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ORIGINAL RESEARCH

EMERGING TECHNOLOGIES AND INNOVATIONS

Mortality Prediction in Patients With or Without Heart Failure Using a Machine Learning Model

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ABSTRACT

BACKGROUND Most risk prediction models are confined to specific medical conditions, thus limiting their application to general medical populations.

OBJECTIVES The MARKER-HF (Machine learning Assessment of RisK and EaRly mortality in Heart Failure) risk model was developed in heart failure (HF) patients. We assessed the ability of MARKER-HF to predict 1-year mortality in a large community-based hospital registry database including patients with and without HF.

METHODS This study included 41,749 consecutive patients who underwent echocardiography in a tertiary referral hospital (4,640 patients with and 37,109 without HF). Patients without HF were further subdivided into those with (n = 22,946) and without cardiovascular disease (n = 14,163) and also into cohorts based on recent acute coronary syndrome or history of atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, hypertension, or malignancy.

RESULTS The median age of the 41,749 patients was 65 years, and 56.2% were male. The receiver operated area under the curves for MARKER-HF prediction of 1-year mortality of patients with HF was 0.729 (95% CI: 0.706-0.752) and for patients without HF was 0.770 (95% CI: 0.760-0.780). MARKER-HF prediction of mortality was consistent across subgroups with and without cardiovascular disease and in patients diagnosed with acute coronary syndrome, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, or hypertension. Patients with malignancy demonstrated higher mortality at a given MARKER-HF score than did patients in the other groups.

CONCLUSIONS MARKER-HF predicts mortality for patients with HF as well as for patients suffering from a variety of diseases. (JACC Adv 2023;2:100554) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

AF = atrial fibrillation

AUC = area under the curve

CKD = chronic kidney disease

COPD = chronic obstructive pulmonary disease

CV = cardiovascular

HF = heart failure

HTN = hypertension

KNUH = Kyungpook National University Hospital

ROC = receiver operating characteristic

UCSD = University of California-San Diego

Predicting the likelihood of death over a period of time helps identify patients at varying degrees of risk, which in turn can influence their medical care. In particular, individuals at high risk can be more intensively monitored, referred for advanced therapies, or counseled regarding end-of-life issues.[1] Identifying patients at high risk of mortality may also help improve the efficiency of clinical trials that include death as a primary or secondary end point.[2] In many settings, however, assessment of a patient's risk of dying over a finite period of time is imprecise, particularly when it is based on clinical judgment or a single variable. As a result, risk prediction models and scoring systems which are based on combinations of a patient's physical signs, laboratory findings, biomarkers, and genetic profile have been developed.[3-5] While often accurate, these risk prediction models tend to be highly disease-specific, so that a score derived from a population with a given disease cannot be applied reliably to another with a different identifying disease or condition.[5] For example, the CHA_2DS_2-VASc score is useful mainly for patients with atrial fibrillation (AF)[4] while the Model For End-Stage Liver Disease (MELD) addresses risk in patients with chronic liver disease.[3]

MARKER-HF (Machine learning Assessment of RisK and EaRly mortality in Heart Failure) is a novel, machine learning-based model that was generated to predict mortality risk of patients with heart failure (HF).[6] Its predictive accuracy was independently validated in a variety of settings including community-based registries and clinical trial populations.[2,6] It also predicts outcomes across all categories of HF defined by left ventricular ejection fraction that are used in major guideline recommendations.[7] Changes in values of the 8 variables used to calculate the MARKER-HF score (ie, diastolic blood pressure, creatinine, blood urea nitrogen, hemoglobin, white blood cell count, platelets, albumin, and red blood cell distribution width), however, are not specific to HF and often occur in other disease settings.

Therefore, we hypothesized that MARKER-HF might be a reliable general indicator of mortality that could predict risk across a variety of diseases that are seen in clinical practice. In the present study, we tested whether this hypothesis by assessing MARKER-HF prediction of mortality in a large cohort of patients, both with and without HF, who were included in a community hospital registry.

METHODS

The study conforms with the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Kyungpook National University Hospital (KNUH).

STUDY POPULATION. All 58,965 patients who underwent echocardiography at KNUH either during hospitalization, in the emergency department, or in an outpatient clinic setting between September 2013 and March 2020 were included in this analysis. Baseline demographic data and laboratory tests were extracted from the clinical data warehouse (SOFTCEN 2017, Republic of Korea) of KNUH.

After excluding 17,216 patients who were missing one or more of the variables required to calculate the MARKER-HF score, the remaining 41,749 patients were included in the final analysis (Supplemental Figure 1). Patients from the KNUH population were initially separated into those with HF using the same International Classification of Disease-10 (ICD-10) codes (Supplemental Table 1) as were used for the original derivation and validation of MARKER-HF,[6] and those without HF. Patients without HF were then divided into subgroups based on the presence of cardiovascular (CV) disease. The presence of CV disease was defined by the patient's having one or more of the diagnostic codes that were applied to patients followed by the CV department at KNUH (as listed Supplemental Table 2) or with a diagnostic code for hypertension (also listed in Supplemental Table 2).

The predictive value of MARKER-HF was further assessed in subgroups of patients with acute coronary syndrome (ACS) diagnosed within 1 month prior to index echocardiography, a history of AF, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension (HTN), or malignancy. Each subgroup was identified using the ICD-10 codes listed in Supplemental Table 1.

These 7 disease-based subgroups were not mutually exclusive, and patients could be included in more than one group. Patients with HF, however, were excluded from these subgroups to cleanly assess the performance of MARKER-HF on HF and non-HF patients.

In the present study, the 1-year survival probability in the KNUH cohorts described above was predicted

using MARKER-HF. A score was derived and validated on 5,822 HF patients followed at the University of California San-Diego (UCSD).[6]

CALCULATION OF MARKER-HF SCORE. Details of the derivation and validation of MARKER-HF are published elsewhere.[6] In brief, MARKER-HF is a machine learning-based model that uses a boosted decision tree algorithm to predict mortality in patients with HF. It relies on 8 variables (diastolic blood pressure, serum creatinine, blood urea nitrogen, hemoglobin, white blood cell count, platelets, albumin, and red blood cell distribution width) to generate a score ranging between −1 and +1. A score closer to +1 indicates higher risk. The variables were chosen based on their discriminating power as well as their general availability. The number of variables was restricted to avoid overfitting the algorithm due to the size of the cohorts on which the algorithm was trained and tested. Corresponding 1-year survival estimates can be calculated from the MARKER-HF score.

STUDY OUTCOME. The primary outcome was 1-year all-cause mortality in the study population. Patients' death was adjudicated based on medical record and the National Health Insurance database of the Republic of Korea.

STATISTICAL ANALYSIS. Baseline characteristics were presented as numbers and frequencies for categorical variables and as median (IQR) for continuous variables. Normality of distribution was assessed using the Anderson-Darling test. For comparisons between groups of categorical variables chi-square test was used, while variables were compared using either an independent *t*-test or Kruskal-Wallis rank sum test. Kaplan-Meier estimates were used to compare 1-year survival between KNUH and UCSD cohorts. A comparison of survival rates between different groups was assessed with log-rank tests and confidence intervals.

We calculated the 1-year survival probability using Kaplan-Meier curves stratified by MARKER-HF score. Survival probabilities were then graphed as a function of MARKER-HF in the overall study population and the various subgroups.

The receiver operating characteristic (ROC) curve was used to measure the predictive power of MARKER-HF. The confidence intervals of an area under the curve (AUC) were calculated with the method of Delong et al.[8] The AUC is obtained in the standard way by examining sensitivity and specificity when scanning MARKER-HF threshold.

A 2-sided P value of <0.05 was considered statistically significant. Statistical tests were performed using R programming version 3.6.0 (The R Foundation for Statistical Computing, Vienna) and custom Python (version 3.9)-based code.

TEST OF MARKER-HF CALIBRATION ON THE KNUH COHORT. An important requirement for a risk score is that its performance be reproducible in cohorts other than the one from which it was derived. Accordingly, we compared the predicted 1-year survival probability to the observed mortality rate in all sub-cohorts studied. For each sub-cohort, we plotted the 1-year survival rate vs MARKER-HF, where the (same) red curve represents the predicted survival rate (based on the relationship between the score's value and survival rate in the UCSD derivation cohort). The data points show the observed mortality rate in the sub-cohort in question. The error bars represent the 95% CI (y-axis) and range of coverage (x-axis). A systematic difference (beyond local statistical fluctuations) between predicted and observed values could be due to a difference in mortality rates between the cohorts/conditions or indicate an uncalibrated score if cohorts/conditions are expected to be similar.

RESULTS

MARKER-HF IN PATIENTS WITH AND WITHOUT HF. **Table 1** summarizes baseline characteristics, including comorbid conditions and variables used to calculate MARKER-HF score for the entire KNUH study population and subgroups defined by presence or absence of HF. The median age of the entire KNUH population was 65 [IQR: 55-75] years, and 56% were males. Patients with HF were older (72 [IQR: 62-79] years vs 65 [IQR: 54-74] years, $P < 0.001$), less likely to be male (51.8% vs 56.8%; $P < 0.001$), and were more likely to have comorbidities (except for malignancy) than patients without HF.

MARKER-HF score was unimodally distributed in the entire population (median of −0.35 [IQR: −0.41 to −0.25]), and in all subgroups listed in **Table 1**. Patients without HF had a lower median MARKER-HF score (indicating lower mortality risk) than those with HF (−0.35 [IQR: −0.41 to −0.25] vs −0.31 [IQR: −0.39 to −0.19]; $P < 0.001$). As depicted in **Figure 1A**, all-cause mortality at 1 year of follow-up was considerably less in KNUH patients without HF than in patients with HF (6.8% vs 11.3%; $P < 0.001$).

Using the ROC curve analysis, MARKER-HF prediction of 1-year mortality had an AUC of 0.767

TABLE 1 Baseline Characteristics of Study Patients

	All (N = 41,749)	HF (n = 4,640)	No HF (n = 37,109)	*P* Value	No HF With CV (n = 22,946)	No HF, No CV (n = 14,163)	*P* Value
Age, y	65.0 (55.0-75.0)	72.0 (62.0-79.0)	65.0 (54.0-74.0)	<0.001	65.0 (55.0-74.0)	65.0 (53.0-75.0)	0.626
Male	23,469 (56.2%)	2,404 (51.8%)	21,065 (56.8%)	<0.001	13,522 (58.9%)	7,543 (53.3%)	<0.001
HTN	10,445 (25.0%)	1,669 (36.0%)	8,776 (23.6%)	<0.001	8,776 (38.2%)	0 (0.0%)	<0.001
DM	5,173 (12.4%)	799 (17.2%)	4,374 (11.8%)	<0.001	2,935 (12.8%)	1,439 (10.2%)	<0.001
COPD	1,007 (2.4%)	225 (4.8%)	782 (2.1%)	<0.001	485 (2.1%)	297 (2.1%)	0.943
CKD	2,312 (5.5%)	418 (9.0%)	1,894 (5.1%)	<0.001	1,585 (6.9%)	309 (2.2%)	<0.001
Malignancy	8,027 (19.2%)	722 (15.6%)	7,305 (19.7%)	<0.001	3,217 (14.0%)	4,088 (28.9%)	<0.001
DBP, mm Hg	73 (64-83)	70 (61-81)	73 (64-83)	<0.001	73 (63-83)	74 (65-84)	<0.001
WBC, $10^3/\mu L$	6.8 (5.4-8.7)	7.0 (5.5-9.0)	6.8 (5.4-8.7)	<0.001	6.8 (5.5-8.6)	6.8 (5.3-8.8)	0.165
Hemoglobin, g/dL	13.1 (11.5-14.4)	12.6 (11.0-14.0)	13.1 (11.6-14.4)	<0.001	13.3 (11.8-14.5)	12.9 (11.3-14.3)	<0.001
Platelet, $10^3/\mu L$	226 (183-274)	212 (170-264)	228 (185-275)	<0.001	226 (185-271)	231 (185.-282)	<0.001
RDW	13.0 (12.5-13.8)	13.4 (12.7-14.3)	12.9 (12.4-13.7)	<0.001	12.9 (12.4-13.6)	13.0 (12.5-13.9)	<0.001
BUN, mg/dL	15.1 (12.0-19.6)	18.1 (13.9-24.6)	14.8 (11.8-19.0)	<0.001	15.2 (12.2-19.6)	14.2 (11.2-18.2)	<0.001
Creatinine, mg/dL	0.8 (0.7-1.0)	0.9 (0.8-1.2)	0.8 (0.7-1.0)	<0.001	0.8 (0.7-1.0)	0.8 (0.6-0.9)	<0.001
Albumin, g/dL	4.2 (3.8-4.5)	4.0 (3.6-4.4)	4.2 (3.8-4.5)	<0.001	4.3 (3.9-4.5)	4.1 (3.6-4.5)	<0.001
MARKER-HF	−0.35 (−0.41 to −0.25)	−0.31 (−0.39 to −0.19)	−0.35 (−0.41 to −0.25)	<0.001	−0.35 (−0.41 to −0.27)	−0.35 (−0.41 to −0.23)	<0.001
1-y mortality	3,046 (7.3%)	525 (11.3%)	2,521 (6.8%)	<0.001	1,223 (5.3%)	1,298 (9.2%)	<0.001

Values are median (IQR) or n (%).

BUN = blood urea nitrogen; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; DBP = diastolic blood pressure; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; RDW = red cell distribution width; WBC = white blood cell.

(95% CI: 0.758-0.776) for the entire KNUH population. MARKER-HF score successfully predicted mortality risk in patients with and without HF with AUCs of 0.729; 95% CI: 0.706-0.752, and 0.770; 95% CI: 0.760-0.780, respectively ($P = 0.001$) (**Figure 1B**). For comparison, the UCSD population of patients with HF is also depicted in **Figure 1B**. **Figure 1C** compares 1-year survival rate predicted by MARKER-HF (red curve) with that observed in the entire KNUH population and in subgroups of patients with and without HF.

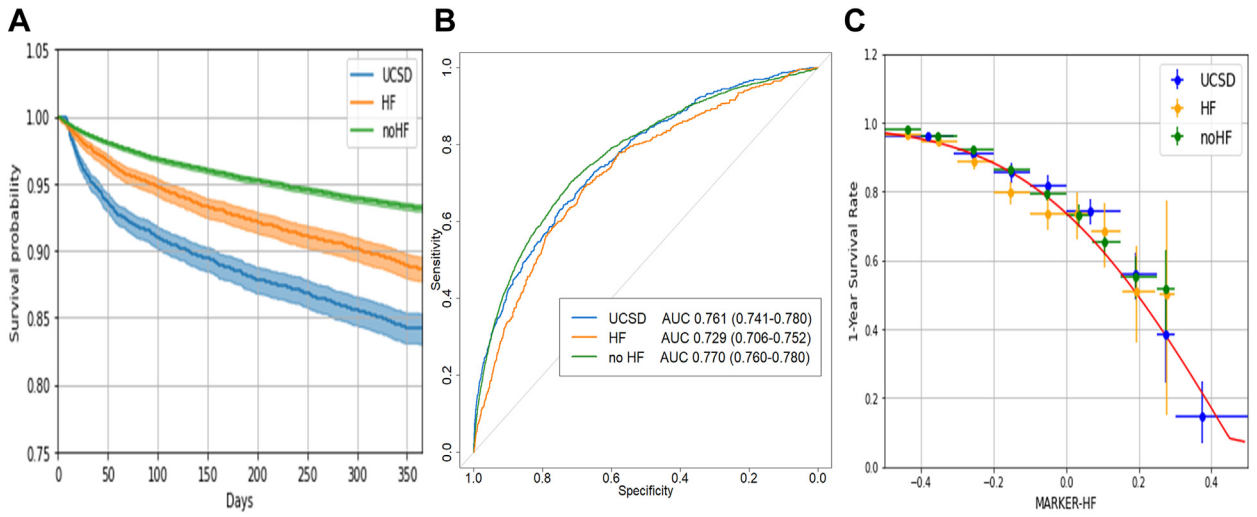
These results show that despite significant differences in 1-year mortality rates between groups, MARKER-HF prediction of mortality was similar in all groups, indicating that the survival estimates derived from the UCSD HF population reliably predicts the survival outcomes in the KNUH population regardless of whether or not they had HF.

MARKER-HF IN PATIENTS WITH AND WITHOUT CARDIOVASCULAR DISEASE. We next focused on testing MARKER-HF in KNUH patients without HF, divided further into subgroups based on whether they had CV disease (**Table 1**). As shown in **Figure 2A**, the group without CV disease had higher 1-year mortality (9.2% vs 5.3%; $P < 0.001$) that that of patients with CV disease, a finding likely due to the significantly higher prevalence of malignancy in the patients without HF and no CV disease compared to those without HF who had CV disease (28.9% vs 14.0%; $P < 0.001$). In the ROC curve analysis, the AUCs for MARKER-HF prediction of 1-year mortalities demonstrated similar performance in both subgroups with a slightly higher AUC for patients with CV disease (0.782; 95% CI: 0.768-0.796) compared to that seen in patients without CV disease (0.754; 95% CI: 0.740-0.769, $P = 0.006$) (**Figure 2B**).

Figure 2C demonstrates that MARKER-HF has comparable ability to predict mortality in the 2 groups with good calibration across a wide range of the risk spectrum.

MARKER-HF IN PATIENTS WITH COMMON MEDICAL CONDITIONS. KNUH patients without HF were then divided into 7 cohorts based on the presence of common medical conditions (ie, ACS, AF, CKD, COPD, diabetes mellitus, HTN, and malignancy). Baseline characteristics and variables used to generate the MARKER-HF score for these groups (summarized in Supplemental Table 3) show considerable variability between groups. The 1-year mortality rates were also very different between groups, ranging from 4.0% to 17.4% (**Figure 3**A). Despite these variations and the absence of a HF diagnosis in any of these patients, the MARKER-HF prediction of mortality was consistent in all subgroups of patients except for those with malignancy where the risk score tended to underestimate mortality (**Figure 3C**, **Central Illustration**, Supplemental Figure 2). The AUCs of the MARKER-HF curves for predicting 1-year mortality in each of the 7

FIGURE 1 Kaplan-Meier 1-Year Survival Rates and Performance of MARKER-HF in Patients With and Without HF in UCSD and KNUH Cohorts

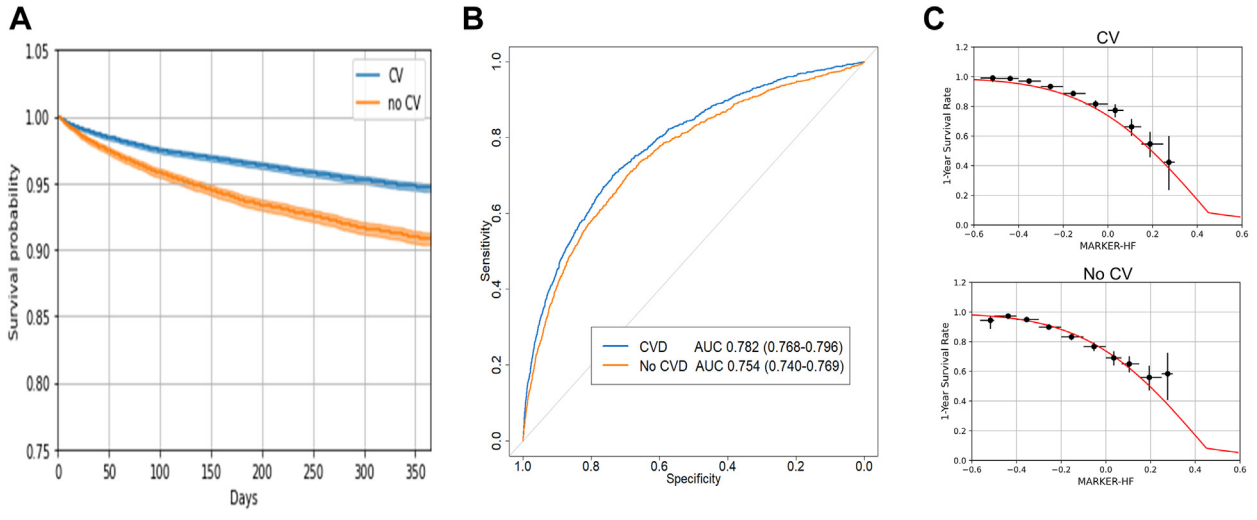


(A) Kaplan-Meier survival curves for the UCSD and KNUH populations. **(B)** Receiver operating characteristic curves of MARKER-HF score for predicting 1-year mortality in patients with and without HF in the KNUH and the UCSD population of patients with HF. **(C)** Predicted and observed 1-year survival rates for the UCSD and KNUH populations. HF = heart failure; KNUH = Kyungpook National University Hospital; UCSD = University of California-San Diego.

subgroups range between 0.671 and 0.738 (**Figure 3B**). The optimal threshold(s) for the corresponding sensitivity and specificity are presented in Supplemental Table 4.

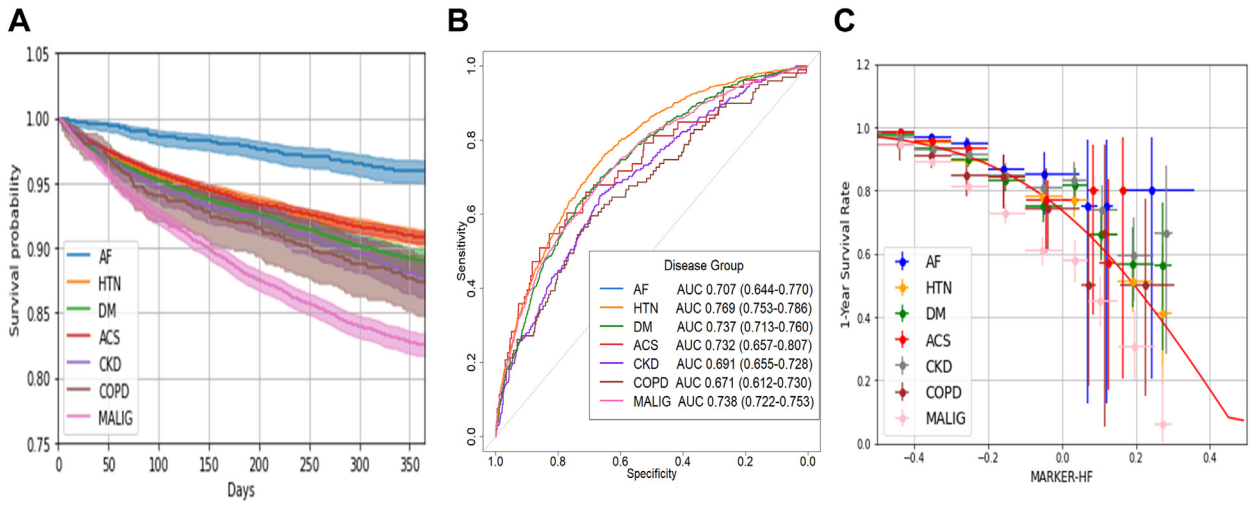
MARKER-HF SCORE IN SUBGROUPS DIVIDED BY AGE AND SEX. As MARKER-HF (intentionally) does not include age, we determined whether there were significant differences in the predictive accuracy of

FIGURE 2 Kaplan-Meier 1-Year Survival Rates and Performance of MARKER-HF in KNUH Patients With and Without CV Disease



(A) Kaplan-Meier survival curves for patients with and without CV disease. **(B)** Receiver operating characteristic curve analysis of the MARKER-HF score for predicting 1-year mortality in patients with and without CV disease. **(C)** Predicted and observed 1-year survival rates for patients with and without CV disease. CV = cardiovascular; HF = heart failure; KNUH = Kyungpook National University Hospital; UCSD = University of California-San Diego.

FIGURE 3 Kaplan-Meier 1-Year Survival Rate and Performance of MARKER-HF in Patients With Common Medical Conditions



(A) Kaplan-Meier survival curves of patients with 7 common medical conditions. **(B)** Receiver operating characteristic curve analysis of the MARKER-HF for predicting 1-year mortality in subgroups of patients with common medical conditions. **(C)** Predicted and observed 1-year survival rates for patients with 7 medical conditions. ACS = acute coronary syndrome; AF = atrial fibrillation; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HTN = hypertension; MALIG = malignancy.

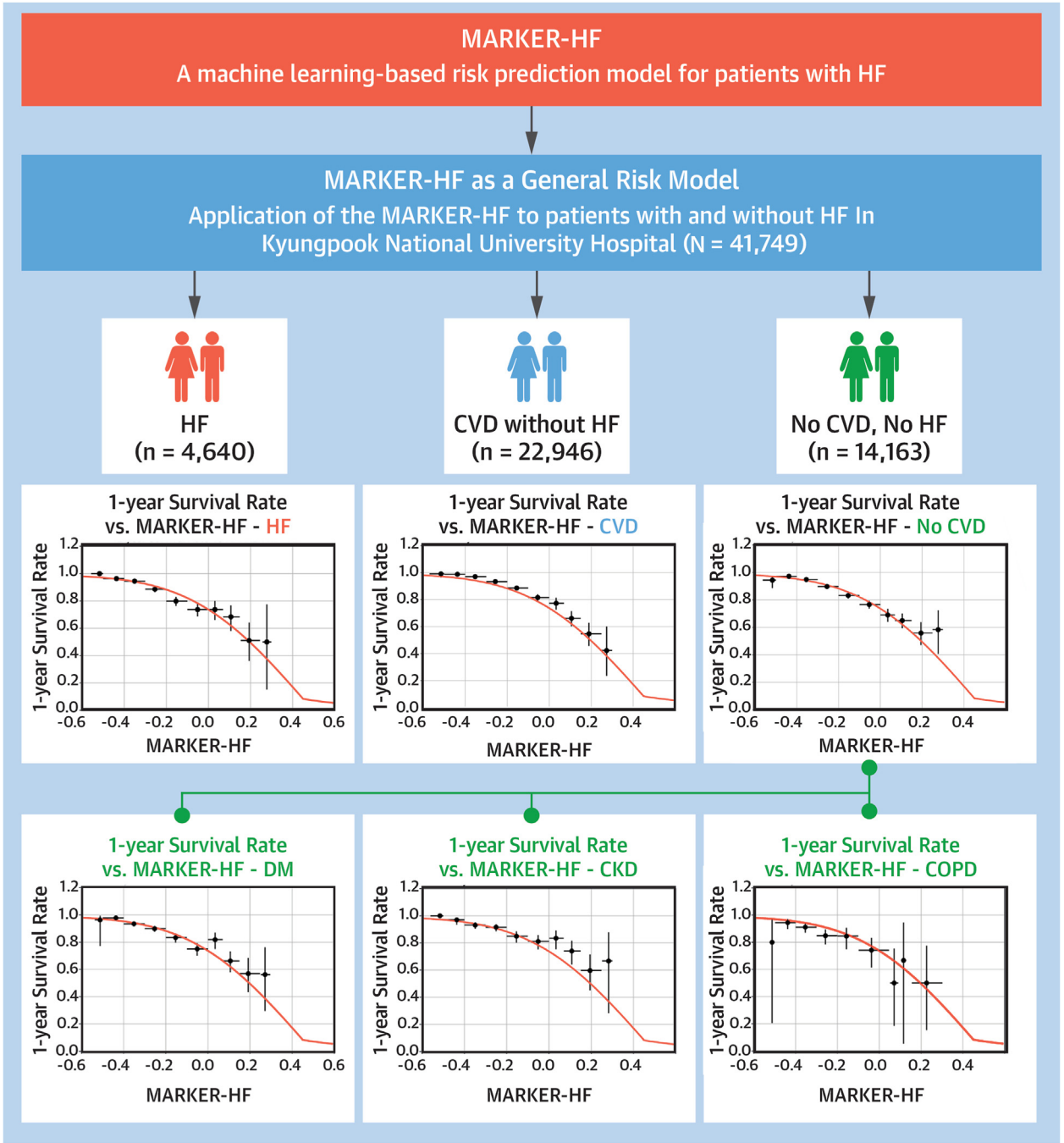
MARKER-HF between age groups. The reason excluding age in the score's training is that it is an obvious and dominant mortality characteristic that would mask the importance of more subtle but salient clinical inputs, thereby weakening the score's discriminating power for the given outcome(s). When MARKER-HF was applied to the KNUH population, MARKER-HF predicted mortality in patients separated into subgroups according to age (above or below 65 years) and in both male and female patients, although the score tended to overestimate 1-year risk in patients who were <65 years of age (Figure 4).

WHY DOES MARKER-HF WORK IN PATIENTS WITHOUT HF? The 8 variables used to calculate the MARKER-HF score can be affected not only by pathophysiologic abnormalities that occur in patients with HF but also by the effects of abnormal organ function that develop in a variety of disease states. Supplemental Figure 3 shows the mean value of MARKER-HF as a function of each of the 8 input variables in patients from the KNUH population. The yellow bands indicate the 'normal' ranges for each variable. Deviation from the normal range of each generally results in a higher MARKER-HF score, indicating higher risk for mortality. Since these ranges were not used as input to the model, it appears the model 'learned' them by associating the combination of the covariates (in their multidimensional space) to the outcomes. Our findings also show that the association between these variables originally detected in UCSD patients with HF also holds in populations without HF.

DISCUSSION

Most risk prediction models are specific to the disease for which they were trained. The MARKER-HF score was developed to predict mortality risk in patients with HF and it has been independently validated in HF registry and clinical trial populations.[2,6] The ability of MARKER-HF to predict outcome is maintained across the spectrum of HF classes defined by left ventricular ejection fraction,[7] and it appears to be superior to several other risk scores used to predict mortality in patients with HF.[6] The 8 variables used to compute MARKER-HF, however, are not uniquely influenced by HF as they are sensitive to the effects of a variety of diseases. This insight motivated the present study of the predictive power of MARKER-HF in patients with medical conditions other than HF. When we applied the MARKER-HF score to the large KNUH community-based hospital registry, we found that MARKER-HF reliably predicted 1-year mortality

CENTRAL ILLUSTRATION **MARKER-HF: A Machine Learning-Based Mortality Score, Derived and Validated on a UCSD Cohort With HF, was a Good Predictor for 1-Year Mortality on KNUH Patients**



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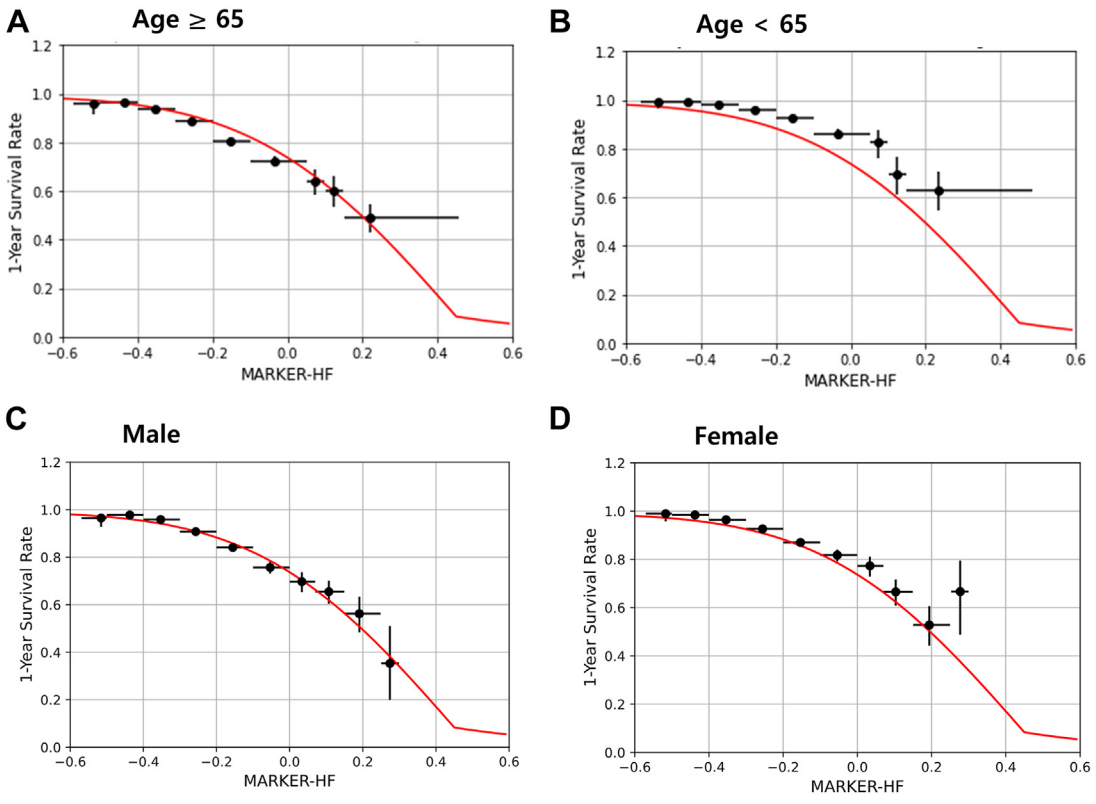
CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HF = heart failure; KNUH = Kyungpook National University Hospital; USCF = University of California-San Francisco.

FIGURE 4 Predicted and Observed 1-Year Survival Rates in Age and Sex Subgroups



Association between the MARKER-HF score and survival at one year was assessed in patients from the KNUH population according to age >65 **(A)**, <65 **(B)**, male sex **(C)** or female sex **(D)**. KNUH = Kyungpook National University Hospital.

regardless of whether HF was present. We also found that the ability of this risk score to predict mortality was maintained in patients without HF, either with or without CV disease and in subgroups of patients identified by diseases commonly seen in medical practice (**Central Illustration**). These results extend the potential utility of the risk score beyond the HF population and suggest that it can be used to screen large populations of patients in order to identify individuals and cohorts of patients at varying levels of risk within those populations.

MARKER-HF PERFORMANCE IN PATIENTS WITH HEART FAILURE. Many risk scores have been developed for predicting mortality in patients with HF including the EFFECT (Enhanced Feedback for Effective Cardiac Treatment score,[9] the acute decompensated heart failure (ADHF)/N-terminal pro-B-type natriuretic peptide (NT-proBNP) score for 1-year mortality,[10] the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) score for 1- and 3-year mortality,[11] the ADHERE (Acute Decompensated Heart Failure National Registry) score for in-hospital and short-term mortality,[12] and Get With The Guideline-HF (GWTG-HF) score for in-hospital mortality.[13] In our initial description of MARKER-HF,[6] we compared the predictive accuracy of MARKER-HF with that of 3 other commonly used risk score systems (the Intermountain Risk Score, GWTG-HF score, and ADHERE score). The results showed that MARKER-HF was superior to these scores in predicting 1-year mortality in 3 independent populations. We also have shown that MARKER-HF maintains its predictive accuracy across classes of HF defined by left ventricular ejection fraction and in independent populations in the United States and Europe as well as in clinical trial populations. In the present study, we extend these findings by demonstrating that MARKER-HF is an accurate predictor of mortality in East Asian patients with HF. Of note is the fact that the AUC for MARKER-HF prediction of mortality is lower in the present study (AUC = 0.76) than in the

initial report (AUC = 0.88).[6] This difference is due to the fact that the present study is based on the separation of patients who died within 365 days from those who survived >365 days. This second set of patients includes many patients at intermediate risk, and as a result, the separation is not expected to be as good as in the initial MARKER-HF manuscript which reported an AUC for the separation of death within 90 days and survival of more than 2 years.

In addition to MARKER-HF, other machine learning-based algorithms for predicting the prognosis of patients with HF have been developed.[1,14,15] Jing et al used a machine learning-based algorithm to generate a mortality risk prediction model based on data from the electronic health record of 26,971 patients with HF. This model which used 26 variables performed slightly better (AUC = 0.77) than a model using linear logistic regression (AUC = 0.74).[14] Kim et al[1] developed a machine learning model incorporating 27 continuous and 44 categorical variables from patients included in the Korean Acute Heart Failure registry. The AUC for predicting 1-year mortality was 0.71, which was comparable to that of the MAGGIC-HF score (AUC = 0.711). Although MARKER-HF has not been compared directly to these other machine learning models as the databases were either not available to us or did not include all the variables required for calculating MARKER-HF, the AUC which we are reporting for 1-year mortality is in a similar range as for the other machine learning models described above. Notably, MARKER-HF requires only 8 physiologic variables, greatly simplifying the utility of this score in clinical practice[6,7] and it has undergone considerably greater independent external validation than the other scores.

MARKER-HF PERFORMANCE IN PATIENTS WITHOUT HEART FAILURE. Baseline clinical characteristics, MARKER-HF scores, and survival rates were substantially different between patients with and without HF in the KNUH population. Nonetheless, MARKER-HF scores defining levels of risk tracked along with demonstrated 1-year mortality in the KNUH patient groups with and without HF with an AUC for the non-HF population slightly higher for the cohort of patients with HF indicating that MARKER-HF can reliably predict outcomes regardless of whether it is being used in patients with or without HF.

MARKER-HF PERFORMANCE IN PATIENTS WITH AND WITHOUT CARDIOVASCULAR DISEASE AND IN COMMON MEDICAL CONDITIONS. Since HF is the final common pathway of a variety of CV diseases, it is of interest whether MARKER-HF predicts outcomes in patients with and without CV disease. Our results show that in patients without HF, MARKER-HF predicted mortality risk in both groups of patients. We further assessed MARKER-HF performance in patients with CV disease by assessing its ability to predict mortality in KNUH cohorts with 3 common CV conditions, that is, hypertension, ACS, and AF, and in 2 conditions that commonly coexist in patients with CV disease, for example, diabetes and CKD. Our results showing that MARKER-HF maintained its predictive accuracy in patients with these conditions imply that this risk score predicts mortality throughout the CV disease continuum.

In the subgroup of patients without CV disease, MARKER-HF predicted mortality in patients with COPD, a finding which further enhances the generalizability of the risk score.

However, MARKER-HF under-predicted (by about 10%) 1-year mortality risk for patients with malignancy. The reasons for the ability of MARKER-HF to predict mortality in the other 6 subgroups but underestimating it in patients with malignancy are uncertain. Regardless, our results do not support use of MARKER-HF in this subgroup of patients.

MARKER-HF AS A GENERAL MORTALITY RISK MODEL. Many risk scores are limited to specific medical conditions, for example, CHA_2DS_2-VASc score for thromboembolic risk in AF.[4] HF is a common disease with poor prognosis and as noted previously many risk prediction models have been developed. However, not all the CV or non-CV diseases have their own risk stratification system. Moreover, many patients in clinical practice have multiple comorbidities in combination, including diabetes, hypertension, and CKD. Our results suggest that the information regarding mortality risk that can be obtained using MARKER-HF in a general medical population (as well as in cohorts defined by specific medical conditions) could be quite useful in providing a broad picture of the patients' physiologic state. For example, patients with HTN in the present study had a high prevalence of comorbid conditions including diabetes in 25.0%, CKD in 15.4, malignancy in 20.1%, and CKD (evidenced by a serum creatinine that averaged 2.2 mg/dL). The 1-year mortality of patients with HTN was very high (17.4%). Patients in the HTN cohort without any of the comorbidities mentioned above had a 1-year mortality of low as 3.5%, nonetheless, the predictive power of MARKER-HF was excellent with an AUC of 0.769 in this subgroup. While our results suggest that MARKER-HF would be useful in screening large general medical clinic populations where patients often have multiple diseases and

comorbidities or in a health care system database, to help identify those at high risk of mortality, they should not be misinterpreted as showing that MARKER-HF is preferable to disease-specific risk scores in patients who are being managed for specific conditions, for example, CHA_2DS_2-VASc score for thromboembolic risk and MELD score for chronic liver disease.

The ability of MARKER-HF to predict mortality risk in a large general medical population regardless of whether HF is present can be explained by the fact that all 8 variables used to construct the score are sensitive to changes in the function of several organ systems that may develop during the course of a variety of common diseases. During the training phase of MARKER-HF, variables from HF patients in the UCSD population were included in a Boosted Decision Tree algorithm and exposed to 2 extreme outcomes—imminent death (<90 days) or survival time exceeding 2 years. The associations between the 8 input variables and each of the 2 outcomes learned by the model were captured in the calculation of the multidimensional space of the 8 covariates used to construct the MARKER-HF risk score. This and the temporal proximity of the input variables which were collected over a limited time frame ensure that the state of the patient is captured with minimal dilution. We observed earlier[6] that no single variable has good discrimination between the 2 survival extrema that MARKER-HF was trained to identify. Rather, it is the ensemble of the 8 covariates and the way they are changing in a correlated way that indicates the state of the patient, or the risk. As the variables used to calculate MARKER-HF are fundamental indicators of perturbations to normal human physiology, combination of them which are captured in the score can identify varying degrees of organ dysfunction within the patient and relate them to the subsequent risk of survival over a finite period of time. This same argument applies to a healthy, stable person's condition, as exemplified by the fact that as shown in Supplemental Figure 3, the model 'learned' the healthy ranges for these variables on its own.

STUDY LIMITATIONS. This study has several limitations. Although MARKER-HF has been validated in patients with HF from several community-based registry and clinical trial populations from the United States and Europe, this is the first time the risk score has been applied to non-HF patients. Future studies are needed to validate MARKER-HF in diverse non-HF populations that include Caucasian and Black patients. The study was retrospective in nature and based on data from a single center enrolling only East Asian patients. Future studies should consider further prospective validation in other populations. The underestimation of MARKER-HF in patients with malignancy requires further exploration including assessing the score in patients with various types of malignancy (eg, solid organ tumors vs hematologic malignancies). In addition, the performance of MARKER-HF needs to be validated in other conditions including neurologic and autoimmune diseases, if it is to be used in these contexts.

There are a variety of factors that might weaken the performance of the model including time variations in the collection of input variables so that the physiologic state of the patient at a specific point in time is not accurately captured and imputation of missing variables. These conditions were avoided in this analysis of MARKER-HF by maintaining a narrow window for collection of the 8 variables and by excluding patients with missing data.

CONCLUSIONS

The MARKER-HF risk score provided excellent prediction of mortality in patients with and without HF. Its ability to predict mortality was maintained regardless of whether patients had CV disease and across a variety of common medical conditions (other than malignancy), suggesting that MARKER-HF can be used as a mortality risk model for a general medical population which includes patients with a variety of conditions. To the best of our knowledge, MARKER HF is the first general mortality prediction model that can be applied to patients independent of underlying disease.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In this cohort study of 41,749 patients included in a hospital registry data base, MARKER-HF predicted 1-year mortality in patients with and without heart failure, in patients with and without cardiovascular disease and in sub-groups with various common medical conditions. These findings demonstrate that MARKER-HF is not specific for patients with heart failure and could be used to predict mortality risk in patients without heart failure suffering from a variety of diseases.

TRANSLATIONAL OUTLOOK: These results provide evidence that the MARKER-HF risk score can be used to assess mortality risk in a variety of clinical settings.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.