Transthyretin amyloid cardiomyopathy among patients hospitalized for heart failure and performance of an adapted wild-type ATTR-CM machine learning model: Findings from GWTG-HF

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Background An 11-factor random forest model has been developed among ambulatory heart failure (HF) patients for identifying potential wild-type amyloidogenic TTR cardiomyopathy (wtATTR-CM). The model has not been evaluated in a large sample of patients hospitalized for HF.

Methods This study included Medicare beneficiaries aged ≥65 years hospitalized for HF in the Get With The Guidelines-HF® Registry from 2008-2019. Patients with and without a diagnosis of ATTR-CM were compared, as defined by inpatient and outpatient claims data within 6 months pre- or post-index hospitalization. Within a cohort matched 1:1 by age and sex, univariable logistic regression was used to evaluate relationships between ATTR-CM and each of the 11 factors of the established model. Discrimination and calibration of the 11-factor model were assessed.

Results Among 205,545 patients (median age 81 years) hospitalized for HF across 608 hospitals, 627 patients (0.31%) had a diagnosis code for ATTR-CM. Univariable analysis within the 1:1 matched cohort of each of the 11-factors in the ATTR-CM model found pericardial effusion, carpal tunnel syndrome, lumbar spinal stenosis, and elevated serum enzymes (e.g., troponin elevation) to be strongly associated with ATTR-CM. The 11-factor model showed modest discrimination (c-statistic 0.65) and good calibration within the matched cohort.

Conclusions Among US patients hospitalized for HF, the number of patients with ATTR-CM defined by diagnosis codes on an inpatient/outpatient claim within 6 months of admission was low. Most factors within the prior 11-factor model were associated with greater odds of ATTR-CM diagnosis. In this population, the ATTR-CM model demonstrated modest discrimination. (Am Heart J 2023;265:22–30.)

Background

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a restrictive cardiomyopathy that results from extracellular transthyretin protein deposition,[1] with complications that can include heart failure (HF), conduction abnormalities, arrhythmias, among other sequelae.[2] Although historically considered a rare disease reserved for diagnosis at expert centers, there is growing appreciation that the disease is under-recognized and often misdiagnosed.[1-3] For example, studies of active screening strategies suggest that the disease may represent 5% to 20% of patients with heart failure with preserved ejection fraction (HFpEF).[4-6] With the recent availability of approved disease-modifying therapy to improve survival and quality of life for patients with ATTR-CM such as tafamidis, timely and accurate identification has potential to significantly improve patient-centered outcomes.[3,7,8]

Given challenges with under- or misdiagnosis of ATTR-CM, developing systematic and evidence-based strategies to identify patients with ATTR-CM in clinical prac-

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tice remains an important unmet need. Utilizing medical claims data of >2,000 derivation and ~60,000 validation ambulatory HF patients aged ≥50 years, a prior analysis developed and validated a predictive model that was able to distinguish HF patients with vs without wild-type ATTR-CM (wtATTR-CM) with strong discrimination and reclassification of risk: area under the receiver operating curve 0.76 to 0.95; positive likelihood ratio 2.9 to 16 with post-test probability of ATTR-CM rising 11% to 40% from 4%.[9] Within this 11-factor model, features such as carpal tunnel syndrome and pericardial effusion/pericarditis demonstrated leading roles with odds ratios of 5.5 and 5.2, respectively, for wtATTR-CM. While this model was internally and externally validated in multiple cohorts, it has not been studied among patients hospitalized for HF. An evidence-based strategy to improve screening and identification of ATTR-CM during the hospitalization for HF could represent an efficient and effective means of implementing disease-modifying therapies in a high-risk population in clinical practice. Likewise, in-hospital initiation of appropriate therapy is recognized as one of the most powerful and consistent means to improve short-term and long-term use of HF therapies and improve clinical outcomes.[10,11] Accordingly, an evidence-based strategy to improve screening and identification of ATTR-CM during the hospitalization for HF could represent an efficient and effective means of implementing disease-modifying therapies in clinical practice. In this context, the Get With The Guidelines-Heart Failure (GWTG-HF) registry offers a unique opportunity to (1) compare the clinical profile of patients hospitalized for HF with and without ATTR-CM, (2) characterize factors associated with ATTR-CM, and (3) assess the performance of the previously developed predictive model for identifying ATTR-CM in a large representative cohort of patients hospitalized for HF.

Methods

Data source

GWTG-HF is an ongoing, quality improvement registry among US hospitals started in 2005 by the American Heart Association.[12] The registry includes patients hospitalized for HF. Trained personnel at participating centers use an internet-based patient management tool (IQVIA, Parsippany, New Jersey) to collect patient-level data on consecutive HF patients admitted to the hospital. IQVIA serves as the data collection and coordinating center for the American Heart Association's GWTG programs, and the Duke Clinical Research Institute serves as the data analytic center. The GWTG-HF protocol was approved by the institutional review boards at each participating center. As the main purpose of the registry is quality improvement, patient informed consent is waived under the common rule. For the present study, participants ≥65 years of age with fee for-service Medicare coverage were linked to Medicare data using a validated technique.[13]

Study design and population

The study population included patients age ≥65 years who were hospitalized for a primary diagnosis of HF in GWTG-HF from January 1, 2008 to July 1, 2019 and who were enrolled in Medicare fee-for-service benefits ≥6 months prior to index admission. If multiple hospitalizations were found, the first hospitalization was kept as the index hospitalization and other hospitalizations were excluded. Patients with missing data for quantitative EF or unavailable CMS data for 6 months postdischarge for reasons other than death were excluded. Furthermore, in order to reduce likelihood of including patients with amyloid light chain amyloidosis, and consistent with methodology in the development of the wt-ATTR predictive model, patients with an inpatient or outpatient diagnosis code for any of the following were excluded: multiple myeloma or monoclonal gammopathy of undetermined significance, blood cancer, end-stage renal disease or dialysis, light chain amyloidosis, intracranial hemorrhage, or cerebral amyloid angiopathy (Supplemental Table 1).[9] Patients with a history of chronic dialysis therapy or in-hospital receipt of dialysis (as captured in the GWTG registry) were also excluded.

Diagnosis of ATTR-CM

Consistent with other analyses, the diagnosis of ATTR-CM during or within 6 months pre/postindex hospitalization was defined by presence of International Classification of Diseases, 9th Edition (ICD-9) codes 277.3x[2,14-16] or ICD-10 codes E85.82 or E85.4, captured on any inpatient, outpatient, or carrier claims. This approach was adapted from the original wt-ATTR-CM model, which, prior to training the machine learning algorithms, converted all ICD-9 codes to ICD-10 codes.[9]

Risk factor model

The original wt-ATTR-CM model included 11 clinical risk factors as defined by ICD-9/ICD-10 codes.[9] These included the following cardiac conditions: HFpEF (EF≥50%), elevated serum enzymes (ie, troponin or N-terminal pro-B-type natriuretic peptide [NT-proBNP]), arrhythmias (ie, atrial fibrillation/flutter), pericardial effusion, increased left ventricular wall thickness, and conduction disease (ie, heart block, bundle branch block); and the following noncardiac conditions: carpal tunnel syndrome (bilateral or unilateral), shoulder/hip/knee degenerative joint disease, lumbar spinal stenosis, nontraumatic tendon rupture (eg, biceps, Achilles), and non-diabetic polyneuropathy. The current analysis utilized these same ICD-9/ICD-10 code definitions, further supplemented by precise quantitative EF data from the GWTG-HF registry, as well as prespecified Current Procedural Terminology/Healthcare Common Procedure Coding System procedure codes for treatment of carpal tunnel syndrome and atraumatic tendon rupture (Supplemental Table 2). CMS claims (inpatient, outpatient, and carrier claims) were scanned for the corresponding codes during the index hospitalization and the 6-month periods before and after hospitalization.

Statistical analysis

Baseline characteristics were compared between patients with or without diagnosis of ATTR-CM, and separately between patients with a diagnosis of ATTR-CM and age- and sex-matched controls with HF. For each HF patient with ATTR-CM, 1 HF patient without ATTR-CM diagnosis who matched on age (integer years) and sex was selected at random. Continuous variables were reported as median (25th percentile, 75th percentile) and compared by using Wilcoxon Rank Sum tests. Categorical variables were presented as frequencies and percentages and were compared by using the Pearson χ^2 test or the Fisher exact test, as appropriate. Counts smaller than 11 were suppressed, as required by the CMS data use agreement. Further, the different groups were compared using percentage absolute standardized mean differences with an absolute standardized mean differences >10% indicating a meaningful difference. We then calculated univariable odds ratios to evaluate the association between each of the 11 factors and ATTR-CM diagnosis in the matched study cohort.

The 11-factor model was evaluated in a 1:1 sex and age matched cohort, as in the original derivation analysis,[9] in which matching was performed to improve efficiency and remove confounding for age and sex. Since the goal of the present analysis was to evaluate the original model, it was necessary to reproduce this matching strategy in order to achieve an accurate comparison. However, such a ratio sets the prevalence of ATTR-CM to 50% by construction. To reflect estimated rates in the full study population, the model was recalibrated from the prevalence in the matched sample to account for the age and sex distributions among cases and controls in the validation cohort, as well as to assume an estimated prevalence of 5% in the national heart failure population, as was done in the original model calculations.

The performance of the previously developed 11-factor ATTR-CM model was evaluated in both the overall and matched cohorts, including sensitivity, specificity, and accuracy at probability thresholds ranging from 0.25 to 0.75, and area under the receiver operating curve (AUROC). Using Python code provided by the developers of the model, the model was run without any refitting in the matched and overall cohorts to obtain a predicted probability of ATTR-CM overall and in 1:1 sex and age matched patients. This predicted probability in the overall cohort was then recalibrated to reflect the predicted probability of ATTR-CM given the patient's age and sex, by using a naïve Bayes adjustment formula to account for the population prevalence of ATTR-CM (assumed to be 5%), and distribution of age and sex within the GWTG-HF cohorts with and without ATTR-CM (Supplemental Table 3). Calibration plots of the predicted probabilities in the matched cohort and of the naïve Bayes adjusted probabilities in the overall cohort were developed. Recognizing that challenges with ATTR-CM under-diagnosis could conceivably lead to patients in the control group having undiagnosed ATTR-CM, prespecified sensitivity analyses assessed discrimination and calibration of the model using a more conservative control population (termed the "conservative control" cohort) who had undergone testing for ATTR-CM (billing procedure code for an endomyocardial biopsy without a history of heart transplantation, cardiac pyrophosphate scan or cardiac magnetic resonance imaging - Supplemental Table 4) during the index hospitalization or 6 months pre-/posthospitalization but remained without a diagnosis code for ATTR-CM. All statistical analyses were performed using Python version 3.8.8 (Python Software Foundation) and SAS, version 9.4 (SAS Institute, Cary, NC). Two-sided $P < .05$ was considered statistically significant.

Results

Diagnosis of ATTR-CM

Among 205,545 patients hospitalized for HF across 608 US hospitals, 627 patients (0.31%) had a diagnosis code for ATTR-CM (Table I). The proportion of patients with a diagnosis rose from 0.20% in 2008 to 0.52% in 2019, including a sharper increase from 2016 to 2017 corresponding with the shift from ICD-9 to ICD-10 on 10/1/2015, and introduction of ICD-10 code E85.82 (ATTR amyloidosis) on October 1, 2017. Diagnosis rate was higher in patients age ≥75 years (0.32% vs 0.26% in those age <75 years), male patients (0.45% vs 0.18% in female patients), and Black patients (0.80% vs 0.25% in white patients). Cases of ATTR-CM were proportionally overrepresented in the Northeast region of the US, with this region contributing 40% of ATTR-CM cases and 28% of the overall study population. In contrast, the South region of the US was relatively underrepresented in terms of ATTR-CM cases, contributing 22% of cases and 34% of the overall study population.

Patient characteristics

Compared to unmatched patients without ATTR-CM diagnosis, patients with ATTR-CM were similar with respect to age (median 81 years), but more likely to be male (69% vs 47%) and Black race (23% vs 9%; Supplemental Table 5).

After 1:1 matching by age and sex, patients with ATTR-CM were more likely to be Black race (23% vs 8%) and more likely to have history of atrial fibrillation (53% vs 46%), lower eGFR at admission (48 vs 55 mL/min/1.73 m^2) and discharge (50 vs 56 mL/min/1.73m^2), lower

Table I. Diagnosis of ATTR-CM by year of admission and baseline characteristics of ATTR-CM diagnosis cohort

Group	Diagnosis of ATTR-CM using billing codes, *n/N (%)*
Overall study population	627/205,545 (0.31%)
Year of admission	
2008	17/8,295 (0.20%)
2009	17/9,350 (0.18%)
2010	27/11,762 (0.23%)
2011	31/13,872 (0.22%)
2012	38/14,912 (0.25%)
2013	43/16,732 (0.26%)
2014	41/18,135 (0.23%)
2015	58/20,999 (0.28%)
2016	70/26,190 (0.27%)
2017†	106/26,148 (0.41%)
2018†	107/25,252 (0.42%)
2019†	72/13,898 (0.52%)
Age	
<75	145/56,213 (0.26%)
≥75	482/149,332 (0.32%)
Gender	
Female	195/108,784 (0.18%)
Male	432/96,761 (0.45%)
Race*	
White	427/168,518 (0.25%)
Black	147/18,352 (0.80%)
Other	43/15,978 (0.27%)

* 2,697 records are missing on race.
† ICD-10-CM code E85.82 (Wild-type transthyretin-related [ATTR] amyloidosis) effective from October 1, 2015. ICD-10-CM code E85.4 (Organ-limited amyloidosis) effective from October 1, 2015. ICD-9-CM codes (277.3x) effective until September 30, 2015.ATTR-CM, transthyretin amyloid cardiomyopathy.

systolic blood pressure at admission (median 124 vs 137 mmHg) and discharge (112 vs 119 mmHg), and lower body mass index (26 vs 28 kg/m^2); Table II). NT-proBNP/BNP were similar among patients with and without ATTR-CM.

Factors associated with ATTR-CM diagnosis

Univariable analysis within the 1:1 matched cohort of each of the 11-factors in the ATTR-CM model found multiple factors strongly associated with ATTR-CM, including pericardial effusion (20.1% vs 4.6%; odds ratio[OR]: 5.19 [3.40, 7.90]), carpal tunnel syndrome (>3.7% vs <1.8%; OR 3.94 [1.87, 8.28]), lumbar spinal stenosis (11.5% vs 5.3%; OR 2.34 [1.52, 3.58]), and elevated serum enzymes (26.3% vs 13.4%; OR 2.31 [1.73, 3.09]; Table III). Increased left ventricular wall thickness, conduction disease, arrhythmias, shoulder/hip/knee degenerative joint disease were also significantly associated with diagnosis with ATTR-CM. Preserved EF ≥50% and nontraumatic tendon rupture, and nondiabetic polyneuropathy were not significantly associated with ATTR-CM diagnosis.

Sensitivity analysis using 1:1 matching with conservative controls who had undergone testing for ATTR-CM but did not carry a diagnosis demonstrated fewer factors significantly associated with ATTR-CM diagnosis (only preserved EF, arrhythmias, carpal tunnel syndrome, and nondiabetic polyneuropathy, Supplemental Table 6).

Discrimination and calibration performance

In the matched cohort, the 11-factor model showed modest discrimination with c-statistic of 0.65 with good calibration (Figure). High sensitivity was observed with low specificity and vice versa (Table IV). At a probability threshold of 0.5, the model demonstrated sensitivity of 43% and specificity of 80% in the matched cohort (Table IV). Performance in the overall unmatched cohort, "conservative control" cohort, and matched "conservative control" cohort was similar with AUROCs of 0.64, 0.60, and 0.58, respectively (Supplemental Tables 7-9, Supplemental Figures 1-3).

Discussion

In this large cohort of older patients hospitalized for HF across >600 US hospitals, the proportion of patients diagnosed with ATTR-CM more than doubled over the 11-year study period, but absolute rates remained low with a peak of 0.52% in 2019. Patients with ATTR-CM were older, more likely to be male and Black race, and more likely to have atrial fibrillation, lower blood pressure, lower eGFR and lower body mass index, compared with those without ATTR-CM diagnosis. From the previously established 11-factor model, several factors were strongly associated with ATTR-CM diagnosis, led by pericardial effusion, carpal tunnel syndrome, lumbar spinal stenosis, and elevated serum cardiac enzymes (eg, troponin elevation). In the cohort matched by age and sex, the 11-factor model showed modest discrimination with a c-statistic of 0.65 with good calibration and similar performance in sensitivity analyses. Thus, although several of these 11 factors may aid clinicians in assessing likelihood of ATTR-CM diagnosis, further studies are needed to confirm a systematic, efficient, and scalable approach for identifying patients hospitalized for HF who are at high-risk for ATTR-CM.

To our knowledge, we present the first assessment of an ATTR-CM detection model in a large, contemporary US population hospitalized for HF. Hospitalizations of patients diagnosed with amyloidosis are notably increasing with an estimated 9% of these admissions primarily driven by heart failure.[16] This analysis highlights trends in the diagnosis rates of ATTR-CM in US patients hospitalized for HF in routine practice. This diagnosis rate of 0.2% to 0.5% (2008-2019) is consistent with rates from a prior national analysis (2010-2015) based on diagnosis codes[2] and remains well below the prevalence rate of 5% to 20% in HFpEF suggested by smaller local studies with active screening strategies.[4-7] Although prevalence rates in such studies may be affected by referral bias, this rate was consistent (6.3%) in a population-based cohort study of a largely White population, which likely under-

Table II. Baseline characteristics of patients with ATTR-CM diagnosis vs age and sex-matched controls

	Overall (*N* = 1,254)	ATTR-wt diagnosis (*N* = 627)	No ATTR-wt diagnosis (*N* = 627)	*P* -value	Absolute std. diff* (%)
Demographics					
Age, y	81 (75-87)	81 (75-87)	81 (75-87)	-	-
Female sex	390 (31.1%)	195 (31.1%)	195 (31.1%)	-	-
Race				<.001	44.39
White	958 (76.4%)	427 (68.1%)	531 (84.7%)		
Black	198 (15.8%)	147 (23.4%)	51 (8.1%)		
Other	81 (6.5%)	43 (6.9%)	38 (6.1%)		
Insurance				.87	5.52
private/other	>296 (>23.3%)†	>140 (>22.3%)†	>145 (>23.0%)†		
Medicaid	63 (5.0%)	35 (5.6%)	28 (4.5%)		
Medicare	743 (59.3%)	374 (59.6%)	369 (58.9%)		
No insurance/not documented/UTD	<11 (<1.2%)†	<11 (<1.8%)†	<11 (<1.8%)†		
Medical history					
Atrial fibrillation	618 (49.3%)	332 (53.0%)	286 (45.6%)	.013	14.42
Diabetes	365 (29.1%)	154 (24.6%)	211 (33.7%)	<.001	21.51
Hypertension	953 (76.0%)	465 (74.2%)	488 (77.8%)	.045	11.62
Dyslipidemia	87 (6.9%)	34 (5.4%)	53 (8.5%)	.68	6.40
Prior MI	214 (17.1%)	84 (13.4%)	130 (20.7%)	<.001	20.66
Prior CVA/TIA	173 (13.8%)	92 (14.7%)	81 (12.9%)	.41	4.82
Prior PCI	203 (16.2%)	89 (14.2%)	114 (18.2%)	.045	11.62
Prior CABG	200 (15.9%)	59 (9.4%)	141 (22.5%)	<.001	37.86
COPD / asthma	328 (26.2%)	125 (19.9%)	203 (32.4%)	<.001	30.22
Smoker	102 (8.1%)	25 (4.0%)	77 (12.3%)	<.001	30.62
ICD or CRT-D device	148 (11.8%)	72 (11.5%)	76 (12.1%)	.68	2.41
Presence of CRT device	89 (7.1%)	45 (7.2%)	44 (7.0%)	.95	0.35
Ischemic heart disease	597 (47.6%)	255 (40.7%)	342 (54.5%)	<.001	30.50
Peripheral vascular disease	152 (12.1%)	63 (10.0%)	89 (14.2%)	.020	13.48
Atrial fibrillation (at presentation or during hospitalization)	504 (40.2%)	264 (42.1%)	240 (38.3%)	.13	8.89
Atrial flutter (at presentation or during hospitalization)	64 (5.1%)	40 (6.4%)	24 (3.8%)	.10	10.81
GWTG-HF admission vitals & labs					
Ejection fraction	45 (30-57)	45 (32-55)	45 (30-58)	.84	3.16
HFpEF (EF≥50%)	549 (43.8%)	262 (41.8%)	287 (45.8%)	.16	8.04
Heart rate, bpm	81.0 (69.0-95.0)	79.0 (68.0-90.0)	83.0 (70.0-98.5)	<.001	21.57
SBP, mmHg	130.0 (114.0-149.0)	124.0 (110.0-143.0)	137.0 (119.0-156.0)	<.001	40.37
BMI, kg/m^2	26.6 (23.4-30.8)	26.0 (23.5-29.4)	27.7 (23.1-32.7)	.014	29.27
Obesity (BMI ≥30 kg/m^2)	158 (12.6%)	55 (8.8%)	103 (16.4%)	<.001	30.65
Troponin, ng/ml	0.06 (0.02-0.16)	0.10 (0.04-0.21)	0.05 (0.02-0.10)	<.001	18.70
NT-proBNP, pg/mL	5,771 (2,605-9,814)	5,746 (2,965-9,646)	5,796 (2,550-10,365)	1.00	10.42
BNP, pg/mL	774 (444-1433)	756 (485-1317)	821 (381-1560)	.70	5.18
Creatinine, mg/dL	1.3 (1.0-1.8)	1.4 (1.1-1.8)	1.2 (1.0-1.7)	.002	3.37
Sodium, mmol/L	139 (136-141)	138 (135-141)	139 (136-141)	.016	18.21
Potassium, mEq/L	4.2 (3.8-4.5)	4.2 (3.8-4.5)	4.2 (3.8-4.5)	.88	1.37
Hemoglobin, g/dL	12.1 (10.6-13.5)	12.4 (10.9-13.8)	11.9 (10.5-13.4)	.056	16.42
Albumin, g/dL	3.5 (3.1-3.8)	3.5 (3.2-3.8)	3.4 (3.1-3.7)	.085	16.13
eGFR (CKD-EPI formula), mL/min/1.73 m^2	51 (37-68)	48 (36-63)	55 (37-75)	.002	22.91
GWTG discharge vitals & labs‡					
Heart rate, bpm	75 (67-86)	75 (67-85)	75 (67-87)	.47	6.38
SBP, mmHg	116 (103-131)	112 (101-126)	119 (107-136)	<.001	35.11
Potassium, mEq/L	4.0 (3.7-4.4)	4.0 (3.7-4.4)	4.0 (3.6-4.3)	.56	5.41
eGFR (CKD-EPI formula), mL/min/1.73 m^2	53 (38-70)	50 (37-65)	56 (39-74)	.021	16.83
Sodium, mmol/L	138 (136-141)	138 (135-140)	139 (136-141)	<.001	27.05
Discharge medications§					
ACEI/ARB	526 (41.9%)	220 (35.1%)	306 (48.8%)	<.001	30.93
ARNI	13 (1.0%)	<11 (<2.0%)	<11 (<2.0%)	.16	
Beta-blocker	863 (68.8%)	392 (62.5%)	471 (75.1%)	<.001	34.61
Aldosterone antagonist	228 (18.2%)	130 (20.7%)	98 (15.6%)	.039	15.10
Digoxin	60 (4.8%)	17 (2.7%)	43 (6.9%)	<.001	19.52
Loop diuretic	524 (41.8%)	253 (40.4%)	271 (43.2%)	.001	27.46
Calcium channel blocker	106 (8.5%)	38 (6.1%)	68 (10.8%)	.002	17.26

(*continued on next page*)

Table II. (*continued*)

	Overall (N = 1,254)	ATTR-wt diagnosis (N = 627)	No ATTR-wt diagnosis (N = 627)	P -value	Absolute std. diff* (%)
Anticoagulant	574 (45.8%)	326 (52.0%)	248 (39.6%)	<.001	
Hospital characteristics					
Region				<.001	34.19
Northeast	416 (33.2%)	253 (40.4%)	163 (26.0%)		
Midwest	298 (23.8%)	143 (22.8%)	155 (24.7%)		
South	352 (28.1%)	139 (22.2%)	213 (34.0%)		
West	188 (15.0%)	92 (14.7%)	96 (15.3%)		
Academic/teaching hospital	1,022 (81.5%)	536 (85.5%)	486 (77.5%)	<.001	21.41
No. of beds	394 (250-595)	457 (264-648)	361 (226-537)	<.001	28.93
Rural location	26 (2.1%)	12 (1.9%)	14 (2.2%)	.70	2.18

* Absolute standardized difference >10% indicates more than negligible imbalance between groups.
† CMS suppression policy prohibits printing cell counts <11.
‡ Among patients discharged alive.
§ Missing included in denominator.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTR-wt, amyloidogenic transthyretin cardiomyopathy-wild-type; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy plus defibrillator; CVA, cerebrovascular accident; GWTG, Get With The Guidelines-Heart Failure; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischemic attack; UTD, unable to determine.

Table III. Univariable associations of 11 ATTR-CM risk factors with ATTR-wt diagnosis in amyloidosis case and control patients matched on age and sex

Risk factor*	Cases: ATTR-CM diagnosis (N = 627)	Controls: nonamyloid HF (N = 627)	Odds ratio (95% CI)
Preserved ejection fraction (EF ≥50%)	262 (41.8%)	287 (45.8%)	0.85 (0.68, 1.06)
Elevated serum enzymes†	165 (26.3%)	84 (13.4%)	2.31 (1.73, 3.09)
Pericardial effusion	126 (20.1%)	29 (4.6%)	5.19 (3.40, 7.90)
Increased left ventricular wall thickness	402 (64.1%)	306 (48.8%)	1.87 (1.49, 2.35)
Conduction disease‡	310 (49.4%)	198 (31.6%)	2.12 (1.68, 2.67)
Arrhythmias‡	483 (77.0%)	425 (67.8%)	1.59 (1.24, 2.05)
Carpal tunnel syndrome	>23 (>3.7%)‖	<11 (<1.8%)‖	3.94 (1.87, 8.28)
Shoulder/hip/knee degenerative joint disease	142 (22.7%)	90 (14.4%)	1.75 (1.31, 2.34)
Lumbar spinal stenosis	72 (11.5%)	33 (5.3%)	2.34 (1.52, 3.58)
Nontraumatic tendon rupture	<11 (<1.8%)‖	<11 (<1.8%)‖	0.67 (0.11, 4.00)
Nondiabetic polyneuropathy	63 (10.1%)	46 (7.3%)	1.41 (0.95, 2.10)

* See Supplemental Table 2 for specific ICD-9/10 codes utilized for each risk factor.
† Elevated troponin and/or elevated NT-proBNP above normal threshold.
‡ Heart block and/or bundle branch block.+Atrial fibrillation and/or atrial flutter.
‖ CMS suppression policy prohibits printing cell counts <11.
ATTR-CM, transthyretin amyloid cardiomyopathy; ATTR-wt, amyloidogenic transthyretin cardiomyopathy-wild-type.

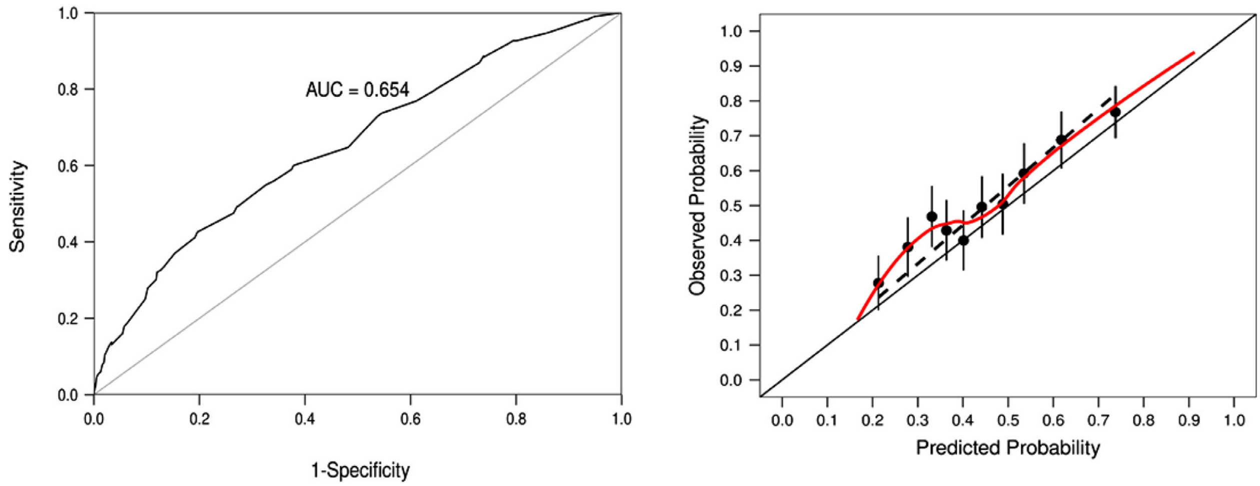
Table IV. Discriminatory performance of the 11 ATTR-CM risk factors in the matched cohort

	Probability threshold							
Metric	0.25	0.30	0.35	0.40	0.45	0.50	0.55	0.75
Sensitivity, %	94.74	88.68	76.87	64.59	54.86	42.58	32.54	5.58
Specificity, %	14.04	26.16	38.92	52.15	67.46	80.38	87.40	99.04
Accuracy, %	54.39	57.42	57.89	58.37	61.16	61.48	59.97	52.31

AUCROC = 0.654 (from the full ROC curve).
ATTR-CM, transthyretin amyloid cardiomyopathy.

estimated prevalence in a broader diverse population.[4] Consistent with prior analyses,[14] frequency of diagnosis appeared to vary by geographic region, with modest underrepresentation of ATTR-CM cases in the Southern and Western US and overrepresentation in the Northeast US, relative to the overall cohort composition. Further, as compared with prior analyses limited to claims data alone, the current study is enhanced by granular clini-

Figure



Receiver operating characteristic curve and calibration plot for the 11-factor model in the matched cohort. The 11-factor model was run without any refitting to obtain predicted probabilities of ATTR-CM in 1:1 sex and age matched patients. A calibration curve was plotted to demonstrate the agreement in predicted and observed probabilities of ATTR-CM diagnosis status. ATTR-CM, transthyretin amyloid cardiomyopathy; AUC, area under receiver operating characteristic curve; GWTG-HF, get with the guidelines-heart failure.

cal data on vital signs, laboratories, and ejection fraction captured within the large GWTG-HF sample, enabling more detailed characterization of patients hospitalized for HF with ATTR-CM. These data suggest that patients hospitalized for HF with a diagnosis of ATTR-CM tend to be male (~70%) with reduced renal function and lower blood pressure compared to counterparts without ATTR-CM diagnosis. Notably, age and ejection fraction did not significantly distinguish patients with or without ATTR-CM diagnosis.

In a prior analysis using claims data to predict wtATTR-CM in outpatient cohorts, the 11-factor random forest model showed strong discrimination (AUROC 0.76-0.95).[9] In contrast, performance in the current cohort of patients hospitalized for HF was more modest (AUROC 0.65), and multiple reasons may explain this difference in performance. First, the original study showing strong discrimination focused exclusively on ICD-10 codes, and specifically the dedicated code for wt-ATTR. (ie, E85.82). The present study utilized a longer timeframe spanning both the ICD-9 and ICD-10 eras. ICD-9 coding did not include specific coding for wt-ATTR, and the wt-ATTR specific ICD-10 code E85.82 was only introduced in October 1, 2017 thus increasing the possibility that patients with hereditary ATTR or other types of amyloid may have been included in this analysis. This possibility of inclusion of hereditary ATTR is further supported by the higher predominance of Black patients among cases vs controls, with prior data suggesting hereditary ATTR disproportionally affects patients of Black race[17].

Second, it is possible that the differences between hospitalized and ambulatory cohorts, in and of themselves, contributed to the model having less discrimination in the current study. For example, in the current analysis, 3 of the 11 factors in the original model (preserved EF, nontraumatic tendon rupture, and nondiabetic polyneuropathy) were not significantly associated between ATTR-CM cases and noncases.

Third, prevalence rates of several of the predictive factors were substantially lower in the current analysis as compared with the original derivation cohort. This could reflect differing epidemiology of a hospitalized cohort, and/or clinicians being less likely to code non-HF diagnosis during the time surrounding an index HF hospitalization. For example, despite both studies primarily relying on diagnosis codes to define each of the 11 conditions, rates of tendon rupture in ATTR cases were 9% in the prior study vs <2% in the current study, and rates of carpal tunnel syndrome in ATTR cases were 32% in the prior study vs 4% in the current study. Alternatively, the scanning window of 6 months pre/postindex hospitalization may have failed to capture more historic diagnoses made years prior to index HF hospitalization if these diagnoses were not documented on recent Medicare claims. Nonetheless, even if more historic diagnoses of ATTR-CM risk factors may not have been coded, the current analysis may better reflect the degree to which these clinical conditions actually detected by clinicians managing patients hospitalized for HF, and the level to which these factors may actively inform medical decision-making.

Given its modest performance, this specific model may not provide substantial incremental clinical utility for diagnosing ATTR-CM in this population. Despite the modest overall performance of the model, several individual clinical factors stood out as strongly associated with ATTR-CM diagnosis. These features were led by pericardial effusion, carpal tunnel syndrome, lumbar spinal stenosis, and elevated serum enzymes (eg, troponin elevation). Pericardial effusion is known to be common in ATTR cardiac amyloidosis (ranging from 26%-49% based on small studies),[4,6,18,19] and the frequent presence in this large hospitalized HF cohort (prevalence 20% and OR 5.2 compared to non-ATTR-CM HF controls) is consistent with the prior model derivation analysis (prevalence 19% and OR 5.2 compared to non-ATTR-CM HF controls).[9] Notably, elevated cardiac serum enzymes also differentiated patients with or without ATTR-CM, but this was driven primarily by troponin elevation while natriuretic peptide levels alone did not significantly differ between cases and HF controls. Other well-known features of ATTR-CM including left ventricular hypertrophy, conduction disease, and arrhythmias were associated with ATTR-CM in this study, albeit not as strongly as the previously noted features. This may reflect, in part, the burden of these conditions in non-ATTR-CM HF as well. Only atrial fibrillation/flutter arrhythmias and carpal tunnel syndrome persisted as discriminating factors in the matched analysis and sensitivity analysis with conservative controls.

Limitations

Limitations of this study should be noted. First, the original analysis and this present study both relied on billing coding/claims data for predictive clinical factors and diagnosis of ATTR-CM, as endomyocardial biopsy, cardiac pyrophosphate imaging, and cardiac magnetic resonance imaging were not available. This may limit the sensitivity and/or accuracy of ATTR-CM diagnosis, but is consistent with prior, population-based analyses.[2,9,14-16] Still, further data are needed to confirm these findings in biopsy/imaging-proven ATTR-CM. Second, GWTG-HF is a voluntary registry, and patient characteristics and diagnosis rates of ATTR-CM may not generalize to all US hospitals. Nonetheless, prior studies have suggested GWTG-HF and predecessor registries to be broadly representative of US clinical practice,[20] and the diagnosis rates for ATTR-CM seen here are consistent with prior analyses using claims data from US clinical practice.[2] Third, as described above, absence of codes for conditions such as carpal tunnel syndrome in inpatient encounters and recent outpatient encounters does not necessarily indicate that there is not a historical diagnosis for that patient, and this could have affected model performance. Fourth, the current study was limited to Medicare beneficiaries with age ≥65 years. Although ATTR-CM is primarily a disease of older adults, the degree to which these findings may generalize to cohorts of hospitalized HF patients with differing age or insurance status is unclear.

Conclusions

Among patients aged ≥65 years hospitalized for HF in US practice, the diagnosis rate of ATTR-CM by billing code increased over the 11-year study period, but the peak of 0.52% in 2019 remains substantially lower than the estimated prevalence by active surveillance studies. Patients with a diagnosis of ATTR-CM have a distinct clinical profile characterized by male sex, Black race, low blood pressure, more impaired kidney function, as well as clinically and statistically significant higher rates of pericardial effusion, carpal tunnel syndrome, and lumbar spinal stenosis. Most factors within the prior 11-factor predictive model were associated with greater odds of ATTR-CM diagnosis, but, in this large population of patients hospitalized for HF, the ATTR-CM model demonstrated modest discrimination. Although these 11-factors may help clinicians when considering likelihood of an ATTR-CM diagnosis, further studies are needed to develop and optimize a systematic, efficient, and scalable approach for identifying patients hospitalized for HF who are at high-risk for underlying ATTR-CM.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.06.013.

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