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One-Year Mortality Risk Stratification in Patients Hospitalized for Acute Decompensated Heart Failure: Construction of TSOC-HFrEF Risk Scoring Model

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Background: Most previous risk prediction models in patients hospitalized for heart failure (HF) are derived from populations in Western countries, and it is unclear whether these models are applicable to Asian populations. This study aimed to construct a risk score system for predicting one-year mortality risk in Asian patients and to compare the applicability of this risk score system with the 3C-HF score system.

Methods: We used the population in the Taiwan Society of Cardiology-Heart Failure with Reduced Ejection Fraction (TSOC-HFrEF) registry, which is a prospective cohort of patients admitted for acute decompensated heart failure (ADHF) in Taiwan. The risk score system was constructed using multivariate Cox-model derived coefficients. A bootstrapping procedure was also used for bias-corrected evaluations. Comparisons between this constructed model and the 3C-HF score prediction model were evaluated using calibration plots and area under curve(AUC) /receiver operating characteristic (ROC) curve.

Results: Patients with complete data (n = 1127) in the TSOC-HFrEF registry were analyzed. During one year of follow-up, 14.5% (n = 163) of the patients died. A risk score system was constructed with the following predictors: body mass index, diastolic blood pressure, dyslipidemia, diabetes, aortic regurgitation, QRS duration, hemoglobin concentration, and digoxin usage. Compared to the 3C-HF score system, this risk score system had a similar discriminatory ability (AUC/ROC values of 0.675 and 0.636, p = 0.127) and both were well-calibrated in the Taiwan population.

Conclusions: The proposed risk score system for predicting one-year all-cause mortality in Taiwanese patients with ADHF may facilitate risk stratification in Asian patients with HF.

Key Words: Heart failure • Mortality • Risk stratification • Scoring system

INTRODUCTION

Heart failure (HF) is a worldwide epidemic that results in considerable morbidity and mortality. A recent study showed a high one-year mortality rate (around 30%) in patients who were admitted to hospitals for acute decompensated HF (ADHF).[1] The mortality rate was even higher in patients with reduced left ventricular ejection fraction. Therefore, risk stratification in patients with HF to predict the high-risk group is essential for clinical decision making and appropriate management.

An increasing number of risk prediction models for mortality in patients with HF have been proposed. Although most previous models are comprehensive and well-validated, there are still some limitations. First, some models were constructed in the period before the

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era of guideline-directed pharmacological treatment.[2-5] Second, under the setting of ADHF, most previous models aimed to predict the short-term mortality rate (from in-hospital mortality to 90-day mortality), and the predictive ability for intermediate- or long-term mortality rates (beyond one-year mortality) were unknown.[4,6] In addition, most of these models were constructed using populations in Western countries, and data derived from Asian countries are still lacking.

A simplified risk score system is a popular method to guide clinical management, and several scoring systems have been developed for HF patients.[2-9] Among these models, the 3C-HF score system proposed by Senni et al. seems to be one of the most promising.[8] This model was constructed from a large cohort of 6274 patients with HF and a variety of different clinical settings. This model has also been well-validated externally and has been shown to have a very good discriminatory ability for predicting death in one year. However, the population tested in this model was primarily Caucasian, and whether this model can be applied to Asian patients is still unknown.

The objective of this study was to construct a risk prediction model for one-year all-cause mortality using an observational registry database of patients hospitalized for ADHF in Taiwan (the TSOC-HFrEF registry). A risk score system was further developed and compared with the application of the 3C-HF score system in this population.

METHODS

TSOC-HFrEF registry design and population

The Taiwan Society of Cardiology-Heart Failure with Reduced Ejection Fraction (TSOC-HFrEF) registry is a prospective, multicenter, and observational survey of patients admitted for ADHF to 21 hospitals in Taiwan. The institutional review board of each hospital approved the registry protocol. Details about the enrollment of patients, patient population characteristics, patient management during hospitalization and outcomes have been described previously.[10,11] Briefly, this survey enrolled patients with acute new-onset HF or acute decompensation of chronic HF with left ventricular ejection fraction (LVEF) less than 40%. LVEF was measured by either echocardiography or left ventriculography during the index hospitalization. All baseline data were collected at the index hospitalization, including demographics, clinical characteristics, basic laboratory data, and other associated diseases. Electrocardiographic and echocardiographic parameters were recorded if measured. Medications at discharge were also documented. The period of patient enrollment was from May 2013 to October 2014. The outcomes were collected at six months and one year after the enrollment. If patients did not return to the hospitals, phone calls were conducted. Follow-up data collection was completed in October 2015.

Statistical analysis

Construction of prediction models

The primary endpoint of this study was one-year all-cause mortality. Patients who had missing important baseline characteristics or outcome results (see Table 1) were excluded from the analyses. Univariate Cox regression analysis was performed to test all variables to screen potential prognostic predictors. Variables with p values < 0.20 were considered to be significant and were included in multivariate Cox regression analysis. Automatic backward selection was performed in multivariate Cox regression analysis to eliminate non-significant variables ($p > 0.05$) with the likelihood ratio test. The variables conserved after backward selection were definitive predictors in the prediction model.

Model performance and TSOC-HFrEF risk score system development

The discrimination of this constructed model was assessed using the concordance index (C-index). For a binary outcome, the C-index is an equivalent of the area under the receiver operating characteristic curve (AUC/ROC curve), which plots (1 - specificity) as the x-axis and sensitivity as the y-axis for consecutive cutoff values of the probability of the outcome. The constructed model was then validated internally using the bootstrap resampling procedure with 200 repetitions to obtain a bias-corrected C-index.

Calibration denotes agreement between predicted outcomes and observed outcomes. In this study, the predicted outcomes indicated the predicted survival probability at a single time point, and the observed outcomes referred to the observed survival probability estimated

Table 1. Baseline characteristics of the study cohort by survival or non-survival within one year

Variables	Total (n = 1127)	Survival (n = 964)	Non-survival (n = 163)	p value
Age, years	63.2 ± 16.1	62.3 ± 16.2	68.9 ± 14.5	< 0.001
Males, n (%)	823 (73.0)	713 (74.0)	110 (67.5)	0.085
BMI, kg/m^2	25.3 ± 5.1	25.5 ± 5.0	23.9 ± 5.2	< 0.001
Height, cm	163.0 ± 9.0	163.4 ± 9.0	160.9 ± 8.5	0.001
Weight, kg	67.7 ± 17.0	68.7 ± 17.0	62.1 ± 16.3	< 0.001
Admission vital signs				
Heart rate, bpm	93.6 ± 22.6	93.5 ± 22.7	94.3 ± 21.9	0.683
Systolic BP, mmHg	131.8 ± 28.1	132.3 ± 28.0	128.7 ± 28.7	0.124
Diastolic BP, mmHg	81.4 ± 19.8	82.2 ± 20.1	76.2 ± 17.2	< 0.001
Admission NYHA class = III or IV, n (%)	994 (88.2)	847 (87.9)	147 (90.2)	0.396
Past or personal history, n (%)				
Smoking	570 (50.6)	496 (51.5)	74 (45.4)	0.153
Alcohol	386 (34.3)	336 (34.9)	50 (30.7)	0.298
CAD	463 (41.1)	384 (39.8)	79 (48.5)	0.038
Peripheral vascular disease	78 (6.9)	59 (6.1)	19 (11.7)	0.010
TIA/stroke	104 (9.2)	85 (8.8)	19 (11.7)	0.247
Hypertensive heart disease	396 (35.1)	347 (36.0)	49 (30.1)	0.142
Atrial fibrillation	302 (26.8)	253 (26.2)	49 (30.1)	0.309
Hypercholesterolemia	262 (23.2)	228 (23.7)	34 (20.9)	0.435
Atherogenic dyslipidemia	240 (21.3)	194 (20.1)	46 (28.2)	0.020
Diabetes mellitus	489 (43.4)	399 (41.4)	90 (55.2)	0.001
Chronic kidney disease	338 (30.0)	267 (27.7)	71 (43.6)	< 0.001
COPD/asthma	121 (10.7)	95 (9.9)	26 (16.0)	0.020
Echocardiography				
LVEF, %	28.3 ± 8.6	28.5 ± 8.5	27.6 ± 9.1	0.240
Mitral regurgitation	568 (50.4)	473 (49.1)	95 (58.3)	0.030
Tricuspid regurgitation	429 (38.1)	361 (37.4)	68 (41.7)	0.299
Aortic regurgitation	140 (12.4)	110 (11.4)	30 (18.4)	0.012
Aortic stenosis	22 (2.0)	16 (1.7)	6 (3.7)	0.085
ECG				
QRS duration, ms	110.8 ± 28.6	109.7 ± 28.2	117.2 ± 30.4	0.002
QTc interval, ms	468.5 ± 47.1	467.3 ± 47.2	476.1 ± 45.7	0.026
LBBB, n (%)	97 (8.6)	78 (8.1)	19 (11.7)	0.133
LVH, n (%)	224 (19.9)	203 (21.1)	21 (12.9)	0.016
Pathologic Q waves, n (%)	54 (4.8)	51 (5.3)	3 (1.8)	0.056
Laboratory data				
Creatinine, mg/dL	2.0 ± 3.3	1.9 ± 3.5	2.3 ± 2.0	0.247
Sodium, mmol/L	137.7 ± 4.4	137.8 ± 4.2	136.9 ± 5.0	0.011
Potassium, mmol/L	4.0 ± 0.6	4.0 ± 0.6	4.1 ± 0.7	0.166
Hemoglobulin, g/dL	12.9 ± 2.5	13.1 ± 2.4	12.0 ± 2.4	< 0.001
Discharge medication, n (%)				
RAS inhibitors	693 (61.5)	610 (63.3)	83 (50.9)	0.003
Beta blockers	695 (61.7)	610 (63.3)	85 (52.1)	0.007
Diuretics	920 (81.6)	790 (82.0)	130 (79.8)	0.503
Calcium channel blockers	147 (13.0)	125 (13.0)	22 (13.5)	0.853
Digoxin	300 (26.6)	248 (25.7)	52 (31.9)	0.099
Antiplatelet agents	670 (59.4)	571 (59.2)	99 (60.7)	0.718
Anticoagulants	245 (21.7)	216 (22.4)	29 (17.8)	0.186
Nitrates	406 (36.0)	342 (35.5)	64 (39.3)	0.352
Hydralazine	55 (4.9)	44 (4.6)	11 (6.7)	0.231
Antiarrhythmic agents	175 (15.5)	145 (15.0)	30 (18.4)	0.273

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; RAS, renin-angiotensin system; SD, standard deviation; TIA, transient ischemic attack.
Only moderate or severe regurgitation/stenosis was considered significant valvular heart diseases.
All the data are presented as mean ± SD or frequencies as appropriate.

with the Kaplan-Meier method. The calibration of the constructed model was assessed visually by splitting the data into seven risk groups and plotting the observed survival probability against its mean predicted survival probability. Bootstrapping with 200 repetitions was used simultaneously to obtain a bias-corrected calibration plot. A perfectly calibrated prediction would be represented as a 45° line.[12] Linear regression lines for the plotted points were also drawn to assist the calibration evaluation.

The TSOC-HFrEF risk score system was developed using the method demonstrated by Sullivan and colleagues.[13] In summary, the median value of each predictor was set as a referent value, and the predictors were categorized into several levels according to the mortality impact of the particular predictor. Second, the category with the lowest mortality risk for each predictor was selected as the base category to obtain a baseline risk profile. The value of each step of a category was computed in terms of regression units. Third, a constant *B* was defined to correspond to a score of one point and reflect the increase in risk associated with a 3-unit increase in body mass index (BMI). A score for each category was derived from each regression unit divided by *B*. A sum score for an individual was calculated to estimate his/her corresponding predicted risk using the following formula:

$$\text{Risk} = 1 - S_0(t)^{\exp(\Sigma\beta x - \Sigma\beta\bar{X})}$$

S_0 (t) was the average survival at time t or the survival rate at mean values (or proportions) of the predictors. $\Sigma\beta X$ could be approximated from the sum of baseline risk and product of score totals and the constant. $\Sigma\beta\bar{X}$ was the sum of the product of the regression coefficients and the means (or the proportions) of the predictors.

Model comparison

First, the 3C-HF score system was applied to our population. A logistic regression model constructed with the proposed 11 predictors[8] was used to predict the outcome probability. The calibration was evaluated visually by plotting the predicted outcomes against observed outcomes. To plot the observed outcomes, we divided our population into 10 groups by decile of the predicted survival probability, and the observed survival proportion was calculated in each group. The mean predicted probability of each group was plotted as the x-axis, and the observed survival proportion was plotted as the y-axis. A linear regression line was also drawn for further evaluation and comparison with our constructed model.[12]

Next, the TSOC-HFrEF risk score system and the 3C-HF score[8] were both applied to this ADHF patient population. The score sum of each individual was calculated according to the risk score system. ROC curves were generated for each applied risk score system to illustrate its discriminatory ability, and differences between the areas under each curve were evaluated using the method reported by Delong et al.[14]

All data were analyzed using SPSS version 22 and R-studio (1.0.143, R v3.4.0) with the "rms", "Hmisc", and "pROC" packages.[15] Significance for the statistical tests was defined as $p < 0.05$ unless otherwise stated.

RESULTS

A total of 1509 patients were enrolled in the TSOC-HFrEF registry. After excluding patients with missing data or outcomes, 1127 patients were included in this study. The baseline characteristics of the patients with complete and missing data are listed in Supplementary Table S1. During one year of follow-up, 163 (14.5%) patients died. Table 1 shows the baseline characteristics of the survival and non-survival groups. Patients in the non-survival group were significantly older and had lower diastolic blood pressure (DBP) than those in the survival group. The prevalence rates of coronary artery disease, peripheral vascular disease, atherogenic dyslipidemia, diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disease or asthma were significantly higher in the non-survival group. In addition, more mitral regurgitation, more aortic regurgitation, prolonged QRS duration, longer QTc duration, less left ventricular hypertrophy, lower serum sodium level, and lower hemoglobin concentration were also observed in the non-survival group. Renin-angiotensin system (RAS) inhibitors and beta-blockers were prescribed more frequently in the survival group than in the non-survival group.

Thirty-one candidate predictors of one-year mortality were derived from univariate Cox regression analysis

(Supplementary Table S2). After performing backward selection in multivariate Cox regression analysis, eight predictors were conserved in the multivariate prediction model. The final prediction model is summarized in Table 2. Only DBP but not systolic blood pressure (SBP) was included in the multivariate analysis to prevent collinearity between these two variables. The constructed prediction model had a moderate discriminatory ability with a C-index of 0.694 and a bias-corrected C-index of 0.677. Figure 1A depicts a calibration plot of the constructed model. As indicated in the figure, the predicted survival probability was closely related to the observed survival probability (red circles), and the bootstrapping plots (blue diamonds) were close to the original plots. The slopes of the regression lines for both sets of points were close to 1 (1.039 and 0.936), and the intercepts of the lines were also close to 0 (-0.033 and 0.054). Because of the small differences between the regression lines and the ideal line, both the calibration and the bias-corrected calibration plots appeared to agree on the prediction of the constructed model.

The TSOC-HFrEF risk score system was developed to estimate the absolute risk of one-year mortality according to the constructed prediction model. The scores of each predictor and the corresponding risk of one-year mortality are summarized in Table 3. The total score of an individual ranged from 0 to 27, and could estimate the mortality risk from 2.2% to 84.2%.

The 3C-HF score system is summarized in Table 4. A total of 11 parameters were used to predict the one-year mortality risk. Figure 1B depicts the calibration plot of the 3C-HF score system after applying it to our population. The points were generally close to the ideal line. The slope (1.014) and intercept (-0.012) of the regression line were also close to the ideal line. Therefore, the 3C-HF score system seemed to be well-calibrated for our

Table 2. Multivariate predicting model for one-year all-cause mortality

Variables	β-coefficient	HR (95% CI)	p value
BMI, per kg/m^2	-0.055	0.95 (0.910-0.985)	0.007
Diastolic BP, per 10 mmHg	-0.091	0.91 (0.834-1.000)	0.051
Atherogenic dyslipidemia	0.407	1.50 (1.059-2.134)	0.023
Diabetes mellitus	0.409	1.51 (1.089-2.079)	0.013
Aortic regurgitation	0.496	1.64 (1.089-2.479)	0.018
QRS duration, per 10 ms	0.062	1.06 (1.013-1.117)	0.013
Hemoglobin, per g/dL	-0.128	0.88 (0.823-0.940)	< 0.001
Digoxin	0.350	1.42 (1.018-1.980)	0.039

BMI, body mass index; BP, blood pressure; CI, confidence interval; HR, hazard ratio.

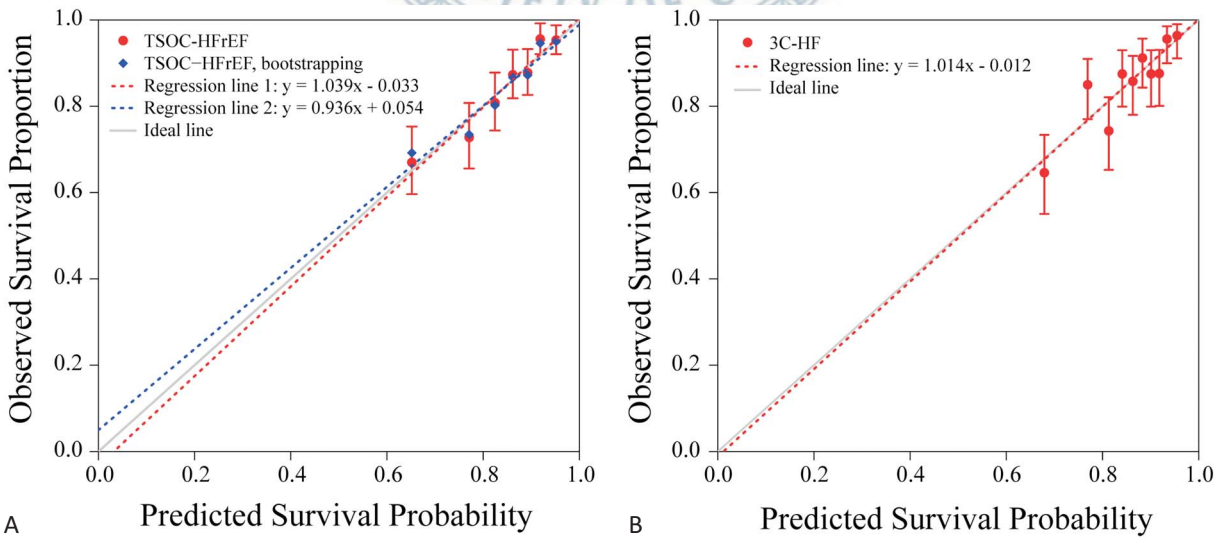

Figure 1. *Calibration plots of (A) the constructed model and (B) the 3C-HF score system. HF, heart failure.*

Table 3. TSOC-HFrEF risk score system derived from the multivariate predicting model and the estimated risk of one-year mortality according to total scores

Risk factor	Category	Score	Total score	Estimated risk
BMI, kg/m^2	< 18.5	6	0	0.022
	18.5-23.9	5	1	0.026
	24-26.9	3	2	0.030
	27-29.9	2	3	0.036
	≥ 30	0	4	0.042
Diastolic BP, mmHg	< 70	3	5	0.049
	70-89	2	6	0.057
	≥ 90	0	7	0.067
Atherogenic dyslipidemia	Yes	2	8	0.079
	No	0	9	0.092
Diabetes mellitus	Yes	2	10	0.108
	No	0	11	0.125
Aortic regurgitation	Yes	3	12	0.146
	No	0	13	0.170
QRS duration, ms	< 90	0	14	0.197
	90-119	1	15	0.228
	≥ 120	3	16	0.262
Hemoglobin, g/dL	< 8	6	17	0.301
	8-12.9	4	18	0.344
	≥ 13	0	19	0.392
Digoxin	Yes	2	20	0.443
	No	0	21	0.498
			22	0.556
			23	0.616
			24	0.676
			25	0.735
			26	0.791
			27	0.842

BP, blood pressure.

Table 4. Summary of the 3C-HF score

Variable	Points (additive score)
Age (per 10 years ≥ 40)	1
NYHA class III-IV vs. I-II	13
LVEF < 20% vs. ≥ 20%	11
No RAS inhibitors	8
Severe valvular heart disease	7
Atrial fibrillation	7
No beta blocker	4
Chronic kidney dysfunction	6
Diabetes with target organ damage	6
Anemia	4
Hypertension	-4

HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin-angiotensin system. Each variable is dichotomized except age.

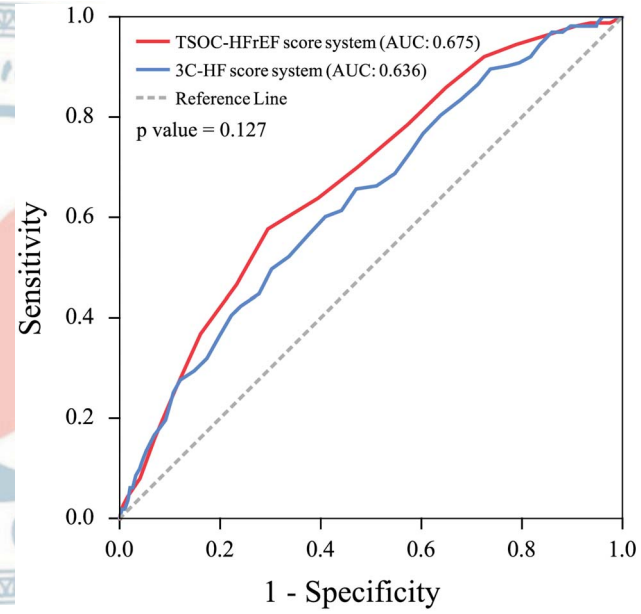

Figure 2. *Receiver operating characteristic (ROCs) curves for TSOC-HFrEF risk score system and 3C-HF score system. AUC, the area under the curve.*

population. The ROC curves of both score systems applied to the TSOC-HFrEF registry population are demonstrated in Figure 2. The TSOC-HFrEF score system seemed to have increased discriminatory ability compared with the 3C-HF score system (AUC/ROC values of 0.675 vs. 0.636, respectively, p = 0.127), but the difference was not statistically significant.

DISCUSSION

We developed a simple risk score system with eight parameters from the TSOC-HFrEF registry. Low BMI, low DBP, dyslipidemia, diabetes, aortic regurgitation, prolonged QRS duration, low hemoglobin concentration, and digoxin usage were associated with a higher one-year mortality risk. To the best of our knowledge, this is the first model derived from an Asian population. The proposed TSOC-HFrEF risk score system had a modest discriminatory ability (C-index 0.694). In this study, we also applied the 3C-HF score system to the TSOC-HFrEF registry patients, and both models seemed to be well-calibrated in our population. However, the results also indicated that the application of the 3C-HF score system

in our Asian population had a relatively lower discriminatory power compared to the application in Western populations.

Low BMI and low hemoglobin concentration were the strongest predictors of mortality in this model. High BMI is generally used to define obesity, and it is a well-known risk factor for cardiovascular (CV) diseases. Despite many adverse effects of obesity on the development of HF, numerous studies have demonstrated an "obesity paradox", where obese patients with established HF appear to have a better outcome than their leaner counterparts.[16] This phenomenon was also observed in a previous study on the TSOC-HFrEF registry, and seems to be consistent across most Asian populations.[17] We confirmed the inverse association between BMI and one-year mortality rate in our patients with ADHF. In this study, we divided the hemoglobin concentration into three categories: less than 8 mg/dL as severe anemia, 8-12.9 mg/dL as anemia, and more than 13 mg/dL as non-anemia. This association between anemia and higher mortality rate in this population is consistent with a previous study.[18]

Individuals with lower SBP[19] or lower DBP[3,9] at admission have been shown to have a higher mortality risk. The findings in this study are consistent with the previous studies about the association between lower blood pressure and worse outcomes. We chose DBP as a predictor rather than SBP because DBP had a higher predictive ability than SBP in this study.

Lipid profile and sugar are two important measurements used to indicate metabolic status. High atherogenic dyslipidemia and hyperglycemia have been shown to contribute to cardiac and microvascular dysfunction, concentric ventricular hypertrophy, atherosclerosis, vascular calcification, and increased risk of cardiovascular mortality.[20] In this study, we observed similar findings. Atherogenic dyslipidemia, or diminished HDL cholesterol, and a history of diabetes were both independently related to a higher risk of mortality in the TSOC-HFrEF population.

Electrocardiography (ECG) and echocardiography were performed in almost all individuals in this study (both examinations were performed in 92% of all patients). Several characteristics of ECG have been proved to be independent risk factors for increased mortality in patients with HF, including prolonged QRS duration, prolonged QTc interval, and left bundle branch block.[21-23] In this study, QRS prolongation seemed to be the strongest predictor for one-year mortality in the TSOC-HFrEF population. Lower LVEF has also been linked to worse outcomes in patients with HF in a chronic care setting[9] or mixed hospital and chronic care setting.[2] In this model, however, LVEF did not seem to have strong predictive value in patients solely under an ADHF setting. In a recent study, severe valvular heart disease was suggested to be a risk factor for increased mortality in HF.[8] In the present study, mitral regurgitation and aortic regurgitation were both associated with a worse outcome in the univariate analysis, but only aortic regurgitation remained a risk predictor of one-year mortality in the following multivariate analysis.

The incorporation of pharmacological treatment into the analysis was crucial, because medical therapies are modifiable factors. In the current guidelines, angiotensin-converting enzyme inhibitors (ACEis), angiotensin-receptor blockers (ARBs), beta-blockers and aldosterone antagonists are recommended (class I indications) for all patients with HFrEF to reduce mortality.[24,25] Some risk prediction models have found that prescriptions of these drugs are independent protective factors for reduced mortality.[6-8] Digoxin is also recommended (class IIa) as an add-on therapy for patients with HFrEF and with persistent HF symptoms.[24] However, although digoxin seems to reduce the risk of rehospitalization, its role in reducing mortality is still unclear. In the TSOC-HFrEF population, the percentages of ACEi/ARB, beta-blocker and digoxin prescriptions were 61.5%, 61.7%, and 26.6%, respectively. The reduced prescription percentage of these essential medications is probably associated with the higher prevalence of chronic obstructive pulmonary disease/asthma (10.7%) and chronic kidney disease (30.0%).

In our univariate analyses, the prescription of RAS inhibitors and beta blockers was strongly significantly associated with better outcomes, and the relationship between worse outcomes and prescriptions of digoxin was relatively insignificant (Supplementary Table S2). However, in this study, the predictive value of digoxin usage outweighed the predictive value of other medications after multivariate analysis. Evidence from clinical trials has shown a substantial survival benefit of RAS inhibitors and beta blockers, and our initial univariate analysis support this point of view. However, in clinical

practice, RAS inhibitors and beta blockers are not tolerated in some patients with lower blood pressure, and patients who receive these medications generally have better blood pressure. Adjusting for these factors may weaken the significance of RAS inhibitor and beta blocker usage, and this may be one of the possible reasons for our results.

On the other hand, digoxin is usually prescribed for symptomatic HF or to control the ventricular rate in patients with atrial fibrillation. The presence of symptomatic HF or atrial fibrillation with rapid ventricular rate represents a worse outcome. Effective heart rate lowering led to improvements in diastolic function in HF patients.[26] This situation in clinical practice may be another reason why digoxin was linked to a worse outcome. In the DIG trial, digoxin did not affect survival, but the use of digoxin reduced the risk of HF death and hospitalization.[27] Although the DIG trial indicated that digoxin therapy did not affect mortality, the use of digoxin may be associated with a higher prevalence of atrial fibrillation, and with the lower LVEF in our population. Lower BMI and SBP were also found in the patients prescribed with digoxin. Some of the above differences, especially the factors which were not included in our final model, may be another reason why digoxin was linked to a worse outcome. Clinical decisions about the use of digoxin may make digoxin an associated risk factor.

The 3C-HF score system shows an excellent discriminatory ability in most populations with a C-index ranged from 0.82 to 0.85 in the original study. However, the majority of patients involved in the development of the 3C-HF score system were Caucasians. When we applied the 3C-HF score system to our TSOC-HFrEF population, the discriminatory power was relatively low. The results suggest that Western prediction models should be applied to predict the risk in Asian populations with caution.

Limitations

This study has several limitations. First, the sample size of the TSOC-HFrEF population is relatively small and the population was mainly composed of patients hospitalized for ADHF with reduced ejection fraction. Second, we did not validate the new risk score on an external dataset. Therefore, the applicability of the TSOC-HFrEF score system to different clinical conditions and the generalizability to different population is unknown. However, we tried to provide a more accurate estimate of model performance in new subjects by applying a bootstrapping resampling procedure. Third, the TSOC-HFrEF score system did not include all variables which could contribute to the outcome. For example, brain natriuretic peptide and N-terminal pro-brain natriuretic peptide are two potentially strong predictors of outcomes.[28] However, these two variables are not routinely obtainable in many hospitals. In this study, not including these variables was an acceptable trade-off for a more easily usable score system. Some important parameters, such as the use of ACEis/ARBs, LVEF and age were not significant in this scoring system, but that does not exclude the importance of these medications and parameters. The purpose of this scoring system was to identify the independent parameters associated with mortality risk rather than determining the causal relationship with mortality. In this scoring system, most of the significant parameters are not modifiable, and therefore the aim of this scoring system is to help clinicians to pay more attention to patients at high risk of mortality during and after hospitalization.

CONCLUSION

In this study, we constructed a simple risk score system for predicting one-year all-cause mortality using eight risk predictors. This relatively unsophisticated TSOC-HFrEF score system may facilitate the risk stratification of patients with acute HF. The relatively lower discriminatory ability of the 3C-HF score system suggests that Western prediction models should be applied to predict the risk in Asian patients with caution.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPLEMENT

Supplementary Table S1. Baseline characteristics between complete and missing data groups

Variables	Missing, n (%)	Complete (n = 1127)	Missing (n = 382)	p value
Age, years	1 (0.1)	63.2 ± 16.1	65.9 ± 16.0	0.006
Males, n (%)	0 (0.0)	823 (73.0)	270 (70.7)	0.375
BMI, kg/m^2	38 (2.5)	25.3 ± 5.1	24.7 ± 5.0	0.072
Height, cm	34 (2.3)	163.0 ± 9.0	163.1 ± 8.8	0.949
Weight, kg	18 (1.2)	67.7 ± 17.0	66.2 ± 16.6	0.139
Admission vital signs				
Heart rate, bpm	1 (0.1)	93.6 ± 22.6	90.3 ± 21.3	0.007
Systolic BP, mmHg	5 (0.3)	131.8 ± 28.1	127.7 ± 24.7	0.002
Diastolic BP, mmHg	5 (0.3)	81.4 ± 19.8	78.1 ± 16.8	0.004
Admission NYHA class = III or IV, n (%)	0 (0.0)	994 (88.2)	336 (88.0)	0.900
Past or personal history, n (%)				
Smoking	0 (0.0)	570 (50.6)	192 (50.3)	0.915
Alcohol	0 (0.0)	386 (34.3)	127 (33.2)	0.720
CAD	0 (0.0)	463 (41.1)	168 (44.0)	0.321
Peripheral vascular disease	0 (0.0)	78 (6.9)	20 (5.2)	0.248
TIA/stroke	0 (0.0)	104 (9.2)	35 (9.2)	0.969
Hypertensive heart disease	0 (0.0)	396 (35.1)	123 (32.2)	0.296
Atrial fibrillation	0 (0.0)	302 (26.8)	91 (23.8)	0.252
Hypercholesterolemia	0 (0.0)	262 (23.2)	73 (19.1)	0.093
Atherogenic dyslipidemia	0 (0.0)	240 (21.3)	67 (17.5)	0.115
Diabetes mellitus	0 (0.0)	489 (43.4)	169 (44.2)	0.772
Chronic kidney disease	0 (0.0)	338 (30.0)	138 (36.1)	0.026
COPD/asthma	0 (0.0)	121 (10.7)	45 (11.8)	0.573
Echocardiography				
LVEF, %	0 (0.0)	28.3 ± 8.6	29.2 ± 9.1	0.138
Mitral regurgitation	75 (5.0)	568 (50.4)	180 (58.6)	0.010
Tricuspid regurgitation	75 (5.0)	429 (38.1)	136 (44.3)	0.048
Aortic regurgitation	75 (5.0)	140 (12.4)	60 (19.5)	0.001
Aortic stenosis	75 (5.0)	22 (2.0)	7 (2.3)	0.717
ECG				
QRS duration, ms	71 (4.7)	110.8 ± 28.6	111.8 ± 32.6	0.609
QTc interval, ms	70 (4.6)	468.5 ± 47.1	478.3 ± 51.9	0.002
LBBB, n (%)	48 (3.2)	97 (8.6)	37 (11.1)	0.169
LVH, n (%)	48 (3.2)	224 (19.9)	62 (18.6)	0.595
Pathologic Q waves, n (%)	48 (3.2)	54 (4.8)	20 (6.0)	0.381
Laboratory data				
Creatinine, mg/dL	23 (1.5)	2.0 ± 3.3	2.1 ± 3.6	0.516
Sodium, mmol/L	31 (2.1)	137.7 ± 4.4	137.6 ± 5.2	0.813
Potassium, mmol/L	24 (1.6)	4.0 ± 0.6	4.0 ± 0.7	0.737
Hemoglobulin, g/dL	61 (4.0)	12.9 ± 2.5	12.8 ± 2.3	0.359
Discharge medication, n (%)				
RAS inhibitors	47 (3.1)	693 (61.5)	209 (62.4)	0.767
Beta blockers	47 (3.1)	695 (61.7)	177 (52.8)	0.004
Diuretics	47 (3.1)	920 (81.6)	282 (84.2)	0.285
Calcium channel blockers	47 (3.1)	147 (13.0)	32 (9.6)	0.087
Digoxin	47 (3.1)	300 (26.6)	79 (23.6)	0.265
Antiplatelet agents	47 (3.1)	670 (59.4)	200 (59.7)	0.934
Anticoagulants	47 (3.1)	245 (21.7)	67 (20.0)	0.495
Nitrates	47 (3.1)	406 (36.0)	124 (37.0)	0.741
Hydralazine	47 (3.1)	55 (4.9)	16 (4.8)	0.938
Antiarrhythmic agents	47 (3.1)	175 (15.5)	54 (16.1)	0.794

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiography; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; RAS, renin-angiotensin system; TIA, transient ischemic attack.

Supplementary Table S2. Hazard ratios of candidate predictors (p value < 0.20) derived from univariate Cox regression analysis

Variables	HR (95% CI)	p value
Age, years	1.03 (1.02-1.04)	< 0.001
Gender (male)	0.77 (0.55-1.07)	0.184
Height, cm	0.97 (0.96-0.99)	0.001
Weight, kg	0.97 (0.96-0.99)	< 0.001
BMI, kg/m^2	0.93 (0.89-0.96)	< 0.001
Systolic BP, mmHg	1.00 (0.99-1.00)	0.107
Diastolic BP, mmHg	0.98 (0.98-0.99)	< 0.001
Smoking	0.79 (0.58-1.08)	0.140
CAD	1.36 (1.00-1.85)	0.049
Peripheral vascular disease	1.95 (1.21-3.15)	0.006
Hypertensive heart disease	0.80 (0.57-1.12)	0.192
Atherogenic dyslipidemia	1.47 (1.04-2.07)	0.027
Diabetes mellitus	1.62 (1.19-2.21)	0.002
Chronic kidney disease	1.93 (1.42-2.63)	< 0.001
COPD/asthma	1.67 (1.10-2.54)	0.016
Mitral regurgitation	1.42 (1.04-1.94)	0.027
Aortic regurgitation	1.76 (1.19-2.62)	0.005
Aortic stenosis	2.16 (0.96-4.88)	0.064
QRS duration, ms	1.01 (1.00-1.01)	0.002
QTc interval, ms	1.00 (1.00-1.01)	0.023
LBBB	1.48 (0.92-2.39)	0.108
LVH	0.59 (0.37-0.93)	0.024
Pathologic Q waves	0.37 (0.12-1.15)	0.085
Sodium, mmol/L	0.96 (0.93-0.99)	0.011
Potassium, mmol/L	1.19 (0.94-1.51)	0.148
Hemoglobulin, g/dL	0.84 (0.79-0.90)	< 0.001
RAS inhibitors	0.61 (0.45-0.83)	0.002
Beta blockers	0.65 (0.48-0.89)	0.006
Digoxin	1.29 (0.93-1.80)	0.126
Anticoagulants	0.76 (0.51-1.13)	0.175
Hydralazine	1.55 (0.84-2.85)	0.162

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; RAS, renin-angiotensin system.