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

Shintaro Kasahara [a], Yasuhiko Sakata [a,b,*], Kotaro Nochioka [a], Wan Ting Tay [c,1], Brian Lee Claggett [d,2], Ruri Abe [a], Takuya Oikawa [a], Masayuki Sato [a], Hajime Aoyanagi [a], Masanobu Miura [a], Takashi Shiroto [a], Jun Takahashi [a], Koichiro Sugimura [a], Tiew-Hwa Katherine Teng [c], Satoshi Miyata [e], Hiroaki Shimokawa [a,b,e,3]

[a] Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[b] The Big Data Medicine Center, Tohoku University, Sendai, Japan
[c] National Heart Centre Singapore, Singapore
[d] Brigham and Women's Hospital, Boston, MA, United States of America
[e] Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

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ABSTRACT

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/m^2, 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.

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

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* Corresponding author at: Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
E-mail address: sakatayk@cardio.med.tohoku.ac.jp (Y. Sakata).

[1] On behalf of the ASIAN-HF investigators.
[2] On behalf of the TOPCAT investigators.
[3] On behalf of the CHART-2 investigators.

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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 (Stage A, N = 868), asymptomatic 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 [18]. 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 'rpart' 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/m^2; B-type natriuretic peptide (BNP), 331 pg/ml; systolic blood pressure (BP), 141 mm Hg; heart rate, 59 bpm; hemoglobin, 13.0 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 m^2. Based on these results and the WHO definition of anemia, we defined the following cut-offs; age, 75 year-old; BMI, 22 kg/m^2; 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 m^2. 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 formula to convert BNP to NT-proBNP levels. As a result, we obtained the conversion formula; $\log_2$ NT-proBNP = 0.8618 + 1.1628 * $\log_2$ 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]. Multiple imputation was 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 discrimination of the risk score, and examined internal validation 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/m^2, 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 m^2, BMI <22 kg/m^2, 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/m^2), higher BNP (≥300 pg/ml), and higher BUN (≥25 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

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Table 1
Baseline characteristics of patients.

	Alive (N = 701)	Dead (N = 576)	*P* value
Age (years)	70 ± 10.7	77.1 ± 8.6	<0.001
Men (N, %)	385 (55)	352 (61)	0.027
BMI (kg/m^2)	24.0 ± 3.8	22.5 ± 3.7	<0.001
NYHA class III/IV (N, %)	57 (8)	105 (18)	<0.001
Smoking (N, %)	266 (40)	235 (43)	0.241
Etiology of CHF (N, %)			
Ischemic heart disease	256 (37)	253 (44)	0.008
Dilated cardiomyopathy	40 (6)	24 (4)	0.246
Hypertrophic cardiomyopathy	52 (7)	25 (4)	0.024
Hypertension	193 (28)	146 (25)	0.408
Valvular heart disease	106 (15)	103 (18)	0.197
Previous history (N, %)			
Admission for heart failure	365 (52)	368 (64)	<0.001
Hypertension	631 (90)	533 (93)	0.137
Diabetes mellitus	237 (34)	236 (41)	0.009
Dyslipidemia	550 (78)	424 (74)	0.047
Stroke	128 (18)	164 (28)	<0.001
Cancer	95 (14)	130 (23)	<0.001
Myocardial infarction	152 (22)	153 (27)	0.048
Atrial fibrillation	417 (59)	348 (60)	0.774
Hemodynamic and LV function			
Systolic BP (mm Hg)	127.4 ± 19.6	128.6 ± 21.1	0.309
Diastolic BP (mm Hg)	73.1 ± 12.1	69.9 ± 13.0	<0.001
Heart rate (bpm)	71.5 ± 15.1	72.9 ± 16.1	0.109
LVEF (%)	65.2 ± 9.1	64.3 ± 8.8	0.095
LAD (mm)	44.7 ± 8.1	45.3 ± 10.1	0.242
LVDd (mm)	49.1 ± 7.5	49.8 ± 8.3	0.086
Laboratory findings			
Hemoglobin (g/dl)	13.1 ± 1.8	11.9 ± 2.0	<0.001
Albumin (g/dl)	4.0 ± 0.5	3.8 ± 0.5	<0.001
Na (mEq/l)	141.3 ± 2.8	140.9 ± 2.9	0.019
K (mEq/l)	4.4 ± 0.4	4.4 ± 0.5	0.079
LDL-C (mg/dl)	104.2 ± 30.6	100.8 ± 30.5	0.097
BUN (mg/dl)	19.1 ± 8.2	25.6 ± 14.2	<0.001
Cre (mg/dl)	1.0 ± 0.6	1.3 ± 1.1	<0.001
eGFR (ml/min/1.73 m^2)	60.9 ± 19.5	49.1 ± 21.7	<0.001
BNP (pg/ml)	198 (137, 291)	238 (156, 383)	<0.001
Medications (N, %)			
Beta-blockers	379 (54)	243 (42)	<0.001
ACE-I/ARB	506 (72)	422 (73)	0.705
Aldosterone antagonists	142 (20)	148 (26)	0.023
Loop diuretics	354 (50)	375 (65)	<0.001
CCB	302 (43)	261 (45)	0.428
Digitalis	210 (30)	165 (29)	0.622
Statins	227 (32)	142 (25)	0.003
Antiplatelets	374 (53)	324 (56)	0.310
Warfarin	358 (51)	256 (44)	0.021

Results are expressed as mean ± SD or frequency (%).
ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CCB, calcium channel blockers; CHF, chronic heart failure; Cre, creatinine; eGFR, estimated glomerular filtration rate; K, potassium; LA, left atrium; LAD, left atrial dimension; LDL-C, low-density lipoprotein cholesterol; LV, left ventricle; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; Na, sodium; NYHA, New York Heart Association.

points to higher age and 1 point to the other 5 variables, naming the risk score as the 3A3B risk score (Fig. 1A). We confirmed that CCA provided the same 6 prognostic variables with the same corresponding points.

3.3. Discrimination and calibration

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). Fig. S1 compares observed and predicted 5-year mortality risk in subgroups. Five-year mortality of women was several percent lower compared with that of men, whereas the risk gradient was well captured by the score in all subgroups.

3.4. External validation of the 3A3B 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 3A3B 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 3A3B score; mortality was clearly stratified by the scores 0, 1, 2, 3, 4, 5, and ≥6 in the TOPCAT cohorts as well as by the scores 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 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

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 3A3B risk score for HFpEF patients

Using the database of the CHART-2 Study, we were able to develop the 3A3B 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 3A3B score has excellent goodness-of-fit to the data. Especially, the score facilitates identification of mortality in daily practice; for example, scores 1, 2, 3, and 4 predict 15, 25, 35, and 45% mortality at 5 years, respectively (Table S5).

4.2. Simplicity of the risk score

One of the significant strengths of the 3A3B score is its simplicity, which is important to be used in daily practice [4]. In the present study, we employed the multivariable Cox proportional hazard models with forward stepwise method with BIC and RSF analysis, in order to minimize the number of items used in the risk score. In addition, the CART analysis enabled us to identify the most useful cut-off values so that we may produce practical binary scoring for each item. As a result,

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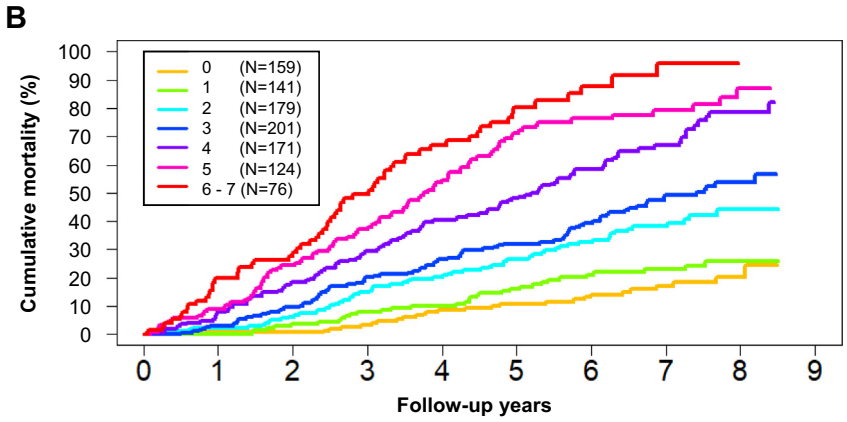
A

	Beta coefficient	Hazard ratio (95% CI)	P value	Points
Age≥75 years	0.952	2.59 (2.15 - 3.12)	<0.001	2
Albumin<3.7 g/dl	0.368	1.45 (1.20 - 1.74)	<0.001	1
Anemia	0.432	1.54 (1.28 - 1.85)	<0.001	1
BMI<22 kg/m^2	0.405	1.50 (1.27 – 1.77)	<0.001	1
BNP≥300 pg/ml	0.405	1.50 (1.27 - 1.77)	0.003	1
BUN≥25 mg/dl	0.595	1.81 (1.52 - 2.17)	<0.001	1
Total score				0 - 7



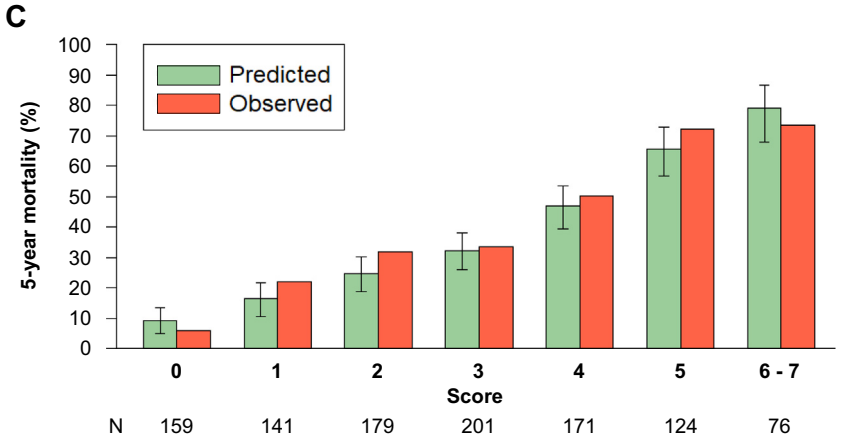


Fig. 1. Risk stratification of HFpEF patients by the 3A3B score. (A) The 3A3B score. BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CI, confidence interval. (B) Kaplan-Meier curves for mortality by the 3A3B score point in the CHART-2 Study. (C) Predicted and observed 5-year mortality by the 3A3B score in the CHART-2 Study.

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 $CHADS_2$ 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 as 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 HFrEF patients but also for HFpEF patients [37]. Finally, worsening renal function was

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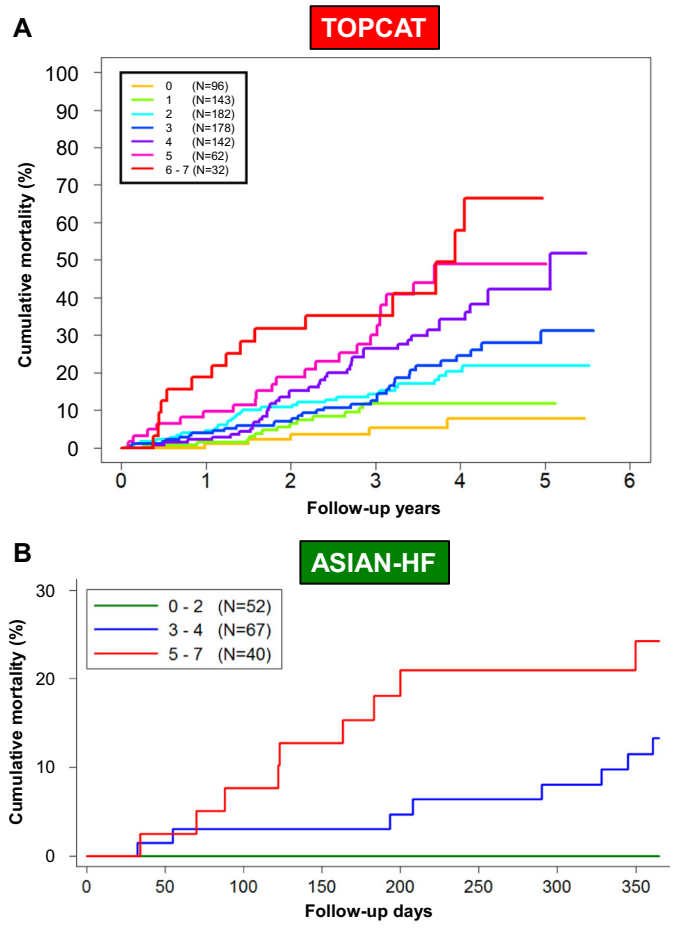

Fig. 2. Kaplan-Meier curves for mortality by the 3A3B score in the external validation cohorts. Estimated incidence of mortality (A) by the scores 0, 1, 2, 3, 4, 5 and ≥6 for the TOPCAT cohort and (B) by the scores 0–2, 3–4 and 5–7 for the ASIAN-HF registry cohort.

associated with worse clinical outcomes, particularly for HF hospitalization in HFrEF, and mortality in HFpEF [35]. BUN represents a surrogate marker for "renal response" to systemic hemodynamic changes related to pathophysiologic mechanisms of HF [36].

4.4. External validation of the 3A3B score

The present 3A3B risk score showed satisfactory risk discrimination power in both Asian and American cohorts. Thus, we may conclude that the 3A3B risk score can be widely used to stratify the mortality risk of HFpEF patients in each region. However, it should be noted that estimated annual incidence of all-cause death in the TOPCAT validation cohort was lower than those in the CHART-2 and ASIAN-HF registry cohorts. This discrepancy of mortality among the cohorts could be attributable to the differences in regions (Asia vs. America) as well as those in study designs (randomized vs. observational). Indeed, regional variations in mortality have been reported in HFpEF patients [38–40]. In the post hoc analysis of the TOPCAT trial, it was reported that both of unadjusted 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 HFrEF 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 HFpEF and HFrEF 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 HFrEF 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 HFmrEF or borderline HFpEF, respectively) has an intermediate clinical characteristics and prognostic factors between HFpEF and HFrEF, indicating that HFmrEF 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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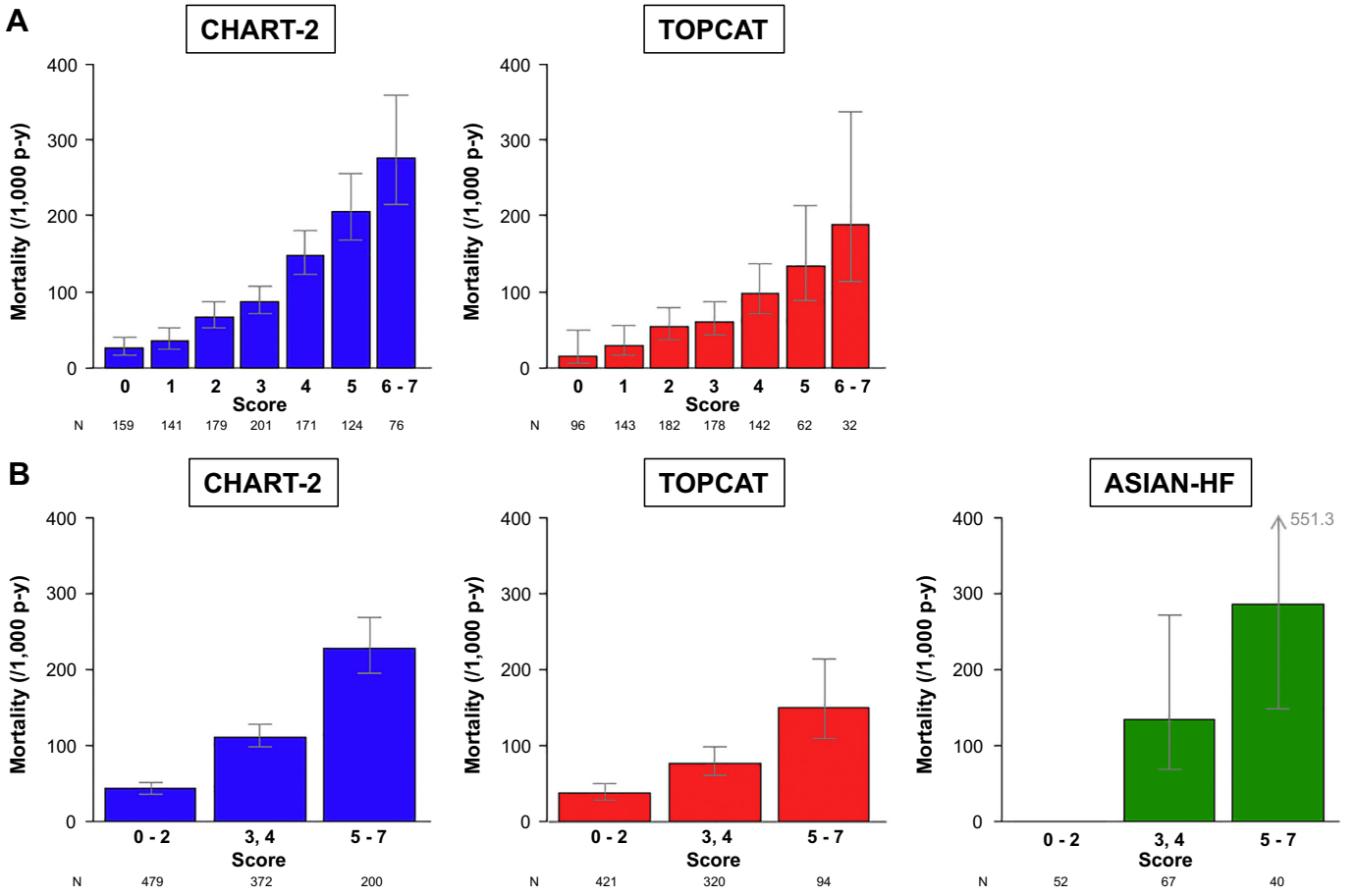

Fig. 3. Annual incidence of all-cause mortality per 1000 persons based on the 3A3B score. Comparison of incidence (A) by the scores 0, 1, 2, 3, 4, 5 and ≥6 between the CHART-2 and the TOPCAT cohorts and (B) by the scores 0–2, 3–4 and 5–7 among the CHART-2, the TOPCAT and the ASIAN-HF registry cohorts.

cardiac conditions in HFpEF patients. In other words, management of non-cardiac factors/comorbidities is important to improve prognosis of HFpEF patients [44], although post-hoc analyses of recent HFpEF trials indicated that elevated BNP/NT-proBNP in HFpEF identify patients at higher risk for events but without significant responsiveness to treatment [45,46]. Lund et al. reported that, in HFpEF 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 HFpEF 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 HFpEF 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 HFpEF patients, analyses from observational studies, enrolling more HFpEF 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 HFpEF 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 HFpEF 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 HFpEF patients. Thus, it should help physicians estimate mortality risk of HFpEF patients in daily practice.

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References

[1] D.S. Lee, J.V. Tu, D.N. Juurlink, et al., Risk-treatment mismatch in the pharmacotherapy of heart failure, JAMA 294 (2005) 1240–1247.
[2] K. Rahimi, D. Bennett, N. Conrad, et al., Risk prediction in patients with heart failure: a systematic review and analysis, JACC Heart Fail. 2 (2014) 440–446.
[3] B.F. Gage, A.D. Waterman, W. Shannon, M. Boechler, M.W. Rich, M.J. Radford, Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation, JAMA 285 (2001) 2864–2870.
[4] L.M. Sullivan, J.M. Massaro, R.B. D'Agostino, Presentation of multivariate data for clinical use: the Framingham Study risk score functions, Stat. Med. 23 (2004) 1631–1660.
[5] B.A. Steinberg, X. Zhao, P.A. Heidenreich, et al., Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes, Circulation 126 (2012) 65–75.
[6] N. Shiba, K. Nochioka, M. Miura, H. Kohno, H. Shimokawa, CHART-2 Investigators, Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan -first report from the CHART-2 study, Circ. J. 75 (2011) 823–833.
[7] A.A. Oktay, J.D. Rich, S.J. Shah, The emerging epidemic of heart failure with preserved ejection fraction, Curr. Heart Fail. Rep. 10 (2013) 401–410.
[8] S.M. Dunlay, V.L. Roger, M.M. Redfield, Epidemiology of heart failure with preserved ejection fraction, Nat. Rev. Cardiol. 14 (2017) 591–602.
[9] K. Tsuji, Y. Sakata, K. Nochioka, et al., Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study, Eur. J. Heart Fail. 19 (2017) 1258–1269.
[10] O. Chioncel, M. Lainscak, P.M. Seferovic, et al., Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry, Eur. J. Heart Fail. 19 (2017) 1574–1585.
[11] R.C. Jones, G.S. Francis, M.S. Lauer, Predictors of mortality in patients with heart failure and preserved systolic function in the Digitalis Investigation Group Trial, J. Am. Coll. Cardiol. 44 (2004) 1025–1029.
[12] M. Komajda, P.E. Carson, S. Hetzel, et al., Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE), Circ. Heart Fail. 4 (2011) 27–35.
[13] B. Pitt, M.A. Pfeffer, S.F. Assmann, et al., Spironolactone for heart failure with preserved ejection fraction, N. Engl. J. Med. 370 (2014) 1383–1392.
[14] J. Tromp, T.H. Teng, W.T. Tay, et al., Heart failure with preserved ejection fraction in Asia, Eur. J. Heart Fail. 16 (2018 Aug) (Epub ahead of print).
[15] T. Yamauchi, Y. Sakata, T. Takada, et al., Prognostic impact of anemia in patients with chronic heart failure- with special reference to clinical background: report from the CHART-2 Study, Circ. J. 79 (2015) 1984–1993.
[16] S.A. Hunt, W.T. Abraham, M.H. Chin, et al., ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society, Circulation 112 (2005) e154–e235.
[17] C.W. Yancy, M. Jessup, B. Bozkurt, et al., 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, Circulation 128 (2013) e240–e327.
[18] A.S. Desai, E.F. Lewis, R. Li, et al., Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction, Am. Heart J. 162 (2011) 966–972. e10.
[19] C.S. Lam, I. Anand, S. Zhang, et al., Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry, Eur. J. Heart Fail. 15 (2013) 928–936.
[20] L. Breiman, J. Friedman, R. Olshen, C. Stone, Classification and Regression Trees, Wadsworth, Belmont, California, 1984.
[21] I. Bou-Hamad, D. Larocque, H. Ben-Ameur, A review of survival trees, Stat. Surv. 5 (2011) 44–71.
[22] S.V. Buuren, K. Groothuis-Oudshoom, Mice: multivariate imputation by chained equations in R, J. Stat. Softw. 45 (2011) 1–67.
[23] H. Ishwaran, U.B. Kogalur, E.H. Blackstone, M.S. Laueret, Random survival forests, Ann. Appl. Stat. 2 (2008) 841–860.
[24] E. Hsich, E.Z. Gorodeski, E.H. Blackstone, H. Ishwaran, M.S. Lauer, Identifying important risk factors for survival in patient with systolic heart failure using random survival forests, Circ. Cardiovasc. Qual. Outcomes 4 (2011) 39–45.
[25] D.B. Rubin, Multiple Imputation for Nonresponse in Surveys, Wiley, New York; Chichester, 1987.
[26] R Core Team, R: a language and environment for statistical computing, R Foundation for Statistical Computing, Austria, Vienna, 2016 , URL https://www.R-project.org/.
[27] S.J. Pocock, D. Wang, M.A. Pfeffer, et al., Predictors of mortality and morbidity in patients with chronic heart failure, Eur. Heart J. 27 (2006) 65–75.
[28] S.J. Pocock, C.A. Ariti, J.J. McMurray, et al., Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies, Eur. Heart J. 34 (2013) 1404–1413.
[29] S. Barlera, L. Tavazzi, M.G. Franzosi, et al., Predictors of mortality in 6975 patients with chronic heart failure in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure trial: proposal for a nomogram, Circ. Heart Fail. 6 (2013) 31–39.
[30] G.M. Felker, L.K. Shaw, W.G. Stough, C.M. O'Connor, Anemia in patients with heart failure and preserved systolic function, Am. Heart J. 151 (2006) 457–462.
[31] C.W. Yancy, M. Jessup, B. Bozkurt, et al., 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, Circulation 136 (2017) e137–e161.
[32] M. Liu, C.P. Chan, B.P. Yan, et al., Albumin levels predict survival in patients with heart failure and preserved ejection fraction, Eur. J. Heart Fail. 14 (2012) 39–44.
[33] R. Jabbour, H.Z. Ling, K. Norrington, et al., Serum albumin changes and multivariate dynamic risk modelling in chronic heart failure, Int. J. Cardiol. 176 (2014) 437–443.
[34] A. Sharma, C.J. Lavie, J.S. Borer, et al., Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure, Am. J. Cardiol. 115 (2015) 1428–1434.
[35] K. Damman, S.D. Solomon, M.A. Pfeffer, et al., Worsening renal function and outcome in heart failure patients with reduced and preserved ejection fraction and the impact of angiotensin receptor blocker treatment: data from the CHARM-study programme, Eur. J. Heart Fail. 18 (2016) 1508–1517.
[36] A. Kazory, Emergence of blood urea nitrogen as a biomarker of neurohormonal activation in heart failure, Am. J. Cardiol. 106 (2010) 694–700.
[37] M. Oremus, A. Don-Wauchope, R. McKelvie, et al., BNP and NT-proBNP as prognostic markers in persons with chronic stable heart failure, Heart Fail. Rev. 19 (2014) 471–505.
[38] M.A. Pfeffer, B. Claggett, S.F. Assmann, et al., Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, Circulation 131 (2015) 34–42.
[39] S.L. Kristensen, L. Køber, P.S. Jhund, et al., International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction, Circulation 131 (2015) 43–53.
[40] H. Shimokawa, M. Miura, K. Nochioka, Y. Sakata, Heart failure as a general pandemic in Asia, Eur. J. Heart Fail. 17 (2015) 884–892.
[41] P. Ponikowski, A.A. Voors, S.D. Anker, et al., 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. J. Heart Fail. 18 (2016) 891–975.
[42] J.R. Kapoor, R. Kapoor, C. Ju, et al., Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction, JACC Heart Fail. 4 (2016) 464–472.
[43] M. Vaduganathan, A. Michel, K. Hall, et al., Spectrum of epidemiological and clinical findings in patients with heart failure with preserved ejection fraction stratified by study design: a systematic review, Eur. J. Heart Fail. 18 (2016) 54–65.
[44] R.J. Mentz, J.P. Kelly, T.G. von Lueder, et al., Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction, J. Am. Coll. Cardiol. 64 (2014) 2281–2293.
[45] I.S. Anand, T.S. Rector, J.G. Cleland, et al., Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial, Circ. Heart Fail. 4 (2011) 569–577.

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[46] I.S. Anand, B. Claggett, J. Liu, et al., Interaction between spironolactone and natriuretic peptides in patients with heart failure and preserved ejection fraction: from the TOPCAT trial, JACC Heart Fail. 5 (2017) 241–252.
[47] L.H. Lund, E. Donal, E. Oger, et al., Association between cardiovascular vs. non-cardiovascular co-morbidities and outcomes in heart failure with preserved ejection fraction, Eur. J. Heart Fail. 16 (2014) 992–1001.
[48] K. Nochioka, Y. Sakata, S. Miyata, et al., Prognostic impact of statin use in patients with heart failure and preserved ejection fraction, Circ. J. 79 (2015) 574–582.
[49] L.H. Lund, L. Benson, U. Dahlström, M. Edner, L. Friberg, Association between use of β-blockers and outcomes in patients with heart failure and preserved ejection fraction, JAMA 312 (2014) 2008–2018.
[50] L.H. Lund, L. Benson, U. Dahlström, M. Edner, Association between use of renin–angiotensin system antagonists and mortality in patients with heart failure and preserved ejection fraction, JAMA 308 (2012) 2108–2117.

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