A multi-state model to predict heart failure hospitalizations and all-cause mortality in outpatients with heart failure with reduced ejection fraction: Model derivation and internal validation

A thesis

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Abstract:

Among outpatients with heart failure (HF), early identification of those at high risk for HF hospitalization and/or death may help direct disease management services or advanced HF therapies. Currently, however, there are no models in this population to predict both heart failure hospitalization and all-cause mortality as individual outcomes as well as a composite outcome. Thus, we developed a model to predict both HF hospitalization and mortality, accounting for the semi-competing nature of the two outcomes. A multi-state model to predict HF hospitalization and all-cause mortality was derived using data from the Heart Failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study cohort, a multicenter, randomized trial of 3,834 symptomatic patients with reduced left ventricular ejection fraction. The following predictors were pre-specified for model inclusion: age, gender, New York Heart Association class III vs II, left ventricular ejection fraction, serum creatinine, serum sodium, systolic blood pressure, weight, history of diabetes mellitus, ischemic heart disease, atrial fibrillation, peripheral vascular disease or prior stroke. In this model, all patients were in the initial state of prevalent HF and were at risk for a HF hospitalization (transition 1, n=944) or death without a preceding HF hospitalization (transition 2, n=757). In addition, those who were hospitalized for HF were also at risk for death after a HF hospitalization (transition 3, n=528). To demonstrate model use, patients were grouped by quartile of predicted risk and the predicted probabilities of the patient with the median risk in each quartile were plotted over 7 years of follow-up. At one year of follow up, patient A (the patient with the median risk from the lowest risk quartile) has a 2% predicted probability of death with or without a preceding HF hospitalization and 2% probability of HF hospitalization without subsequent death. The same predicted probabilities are 11% and 12%, respectively for patient D in the highest risk quartile. This discrimination between low and high-risk patients continued throughout the 7-year duration of follow up of this cohort. Model

discrimination was 0.72 and calibration was adequate as assessed by quartiles of predicted risk.

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List of Abbreviations

HF:	Heart failure
HEAAL: Losartan	Heart failure Endpoint evaluation of Angiotensin II Antagonist
NYHA :	New York Heart Association
LVEF:	Left ventricular ejection fraction
DM:	Diabetes mellitus
IHD:	Ischemic heart disease
AF:	Atrial fibrillation
PVD:	Peripheral vascular disease
AIC:	Akaike information criterion
HR:	Hazard ratio

Introduction:

There are nearly 6 million adults living with heart failure (HF) in the United States with an estimated 670,000 new annual diagnoses(1). Due, in part, to aging of the American population, the prevalence of HF is expected to increase by upwards of 25% over the next 20 years(1). Although pharmacologic and device therapies have improved the survival and quality of life for many patients with HF, the median survival after a HF diagnosis remains only 3-5 years (2, 3), and hospitalizations and re-hospitalizations are common(4, 5). Discriminating between high and low risk ambulatory patients with HF can improve care by preventing delays in appropriate treatment for high-risk patients including referral for consideration of advanced therapies or palliative care. In addition, prediction models can help direct costly disease management services to high-risk patients, select patients for clinical trials, and risk-adjust patient populations for quality improvement efforts.

Heart failure is the most common cause of hospitalization in patients 65 and older and, aside from hospitalizations for labor and delivery, is the most common cause of hospitalization in all adults(34). Total direct and indirect costs related to heart failure in the United States were 39.2 billion in 2010 with more than 75% of these costs due to hospitalizations(1). Disease management programs have been shown to reduce hospitalizations and improve survival(35, 36). As disease management programs cost money to implement it may be wise to direct resources to patients at highest risk of hospitalization and death. While current disease management programs mostly focus on patients recently hospitalized for heart failure, there may be significant opportunity to enroll outpatients with heart failure who have elevated predicted risk of hospitalization or mortality.

Currently available prediction models in ambulatory patients with HF either focus on mortality alone (6-22), a composite of death or hospitalization, but not each endpoint individually(11, 19) or HF hospitalization alone(23). Most ambulatory HF models have not been externally validated(9, 11-22) or contain variables that are not routinely collected in clinical practice (6-8, 13, 14, 16-18, 20, 22). Several models have been developed using cohorts of patients with end-stage HF either with New York Heart Association IIIb-IV symptoms(7) or in patients referred for heart transplant evaluation(6) and thus may not pertain to patients with less severe symptoms. In addition, many models were derived in patient cohorts enrolled more than 20 years ago when evidence based treatment for HF did not include routine beta-blockers, aldosterone antagonists or implantable cardioverters-defibrillators (ICDs) (6, 7, 12, 13, 15, 16). Models developed from more contemporary patient cohorts undergoing ICD implantation included patients that did not have a history of HF (9, 10) or were restricted to the Medicare population(10).

Recently, statistical software(24) and analytic approaches(24, 25) have made it feasible to construct multi-state prediction models of semi-competing risks, such as HF hospitalization and death. Unlike other models of HF hospitalization (23) that failed to account for the competing risk of death, and thus may be predisposed to biased estimates due to informative censoring, multistate models allow for unbiased estimates of each outcome separately or as a composite(25). Thus, we developed a multi-state model employing easily and reliably obtainable demographic and clinical variables for purposes of predicting HF hospitalization and all-cause mortality in outpatients with symptomatic HF with reduced ejection fraction, based on a population receiving current evidence-based care.

Methods:

Model Derivation Cohort: The prediction model was developed from the Heart Failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study cohort (26). HEAAL was an international, multicenter, randomized trial of low dose (50mg) versus high dose (150mg) losartan in stable outpatients with HF with reduced ejection fraction. The study methods and population characteristics have been described previously(26, 27). To be enrolled in the trial, participants had to have New York Heart Association (NYHA) Class II-IV HF with left ventricular ejection fraction (LVEF) <40%, be on stable cardiovascular therapy for at least 2 weeks at the time of enrollment and be intolerant to angiotensin-converting enzyme inhibitor therapy. The complete list of inclusion and exclusion criteria has been published previously(27). Participants were enrolled from 55 sites in 30 countries and 5 geographical regions including Western Europe, Eastern Europe, the Middle East and Africa, Asia and the Pacific Region, and Latin America. Enrollment took place between November, 2001 and March, 2005. Participants were randomized on a 1:1 basis to the receipt of either 50mg or 150mg of losartan and followed for a median of 4.7 years with the study ending on March, 2009. The study was approved by the institutional review board at each site and all patients provided written informed consent.

Outcomes: HF hospitalization and all-cause mortality were selected as the primary outcomes of interest for the prediction model. The HEAAL study captured all hospitalizations and cause of death for all study participants throughout the duration of follow up. All mortality and hospitalization endpoints were adjudicated by an Endpoint Classification Committee. A HF hospitalization was defined as "an overnight stay to any health-care facility with the primary cause being treatment of worsening heart failure and during which an additional diuretic drug, intravenous or oral nitrate, or intravenous

inotropic agent was given"(26). The current analysis was restricted to the patient's first HF hospitalization after enrollment.

Predictors: Candidate predictor variables were selected *a priori* based upon 3 characteristics. First, the predictor variable must have been consistently associated with HF hospitalization or mortality in prior studies. Second, binary predictors could not be rare (<5%). Lastly, predictors were only selected if, by a consensus of the investigators, it was believed they could be reliably assessed with little inter-observer variability in routine clinical practice and are routinely collected in a stable heart failure population. The following variables, which were collected at the time of enrollment, were included in the multi-state model: age, gender, NYHA class (binary outcome III vs II), LVEF as assessed by echocardiogram (%), serum creatinine (mg/dl) and serum sodium (mEq/L), systolic blood pressure (SBP) (mmHg), weight (kg), history of diabetes (DM), ischemic heart disease (IHD), atrial fibrillation (AF), peripheral vascular disease (PVD) or prior stroke..

Sample Size: There were three total transitions in the model. As described above, predictor variables were selected based upon clinical reasoning. We did not use any data-driven variable selection procedures and ensured that there were more than 20 events per degree of freedom per transition to achieve model parsimony and prevent model overfitting.

Missing Data: Since there were few missing data (<1%), a complete case analysis was used.

Multi-state model: Since HF hospitalization and death are semi-competing risks in that death prevents a subsequent HF hospitalization but death can still occur after a HF hospitalization, an illness-death, acyclic, multi-state model was used(24, 25). In this model, all participants are in the initial state of prevalent HF and are at risk of a HF hospitalization (transition 1) or death without a preceding HF hospitalization (transition 2). In addition, those who were hospitalized for HF are also at risk for death after a HF hospitalization (transition 3). To demonstrate model use, patients were grouped by quartile of predicted risk and the predicted probabilities of the patient with the median risk in each quartile were calculated and plotted.

Effect of HF hospitalization on risk of death: The baseline hazards of transitions 2 and 3 (into the same state, death) were assessed graphically for proportionality. If the proportionality assumption was met, then a proportional hazards multi-state model was used in which transition 1 has a separate baseline hazard and transitions 2 and 3 have proportional baseline hazards. A proportional hazards multi-state model provides an estimate of the effect of HF hospitalization on the risk of death – acting as both an outcome variable and a time-dependent covariate. The effect of a HF hospitalization on the risk of dying was analyzed in an unadjusted model, a full model with transition specific covariates and a simplified model with all 13 covariates but without transition-specific estimates.

Statistical analysis:

A semi-parametric, Cox proportional hazards regression model was used in which each of the three transitions were entered as strata with a different non-parametric baseline hazard and with transitions into the same disease state modeled as having proportional baseline hazards(24). In this type of model, coefficients for predictors can be modeled as

either transition-specific with a different effect estimate allowed for each of the three transitions or with an identical effect estimate for all transitions. For each of the 13 predictors, univariate multistate models were used to compare the model fit with transition-specific coefficients versus identical coefficients for each transition and decisions of whether to include transition-specific coefficients were made by likelihood-ratio testing and comparison of the Akaike information criterion (AIC). No data-driven variable selection procedures were used. Linearity assumptions were assessed for all continuous variables and appropriate transformations performed as necessary. The proportional hazards assumptions were evaluated using log(-log(Survival)) plots and Schoenfeld residuals. Discrimination was assessed by concordance, a variation on the c-statistic for time-to-event data with censoring. Concordance in time to event analyses refers probability that a patient with a shorter survival time also had a higher predicted probability of the event than a patient with a longer survival time, factoring in ties and non-comparable pairs due to censoring and is calculated as part of the survival package in R. Calibration was assessed by plotting the cumulative incidence for each transition by quartiles of predicted risk. Internal validation was performed by creating 200 bootstrap samples from the original dataset, re-estimating the model coefficients in each bootstrap sample and applying the bootstrapped model coefficients to the original dataset. Optimism of the concordance was calculated as the difference between the concordance of the 200 bootstrap samples and the concordance of the original sample. Optimism-corrected concordance was calculated as the concordance in the original sample minus the optimism. All analyses were performed using R version 3.0.2 and the mstate and survival packages for multistate modeling.

Results:

Study Population: There were a total of 3834 participants enrolled in the HEAAL trial between 2001 and 2005. There was a high use of beta-blockers (72%) and moderately high use of aldosterone antagonists (38%) in this population. Baseline characteristics of the study population stratified by the two outcomes of interest, HF hospitalization and death, are shown in Table 1.

Table One: Baseline characteristics of the derivation cohort stratified by the two outcomes of interest

Variable	**Death endpoint**		**HF hospitalization endpoint**	
	Died [n=1285]	Alive [n=2524]	HF hospitalization (+) [n=944]	No HF hospitalization (-) [n=2865]
Age,yrs (mean±SD) [n=3809]	66.9 ± 11.7	62.9 ± 11.5	65.4 ± 11.6	63.8 ± 11.7
Female gender: n(%) [n=3809]	329 (25.6%)	807 (32.0%)	247 (26.2%)	889 (31.0%)
NYHA Class III n(%) [n=3808]	514 (40.0%)	638 (25.3%)	372 (39.4%)	780 (27.2%)
LVEF, % (median, IQR) [n=3808]	31 (25-35)	34 (29-37)	30 (25-35)	34 (28-37)
Serum creatinine, mg/dl (mean±SD) [n=3792]	1.2 ± 0.4	1.1 ± 0.3	1.2 ± 0.4	1.1 ± 0.3
Serum sodium, mEq/L (mean±SD) [n=3793]	139.9 ± 3.4	140.4 ± 3.6	139.8 ± 3.4	140.4 ± 3.5
Systolic blood pressure, mmHg (mean±SD) [n=3808]	124.2 ± 18.6	127.3 ± 18.0	123.1 ± 18.9	127.3 ± 17.9
Weight, kg (mean±SD) [n=3804]	73.4 ± 16.3	77.7 ± 17.0	74.9 ± 16.2	76.7 ± 17.1
Diabetes n(%)	497	691	354	834

[n=3809]	(38.7%)	(27.4%)	(37.5%)	(29.1%)
Ischemic etiology n(%) [n=3809]	880 (68.5%)	1558 (61.8%)	588 (62.3%)	1850 (64.6%)
Atrial fibrillation n(%) [n=3809]	424 (33.0%)	640 (25.4%)	311 (32.9%)	753 (26.3%)
Peripheral vascular disease n(%) [n=3809]	184 (14.3%)	179 (7.1%)	100 (10.6%)	263 (9.2%)
Prior stroke n(%) [n=3809]	150 (11.7%)	152 (6.0%)	94 (10.0%)	208 (7.3%)
Beta-blockers n(%) [n=3809]	811 (63.1%)	1928 (76.4%)	647 (68.5%)	2092 (73.0%)
Aldosterone antagonist n(%) [n=3809]	535 (41.6%)	887 (35.1%)	432 (45.8%)	990 (34.6%)

HF refers to heart failure, LVEF left ventricular ejection fraction, NYHA New York Heart Association

In general, the direction of association of the 13 predictors of interest were similar for the two outcomes – patients with a HF hospitalization or who died were older, more likely to be male, have a higher NYHA class, a history of DM, AF, prior stroke, or PVD than those without a HF hospitalization or death. In addition, patients with a HF hospitalization or who died had a lower LVEF, lower systolic blood pressure (SBP), lower weight, lower serum sodium levels and higher serum creatinine levels than those without a HF hospitalization or death. Patients who died were more likely to have ischemic etiology but there was no association between ischemic etiology and risk for HF hospitalization.

Missing Data: Of the predictors of interest, there were few missing data (24 total participants missing data for one or more covariates, 0.6% of the population). There were no missing data for age, gender, DM, IHD, AF or prior stoke (Table 1). There was

one missing value each for LVEF and NYHA Class, 5 missing values for weight and 16 missing values for sodium and 17 missing values for creatinine (16 of these were also missing for sodium). A total of 95 patients were lost to follow up during the study (2.5%), and thus censored at the time of last known follow up and included in this analysis.

Model development cohort: Given the small number of New York Heart Association (NYHA) Class IV participants (0.5% of the total population), these participants were excluded as predictions were unlikely to be accurate for such a small population. In addition, while the HEAAL study inclusion criteria required the presence of NYHA II-IV HF, there were 2 additional participants with NYHA Class I HF who were also excluded and one patient with missing information on NYHA Class, leaving a total of 3,809 participants (Figure 1). Of the remaining predictors of interest there were 23 missing values (0.6% of the population). A complete case analysis was used, leaving 3,786 participants with data for model development. The final cohort for model development had 944 participants who were hospitalized at least once, 757 deaths without a HF hospitalization, and 528 deaths at any time after HF hospitalization.

Figure One: Flow diagram of model development cohort selection and illness-death multistate model transitions

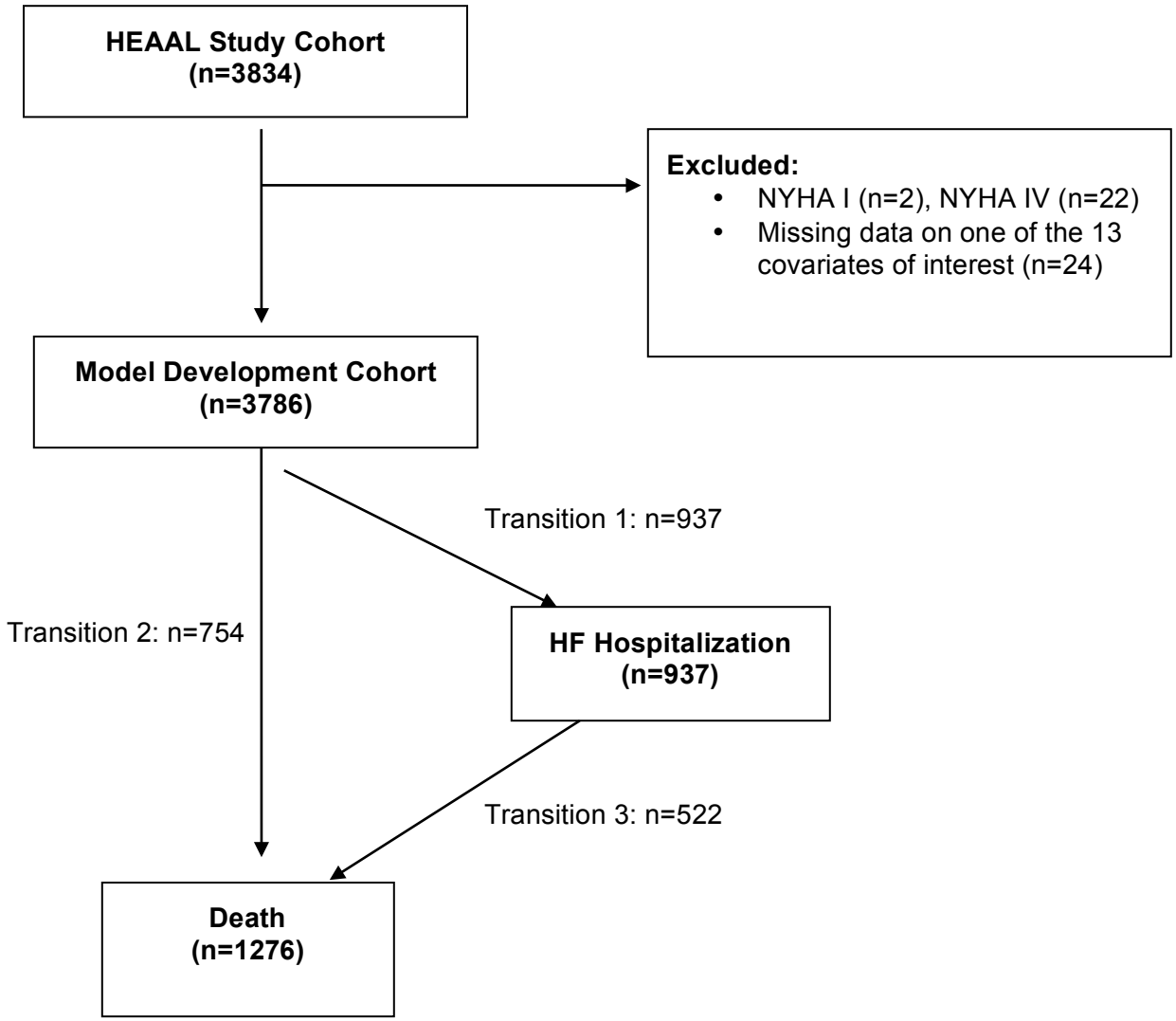

Figure 1: Selection of model development cohort and the number of participants with each of the illness-death multistate model transitions. HEAAL, Heart Failure Endpoint evaluation of Angiotensin II Antagonist Losartan; NYHA, New York Heart Association; HF, heart failure

Model development and specification: Of the 13 predictors, transition-specific covariates were associated with lower model AIC and better model fit by likelihood ratio testing for all covariates except serum sodium. The proportional hazards assumption

was met for all 13 covariates. For all 6 continuous variables a linear association appeared reasonable based on lowess curves and was associated with better model fit than piecewise linear or other transformations in univariate multistate analysis. The multivariate effects of the 13 predictors for the three transitions are shown in Table 2.

Table Two: Transitional hazard ratios for multi-state prediction model:

Predictor	T1: Prevalent HF to HF hospitalization		T2: Prevalent HF to Death		T3: HF hospitalization to Death	
	HR	95% CI	HR	95% CI	HR	95% CI
Age per 10 year increase	1.09	1.02-1.16	1.22	1.13-1.32	1.09	1.00-1.19
Female gender	0.81	0.69-0.96	0.69	0.57-0.83	0.93	0.75-1.17
NYHA III vs II	1.62	1.41-1.85	1.41	1.21-1.64	1.38	1.16-1.65
LVEF per 10% increase	0.73	0.66-0.80	0.76	0.68-0.85	0.88	0.77-1.01
Creatinine per 1mg/dl increase	2.22	1.83-2.68	1.62	1.30-2.01	1.78	1.39-2.29
Sodium (per 10mEQ/L increase)	0.77	0.68-0.88	0.77	0.68-0.88	0.77	0.68-0.88
Systolic Blood Pressure per 10mmHg increase	0.91	0.87-0.94	0.98	0.94-1.02	0.94	0.89-0.99
Weight per 10kg increase	0.92	0.88-0.96	0.86	0.82-0.91	0.84	0.79-0.90
Diabetes mellitus	1.50	1.30-1.72	1.47	1.26-1.71	1.13	0.94-1.36
Ischemic etiology	0.90	0.78-1.03	1.15	0.97-1.35	1.13	0.93-1.37
Atrial fibrillation	1.21	1.05-1.40	1.28	1.09-1.50	0.89	0.73-1.08
Peripheral vascular disease	1.03	0.83-1.28	1.45	1.18-1.78	1.52	1.17-1.98
Prior stroke	1.28	1.03-1.60	1.52	1.22-1.89	1.16	0.87-1.53

HR indicates hazard ratio, CI confidence interval, HF heart failure, NYHA New York Heart Association, LVEF left ventricular ejection fraction

NYHA Class, sodium, SBP and weight had similar effects on all three transitions in multivariate analysis with higher NYHA Class increasing the risk and higher sodium, SBP and weight decreasing the risk for all three transitions. For the majority of predictors, there was a similar effect of the predictor on the risk of transition 1 (HF

hospitalization) and transition 2 (Death) with an attenuated effect of the predictor on the risk of transition 3 (Death after HF hospitalization). Higher LVEF values significantly decreased the risk of transitions 1 and 2 with a similar yet attenuated and non-significant trend for transition 3. Similar findings were seen with age, diabetes and prior stroke. Male gender and a history of AF both increased the risk of transitions 1 and 2 but there was no effect on transition 3. Peripheral vascular disease and ischemic etiology increased the risk of death (transitions 2 and 3) with no effect on HF hospitalization risk (transition 1). The full model is available in the supplemental materials.

Risk prediction: The baseline characteristics of the patient with median risk from each quartile of predicted risk for transition two are shown in Table 3 with the predicted probability of being in each outcome state over 7 years of follow up shown in Figure 2. In addition, the predicted probability of being in each of the four possible states (alive without HF hospitalization, alive having experienced a HF hospitalization, death having experienced a HF hospitalization, death without HF hospitalization) are listed in Table 3 for the four patients at 1, 3 and 6 years of follow up. As can be seen, the probability of transitioning to these different clinical states varied tremendously in these typical patients. At one year of follow up, patient A (the patient with the median risk from the lowest risk quartile) has a 2% predicted probability of death with or without a preceding HF hospitalization and 2% probability of HF hospitalization without subsequent death. The same predicted probabilities are 11% and 12%, respectively for patient D in the highest risk quartile. After six years of follow up, patient A has a 16% predicted probability of death either with or without a preceding HF hospitalization and a 5% probability HF hospitalization without subsequent death. The same probabilities for patient D at six years are 67% and 9%, respectively. In addition, composite outcomes can be obtained from the predicted probabilities directly. For patient A, the predicted

probability of being alive with or without a HF hospitalization (state 1 or state 2) at 1 year is 98% and the risk of HF hospitalization or death (states 2 and 4) is 4% at 1 year. For patient D the predicted probability of being alive with or without HF hospitalization (state 1 or 2) is 90% and HF hospitalization or death (state 2 or 4) is 20% at 1 year.

Table 3: Baseline characteristics and predicted outcomes of the patient with median risk from each quartile of predicted risk of transition two

		Patient A (Q1)	Patient B (Q2)	Patient C (Q3)	Patient D (Q4)
Age (yrs)		73	53	64	63
Gender (M/F)		F	M	M	M
NYHA Class (II or III)		II	II	II	III
LVEF (%)		40	29	35	32
Creatinine (mg/dl)		0.9	0.9	1.7	1.3
Serum sodium (mEq/L)		143	142	145	138
Systolic blood pressure (mmHg)		164	120	135	100
Weight (kg)		65	57	77	63
Diabetes (Y/N)		-	-	+	-
Ischemic etiology (Y/N)		+	+	+	+
Atrial fibrillation (Y/N)		-	-	-	+
Peripheral vascular disease (Y/N)		-	-	-	-
Prior stroke (Y/N)		-	-	-	-
1 yr probabilities of being in a given outcome state	Alive without HFH	96.0%	91.9%	87.4%	77.1%
	HFH, still alive	1.8%	4.2%	6.8%	11.8%
	Death without HFH	2.1%	3.3%	4.8%	7.9%
	HFH followed by death	0.1%	0.6%	1.0%	3.2%
3 yr probabilities of being in a given outcome state	Alive without HFH	88.8%	78.6%	68.2%	48.2%
	HFH, still alive	3.8%	7.9%	11.9%	15.3%
	Death without HFH	6.4%	9.8%	13.7%	20.1%
	HFH followed by death	1.0%	3.7%	6.1%	16.4%
6 yr probabilities of being in a given	Alive without HFH	78.7%	62.0%	46.9%	23.8%
	HFH,	5.1%	10.8%	11.6%	9.2%

outcome state	still alive				
	Death without HFH	12.8%	18.7%	24.4%	31.3%
	HFH followed by death	3.4%	10.8%	17.1%	35.7%

Q1 refers to quartile 1 (lowest risk), Q2 quartile 2, Q3 quartile 3, Q4 quartile 4 (highest risk), M male, F female, NYHA New York Heart Association, LVEF left ventricular ejection fraction, HFH heart failure hospitalization, (+) refers to present and (-) refers to absent at baseline

Figure 2: Prediction probabilities for the patient with median risk from each quartile of predicted risk of transition two

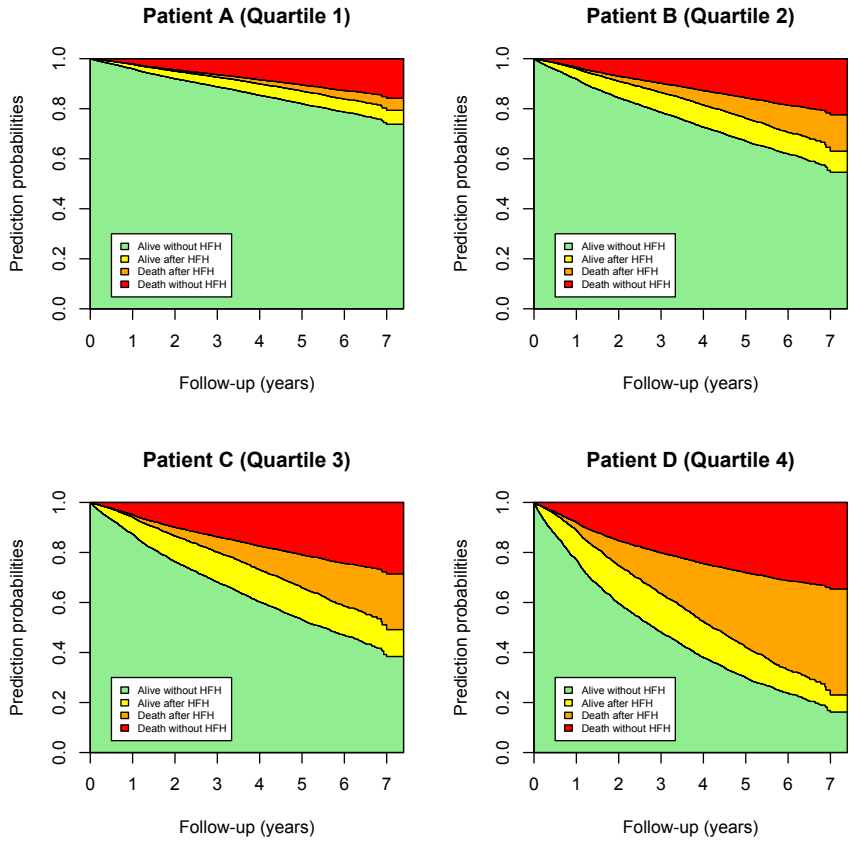

Figure 2: Prediction probabilities for the patient with the median risk from each quartile of risk for transition 2. The development cohort was divided into quartiles of predicted risk for transition 2 (from prevalent heart failure to death). The median patient from each quartile was selected and the predicted probabilities of being alive without heart failure hospitalization, alive after heart failure hospitalization, dead after heart failure hospitalization and dead without heart failure hospitalization are shown. Patient A is the median risk patient in quartile 1 (lowest risk), patient B quartile 2, patient C quartile 3 and patient D quartile 4 (highest risk).

Effect of HF hospitalization on risk of death: In an unadjusted model without other covariates, there was a 5.9-fold higher hazard of death after a HF hospitalization as compared to patients who were not hospitalized for HF (HR=5.9, 95% CI 5.2-6.6). In the full final prediction model, the effect of a HF hospitalization on the risk of death remained clinically substantial and statistically significant (HR=14.1, 95% CI 4.3-45.7). In a sensitivity analysis, a simplified model with all 13 covariates but without transition specific coefficients resulted in more precise estimates (HR 4.4, 95% CI 3.9-4.9).

Model performance: Concordance was 0.72 for the entire model. Dividing the cohort into quartiles of predicted risk and plotting the cumulative incidence of each state revealed a separation of risk of HF hospitalization and death (Figure 3). Patients in the lowest risk quartile had a 1-, 2- and 5-year risk of death of 0.9%, 2.0% and 5.2% respectively and patients in the highest risk quartile had a 1-,2- and 5 year risk of dying of 11.5%, 25.0% and 55%.

Internal validation and optimism-corrected performance: The optimism-corrected concordance from re-estimating the model parameters on 200 bootstrap samples and reapplying these to the original dataset was 0.72

Figure 3: Observed cumulative incidence of being in a given health state by quartiles of predicted risk

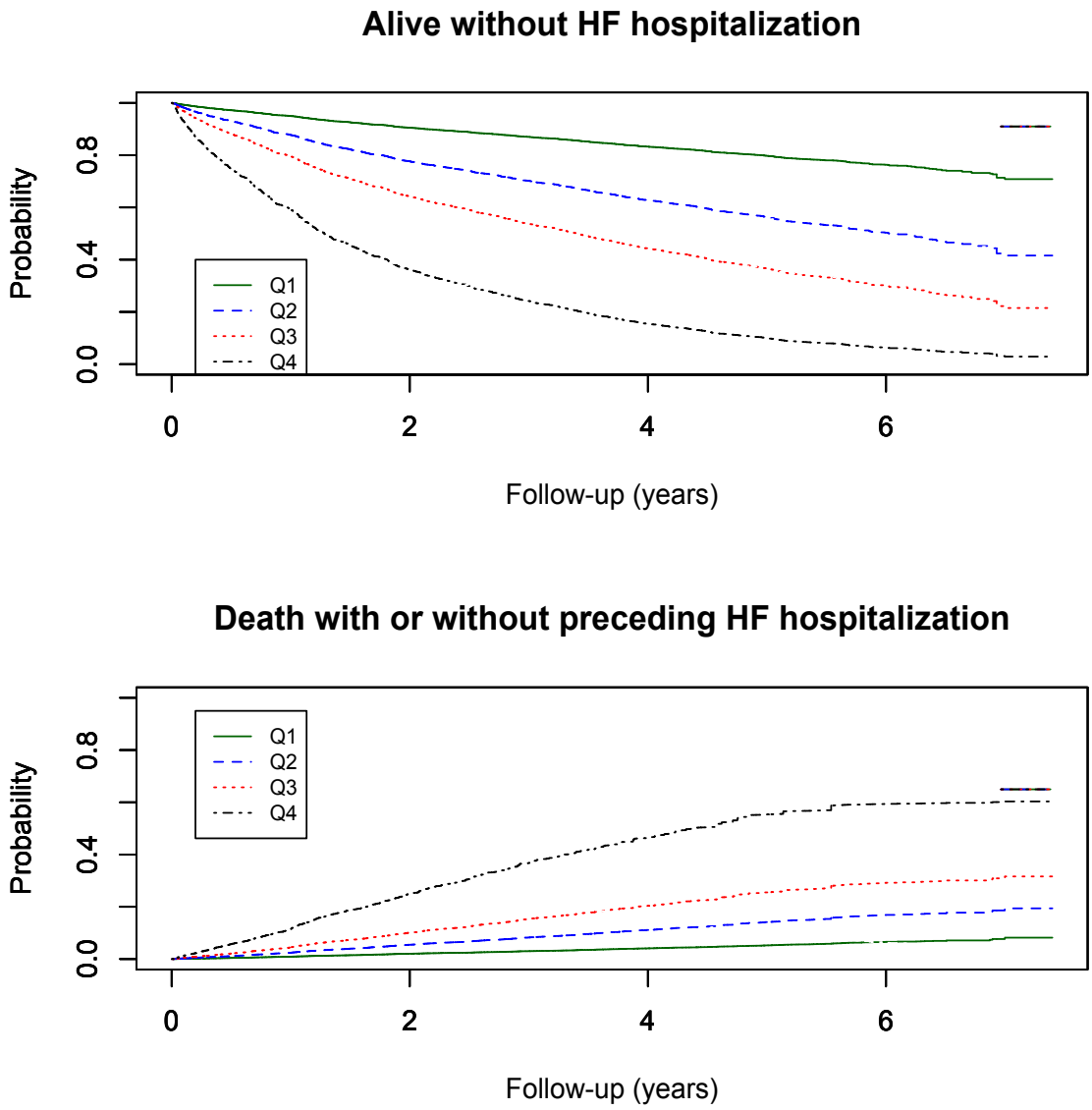

Figure 3: Observed cumulative incidence of being in each health state by quartiles of predicted risk. Quartile 1 (Q1) refers to the lowest risk quartile and quartile 4 (Q4) refers to the highest risk quartile. HFH refers to heart failure hospitalization. Patients were divided into quartiles of predicted risk and the cumulative incidence of being in each health state was plotted. Cumulative incidence curves are similar to survival curves but account for semi-competing or competing risks.

Discussion:

We describe the first multistate model for risk prediction in ambulatory patients with HF. Using routinely collected demographic, clinical, and laboratory information, we have developed a model that can predict HF hospitalization, all-cause death or the composite of HF hospitalization or death over 7 years of follow-up. We found wide variation in risk with the lowest risk quartile having an excellent 1-year prognosis with low risk of HF hospitalization or death (2% each), while the highest risk quartile had much higher event rates at 1 year (12% and 11%, respectively). This discrimination between low and high-risk patients continued throughout the 7 year duration of follow up of this cohort. The concordance of the overall model was 0.72 consistent with good discrimination and is in the range of most published predictive models for HF outcomes.

While there are several published models to predict HF readmission in patients admitted with acute HF, there is only one published model to predict HF hospitalization in ambulatory patients with HF and reduced ejection fraction(23). This model did not include the competing risk of death thus predisposing to biased risk estimates due to informative censoring(25). In contrast, multistate models such as the one described here account for transition states, such as HF hospitalization, and absorbing states, such as death, and allow for valid predictions in the presence of semi-competing risks(25). This report demonstrates the utility and feasibility of using multistate models to improve prediction of semi-competing events and to gain additional insight into factors that modify risk of outcomes in patients with HF.

An advantage of using a multistate modeling approach is the ability to examine the effect of predictor variables on each of the individual component outcomes. This study demonstrates the similar effect of many predictors on the outcomes of HF hospitalization

and all-cause mortality with an attenuated effect of these predictors on subsequent risk of death after HF hospitalization. The attenuated effect of known predictors of death in HF on transition 3 may be related to index event bias, whereby conditioning on a first event dilutes the effect of shared risk factors on related subsequent events—since all patients who experience hospitalization are by definition at higher risk (28). Effect modification or bias related to the fact that all predictors were measured at baseline may also contribute to the attenuated effect of some predictors on the risk of death after HF hospitalization. Notably, this effect is not apparent for NYHA Class, sodium, SBP and weight, in which similar effects were seen for all three transitions. Finally, ischemic etiology and peripheral vascular disease were the only predictors that were found to be important for death (transitions 2 and 3) but not for HF hospitalization (transition 1) in the multistate model.

Another benefit to using a multistate model is that the effect of a transition state, such as HF hospitalization, on the subsequent cumulative hazard of death can be analyzed. Similar to prior studies that showed a higher risk of death after a HF hospitalization(29, 30), we found that HF hospitalization was an extremely powerful predictor of subsequent risk of death.

Recent meta-analyses(31-33) have identified 15-20 published models for the prediction of mortality in ambulatory patients with HF, 4 of which have been externally validated(6-8, 10). Some of these models have limited applicability because they include variables that are not routinely collected in the general HF population such as cardiopulmonary exercise stress testing(6, 14, 16, 22), six minute walk testing(8), magnetic resonance imaging(17) or difficult to obtain laboratory tests such as measures of cytokine levels(20, 22). Several models(7, 11) have more than 20 variables, which may be burdensome to

calculate in clinical practice. In addition, some models include variables without precise definitions or with considerable inter-observer variability in routine clinical practice such as physical exam findings(11, 12) or the appearance of left ventricular hypertrophy on electrocardiogram(13). More recently reported models were developed in populations of patients undergoing ICD(9, 10) implantation and included patients without HF. Many models(6, 7, 12, 13, 15, 16) were developed in cohorts that were not treated with current evidence-based therapy such as beta-blockers, aldosterone antagonists, ICD or CRTs, which may lead to poor performance in current practice. In contrast, we developed this model in a cohort of patients with high rates of beta-blocker and aldosterone antagonist therapy and only used variables that are routinely collected and reliably assessed in clinical practice.

We anticipate that this model will be useful to identify patients who are at high risk for a HF hospitalization, who may benefit from more frequent clinic visits, disease management services or aggressive titration of neurohormonal therapy. In addition, patients with an elevated predicted risk for mortality over the next one to two years may benefit from referral to a transplant center in addition to the above interventions. This model can also be used to select patients for inclusion or explore heterogeneity of treatment effect in clinical trials, allowing for a better estimation of a target event rate of the composite of HF hospitalization or death or a comparison of the effect of an intervention in high versus low risk patients. Finally, this model can be used for risk adjustment for hospitals or providers to identify areas for quality improvement.

Study Strengths and Limitations: Compared with many existing models, the HEAAL study population had higher rates of beta-blocker, aldosterone antagonist and ICD use. There were sufficient events to avoid the problem of overfitting and there was

standardized collection of baseline clinical characteristic and prospective adjudicated recording of mortality and HF hospitalization endpoints. Finally, the multi-state model allows for valid and non-biased modeling of semi-competing risk data. On the other hand, there were several limitations that must be kept in mind when interpreting our study results. Participants in the HEAAL study were enrolled between 2001 and 2005 before the Emphasis-HF study (published in 2010) showed benefit of aldosterone antagonists in NYHA Class II HF. The HEAAL study was conducted in 30 countries but there were no North American sites, possibly affecting generalizability to the US population. This model was developed in a population with mild to moderate HF symptoms (NYHA Class II-III) and should not be applied to NYHA Class I or IV symptoms or those with a reduced ejection fraction without HF or patients with HF with preserved LVEF. Finally, some potentially important predictor variables were not collected such as natriuretic peptide levels, baseline diuretic dose and prior HF hospitalization data.

In conclusion, using well-established and routinely available predictors, we have developed a multi-state model for the prediction of HF hospitalization and death in patients with HF with reduced ejection fraction. This model can be used to generate valid predictions of HF hospitalization alone, the composite of HF hospitalization and death or death alone. This model will need to be externally validated in additional patient cohorts prior to widespread dissemination and use.

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