ORIGINAL RESEARCH

Diuretic Dose and NYHA Functional Class Are Independent Predictors of Mortality in Patients With Transthyretin Cardiac Amyloidosis

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ABSTRACT

BACKGROUND With increasing diagnoses and available treatment options for transthyretin amyloidosis cardiomyopathy (ATTR-CM), risk stratification of ATTR-CM patients is imperative.

OBJECTIVES We hypothesized that diuretic dose and New York Heart Association (NYHA) functional class are independent predictors of mortality in ATTR-CM and would be incrementally additive to existent risk scores.

METHODS Consecutive ATTR-CM patients referred to a single center were identified. Adjusted Cox proportional hazards models determined the association between diuretic dose (furosemide equivalent in mg/kg) at time of diagnosis and the primary outcome of all-cause mortality. The incremental value of adding diuretic dose and NYHA functional class to existing ATTR-CM risk scores was assessed for discrimination and calibration.

RESULTS 309 patients were identified, with mean age 73.2 ± 9.8 years, 84.1% male, and 66% wild type. Daily mean diuretic dose was 0.6 ± 1.0 mg/kg and significantly associated with all-cause mortality (unadjusted hazard ratio: 2.12 per 1-mg/kg increase, [95% confidence interval: 1.71 to 2.61] and fully adjusted hazard ratio: 1.43 [95% confidence interval: 1.06 to 1.93]). Testing previously published ATTR risk scores, adding diuretic dose as categories (0 mg/kg, >0 to 0.5 mg/kg, >0.5 to 1 mg/kg, and >1 to 2 mg/kg) improved the area under the curve of the Mayo risk score from 0.693 to 0.767 and the UK risk score from 0.711 to 0.787 while preserving calibration. Adding NYHA functional class further improved the area under the curve to 0.798 and 0.816, respectively.

CONCLUSIONS Diuretic dose and NYHA functional class are independent predictors of mortality in ATTR-CM patients and provide incremental value to existing ATTR-CM risk scores. (J Am Coll Cardiol CardioOnc 2020;2:414–24) © 2020 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/).

Transthyretin amyloid cardiomyopathy (ATTR-CM) is being increasingly diagnosed, secondary to growing clinical recognition, the emergence of noninvasive methods to confirm ATTR-CM such as nuclear scintigraphy, and the availability of treatment with transthyretin tetramer stabilizers ([1]). The ability to accurately risk stratify these patients is essential for guiding clinical care and treatment options.

There are 2 commonly used risk models for the ATTR-CM population. The Mayo risk model includes the cardiac biomarkers N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin-T, stratifying wild-type ATTR-CM (wtATTR) patients into 3 stages ([2]). The UK risk model includes both wtATTR and hereditary ATTR-CM (hATTR) patients, and uses NT-proBNP and estimated glomerular filtration rate (eGFR) ([3]). However, neither model incorporates well-established, easily obtained predictors of outcomes in heart failure (HF), including diuretic dose ([4-7]) and New York Heart Association (NYHA) functional class. Further, the Seattle Heart Failure Model (SHFM) ([7]) is another widely used risk score that has been validated in other HF cohorts but has not been tested in ATTR-CM.

We hypothesized that diuretic dose and NYHA functional class would be robust predictors of mortality in ATTR-CM. We thus sought to define the associations of diuretic dose and NYHA functional class with all-cause mortality in ATTR-CM and assess whether diuretic dose and NYHA functional class are additive to the existing Mayo and UK ATTR-CM risk models. We applied the SHFM to this cohort to both test and compare its ability to predict risk in ATTR-CM patients.

METHODS

Consecutive ATTR-CM patients referred to a single, quaternary care center (Columbia University, New York, New York) between February 2002 and November 2018 were enrolled in a registry. All patients over 18 years of age with either wtATTR or hereditary hATTR were included. Approval for the study was obtained from the Columbia University Irving Medical Center Institutional Review Board. Demographics, clinical characteristics, and laboratory data including diuretic dose and NYHA functional class assessment were obtained at the baseline clinical visit. Patients were followed over time. Outcomes, including death and cardiac transplantation, were adjudicated manually from chart review. The current study is a retrospective cohort analysis of these previously collected data. The date of data lock was August 1, 2019.

Daily loop diuretic dose was converted to furosemide equivalence normalized by body weight, with standard conversion factors of bumetanide 1 mg oral = torsemide 20 mg oral = furosemide 40 mg oral and divided by weight (in kilogram). Diuretic dose was treated as a continuous variable and also categorized into furosemide equivalent dosages of 0, >0 to 0.5, >0.5 to 1, and >1 mg/kg for comparison in risk models and for ease of interpretation. For diuretic dosing in the risk models, and to facilitate comparisons with the Mayo and UK models, 0 points were assigned for 0 mg/kg, 1 point for >0 to 0.5 mg/kg, 2 points for >0.5 to 1 mg/kg, and 3 points for >1 mg/kg. NYHA functional class was obtained using the standard convention and assigned 1 point per NYHA functional class, respectively, ranging from 1 to 4 points.

Current ATTR-CM risk stratification models are from the Mayo Clinic ([2]) and the UK data ([3]). The Mayo classification identified elevated NT-proBNP >3,000 pg/ml and troponin-T >0.05 ng/ml as risk factors. The UK classification used an elevated NT-proBNP >3,000 pg/ml and decreased eGFR <45 ml/min/1.73 m². As our patients had a combination of BNP and NT-proBNP at baseline, we estimated a BNP cutoff >600 pg/ml to correspond to NT-proBNP >3,000 pg/ml (on the basis of a commonly used 5- to 6-fold estimated conversion in clinical settings) ([8]). Similarly, there was a combination of troponin-T and troponin-I assays at baseline. We chose a troponin-I cutoff of >0.1 ng/ml to correspond to troponin-T >0.05 ng/ml; this was based on the Boston University analysis on light chain amyloid patients for equivalence between troponin-I and troponin-T ([9]). All patients had eGFR estimates at baseline. For the Mayo risk score, patients were assigned 1 point for either elevated NT-proBNP or BNP and 1 point for elevated troponin-T or troponin-I, for a range of 0 to 2 points. For the UK risk score, patients were assigned 1 point for either elevated NT-proBNP or BNP and 1 point for eGFR <45 ml/min/1.73 m², for a range of 0 to 2 points.

We additionally evaluated the SHFM model to provide a separate comparator with a well-established risk tool used in other HF cohorts. SHFM includes age, sex, ejection fraction, systolic blood pressure, weight, NYHA functional class, etiology, medications (diuretic dose, allopurinol, statins,

TABLE 1   Baseline Characteristics by Diuretic Dose

		Diuretic Dose			
	Total (N = 309)	0 mg/kg (n = 92)	>0 to 0.5 mg/kg (n = 95)	>0.5 to 1 mg/kg (n = 70)	>1 mg/kg (n = 52)
Age, yrs*	73.2 ± 9.8	70.1 ± 12.2	75.1 ± 7.1	74.2 ± 9.2	74.1 ± 8.7
Male *	84.1	77.2	92.6	81.4	84.6
Race*					
White	72.5	79.3	80.0	60.0	63.5
Black	23.6	18.5	16.8	31.4	34.6
Other	3.9	2.2	3.2	8.6	1.9
ATTR type*					
Wild-type	66.0	56.5	84.2	61.4	55.8
Hereditary	34.0	43.5	15.8	38.6	44.2
Height, cm*	172.9 ± 8.9	171.6 ± 9.1	176.0 ± 8.1	171.5 ± 9.2	171.5 ± 8.2
Weight, kg*	78.8 ± 13.7	76.1 ± 14.3	84.4 ± 12.2	78.4 ± 14.7	73.8 ± 9.8
BMI, kg/m^2*	26.5 ± 4.7	25.7 ± 3.9	27.4 ± 4.8	27.0 ± 6.0	25.3 ± 3.6
SBP, mm Hg*	115.7 ± 16.3	122.4 ± 16.2	118.3 ± 15.9	109.5 ± 13.9	108.0 ± 14.4
DBP, mm Hg*	70.4 ± 9.7	73.7 ± 9.6	72.0 ± 10.0	68.0 ± 8.0	65.1 ± 8.4
Heart rate, beats/min	75.2 ± 13.3	74.6 ± 12.2	74.3 ± 13.7	75.9 ± 14.3	77.4 ± 13.2
NYHA functional class*					
I	9.4	27.2	4.2	0.0	0.0
II	45.3	53.3	56.8	34.3	25.0
III	41.7	17.4	37.9	64.3	61.5
IV	3.6	2.2	1.1	1.4	13.5
Prevalent atrial fibrillation/flutter*	17.2	10.7	12.1	20.9	32.7
Creatinine, mg/dl*	1.3 ± 0.5	1.1 ± 0.4	1.3 ± 0.4	1.6 ± 0.7	1.5 ± 0.6
eGFR, ml/min/1.73 m^2*	60.1 ± 22.6	73.3 ± 25.5	58.6 ± 17.5	51.2 ± 20.4	52.2 ± 18.4
BNP or NT-proBNP elevated*†	40.1	19.5	38.4	56.5	55.9
Troponin-I or troponin-T elevated*‡	37.8	15.6	35.6	55.6	57.1
LVEF, %*	45.1 ± 15.1	51.8 ± 12.8	44.3 ± 15.1	39.4 ± 15.7	42.2 ± 14.4
Lasix dose, mg/kg*	0.6 ± 1.0	0.0 ± 0.0	0.3 ± 0.1	0.7 ± 0.2	1.7 ± 0.8
SHFM score*	1.0 ± 0.8	0.6 ± 0.7	0.8 ± 0.6	1.2 ± 0.7	1.6 ± 0.8
HF GDMT					
ACE inhibitor/ARB	31.7	21.7	38.9	34.3	32.7
Beta-blocker*	49.8	38.0	57.9	51.4	53.8
MRA*	23.3	11.2	22.3	32.9	31.4

Values are mean ± SD or %. *p < 0.05 across diuretic categories. †Defined as NT-proBNP >3,000 pg/ml or BNP >600 pg/ml. ‡Defined as troponin-T >0.05 ng/ml or troponin-I >0.1 ng/ml.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ATTR = transthyretin amyloidosis; BMI = body mass index; BNP = B-type natriuretic peptide; DBP = diastolic blood pressure; eGFR = glomerular filtration rate; GDMT = guideline directed medical therapy; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure; SHFM = Seattle Heart Failure Model.

renin-angiotensin receptor blockers, beta-blockers, potassium sparing diuretics), biventricular pacing or defibrillators, and laboratory values (sodium, total cholesterol, hemoglobin, lymphocyte percentage, and uric acid) (7). The SHFM model does not include BNP or troponin.

STATISTICAL ANALYSIS. Baseline characteristics were compared between the different diuretic groups, as well as Mayo Clinic and UK risk scores 0 to 2. For continuous variables, distributions were assessed for normality, and means were compared using 1-way analysis of variance. All variables were normally distributed. Categorical variables were compared using the chi-square test.

The relationship between each interval increase in diuretic dose category or NYHA functional class was not completely equal. For this reason, we tested weighted models estimated from beta-coefficients for the variables. There was only a modest, nonsignificant gain in discrimination with the more complex weighted scoring system, so we opted to implement the diuretic dose categories and NYHA functional class as a nonweighted increase for simplicity.

Cox proportional hazards models were generated for diuretic dose as a continuous predictor with all-cause mortality as the primary outcome. Patients were censored at time of cardiac transplantation or time of last follow-up. Multivariable models were

TABLE 2 Daily Diuretic Dose as Predictor of All-Cause Mortality and Mortality or Heart Transplantation

Model*	Hazard Ratio (95% CI) per 1 mg/kg Increase (Continuous Scale)	p Value
All-cause mortality		
Unadjusted	2.12 (1.71–2.61)	<0.001
Adjusted 1	1.80 (1.38–2.34)	<0.001
Adjusted 2	1.49 (1.11–2.01)	0.009
Adjusted 3	1.43 (1.06–1.93)	0.020
Mortality or heart transplantation		
Unadjusted	2.09 (1.72–2.54)	<0.001
Adjusted 1	1.73 (1.37–2.19)	<0.001
Adjusted 2	1.49 (1.15–1.93)	0.003
Adjusted 3	1.35 (1.03–1.77)	0.031

*Adjusted 1 = adjusted for age, sex, SBP, hereditary vs. wild type, LVEF; Adjusted 2 = adjusted for age, sex, SBP, hereditary vs. wild type, LVEF, and also adjusted for eGFR, BNP or NT-proBNP elevation, and troponin I or T elevation; Adjusted 3 = adjusted for age, sex, SBP, hereditary vs. wild type, LVEF, eGFR, BNP or NT-proBNP elevation, and troponin I or T elevation, and also adjusted for NYHA functional class.

CI = confidence interval; other abbreviations as in Table 1.

initially adjusted for age, sex, systolic blood pressure, wtATTR versus hATTR, and left ventricular ejection fraction (LVEF). We additionally tested the model after adjusting for renal function, troponin-I or -T elevation, and for either NT-proBNP or BNP elevation; this included variables in the Mayo and UK ATTR-CM risk models. Third, we adjusted for NYHA functional class in the diuretic model. Analyses were repeated with the composite of death or heart transplantation as a secondary outcome. Data are expressed in the tables as hazard ratio (HR) with 95% confidence intervals. Kaplan-Meier curves are used to display survival probabilities for individual risk markers. The final combined scores for Mayo + diuretic dose + NYHA functional class and UK + diuretic dose + NYHA functional class were subdivided into tertiles and plotted to estimate median survival. Comparisons between groups were made using log-rank statistic.

We tested the discrimination of the various risk models using time-dependent receiver-operating characteristic (ROC) curves with estimation of the time-dependent area under the curve (AUC) at the 2-year time point (10). This time point was chosen due to reported median survival of 2.5 years in hATTR V122i mutation subtype (1). Additionally, given the high early mortality and the contemporary enrollment of patients, the models are less stable over time; hence, the point estimates at 2 years for the models are more accurate than with longer follow-up. To test the robustness of our models, we ran sensitivity analyses calculating Harrell's c-statistic, which is the weighted average of the time-dependent AUC across all available survival times. The likelihood ratio test was used to compare nested models to determine whether the addition of diuretic dose and/or NYHA functional class improved the model fit to either the Mayo or UK scores. The continuous net reclassification index (NRI), integrated discrimination improvement, and median improvement (11) were used to determine incremental benefit of adding diuretic dose and NYHA functional class to either the Mayo or the UK risk scores. Calibration was tested with a modified Hosmer-Lemeshow statistic for goodness of fit incorporating survival data (12). Internal validation of the predictive accuracy of each model was performed using 1,000 bootstrap samples to estimate optimism-corrected AUCs and 95% confidence interval (CI).

Statistics were performed using a combination of STATA SE 15 (StataCorp LLC, College Station, Texas) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided p value <0.05 was considered significant.

RESULTS

A total of 309 ATTR-CM patients were included in this study. The mean follow-up time was 1.92 ± 1.82 years for the total cohort. During this time, 33.3% died and 38.8% died or had cardiac transplantation. Cardiac transplantation occurred in 6.8% of the total cohort. The median survival time was 4.0 years, and the estimated 1-year survival was 87.4% (95% CI: 83.3% to 91.8%) and 5-year survival was 36.7% (28.3% to 47.5%).

For the total cohort, the mean age was 73.2 ± 9.8 years, 84.1% were male, and 72.5% were White; 66.0% had wtATTR and 34.0% had hATTR. For those with hATTR, the most common mutation was V122I (61.0%). The majority of patients were NYHA functional class I to III. Mean eGFR was 60.1 ± 22.6 ml/min/1.73 m², 40.1% had elevated BNP or NT-proBNP, and 37.8% had elevated troponin I or T (Table 1). We had no missing data for diuretic dose or NYHA functional class. For the other variables relevant to the Mayo and UK models, we had BNP data on 95.1% of patients (n = 294), troponin data on 95.8% of patients (n = 296), and eGFR on 95.1% of patients (n = 294). The percentage of missing data for these variables was <5%.

Baseline characteristics stratified by diuretic dose categories are shown in Table 1. Patients on higher doses of diuretic agents were more likely to have hATTR, lower weight, lower systolic blood pressure, lower eGFR, elevated BNP or NT-proBNP, elevated

FIGURE 1   Kaplan-Meier Curves for Freedom From All-Cause Mortality
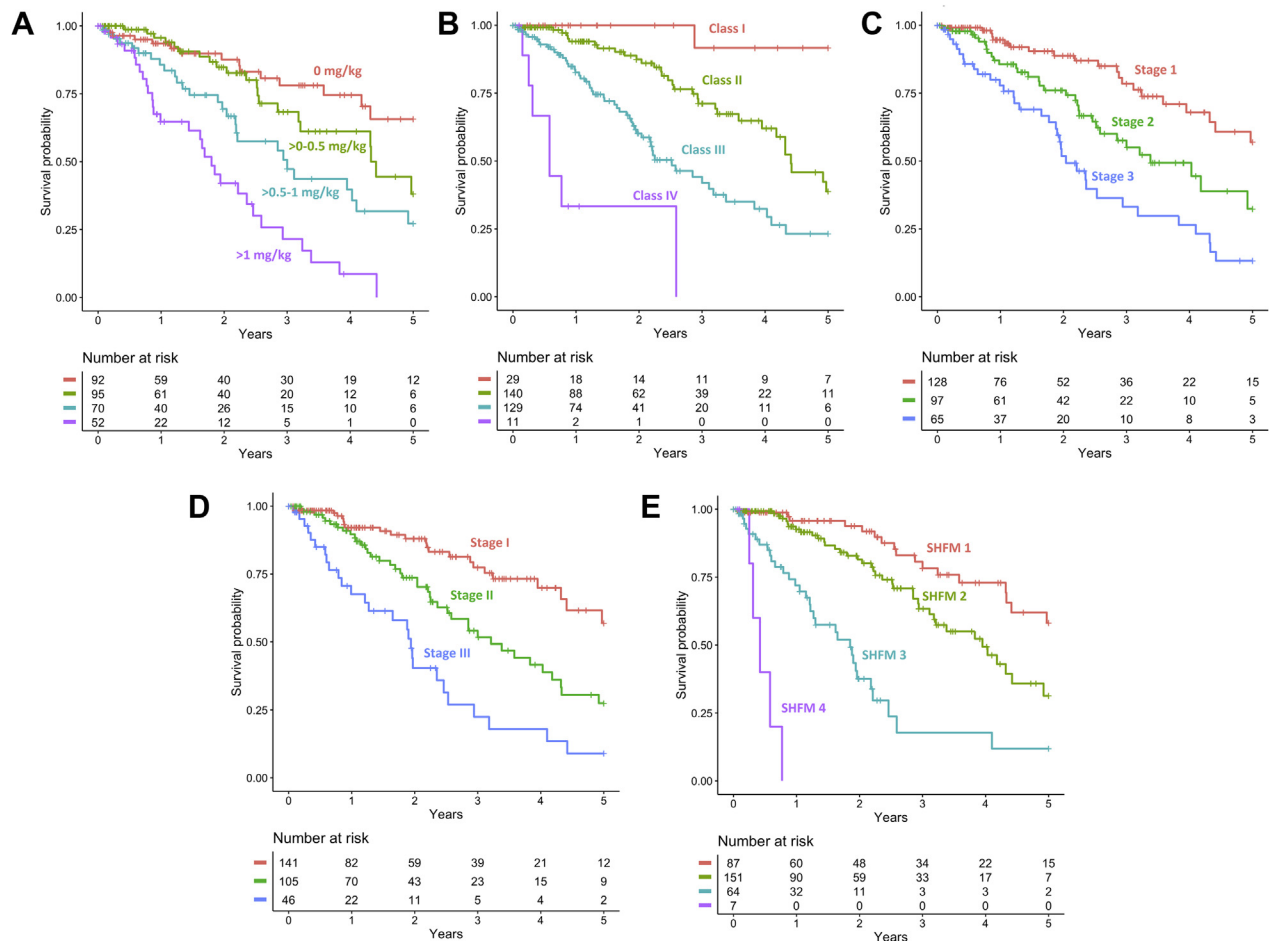
(A) Kaplan-Meier curves are shown for diuretic dose categories. **(B)** New York Heart Association functional class; **(C)** Mayo risk score categories; **(D)** UK risk score categories; and **(E)** Seattle Heart Failure Model (SHFM) score rounded to the nearest integer. For each model, comparison between groups was statistically significant with log-rank p < 0.001.

troponin-I or -T, lower LVEF, and higher NYHA functional class. Characteristics by Mayo stage and UK stage are shown in Supplemental Table 1. Patients with higher Mayo stage were older, had lower weight, lower systolic blood pressure, higher NYHA functional class, lower eGFR, and lower LVEF. Higher UK stage was associated with older age, lower BMI, higher NYHA functional class, and lower LVEF.

Diuretic dose was a strong predictor of all-cause mortality in unadjusted models. It remained significant after consideration of baseline demographics, and after adjusting for BNP, troponin, eGFR, and NYHA functional class (fully adjusted HR: 1.43 per 1 mg/kg increase [95% CI: 1.06 to 1.93]; p = 0.020)

(Table 2). Similarly, diuretic dose predicted the secondary outcome of all-cause mortality or heart transplantation (adjusted HR: 1.35 [95% CI: 1.03 to 1.77]; p = 0.031). NYHA functional class was predictive of both all-cause mortality (adjusted HR: 1.85 [95% CI: 1.22 to 2.80]; p = 0.004) and the composite of mortality or transplantation (adjusted HR: 2.02 [95% CI: 1.39 to 2.93]; p < 0.001). Models with the Mayo and UK scores individually are also shown in Supplemental Table 2.

Kaplan-Meier curves were plotted for the Mayo (log-rank p < 0.001) and UK scores (p < 0.001), as well as for diuretic dose (p < 0.001), SHFM (p < 0.001), and NYHA functional class (p < 0.001) for freedom

TABLE 3 Survival Time ROC Comparisons Between Models (With Mayo or UK Model as Reference)

	All-Cause Mortality AUC (95% CI)	Gain From Reference	p Value	Death or Cardiac Transplantation AUC (95% CI)	Gain From Reference	p Value
Mayo model	0.693 (0.609–0.777)	Reference	Reference	0.685 (0.605–0.764)	Reference	Reference
Diuretic dose only	0.713 (0.627–0.799)	0.020	0.784	0.700 (0.622–0.777)	0.015	0.868
Mayo + diuretic dose	0.767 (0.692–0.843)	0.074	0.046	0.748 (0.673–0.822)	0.063	0.057
Mayo + diuretic dose + NYHA functional class	0.798 (0.729–0.868)	0.105	0.006	0.780 (0.713–0.847)	0.095	0.005
SHFM	0.820 (0.751–0.889)	0.127	<0.001	0.802 (0.732–0.871)	0.117	0.001
UK model	0.711 (0.630–0.792)	Reference	Reference	0.688 (0.608–0.767)	Reference	Reference
Diuretic dose only	0.713 (0.627–0.799)	0.002	0.918	0.700 (0.622–0.777)	0.012	0.818
UK + diuretic dose	0.787 (0.717–0.856)	0.076	0.059	0.757 (0.683–0.831)	0.069	0.048
UK + diuretic dose + NYHA functional class	0.816 (0.749–0.883)	0.105	0.009	0.791 (0.721–0.861)	0.103	0.003
SHFM	0.820 (0.751–0.889)	0.109	0.011	0.802 (0.732–0.871)	0.114	0.001

For diuretic dosing, 0 points were assigned for 0 mg/kg, 1 point for >0 to 0.5 mg/kg daily dose, 2 points for >0.5 to 1 mg/kg daily dose, and 3 points for >1 mg/kg daily dose

AUC = area under the curve; ROC = receiver-operating characteristic; other abbreviations as in **Tables 1 and 2**.

from all-cause mortality (**Figure 1**). Additionally, Kaplan-Meier curves were generated for freedom from death or heart transplantation (Supplemental Figure 1).

Diuretic dose alone yielded an AUC of 0.713 (95% CI: 0.627 to 0.799) for all-cause mortality (**Table 3**). The Mayo model had a baseline AUC of 0.693 (95% CI: 0.609 to 0.777). Adding diuretic dose to the Mayo model improved the AUC to 0.767 (95% CI: 0.692 to 0.843), whereas adding NYHA functional class further increased this to 0.798 (95% CI: 0.729 to 0.868) for Mayo + diuretic dose + NYHA functional class. The UK model had a baseline AUC of 0.711 (95% CI: 0.630 to 0.792) (**Table 3**). Adding diuretic dose improved the AUC to 0.787 (95% CI: 0.717 to 0.856), and adding NYHA functional class further improved the model to 0.816 (95% CI: 0.749 to 0.883) for UK + diuretic dose + NYHA functional class (**Figure 2**).
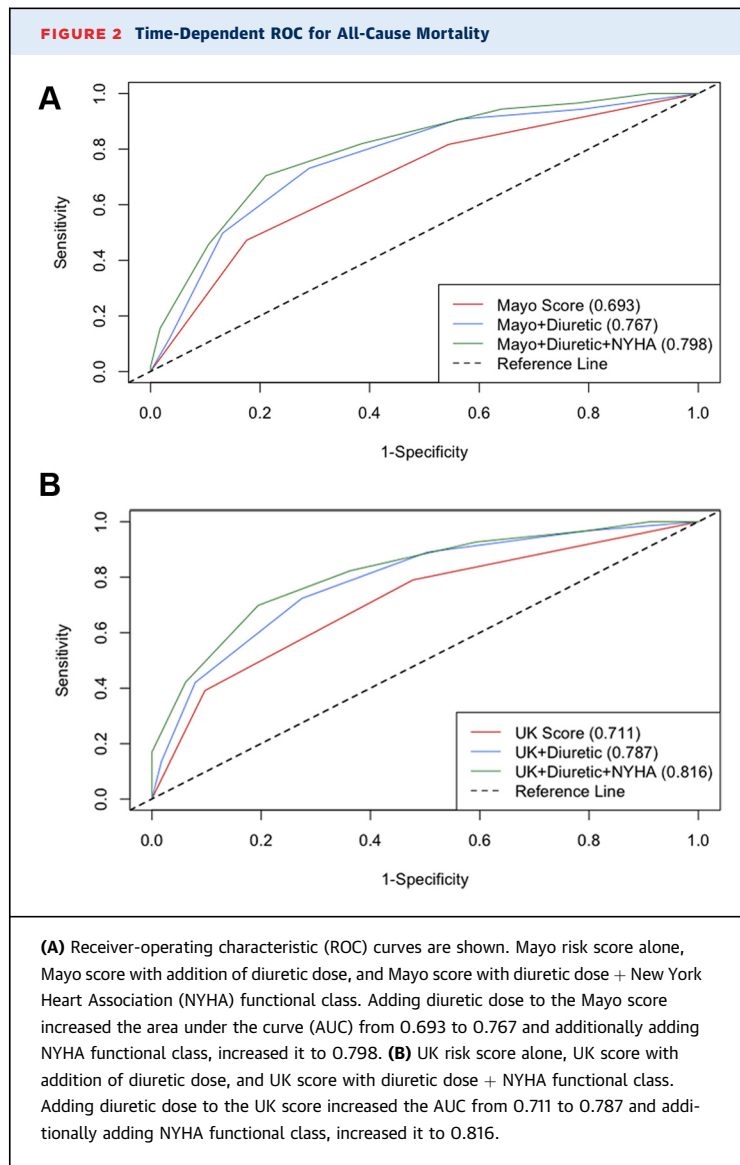
For the final model of Mayo + diuretic dose + NYHA functional class, patients were divided into 3 risk groups (score 1 to 3, 4 to 6, and 7 to 9). The estimated mean survival was 6.5 years for the low-risk group, 4.0 years for the intermediate risk group, and 2.2 years for the high-risk group (log-rank p < 0.001) (**Figure 3A**). Similarly, for the UK + diuretic dose + NYHA functional class model, survival was 6.5 years, 3.8 years, and 1.9 years for the low-, intermediate-, and high-risk groups, respectively (log-rank p < 0.001) (**Figure 3B**).

We also tested the ability of the risk scores to predict a combined outcome of mortality or cardiac transplantation (**Table 3**). The Mayo model had an AUC of 0.685 (95% CI: 0.605 to 0.764), which improved to 0.780 (95% CI: 0.713 to 0.847) when adding diuretic dose and NYHA functional class. The UK model had an AUC of 0.688 (95% CI: 0.608 to 0.767), which improved to 0.791 (95% CI:

0.721 to 0.861) with diuretic dose and NYHA functional class.

We tested SHFM in this cohort because it is widely used in other HF populations. The continuous SHFM score provided an AUC of 0.820 (95% CI: 0.751 to 0.889) for mortality and 0.802 (95% CI: 0.732 to 0.871) for mortality or transplantation. SHFM predicted and observed 1-year survival were similar (88.0% vs. 87.4%), although the 5-year predicted survival was higher than observed (53.7% vs. 36.7%).

To confirm the robustness of our results, we tested Harrell's c-statistic for the different models to incorporate all available follow-up times (Supplemental Table 3), which confirmed that adding diuretic dose and NYHA functional class to the Mayo or UK risk models substantially increased the c-statistic. Likelihood ratio tests between nested models showed that adding diuretic dose and NYHA functional class to each of the Mayo or UK models improved the models significantly in a stepwise manner (**Table 4**). Additionally, to further assess the incremental value of adding diuretic dose and NYHA functional class to either the Mayo or UK scores, we assessed integrated discrimination improvement, NRI, and median improvement (**Table 5**). For all-cause mortality, the addition of diuretic dose and NYHA functional class to both the Mayo and UK scores provided added value compared with either score alone. The results were similar for the combined outcome of mortality or transplantation. The values of the event and nonevent NRI are provided in Supplemental Table 4. Survival-based Hosmer-Lemeshow goodness-of-fit comparisons were nonsignificant across all tested models, suggesting that there were no statistically significant differences between predicted versus observed event rates (Supplemental Table 5). Lastly, we performed internal validation by bootstrapping to calculate the

FIGURE 2 Time-Dependent ROC for All-Cause Mortality

(A) Receiver-operating characteristic (ROC) curves are shown. Mayo risk score alone, Mayo score with addition of diuretic dose, and Mayo score with diuretic dose + New York Heart Association (NYHA) functional class. Adding diuretic dose to the Mayo score increased the area under the curve (AUC) from 0.693 to 0.767 and additionally adding NYHA functional class, increased it to 0.798. **(B)** UK risk score alone, UK score with addition of diuretic dose, and UK score with diuretic dose + NYHA functional class. Adding diuretic dose to the UK score increased the AUC from 0.711 to 0.787 and additionally adding NYHA functional class, increased it to 0.816.

optimism-adjusted AUCs at 2 years (Table 6). The adjusted AUCs were similar to the AUCs calculated in our sample, suggesting the models were well-validated internally.
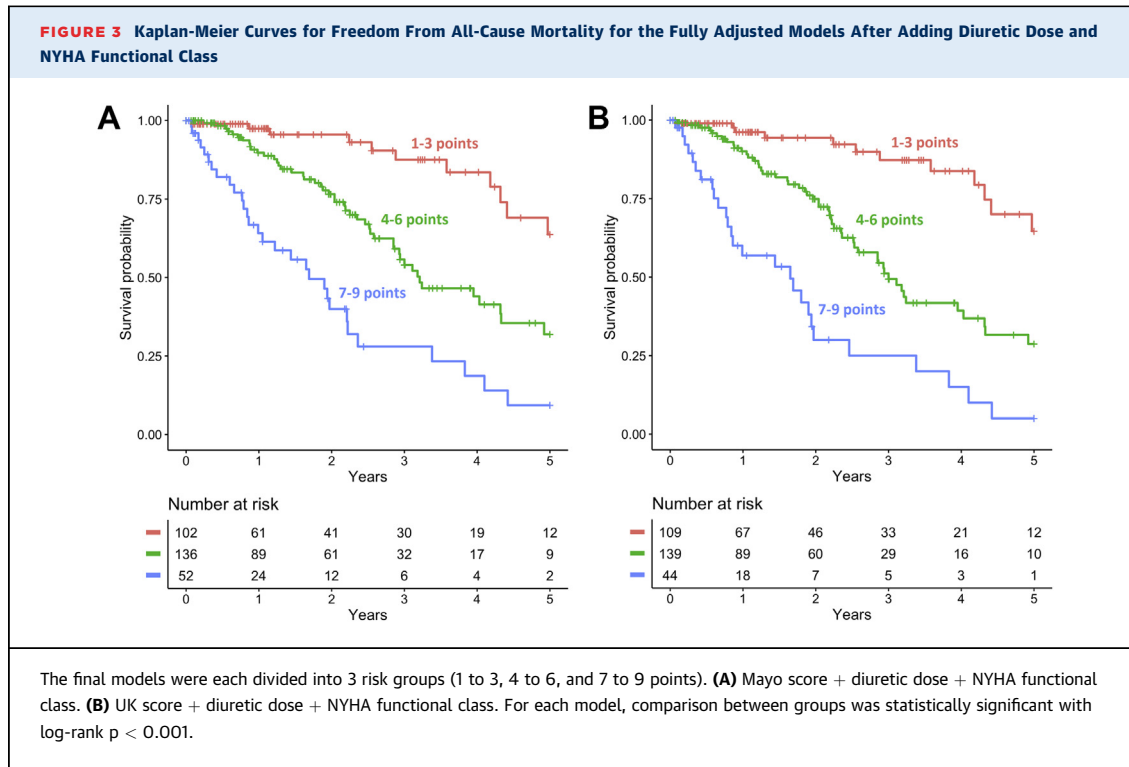
DISCUSSION

ATTR-CM has increasingly been diagnosed in recent years, due to improved accuracy of noninvasive imaging modalities, enhanced awareness, and development of effective disease-specific treatment options. The spectrum of patients diagnosed ranges from pre-clinical hATTR mutation carriers to HF with preserved ejection fraction patients presenting with clinical HF, and to those with end-stage disease. It is critical to accurately risk stratify ATTR-CM patients to

identify those that need closer clinical follow-up and are more likely to benefit from current and future treatments.

Diuretic dose has been shown to be a strong predictor of mortality in other HF cohorts (4-7,13,14). Putative mechanisms for worse outcomes with loop diuretic agents include activation of the renin-angiotensin-aldosterone and sympathetic nervous systems (15) leading to increases in ventricular filling pressures, decreased glomerular filtration rate due to changes in renal blood flow (16), and exacerbation of arrhythmias (17). For ATTR-CM patients with decreased reserve, increased filling pressures, worsening renal function, and arrhythmias could exacerbate an already precarious condition. It has also been proposed that a higher diuretic dose may serve as an indicator of worse disease severity rather than as a mediator of outcomes (4). ATTR-CM results in a predominantly restrictive HF phenotype, resulting in declines in stroke volume and cardiac output with high right atrial pressures. Hence, a decline in renal perfusion pressure leads to progressive cardio-renal syndrome and is likely a contributor to the higher diuretic requirements over time. The UK model has shown that eGFR is a strong predictor of outcomes in ATTR-CM. Although diuretic dose and eGFR may be interrelated, our analyses show that diuretic dose remains an independent predictor of mortality, even after adjusting for eGFR.

The Mayo Clinic (2) and the UK data (3) risk models are most frequently used in clinical practice. There has, however, been interest in other potential predictors of risk in ATTR-CM. For example, despite the effectiveness of nuclear imaging in the diagnosis of ATTR-CM (18,19), its ability to risk stratify those with confirmed ATTR-CM has yielded discordant findings as to whether or not increased radiotracer uptake is associated with mortality (18,20-22). There has also been interest in the use of echocardiographic-derived parameters including global longitudinal strain, early mitral inflow, deceleration time, myocardial performance index, and stroke volume index as predictors of adverse outcomes; however, there is not, as of yet, any formal staging system that incorporates these parameters for ATTR-CM (18). Cardiac magnetic resonance imaging parameters including native T1, extracellular volume, and the presence and pattern of late gadolinium enhancement have also shown promise as prognostic markers in cardiac amyloidosis, but it requires advanced imaging, and much of the data have been with light chain, rather than ATTR, amyloidosis, with extracellular volume perhaps the most robust predictor in ATTR-CM

FIGURE 3 Kaplan-Meier Curves for Freedom From All-Cause Mortality for the Fully Adjusted Models After Adding Diuretic Dose and NYHA Functional Class

The final models were each divided into 3 risk groups (1 to 3, 4 to 6, and 7 to 9 points). **(A)** Mayo score + diuretic dose + NYHA functional class. **(B)** UK score + diuretic dose + NYHA functional class. For each model, comparison between groups was statistically significant with log-rank p < 0.001.

(18,23). In a comprehensive study that included noninvasive parameters including demographics, laboratory testing, electrocardiography, echocardiography, nuclear scintigraphy, and cardiac magnetic resonance imaging, univariable analysis found that NT-proBNP, troponin-T, mitral annular plane systolic excursion and left ventricular hypertrophy index were predictors of mortality; however, on multivariable analysis, only troponin-T predicted survival (22). A more recent analysis included a combination of light chain and ATTR amyloidosis patients, and evaluated parameters that included demographics, right heart catheterization, echocardiography, and biomarkers. In ATTR-CM, the strongest predictors of all-cause mortality were QRS duration, high-sensitivity troponin-T, and NT-proBNP (24). As far as we know, there have not been attempts to assess diuretic dose or NYHA functional class as predictors of adverse outcomes in ATTR-CM, despite the extensive data for diuretic dose and NYHA functional class as risk factors in other HF populations.

In this study, we validate the previously published Mayo and UK ATTR-CM models in a relatively large ATTR-CM cohort. We confirm that they each have moderate discriminatory ability in their current forms. A recent study comparing the 2 risk models in 175 ATTR-CM patients found that the UK model had better discrimination than the Mayo model (25). Our analysis found similar results, with the UK model

performing slightly better than the Mayo model, although the difference was not significant.

We sought to increase the accuracy of risk stratification while keeping the overall model parsimonious with easily obtainable data from the clinical setting. Adding either diuretic dose or NYHA functional class individually resulted in improved discrimination over the Mayo or UK models. Adding both of these variables further improved discrimination. In routine clinical care, diuretic dose and NYHA functional class

TABLE 4 Likelihood Ratios Comparing Nested Models With Addition of Daily Diuretic Dose and NYHA Functional Class to Existent Mayo or UK Risk Scores

Death	
Mayo score + diuretic dose vs. Mayo score	25.9 (<0.001)
Mayo score + diuretic dose + NYHA functional class vs. Mayo score + diuretic dose	13.8 (<0.001)
UK score + diuretic dose vs. UK score	27.2 (<0.001)
UK score + diuretic dose + NYHA functional class vs. UK score + diuretic dose s	15.2 (<0.001)
Death or cardiac transplantation	
Mayo score + diuretic dose vs. Mayo score	24.9 (<0.001)
Mayo score + diuretic dose + NYHA functional class vs. Mayo score + diuretic dose	18.8 (<0.001)
UK score + diuretic dose vs. UK score	27.2 (<0.001)
UK score + diuretic dose + NYHA functional class vs. UK score + diuretic dose	21.1 (<0.001)

Values are chi-square (p value). For diuretic dosing, 0 points were assigned for 0 mg/kg, 1 point for >0 to 0.5 mg/kg daily dose, 2 points for >0.5 to 1 mg/kg daily dose, and 3 points for >1 mg/kg daily dose.

NYHA = New York Heart Association.

TABLE 5 Continuous IDI and NRI

	IDI* (95% CI)	p Value	NRI>0† (95% CI)	p Value	Median Improvement‡ (95% CI)	p Value
2-yr all-cause mortality						
Mayo vs. Mayo + diuretic dose	0.07 (−0.00 to 0.13)	0.073	0.68 (−0.08 to 0.96)	0.12	0.08 (0.00 to 0.20)	0.047
Mayo + diuretic dose vs. Mayo + diuretic dose + NYHA functional class	0.05 (0.01 to 0.07)	<0.001	0.86 (0.36 to 1.12)	<0.001	0.06 (0.01 to 0.09)	<0.001
Mayo vs. Mayo + diuretic dose + NYHA functional class	0.10 (0.04 to 0.19)	<0.001	0.70 (0.38 to 1.02)	<0.001	0.13 (0.05 to 0.25)	<0.001
UK vs. UK + diuretic dose	0.07 (−0.01 to 0.14)	0.027	0.46 (−0.10 to 0.98)	0.126	0.12 (−0.05 to 0.26)	0.146
UK + diuretic dose vs. UK + diuretic dose + NYHA functional class	0.05 (0.02 to 0.09)	0.013	0.88 (0.34 to 1.12)	0.007	0.07 (0.02 to 0.11)	0.007
UK vs. UK + diuretic dose + NYHA functional class	0.12 (0.04 to 0.19)	<0.001	0.66 (0.26 to 1.02)	<0.001	0.15 (0.01 to 0.28)	0.007
2-yr mortality or cardiac transplantation						
Mayo vs. Mayo + diuretic dose	0.06 (0.01 to 0.12)	0.020	0.64 (0.00 to 0.90)	0.047	0.08 (0.00 to 0.16)	0.027
Mayo + diuretic vs. Mayo + diuretic dose + NYHA functional class	0.05 (0.01 to 0.08)	<0.001	0.84 (0.44 to 1.10)	<0.001	0.07 (0.03 to 0.10)	<0.001
Mayo vs. Mayo + diuretic dose + NYHA	0.11 (0.05 to 0.17)	<0.001	0.66 (0.34 to 0.92)	<0.001	0.15 (0.03 to 0.22)	<0.001
UK vs. UK + diuretic dose	0.07 (−0.00 to 0.13)	0.053	0.66 (−0.08 to 0.90)	0.12	0.13 (−0.01 to 0.17)	0.073
UK + diuretic dose vs. UK + diuretic dose + NYHA functional class	0.5 (0.01 to 0.09)	0.007	0.88 (0.38 to 1.16)	0.007	0.07 (0.02 to 0.11)	0.001
UK vs. UK + diuretic dose + NYHA functional class	0.13 (0.05 to 0.20)	<0.001	0.62 (0.22 to 0.92)	0.007	0.16 (0.02 to 0.24)	0.013

For diuretic dosing, 0 points were assigned for 0 mg/kg, 1 point for >0 to 0.5 mg/kg daily dose, 2 points for >0.5 to 1 mg/kg daily dose, and 3 points for >1 mg/kg daily dose. *Difference in discrimination slopes between 2 models, where the discrimination slope is the difference between the mean predicted probabilities for events and nonevents. †Sum of net proportions of persons with and without the event correctly assigned to a different risk category; ranges from −2 to 2. ‡Similar to the IDI except compares difference between median predicted probabilities.

IDI = integrated discrimination improvement; NRI = net reclassification index; other abbreviations as in **Tables 1 and 2**.

are readily available data points. Adding these easily obtainable parameters resulted in a substantial incremental gain in AUC, increasing the AUC for the Mayo risk model from 0.693 to 0.798 and the UK risk model from 0.711 to 0.813 for all-cause mortality (**Central Illustration**). The gain in AUC of ~0.10 for both the Mayo and UK models when adding diuretic dose and NYHA functional class supports the use of these variables for clinical decision-making.

Although not the focus of the current study, we did test the SHFM in this cohort, as it is widely used in other HF populations. Despite the model not being developed for ATTR amyloid patients or HF with preserved ejection fraction, it also showed robust

discriminatory ability in ATTR-CM with an AUC of 0.820, probably due to inclusion of diuretic dose and NYHA functional class in the SHFM. However, the SHFM is complex and includes many variables, which may not be readily available in a routine clinic visit. Further, the benefit of HF medications including neurohormonal blockade, which is included in the SHFM has not been proven in the ATTR-CM population. In fact, there is some concern that standard HF guideline directed medical therapies for reduced LVEF, such as beta-blockers, may be detrimental in this population. We find that the much simpler Mayo or UK models, after the addition of diuretic dose and NYHA functional class, was similar in discriminatory ability to the full SHFM despite containing fewer variables and being more readily accessible.

ATTR-CM is an emerging disease with increasing recognition over the last decade. As more patients are diagnosed, accurate risk stratification will become more important. Currently, the Mayo and UK risk models provide patients with an estimate of their prognosis. The addition of diuretic dose and NYHA functional class to these models offers incremental insight into disease severity. Given the recently observed difference in benefit of treating ATTR-CM for NYHA functional class I to II versus class III with the ATTR-ACT (Tafamidis in the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial) (26), better understanding of disease progression is needed to guide therapeutic decision-making. There may be a "point of no return" due to progressive ATTR amyloid
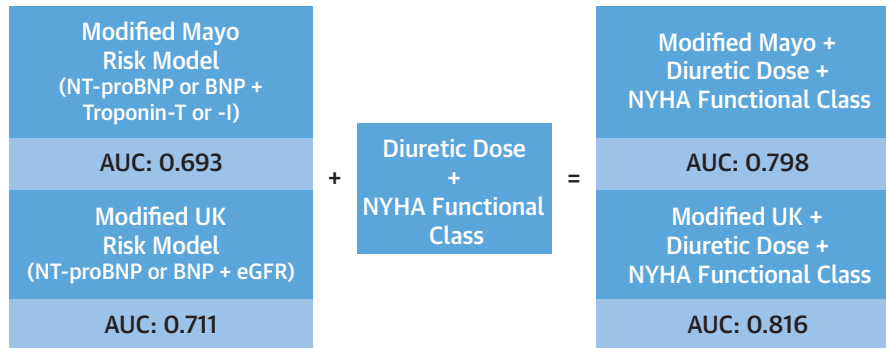
TABLE 6 Internal Validation With Bootstrapping: Optimism-Adjusted Survival-Based AUC

	All-Cause Mortality AUC (95% CI)	Death or Cardiac Transplantation AUC (95% CI)
Mayo model	0.691 (0.633–0.745)	0.687 (0.632–0.738)
Mayo + diuretic dose	0.765 (0.711–0.815)	0.751 (0.696–0.801)
Mayo + diuretic dose + NYHA functional class	0.795 (0.742–0.843)	0.783 (0.731–0.831)
UK model	0.698 (0.638–0.755)	0.678 (0.619–0.733)
UK + diuretic	0.776 (0.724–0.826)	0.753 (0.700–0.803)
UK + diuretic dose + NYHA functional class	0.806 (0.757–0.853)	0.787 (0.783–0.834)
Diuretic dose only	0.715 (0.657–0.771)	0.705 (0.653–0.757)
SHFM	0.785 (0.734–0.836)	0.774 (0.724–0.822)

For diuretic dosing, 0 points were assigned for 0 mg/kg, 1 point for >0 to 0.5 mg/kg daily dose, 2 points for >0.5 to 1 mg/kg daily dose, and 3 points for >1 mg/kg daily dose.

Abbreviations as in **Tables 1 to 3**.

CENTRAL ILLUSTRATION Incremental Benefit of Adding Diuretic Dose and New York Heart Association Functional Class to Existing Transthyretin Amyloidosis Cardiomyopathy Risk Models for All-Cause Mortality

Modified Mayo Risk Model (NT-proBNP or BNP + Troponin-T or -I)		Modified Mayo + Diuretic Dose + NYHA Functional Class
AUC: 0.693	+ Diuretic Dose + NYHA Functional Class =	AUC: 0.798
Modified UK Risk Model (NT-proBNP or BNP + eGFR)		Modified UK + Diuretic Dose + NYHA Functional Class
AUC: 0.711		AUC: 0.816

Cheng, R.K. et al. J Am Coll Cardiol CardioOnc. 2020;2(3):414–24.

Adding diuretic dose + New York Heart Association (NYHA) functional class to the Mayo transthyretin amyloidosis (ATTR) score improved the time-dependent area under the curve (AUC) from 0.693 to 0.798. Adding diuretic dose + NYHA functional class to the UK ATTR score improved the time-dependent AUC from 0.711 to 0.816.

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deposition, where medical therapy may no longer be effective and when patients should be considered for advanced HF options or palliative care. Future studies with stratification by disease severity or responder analysis in already completed trials based on these risk models should be considered, particularly if treatment cost remains prohibitively high for many patients ([27]).

STUDY LIMITATIONS. Our cohort included both wtATTR and hATTR. It is possible that risk markers may be differentially predictive in these distinct cohorts because natural disease progression is more aggressive with hATTR, and there may also be differences between mutation types. Of note, the Mayo risk score ([2]) was derived in only wtATTR; the UK risk model ([3]) included both wtATTR and hATTR. However, we did not separate the data according to these 2 groups due to the limited sample size. With respect to sample size, although our cohort was not large, it is still one of the larger cohorts of ATTR-CM patients studied to date. The study involved a single referral center with primarily NYHA functional class I to III, so its generalizability to other centers, and to those with pre-clinical or end stage disease needs to be tested. Additionally, we did not externally validate our models, given the lack of readily accessible datasets, but plan to do so in future studies. We also did not create separate derivation and validation cohorts secondary to sample size, but we did perform internal validation with bootstrapping. The laboratory values in our dataset included both BNP and NT-proBNP and both troponin-T and troponin-I, which were each combined into a single variable. Ideally, all patients should have the same laboratory test performed at baseline. However, the need to combine different assays arguably reflects real-world practice where different institutions will use different troponin and BNP assays.

CONCLUSIONS

In the current study, we demonstrate that diuretic dose and NYHA functional class are strong independent predictors of all-cause mortality and the composite outcome of all-cause mortality or cardiac transplantation. We validate the Mayo and UK ATTR-CM risk scores, demonstrating that each of these has moderate discriminatory ability in our ATTR-CM cohort. When added to either the Mayo or UK risk scores for ATTR-CM, diuretic dose and NYHA functional class provide incremental predictive and discriminative utility, while maintaining calibration. Given that diuretic dose and NYHA functional class are easily obtainable data points, these should be considered when risk stratifying patients with ATTR-CM in the clinical setting.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The current Mayo and UK risk models for ATTR-CM provide moderate discriminatory ability in our ATTR-CM cohort. Diuretic dose and NYHA functional class are easily obtainable clinical parameters that provide incremental predictive and discriminative value to the existing Mayo and UK risk scores for ATTR-CM.

TRANSLATIONAL OUTLOOK: Further research is needed to validate these findings in larger cohorts and determine if they apply similarly to hATTR and wtATTR. Optimized risk stratification tools can also be used to aid in decision making for targeted therapy in ATTR-CM.

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KEY WORDS cardiac amyloidosis, heart failure, transthyretin

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