3.0T cardiac magnetic resonance quantification of native T1 and myocardial extracellular volume for the diagnosis of late gadolinium enhancement-negative cardiac amyloidosis

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Background: Late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) is useful for the detection of cardiac amyloidosis (CA), but characteristic LGE patterns do not always occur or they appear late in the disease. Native T1 and extracellular volume (ECV) by T1 mapping may improve disease detection and quantify myocardial amyloid load.

Methods: Thirty patients with definite CA, 10 patients with possible CA, 20 patients with hypertrophic cardiomyopathy (HCM) and 40 healthy volunteers were performed 3.0-T CMR including cine, pre- and postcontrast T1 mapping and LGE. Receiver-operating characteristic (ROC) curves were constructed to assess the diagnostic ability of native T1 and ECV for CA. Correlation analysis between native T1 or ECV and cardiac biomarkers, structure, and function indexes were assessed using Pearson or Spearman correlation, as appropriate.

Results: Native T1 values were 1,429±93, 1,290±49, 1,304±42, and 1,225±21 ms, in definite CA, possible CA, HCM, and healthy controls, respectively. ECV values were 44%±9%, 34%±5%, 33%±4%, and 24%±3%, in definite CA, possible CA, HCM, and healthy controls, respectively. Native T1 [area under curve (AUC) =0.89, 95% confidence interval (CI): 0.75–1.00, P<0.001] and ECV (AUC =0.99, 95% CI: 0.98–1.00, P<0.001) showed good ability to differentiate LGE-negative patients with possible CA from healthy controls, especially ECV. Positive correlations were found between native T1 or ECV and New York Heart Association (NYHA) functional class (r=0.673 and r=0.594, respectively; P<0.001), NT-proBNP (r=0.668 and r=0.603, respectively; P<0.001), troponin T (r=0.724 and r=0.591, respectively; P<0.001), left ventricular (LV) mass index (r=0.668 and r=0.579, respectively; P<0.001), and global LV wall thickness (r=0.765 and r=0.629, respectively; P<0.001). Negative correlations were found between native T1 or ECV and left ventricular ejection fraction (LVEF) (r=–0.761 and r=–0.668, respectively; P<0.001) and left ventricular stroke volume (LVSV) (r=–0.777 and r=–0.729, respectively; P<0.001).

Conclusions: Native T1 and ECV, which are able to reflect cardiac biochemistry, structure, and function, have high diagnostic accuracy for detecting CA, especially in LGE-negative patients, and thus could be used for early diagnosis of CA.

Keywords: Cardiac amyloidosis (CA); cardiac magnetic resonance (CMR); native T1; extracellular volume (ECV)

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Introduction

Amyloidosis is a systemic disease caused by extracellular deposition of an insoluble fibril that disrupts the architecture and function of normal tissues and organs (1). Amyloid light-chain (AL) amyloidosis results from the deposition of immunoglobulin light-chain fragments and is the most prevalent and serious form of systemic amyloidosis (2). Cardiac involvement is the most common type of AL amyloidosis and is characterized by rapid progression, mis- and delayed diagnosis, and poor prognosis (3). Therefore, early diagnosis is very important for patients with AL amyloidosis (3). In current clinical practice, endomyocardial biopsy (EMB) is considered the gold standard for cardiac amyloidosis (CA) diagnosis. However, the invasive methodology and complicated sample processing and assessment procedures hinder it as a rapid diagnosis tool (4). Moreover, commonly employed noninvasive CA evaluation methods including electrocardiograph (ECG), echocardiographic and cardiac biomarkers was respectively hindered by only late disease stage identification (5), unstable specificity (6) and not fully verified scoring system (7). For effective evaluation of early stage cardiac involvement during CA process, development of a novel modality for early diagnosis of AL amyloidosis is needed.

Cardiac magnetic resonance (CMR) has recently emerged as a noninvasive technique for CA diagnosis via late gadolinium enhancement (LGE) imaging. As an accurate tool for myocardial mass and thickness evaluation, CMR can provide unique information about tissue composition, with a typical pattern of diffuse subendocardial or transmural enhancement rarely seen in other cardiomyopathies (8-10). Furthermore, CA can also be present in LGE-negative patients with normal left ventricular wall thickness (11,12).

A previous study (13) has reported that T1 mapping techniques combined with gadolinium-based contrast enhancement can be used to assess diffuse myocardial fibrosis and quantitatively measure the progression of cardiac amyloid infiltration from early infiltration with negative LGE to diffuse transmural involvement. Meanwhile, native T1 representing the intrinsic signal of the myocardium and myocardial c(ECV) can be used as an index for CA diagnosis. However, a variety of factors, including differences in field intensity, vendor, center-specific protocols, and pulse sequence, have made specific cut-offs for native T1 and ECV difficult to define. Moreover, most of the data have been obtained from meta-analyses. It is important to standardize local reference ranges for native T1 and ECV values at individual institutions to broaden their clinical use.

Here, we aimed to assess the diagnostic accuracy of native T1 and ECV using 3.0T CMR for the detection of CA, especially for early infiltration with negative LGE, thereby achieving an early diagnosis. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3251/rc).

Methods

Study design

This was a diagnostic test.

Participants

Between July 2017 and October 2020, 40 consecutive AL amyloidosis patients were prospectively recruited from the Department of Radiology at the First Affiliated Hospital of Soochow University. Among them, there were 28 patients with primary systemic amyloidosis, and the remaining patients had secondary amyloidosis due to multiple myeloma or other plasma cell dyscrasias. All patients were confirmed with systemic AL amyloidosis by Congo red and immunohistochemical staining using specimens of subcutaneous abdominal fat (n=22), bone marrow (n=10), kidney (n=7), and upper gastrointestinal tract (n=1). Based on a combination of clinical characteristics, cardiac serum biomarkers, and CMR-LGE features, patients with amyloidosis were categorized as having definite CA (n=30) and possible CA (n=10). Definite CA was defined as the presence of LGE-positive manifestations, including diffuse subendocardial or transmural enhancement, and 1 of the following conditions: (I) left ventricular (LV) wall thickness ≥12 mm in the absence of any other known cause; (II) right ventricular (RV) free-wall thickening coexisting with LV thickening in the absence of systemic or pulmonary hypertension; and (III) elevated cardiac biomarkers, including N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T. Possible CA was defined as LGE-negative presentation and 1 of the following conditions: (I) LV wall thickening with the presence of hypertension; (II) RV thickening with the presence of pulmonary hypertension; and (III) normal wall thickness with diastolic dysfunction and elevated cardiac biomarkers (*Figure 1*). In addition, 20 consecutive patients with hypertrophic cardiomyopathy

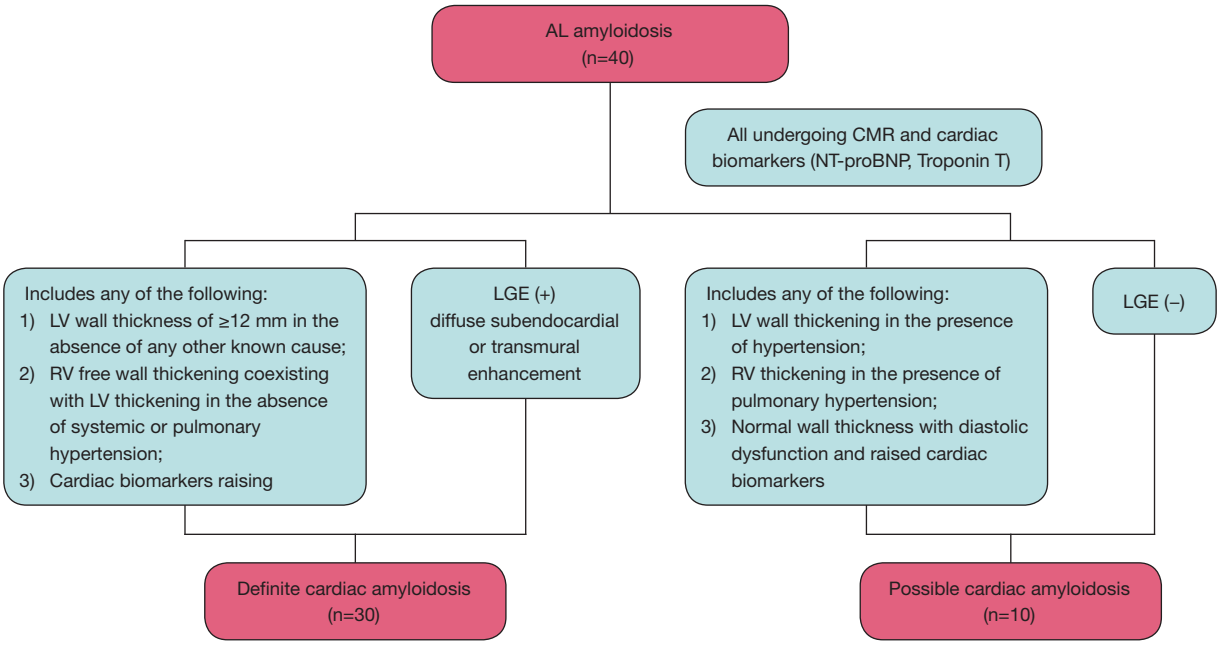

Figure 1 Flow chart of patient inclusion process. AL, amyloid light-chain; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LV, left ventricular; RV, right ventricular; LGE, late gadolinium enhancement.

(HCM) were also included. The diagnostic criteria of HCM was the presence of abnormal increased ventricular wall thickness or mass in the absence of loading conditions, such as hypertension, valve disease, and so on, as per a previous report (14). A total of 16 (80%) patients had an asymmetrical septal hypertrophy pattern and the remaining were with apical predominant hypertrophy. A total of 15 (75%) patients were found to be LGE positive in a variety of locations, including RV insertion points or the LV apex. Further, a total of 40 healthy controls who had no history or symptoms of cardiovascular disease or risk factors (such as, diabetes mellitus, hypertension, and so on) were recruited. A blood sample was obtained from all subjects for biochemical examination and hematocrit at 30 minutes before the CMR scan. The study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (No. 2019112), and was adhered to the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from each included individual.

CMR protocol

All participants underwent standard CMR on a 3.0T clinical scanner (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany) using an anterior 18-channel phased-array surface coil. For cine CMR, short-axis images covering the entire LV and 2-chamber and 4-chamber LV long-axis images were acquired from standard pilot images using a retrospective electrocardiogram (ECG)-gated balance steady-state free precession (SSFP) sequence with the following settings: echo time (TE) =1.4 ms, repetition time (TR) =39.2 ms, field of view (FOV) =174 mm × 208 mm, matrix =256×256, and slice thickness =8 mm. For LGE-CMR, LGE imaging was performed 10 minutes after a bolus injection of gadoterate meglumine (Magnevist, Bayer Healthcare, Berlin, Germany) at 0.1 mmol/kg and a 10-mL saline flush using a breath-hold gradient recalled echo phase-sensitive or magnitude-only inversion recovery sequence to obtain the same short-axis and long-axis images using the following settings: TR =700 ms, TE =1.5 ms, flip angle =20°, FOV =256 mm × 192 mm, matrix =256×256, slice thickness =8 mm, and inversion time =300 ms. For pre- and postcontrast myocardial and blood T1 mapping, 3 short-axis images, including basal, mid-ventricular, and apical, were acquired using the shortened modified look-locker inversion recovery sequence (shMOLLI) in 11 cardiac cycles (5[3]3) before and 15 minutes after administration of contrast agent according to the following settings: TR =277.9, TE =1.1 ms, flip angle =35°, FOV =256 mm × 192 mm, matrix =192×144, and slice thickness =8 mm. Representative imaging figures

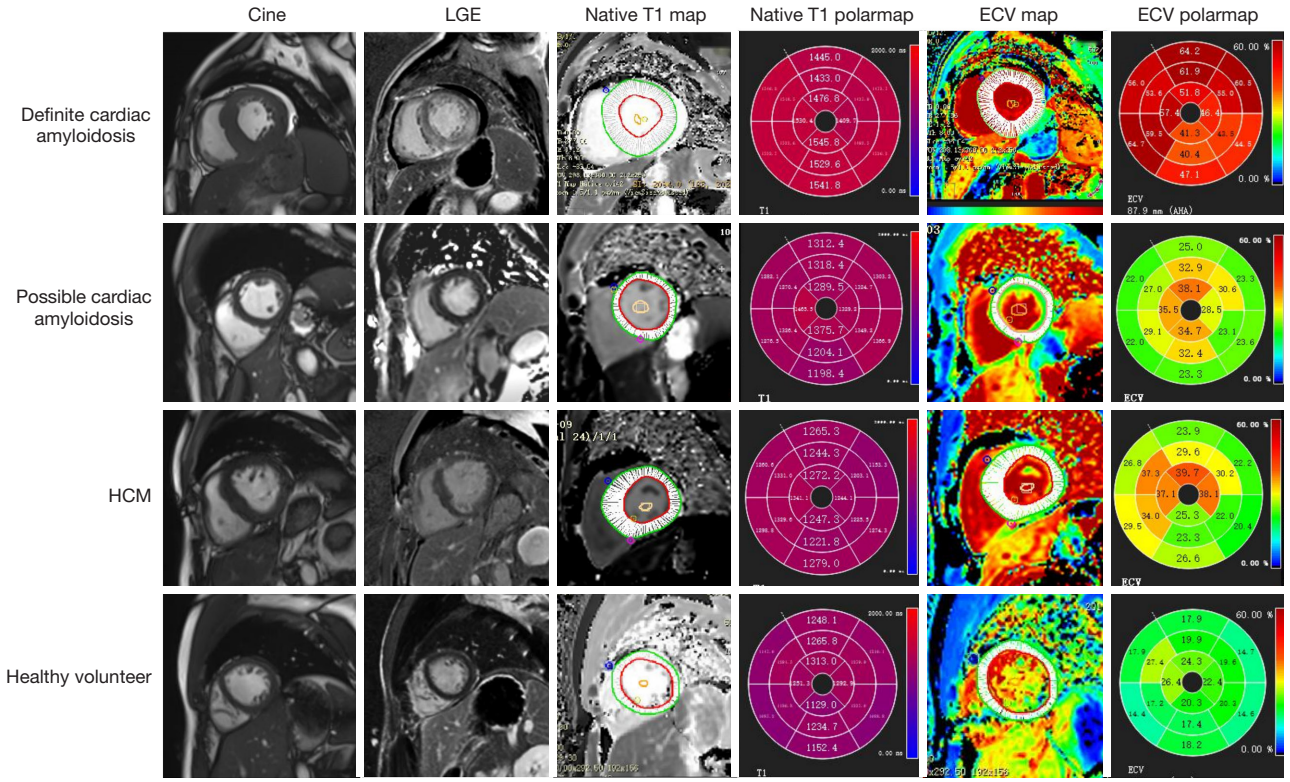

Figure 2 SSFP, LGE, native T1 mapping, and ECV map images in identical short-axis 2 chamber slice of patients with definite cardiac amyloidosis, possible cardiac amyloidosis, and HCM, and healthy controls. SSFP, steady-state free precession; LGE, late gadolinium enhancement; ECV, extracellular volume; HCM, hypertrophic cardiomyopathy.

of definite and possible CA, HCM, and healthy control are provided in *Figure 2*.

CMR image analysis

Quantification of LV volumes, ejection fraction, and LV mass were calculated, respectively, with a dedicated software package (Argus, Siemens Healthineers). The LGE images were visually analyzed for the presence or absence of enhancement. Pre- and postcontrast shMOLLI sequence-generated images with varying inversion times were transferred to a dedicated research software package (CVI42 v5.11.3, Circle Cardiovascular Imaging, Alberta, Canada) to create parametric T1 and ECV pixel maps and corresponding values.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 22.0 (IBM, Chicago, IL, USA) and R version 4.0.0. Continuous data are expressed as mean ± standard deviation (SD) or median and interquartile range based on whether there was a normal distribution or not. Categorical data are expressed as frequencies and percentages. Comparison of native T1 and ECV among 4 groups of subjects (definite CA, possible CA, HCM, and healthy controls) were performed using one-way analysis of variance (ANOVA) and post hoc least significant difference (LSD) test. A Kruskal-Wallis test was used for nonnormal distribution data. Categorical variables were compared by the Chi square test or Fisher's exact test, as appropriate. Correlation analysis between native T1 or ECV and cardiac biomarkers, structure, and function indexes were assessed using Pearson or Spearman correlation, as appropriate. Receiver-operating characteristic (ROC) curve analysis was performed to define the diagnostic accuracy of native T1, ECV and cardiac biomarker, structure and function indexes. The areas under the curves (AUC) were compared statistically for correlated ROC curves with the DeLong method. AUC has a certain diagnostic accuracy between 0.7 and 0.9, while AUC above 0.9 has a high

Table 1 Baseline characteristics of cardiac amyloidosis or HCM patients and healthy controls

Baseline characteristics	Definite cardiac amyloidosis (n=30)	Possible cardiac amyloidosis (n=10)	HCM (n=20)	Healthy volunteers (n=40)	P value
Age (yrs)	60±11	56±11	51±17	45±10	<0.001
Male/female (n/n)	21/9	9/1	15/5	11/29	<0.001
NYHA functional class (%)					
I	13.3	90.0	65.0	100	<0.001
II	33.3	10.0	35.0	–	
III	50.0	–	–	–	
IV	3.3	–	–	–	
Hematocrit (%)	39±5	39±4	41±2	40±3	0.167
NT-proBNP (pg/mL)	2,502 [551–4,465]	457 [221–700]	116 [56–671]	NA	<0.001
Troponin T (pg/mL)	40 [28–565]	13 [12–20]	11 [8–28]	NA	<0.001
Heart rate (beats/min)	84±18	70±8	76±15	79±12	0.033
LVEDVi (mL/m^2)	74±12†	71±17	67±8	64±4*	<0.001
LVESVi (mL/m^2)	30±3†‡	31±4†‡	24±9*	25±3*	<0.001
LVEF (%)	52±8†‡	62±5*‡	69±6*	66±3*	<0.001
LV mass index (g/m^2)	126±17†‡	87±9*†	95±23*†	64±4*‡	<0.001
LVSV (mL)	63±13†‡	79±7*	77±16*	78±9*	<0.001
CO (L/min)	5.0±1.0	4.9±0.5	4.7±0.8	4.8±0.7	0.606
LV wall thickness (mm)					
Basal	13.8±1.3†‡	8.7±0.5*‡	12.1±0.7*†	8.1±0.3*‡	<0.001
Mid	12.1±1.1†‡	7.6±0.4*‡	11.0±0.6*†	7.0±0.4*‡	<0.001
Apical	8.1±0.5†	5.8±0.4*‡	8.3±0.4†	5.4±0.3*‡	<0.001
Global	11.7±1.0†‡	7.7±0.5*‡	10.9±0.5*†	7.2±0.3*‡	<0.001

Data was expressed as mean ± SD or median [interquartile range]. *, †, and ‡ indicate P<0.01 *vs.* definite cardiac amyloidosis, healthy controls, and HCM, respectively. SD, standard deviation; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; CO, cardiac output; NA, not applicable.

diagnostic accuracy. On the ROC curve, the maximum value of the Yorden's index (YI = sensitivity + specificity – 1) is taken as the optimal cutoff value. Statistical significance was defined as P<0.05, two-sided.

Results

Baseline characteristics

The baseline characteristics of all included subjects are provided in *Table 1*. Among the CA, HCM, and healthy control groups, a significant difference could be found for age, male/female ratio, New York Heart Association (NYHA) functional class ratio, NT-proBNP, troponin T, heart rate, left ventricular end-diastolic volume index (LVEDVi), left ventricular end-systolic volume index (LVESVi), left ventricular ejection fraction (LVEF), LV mass index, left ventricular stroke volume (LVSV), and LV wall thickness. No significant difference was found for hematocrit or cardiac output (CO) among the CA, HCM, and healthy control groups.

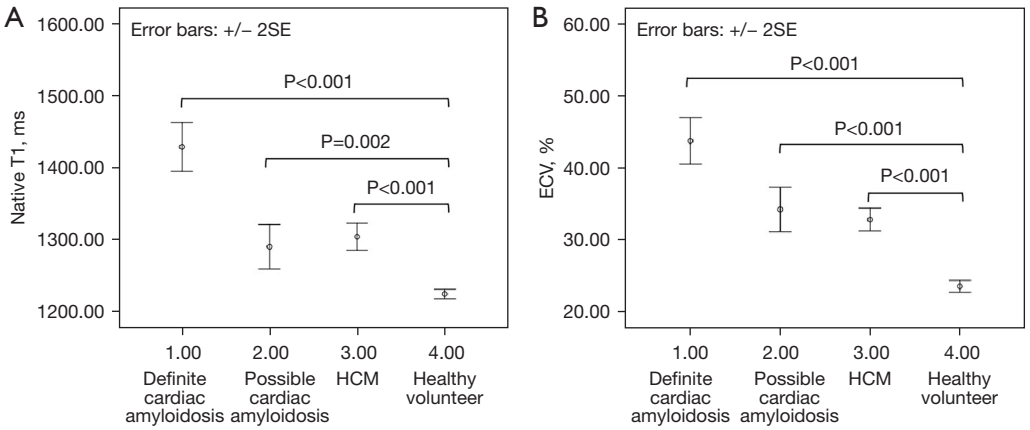

Figure 3 Comparison of native T1 (A) and ECV (B) values in patients with definite cardiac amyloidosis, possible cardiac amyloidosis, and HCM, and healthy controls. ECV, extracellular volume; HCM, hypertrophic cardiomyopathy.

Comparison of native T1 and ECV values in patients with CA, HCM, and healthy controls

All subjects underwent CMR, and the native T1 and ECV values were calculated. As shown in *Figure 3*, native T1 values for definite CA, possible CA, HCM, and healthy controls were 1,429±93, 1,290±49, 1,304±42, and 1,225±21 ms, respectively, and ECV values were 44%±9%, 34%±5%, 33%±4%, and 24%±3%, respectively. The highest and lowest native T1 and ECV values were found in definite CA patients and healthy controls, respectively. Significantly different native T1 and ECV values were found between definite CA and HCM and also between possible CA and healthy controls, whereas no difference was found in native T1 and ECV values between possible CA and HCM. These data indicated that elevated native T1 and ECV were shown in CA and HCM patients, especially those with definite CA.

Diagnostic efficacy of native T1 and ECV values in patients with CA, HCM, and healthy controls

In order to evaluate the diagnostic efficacy of native T1 and ECV values for patient differentiation, we performed ROC curve analysis using native T1 and ECV values. A good AUC of 0.75 for native T1 (95% CI: 0.63–0.87, P=0.002) and 0.77 for ECV (95% CI: 0.66–0.89, P=0.001) could be achieved for differentiation of CA patients from HCM (*Figure 4A*). The optimal cut-off values of native T1 and ECV for identifying definitive or possible CA was 1,270 ms and 29.5%, respectively, with a specificity and sensitivity of 75% and 90% (native T1) and 73.3% and 92.5% (ECV), respectively. Further, for those with LGE-negative phenotype, native T1 (AUC =0.89, 95% CI: 0.75–1.00, P<0.001) and ECV (AUC =0.99, 95% CI: 0.98–1.00, P<0.001) showed good ability to differentiate patients with possible CA from healthy controls, especially ECV (*Figure 4B*). The optimal cut-off values for native T1 and ECV for diagnosing possible CA were 1,258 ms and 27.5%, respectively, with a specificity and sensitivity of 95% and 80% (native T1) and 92.5% and 100% (ECV), respectively. Moreover, cardiac biomarkers (NT-proBNP and troponin T) and cardiac functional and structure indexes (LVESVi and LV mass index) also showed good ability to differentiate CA patients from HCM (*Figure 4C*). These results indicated that native T1 and ECV values could exhibit the ability for CA and HCM differentiation and also showed good ability to differentiate possible CA patients from healthy controls, suggesting their potential role in early CA diagnosis.

Correlations between native T1 or ECV and cardiac biomarkers, structure, and function indexes

We also performed correlation analysis between native T1 or ECV and cardiac biomarkers, structure, and function indexes. Positive correlations were found between native T1 or ECV and NYHA functional class, NT-proBNP, troponin T, LV mass index, and basal, middle, apical, and global LV wall thickness. Negative correlations were found between native T1 or ECV and LVEF or LVSV, and no correlation was found between native T1 or ECV and LVEDVi, LVESVi, or CO (*Figures 5,6*, *Tables 2,3*). These data indicated that native T1 or ECV could reflect the changes

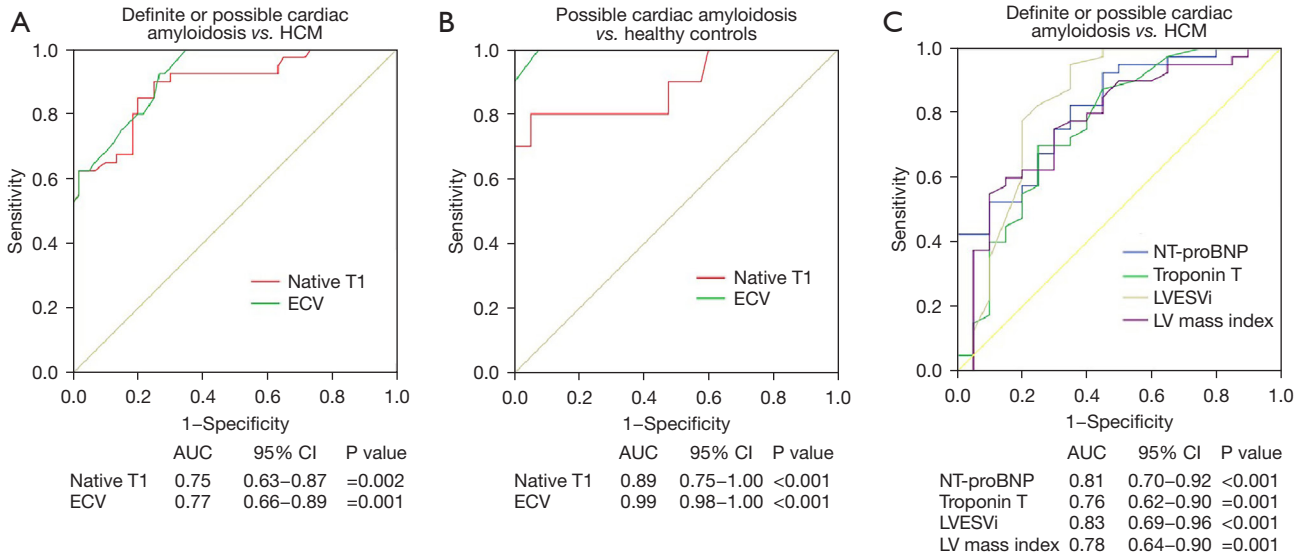

Figure 4 (A) ROC curve for discrimination of definite or possible cardiac amyloidosis from HCM using native T1 and ECV values; (B) ROC curve for discrimination of possible cardiac amyloidosis from healthy controls using native T1 and ECV values; (C) ROC curve for discrimination of definite or possible cardiac amyloidosis from HCM using NT-proBNP, troponin T, LVESVi, and LV mass index. ROC, receiver-operating characteristic; HCM, hypertrophic cardiomyopathy; ECV, extracellular volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVESVi, left ventricular end-systolic volume index; LV, left ventricular.

in cardiac biochemical, structure, and function indexes.

Discussion

Native T1 and ECV determined by CMR have been verified as noninvasive quantitative indexes for evaluation of myocardial fibrosis and progression of cardiac amyloid infiltration (15-17). Since various T1 values could be obtained using different field strengths and sequences, establishment of normal ranges for T1 in a given system via using standardization tools is recommended.

In the present study, we found that patients with definite CA showed obviously elevated native T1 and ECV values which were higher than in patients with HCM (P<0.01). The higher native T1 and ECV values might have reflected either increased proportion of amyloid or greater T1 prolongation compared to myocardial fibrosis with similar degree of increasing wall thickness. More excitingly, in possible CA with negative LGE presentation, native T1 and ECV values were also elevated when compared to healthy controls (P<0.01), although comparable values of native T1 and ECV were found in possible CA and HCM patients. These results suggested that native T1 and ECV values could be used to differentiate CA from HCM, thereby providing a more sensitive early-stage disease detection method than LGE imaging.

Pan *et al.* (18) recently performed a meta-analysis to compare the diagnostic and prognostic efficacy of native T1, ECV, and LGE in CA, and they concluded that ECV exhibited a higher diagnostic ability for assessing CA than LGE and a higher adverse event-prediction ability compared with LGE and native T1. In addition, a similar sensitivity and specificity was found using native T1, ECV, and LGE in a setting with no contrast material. However, due to the study heterogeneity, high quality studies are required to confirm their conclusions (18), and the efficacy of native T1 and ECV in LGE-negative patients should also be assessed. Chamling *et al.* evaluated the diagnostic efficacy of CMR for CA and recommended both LGE and T1-mapping-based ECV for CA determination. However, they only included 2 patients who underwent CMR on a 1.5T scanner (19). Korthals *et al.* reported that both native T1-mapping and ECV measurement were superior to longitudinal strain measurement (with assessment of relative apical sparing) in diagnosis of CA, which supports the better role of native T1 and ECV in CA diagnosis (20). In addition, with the development of novel therapies, accurate tracking of the treatment response in cardiac

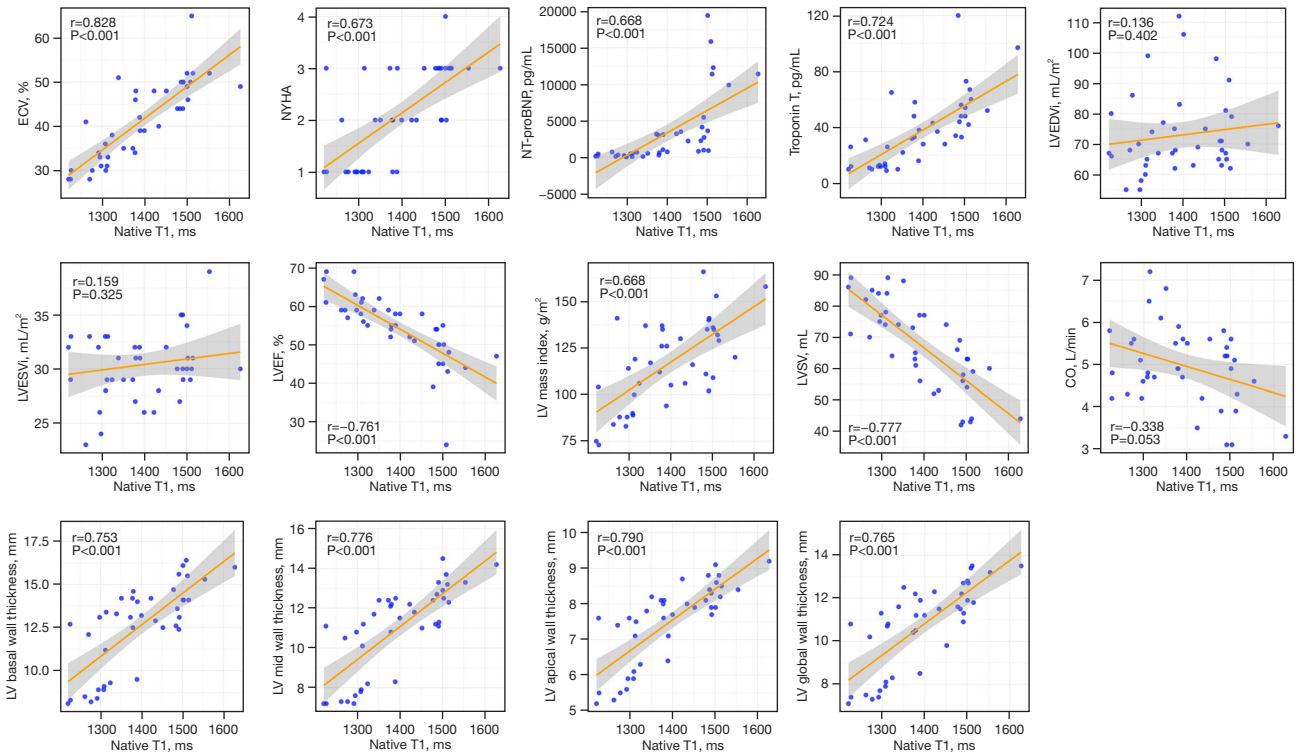

Figure 5 Correlation analysis between native T1 and cardiac biomarkers, structure, and function indexes in patients with AL amyloidosis. AL, amyloid light-chain; ECV, extracellular volume; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LV, left ventricular; SV, stroke volume; LVSV, left ventricular stroke volume; CO, cardiac output.

disease patients is becoming increasingly important (21), and native T1 and ECV could also be considered for these applications. Our results indicated that both native T1 and ECV had a high diagnostic accuracy to differentiate CA from HCM and healthy controls. Moreover, ECV showed a better diagnostic accuracy than native T1. In addition, the diagnostic accuracy of native T1 and ECV was also high in differentiating patients with possible CA from healthy controls. In particular, ECV exhibited a very high diagnostic accuracy (AUC: 0.99, 95% CI: 0.98–1.0), which supports its role as a diagnostic marker in patients with suspected CA for confirming early amyloid infiltration. According to previous studies, native T1 could be prolonged with the increased tissue water content and presence of cardiac and/or renal dysfunction-related myocardial edema caused by fluid retention (22,23), whereas ECV is a direct measure of the extracellular space rather than a composite signal from the myocytes and extracellular space. Therefore, ECV may be a better index to reflect myocardial structural changes. Moreover, since ECV is a T1 ratio [ECV = (1-Hematocrit) × (ΔR1myocardium/ΔR1blood), ΔR1 = (1/T1precontrast – 1/T1postcontrast)], it does not suffer from the limitations of data acquisition standardization as seen in native T1. Thus, ECV is believed to be a more reliable technique for the quantification of amyloid burden and identification of the full spectrum of different stages of CA evolution, possibly allowing the clinician to better diagnose CA.

For those patients with poor renal function, Baggiano *et al.* (15) recently reported the possibility of CA diagnosis using non-contrast CMR. Their results also found that an elevated native T1 between 1,036 and 1,164 ms could serve as the diagnosis criteria for CA, showing a high AUC of 0.93 and 98% negative and positive prediction values. However, in our study, we excluded patients with severe renal impairment and thus failed to acknowledge the clinical usefulness of non-contrast CMR in CA diagnosis.

Our correlation analysis showed a good correlation value between native T1 and ECV (r=0.828, P<0.001) in definite and possible CA. Moreover, positive correlations were found between native T1 or ECV and NYHA

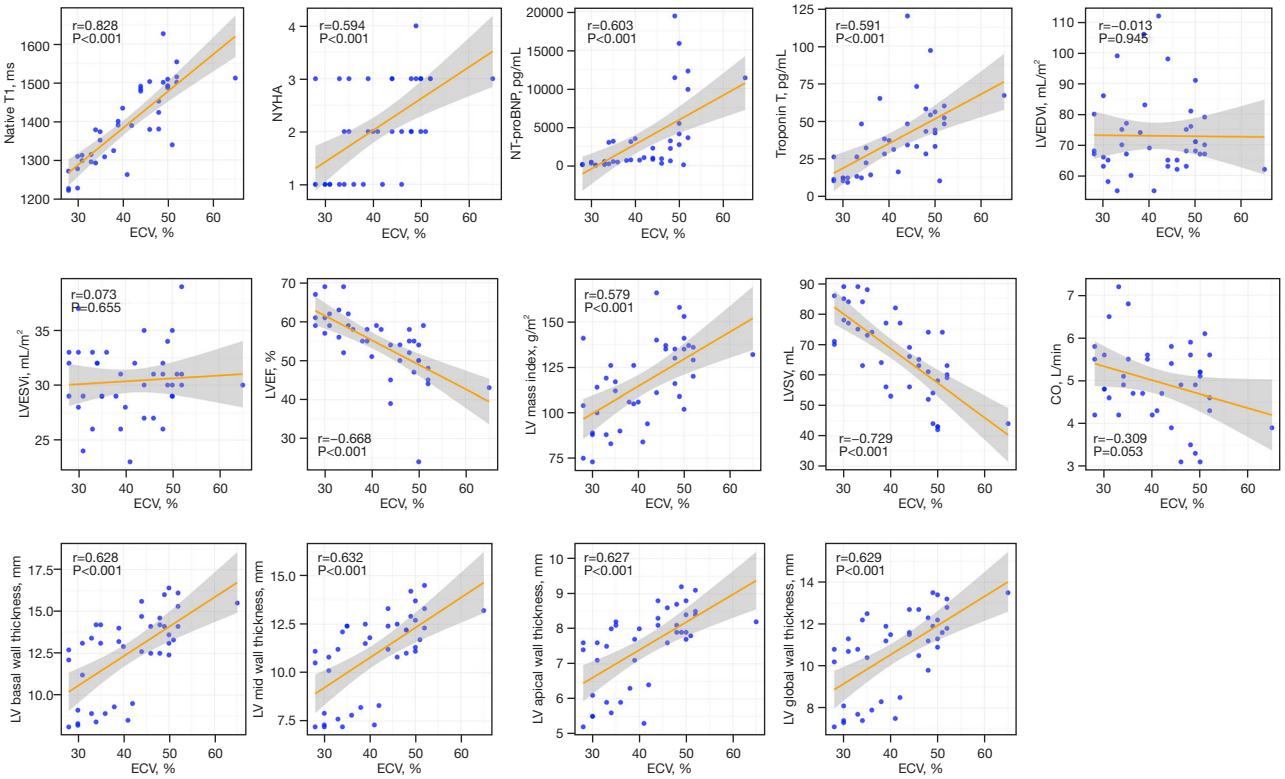

Figure 6 Correlation analysis between ECV and cardiac biomarkers, structure and function indexes in patients with AL amyloidosis. ECV, extracellular volume; AL, amyloid light-chain; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LV, left ventricular; SV, stroke volume; LVSV, left ventricular stroke volume; CO, cardiac output.

functional class, NT-proBNP, troponin T, LV mass index, and basal, middle, apical, and global LV wall thickness. Negative correlations were found between native T1 or ECV and LVEF or LVSV, and no correlation was found between native T1 or ECV and LVEDVi, LVESVi, or CO, indicating a gradual reduction in correlation between native T1 or ECV and the cardiac structure indexes with severity of cardiac involvement. Thus, native T1 and ECV may have potential as a valuable method for diagnosing and quantifying cardiac involvement in AL amyloidosis.

NT-proBNP is a widely recognized biomarker for heart failure. Although the release of NT-proBNP is considered to be due to the elevation of ventricular filling pressure, increased level of NT-proBNP in CA patients could be caused by direct damage of the ventricular myocytes (24). Cardiac troponin T is known as one of the most sensitive biomarkers for myocardial injury (25). Recently, several studies have demonstrated that high levels of NT-proBNP and cardiac troponin T had a strong predictive ability for CA diagnosis and prognosis prediction (26,27). In our study, both elevated NT-proBNP and cardiac troponin T were found in patients with definite and possible CA, which showed a slightly better diagnostic value compared to native T1 and comparable value with ECV, further supporting the equivalent role of native T1 and ECV as diagnosis indexes. In addition, NT-proBNP and troponin T were positively correlated with both native T1 and ECV, which further confirmed the reflecting role of native T1 and ECV in myocardial biochemical events.

There were several limitations in the present study. Firstly, the observational and single-center nature of this study limited the generalizability of the findings and raised the possibility of selection bias. Secondly, the relatively small number of patients could have also led to result bias. Thirdly, all AL amyloidosis patients were not performed EMB, which continues to be the histological gold standard for diagnosing CA. Finally, prognosis results were not included due to the relatively short study period, although Banypersad *et al.* also

Table 2 Correlations between native T1 or ECV and cardiac biomarkers, structure, and function in patients with AL amyloidosis

Variables	r	P value
Native T1 (ms)		
ECV (%)	0.828	<0.001
NYHA functional class	0.673	<0.001
NT-proBNP (pg/mL)	0.668	<0.001
Troponin T (pg/mL)	0.724	<0.001
LVEDVi (mL/m^2)	0.136	0.402
LVESVi (mL/m^2)	0.159	0.325
LVEF (%)	–0.761	<0.001
LV mass index (g/m^2)	0.668	<0.001
LVSV (mL)	–0.777	<0.001
CO (L/min)	–0.338	0.053
LV basal wall thickness (mm)	0.753	<0.001
LV mid wall thickness (mm)	0.776	<0.001
LV apical wall thickness (mm)	0.790	<0.001
LV global wall thickness (mm)	0.765	<0.001
ECV (%)		
Native T1 (ms)	0.828	<0.001
NYHA functional class	0.594	<0.001
NT-proBNP (pg/mL)	0.603	<0.001
Troponin T (pg/mL)	0.591	<0.001
LVEDVi (mL/m^2)	–0.013	0.945
LVESVi (mL/m^2)	0.073	0.655
LVEF (%)	–0.668	<0.001
LV mass index (g/m^2)	0.579	<0.001
LVSV (mL)	–0.729	<0.001
CO (L/min)	–0.309	0.053
LV basal wall thickness (mm)	0.628	<0.001
LV mid wall thickness (mm)	0.632	<0.001
LV apical wall thickness (mm)	0.627	<0.001
LV global wall thickness (mm)	0.629	<0.001

Pearson or Spearman rho correlation analysis was used for analysis. ECV, extracellular volume; AL, amyloid light-chain; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; CO, cardiac output.

Table 3 Correlation analysis between the native T1 or ECV and cardiac biomarkers, structure, and function in all the subjects

Variables	r	P value
Native T1 (ms)		
ECV (%)	0.915	<0.001
NT-proBNP (pg/mL)	0.697	<0.001
Troponin T (pg/mL)	0.699	<0.001
LVEDVi (mL/m^2)	0.368	<0.001
LVESVi (mL/m^2)	0.423	<0.001
LVEF (%)	–0.768	<0.001
LV mass index (g/m^2)	0.822	<0.001
CO (L/min)	–0.106	0.294
LV basal wall thickness (mm)	0.831	<0.001
LV mid wall thickness (mm)	0.821	<0.001
LV apical wall thickness (mm)	0.735	<0.001
LV global wall thickness (mm)	0.800	<0.001
ECV (%)		
Native T1 (ms)	0.915	<0.001
NT-proBNP (pg/mL)	0.642	<0.001
Troponin T (pg/mL)	0.591	<0.001
LVEDVi (mL/m^2)	0.284	0.0042
LVESVi (mL/m^2)	0.360	0.00023
LVEF (%)	–0.709	<0.001
LV mass index (g/m^2)	0.803	<0.001
CO (L/min)	–0.0563	0.578
LV basal wall thickness (mm)	0.807	<0.001
LV mid wall thickness (mm)	0.793	<0.001
LV apical wall thickness (mm)	0.712	<0.001
LV global wall thickness (mm)	0.775	<0.001

ECV, extracellular volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; CO, cardiac output.

showed that higher T1 and ECV values were associated with shorter event-free survival in AL amyloidosis (28). Further, Aus dem Siepen *et al.* reported that native T1 and ECV values were very stable in healthy volunteers during a long-term follow-up period and could be useful for prognostic prediction (29). Therefore, further multicenter studies

with more patients and complete follow-up data should be performed to confirm the data obtained here.

In conclusion, we demonstrated that native T1 and ECV mapping had high diagnostic accuracy for the detection of CA and correlated well with cardiac biomarkers and CMR cardiac structure and function. Native T1 and ECV mapping could offer advantages over LGE imaging for identifying early cardiac disease, although further studies are needed to confirm the results here and to clarify the prognostic significance of native T1 and ECV elevation.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3251/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3251/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3251/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (No. 2019112), and was adhered to the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from each included individual.

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