The 3A3B score: The simple risk score for heart failure with preserved ejection fraction - A report from the CHART-2 Study

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A B S T R A C T

Background: Few simple risk models, without echocardiography have been developed for patients with heart failure (HF) and preserved left ventricular ejection fraction (LVEF) (HFpEF).

Methods: To develop a risk score to predict all-cause death for HFpEF patients, we examined 1277 HF patients with LVEF ≥50% and BNP ≥100 pg/ml in the CHART-2 Study, a large-scale prospective cohort study for HF in Japan. We selected the optimal subset of covariates for the score with Cox proportional hazard models and random survival forests (RSF).

Results: During the median 5.7-year follow-up, 576 deaths occurred. Cox models and RSF analyses consistently indicated age ≥75 years, albumin <3.7 g/dl, anemia, BMI ≥22 kg/m2, BNP ≥300 pg/ml (or NT-proBNP ≥1400 pg/ml), and BUN ≥25 mg/dl, as the important 6 prognostic variables. Incorporating these 6 variables, we developed a scoring system (3A3B score, with 2 points given to age ≥75 years and 1 point to the others based on the hazard ratios. The discrimination ability of the risk score was excellent (c-index 0.708). Regarding model goodness-of-fit, the overall gradient in 5-year risk was well captured by the score. The predictive accuracy of the 3A3B score was confirmed in the external validation cohorts from the TOPCAT trial (N = 835, c-index 0.652) and the ASIAN-HF registry (N = 170, c-index 0.741).

Conclusions: We developed a simple risk score to predict long-term prognosis of HFpEF patients. The 3A3B score, comprising 6 commonly available parameters in daily practice, has potential utility in the risk stratification and management of HFpEF patients.

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1. Introduction

Although therapies for heart failure (HF) have been significantly advanced in the last decades, optimal managements are not achieved yet in HF patients. These suboptimal treatments are often critical, particularly for HF patients at high risk, since disassociation between evaluation of patient’s risk and actual management likely results in worse outcomes [1]. Thus, it is important to establish a reliable measure to estimate the prognostic risk of HF patients, which should help physicians implement proven therapies adequately and minimize such ‘risk-treatment’ mismatches. Furthermore, therapies guided by risk estimation inevitably reduce medical costs, the burden of which is now an emerging issue in the era of HF epidemic worldwide. To address this issue, a number of risk models have been previously developed to predict prognosis of HF patients [2]. However, these models are not widely used in daily clinical practice because they often require complicated calculation.
with many components including echocardiography data, although simplicity is one of the most important factors for useful risk score [3,4].

Recently, both the incidence and prevalence of HF patients with preserved left ventricular ejection fraction (LVEF) (HFpEF) have been rapidly increasing worldwide [5–7], where approximately 50% of HF patients are those with HFpEF [8]. Recently, we and others have reported that prognostic risk factors are different between HFpEF and HF with reduced LVEF (HFrEF) [9,10]. Furthermore, although some risk models have been developed for HFpEF [11,12], they are not easy to be used in daily clinical practice. Thus, in the present study, we aimed to develop a simple risk score to predict long-term prognosis of HFpEF patients based on our large-scale prospective cohort study.

2. Methods

2.1. Study design

In the present study, we developed a risk score to predict all-cause death for HFpEF patients. To derive the score, we used the database of the Chronic Heart Failure Registry and Analysis in the Tohoku District-2 (CHART-2) Study and performed external validation using the dataset of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial [13] and of the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry [14]. The CHART-2 Study is a large-scale prospective observational multicenter cohort study of chronic HF patients in Japan (NCT00418041), which enrolled a total of 10,219 stable patients aged ≥20 years with either coronary artery disease (CAD), chronic stable angina, or structural heart disease (Stage B.N. ≥ 4475), or a current or past history of symptomatic HF (Stage C/D, N = 4876) between October 2006 and September 2010 at the Tohoku University Hospital and 23 affiliated hospitals in the Tohoku District, Japan [6,9,15], based on the American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) guidelines 2005 [16]. In the present study, we enrolled 1277 patients with HFpEF from the CHART-2 Study based on the following criteria: 1) HF in Stage C/D, 2) LVEF ≤ 50% [17], and 3) BNP ≥ 100 pg/ml [18]. The TOPCAT trial was a randomized, double-blind trial to examine whether treatment with spironolactone, an aldosterone antagonist, would improve clinical outcomes in patients with symptomatic HF and relatively preserved LVEF [19]. For the validation of the risk score, we included 835 HF patients with LVEF ≤ 50% and BNP or N-terminal pro B-type natriuretic peptide (NT-proBNP) data enrolled from Americas cohort of the TOPCAT Trial. The ASIAN-HF registry is a prospective observational multinational registry with symptomatic HF involving 44 centers across 11 Asian regions [19]. Although the ASIAN-HF registry was originally designed to include only HF patients with LVEF ≤ 40%, its protocol amendment also included HF patients with LVEF ≤ 50% [14]. For the validation of the risk score, we included 170 HF patients with LVEF ≤ 50% from the ASIAN-HF registry, in whom all of the risk score items were available in the present study.

2.2. Statistical analysis

To derive the risk score, we selected items from the most consistent and strongest predictors in the systematic review [2] and/or prognostic factors in HFpEF in our recent report [9]. We transformed continuous variables into binary categorical variables for usefulness in clinical practice. A cut-off point of each dichotomous variable was determined based on the results of the survival CART (classification and regression trees) analyses with the ‘part’ and the ‘survival’ packages of the R software [20]. The CART analysis provides a binary decision tree for classification and regression based on recursive partitioning of the data space, and sequentially determines conditioning variables and their splitting points for partitioning to fit a simple prediction model within each partition [20]. The survival CART is the CART considering survival time as an outcome [21]. Survival CART analysis showed cut-offs as follows; age, 74 year-old; body mass index (BMI), 22.2 kg/m2; BNP, 300 pg/ml; systolic BP, 140 mm Hg; heart rate, 60 bpm; hemoglobin (anemia), 13 g/dl in men and 12.0 g/dl in women; albumin, 3.7 g/dl; sodium, 136 mEq/l; blood urea nitrogen (BUN), 25.0 mg/dl, and estimated glomerular filtration rate (eGFR), 52.8 ml/min/1.73 m2. Based on these results and the WHO definition of anemia, we defined the following cut-offs; age, 75 year-old; BMI, 22 kg/m2; BNP, 300 pg/ml; systolic BP, 140 mm Hg; heart rate, 60 bpm; hemoglobin (anemia), 13 g/dl in men and 12 g/dl in women; albumin, 3.7 g/dl; sodium, 135 mEq/l; BUN, 25 mg/dl, and eGFR, 50 ml/min/1.73 m2. To determine the cut-off value of NT-proBNP, we selected 100 patients among the present study subjects (Table S1), in whom frozen samples aliquoted were obtained on the same day. In these patients, we performed the simple regression analysis and developed an equation to convert BNP to NT-proBNP levels. As a result, we obtained the conversion formula; log, NT-proBNP = 0.8618 + 1.1628 + b log, BNP. With this formula, we determined the cutoff value of NT-proBNP 1400 pg/ml as the equivalent value to the BNP cut-off value, 300 pg/ml. Missing values were handled by multiple imputations using chained equations by the ‘mice’ package of the R software [22]. The multiple imputations were repeated 20 times, thus 20 imputed data sets were created.

To select the optimal subset of covariates for the risk score, we used Cox proportional hazard models and random survival forests (RSF) for each of these data sets. We performed Cox regression model with stepwise forward variable selection method based on Bayesian information criterion (BIC). Forward selection procedure adds 1 variable at each step, with the goal of optimizing the BIC at each addition step until the most predictive variables are found in the model equation. We also adopted RSF analysis with the ‘randomForestSRC’ package of the R software to select prognostic variables for survival time. RSF analysis is an ensemble learning method for classification and regression of survival data, constructed by averaging over randomly generated binary decision trees based on bootstrap samplings. RSF is consistently better than, or at least as good as, competing methods [23], and have been previously used for HFrEF study [24]. The covariates for our risk score were selected based on the combined rankings of prognostic factors from Cox model and RSF. Then, the Cox regression model was fit with the selected risk factors to the 20 imputed data sets, and the estimates and the standard errors from those 20 replicates were combined using Rubin’s rule [25]. The combined hazard ratios were rounded to integers, and summed up as the risk score. We also conducted complete cases analysis (CCA) only using samples without missing as sensitivity analysis. We calculated Harrell’s c-index to evaluate discriminative performance of the risk score, and measured internal validity by average c-index from 200 bootstrap samples. We calculated Kaplan-Meier curves, probability of death at 1, 3, and 5 years, and person-year mortality by the score, and compared predicted and observed mortality rates to validate the risk score. Finally, we validated the risk score by calculating c-index and estimating Kaplan-Meier curves and person-year mortality for the score in the TOPCAT and the ASIAN-HF registry cohorts.

All continuous variables are reported as mean ± SD or median with interquartile range (IQR) and all categorical variables are reported as frequency (%). To compare the subgroups, we performed Welch’s t-test for continuous variables and Fisher’s exact test for categorical variables. P-value <0.05 was considered to be statistically significant. All statistical analyses were performed using the open-source statistics computing software R version 3.3.1 [26].

3. Results

3.1. Patient characteristics

During the median 5.7-year follow-up, 576 (45.1%) all-cause deaths occurred. Table 1 shows the baseline patient characteristics. Patients who died during the follow-up period, as compared with those who were alive, were characterized by older age, lower BMI, lower hemoglobin and albumin levels, higher BUN levels, and higher prevalence of ischemic HF and prior HF admission. There were no significant differences in LVEF, LV end-diastolic dimension or prevalence of atrial fibrillation (AF). There were no significant differences in all the candidate covariates for the risk score between the full data and one of the model-building imputation cohorts (Table S2). Table S3 shows the number of missing patients for each covariate.

3.2. Risk score derivation

In the initial screening, 14 covariates were selected, including higher age, men, lower BMI, diabetes mellitus (DM), cancer, higher systolic BP, higher heart rate, anemia, lower albumin, lower sodium, higher BUN, lower eGFR, higher BNP, use of diuretics, and treatment without statins (Table S2). The covariates were listed in order of forward selection of Cox proportional hazard model, and in increasing order of the minimal depth for the distance of a covariate from the root of the decision tree for assessment of its predictability in RSF in Table S4. The forward variable selection in the Cox proportional hazard model began with the minimal model only with the intercept, added 1 variable with maximal decrease in BIC at each step until the process achieved the optimum. For example, in the imputation cohort 1, age ≥75 years was chosen as the most prognostic variable, followed by BUN ≤25 mg/dl, anemia, BMI <22 kg/m2, albumin ≤3.7 g/dl, DM, heart rate ≤60 bpm, and BNP ≤300 pg/ml (Table S4). In the RSF analysis, prognostic importance was increased along with a decrease in minimal depth. Among the variables, the RSF analysis gave the smallest minimal depth to age ≥75 years, followed by anemia, BUN ≤25 mg/dl, albumin ≤3.7 g/dl, eGFR ≥50 ml/min/1.73 m2, BMI <22 kg/m2, BNP <300 pg/ml, and cancer in the imputation cohort 1 (Table S4). Among the 20 imputation cohorts, 6 variables consisting of higher age (≥75 years), lower albumin (<3.7 g/dl), anemia, lower BMI (<22 kg/m2), higher BNP (≥300 pg/ml), and higher BUN (≥225 mg/dl) were consistently selected in the Cox proportional hazard model and ranked in the top 8 in the RSF in the same imputation cohort, and thus selected as the final components of the scoring system. Based on the hazard ratios of Cox proportional hazard model with the 6 variables, we gave 2
4.2. Simplicity of the risk score

The present study is the first to develop a simple risk score to predict long-term prognosis of HfPEF patients in the large-scale prospective observational study. The risk score, the 3A3B score, is composed of only 6 simple items (age, albumin, anemia, BMI, BNP/NT-proBNP, and BUN) without echocardiographic data and has a powerful discrimination capability for mortality risk of HfPEF patients for 5 years.

4.1. Development of a simple 3AB score risk score for HfPEF patients

Using the database of the CHART-2 Study, we were able to develop the 3AB score to predict long-term prognosis of HfPEF patients. Since this risk score consists of only 6 simple items without echocardiography data, it should provide physicians with useful prognostic information for HfPEF patients in daily practice. In the present study, the long-term follow-up data of the CHART-2 Study enabled us to estimate the usefulness of the score for up to 5 years, while most previous risk models estimated up to 3-year prognosis [27–29] (Supplementary references). Furthermore, the 3AB score has excellent goodness-of-fit to the data. Especially, the score facilitates identification of mortality in daily practice; for example, scores 1, 3, and 5-year mortality in the CHART-2 and the TOPCAT by the score. Observed 5-year mortality of patients with 0 point were 6.1% and 7.7% and those with 6–7 points were 73.2% and 66.4% in the CHART-2 and the TOPCAT, respectively.

4. Discussion

We found that the discrimination ability of the 3A3B risk score was excellent (c-index 0.708). Results from internal validation resampling showed no over-inflation of the discrimination ability (averaged c-index 0.708). The Kaplan-Meier curves showed that mortality was clearly stratified by the score (Fig. 1B). Comparison of observed and predicted 5-year mortality risk across the 7 groups by the score showed that goodness-of-fit was excellent in this model and that the risk gradient was well captured by the score (Fig. 1C). At 1, 3, and 5 years, patients with 0 point had predicted mortality of 0.5, 2.5, and 9.5% respectively, while those with 6–7 points had predicted mortality of 22.0, 49.0, and 79.2%, respectively (Table S5).

In subgroup analyses, c-index was 0.704 and 0.714 in men and women, 0.725 and 0.679 in patients without ischemic heart disease (IHD) and those with IHD, 0.715 and 0.700 in patients without DM and those with DM, and 0.713 and 0.708 in patients without AF and those with AF, respectively, indicating that the discrimination ability of the score was excellent throughout the subgroups (Table S6).

3.4. External validation of the 3AB score in the TOPCAT and the ASIAN-HF registry cohorts

Table S7 shows baseline patient characteristics of the TOPCAT and ASIAN-HF registry, respectively. External validation showed good discrimination ability by the score point in the TOPCAT validation cohort (c-index 0.652) and excellent discrimination ability in the ASIAN-HF registry validation cohort (c-index 0.741). Kaplan-Meier curves show that the 3AB score was useful to stratify the mortality risk in the external validation cohorts from both the TOPCAT trial and the ASIAN-HF registry (Fig. 2). Fig. 3 shows annual incidence of all-cause mortality per 1000 persons based on the 3AB score; mortality was clearly stratified by the scores of 0, 1, 2, 3, 4, 5, and 6 in the TOPCAT cohorts as well as by the scores of 0–2, 3–4, and 5–7 in the TOPCAT and the ASIAN-HF registry cohorts. Table S5 shows predicted 1, 3, and 5-year mortality and observed 5-year mortality of patients with 0 point were 6.1% and 7.7% and those with 6–7 points were 73.2% and 66.4% in the CHART-2 and the TOPCAT, respectively.

3.3. Discrimination and calibration

We confirmed that CCA provided the data. Especially, the score facilitates identification of mortality in daily practice; for example, scores 1, 3, and 5-year mortality in the CHART-2 and the TOPCAT by the score. Observed 5-year mortality of patients with 0 point were 6.1% and 7.7% and those with 6–7 points were 73.2% and 66.4% in the CHART-2 and the TOPCAT, respectively.

3.2. Validation of the 3AB score in the large-scale prospective observational study

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we have successfully developed the 3A3B risk score, which consists of only 6 simple items, all of which are transformed into binary categorical variables in order to be simply summed up like the CHADS2 score [3]. Thus, in terms of simplicity, the 3A3B score has potential significant application for daily practice, while most of the previous risk models for HF require complicated calculation with many components (Table S8) [11,12,27,28].

4.3. Availability and significance of the score items in daily practice

It was noteworthy that the 6 items used in the 3A3B score (age, albumin, anemia, BMI, BNP/NT-proBNP, and BUN) are easily available in daily practice, requiring only physical examination and blood testing. Among them, age is the most important prognostic factor [2]. Indeed, the Cox proportional hazard models gave higher hazard ratio to age compared with other covariates, and thus we assigned 2 points to age ≥75 years. Hypoalbuminemia is associated with increased risk of death in HfPEF [32]. Albumin is used as an item of model to predict incident HF based on population-based study, although few previous risk models included hypoalbuminemia to predict prognosis of HF patients [33]. Anemia is also an independent predictor of mortality in HFpEF [30] and might be more predictive for mortality in HFpEF than in HFrEF [15]. Indeed, the 2017 ACC/AHA/HFSA Heart Failure Guideline Focused Update advocated recommendations for treatment of anemia, as one of the important comorbidities in HF [31]. BMI is also recognized as prognostic factors. Although its U-shaped relation to adverse events has been reported, risk for mortality is particularly high in HF patients in the lower end of BMI [34]. BNP/NT-proBNP is included in the 3A3B score as an established prognostic factor not only for HFpEF patients but also for HFrEF patients [37]. Finally, worsening renal function was
Similarly, regional variation in mortality in HFpEF may exist between factors. The score for the mortality rates should be further validated with careful marker for tion in HFrEF, and mortality in HFpEF [35]. BUN represents a surrogate marker for pathophysiologic mechanisms of HF [36].

In Western Europe, and lowest in Eastern Europe/Russia, although Russia/Georgia [38]. Kristensen et al. reported that unadjusted rates of the post hoc analysis of the TOPCAT trial, it was reported that both of un-adjusted and adjusted mortality in Americas was higher than that of Russia/Georgia [38]. Kristensen et al. reported that unadjusted rates of mortality in HFpEF was highest in United States/Canada, intermediate in Western Europe, and lowest in Eastern Europe/Russia, although HFpEF had little international geographic variation in mortality [39]. Similarly, regional variation in mortality in HFpEF may exist between Americas and Asia [40]. Thus, predictive performance of the 3A3B score for the mortality rates should be further validated with careful consideration of regionality, selection biases, and other confounding factors.

4.5. Comparison with the previous risk scores

The previous studies developed the risk scores for HFpEF patients (Table S8). The DIG (Digitalis Investigation Group) trial provided the first prognostic risk score for HFpEF based on a large prospective study [11]. The CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) programme developed the score, in a single cohort spanning, for the full range of LVEF, which was proven to be useful to estimate risk for both HFpEF and HFrEF patients [27]. The MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) established a representative risk model for HFpEF based on the individual data with 39,372 patients with both HFrEF and HFpEF from 30 cohort studies, providing a simple integer score that is accessible by the website [28]. As compared with these previous risk scores, the 3A3B score has strength in terms of simplicity and predictive accuracy (Table S8). One of the main factors for the simplicity and predictive accuracy of the score could be attributed to inclusion of BNP (NT-proBNP), since natriuretic peptide (NP) has been established as the most prognostic biomarker for HF [37]. Indeed, it was reported that the introduction of BNP (NT-proBNP) significantly improved prognostic discrimination for mortality as compared with a model with clinical risk factors alone [29].

I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction Study) also provided a unique and excellent risk model for HFpEF patients aged ≥60 years, including NT-proBNP as the most powerful independent prognostic factor for all-cause death [12]. However, this model also requires evaluation of 11 items including NT-proBNP and LVEF to obtain its accuracy (c-index 0.738). In addition, heterogeneity of HFpEF population used for derivation might have caused complexity of the risk scores. It has been recently recognized that HFpEF is a distinct entity of HF from HFrEF, and LVEF 50% has been embraced as a cut-off for HFpEF in order to clearly discern from HFpEF in the clinical guidelines, leaving a gap of LVEF of 40–49% as a borderline zone [17,41].

We [9] and others [42] have recently reported that HF with mid-range (40–49%) or borderline (41–49%) LVEF (named HfMRF or borderline HFpEF, respectively) has an intermediate clinical characteristics and prognostic factors between HFpEF and HFrEF, indicating that HfMRF is a heterogeneous condition. Thus, inclusion of HF patients with LVEF 40–49% in the previous HFpEF risk prediction models may have reduced their simplicity and predictive accuracy (Table S8) [11,12,27,28]. From this viewpoint, we set the cut-off LVEF 50% to define HFpEF to decrease heterogeneity of the score derivation cohort as HFpEF population in the present study, which might have contributed to better simplicity of the 3A3B score.

4.6. Risk score derived from an observational cohort study

It is anticipated that the 3A3B score is used in the broad range of HFpEF patients, since its derivation cohort, the CHART-2 Study, included consecutive HF patients without any exclusion criterion other than age (<20 year-old). As a result, the 3A3B score included anemia and albumin <3.7 g/dl as components, after examining full-range values of hemoglobin and albumin, which is difficult when using the database of randomized clinical trials (RCT). Indeed, RCT exclude patients with severe anemia, hypoalbuminemia, or renal dysfunction, all of which are important prognostic predictors for HFpEF population. Moreover, it has been reported that all-cause mortality tended to be higher in HF registry studies than in RCT as these differences in outcomes persisted even at 5 years of follow-up [43]. Thus, the present 3A3B risk score based on an observational study may reflect real world data more precisely as compared with RCT and should be useful in daily practice.

4.7. Clinical significance of the 3A3B score

It was noteworthy that, in addition to BNP/NT-proBNP, the 3A3B score includes 5 non-cardiac items consisting of age, albumin, anemia, BMI, and BUN, suggesting that majority of mortality risk could be attributed to non-

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cardiac conditions in HFrEF patients. In other words, management of non-cardiac factors/comorbidities is important to improve prognosis of HFrEF patients [44], although post-hoc analyses of recent HFrEF trials indicated that elevated BNP/NT-proBNP in HFrEF identify patients at higher risk for events but without significant responsiveness to treatment [45,46]. Lund et al. reported that, in HFrEF patients, prognosis was affected by non-cardiovascular comorbidities, while use of conventional HF medications was still associated with improved outcomes [47]. In addition, we have recently reported that statins were associated with reduced mortality in HFrEF patients, which was mostly attributable to reduction in sudden death and non-cardiac death, but not that in HF death [48]. These lines of evidence suggest that cardiovascular medications could also be beneficial in HFrEF patients at high risk because of their severe non-cardiac conditions. Indeed, although no randomized clinical trials have ever shown benefits of pharmacological treatments in HFrEF patients, analyses from observational studies, enrolling more HFrEF patients with advanced non-cardiac conditions, including higher age, lower albumin, anemia, lower BMI, and higher BUN, showed that cardiovascular medications (e.g., beta-blockers, renin-angiotensin system inhibitors, and statins) were associated with decreased mortality [48–50]. Thus, to improve prognosis, assessment with the 3A3B score, but not with BNP/NT-proBNP alone, may lead to more appropriate risk stratification and therapies in a multidisciplinary manner for cardiac and non-cardiac risks of individual HFrEF patient [17,41].

4.8. Study limitations

Several limitations should be mentioned for the present study. First, since the 3A3B score items were selected from those collected in the CHART-2 Study, we did not consider other important prognostic factors, e.g. chronic obstructive pulmonary disease (COPD), a common comorbidity in HF patients [12], when developing the 3A3B score. Second, the cut-off value NT-proBNP 1400 pg/ml may need to be re-evaluated, since the number of patients employed to derive the conversion formula between BNP and NT-proBNP values was relatively small in the present study. Finally, we only included Americas cohort from the TOPCAT Trial. In addition, in the ASIAN-HF cohort, we were not able to validate the predictive accuracy for each score point and/or for long-term follow-up, because of relatively small number of patients and pre-specified 1-year follow-up protocol. Thus, several biases might have affected in the external validation of the 3A3B score.

5. Conclusions

We were able to develop the useful and simple 3A3B risk score to predict long-term mortality of HFrEF patients based on the data from the CHART-2 Study, which was validated in the Americas cohort from the TOPCAT trial as well as in the cohort from the ASIAN-HF registry. The score consists of only 6 simple items available in daily practice (age, albumin, anemia, BMI, BNP or NT-proBNP, and BUN) and is simple and easy enough to be used in the management of HFrEF patients. Thus, it should help physicians estimate mortality risk of HFrEF patients in daily practice.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.076.

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