Non-contrast magnetic resonance for the diagnosis of cardiac amyloidosis

Andrea Baggiano, MD[a,b,*], Michele Boldrini, MD[a,c,*], Ana Martinez-Naharro, MD[a], Tushar Kotecha, MBChB[a,d], Aviva Petrie, BSc (Hons), MSc[g], Tamer Rezk, MBBS[a], Maurizio Gritti, MD[a], Cristina Quarta, MD, PhD[a], Daniel S. Knight, MBBS, MD (Res)[a,d], Ashutosh D. Wechalekar, MD, PhD[a], Helen J. Lachmann, MD[a], Stefano Perlini, MD, PhD[c], Gianluca Pontone, MD, PhD[b], James C. Moon, MD[e], Peter Kellman, PhD[f], Julian D. Gillmore, MD, PhD[a], Philip N. Hawkins, PhD, FMedSci[a], Marianna Fontana, MD, PhD[a]

Word count: 4955

[a]National Amyloidosis Centre, University College London, Royal Free Campus, London, UK

[b]Centro Cardiologico Monzino, IRCCS, Milan, Italy

[c]Emergency Department, Amyloid Research and Treatment Center, IRCCS Policlinico San Matteo Foundation, University of Pavia, Pavia, Italy

[d]Department of Cardiology, Royal Free Hospital, London, UK

[e]Barts Heart Centre, St. Bartholomew's Hospital, London, UK

[f]National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

[g]UCL Eastman Dental Institute, London, UK

[*]Andrea Baggiano and Michele Boldrini contributed equally to this work

All authors have nothing to disclose.

Address for Correspondence:
Dr Marianna Fontana,
Cardiac MRI Unit, National Amyloidosis Centre,
University College London, Royal Free Campus,
Rowland Hill Street, London, NW3 2PF, UK
E-mail: m.fontana@ucl.ac.uk
Phone No: +44 2074332764
Fax No: +44 2044332817

ABSTRACT

Background: Cardiac amyloidosis (CA) is a progressive and fatal underdiagnosed cause of heart failure. Cardiovascular magnetic resonance (CMR) has emerged as an extremely useful test for the non-invasive diagnosis of CA, but administration of contrast is still required to make a diagnosis.

Objectives: To assess the diagnostic utility of native T1 to detect cardiac amyloidosis in a large prospective cohort of patients referred for suspected systemic amyloidosis.

Methods: 868 patients with suspected cardiac amyloidosis referred between 2015 and 2017 underwent CMR with late gadolinium enhancement (LGE), T1 mapping, and an array of clinical investigations.

Results: The final diagnosis was cardiac AL amyloidosis in 222, cardiac ATTR amyloidosis in 214 and no cardiac involvement in 427 cases. T1 was significantly elevated in both types of CA and this was associated with high diagnostic accuracy in the overall population (AUC 0.93). A native T1 < 1036ms was associated with 98% negative predictive value for CA whilst a native T1 > 1164ms was associated with 98% positive predictive value for CA. We propose the use of these cut-offs to exclude or confirm CA and to restrict the administration of contrast only to patients with intermediate probability (native T1 between 1036 and 1164 ms), 58% of patients in this population.

Conclusions: Native myocardial T1 enables diagnosis of CA to be made without need for gadolinium contrast in a large proportion of patients with suspected systemic amyloidosis. We propose a diagnostic algorithm for non-contrast CMR applicable to patients with suspected amyloidosis.

CONDENSED ABSTRACT

Native T1 is elevated in cardiac amyloidosis patients. In patients with renal failure, the use of gadolinium-based contrast agents (GBCA) is contraindicated. We sought to see whether native T1 mapping with on-the-fly analysis could reduce the need for GBCAs. We compared diagnostic performance of native T1 and LGE in a large unselected population with possible amyloid. We propose a diagnostic algorithm for non-contrast CMR applicable to the majority of patients.

KEYWORDS

Amyloidosis, Renal Failure, Cardiovascular Magnetic Resonance, Native T1 Mapping, Accuracy

ABBREVIATIONS LIST

CMR = Cardiovascular Magnetic Resonance

LGE = Late Gadolinium Enhancement

AL = Amyloid light-chain

ATTR = Amyloid transthyretin

eGFR = estimated Glomerular Filtration Rate

MOLLI= modified Look-Locker inversion recovery

CKD = chronic kidney disease

INTRODUCTION

Cardiac amyloidosis is a challenging and underdiagnosed cause of heart failure(1,2). The disease is characterized by extracellular deposition of fibrillary protein that disrupts normal tissue architecture and function(3). The types of systemic amyloidosis most frequently associated with clinically relevant cardiac involvement are systemic AL amyloidosis, in which the amyloid fibrils are composed of aggregated misfolded monoclonal immunoglobulin light chains and ATTR amyloidosis, in which the fibrils are derived from transthyretin (TTR), a transport protein synthesized mainly by the liver. ATTR amyloidosis is either hereditary (ATTRm), associated with more than 100 TTR gene mutations, or non-hereditary wild-type (ATTRwt), the latter previously known as "senile" systemic amyloidosis and which predominantly affects the hearts of older men(3,4).

Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) identifies myocardial amyloid infiltration as a characteristic pattern of global subendocardial or transmural LGE coupled with abnormal myocardial and blood-pool gadolinium kinetics(5-9). However, the LGE technique has limitations in evaluating patients with suspected cardiac amyloidosis, since many have severe renal impairment, a condition where gadolinium-based contrast agents should be avoided unless the diagnostic information is essential and not available with non-contrast CMR(10,11). Moreover, concerns regarding accumulation of gadolinium deposits in the brain have lately been raised, leading to the removal of linear agents for most indications and recommendations for using macrocyclic agents in the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable(12).

Native T1 mapping has emerged as a potentially useful diagnostic CMR technique for the identification of both AL and ATTR cardiac amyloidosis without recourse to contrast agents(13,14). However, only small retrospective studies have been performed to date, leaving a knowledge gap on clinical utility and accuracy of native T1 as a diagnostic test. Furthermore, the impact of renal failure on native T1 performance has never been assessed.

The aim of this study was to assess the diagnostic utility of native T1 for the identification of cardiac involvement in a large prospective cohort of patients referred with suspected systemic amyloidosis.

METHODS

A total of 868 consecutive consenting patients referred with suspected cardiac amyloidosis both in the context of increased LV mass or in the context of suspected systemic amyloidosis were prospectively studied between 2015 and 2017 at the National Amyloidosis Centre, London, United Kingdom. All patients underwent a comprehensive clinical assessment including clinical evaluation, echocardiography, CMR with gadolinium contrast, serum and urine biochemistry including N-terminal pro-b-type natriuretic peptide (NT-proBNP)(15), troponin T, NYHA functional class, 6 minute walk test (6MWT), bioimpedance with extracellular body water / total body water ratio calculation (ECW/TBW ratio)(15), SAP scintigraphy(16) and assessment of hematologic disease by serum free light chain (FLC) assay along with serum and urine immunofixation electrophoresis. Patients with eGFR < 30 mL/min received contrast following an individual assessment of risk/benefit. Patients with suspected ATTR amyloidosis also underwent technetium-labeled bone scintigraphy using 3,3-diphosphono-1,2-propanodicarboxylicacid (DPD scintigraphy). Sixty-five patients were included in previous publication(17).

Thirty healthy volunteers (16 male, mean age 46±7 years) were recruited through advertising in the hospital, university and general practices. All had no history of cardiovascular disease, hypertension, or diabetes. This cohort was only used to calculate the z-scores for the different native T1 cut-offs.

The study was approved by the local Committee on the Ethics of Human Research and all participants provided written informed consent.

Cardiac ATTR was defined as the combination of typical features on CMR, grade 2 or 3 cardiac uptake on 99mTc-DPD scintigraphy in the absence of monoclonal gammopathy, or in the presence of monoclonal gammopathy, a cardiac biopsy positive for TTR(18). Cardiac AL amyloidosis was defined as the combination of typical features on CMR and biopsy proven

systemic AL amyloidosis on cardiac or non-cardiac biopsy. All patients with cardiac amyloidosis had also typical features on LGE enhancement imaging(9).

CMR protocol. All participants underwent standard CMR on a 1.5-T clinical scanner (Aera, Siemens Healthcare, Erlangen, Germany). A standard volume and LGE study was performed. The gadolinium-based contrast agent used was 0.1 mmol/kg gadoterate meglumine. LGE imaging was acquired with magnitude reconstruction and phase sensitive inversion recovery (PSIR) reconstruction in all patients. For native T1 and post-contrast mapping, basal, mid and apical ventricular short-axis and 4-chamber long-axis images were acquired by the modified Look-Locker inversion recovery (MOLLI) after regional shimming before the administration of contrast, as previously described in literature (see supplemental material for sequence details)(19,20). At fifteen minutes after the bolus of gadoterate meglumine and standard LGE imaging (standard fast low-angle shot inversion recovery or balanced steady-state free-precession sequence with magnitude reconstruction and PSIR reconstruction), the T1 measurement was repeated with the MOLLI sequence(21) and inline extracellular volume maps (ECV) were automatically generated(22).

CMR image analysis. All CMR images and maps were analyzed offline. T1 measurement was performed by drawing a region of interest in the basal to mid septum of the 4-chamber T1 map (this was done blinded to the LGE images). The LGE pattern was classified into characteristic for cardiac amyloidosis and negative for cardiac amyloidosis(5,8,9). The presence of LVH was defined as increased left ventricular (LV) mass based on age and sex-indexed reference values.

Statistical Analysis. The diagnosis endpoint was defined as the presence of typical features on LGE enhancement imaging(9). The overall sample was divided into training and validation samples. This was done by randomly selecting 694 patients (80%) from the total of 868 patients to provide the training sample. The remaining 174 patients, 20% of the total, made up the validation sample. Calibration, the agreement between observed and predicted events, was assessed by examining the mean Brier score (ranging from 0 (perfect agreement) to 1 (perfect

disagreement)) with its associated Speiegelhalter test (a significant result indicates poor calibration) and by performing the Hosmer-Lemeshow goodness-of-fit test (a significant result indicates poor calibration). Discrimination, distinguishing between patients who do and do not experience the endpoint, was evaluated by determining the area (AUC or *c*-statistic) under the receiver operating curve (ROC).

Training sample. The Hosmer-Lemeshow goodness of fit test was executed after performing a logistic regression analysis with native T1 as the explanatory variable and the diagnostic endpoint as the outcome. Three cut-offs for native T1 were chosen by giving consideration to the negative predictive value (NPV) and positive predictive value (PPV) of different points of the ROC: 1) the optimal cut-off was calculated using the Youden and Liu methods; 2) a second cut-off had approximately 98% NPV and the greatest possible PPV; 3) a third cut-off had approximately 98% PPV and the greatest possible NPV. For each T1 cut-off, the following parameters were calculated after performing a logistic regression analysis, with the relevant cut-off as the explanatory variable and the diagnostic endpoint as the outcome, and then creating a ROC: area under the curve (AUC) with its associated confidence interval (CI), predictive probabilities, sensitivity, specificity, positive and negative predictive values, the mean Brier score and the odds ratio (OR).

For each of the three T1 cut-offs the respective z-score was calculated according to the formula: $z = (x - \mu) / \sigma$, where (x) is the diagnostic T1 cut-off value, (μ) is the mean T1 from the healthy volunteers cohort and (σ) its standard deviation.

A univariable linear regression analysis was performed to assess the effect of each of a number of clinical variables (the explanatory variable) on native T1 (the outcome variable), and the r^2 (the proportion of the total variation in native T1 explained by its relationship with the relevant explanatory variable) was calculated.

Validation sample. Predicted probabilities of disease were calculated using the training sample logistic regression model coefficients in the validation data set. Five cut-offs were created

representing the quintiles of predicted probabilities. The observed frequencies of disease in each of the 5 ordered predicted probability groups were calculated. To assess good calibration, a bar chart showing observed percentage with the disease in each quintile group was plotted against the predicted risk of disease when the training model was applied to the validation data set. Good calibration was also assessed using calibration curves. For each cut-off of native T1, the logistic regression coefficients from the training sample model were applied to the validation dataset and all relevant parameters, as described above, were determined and compared to those obtained from the training sample.

Two sided tests were used for all analysis and a $p < 0.05$ was considered significant. The data were analysed using Stata (StataCorp. 2015. Stata Statistical Software: Release 14; StataCorp LP, College Station, TX, USA).

RESULTS

Baseline characteristics of all 868 patients divided into Cardiac Amyloidosis and Non-Cardiac Amyloidosis (suspected), and the 30 healthy volunteers are shown in Table 1. The prevalence of cardiac amyloidosis was 50.8%. The final diagnosis was cardiac AL amyloidosis in 222 patients (25.6%), cardiac ATTR amyloidosis in 214 patients (of which 146 ATTRwt amyloidosis and 68 ATTRm amyloidosis), systemic AL amyloidosis with no cardiac involvement in 166, other types of amyloidosis with no cardiac involvement in 50, other types of heart disease in 139, normal heart in 72 patients (Table 2). Baseline characteristics of patients with cardiac AL and ATTR diagnosis are reported in Table 3. Three patients died before a definitive diagnosis could be confirmed.

Training sample. Supplemental Table 1 summarizes baseline characteristics of the overall population divided into Training sample and Validation sample. The model showed good calibration as assessed by the Hosmer-Lemeshow goodness-of-fit test ($p = 0.25$), Mean Brier score (0.10) and the Spiegelhalter's p value for the Brier score ($p = 0.83$).

Native myocardial T1 showed a high diagnostic accuracy to discriminate cardiac amyloidosis (AUC 0.93) (Figure 1). For native T1 the optimal cut-off was 1091ms (z-score 1.7), which gave a NPV of 85% and a PPV of 87%. The cut-off with 98% NPV was 1036ms (z-score 0.4), which gave a PPV of 65%. The cut-off with 98% PPV was 1164ms (z-score 3.5), which gave a NPV of 60%. Fifty-eight percent of patients had a native T1 between 1036 and 1164 ms, defining the group with intermediate probability. In patients with intermediate probability, ECV was associated with a very high diagnostic accuracy (AUC 0.976, CI 0.965-0.987, $p < 0.0001$, optimal cut-off 0.37). Supplemental table 2 summarises the model accuracy, discrimination and calibration for native T1 from the training sample as well as the relevant parameters for each of the chosen cut-offs of native T1.

There was no evidence of a difference ($p = 0.12$) in diagnostic accuracy of native myocardial T1 in the five categories of renal failure (No chronic kidney disease, CKD, (n = 195) AUC =

0.96 [CI 0.93-0.99], CKD 1 (n = 31) AUC = 0.93 [CI 0.85-1], CKD 2 (n = 342) AUC = 0.95 [CI 0.92-0.98], CKD 3 (n = 248) AUC = 0.89 [0.84-0.94], CKD 4-5 (n = 45) AUC = 0.89 [CI 0.79-0.99]). Similarly, there was no evidence of a difference (p = 0.14) in diagnostic accuracy of native myocardial T1 in patients with anaemia (Hb < 13 g/dl for men and < 12 g/dl for women AUC 0.91 [CI 0.87-0.95], Hb > 13 g/dl for men and > 12 g/dl for women AUC 0.95 [0.93-0.97]) (Supplemental table 3). Finally, there was no evidence of a difference (p = 0.27) in diagnostic accuracy of native myocardial T1 in patients with nephrotic range proteinuria (Proteinuria ≥ 3g/die AUC 0.92 [CI 0.88-0.97], Proteinuria < 3g/die AUC 0.93 [0.91-0.96]) (Supplemental Figure 1). Univariable linear regression analysis of native T1 on each of ECW/TBW ratio, eGFR, albumin, proteinuria, haemoglobin and haematocrit showed poor association (r^2 = 0.002, r^2 = 0.11, r^2 = 0.05, r^2 = 0.025, r^2 = 0.007, r^2 = 0.0003 respectively, Supplemental Figure 2). There was no evidence of a difference (p = 0.35) in diagnostic accuracy of native myocardial T1 between patients with increased left ventricular mass indexed compared to patients with normal left ventricular mass indexed (Figure 2).

Validation sample. The model showed good calibration as assessed by the stepwise increase in the observed percentage of patients with cardiac involvement as the predicted probability from the model increases (Supplemental Figure 3). The calibration curves also confirmed good calibration (Supplemental Figure 4). Supplemental table 2 summarises the model accuracy, discrimination and calibration from the validation sample as well as the relevant parameters for each of the cut-offs. The training and validation sample gave comparable results (Supplemental table 2).

Diagnostic performance. The diagnostic accuracy of native T1 was compared against other CMR, clinical and echocardiographic diagnostic markers. The comparison was performed in the overall population (Table 4, Figure 3), in AL and ATTR separately (Table 5) and in the training and validation cohort (Supplemental table 4).

Multivariable regression. A multivariable regression analysis of variables explanatory of native T1 using all other clinical, echocardiographic and CMR variable was performed: only ECV and T2 remained independent predictors (both $p < 0.001$).

DISCUSSION

Our study, which is the first prospective study to investigate the diagnostic accuracy of native myocardial T1 in a large cohort of patients with suspected systemic amyloidosis, supports the role of native T1 mapping as a sensitive and specific diagnostic tool for identification of cardiac amyloid. Furthermore, our findings support the use of native myocardial T1 also in patients with renal disease, a common comorbidity in this patient population.

Non-contrast T1 mapping is a technique where direct quantitative signal from the myocardium is measured before the administration of contrast (native myocardial T1)(21,23-26). Each pixel in the image is coded in colour, reflecting the absolute value of T1 (Figure 4). Native myocardial T1 mapping measures myocardial intrinsic signal, and T1 ‘‘maps’’ are now available from all MRI manufacturers(13,14,23). Several studies have shown changes in myocardial T1 with pathology: native T1 is reduced in iron overload and fat infiltration such as Fabry disease(27-29), whilst a slight increase in native T1 occurs in focal and diffuse fibrosis(30-36), oedema and inflammation(37-40). Native T1 is substantially elevated in the presence of AL and ATTR cardiac amyloidosis(14,41). Native myocardial T1 mapping has been associated in single centre studies with a high diagnostic accuracy for cardiac amyloidosis(42). However, these studies were performed in small retrospective cohorts of patients with AL and ATTR amyloidosis and these patients were retrospectively compared to healthy volunteers, patients with aortic stenosis or hypertrophic cardiomyopathy, leaving a knowledge gap on the diagnostic utility of native T1. Furthermore, native myocardial T1 is prolonged with increasing water content in the tissue and the presence of myocardial oedema due to fluid retention associated with cardiac and/or renal dysfunction has potential to be a diagnostic confounder(38,40).

Our analysis of 694 patients, corroborated in the validation cohort of 174 patients, indicates that non-contrast T1 mapping is a sensitive and specific tool for diagnosis of cardiac amyloidosis, both in the overall population of patients referred with suspected cardiac

amyloidosis and in the subset with reduced kidney function. The diagnostic accuracy of native T1 is not different in patients with different degrees of kidneys failure, nephrotic range proteinuria or in the presence of anaemia. We also did find poor association between native T1 and parameters related to the severity of proteinuria (24-hour proteinuria, serum albumin), kidney failure (eGFR), fluid overload (ECW ratio, a measure of the extracellular water content in the body), haemoglobin or haematocrit. Furthermore, the diagnostic accuracy of native T1 was high in the subgroup of patients with normal left ventricular mass and comparable to the subgroup with increased left ventricular mass, highlighting the role of native T1 as an early disease marker.

These findings have important immediate clinical implications in patients with severe reduction in the kidney function, in whom administration of gadolinium-based contrast agents is relatively contraindicated. In addition, there are recent concerns more widely regarding brain deposits following use of gadolinium-based contrast agents. Non-contrast CMR techniques have therefore become an appealing strategy in the general population irrespective of kidney function, which has previously been considered the only relevant parameter to consider before administration of gadolinium. This study shows that native T1 has excellent diagnostic accuracy in an overall population of patients with clinical suspicion of amyloidosis, potentially supporting the routine use of non-contrast CMR in this setting. When the diagnostic accuracy of native T1 was compared against other CMR, clinical and echocardiographic diagnostic markers, native T1 showed the best diagnostic accuracy with the only exception of ECV. This is not surprising, as ECV is a direct measure of the extracellular space rather than a composite signal from the myocytes and extracellular space but requires, similarly to LGE, administration of contrast. However, because it is so crucial to avoid misdiagnosis of cardiac amyloidosis, we have developed a clinical algorithm to provide guidance on the indications for contrast. The aim of this is to provide reliable cut-offs for native myocardial T1 that exclude or confirm the diagnosis of cardiac amyloidosis and restrict administration of contrast only to patients with

intermediate probability, in this cohort 58 percent of patients (Figure 5). We therefore propose that in patients with intermediate native T1 values, macrocyclic gadolinium-based contrast agent administration should still be considered for diagnostic purpose. Using this algorithm, the diagnosis of cardiac amyloidosis could be obtained in a 42 percent of patients with suspected cardiac amyloidosis without need for a contrast. This would not only limit the exposure of patients to contrast but could also have implications in the diagnostic workflow, as non-contrast CMR studies that includes T1 mapping, volume and functional assessment can be performed in less than 15 minutes, reducing scan time by two thirds.

In patients with intermediate probability based on the native T1, an ECV cut-off of 0.37 was associated with a very high diagnostic accuracy (AUC 0.976, CI 0.965-0.987, $p < 0.0001$). These results support the role of ECV as diagnostic marker in patients with suspected cardiac amyloidosis undergoing a CMR that includes the administration of contrast. ECV has advantages over the LGE evaluation, providing the ability to quantify the expansion of the extracellular space by simply drawing a region of interest on ECV maps. ECV maps offer a rapid fully-automated approach to generate online pixelwise ECV maps, enabling the clinician to obtain ECV values immediately after the acquisition of post-contrast T1 maps.

Importantly, the findings and recommendations documented here do not eliminate the need for typing of amyloid among patients with cardiac amyloidosis. Native T1, as well as other CMR features, cannot be reliably used to differentiate amyloid type. Whilst tissue characterization and morphological features can give a strong suggestion of ATTR versus AL amyloid type, there is significant overlap.

Study limitations. Firstly, our study is a single centre study; we are therefore unable to provide information on the diagnostic accuracy when the test is used at multicentre level. Non-invasive diagnostic algorithms were used, which means a cardiac biopsy was available only in a minority of patients (5%). However, the concordance between the cardiac biopsy and the diagnostic criteria used was 100%.

Secondly, it should be noted that the patients presented here were not unselected but rather were referred to a specialist amyloid centre for the evaluation of suspected amyloidosis (therefore with a high pretest-likelihood of amyloidosis). Further study is required to validate these results in the general population. Furthermore, cut-points for good NPV and good PPV are important. However, NPV and PPV depend on prevalence. Therefore, the NPV and PPV would be different if the prevalence in the referral population was higher or lower. Nonetheless, the prevalence in this manuscript is very similar to other reports. The most recent and largest study done so far in amyloidosis that assessed the diagnostic accuracy of DPD scintigraphy in a large cohort of patients (1217 patients recruited from 8 centers from Europe and the US) had a prevalence of cardiac amyloidosis of 59%(43). Our prevalence is therefore very similar to other reports and likely to represent a "real world" clinical situation where amyloidosis is suspected. Finally, different CMR systems and T1 mapping sequences have different normal ranges(44). Normal T1 values are higher when measured at 3T, with different sequences, and typically with newer variants of mapping compared to older ones. Current recommendations are for normal reference ranges to be defined locally, but this may change over time. This is a significant obstacle for the implementation of native T1 in clinical practice. Standardization is only now commencing, but consensus guidelines are now available(45,46).

CONCLUSIONS

Native myocardial T1 enables the diagnosis of cardiac amyloidosis to be made reliably without need for gadolinium contrast in a 42 percent of patients with suspected systemic amyloidosis. We propose a clinical algorithm to minimize use of contrast in the CMR evaluation of patients with suspected amyloidosis (Central Illustration).

CLINICAL PERSPECTIVES

Competency in Medical Knowledge: Native T1 mapping has emerged as a robust CMR technique in the evaluation of patients with suspected cardiac amyloidosis thanks to its high diagnostic accuracy.

Competency in Patient Care: Patients with suspected cardiac amyloidosis frequently exhibit renal failure at presentation. Non-contrast CMR with native T1 mapping gives reliable assessment in the subset of patients in which contrast administration is contraindicated for safety reasons.

Translational Outlook 1: Capability of non-contrast T1 mapping to track disease progression/remission after medical treatment with serial non-contrast CMR exams should be investigated.

Translational Outlook 2: Capability of non-contrast T1 mapping to depict amyloid infiltration at the level of other organs than heart should be investigated.

REFERENCES

1. Falk RH, Comenzo RL, Skinner M. The Systemic Amyloidoses. N Engl J Med 1997;337:898-909.
2. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016;387:2641-2654.
3. Rapezzi C, Merlini G, Quarta CC et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation 2009;120:1203-12.
4. Lachmann HJ, Booth DR, Booth SE et al. Misdiagnosis of Hereditary as AL (Primary) Amyloidosis. N Engl J Med 2002;346:1786-91.
5. Fontana M, Pica S, Reant P et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation 2015;132:1570-9.
6. Dungu JN, Valencia O, Pinney JH et al. CMR-based differentiation of AL and ATTR cardiac amyloidosis. J Am Coll Cardiol Img 2014;7:133-42.
7. Vogelsberg H, Mahrholdt H, Deluigi CC et al. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: noninvasive imaging compared to endomyocardial biopsy. J Am Coll Cardiol 2008;51:1022-30.
8. Maceira AM, Prasad SK, Hawkins PN, Roughton M, Pennell DJ. Cardiovascular magnetic resonance and prognosis in cardiac amyloidosis. J Cardiovasc Magn Reson 2008;10:54.
9. Maceira AM, Joshi J, Prasad SK et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005;111:186-93.
10. Bollee G, Guery B, Joly D et al. Presentation and outcome of patients with systemic amyloidosis undergoing dialysis. Clin J Am Soc Nephrol 2008;3:375-81.
11. Lachmann HJ, Gillmore JD. Renal Amyloidosis. British Journal of Hospital Medicine 2010;71:83-86.

12. Agency EM. EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans. European Medicines Agency 2017;457616:1-4.
13. Karamitsos TD, Piechnik SK, Banypersad SM et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. J Am Coll Cardiol Img 2013;6:488-97.
14. Fontana M, Banypersad SM, Treibel TA et al. Native T1 mapping in transthyretin amyloidosis. J Am Coll Cardiol Img 2014;7:157-65.
15. Bandula S, Banypersad SM, Sado D et al. Measurement of Tissue interstitial volume in healthy patients and those with amyloidosis with equilibrium contrast-enhanced MR imaging. Radiology 2013;268:858-64.
16. Hawkins PN, Lavender JP, Pepys MB. Evaluation of systemic amyloidosis by scintigraphy with ^{123}I-labeled serum amyloid P component. N Engl J Med 1990;323:508-513.
17. Martinez-Naharro A, Treibel TA, Abdel-Gadir A et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol 2017;70:466-477.
18. Rapezzi C, Quarta CC, Guidalotti PL et al. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. J Am Coll Cardiol Img 2011;4:659-70.
19. Kellman P, Hansen MS. T1 mapping in the heart: accuracy and precision. J Cardiovasc Magn Reson 2014;16:20.
20. Kellman P, Bandettini WP, Mancini C, Hammer-Hansen S, Hansen MS, Arai AE. Characterization of myocardial T1-mapping bias caused by intramyocardial fat in inversion recovery and saturation recovery techniques. J Cardiovasc Magn Reson 2015;17:33.
21. Taylor AJ, Salerno M, Dharmakumar R, Jerosch-Herold M. T1 Mapping: Basic Techniques and Clinical Applications. J Am Coll Cardiol Img 2016;9:67-81.

22. Spottiswoode BS, Ugander M, Kellman P. Automated inline extracellular volume (ECV) mapping. Journal of Cardiovascular Magnetic Resonance 2015;17:W6.

23. Dabir D, Child N, Kalra A et al. Reference values for healthy human myocardium using a T1 mapping methodology: results from the International T1 Multicenter cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 2014;16:69-81.

24. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: a comprehensive review. J Cardiovasc Magn Reson 2016;18:89.

25. Schelbert EB, Messroghli DR. State of the Art: Clinical Applications of Cardiac T1 Mapping. Radiology 2016;278:658-76.

26. Muscogiuri G, Suranyi P, Schoepf UJ et al. Cardiac Magnetic Resonance T1-Mapping of the Myocardium: Technical Background and Clinical Relevance. J Thorac Imaging 2017.

27. Sado DM, White SK, Piechnik SK et al. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. Circ Cardiovasc Imaging 2013;6:392-8.

28. Pica S, Sado DM, Maestrini V et al. Reproducibility of native myocardial T1 mapping in the assessment of Fabry disease and its role in early detection of cardiac involvement by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2014;16:99-107.

29. Alam MH, Auger D, Smith GC et al. T1 at 1.5T and 3T compared with conventional T2* at 1.5T for cardiac siderosis. J Cardiovasc Magn Reson 2015;17:102.

30. Bull S, White SK, Piechnik SK et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. Heart 2013;99:932-7.

31. O h-Ici D, Jeuthe S, Al-Wakeel N et al. T1 mapping in ischaemic heart disease. Eur Heart J Cardiovasc Imaging 2014;15:597-602.

32. Dall'Armellina E, Ferreira VM, Kharbanda RK et al. Diagnostic value of pre-contrast T1 mapping in acute and chronic myocardial infarction. J Am Coll Cardiol Img 2013;6:739-42.

33. Hinojar R, Varma N, Child N et al. T1 Mapping in Discrimination of Hypertrophic Phenotypes: Hypertensive Heart Disease and Hypertrophic Cardiomyopathy: Findings From the International T1 Multicenter Cardiovascular Magnetic Resonance Study. Circ Cardiovasc Imaging 2015;8.

34. aus dem Siepen F, Buss SJ, Messroghli D et al. T1 mapping in dilated cardiomyopathy with cardiac magnetic resonance: quantification of diffuse myocardial fibrosis and comparison with endomyocardial biopsy. Eur Heart J Cardiovasc Imaging 2015;16:210-6.

35. Reiter U, Reiter G, Kovacs G et al. Native myocardial T1 mapping in pulmonary hypertension: correlations with cardiac function and hemodynamics. Eur Radiol 2017;27:157-166.

36. Ntusi NAB, Piechnik SK, Francis JM et al. Subclinical myocardial inflammation and diffuse fibrosis are common in systemic sclerosis – a clinical study using myocardial T1-mapping and extracellular volume quantification. J Cardiovasc Magn Reson 2014;16:21-33.

37. Ugander M, Bagi PS, Oki AJ et al. Myocardial edema as detected by pre-contrast T1 and T2 CMR delineates area at risk associated with acute myocardial infarction. J Am Coll Cardiol Img 2012;5:596-603.

38. Ferreira VM, Piechnik SK, Dall'Armellina E et al. Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents. J Cardiovasc Magn Reson 2014;16:36-47.

39. Ferreira VM, Piechnik SK, Dall'Armellina E et al. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2012;14:42.

40. Ferreira VM, Piechnik SK, Dall'Armellina E et al. T(1) mapping for the diagnosis of acute myocarditis using CMR: comparison to T2-weighted and late gadolinium enhanced imaging. J Am Coll Cardiol Img 2013;6:1048-1058.

41. Banypersad SM, Fontana M, Maestrini V et al. T1 mapping and survival in systemic light-chain amyloidosis. Eur Heart J 2015;36:244-51.

42. Fontana M, Banypersad SM, Treibel TA et al. Native T1 mapping in ATTR cardiac amyloidosis - comparison with AL cardiac amyloidosis - a 200 patient study. J Cardiovasc Magn Reson 2014;16.

43. Gillmore JD, Maurer MS, Falk RH et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016;133:2404-12.

44. Roujol S, Weingärtner S, Foppa M et al. Accuracy, Precision, and Reproducibility of Four T1 Mapping Sequences: A Head-to-Head Comparison of MOLLI, ShMOLLI, SASHA, and SAPPHIRE. Radiology 2014;272:6.

45. Moon JC, Messroghli DR, Kellman P et al. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. J Cardiovasc Magn Reson 2013;15:12.

46. Messroghli DR, Moon JC, Ferreira VM et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017;19:75.

FIGURE LEGENDS

Figure 1. Receiver operating characteristic (ROC) curve for the discrimination of cardiac amyloidosis. Three cut-offs are presented: the optimal cut-off (1091ms, z-score 1.7), the one with 98% PPV (1164ms, z-score 3.5), the one with 98% NPV (1036ms, z-score 0.4).

Figure 2. Native T1 diagnostic accuracy according to Left Ventricular Hypertrophy. Receiver operating characteristic (ROC) curve for native T1 diagnostic accuracy for cardiac amyloidosis in patients with and without Left Ventricular Hypertrophy (LVH).

Figure 3. Receiver operating characteristic (ROC) curves for comparison of the diagnostic accuracy of Native T1 with other parameters. Left panel: Native T1 vs NT-proBNP and other CMR parameters. Right Panel: Native T1 vs echocardiographic parameters. EF, Ejection Fraction; ESVi, End Systolic Volume index; EDVi, End Diastolic Volume index; SVi, Stroke Volume index; MASSi, Left Ventricular Mass index; ECV, Extra Cellular Volume; DT, E wave deceleration time; E/e', early transmitral inflow wave E over early tissue Doppler imaging e' wave of the mitral annulus; LAA, left atrium area.

Figure 4. Native T1 mapping and LGE appearance in different clinical scenarios. CMR end-diastolic cine still (top), MOdified Look-Locker Inversion recovery native T1 map (middle), and late gadolinium enhancement (LGE) images (bottom) in (left to right) healthy volunteer, patients with end stage kidney failure on hemodialysis, hypertrophic cardiomyopathy (HCM), immunoglobulin light-chain amyloidosis (AL amyloidosis), and transthyretin amyloidosis (ATTR amyloidosis) patients.

Figure 5. Diagnostic algorithm in patients with suspected cardiac amyloidosis. Algorithm for requirement for contrast among patients with suspected cardiac amyloidosis. In patients with myocardial native T1 < 1036ms (z-score 0.4), cardiac amyloidosis can be excluded with very high diagnostic accuracy (NPV 98%). In patients with native myocardial T1 > 1164ms (z-score 3.5), cardiac amyloidosis can be diagnosed with very high diagnostic accuracy (PPV

98%). When native myocardial T1 ranges between 1036ms (z-score 0.4) and 1164ms (z-score 3.5), administration of contrast should be considered.

Central Illustration. Native T1 in Cardiac Amyloidosis. In this study, we sought to see whether non-contrast cardiovascular magnetic resonance (CMR) and native T1 mapping with on-the-fly analysis could reduce the need for gadolinium-based contrast agents (GBCAs). We found that non-contrast T1 mapping is a sensitive and specific tool for diagnosis of cardiac amyloidosis in a large unselected population with possible amyloid. Considering this excellent performance in discriminating cardiac infiltration, preserved in the different cardiac amyloidosis subtypes, in the presence of chronic kidney disease and anaemia, we propose a diagnostic algorithm for non-contrast CMR applicable to the majority of patients.

TABLES

Table 1. Baseline characteristics of the overall population divided into Cardiac Amyloidosis, Non-Cardiac Amyloidosis (suspected) and healthy volunteers.

	Cardiac Amyloidosis (n = 441)	**Non-Cardiac Amyloidosis (suspected) (n = 427)**	**Healthy volunteers (n = 30)**	**p value Cardiac Amyloidosis Non-Cardiac Amyloidosis**
General parameters				
Age, years	71 ± 11	64 ± 13	46 ± 7	< 0.001
Male, %	75	58	53	< 0.001
BMI, kg/m^2	26 ± 5	28 ± 5	25 ± 4	< 0.001
SBP, mmHg	120 ± 23	131 ± 24	128 ± 21	< 0.001
DBP, mmHg	72 ± 12	77 ± 13	75 ± 11	< 0.001
Hemoglobin, gr/dl	13.4 ± 1.8	13.0 ± 1,9	13.7	0.004
Hematocrit, %	39.6 ± 5.1	39.8 ± 5.5	40.3 ± 3.5	0.603
eGFR, $ml/min/1.73m^2$	69 ± 22	72 ± 25	83 ± 12	0.040
Albumin, g/L	3.9 ± 0.8	4.0 ± 0.8	-	0.081
Proteinuria, g/24h	0.23 (0.13-1.42)	0.20 (0.13-1.27)	-	0.255
NYHA Class, %	I = 26.3 % II = 60.4 % III = 13.3 % IV = 0 %	I = 56.9 % II = 39.1 % III = 3.7 % IV = 0.3 %	I = 100%	< 0.001
6-minute walking test, mt	351 ± 136	410 ± 142	-	< 0.001
Heart rate, bpm	73 ± 14	72 ± 14	-	0.693
Biomarkers				
NT-proBNP, ng/l	2897 (1446-5546)	228 (85-903)	-	< 0.001
Echocardiographic parameters				
LA area, cm^2	25 ± 7	20 ± 6	-	< 0.001
Lateral E', cm/s	0.07 ± 0.03	0.10 ± 0.04	-	< 0.001
E/E'	16 ± 8	9 ± 5	-	< 0.001
E-wave deceleration time, ms	197 ± 60	223 ± 67	-	< 0.001

CMR parameters				
LV mass, g	220 ± 75	139 ± 63	114 ± 17	< 0.001
LV mass index, g/m^2	116 ± 36	72 ± 28	61 ± 8	< 0.001
LVEDV, ml	122 ± 38	134 ± 41	157 ± 19	< 0.001
LVEDV index, ml/m2	65 ± 18	70 ± 18	84 ± 10	< 0.001
LVESV, ml	51 ± 30	47 ±31	51 ± 8	0.044
LVESV index, ml/m2	27 ± 15	24 ± 15	27 ± 4	0.007
LVSV, ml	71 ± 21	88 ± 24	106 ± 19	< 0.001
LVSV index, ml/m2	38 ± 10	46 ± 10	56 ± 10	< 0.001
LVEF, %	60 ± 13	67 ± 12	61 ± 21	< 0.001
Native T1, ms	1149 ± 63	1038 ± 50	1020 ± 41	< 0.001
T2, ms	51 ± 4	48 ± 3	48 ± 4	< 0.001
ECV, %	52 ± 9	30 ± 5	30 ± 3	< 0.001

Values are mean ± SD, %, or median (interquartile range).
BMI = Body Mass Index; SPB = systolic blood pressure; DBP = diastolic blood pressure; eGFR = estimated Glomerular Filtration Rate; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LA = left atrium; CMR = cardiac magnetic resonance; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end systolic volume; LVSV = left ventricular stroke volume; LVEF = left ventricular ejection fraction; ECV = extracellular volume.

Table 2. Final diagnosis in the overall population.

Patients	**868**
Cardiac amyloidosis	**441 (50.8%)**
Cardiac AL amyloidosis	222
Cardiac ATTR amyloidosis	214
Cardiac ApoAI amyloidosis	1
Cardiac amyloidosis of unknown type	3
Cardiac gelsolin amyloidosis	1
No cardiac amyloid	**427 (49.2%)**
Amyloidosis without cardiac involvement	216 (24.9%)
Systemic AL amyloidosis, no cardiac involvement	166
ATTR amyloidosis, no cardiac involvement	18
AA amyloidosis, no cardiac involvement	7
LECT 2 amyloidosis, no cardiac involvement	2
Localized AL amyloidosis, no cardiac involvement	23
No amyloidosis	211 (24.3%)
Hypertrophic cardiomyopathy	16
Hypertensive heart disease	48
Fabry disease	1
Ischemic dilated cardiomyopathy	1
Non-ischemic dilated cardiomyopathy	8
Ischemic heart disease	15
Chemotherapy Toxicity	4
Acute myocarditis	2
Previous myocarditis	5
Cardiac sarcoidosis	4
Valvular heart disease	10
Arrhythmogenic right ventricular cardiomyopathy	1
Primary pulmonary hypertension	1
Undetermined cardiomyopathy	21
Light-chain deposition disease	2
Normal heart	72

Table 3. Baseline characteristics of Cardiac AL and ATTR Amyloidosis patients.

	Cardiac AL Amyloidosis (n = 222)	**Cardiac ATTR Amyloidosis (n = 214)**	**p value Cardiac AL Amyloidosis vs Cardiac ATTR Amyloidosis**
General parameters			
Age, years	65 ± 10	76 ± 10	< 0.001
Male, %	60	88	< 0.001
BMI, kg/m^2	26 ± 5	27 ± 4	0.173
SBP, mmHg	113 ± 22	127 ± 22	< 0.001
DBP, mmHg	70 ± 13	75 ± 12	< 0.001
Hemoglobin, gr/dl	12.9 ± 1.9	13.8 ± 1.5	< 0.001
Hematocrit, %	39,3 ±5,1	39.9 ± 5.2	< 0.001
eGFR, $ml/min/1.73m^2$	72 ± 24	66 ± 20	0.003
Albumin, g/L	34 ± 8	44 ± 4	< 0.001
Proteinuria, g/24h	1.44 (0.28-4.60)	0.15 (0.11-0.21)	< 0.001
NYHA Class, %	I = 16.7 % II = 16.7 % III = 53.0 % IV = 13.6 %	I = 15.1 % II = 3.6 % III = 68.2 % IV = 13.0 %	< 0.001
6-minute walking test, mt	352 ± 140	354 ± 131	0.874
Heart rate, bpm	75 ± 14	72 ± 14	0.586
Biomarkers			
NT-proBNP, ng/l	3480 (1160-6755)	2496 (1446-4702)	0.003
Echocardiographic parameters			
LA area, cm^2	22 ± 6	28 ± 6	< 0.001
Lateral E', cm/s	- 0.07 ± 0.03	- 0.07 ± 0.02	0.866
E/E'	16 ± 9	16 ± 8	0.994
E-wave deceleration time, ms	198 ± 60	198 ± 60	0.959
CMR parameters			
LV mass, g	191 ± 72	253 ± 64	< 0.001
LV mass index, g/m^2	102 ± 34	132 ± 32	< 0.001
LVEDV, ml	112 ± 38	134 ± 36	< 0.001
LVEDV index, ml/m2	60 ± 16	70 ± 18	< 0.001

LVESV, ml	43 ± 28	60 ± 31	< 0.001
LVESV index, ml/m2	23 ± 14	31 ± 16	< 0.001
LVSV, ml	69 ± 23	73 ± 20	0.035
LVSV index, ml/m2	37 ± 10	38 ± 10	0.091
LVEF, %	63 ± 13	57 ± 14	< 0.001
Native T1, ms	1166 ± 64	1133 ± 58	< 0.001
T2, ms	52 ± 4	49 ± 3	< 0.001
ECV, %	49 ± 9	54 ± 8	< 0.001

Values are mean ± SD, %, or median (interquartile range).
BMI = Body Mass Index; SPB = systolic blood pressure; DBP = diastolic blood pressure; eGFR = estimated Glomerular Filtration Rate; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LA = left atrium; CMR = cardiac magnetic resonance; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end systolic volume; LVSV = left ventricular stroke volume; LVEF = left ventricular ejection fraction; ECV = extracellular volume.

Table 4. Diagnostic performance of relevant laboratory, echocardiographic and CMR parameters in the overall population.

	AUC (95% CI)	**p value vs Native T1 mapping**
Biomarkers		
NT-proBNP, ng/l	0.88 (0.85-0.92)	0.0018
Echocardiographic parameters		
LA area, cm^2	0.76 (0.72-0.81)	< 0.001
Lateral E', cm/s	0.75 (0.72-0.79)	< 0.001
E/E'	0.84 (0.81-0.88)	< 0.001
E-wave deceleration time, ms	0.65 (0.59-0.70)	< 0.001
CMR parameters		
LV mass, g	0.82 (0.78-0.86)	< 0.001
LV mass index, g/m^2	0.86 (0.82-0.89)	< 0.001
LVEDV, ml	0.61 (0.55-0.66)	< 0.001
LVEDV index, ml/m2	0.63 (0.58-0.68)	< 0.001
LVESV, ml	0.55 (0.50-0.61)	< 0.001
LVESV index, ml/m2	0.57 (0.51-0.62)	< 0.001
LVSV, ml	0.72 (0.67-0.77)	< 0.001
LVSV index, ml/m2	0.75 (0.71-0.80)	< 0.001
LVEF, %	0.67 (0.62-0.72)	< 0.001
Native T1, ms	0.93 (0.92-0.96)	-
T2, ms	0.69 (0.64-0.74)	< 0.001
ECV, %	0.99 (0.98-1.00)	< 0.001

AUC = area under curve; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LA = left atrium; CMR = cardiac magnetic resonance; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end systolic volume; LVSV = left ventricular stroke volume; LVEF = left ventricular ejection fraction; ECV = extracellular volume.

Table 5. Diagnostic performance of relevant laboratory, echocardiographic and CMR parameters in Cardiac AL Amyloidosis and Cardiac ATTR Amyloidosis.

	Cardiac AL Amyloidosis (n = 222)	**Cardiac ATTR Amyloidosis (n = 214)**	**p value Cardiac AL Amyloidosis vs Cardiac ATTR Amyloidosis**
	AUC (95% CI)	**AUC (95% CI)**	
Biomarkers			
NT-proBNP, ng/l	0.87 (0.83-0.90)	0.86 (0.73-0.98)	0.89
Echocardiographic parameters			
LA area, cm^2	0.68 (0.62-0.75)	0.80 (0.60-0.99)	0.43
Lateral E', cm/s	0.73 (0.68-0.80)	0.62 (0.41-0.84)	0.29
E/E'	0.82 (0.77-0.87)	0.75 (0.57-0.92)	0.46
E-wave deceleration time, ms	0.71 (0.65-0.77)	0.73 (0.58-0.89)	0.56
CMR parameters			
LV mass, g	0.78 (0.73-0.83)	0.92 (0.83-1.00)	0.016
LV mass index, g/m^2	0.83 (0.79-0.88)	0.94 (0.86-1.00)	0.04
LVEDV, ml	0.63 (0.57-0.70)	0.55 (0.38-0.72)	0.37
LVEDV index, ml/m2	0.63 (0.56-0.69)	0.56 (0.41-0.71)	0.43
LVESV, ml	0.53 (0.46-0.60)	0.67 (0.49-0.85)	0.16
LVESV index, ml/m2	0.55 (0.49-0.62)	0.69 (0.53-0.86)	0.14
LVSV, ml	0.72 (0.66-0.78)	0.73 (0.57-0.89)	0.84
LVSV index, ml/m2	0.73 (0.67-0.78)	0.75 (0.60-0.91)	0.82
LVEF, %	0.65 (0.59-0.71)	0.75 (0.62-0.88)	0.2
Native T1, ms	0.94 (0.92-0.97)	0.96 (0.92-1.00)	0.46
T2, ms	0.77 (0.72-0.82)	0.72 (0.54-0.90)	0.59
ECV, %	0.98 (0.97-0.99)	0.99 (0.99-1.00)	0.37

AUC = area under curve; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LA = left atrium; CMR = cardiac magnetic resonance; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end systolic volume; LVSV = left ventricular stroke volume; LVEF = left ventricular ejection fraction; ECV = extracellular volume.