

ORIGINAL RESEARCH

Native T1 for Diagnosis and Risk Prediction in Amyloid Transthyretin Cardiomyopathy

An Observational Study on 1,675 Subjects

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ABSTRACT

BACKGROUND Native T1 mapping is a contrast-free cardiac magnetic resonance (CMR) marker of myocardial amyloid infiltration, but center-specific diagnostic cutoffs and prognostic strata remain incompletely defined across transthyretin amyloidosis (ATTR).

OBJECTIVES This study aims to define native T1 thresholds and risk strata across the ATTR spectrum and compare its diagnostic and prognostic performance with extracellular volume (ECV).

METHODS In a cohort at a national referral amyloidosis center (2011-2025), 1,675 individuals undergoing CMR for suspected or confirmed ATTR were classified as asymptomatic *TTR*-variant carriers ($n = 125$), extracardiac ATTR ($n = 44$), early ATTR-CM ($n = 73$), or overt ATTR-CM ($n = 1,433$). Diagnostic targets were: 1) any cardiac involvement (early/overt ATTR-CM); and 2) overt vs early ATTR-CM. All-cause mortality from national records was analyzed with Cox models; native T1 strata were calibrated to predefined ECV strata using 3-year mortality.

RESULTS Native T1 rose stepwise across disease categories and correlated with ECV ($r = 0.62$), with weaker coupling in advanced disease. Over a median 3.3 years, 822 of 1,675 (49%) participants died. Native T1 $\leq 1,050$ ms (z-score $+1.14$) identified a low likelihood of cardiac involvement with 93% sensitivity and 84% specificity, whereas native T1 $\geq 1,100$ ms (z-score $+2.40$) identified overt ATTR-CM with 75% sensitivity and 88% specificity. Calibration against ECV strata yielded native T1 risk categories that reproduced a stepwise 3-year mortality gradient, with a stronger gradient at low to intermediate T1 and relative plateauing at higher T1; adding native T1 strata improved prognostic information beyond clinical variables.

CONCLUSIONS Native T1 can provide pragmatic diagnostic supportive thresholds, whereas ECV-calibrated native T1 strata reproduced a graded 3-year mortality risk. Native T1 offers a practical contrast-free approach to support diagnosis and risk stratification, although ECV remains the preferred quantitative marker when contrast CMR is available. Thresholds and z-score based approaches still require local recalibration and external validation before adoption at other centers. (JACC Cardiovasc Imaging. 2026;■:■-■) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

ABBREVIATIONS
AND ACRONYMS**ATTR** = transthyretin amyloidosis**ATTR-CM** = amyloid transthyretin cardiomyopathy**AUC** = area under the curve**CMR** = cardiac magnetic resonance**ECV** = extracellular volume**LGE** = late gadolinium enhancement**NAC** = National Amyloidosis Centre**ROC** = receiver operating characteristic

Cardiac involvement in transthyretin amyloidosis (ATTR) manifests as a biological continuum, from asymptomatic gene carriers or patients with extracardiac deposits to overt amyloid cardiomyopathy (ATTR-CM).¹ Accurate quantification of myocardial amyloid burden is essential for diagnosis, staging, and monitoring response to disease-modifying and amyloid-clearing therapies.² Cardiac magnetic resonance (CMR) has become the noninvasive reference standard for this purpose.³⁻⁵ Contrast-enhanced extracellular volume (ECV) mapping directly quantifies expansion of the myocardial extracellular compartment due to amyloid fibril deposition

and has been shown to define thresholds that stratify risk and guide management in ATTR-CM.⁶

ECV measurement requires administration of gadolinium-based contrast agents, which is less desirable in patients with renal impairment, lengthens examination time, and limits the feasibility of serial assessments.⁷ Native T1 mapping is a noncontrast CMR marker of myocardial tissue composition⁸ that is elevated in ATTR-CM,⁸ shows high diagnostic accuracy for amyloid CM,^{9,10} and correlates with established markers of disease severity,^{7,8} making it attractive when contrast administration is undesirable or streamlined evaluation is needed. Despite promising results, translation of native T1 mapping into broad clinical use remains limited by the lack of information about its relationship to absolute amyloid burden and independent prognostic value across the ATTR spectrum.

This study builds on the evolving ECV framework to evaluate how noncontrast native T1 mapping relates to myocardial amyloid infiltration and clinical outcomes in ATTR-CM. The objectives are to define clinically meaningful native T1 categories that correspond to ECV strata and to assess their diagnostic and prognostic value. By situating native

T1 within this calibrated quantitative framework, the study examines whether a rapid, contrast-free approach can serve as a practical tool for disease staging and serial monitoring in ATTR amyloidosis.

METHODS

STUDY COHORT AND DIAGNOSTIC WORKUP. We included all consecutive eligible patients undergoing CMR at the NAC (National Amyloidosis Centre) between February 2011 and June 2025. Eligible participants had a definitive ATTR diagnosis or were TTR-variant carriers, underwent standardized 1.5-T mapping with analyzable native T1 (and, where applicable, ECV), and had sufficient clinical and scintigraphic data for phenotypic classification. Patients with alternative or uncertain diagnoses, inadequate image quality, or missing key CMR or laboratory data were excluded (Supplemental Figure 1).

The final study cohort comprised 1,675 individuals, categorized as TTR-variant carriers, extracardiac ATTR, early ATTR-CM, or overt ATTR-CM according to prespecified criteria:

- Asymptomatic TTR-variant carriers: no myocardial uptake on ^{99m}technetium labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy; N-terminal pro-B-type natriuretic peptide and troponin T within upper reference limits, and echocardiography judged normal for age by the evaluating cardiologists.
- Extracardiac ATTR: biopsy-proven peripheral ATTR deposits (eg, transverse carpal ligament) with no clinical cardiac involvement as defined previously.
- Early-stage ATTR-CM: Perugini grade 1 myocardial uptake on ^{99m}Tc-DPD scintigraphy, no monoclonal gammopathy, and biopsy-proven ATTR amyloidosis.
- Overt ATTR-CM: characteristic echocardiogram or CMR, and either direct endomyocardial biopsy proof of ATTR amyloid or presence of ATTR amyloid in an extracardiac biopsy along with cardiac uptake, or grade 2 to 3 cardiac uptake in the

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

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absence of biochemical evidence of a plasma cell dyscrasia.¹¹

No formal sample size calculation was performed; we included all consecutive eligible patients over the study period. Patients provided written informed consent for analysis and publication of data (Research Ethics Committee reference 21/PR/0620) and were managed in accordance with the Declaration of Helsinki. Follow-up began with the date of CMR and was censored in October 2025. Mortality data were obtained via the UK Office of National Statistics. All-cause mortality was ascertained through national records; no patients were lost to follow-up for the primary outcome.

CMR PROTOCOL. See the [Supplemental Material](#).

STATISTICAL ANALYSIS. See the [Supplemental Material](#).

RESULTS

STUDY POPULATION AND SUBGROUPS. The study cohort comprised 1,675 participants classified as asymptomatic carriers ($n = 125$ [8%]), patients with extracardiac ATTR deposits ($n = 44$ [3%]), early-stage ATTR-CM ($n = 73$ [4%]), or overt ATTR-CM ($n = 1,433$ [86%]). Two-thirds ($n = 1,134$ [67%]) harbored no *TTR* variant, 213 (13%) carried Val122Ile, and 328 (20%) carried other *TTR* variants. The main participant characteristics across groups are reported in [Table 1](#). Missing data for each variable are reported in [Supplemental Table 1](#).

At the time of baseline CMR, 419 of 1,675 patients (25.0%) were enrolled in a clinical trial and 388 of 1,675 (23.2%) were receiving tafamidis, all of whom had early or overt ATTR-CM.

NATIVE T1 VS ECV. Native T1 values increased progressively across the amyloidosis spectrum, from asymptomatic *TTR*-variant carriers and patients with extracardiac ATTR to early and overt ATTR-CM ([Table 1](#), [Figure 1](#)).

We then examined the relationship between native T1 and ECV in the whole cohort and in prespecified subgroups. In the overall cohort, native T1 and ECV were moderately correlated and showed an approximately linear association, with an increase of about 30 ms in native T1 per 10% higher ECV. This association was strongest in variant carriers, extracardiac/early ATTR, younger patients, and women, and became shallower at very high ECV ($ECV \geq 60\%$). Accordingly, native T1 increased stepwise from low to very high ECV, but within the highest ECV range ($\geq 60\%$) the association between T1 and ECV became flatter. Native T1 and ECV both increased across Perugini

grades. The strength of the T1-ECV correlation varied with scintigraphic uptake: the regression slope was steep in Perugini 0 and 1 (6.5 and 3.8 ms per 1% ECV; $r = 0.50$ and 0.59 , respectively) but flatter in Perugini 2 and 3 (around 1.5 ms per 1% ECV; $r = 0.27$ - 0.28); 95% CIs for all correlation coefficients are reported in [Supplemental Table 2](#).

NATIVE T1 TO PREDICT CARDIAC INVOLVEMENT: DIAGNOSTIC CUTOFFS.

For the prediction of any cardiac involvement (ie, early or overt ATTR-CM) in the overall cohort, the area under the curve (AUC) for native T1 was 0.957. The 1,041-ms native T1 threshold showed 95% sensitivity and 78% specificity for identifying patients with a low likelihood of cardiac involvement, although its negative predictive value was lower than that of ECV ([Table 2](#)). Among individuals with either early or overt ATTR-CM, native T1 discriminated overt disease with an AUC of 0.900, compared with ECV AUC 0.988 ($P < 0.001$). A threshold of 1,119 ms yielded 59% sensitivity and 96% specificity for identifying overt ATTR-CM. For pragmatic clinical use, these thresholds were approximated to 1,050 and 1,100 ms, respectively. These cutoffs displayed a good diagnostic performance, broadly similar to ECV rule-out and rule-in cutoffs previously defined ([Table 2](#)). The diagnostic performance was good also across a variety of subgroups ([Supplemental Table 3](#)).

The exact receiver operating characteristic (ROC)-derived native T1 thresholds of 1,041 ms and 1,119 ms corresponded to z-scores of +0.91 and +2.88, respectively, relative to the local healthy reference cohort. The pragmatic thresholds used for clinical reporting, 1,050 ms and 1,100 ms, corresponded to z-scores of +1.14 and +2.40, respectively. At these rounded thresholds, native T1 $\leq 1,050$ ms identified a low likelihood of cardiac involvement with 93% sensitivity and 84% specificity, whereas native T1 $\geq 1,100$ ms identified overt ATTR-CM with 75% sensitivity and 88% specificity.

NATIVE T1 FOR RISK PREDICTION. During a median follow-up of 3.3 years (Q1-Q3: 1.8-5.1 years), 822 patients (49%) died, with 22 deaths (9%) over 4.3 years (Q1-Q3: 2.8-6.7 years) in the subgroup without overt ATTR-CM, and 815 deaths (54%) over 3.3 years (Q1-Q3: 1.8-5.0 years) in the subgroup with either early or overt ATTR-CM. After the baseline CMR, 175 patients (10%) were subsequently enrolled in a clinical trial and 63 (4%) started tafamidis during follow-up.

In the whole cohort, we derived native T1 categories intended to mirror the prognostic information conveyed by established ECV strata ($<30\%$, 30% - 39% , 40% - 49% , 50% - 59% , and $\geq 60\%$).

TABLE 1 Participant Characteristics

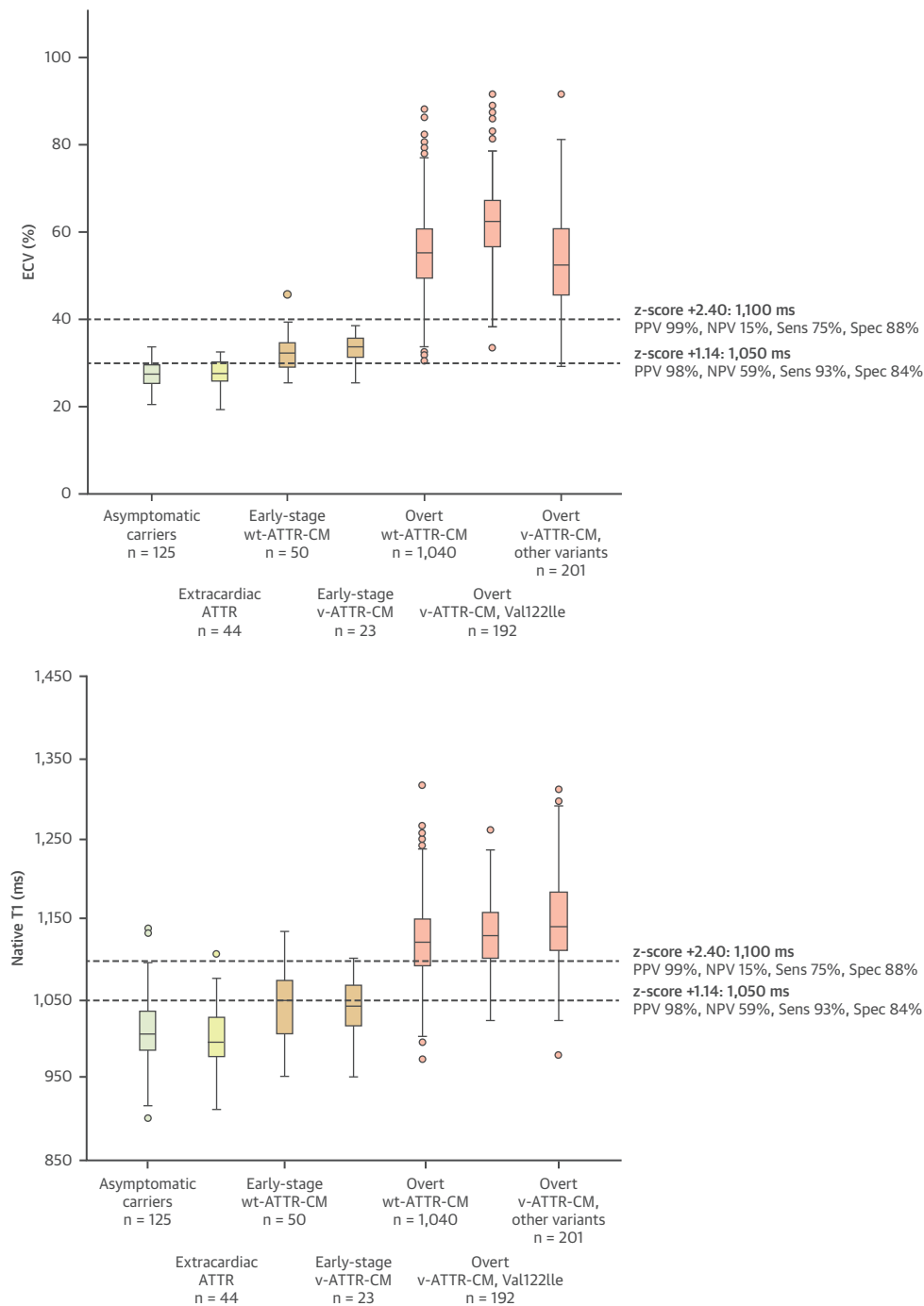
	Asymptomatic Carriers (n = 125)	Extracardiac ATTR (n = 44)	Early-Stage ATTR-CM (n = 73)	Overt ATTR-CM (n = 1,433)
Age, y	55 (45-64)	81 (76-87) ^a	79 (71-88) ^b	80 (74-85) ^c
wt form	0 (0)	44 (100) ^a	50 (69) ^b	1,040 (73) ^{c,d}
v genotype	125 (100)	0 (0) ^a	23 (32) ^b	393 (27) ^{c,d}
Val122Ile	19 (15)	0 (0) ^a	2 (3) ^b	192 (13) ^{c,d}
Other variants	106 (85)	0 (0) ^a	21 (29) ^b	201 (14) ^{c,d}
Comorbidities				
Diabetes	9 (7)	4 (9)	9 (12)	202 (14)
Ischemic heart disease	1 (1)	9 (21) ^a	14 (19) ^b	265 (19) ^c
Hypertension	14 (11)	18 (41) ^a	21 (29) ^b	474 (33) ^c
Atrial fibrillation	1 (1)	6 (14) ^a	16 (22) ^b	716 (50) ^{c,d}
NYHA I/II/III/IV	122/3/0/0 (98/2/0/0)	34/10/0/0 (77/23/0/0) ^a	55/15/3/0 (75/21/4/0) ^b	1/226/981/223/2 (0/16/69/16/0) ^{c,d}
Laboratory exams				
NT-proBNP, ng/L	50 (50-88)	161 (92-302) ^a	276 (86-1,090) ^b	2,537 (1,319-4,740) ^{c,d,e}
hs-troponin T, ng/L	4 (3-8)	12 (10-17) ^a	19 (12-33) ^{b,f}	57 (38-80) ^{c,d,e}
eGFR, mL/min/1.73 m ²	88 (75-90)	73 (57-84) ^a	72,854-85) ^b	60 (47-75) ^{c,d,e}
NAC stage 1/2/3	120/1/2 (96/1/2)	39/2/0 (95/5/0)	60/80/4 (82/11/6) ^b	794/459/166 (56/32/12) ^{c,d}
Perugini grade 0/1/2/3	123/0/0/0 (100/0/0/0)	38/4/0/0 (90/0/0/0) ^a	3/70/0/0 (4/96/0/0) ^b	1/19/1,113/289 (0/1/78/20) ^{c,d}
CMR				
Mean wall thickness, mm	10 (9-11)	12 (10-12) ^a	12 (10-14) ^b	19 (17-22) ^{c,d,e}
LVMI, g/m ²	56 (48-66)	63 (52-73)	69 (61-81) ^b	122 (101-145) ^{c,d,e}
LVEDVi, mL/m ²	69 (59-77)	69 (61-77)	72 (857-81)	69 (59-82)
LVSVi, mL/m ²	47 (41-52)	46 (42-52)	47 (39-51)	40 (33-46) ^{c,d,e}
LVEF, %	69 (64-73)	69 (64-73)	68 (62-74)	58 (47-67) ^{c,d,e}
MAPSE, mm	13 (12-15)	12 (11-13)	11 (10-13) ^{b,f}	7 (6-9) ^{c,d,e}
LA area index, cm ² /m ²	11 (10-13)	14 (12-16) ^a	14 (11-16) ^b	17 (15-19) ^{c,d,e}
RA area index, cm ² /m ²	10 (9-12)	12 (10-14) ^a	11 (9-14) ^b	15 (13-18) ^{c,d,e}
RVEDVi, mL/m ²	77 (58-84)	76 (62-83)	70 (59-75)	70 (59-89)
RVEF, %	64 (62-67)	60 (62-74)	66 (56-72)	51 (41-60) ^{c,d,e}
TAPSE, mm	23 (20-26)	23 (19-26)	20 (16-22) ^{b,f}	12 (9-16) ^{c,d,e}
LGE presence	22 (19)	16 (39)	47 (77) ^{b,f}	1,165 (100) ^{c,d,e}
LGE pattern: absent/subendocardial/transmural/patchy	110/0/0/4 (96/0/0/4)	35/0/1/5 (85/0/2/12)	27/13/2/19 (44/21/3/31) ^{b,f}	6/364/765/34 (1/31/65/3) ^{c,d,e}
ECV, %	28 (26-30)	29 (26-31)	33 (31-36) ^{b,f}	56 (49-62) ^{c,d,e}
Native T1, ms	1,010 (989-1,040)	1,001 (981-1,031)	1,051 (1,010-1,080) ^{b,f}	1,129 (1,099-1,160) ^{c,d,e}

Values are median (Q1-Q3) or n (%), unless otherwise indicated. For categorical variables, the percentages were calculated out of the available values. Lower case letters indicate significant *P* values after the Bonferroni correction (*P* < 0.008) for the following comparisons: ^aasymptomatic carriers vs extracardiac ATTR; ^basymptomatic carriers vs early-stage ATTR-CM; ^casymptomatic carriers vs overt ATTR-CM; ^dearly-stage ATTR-CM vs overt ATTR-CM; ^eextracardiac ATTR-CM vs overt ATTR-CM; ^fextracardiac ATTR vs early-stage ATTR-CM.

ATTR = amyloid transthyretin; CM = cardiomyopathy; CMR = cardiac magnetic resonance; ECV = extracellular volume; eGFR = estimated glomerular filtration rate; hs = high-sensitivity; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LVSVi = left ventricular stroke volume index; MAPSE = mitral annular plane systolic excursion; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RA = right atrial; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVSVi = right ventricular stroke volume index; TAPSE = tricuspid annular plane systolic excursion; v = variant; wt = wild-type.

Among patients with both ECV and native T1 available, we estimated 36-month Kaplan-Meier mortality within each ECV stratum and then searched for 4 native T1 thresholds that defined 5 T1 strata whose category-specific 36-month mortality best approximated that of the corresponding ECV strata. Candidate T1 cutpoints were iteratively adjusted to minimize the sum of squared differences between ECV- and T1-based 3-year mortality. This procedure yielded initial native T1 ranges of <980, 980-1,029, 1,030-1,049, 1,050-1,259, and ≥1,260 ms. To reduce the large imbalance in sample size in the 1,050-1,259 ms category while preserving a similar 3-year

mortality to the ECV 50% to 59% stratum, the upper cutoff was subsequently refined to 1,130 ms. This calibration yielded native T1 ranges <980, 980-1,029, 1,030-1,049, 1,050-1,129, and ≥1,130 ms, which showed similar 3-year mortality to the corresponding ECV ranges, with the partial exception of the highest native T1 and ECV ranges ([Supplemental Table 4](#)). Survival curves showed a good separation across native T1 strata except for the 2 highest strata ([Figure 2](#)). This was in line with the risk of mortality displaying a plateau for native T1 values higher than 1,130 ms, as opposed to the continuous increase in risk for ECV values ([Figure 2](#)).

FIGURE 1 ECV and Native T1 Values Across Diagnostic Categories

The horizontal dashed line on the left graph corresponds to the rule-out and rule-in extracellular volume (ECV) cutoffs previously established (30% and 40%), and those on the right graph to the native T1 cutoffs identified in the present study as conveying a similar diagnostic information (1,050 and 1,100 ms). ATTR = transthyretin amyloidosis; ATTR-CM = amyloid transthyretin cardiomyopathy; NPV = negative predictive value; PPV = positive predictive value; Sens = sensitivity; Spec = specificity; v = variant; wt = wild-type.

TABLE 2 Diagnostic Performance of Native T1 Cutoffs

	Outcome	Measure	Metric	Threshold	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Whole cohort	Early or overt ATTR-CM	Native T1	Rule-out	1,050 ms	93 (92-95)	84 (78-89)	98 (97-99)	59 (52-65)
		ECV	Rule-out	30%	99 (98-100)	68 (61-76)	96 (95-97)	90 (83-95)
Early or overt ATTR-CM	Overt ATTR-CM	Native T1	Rule-in	1,100 ms	75 (73-77)	88 (78-94)	99 (98-100)	15 (12-19)
		ECV	Rule-in	40%	96 (95-97)	95 (87-99)	100 (99-100)	54 (44-63)

NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 1.

The 2 higher native T1 ranges were then merged. When added to the clinical model (age, sex, genotype, left ventricular ejection fraction), native T1 strata (<980, 980-1,029, 1,030-1,049, and ≥1,050 ms) provided only a modest improvement in 1-year risk reclassification but a more evident incremental value for 3- and 5-year mortality prediction (Supplemental Table 5).

Late gadolinium enhancement (LGE) was evaluated as an additional qualitative imaging covariate for prognosis. In the whole cohort, both LGE presence and LGE pattern provided incremental prognostic information beyond the clinical models (Supplemental Table 6). When added to models already including native T1 strata, LGE presence remained independently associated with mortality, and LGE pattern also improved model fit, with transmural LGE showing the strongest adverse association. By contrast, neither LGE presence nor LGE pattern added significant prognostic information once ECV strata were included (Supplemental Table 6).

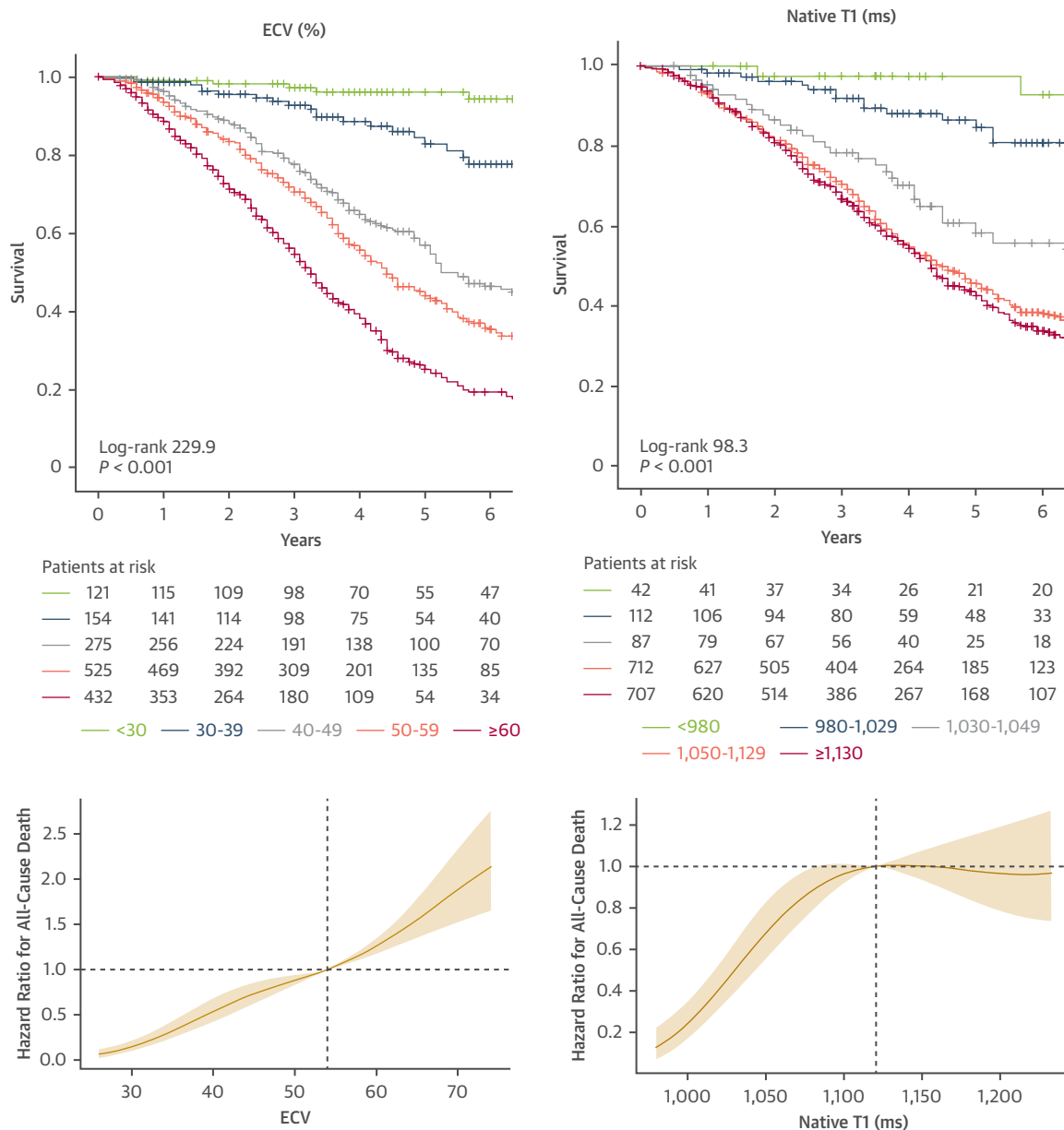
In sensitivity analyses adjusting for baseline tafamidis use and baseline trial enrollment, the prognostic associations of both native T1 and ECV remained robust. Adding native T1 strata to the treatment-adjusted clinical models improved model fit both before and after inclusion of NAC stage (likelihood ratio chi-square 73.8 and 69.4, respectively; both $P < 0.001$). In the fully adjusted model, compared with native T1 <980 ms, HRs were 4.38 (95% CI: 1.01-19.13; $P = 0.049$) for 980-1,029 ms, 11.82 (95% CI: 2.80-49.85; $P < 0.001$) for 1,030-1,049 ms, and 15.67 (95% CI: 3.84-63.87; $P < 0.001$) for ≥1,050 ms. Likewise, ECV strata retained strong prognostic value after treatment adjustment (likelihood ratio chi-square 122.4 and 114.1 before and after inclusion of NAC stage, respectively; both $P < 0.001$). In the fully adjusted model, compared with ECV <30%, HRs were 3.06 (95% CI: 1.36-6.90; $P = 0.007$) for 30% to 39%, 8.07 (95% CI: 3.87-16.82; $P < 0.001$) for 40% to 49%, 8.91 (95% CI: 4.32-18.39; $P < 0.001$) for 50% to 59%, and 11.96 (95% CI: 5.79-24.72; $P < 0.001$) for ≥60%.

DISCUSSION

In this large single-center cohort spanning the full spectrum of transthyretin amyloidosis, we compared native T1 mapping and ECV for the diagnosis and risk stratification of ATTR-CM. The main findings are that both markers showed high diagnostic accuracy for cardiac involvement; that pragmatic native T1 thresholds of 1,050 ms and 1,100 ms provide a clinically useful, contrast-free framework to support diagnostic interpretation; and that native T1 categories calibrated against ECV reproduce a graded mortality signal and add prognostic information beyond contemporary clinical models. Overall, these data support complementary roles for ECV and native T1, with ECV remaining the preferred contrast-based quantitative marker and native T1 serving as a robust contrast-free alternative within a standardized local acquisition and analysis framework (Central Illustration).

A key observation is that the relationship between native T1 and ECV is stage-dependent. Across the disease spectrum, both markers increased with cardiac involvement and scintigraphic burden, consistent with their shared relation to myocardial interstitial expansion. However, their coupling was strongest in earlier disease and weaker in advanced infiltration, where ECV continued to rise despite a flatter increase in native T1. This suggests that the 2 markers capture overlapping but not identical aspects of myocardial involvement. A plausible explanation is that in earlier disease both markers are strongly influenced by interstitial expansion, whereas in advanced disease ECV continues to track extracellular amyloid burden more linearly while native T1 shows relative saturation. Although this interpretation remains inferential, it is biologically plausible and helps explain why native T1 appears particularly informative at lower to intermediate disease burden, whereas ECV better preserves discrimination in advanced disease.

These findings extend previous work on native T1 in ATTR from proof-of-concept to practical implementation across the disease continuum.

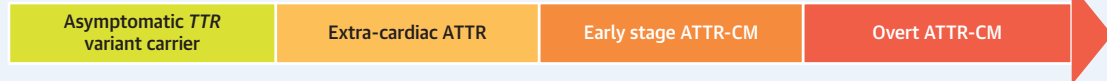
FIGURE 2 ECV, Native T1, and Outcome

Kaplan-Meier survival curves (top) and restricted spline curve analyses (bottom). In the Kaplan-Meier graphs, patients are stratified based on previously established ECV ranges and native T1 ranges. In the spline curves, the horizontal dashed line marks the HR = 1 value, and the vertical dashed line the corresponding ECV and native T1 values (54% and 1,120 ms, respectively). Abbreviation as in [Figure 1](#).

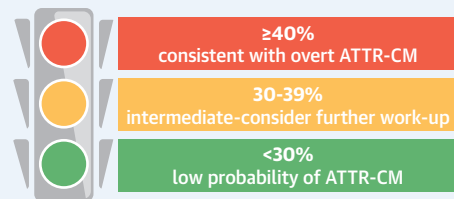
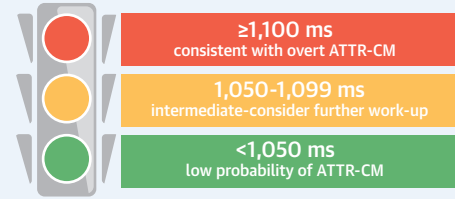
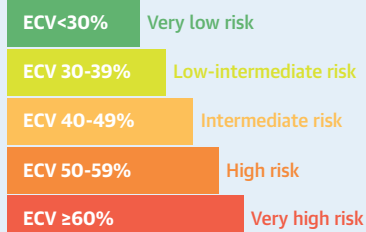
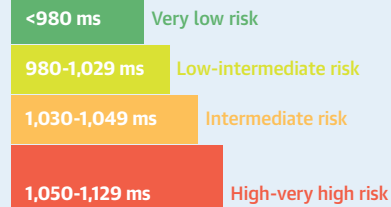
Earlier studies showed that native T1 is elevated in ATTR-CM, correlates with disease severity, and can distinguish amyloid cardiomyopathy from other phenotypes, but they were smaller, often focused on overt cardiomyopathy, and were not designed to define clinically actionable thresholds within the contemporary ATTR-CM diagnostic pathway.^{7,8}

By contrast, the present cohort included asymptomatic TTR-variant carriers, extracardiac ATTR, early ATTR-CM, and overt ATTR-CM, allowing us to position native T1 as a quantitative myocardial signal across the full spectrum of disease.

From a diagnostic perspective, native T1 performed well across the ATTR spectrum. Native T1

CENTRAL ILLUSTRATION Native T1 for Diagnosis and Risk Stratification in ATTR-CM**Quantitative CMR in ATTR-CM**
ECV as Reference Standard, Native T1 as Contrast-Free Alternative**ATTR-CM disease continuum**

Both ECV and native T1 increase with myocardial amyloid burden; native T1 tends to plateau at highest burden

**ECV-Based Diagnostic Pathway****Native T1-Based Diagnostic Pathway****Risk Stratification****ECV-based risk strata****Calibrated native T1 risk strata**

Calibrated native T1 strata approximate ECV-based risk and add independent prognostic information (with a plateau at the highest T1 levels)



Prefer ECV, when contrast is feasible, as the primary quantitative marker for myocardial amyloid burden and risk stratification across the full disease spectrum.

Use native T1 as a contrast-free adjunct: diagnostic cut-offs are supportive within multimodality pathways, and native T1 categories may support risk stratification

Aimo A, et al. JACC Cardiovasc Imaging. 2026;■(■):■-■.

ATTR = transthyretin amyloidosis; ATTR-CM = amyloid transthyretin cardiomyopathy; ECV = extracellular volume.

rose progressively from carriers and extracardiac ATTR to early and overt ATTR-CM, paralleling ECV and capturing the continuum of myocardial amyloid infiltration without contrast administration. Within this framework, a value around 1,050 ms identified a low likelihood of cardiac involvement, whereas a value around 1,100 ms strongly favored overt ATTR-CM. These operating points were derived from prespecified sensitivity and specificity targets: a high-sensitivity rule-out threshold to minimize false-negative classifications when assessing cardiac involvement, and a high-specificity rule-in threshold to minimize false-positive classifications when identifying overt ATTR-CM. Importantly, these cutoffs should be regarded as supportive decision thresholds within a multimodality diagnostic pathway, not as stand-alone diagnostic criteria. They may increase or decrease suspicion for cardiac involvement, but they do not replace scintigraphy, serological testing, clinical assessment, or echocardiography.

The local reference framework is central to the interpretation of these thresholds. In our center, the exact ROC-derived native T1 thresholds of 1,041 ms and 1,119 ms corresponded to *z*-scores of +0.91 and +2.88, respectively, relative to the healthy reference cohort, whereas the pragmatic reporting thresholds of 1,050 ms and 1,100 ms corresponded to *z*-scores of +1.14 and +2.40. The exact ROC-derived values were rounded to these pragmatic thresholds to improve clinical interpretability and avoid false precision. This is important because operating points derived from empirical ROC curves, particularly in high-sensitivity or high-specificity regions, may be less stable in small samples or sparse subgroups. Expressing native T1 relative to a reference population in *z*-score terms may improve interpretability and may support better cross-site comparability than raw millisecond values alone.

The translational role of native T1 should therefore be interpreted in the context of the diagnostic framework used in this study. Cardiac involvement was not defined by CMR alone, but by multimodality assessment integrating clinical evaluation, laboratory testing, echocardiography, and bone scintigraphy. Our data therefore do not support native T1 as a replacement for the established diagnostic pathway. Rather, its main value is that it provides a continuous, contrast-free myocardial signal that can support phenotypic characterization, triage, and follow-up, particularly when gadolinium is contraindicated or when a streamlined noncontrast CMR protocol is desirable. At the same time, the relatively small numbers of patients with early ATTR-CM and

extracardiac ATTR mean that diagnostic performance estimates in these subgroups remain less precise and should be interpreted cautiously until confirmed in larger and less selected cohorts.

For risk prediction, native T1 and ECV showed overlapping but nonidentical relationships with outcome. ECV displayed a near-linear association with mortality across its range, whereas native T1 showed its clearest risk gradient at low to intermediate values, with relative plateauing at the highest values, consistent with the stage-dependent divergence between the 2 markers. Calibrating native T1 against predefined ECV strata allowed us to derive practical T1 categories that reproduced a clear stepwise increase in 3-year mortality. Although the highest native T1 category did not fully recapitulate the very high risk observed for ECV $\geq 60\%$, it still identified patients with clearly adverse outcomes. When added to clinical models, these native T1 strata provided independent prognostic information, with modest value for short-term reclassification but clearer incremental value for 3- and 5-year risk prediction.

Qualitative LGE further refines this framework. In the whole cohort, both LGE presence and LGE pattern provided incremental prognostic information beyond the clinical models, and transmural LGE showed the strongest adverse association. However, once ECV strata were included, LGE no longer provided significant additional prognostic information, whereas it remained informative in models containing native T1 strata. This supports the concept that ECV captures myocardial disease burden more comprehensively, whereas native T1 benefits from complementary qualitative tissue characterization. Taken together, these findings support a pragmatic imaging hierarchy: when contrast CMR is feasible, ECV should remain the preferred quantitative marker for staging and prognostication, with LGE providing complementary qualitative information; when gadolinium cannot be used or when a non-contrast protocol is preferred, native T1 offers a practical framework for supportive diagnostic interpretation and risk stratification.

STUDY STRENGTHS AND LIMITATIONS. This study has important strengths, including its large sample size, inclusion of the full ATTR spectrum, and linkage of imaging findings to hard outcome data. Several limitations also should be acknowledged. First, this was a single-center study performed on a single 1.5-T platform with a specific Modified Look-Locker Inversion-Recovery implementation and post-processing workflow, which limits generalizability. Although expressing native T1 relative to a healthy

reference population as z-scores may improve standardization and comparability beyond absolute millisecond thresholds, z-scores do not eliminate the need for local recalibration and external validation. Second, overt ATTR-CM represented most of the cohort, whereas early ATTR-CM and extracardiac ATTR were comparatively small groups, reducing precision for inferences in earlier disease. Similarly, diagnostic operating points in high-sensitivity or high-specificity regions may be less stable in smaller subgroups, and the subgroup diagnostic estimates should therefore be interpreted cautiously. Third, analyses were based on complete cases. Fourth, although sensitivity analyses adjusting for baseline tafamidis use and baseline trial enrollment did not materially change the prognostic associations, residual treatment-related confounding cannot be fully excluded in a cohort spanning a period during which disease-modifying therapies became increasingly available. Finally, the present analysis was based on baseline imaging, and longitudinal studies are needed to determine whether serial changes in native T1 track treatment response and improve monitoring strategies.

CONCLUSIONS

ECV remains the preferred quantitative marker of myocardial amyloid burden and prognosis when contrast-enhanced CMR is available. Native T1 provides a practical contrast-free alternative for characterizing myocardial involvement and staging risk using locally derived thresholds and ECV-informed categories. Its principal value is as a continuous quantitative marker that complements, rather than replaces, the current diagnostic pathway. The proposed native T1 cutoffs should therefore be regarded as supportive thresholds for clinical interpretation. Reporting native T1 relative to a local healthy reference population as z-scores may facilitate interpretation and may improve comparability beyond raw millisecond values alone, but both thresholds and z-score-based approaches still require local recalibration and external validation before adoption at other centers.

DATA AVAILABILITY Data are available on reasonable request to the corresponding author.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Native T1 mapping is a contrast-free CMR marker that rises with myocardial transthyretin amyloid involvement and can provide a continuous quantitative estimate of myocardial infiltration across the ATTR spectrum. Its greatest clinical value may be in disease characterization, triage, and follow-up when gadolinium is undesirable or contraindicated. Native T1 should be interpreted alongside biomarkers, and clinical staging, and should not be used as a stand-alone rule-out test. When contrast CMR is available, ECV remains the preferred quantitative marker for amyloid burden and risk stratification, with LGE providing complementary qualitative information. Native T1 categories aligned to ECV may aid decisions about referral urgency, follow-up intensity, and treatment discussions, particularly in settings where a streamlined noncontrast approach is needed. Expressing native T1 relative to a local healthy reference population as z-scores may aid interpretation, but both z-scores and absolute thresholds remain protocol dependent and should be used only within a validated local framework.

TRANSLATIONAL OUTLOOK: Multicenter studies are needed to confirm the performance of native T1 thresholds and risk strata across scanners, field strengths, mapping sequences, post-processing workflows, and patient populations, and to establish harmonized reporting that supports cross-site comparability. Future work should define practical strategies for local recalibration, including site-specific normal ranges, phantom- or z-score-based normalization, and prospective validation against diagnostic and prognostic endpoints. Additional studies should clarify how native T1 can be integrated with ECV and LGE in multimodality risk models, why native T1-ECV coupling weakens in advanced disease, and whether serial native T1 changes track treatment response and improve clinical decision-making.

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KEY WORDS CMR, diagnosis, magnetic resonance, risk prediction, T1 mapping, transthyretin amyloidosis

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