Risk stratification in patients hospitalized for acute heart failure in Asian population

Hao-Chih Chang[a,b], Hao-Min Cheng[b,c,d], Wei-Ming Huang[a,b], Ching-Wei Lee[a,b], Chao-Yu Guo[e], Wen-Chung Yu[a,b,d], Chen-Huan Chen[b,c,d,e], Shih-Hsien Sung[a,d,e,*]

[a]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan, ROC; [c]Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC; [e]Institute of Public Health, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC

Abstract

Background: The AHEAD (A: atrial fibrillation; H: hemoglobin; E: elderly; A: abnormal renal parameters; D: diabetes mellitus) score may be suboptimal in predicting long-term mortality in Asian patients with acute heart failure (AHF). We aimed to propose and validate a risk score incorporating easily available echocardiographic parameters to improve risk stratification in Asian patients with AHF.

Methods: A total of 3537 patients hospitalized for AHF were enrolled and divided into generation and validation cohorts. Independent predictors of all-cause mortality were identified by Cox regression analysis and scored by hazard ratios to constitute the model. Model performance was validated and evaluated by receiver operating characteristic (ROC) curves and net reclassification improvement (NRI).

Results: In the generation cohort of 1775 patients (74.3±13.0 years, 69.9% men), there were 870 deaths (49.0%) during a mean follow-up of 24.7±13.8 months. Age, anemia, estimated glomerular filtration rate <50 ml/min/1.73 m^2, hyperuricemia, left ventricular ejection fraction <50% and right ventricular systolic pressure (RVSP) >40 mmHg were independently related to mortality, which constituted "UR-HEARt" (U: uric acid, R: renal function, H: hemoglobin, E: ejection fraction of left ventricle, A: age, Rt: RVSP) score. Model performance was evaluated in the validation cohort (n = 1762), which outperformed AHEAD score by comparison of ROC curves in predicting all-cause mortality (area under curve [AUC] of UR-HEARt vs. AHEAD: 0.66 [95% CI 0.62–0.70] vs. 0.58 [95% CI 0.54–0.62]; $p < 0.001$), with NRI by 10.9% for all-cause mortality ($p < 0.001$) and 18.4% for cardiovascular death ($p < 0.001$).

Conclusion: UR-HEARt score, an easily accessible racial-specific risk score with integration of echocardiographic indices, improved risk stratification in Asian patients hospitalized for AHF.

Keywords: Acute heart failure; Asian population; Risk stratification

1. INTRODUCTION

Acute heart failure (AHF), one of the leading causes of hospitalization in the developed centuries, and its adverse consequences, including a 4% to 6.7% in-hospital mortality rate,[1,2] more than 50% rehospitalization rate within 6 months[3] and 21% to 32.3% post-discharge mortality rate at 1 year,[4] impose a significant economic burden. Considering the heterogeneous characteristics of the patients with AHF, the therapeutic strategies of AHF vary and its prognoses could be diametrical. Therefore, an accurate prognostication may play an essential role in identifying high-risk patients and optimizing the clinical management of patients with AHF.

The Seattle Heart Failure Model[5] and the Heart Failure Survival Score[6] have been validated to predict the clinical outcomes of patients with chronic heart failure (CHF). However, patients with AHF may have distinct prognostic factors from those with CHF.[7] The AHEAD (A: atrial fibrillation; H: hemoglobin; E: elderly; A: abnormal renal parameters; D: diabetes mellitus) score has been associated with the clinical outcomes of AHF. We have previously validated the AHEAD score in an Asian cohort of AHF with either preserved or reduced left ventricular systolic function and improved its risk stratification by the incorporation of uric acid into the score.[8] However, its generalizability remains unclear, while some, but not all, cardiovascular (CV) risk factors in the Asians are similar to those living in other geographic regions. Moreover, growing evidence has shown that echocardiography is a valuable tool for predicting both short-term and long-term outcomes among patients with AHF.[9,10] Therefore, we aimed to generate and validate a new risk prediction model for Asian AHF patients with the integration of echocardiographic indices.

2. METHODS

2.1. Study participants

The study population was drawn from an on-going Heart Failure Registry of Taipei Veterans General Hospital for

*Address correspondence: Dr. Shih-Hsien Sung, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: mr.sungsh@gmail.com (S.-H. Sung)

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 544-550.

Received November 10, 2019; accepted December 26, 2019.

doi: 10.1097/JCMA.0000000000000340.

patients hospitalized due to AHF, defined as new-onset or gradually or rapidly worsening heart failure symptoms and signs requiring urgent therapy during the time frame from August 2003 to June 2014. Subjects with severe infection or severe hepatic disease were excluded from the analysis. Medical history, findings of physical examination, and prescribed medications were recorded in detail. Blood samples were obtained from every subject for the measurement of hemograms and biochemistries on admission. When patients were stabilized, the study subjects underwent comprehensive echocardiogram evaluation before discharge. The investigation conformed to the principles outlined in the Declaration of Helsinki. Informed consent was waived considering the nature of the administrative registry and was approved by the institutional review board of Taipei Veterans General Hospital.

2.2. Definitions of variables

Echocardiographic indices were measured using two-dimensional, M-mode, and Doppler echocardiogram. Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson's method. Transmitral inflow parameters including the peak of early (E) and late (A) diastolic filling velocities were measured by pulsed-wave Doppler echocardiogram. Right ventricular systolic pressure (RVSP) was calculated as the sum of the estimated right atrial pressure and pressure gradient of right ventricle to right atrium during systole, approximated by the modified Bernoulli equation.[11] Estimated glomerular filtration rate (eGFR) was calculated from the Modification of Diet in Renal Disease equation for Asians.[12] Serum levels of blood urea nitrogen (BUN), lipid profiles, and uric acid were also measured.

2.3.Clinical outcomes

All participants were followed up either at outpatient clinics or by telephone consultations to determine whether there was any mortality event. The primary end-point was all-cause mortality with a follow-up duration of up to 3 years. The secondary end-point was CV death, including sudden cardiac death, death due to heart failure, acute myocardial infarction, pulmonary embolism, or cerebrovascular events by documented medical records.

2.4. Statistical analyses

Patients enrolled before January 1, 2010 comprised the generation cohort, whereas the other patients comprised the validation cohort. The baseline characteristics were compared by Student's t test for continuous variables and chi-squared test for categorical variables. Univariate Cox regression analysis was performed to evaluate the associations between each variable and mortality. The independent predictors were subsequently identified using multivariate Cox models. Receiver operating characteristic (ROC) analysis was applied to dichotomize the continuous variables to compute the risk prediction model. The prognostic value of the risk prediction model was demonstrated using the Kaplan–Meier survival curve analysis. The model performance of the new risk prediction model was compared to the AHEAD risk score by ROC curves and the net reclassification improvement (NRI). Statistical analyses were performed using the IBM SPSS version 22.0, MedCalc version 18.10, and SAS version 9.4.

Table 1

Baseline characteristics of the generation cohort (n = 1775)

Variables	Survival, n = 905	Mortality, n = 870	All, n = 1775	*p*
Age, years	71.7±14.4	77.0±10.8	74.3±13.0	<0.001
Men, n (%)	628 (69.4)	613 (70.5)	1241 (69.9)	0.624
Comorbidities, n (%)				
Hypertension	559 (61.8)	501 (57.6)	1060 (59.7)	0.073
Diabetes mellitus	296 (32.7)	338 (38.9)	634 (35.7)	0.007
Coronary artery disease	316 (34.9)	288 (33.1)	604 (34.0)	0.420
Myocardial infarction	123 (13.6)	117 (13.4)	240 (13.5)	0.930
Atrial fibrillation	246 (27.2)	227 (26.1)	473 (26.6)	0.603
COPD	113 (12.5)	167 (19.2)	280 (15.8)	<0.001
Laboratory data				
Hemoglobin, g/dL	12.3±2.6	11.5±2.2	11.9±1.3	<0.001
BUN, mg/dL	35.9±22.7	42.6±25.8	35.4±23.3	<0.001
Creatinine, mg/dL	1.7±1.5	2.1±1.4	1.9±1.5	<0.001
eGFR, mL/min/1.73m^2	55.1±26.5	43.4±25.0	49.4±26.4	<0.001
Total cholesterol, mg/dL	163.5±46.3	156.5±44.8	160.2±45.8	0.005
HDLc, mg/dL	43.6±13.5	43.3±14.6	43.4±14.0	0.331
LDLc, mg/dL	100.5±36.1	94.4±34.7	97.7±35.5	0.002
Triglyceride, mg/dL	117.7±171.9	100.8±66.9	109.7±133.6	0.016
Uric acid, mg/dL	8.2±2.9	9.1±3.2	8.7±3.1	<0.001
NT-pro-BNP[a], pg/mL	3.8±0.6	3.9±0.7	3.8±0.6	0.234
Total bilirubin, mg/dL	0.9±0.7	0.9±0.7	0.9±0.8	0.898
Echocardiography				
HFpEF, n (%)	503 (56.7)	414 (48.7)	917 (52.8)	0.001
LVEF, %	51.2±18.6	48.8±19.3	50.1±18.5	0.007
MV E velocity, m/s	85.7±31.3	84.9±31.3	91.6±31.1	0.754
MV A velocity, m/s	84.2±30.9	89.5±30.9	87.5±30.6	0.063
MV deceleration time, ms	196.4±74.4	202.4±81.5	199.2±70.0	0.346
RVSP, mmHg	41.1±15.8	45.8±17.1	44.7±17.0	<0.001

[a]N-terminal pro-B type natriuretic peptide (NT-pro-BNP) was taken logarithmic transformation.

BUN=blood urea nitrogen; COPD=chronic obstructive pulmonary disease; eGFR=estimated glomerular filtration rate; HDLc=high-density lipoprotein cholesterol; HFpEF=heart failure with preserved ejection fraction; LDLc=low-density lipoprotein cholesterol; LVEF=left ventricular ejection fraction; MV=mitral valve; RVSP=right ventricular systolic pressure.

3. RESULTS

Among the generation cohort comprising 1775 subjects (age 74.3±13.0 years, 69.9% men), 1060 (59.7%) had hypertension, 634 (35.7%) had diabetes mellitus, 604 (34.0%) had coronary artery disease, 240 (13.5%) had previous myocardial infarction, 473 (26.6%) had atrial fibrillation, and 280 (15.8%) had chronic obstructive pulmonary disease (COPD) (Table 1). During a mean follow-up duration of 24.7±13.8 months, there were 870 (49.0%) deaths, of whom 379 (43.6%) died of CV causes. Compared to the survivors, the deceased were older; had diabetes mellitus and COPD; had lower hemoglobin, total cholesterol, low-density lipoprotein cholesterol (LDLc), triglyceride, and eGFR levels; and had higher BUN, creatinine, and uric acid levels (Table 1). Moreover, the deceased patients had lower LVEF and higher RVSP than the survivors.

3.1. Generation of the risk prediction model

Age; presence of COPD and diabetes mellitus; LDLc, hemoglobin, eGFR, and uric acid levels; LVEF and RVSP were all crudely associated with long-term mortality (Table 2). When all the significant risk factors were adjusted in a multivariate Cox regression analysis, age; hemoglobin, eGFR, and uric acid levels; LVEF and RVSP were independently associated with the clinical outcomes (Table 2). After dichotomizing by ROC analysis, age >65 years, hemoglobin <12 g/L, eGFR <50 mL/min/1.73 m^2, uric acid level >8.6 mg/dL in men, or >7.9 mg/dL in women, LVEF <50% and RVSP >40 mmHg comprised the risk score (Table 3). Each variable was assigned with one point according to the hazard ratios, except for age >75 years, which was assigned with two points, to obtain a seven-point score, the UR-HEARt (U: uric acid, R: renal function, H: hemoglobin, E: ejection fraction of left ventricle, A: age, Rt: RVSP) risk score. The study population was categorized into the following four risk strata: low (scores 0, 1), intermediate-low (scores 2, 3), intermediate-high (scores 4, 5), and high (scores 6, 7). The absolute risks of CV death and all-cause mortality within a year increased along with the risk categories (Supplementary Table 1, http://links.lww.com/JCMA/A51). The Kaplan–Meier survival analysis further demonstrated that the 3-year mortality risk was aggravated along with the increased UR-HEARt risk score (log-rank test $p < 0.001$) (Fig. 1A).

3.2. Validation of the risk prediction model

The baseline characteristics of the validation cohort (age 76.5±13.6 years, 65.8% men) were compared to the generation cohort in Table 4. In brief, the validation cohort was older, was less likely to be men, had more prevalence with hypertension and atrial fibrillation, and had less history of myocardial infarction than the generation cohort. Moreover, the validation cohort had lower hemoglobin, cholesterol, triglyceride, and uric acid levels, and higher BUN levels, mitral inflow E flow velocity, and RVSP than the generation cohort (Table 4).

Table 2

Predictors of mortality in the generation cohort-HR per 1 SD increase in the generation cohort

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age, 1 SD = 13.3 years	1.37 (1.27–1.49)	<0.001	1.34 (1.19–1.51)	<0.001
Men	1.04 (0.90–1.21)	0.581		
COPD [a]	1.38 (1.16–1.63)	<0.001	1.20 (0.93–1.54)	0.158
Diabetes mellitus[a]	1.17 (1.02–1.34)	0.026	1.21 (1.00–1.48)	0.050
Atrial fibrillation[a]	0.95 (0.82–1.11)	0.541		
LDLc, 1 SD = 35.4 mg/dL	0.85 (0.78–0.93)	<0.001	0.95 (0.86–1.05)	0.289
Hb, 1 SD = 2.3 gm/dL	0.77 (0.72–0.83)	<0.001	0.87 (0.78–0.97)	0.012
eGFR, 1 SD = 28.2 mL/min/1.73 m^2	0.70 (0.64–0.75)	<0.001	0.79 (0.69–0.90)	<0.001
Uric acid, 1 SD = 3.0 mg/dL	1.23 (1.15–1.32)	<0.001	1.16 (1.06–1.27)	0.002
LVEF, 1 SD = 18.5 %	0.91 (0.85–0.96)	0.002	0.83 (0.77–0.89)	<0.001
RVSP, 1 SD = 17.0 mmHg	1.24 (1.16–1.32)	<0.001	1.12 (1.02–1.23)	0.024

[a]Indicated yes versus no.

CI=confidence interval; COPD=chronic obstructive pulmonary disease; eGFR=estimated glomerular filtration rate; Hb=hemoglobin; HR=hazard ratio; LDLc=low-density lipoprotein cholesterol; LVEF=left ventricular ejection fraction; RVSP=right ventricular systolic pressure; SD=standard deviation; UA=uric acid.

Table 3.

Dichotomized variables and HR (95% CI) in the generation cohort

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age <65	…	…	…	…
Age 65–75	1.78 (1.40–2.26)	<0.001	1.65 (1.24–2.21)	0.001
Age >75	2.01 (1.68–2.53)	<0.001	1.97 (1.54–2.52)	<0.001
Anemia[a]	1.66 (1.44–1.91)	<0.001	1.39 (1.17–1.65)	<0.001
eGFR <50 mL/min/1.73 m^2	1.92 (1.67–2.21)	<0.001	1.37 (1.14–1.64)	0.001
Hyperuricemia[b]	1.64 (1.42–1.90)	<0.001	1.48 (1.25–1.76)	<0.001
LVEF <50%	1.29 (1.13–1.48)	<0.001	1.46 (1.24–1.72)	<0.001
RVSP >40 mmHg	1.57 (1.36–1.81)	<0.001	1.30 (1.10–1.53)	0.002

[a]Definition of anemia: hemoglobin <12 g/dL.

[b]Definition of hyperuricemia: male: Uric acid >8.6 mg/dL, female: Uric acid >7.9 mg/dL.

CI=confidence interval; eGFR=estimated glomerular filtration rate; HR=hazard ratio; LVEF=left ventricular ejection fraction; RVSP=right ventricular systolic pressure.

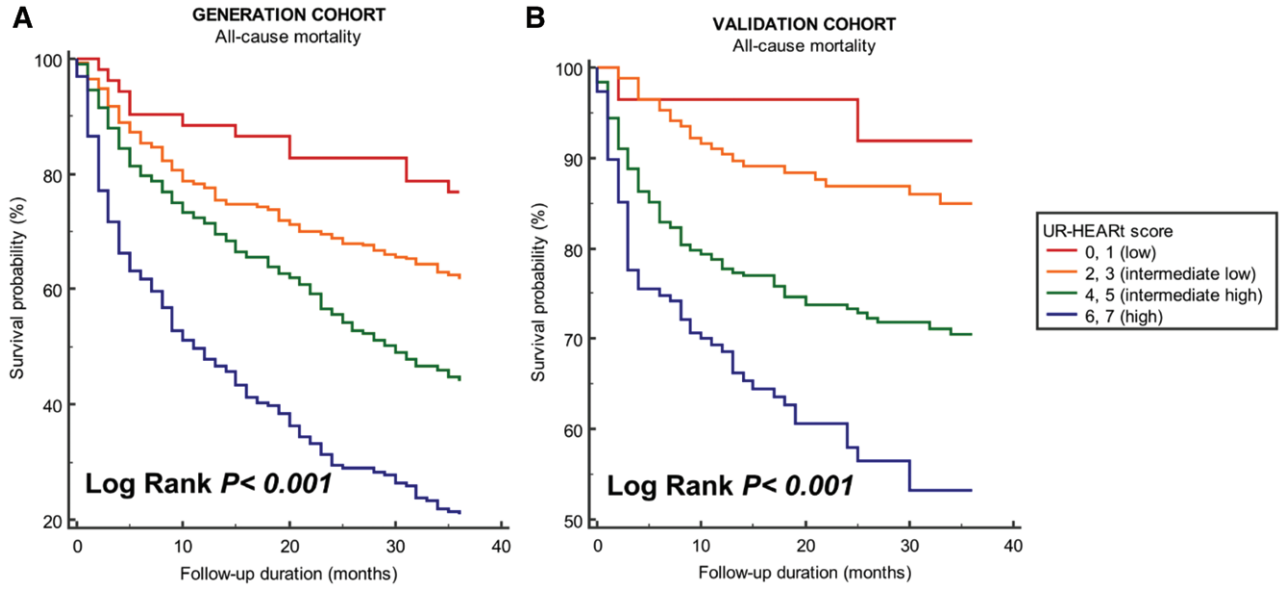

Fig. 1. Kaplan–Meier survival curve. A, generation. B, validation cohort-stratified by UR-HEARt score.

Table 4

Baseline characteristics of the generation cohort vs. the validation cohort

Variables	Generation cohort (n=1775)	Validation cohort (n=1762)	*p*
Age	74.3±13.0	76.5±13.6	<0.001
Men, n (%)	1241 (69.9)	1160 (65.8)	0.009
Comorbidities, n (%)			
Hypertension	1060 (59.7)	1141 (64.8)	0.002
Diabetes mellitus	634 (35.7)	662 (37.6)	0.253
Coronary artery disease	604 (34.0)	551 (31.3)	0.080
Myocardial infarction	240 (13.5)	198 (11.2)	0.039
Atrial fibrillation	473 (26.6)	591 (33.5)	<0.001
COPD	280 (15.8)	294 (16.7)	0.463
Laboratory data			
Hemoglobin, g/dL	11.9±1.3	11.4±2.3	<0.001
BUN, mg/dL	35.4±23.3	37.3±23.5	0.015
Creatinine, mg/dL	1.9±1.5	2.0±1.7	0.136
eGFR, mL/min/1.73 m^2	49.4±26.4	50.3±29.9	0.330
Total cholesterol, mg/dL	160.2±45.8	153.9±42.7	0.001
HDLc, mg/dL	43.4±14.0	42.0±14.2	0.017
LDLc, mg/dL	97.7±35.5	93.9±35.2	0.014
Triglyceride, mg/dL	109.7±133.6	96.0±60.0	0.001
Uric acid, mg/dL	8.7±3.1	8.2±3.0	<0.001
NT-pro-BNP[a], pg/mL	3.8±0.6	3.7±0.6	0.122
Total bilirubin	0.9±0.7	0.9±0.9	0.423
Echocardiography			
HFpEF, n (%)	917 (52.8)	940 (54.5)	0.325
LVEF, %	50.0±19.0	50.1±17.9	0.864
MV E velocity, m/s	85.3±31.3	94.5±30.6	<0.001
MV A velocity, m/s	86.4±31.0	88.1±30.4	0.329
RVSP, mmHg	43.4±16.7	45.9±17.3	<0.001

[a]N-terminal pro-B type natriuretic peptide (NT-pro-BNP) was taken logarithmic transformation.
BUN=blood urea nitrogen; COPD=chronic obstructive pulmonary disease; eGFR=estimated glomerular filtration rate; HDLc=high-density lipoprotein cholesterol; HFpEF=heart failure with preserved ejection fraction; LDLc=low-density lipoprotein cholesterol; LVEF=left ventricular ejection fraction; MV=mitral valve; RVSP=right ventricular systolic pressure.

In the validation cohort comprising 1762 subjects, 387 patients (22.0%) died, of whom 192 (49.6%) died of CV causes, during a mean follow-up duration of 23.8±11.9 months. The absolute risks of CV death and all-cause mortality within a year increased along with the risk categories (Supplementary Table 2, http://links.lww.com/JCMA/A51). The Kaplan–Meier survival analysis clearly showed that the survival rate was distinct in each risk stratum of the UR-HEARt score (Figure 1B).

The area under curve of the UR-HEARt score to predict all-cause mortality (0.66; 95% confidence interval, [CI] 0.62–0.70) was significantly higher than that of the AHEAD score (0.58; 0.54–0.62) in the validation cohort ($p < 0.001$) (Table 5). The UR-HEARt score was associated with NRIs of 10.9% ($p < 0.001$) for total mortality and 18.4% ($p < 0.001$) for CV death in the Cox regression analysis.

4. DISCUSSION

In the present study, we proposed and validated a new risk prediction model, the UR-HEARt score, based on an Asian heart failure registry for the risk classification of patients hospitalized for AHF. Each stratum increase of the UR-HEARt score was associated with an excessive risk of 13.4% for all-cause mortality and 7.0% for CV death at one year after discharge. This study demonstrated that the racial-specific prediction model, the UR-HEARt score, outperformed the existing scoring system in recognizing patients at risk of mortality in Asian populations.

4.1. Population-specific risk prediction model

While the Acute Decompensated Heart Failure National Registry (ADHERE) risk score, Get With the Guidelines-Heart Failure (GWTG-HF) risk score, and Cardiac Comorbid Conditions Heart failure (3C-HF) risk score have been proposed to evaluate the clinical risks for mortality in patients hospitalized for HF, their practicability remains limited. When the GWTG-HF risk score comprises vital signs and laboratory data, the 3C-HF risk score comprises comorbidities, renal function, and LVEF. However, the aforementioned risk scores contain continuous

Table 5

Comparison of model performance AHEAD versus UR-HEARt in the validation cohort

	All-cause mortality (event number = 387)				Cardiovascular death (event number = 192)			
	AUC (95% CI)	*p*	NRI[a]	*p*	AUC (95% CI)	*p*	NRI[a]	*p*
AHEAD	0.58 (0.54–0.62)	…	…	…	0.56 (0.52–0.60)	…	…	…
UR-HEARt	0.66 (0.62–0.70)	<0.001	0.109	<0.001	0.64 (0.61–0.68)	0.006	0.184	<0.001

[a]The NRI was calculated and classified by the base risk prediction Cox model incorporating parameters of the AHEAD and UR-HEARt into low, intermediate, and high-risk group for both all-cause mortality and cardiovascular death (cutoff points 0.10 and 0.90).

AUC=area under curve; NRI=net reclassification improvement.

variables requiring calculators or flow-charts that jeopardize the clinical application. Spinar *et al*. therefore computed the AHEAD score, a dichotomized and mnemonic model for the risk assessment of AHF, to facilitate its popularization.[4] We previously have validated the AHEAD score to demonstrate its prognostic value in an Asian population with AHF. We further refined the AHEAD score into the AHEAD-U score to present a better model performance in the prediction of long-term mortality.[8] Considering that the etiologies of HF, prevalence of comorbidities, HF phenotypes, and clinical practice patterns varied widely in Western and Asian countries,[12] we reconstructed a population-specific risk prediction model, the UR-HEARt risk score, which could be applicable to Asian populations.

It is also worth mentioning that most of the published AHF risk models, including the AHEAD, GWTG-HF, and 3C-HF risk scores, predicted the intermediate- or short-term mortality of patients hospitalized for AHF for up to 1 year. In the present study, the study population was followed for up to 3 years to construct and validate the UR-HEARt score to stratify the time-varied mortality risks for immediate-, short-, and long-term predictions. Therefore, the study may further extend the risk prediction for a long-term period in AHF.

4.2. Individual risk factors

Compared to the AHEAD score of clinical characteristics, only age, renal function, and anemia, but not diabetes or atrial fibrillation, remained independently associated with mortality in the study population. Additionally, we incorporated echocardiographic features into the UR-HEARt risk score. LVEF and RVSP were the major echocardiographic indices used to characterize the phenotype and severity of HF, both of which were associated with clinical outcomes in the study population. In this study, the population-specific risk prediction model, the UR-HEARt score, certainly outperformed the AHEAD score to provide clinicians in Asia a feasible tool to easily conduct risk stratification easily and was applicable to all hospitalized patients with AHF, irrespective of their LVEF.

4.2.1. Diabetes mellitus

Although diabetes has been proposed as an independent predictor of CV death or HF hospitalization in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) study,[13] the controversies have been illustrated in other clinical trials that diabetes was not associated with in-hospital mortality or long-term survival.[14,15] In the cohort of 39 783 patients from the GWTG-HF program, diabetes was even more prevalent in the survivors, so was the presence of hypertension.[16] The neutrally prognostic impacts of diabetes in AHF were also observed in other Asian cohorts.[17,18] Although data from the Singapore cohort of patients with AHF suggested that diabetes may only deteriorate the clinical outcomes in patients with impaired LVEF,[19] the association was inconsistent in another AHF cohort with reduced LVEF.[20] Our study population comprised 36.6% of diabetic patients, similar to other series, and did not support diabetes as an independent risk factor of mortality.

4.2.2. Atrial fibrillation

A total of 30.1% of the study patients had atrial fibrillation, which might be more underestimated compared to the other series.[21] Although it has been demonstrated that atrial fibrillation was associated with 1.4-fold to 1.8-fold mortality risk in CHARM study of chronic stable HF,[22] atrial fibrillation was not associated with the long-term survival of patients with AHF in the ASCEND-HF trial.[23] In a Japanese cohort of 2659 patients with AHF, AF was neither a prognostic factor.[17] The study findings, regarding the neutral impacts of atrial fibrillation on mortality, were consistent with the other Asian cohorts of AHF.[20,24] Considering that atrial fibrillation and HF mutually begets each other, the incident atrial fibrillation after the index hospitalization might confound the true prognostic effects of atrial fibrillation.

4.2.3. Hyperuricemia

Hyperuricemia has been an independent predictor of unfavorable outcomes both in patients with either chronic stable HF or AHF, irrespective of the underlying LVEF.[25] In a Japanese registry of 1869 patients hospitalized for HF, hyperuricemia was independently associated with total and CV deaths.[22] Both Asian and Western patients with AHF may share hyperuricemia as a common risk factor. We have also previously proposed that the integration of hyperuricemia with the AHEAD score would result in an NRI of 20% for both all-cause and CV mortalities.[8] Although there are conflicting results regarding the therapeutic benefits of hyperuricemia in patients with AHF, hyperuricemia remains a remarkable indicator of outcomes in the study population.

4.2.4. Left ventricular systolic function

An LVEF of 50% is the cutoff value to identify patients with heart failure and preserved LVEF (HFpEF), in contrast to those with reduced LVEF (HFrEF). While it has been suggested that patients with either HFpEF or HFrEF might share similar clinical outcomes in the past, recent publications have indicated that patients with HFpEF would have better survival than those with HFrEF.[26] Since patients with HFrEF may die predominantly of CV causes, and patients with HFpEF would die majorly of non-CV events,[27] the incorporation of LVEF into the risk score was able to distinguish the phenotypes of HF. In this study, the UR-HEARt score improved the risk stratification of the AHEAD score for not only all-cause mortality but also for CV death.

4.2.5. Right ventricular systolic pressure

The prevalence of pulmonary hypertension (PH) was conceivably high among patients with either HFpEF or HFrEF. Left

heart disease-related PH was initially associated with the backward transmission of increased left ventricular filling pressure. Sustained increased pulmonary arterial pressure and hypoxia might trigger the pre-capillary vascular remodeling leading to combined pre- and post-capillary PH.[28] The presence of PH may indicate the severity of HF. The ominous association between PH and unfavorable outcomes was found both in acute and chronic stable HF patients with a dose-response relationship, irrespective of LVEF.[29] In the study population, the prevalence of PH, defined by an echocardiographic estimation of RVSP >40 mmHg, was 45.1%. Considering its evident prognostic implications, it is imperative to integrate PH into the risk stratification model.

4.3. Study limitations

This study had several limitations that may require further investigation. First, our prediction model was validated internally, using a single dataset from which the model was derived. Considering that the generation and validation cohorts were stratified by time, there was certainly an immortal time bias between the two cohorts that the validation cohort had a better survival rate than the generation cohort (Supplementary Figure, http://links.lww.com/JCMA/A51). Therefore, assessment of the model performance by external validation would have better discriminative power and higher level of validity. The generalizability of the UR-HEARt score to other populations requires further study. Second, we dichotomized the continuous variables for clinical accessibility, which might compromise the predictive accuracy. Third, some parameters reported to be associated with the outcomes of HF, such as body mass index,[30] smoking behavior, high-sensitivity C-reactive protein, and N-terminal pro-B-type natriuretic peptide, were excluded in this study. Considering that the majority of the AHF patients were initially edematous, the on-admission body weight might be over-estimated, and some novel biomarkers are not always available and costly. Models with more variables and complex calculations might have better prediction power, but limited utility would be restricted in real-world clinical practice.

In conclusion, the UR-HEARt score, an easily accessible risk prediction model, improved the risk stratification in Asian patients hospitalized for AHF. To the best of our knowledge, this study is the first to construct a risk prediction model for hospitalized AHF patients based on an Asian population. We also integrated the easily accessible echocardiographic features into the risk model to enhance model performance. Whether the modifiable risk factors could be potential therapeutic targets or merely indicators of disease severity requires further investigation. It is noteworthy to bear in mind that precise and practical prognostication assisted clinical judgement, but did not replace the intuitive predictions of physicians in individual cases.

ACKNOWLEDGMENTS

The study was supported by Taipei Veterans General Hospital (V100C-145, V101C-092, V102C-119, V103B-017, V104C-172, V106C-098, V107C-072, V109C-134), Ministry of Science and Technology (MOST 103-2314-B-010-050-MY2), and Ministry of Health and Welfare, Taiwan with grant (MOHW-104-TDU-B-211-113003 and MOHW-105-TDU-B-211-133017, MOHW106-TDU-B-211-113001) and the death registry.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1097/JCMA.0000000000000340.

REFERENCES

1. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006; **27**: 2725–36.
2. Adams KF, Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; **149**: 209–16.
3. Desai AS, Stevenson LW. Rehospitalization for heart failure: predict or prevent? *Circulation* 2012;**126**:501–6.
4. Spinar J, Jarkovsky J, Spinarova L, Mebazaa A, Gayat E, Vitovec J, et al. AHEAD score – long-term risk classification in acute heart failure. *Int J Cardiol* 2016;**202**:21–6.
5. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006;**113**:1424–33.
6. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997;**95**:2660–7.
7. Lee DS, Alba AC. Risks and benefits of risk prediction in acute heart failure. *JACC Heart Fail* 2015;**3**:748–50.
8. Chen YJ, Sung SH, Cheng HM, Huang WM, Wu CL, Huang CJ, et al. Performance of AHEAD score in an Asian cohort of acute heart failure with either preserved or reduced left ventricular systolic function. *J Am Heart Assoc* 2017; **6**(5): e00249.
9. Papadimitriou L, Georgiopoulou VV, Kort S, Butler J, Kalogeropoulos AP. Echocardiography in acute heart failure: current perspectives. *J Card Fail* 2016;**22**:82–94.
10. Dokainish H, Zoghbi WA, Lakkis NM, Ambriz E, Patel R, Quinones MA, et al. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. *J Am Coll Cardiol* 2005;**45**:1223–6.
11. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006;**17**:2937–44.
12. Mentz RJ, Roessig L, Greenberg BH, Sato N, Shinagawa K, Yeo D, et al. Heart Failure Clinical Trials in East and Southeast Asia: understanding the importance and defining the next steps. *JACC Heart Fail* 2016;**4**:419–27.
13. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008; **29**: 1377–85.
14. Sarma S, Mentz RJ, Kwasny MJ, Fought AJ, Huffman M, Subacius H, et al. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. *Eur J Heart Fail* 2013; **15**: 194–202.
15. Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2007;**154**:277.e1–8.
16. Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, et al. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. *Circ Cardiovasc Qual Outcomes* 2010;**3**:25–32.
17. Hamaguchi S, Yokoshiki H, Kinugawa S, Tsuchihashi-Makaya M, Yokota T, Takeshita A, et al. Effects of atrial fibrillation on long-term outcomes in patients hospitalized for heart failure in Japan: a report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *CIRC J* 2009;**73**:2084–90.
18. Sawano M, Shiraishi Y, Kohsaka S, Nagai T, Goda A, Mizuno A, et al. Performance of the MAGGIC heart failure risk score and its modification with the addition of discharge natriuretic peptides. *ESC Heart Fail* 2018;**5**:610–9.
19. Go YY, Allen JC, Chia SY, Sim LL, Jaufeerally FR, Yap J, et al. Predictors of mortality in acute heart failure: interaction between diabetes and impaired left ventricular ejection fraction. *Eur J Heart Fail* 2014;**16**:1183–9.

20. Chang HY, Wang CC, Wu YW, Chu PH, Wu CC, Hsu CH, et al. One-year outcomes of acute decompensated systolic heart failure in Taiwan: lessons from TSOC-HFrEF Registry. *Acta Cardiol Sin* 2017;**33**:127–38.
21. Farmakis D, Parissis J, Lekakis J, Filippatos G. Acute heart failure: epidemiology, risk factors, and prevention. *Rev Esp Cardiol (Engl Ed)* 2015;**68**:245–8.
22. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart Failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997–2004.
23. Abualnaja S, Podder M, Hernandez AF, McMurray JJ, Starling RC, O'Connor CM, et al. Acute heart failure and atrial fibrillation: insights from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) Trial. *J Am Heart Assoc* 2015;**4**:e002092.
24. Ajlan M, Almazroa L, AlHabib KF, Elasfar AA, Alfaleh H, Albackr H, et al. Atrial fibrillation in patients hospitalized with heart failure: patient characteristics and outcomes from the HEARTS registry. *Angiology* 2018; **69**: 151–7.
25. Palazzuoli A, Ruocco G, Pellegrini M, Beltrami M, Giordano N, Nuti R, et al. Prognostic significance of hyperuricemia in patients with acute heart failure. *Am J Cardiol* 2016; **117**: 1616–21.
26. Meta-analysis Global Group in Chronic Heart Failure. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012; **33**: 1750–7.
27. Vaduganathan M, Patel RB, Michel A, Shah SJ, Senni M, Gheorghiade M, et al. Mode of death in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2017;**69**:556–69.
28. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. *Eur Heart J* 2016;**37**:942–54.
29. Merlos P, Núñez J, Sanchis J, Miñana G, Palau P, Bodí V, et al. Echocardiographic estimation of pulmonary arterial systolic pressure in acute heart failure. Prognostic implications. *Eur J Intern Med* 2013;**24**:562–7.
30. Powell-Wiley TM, Ngwa J, Kebede S, Lu D, Schulte PJ, Bhatt DL, et al. Impact of body mass index on heart failure by race/ethnicity from the get with the Guidelines-Heart Failure (GWTG-HF) Registry. *JACC Heart Fail* 2018;**6**:233–42.