, aldosterone antagonists, and statins were higher in the HFrEF patients than in the HFpEF patients. In addition, device therapies were more frequently used in the HFrEF patients.

SHFM Performance

Overall, 572 patients (23.2%) died during a mean (±SD) follow-up of 2.1 ± 1.2 years (median 2.0 [IQR 1.0−2.8]). In the entire cohort, the observed 1-year survival rate was 88.4% and predicted 1-year survival rate was 89.2%. Figure 2 shows that, in the entire cohort, SHFM showed good discrimination (c-statistic for 1-year survival = 0.72) and calibration, and tended to slightly underestimate 1-year survival (slope = 1.04; intercept = −0.02; $R^2 = 0.97$). Among HFrEF patients, the observed 1-year postdischarge survival rate was 87.1% and predicted 1-year survival rate was 90.0%: SHFM showed good discrimination (c-statistic for 1-year survival = 0.75) but miscalibration, tending to overestimate 1-year survival (slope = 0.78; intercept = 0.22; $R^2 = 0.97$). In contrast, among HFpEF patients, the predicted 1-year postdischarge survival rate was 89.7% and predicted 1-year survival rate was 88.6%: SHFM showed modest discrimination (c-statistic = 0.69) and calibration and tended to underestimate 1-year survival (slope = 1.18; intercept = −0.16; $R^2 = 0.91$; Fig. 3). After intercept recalibration (with $\lambda = -0.059$), the calibration was corrected in HFrEF patients (slope = 1.03; intercept = −0.04; $R^2 = 0.97$; Fig. 4), but not in HFpEF patients. In HFrEF patients, the recalibrated model enabled the stratification of survival rates, across deciles, from >90% in the highest 5 deciles to 58% in the lowest decile.

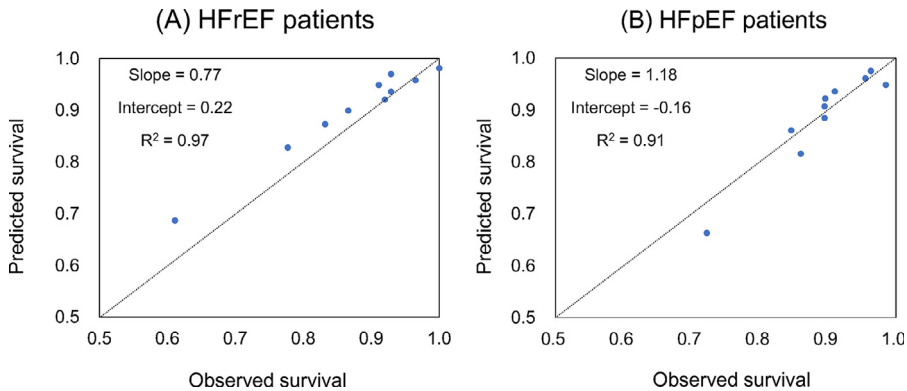

Fig. 3. Calibration plots for patients with heart failure with (A) reduced (HFrEF) and (B) preserved (HFpEF) ejection fraction. The Seattle Heart Failure Model demonstrated good discrimination (c-statistic = 0.75) but poor calibration in HFrEF patients, and modest discrimination (c-statistic = 0.69) and calibration in HFpEF patients.

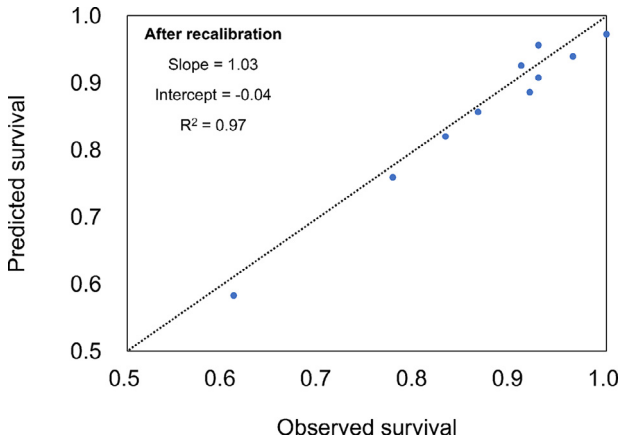

Fig. 4. Calibration plot after the intercept recalibration (for patients heart failure with reduced ejection fraction only).

Discussion

In this collaborative analysis of 2 large-scale registries, we externally validated SHFM in real-world AHF patients. We found that, despite significant differences in baseline characteristics compared with the original derivation cohort, SHFM showed adequate performance after recalibration among our HFrEF patients. At the present time, SHFM plays an important role in timely triaging of eligible patients for VAD and/or heart transplantation in Western countries, especially among patients who do not depend on inotropes or mechanical circulatory supports and are at borderline candidacy for such treatments (eg, Interagency Registry for Mechanically Assisted Circulatory Support profile 4−5). Given the satisfactory discrimination and calibration in the Japanese registries, our study suggests that the application of SHFM can be expanded to non-Western populations. However, the performance of SHFM was inadequate in HFpEF patients after an update of intercept recalibration; risk stratification and the exploration of effective treatment strategies for HFpEF patients remain challenging.

The performance of SHFM has been validated in a broad range of HF patients,[7−12] and some have suggested that SHFM has a tendency to overestimate survival rates (ie, underestimate mortality rates) in certain subgroups, such as patients that require advanced HF therapy (eg, VAD and heart transplantation).[10−12] Allen et al[21] recently reported that SHFM consistently overestimated survival rates even in ambulatory HF patients receiving standard therapies, albeit there was a very high rate of missing data, with NYHA functional class not available for the entire cohort. This mismatch is possibly due to differences in patient characteristics and treatment strategies; in fact, profound differences in medical therapies (eg, beta-blockers and aldosterone antagonists) existed between each cohort in the present study. SHFM is a statistical model that was derived and validated in randomized controlled trial settings as well as in the ambulatory setting, where strict enrollment criteria are applied. Risk models, as such, tend to overestimate when applied in real-world practice, such as discharge after AHF, as was the case in the present study. The patient characteristics in our study are similar to those in a previous report.[21]

Generally, model performance is influenced by the degree of similarity of incidence of outcome in derivation and validation populations.[22] When a risk model is externally validated but not well applied, model updating is necessary and practically relevant. Although estimates of regression parameters of risk models derived from large derivation cohorts are clearly precise, the corresponding predicted risks may still be biased in validation cohorts, mainly because of different associations of the predictors in validation cohorts or the presence of important predictors that were not included in the model. In the latter case, adjustment of the intercept is often sufficient and preferable. Previous studies have suggested that simple recalibration methods (adjusting the intercept and/or overall slope) are reasonable compared with more complicated model revision when model validation is performed in relatively small samples or the discriminative ability of risk models are sufficient.[18,19] Indeed, by simple recalibration without complex adjustments for the coefficients, conventional SHFM scoring was adequately performed in the Japanese HF population. This suggests that the risk models can overcome the difference in international practice patterns. Despite the need for recalibration, the factors that predict the outcome of HF patients are similar between Japan and North America. Whether the application of medical resources differ between these countries should be determined to help define the better strategy among these patients.

Regarding the clinical implication of our study results, the shortage of donors for heart transplantation remains an important issue, even in non-Western countries; the mean waiting period for heart transplantation exceeds ∼3 years in Japan. The number of heart transplantations is low, with an average of 30−40 procedures annually.[5] Destination therapy with VAD is likely to be introduced in Japan as well as other countries. In this context, it is favorable that patients who are implanted with VADs have had better prognoses in Japan compared with other countries,[23] which emphasizes the importance of precise risk prediction by means of risk models. The present study demonstrates that, especially in HFrEF patients, the traditional SHFM can assist clinicians in identifying patients who should be listed for heart transplantation or VAD implantation. The 2016 International Society for Heart Lung Transplantation updated criteria for heart transplantation suggests that an estimated 1-year survival of <80% (in patients <65 y of age), as calculated by means of the SHFM, should be considered as a reasonable cutoff point for listing.[24] In the present analysis, 15%−20% of the HFrEF patients had <80% of 1-year predicted survival after recalibration. SFHM scoring creates opportunities for reviewing patients' care and excludes missing the appropriate timing of listing for heart transplantation; furthermore, its combination with a clinician support application (eg, sending e-mail automatically to providers identifying advanced HF patients)[25] and/or

automatic systems to provide detailed risk profiles from the electronic medical record for clinicians might improve patients' prognoses.

Study Limitations

This study has inherent limitations. First, the registries consist of only 6 institutions, and the results may not be applicable to other countries or even other areas in Japan. However, patient characteristics and demographics in our cohorts are similar to those in the ATTEND registry, which covers the entire Japanese population and is considered to be representative of the general population of AHF patients in Japan.[17] Second, we did not attempt to further update the model (eg, reestimation of the intercept and the regression coefficients of all predictors with the use of the validation dataset), especially for HFpEF patients, because prognostic indicators of HF patients differed among LVEF groups.[26] Based on the data from the European Society of Cardiology Heart Failure Long-Term Registry, Chioncel et al[26] reported that atrial fibrillation was one of the predictors in HFpEF patients only. In addition, Chen et al[27] reported that atrial fibrillation, 1 of 5 variables included in the risk model they proposed, was associated with long-term mortality in HFpEF patients, but the calibration of the model was not verified. One of the reasons for the inadequate amount of research in this area is the scarcity of effective strategies to improve outcomes. However, recently, rhythm control via catheter ablation for atrial fibrillation has been reported as effective for improving left ventricular function and exercise capacity in HFpEF patients.[28,29] Further studies are required to identify patients who would benefit the most from medical interventions and to clarify successful approaches for HFpEF. Third, this study could not evaluate several important prognostic indicators, such as peak oxygen consumption (VO_2). Peak VO_2 is a standard criterion for heart transplantation, but has limitations regarding discrimination between risk strata, and it calibrates poorly in some populations.[30,31] Risk stratification for HF patients should not rely on peak VO_2 alone; combining risk models and peak VO_2 is recommended to adequately risk-stratify HF patients.[32] Fourth, it may be difficult to interpret the patients' NYHA functional class at discharge, because they were AHF patients after in-hospital treatment, even with a long hospital stay and sufficient decompensation. Such patients hospitalized for HF may have a different trajectory compared with ambulatory outpatients. Finally, ~25% of the patients were excluded because of missing data that were required for SHFM score calculation.

Conclusion

We externally and internationally validated the SHFM with the use of a Japanese cohort of HF patients with a recent episode of acute decompensation requiring hospital admission. The SHFM showed adequate performance after recalibration among HFrEF patients. However, the performance was suboptimal in HFpEF patients. To improve the quality of care in HF patients, especially HFrEF patients who should be considered for VAD and heart transplantation, the SHFM could be applied to Japanese HF patients. However, risk stratification for HFpEF patients remains a challenge. Further studies are needed to establish successful approaches for HFpEF based on sufficient risk stratification.

Disclosures

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