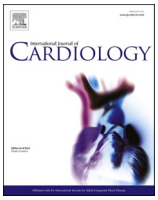
International Journal of Cardiology 403 (2024) 131892

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Tissue mapping by cardiac magnetic resonance imaging for the prognostication of cardiac amyloidosis: A systematic review and meta-analysis

Sean Cai [a], Hourmazd Haghbayan [b], Kelvin K.W. Chan [a,c], Djeven P. Deva [d,e,f], Laura Jimenez-Juan [d,f], Kim A. Connelly [a,e,g], Ming-Yen Ng [h], Raymond T. Yan [a], Andrew T. Yan [a,d,f,g,*]

[a] Department of Medicine, University of Toronto, Toronto, Canada
[b] Department of Medicine, Mackenzie Health Network, Toronto, Canada
[c] Department of Medical Oncology, Sunnybrook Hospital, Toronto, Canada
[d] Department of Medical Imaging, University of Toronto, Toronto, Canada
[e] Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Canada
[f] Department of Medical Imaging, St. Michael's Hospital, Toronto, Canada
[g] Terrence Donnelly Heart Centre, Division of Cardiology, St. Michael's Hospital, Toronto, Canada
[h] Department of Diagnostic Radiology, The University of Hong Kong, HKU-Shenzhen Hospital, China

ARTICLE INFO

Keywords:
Cardiac MRI
Tissue mapping
Cardiac amyloidosis
Prognosis

ABSTRACT

Background: Cardiac amyloidosis is increasingly recognized as a significant contributor to cardiovascular morbidity and mortality. With the emergence of novel therapies, there is a growing interest in prognostication of patients with cardiac amyloidosis using cardiac magnetic resonance imaging (CMR). In this systematic review and meta-analysis, we aimed to examine the prognostic significance of myocardial native T1 and T2, and extracellular volume (ECV).

Methods: Observational cohort studies or single arms of clinical trials were eligible. MEDLINE, EMBASE and CENTRAL were systematically searched from their respective dates of inception to January 2023. No exclusions were made based on date of publication, study outcomes, or study language. The study populations composed of adult patients (≥18 years old) with amyloid cardiomyopathy. All studies included the use of CMR with and without intravenous gadolinium contrast administration to assess myocardial native T1 mapping, T2 mapping, and ECV in association with the pre-specified primary outcome of all-cause mortality. Data were extracted from eligible primary studies by two independent reviewers and pooled via the inverse variance method using random effects models for meta-analysis.

Results: A total of 3852 citations were reviewed. A final nine studies including a total of 955 patients (mean age 65 ± 10 years old, 32% female, mean left ventricular ejection fraction (LVEF) 59 ± 12% and 24% had NYHA class III or IV symptoms) with cardiac amyloidosis [light chain amyloidosis (AL) 50%, transthyretin amyloidosis (ATTR) 49%, other 1%] were eligible for inclusion and suitable for data extraction. All included studies were single centered (seven with 1.5 T MRI scanners, two with 3.0 T MRI scanners) and non-randomized in design, with follow-up spanning from 8 to 64 months (median follow-up = 25 months); 320 patients died during follow-up, rendering a weighted mortality rate of 33% across studies. Compared with patients with AL amyloid, patients with ATTR amyloid had significantly higher mean left ventricular mass index (LVMi) (102 ± 34 g/m^2 vs 127 ± 37 g/m^2, $p = 0.02$). N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin T levels, mean native T1 values, ECV and T2 values did not differ between patients with ATTR amyloid and AL amyloid (all $p > 0.25$). Overall, the hazard ratios for mortality were 1.33 (95% CI = [1.10, 1.60]; $p = 0.003$; $I^2 = 29\%$) for every 60 ms higher T1 time, 1.16 (95% CI = [1.09, 1.23], $p < 0.0001$; $I^2 = 76\%$) for every 3% higher ECV, and 5.23 (95% CI = [2.27, 12.02]; $p < 0.0001$; $I^2 = 0\%$) for myocardial-to-skeletal T2 ratio below the mean (vs above the mean).

Conclusion: Higher native T1 time and ECV, and lower myocardial to skeletal T2 ratio, on CMR are associated with worse mortality in patients with cardiac amyloidosis. Therefore, tissue mapping using CMR may offer a

* Corresponding author at: St Michael's Hospital, Division of Cardiology, 30 Bond St, Room 6-030 Donnelly, Toronto, ON M5B 1W8, Canada.
E-mail address: Andrew.yan@unityhealth.to (A.T. Yan).

https://doi.org/10.1016/j.ijcard.2024.131892
Received 26 October 2023; Received in revised form 5 February 2024; Accepted 18 February 2024
Available online 19 February 2024

useful non-invasive technique to monitor disease progression and determine prognosis in patients with cardiac amyloidosis.

1. Introduction

Amyloid cardiomyopathy is caused by the abnormal deposit of misfolded proteins (amyloid fibrils) in the myocardium and has become increasingly recognized as a prevalent cause of heart failure with preserved ejection fraction (HFpEF) worldwide [1]. Transthyretin cardiac amyloidosis (ATTR) is the most common form of cardiac amyloidosis with novel and emerging treatment options available, while immunoglobulin light chain cardiac amyloidosis (AL) currently has no targeted treatment and is generally characterized by rapid progression of cardiomyopathy and high mortality rate [2,3]. Along with the increasing recognition of cardiac amyloid as highly prevalent in the elderly heart failure population and the availability of effective targeted therapies, the accurate prognostication of cardiac amyloidosis has become a subject of intensive investigation.

Cardiac magnetic resonance (CMR) is a highly sensitive, non-invasive, and non-ionizing imaging modality which permits detailed tissue characterization of the myocardium and extracellular space in vivo. By employing tissue mapping sequences, three interrelated measurements on CMR have been hypothesized to correlate with prognosis in patients with cardiac amyloidosis: pre-contrast native T1, longitudinal relaxation time of the myocardium; extracellular volume (ECV), a marker of myocardial tissue remodelling due to amyloid fibril deposition in the extracellular matrix of the myocardium; and native T2 mapping, a quantitative measure of myocardial edema. Multiple prior studies have examined the relationship between these CMR tissue mapping characteristics and mortality, with some conflicting results. However, there is substantial heterogeneity between the studies due to small patient numbers, differences in MRI sequences and field strengths used, patient populations, methods of amyloid diagnosis, and reported variables [4]. In this systematic review and meta-analysis, we therefore sought to examine whether T1, ECV, and T2 values measured on CMR predict mortality in patients with amyloid cardiomyopathy.

2. Methods

Studies were eligible for inclusion into the meta-analysis if they were observational cohort studies or single arms of clinical trials composed of adult patients (≥18 years old) with amyloid cardiomyopathy (diagnosed by biopsy or another non-invasive diagnostic cardiac test, as defined by the authors of the primary studies) of any sub-type, and contained use of CMR with and/or without intravenous gadolinium contrast administration to assess native myocardial T1 and T2 mapping, and ECV in association with mortality in follow-up. Studies were excluded if they did not include the patient population of interest, CMR parameters of interest, any mortality as outcome, or longitudinal follow-up. No exclusions were made based on article language, country of study, date of publication, and duration or method of follow-up.

Review methods were defined in a protocol a priori to the initiation of the formal search strategy and subsequently indexed online following internal revisions to methods (PROSPERO registration CRD42023389620, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023389620). There were no amendments or deviations from original study protocol at the end of the study. MEDLINE, EMBASE, and CENTRAL were systematically searched from their respective dates of inception to June 2023 (Appendix). Two reviewers (S.C. and H.H.) undertook two-stage selection of retrieved citations, first by title and abstract screening, followed by full-text review for confirmation of eligibility prior to inclusion in the systematic review. There were no disagreements between reviewers during the screening process. At both stages, if disagreement arose, the plan was to resolve any disagreement by consensus and discussion with a third reviewer (A.T.Y.).

Employing a standardized and piloted abstraction form, data were extracted from eligible primary studies by two reviewers (S.C. and H.H.) in parallel on study characteristics such as methodological design, setting, year, duration of follow-up, sample size, loss to follow-up, eligibility criteria, sources of funding, and conflicts of interest; baseline participant characteristics such as age, sex, cardiac risk factors, renal function, concomitant diagnosis of ischemic heart disease, New York Heart Association (NYHA) class status, previous hospitalizations for heart failure, and common serological cardiac biomarkers (such as troponin, creatine kinase-myocardial band, and natriuretic peptide levels); CMR imaging characteristics such as field strength, brand, types and dose of gadolinium contrast administered, types of pulse sequences procured, and duration of imaging study; CMR measurements such as left ventricular volume, left ventricular ejection fraction, left ventricular mass, extent of late gadolinium enhancement, myocardial native T1 time, T2 time, and ECV fraction quantification; other prognosticators or prognostic model scores presented by the primary study authors; outcome measures (as defined previously) at all time points presented by study authors such as hazard ratios (HR) for mortality; statistical methods used to relate CMR findings to clinical outcome, covariates considered, and methods for creation of and inclusion of variables in multivariable models. The outcome of interest was all-cause mortality, but all other clinical outcomes reported by investigators in the primary studies were considered as secondary outcomes if adequate data were available for synthesis. When HR was not reported by studies, we first reached out to the original study authors for additional data. In the case where such data could not be obtained, we reconstructed individual-level survival data from the published Kaplan-Meier curves using previously validated digitizeit (https://www.digitizeit.xyz/) by the Guyot method [5,6]. HRs and their 95% CIs were then computed using univariable proportional hazards model based on these reconstructed survival data.

Two reviewers (S.C. and H.H.) independently employed the updated Quality in Prognosis Studies (QUIPS) risk of bias tool to assess the methodological quality of all included studies. Any discrepancies in data extraction and risk of bias assessments between the two reviewers were resolved by consensus or discussion with a third author (A.T.Y.).

2.1. Statistical analysis

Studies were quantitatively synthesized if at least two inclusion studies presented a relationship between a tissue mapping parameter of interest and the primary outcome of all-cause mortality. Univariate analyses were undertaken separately for each CMR parameter (T1, ECV, and T2) by type of statistical relationship (continuous and dichotomous) with HRs for mortality. Wherever such meta-analysis was possible, data were pooled utilizing random effects models and presented graphically via forest plots. Studies using continuous variables and studies using dichotomous variables were not pooled into the same meta-analysis. Meta-analysis of continuous and time-to-event outcomes were undertaken using the generic inverse-variance method to combine study results with a random effects model (DerSimonian and Laird) if both estimates and either their CIs or standard errors are reported in the primary studies to allow pooling. Differing units for linear variables (i.e. per 1–3% increase in ECV between different studies) were adjusted to a standard unit (i.e. per 3% increase in ECV, per 1 standard deviation increase in ECV) while preserving the underlying variable to outcome relationship to homogenously incorporate different studies into the meta-analysis whilst maintaining data integrity. When relevant, cut-offs

defined by the original study authors were retained (commonly defined as the median in studies undertaking dichotomized comparisons). In addition, since tissue mapping values such as native T1 and T2 times are affected by a variety of factors such as MRI magnet strengths, MRI vendors, mapping sequences used, separate analyses were also performed to standardize HRs per increase in standard deviation. Statistical heterogeneity was evaluated by the I^2 statistic on a 0 to 100 scale. A two-tailed alpha of 0.05 was used for all tests and CIs. Multivariable analyses for other clinical variables outside of CMR parameters were not performed due to low sample size.

Descriptive data on study-level characteristics and patient demographics are presented in tabular format. Categorical variables are expressed as a percentage whilst continuous variables are either expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), with overall descriptive statistics pooled as weighted point estimates with associated measures of dispersion or 95% confidence intervals (95% CI).

Management and selection of citations retrieved from database searching were conducted with Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia (http://www.covidence.org). Data analysis was undertaken utilizing Microsoft Excel version 15.30 (Microsoft, USA, 2017) and Cochrane Review Manager version 5.3.5 (The Cochrane Collaboration, Denmark, 2014).

3. Results

Our search identified 3852 total citations for review following removal of duplicates. Of these studies, 3778 were excluded based on title and abstract screening, with 74 studies assessed for eligibility criteria in full text. Common reasons of ineligibility included lack of longitudinal follow-up, lack of mortality as an outcome, or different patient populations examined. A final nine studies including a total of 955 patients with cardiac amyloidosis were thus determined as eligible for inclusion and suitable for data extraction (Fig. 1) [7–15]. Five studies were rated as low risk of bias, whereas the remaining four were moderate, principally due to lack of control of confounding and lack of blinding of CMR interpretation to clinical data (Table 1, Supplemental table).

All included studies were single-center and non-randomized in design, with follow-up spanning from 8 to 64 months (median follow-up 25 months) (Table 1–2). The mean age of included participants was 65 ± 10 years old and 32% of patients were female. Mean LVEF was 59 ± 12% and 24% of patients had NYHA class III or IV symptoms. Five out of nine studies included biopsy and seven out of nine studies included imaging modalities such as CMR, echocardiography or nuclear medicine for diagnosis of amyloid cardiomyopathy. 320 patients died during over a median follow-up of 25 months.

Breakdown by amyloid subtype for AL (n = 475), ATTR (n = 471), and others (n = 9) was 50%, 49% and 1% respectively (Table 2).

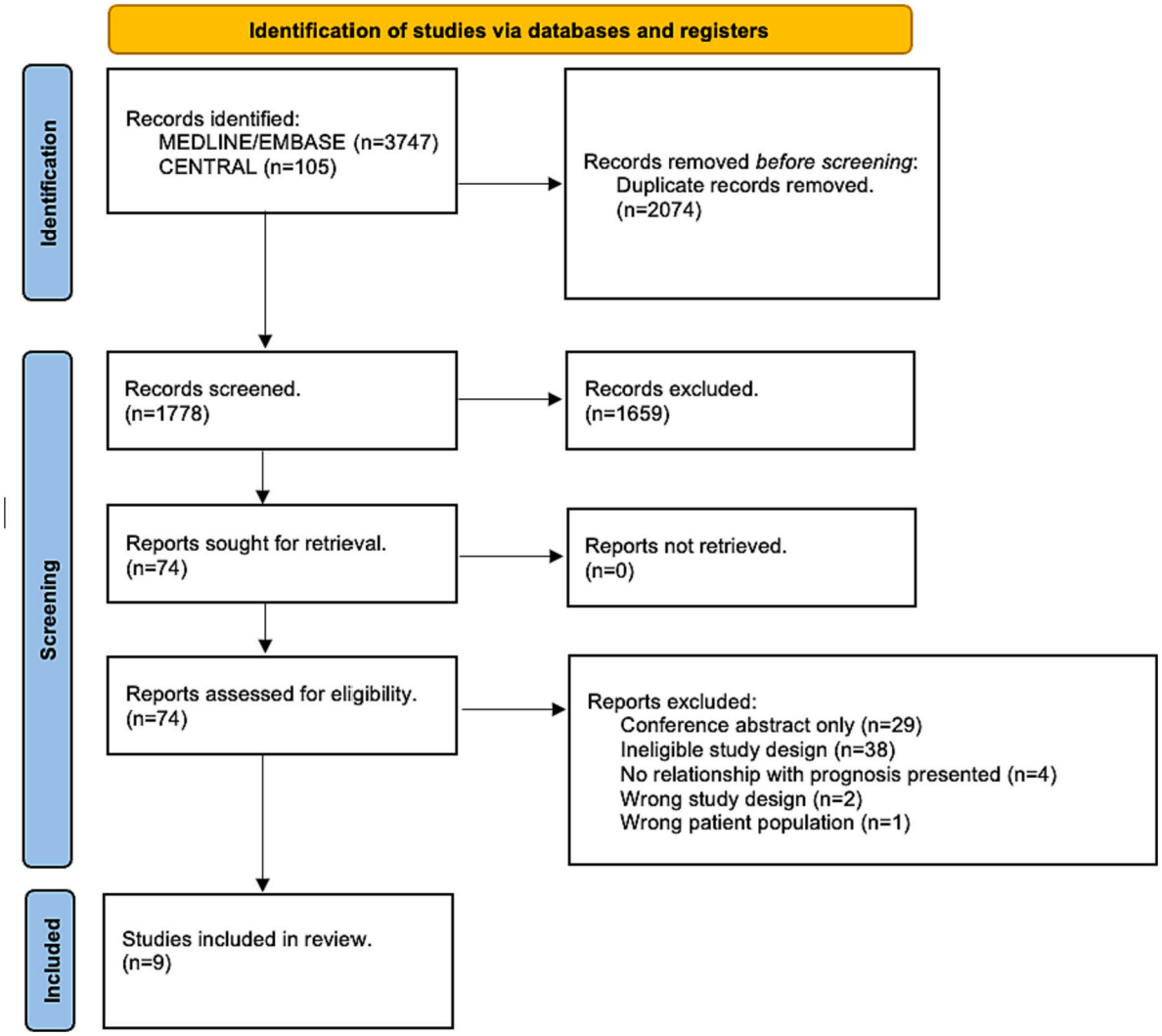


Fig. 1. PRISMA flow diagram regarding study selection.

Table 1
Study characteristics.

First Author Year	Country	Type of study	Total amyloid patients	Number of centers	Reference Diagnostic Tests	MRI strength	MRI sequences used	Blinding	CMR characteristics examined	Outcome examined	Risk of Bias
Banypersad 2015	United Kingdom	Prospective observational	100	1	Biopsy	1.5 T	ShMOLLI	Not specified	Myocardial ECV, T1	Mortality	Low
Ridouani 2018	France	Prospective observational	42	1	Biopsy; Nuclear; Genetic testing for ATTR	1.5 T	MOLLI	Image analysis blinded to clinical data	Myocardial ECV, T1, T2	Mortality	Low
Wan 2019	China	Prospective observational	77	1	CMR LGE patterns; Echocardiogram	3.0 T	MOLLI	Not specified	Myocardial ECV, T1	Mortality	Moderate
Martinez-Naharro 2019	United Kingdom	Prospective observational	227	1	Echocardiogram; Nuclear; Genetic testing for ATTR	1.5 T	ShMOLLI	Not specified	Myocardial ECV, T1	Mortality	Low
Lin 2018	China	Prospective observational	82	1	N/A	3.0 T	MOLLI	Not specified	Myocardial ECV, T1	Mortality	Moderate
Kotecha 2018	United Kingdom	Prospective observational	286	1	Echocardiogram; Nuclear; Biopsy; Genetic testing for ATTR	1.5 T	ShMOLLI; single-shot T2-prepared SSFP readouts	Not specified	Myocardial ECV, T2	Mortality	Low
Agha 2021	United States	Retrospective observational	44	1	CMR	1.5 T	MOLLI; FLASH sequence with T2 preparation pulses	Not specified	Myocardial ECV, T2	Mortality	Moderate
Wassmuth 2011	Germany	Prospective observational	36	1	Biopsy; Echocardiogram; ECG	1.5 T	Short tau-inversion T2-weighted fast spin echo	Not specified	Myocardial signal intensity indexed to skeletal muscle on T2 weighted images	Mortality	Moderate
Legou 2017	France	Prospective observational	73	1	CMR LGE patterns; Biopsy; Nuclear	1.5 T	Short tau-inversion T2-weighted fast spin echo	Image analysis blinded to clinical data	Myocardial signal intensity indexed to skeletal muscle on T2 weighted images	Mortality	Moderate

NYHA class, New York Heart Association class; LVEF, left ventricular ejection fraction; MRI, Magnetic resonance imaging; CMR, cardiac MRI; AL, lightchain amyloid; ATTR, transthyretin amyloid; wt, wild-type; m, mutation; AA, serum amyloid A protein amyloid; LGE, late gadolinium enhancement; ECG, electrocardiogram; ECV, extracellular volume; MOLLI, Modified Look-Locker inversion recovery; ShMOLLI, Shortened Modified Look-Locker inversion recovery.
Values are expressed as median (IQR) or mean ± SD, where appropriate.

Compared with patients with AL amyloid, patients with ATTR amyloid had significantly higher mean indexed left ventricular mass (LVMi) (127 ± 37 g/m2 vs 102 ± 34 g/m^2, $p = 0.02$). NT-proBNP, troponin T levels were not significantly different between patients with ATTR and AL amyloid (all $p > 0.25$). Mean native myocardial T1 values, ECV and T2 values did not differ between patients with ATTR amyloid and AL amyloid. Mean native T1 for patients with ATTR amyloid and AL amyloid were 1094 ± 116 ms and 1292 ± 104 ms ($p = 0.29$) (Table 3a). Mean myocardial ECV for patients with ATTR amyloid and AL amyloid were 0.61 ± 0.11 and 0.49 ± 0.12 ($p = 0.19$) (Table 3b). Mean myocardial T2 value for patients with ATTR amyloid and AL amyloid were 57 ± 5 ms and 54 ± 4 ms ($p = 0.56$) (Table 3c).

Four studies examined the association between native myocardial T1 time and mortality. Two studies involving 304 patients expressed hazard ratios for mortality based on incremental increase in T1 times (Fig. 2a and 2b). Point estimate for hazard ratio for mortality, for every 60 ms increase in T1 time was 1.33 (95% CI = [1.10, 1.60]; $p = 0.003$; I^2 29%); for every 1 standard deviation increase in T1 time was 1.93 (95% CI = [1.33, 2.80]; $p = 0.0005$; I^2 66%). Two studies involving 171 patients expressed hazard ratios for mortality using median T1 time as binary cut-off for comparison (Fig. 2c). Point estimate for hazard ratio for mortality, using median T1 time as cut-off was 2.24 (95% CI = [1.20, 4.1]; $p = 0.01$; I^2 0%).

Seven studies examined the association between myocardial ECV and mortality. Four studies involving 632 patients expressed hazard ratios for mortality based on incremental increase in ECV (Fig. 3a and 3b). Point estimate for hazard ratio for mortality, for every 3% increase in ECV was 1.16 (95% CI = [1.09,1.23]; $p < 0.0001$; I^2 76%); for every 1 standard deviation increase in ECV was 1.92 (95% CI = [1.67, 2.22]; $p < 0.0001$; I^2 0%). Four studies involving 282 patients expressed hazard ratios for mortality using median ECV as cut-off for comparison (Fig. 3c) (HR = 5.31, 95% CI = [2.92, 9.63] $p < 0.0001$; I^2 0%).

Five studies examined myocardial T2 time and mortality (Table 3c). Three studies used T2 time to skeletal muscle ratio as the variable of interest: two of the three studies involving 109 patients concluded that having a T2 ratio lower than the mean T2 ratio of the study population is associated with higher mortality (Fig. 4, HR = 5.23, 95% CI = [2.27, 12.02]; $p < 0.0001$; I^2 0%) [14,15]. However, the mean T2 to skeletal ratio varied between two studies (1.5 ± 0.4 in Wassmuth 2011, 1.16 ± 0.30 in Legou 2017); one study found that T2 ratio was not significantly different between patients with AL, ATTR CA or healthy controls ($p = 0.2$), and did not report hazard ratio for T2 ratio and mortality [8]. Two

Table 2
Patient characteristics.

First Author Year	Age	Amyloid type and patient numbers	Follow-up duration (Months)	Mortality rate	Female	NYHA class I/ II/III/ IV	LVEF (%)	LVMi (g/m2)	LVEDVi (mL/ m2)	LVESVi (mL/ m2)	Troponin (ng/ L)	NT-proBNP (pg/ mL)	Creatinine (mmol/L)	ECV	T1 (ms)	T2
Banypersad 2015	62 ± 10	AL (n = 100)	23	25%	33%	29% / 56% / 15% / 0%	66 ± 11	96 ± 34	60 ± 14	19 ± 10	Troponin T: 0.03 (0.01–0.06)	(pmol/L) 146 (38–359)	89 ± 32	0.44 ± 0.12	1080 ± 87 ms	N/A
Ridouani 2018	69 ± 13	AL (*n* = 22), ATTRwt (*n* = 11), ATTRm (n = 9)	27 (14–40)	43%	30%	11% / 39% / 41% / 9%	54 ± 15	AL: 97 ± 28; ATTR: 115 ± 31	AL: 74 ± 23; ATTR: 89 ± 27	AL: 35 ± 21; ATTR: 47 ± 28	Troponin T: AL: 52 (14–112); ATTR: 38 (8–54)	AL: 6317 (340–18,908); ATTR: 2384 (541–9129)	AL: 110 (78–275); ATTR: 101 (89–167)	AL: 0.53 ± 0.17, ATTR: 0.46 ± 0.11	AL: 1105 ± 54 ms; ATTR: 1066 ± 42 ms	Native T2: AL 63.2 ± 4.7 ms, ATTR 56.2 ± 3.1 ms
Wan 2019	58 ± 10	AL (*n* = 77)	38 (27–46)	60%	34%	> II: 45%	48 ± 12	110 ± 38	69 ± 16	43 ± 14	Troponin T: 83.3 (127.8–219.8)	5347 (11012–24,649)	N/A	0.55 ± 0.11	1470 ± 123 ms	N/A
Martinez-Naharro 2019	72 ± 11	ATTRwt (*n* = 134), ATTRm (*n* = 81), ATTRm carriers (*n* = 12)	32 ± 17	42%	N/A	N/A	56 ± 14	120 ± 41	71 ± 18	32 ± 16	N/A	286 (142–538)	N/A	0.61 ± 0.12	1096 ± 51 ms	N/A
Lin 2018	56 ± 9	AL (*n* = 82)	8	27%	37%	36% / 29% / 28% / 7%	63 ± 15	93.5 ± 29	58.3 ± 16.0	22.1 ± 12.4	Troponin I: 43 (15–146)	2056 (348–6096)	87.3 ± 21.6	0.439 ± 0.109	1438 ± 120 ms	N/A
Kotecha 2018	64 ± 9	AL (*n* = 100), ATTR (*n* = 175), ATTRm carrier (*n* = 11)	23 ± 15	26%	23%	AL: 25% / 36% / 39% / 0% ATTR: 12% / 68% / 20% / 1%	64 ± 11	AL: 113 ± 36 ATTR: 137 ± 33	AL: 61 ± 16 ATTR: 71 ± 19	AL: 26 ± 13; ATTR: 33 ± 16	N/A	AL: 241 (156–895); ATTR: 329 (177–589)	N/A	AL: 0.55 ± 0.10, ATTR: 0.63 ± 0.09	N/A	Native T2: AL 56.6 ± 5.1 ms, ATTR 54.2 ± 4.1 ms
Agha 2021	N/A	AL (*n* = 44)	14	25%	55%	N/A	N/A	N/A	N/A	N/A	Troponin I: 120 (10–1050)	BNP (pg/mL): 794.4 (82–3830)	N/A	0.48 (0.27–0.88)	N/A	Native T2: 53.30 (41.00–60.00) ms
Wassmuth 2011	63 (39–77)	AL (*n* = 31),AA (*n* = 2), ATTR (n = 2), senile (n = 1)	31 (8–64)	64%	50%	N/A	55 ± 12	111 ± 36	68 ± 19	N/A	N/A	N/A	N/A	N/A	N/A	T2 to skeletal ratio 1.5 ± 0.4
Legou 2017	63 ± 15	AL (*n* = 19), ATTR (*n* = 48), senile (*n* = 6)	18 ± 6	11%	34%	N/A	52 ± 15	N/A	N/A	N/A	N/A	3904 ± 5722	N/A	N/A	N/A	T2 to skeletal ratio 1.16 ± 0.30

NYHA class, New York Heart Association class; LVEF, left ventricular ejection fraction; MRI, Magnetic resonance imaging; CMR, cardiac MRI; AL, light chain amyloid; ATTR, transthyretin amyloid; wt, wild-type; m, mutation; AA, serum amyloid A protein amyloid; LGE, late gadolinium enhancement; ECG, electrocardiogram; ECV, extracellular volume.
Values are expressed as median (IQR) or mean ± SD, where appropriate.

Table 3a
Characteristics of studies that examined association between T1 and mortality.

Article	Variable(s) examined	Patients (n)	Death (n)	Outcomes
Banypersad 2015	Native T1	100	25	• Native T1 values were higher in patients with AL cardiac amyloidosis compared with healthy controls (1080 ± 87 ms vs 954 ± 34 ms, $p <$ 0.001) • Native T1 > 1080 ms is associated with worse survival ($p = 0.035$)
Ridouani 2018	Native T1; Post-contrast T1	42	18	• Native T1 values were higher in patients with AL and ATTR cardiac amyloidosis compared with healthy controls (AL: 1105 ± 54 ms; ATTR: 1066 ± 42 ms; vs 975 ± 26 ms; $p < 0.001$) • Higher post contrast T1 values was associated with worse survival ($p =$ 0.0005). The relationship between native T1 values and mortality was not examined.
Wan 2019	Native T1	77	18	• Native T1 values were higher in patients with AL cardiac amyloidosis compared with healthy controls (1470 ± 123 ms vs 1203 ± 47 ms, p < 0.001) • Higher native T1 values was associated with worse survival (p < 0.001)
Martinez-Naharro 2019	Native T1	227	95	• Native T1 values were higher in patients with ATTR cardiac amyloidosis compared with hypertrophic cardiomyopathy controls (1096 ± 51 ms vs 1013 ± 64 ms, p < 0.001) • Native T1 > 1078 ms was associated with worse survival ($p < 0.05$)
Lin 2018	Native T1	82	11	• Native T1 values were higher in patients with AL cardiac amyloidosis compared with healthy controls (1438 ± 120 ms vs 1283 ± 46 ms, $p =$ 0.001) • Native T1 > 1456 ms was associated with worse survival, though not statistically significant ($p = 0.069$)

studies examined the relationship between measured T2 values and mortality: Ridouani 2018 showed that T2 values was not associated with mortality in patients with cardiac amyloidosis ($p = 0.53$) [8]; Kotecha et al. showed that native T2 < 55 ms was associated with better survival in patients with cardiac amyloidosis and T2 values predicted mortality in a multivariable model ($p < 0.01$) [12]. One study examined T2 time to ECV ratio found that T2/ECV ratio ≤ 100 was associated with worse survival ($p = 0.017$) [13].

Table 3b
Characteristics of studies that examined association between ECV and mortality.

Article	Variable(s) examined	Patients (n)	Death (n)	Outcomes
Banypersad 2015	ECV	100	25	• Patients with AL cardiac amyloidosis had higher ECV values compared with healthy controls (0.44 ± 0.12 vs 0.25 ± 0.02, p < 0.001) • ECV > 0.45 was associated with worse survival ($p = 0.004$)
Ridouani 2018	ECV	42	18	• Patients with AL and ATTR cardiac amyloidosis did not differ in ECV values (0.53 ± 0.17 vs 0.46 ± 0.11, $p =$ 0.2). • ECV > 0.59 was associated with worse survival (p = 0.004)
Wan 2019	ECV	77	18	• Patients with AL cardiac amyloidosis had higher ECV values compared with healthy controls (0.55 ± 0.11 vs 0.28 ± 0.03, p < 0.001) • Higher ECV is associated with worse survival (p < 0.001)
Martinez-Naharro 2019	ECV	227	95	• Patients with ATTR cardiac amyloidosis had higher ECV values compared with hypertrophic cardiomyopathy controls (0.61 ± 0.12 vs 0.36 ± 0.13, p < 0.001) • ECV > 0.59 was associated with worse survival (p < 0.001)
Lin 2018	ECV	82	11	• Patients with AL cardiac amyloidosis had higher ECV values compared with healthy controls (0.439 ± 0.109 vs 0.270 ± 0.017, $p =$ 0001) • ECV > 0.44 was associated with worse survival (p = 0.001)
Kotecha 2018	ECV	274	75	• Patients with AL and ATTR cardiac amyloidosis had higher ECV values compared with healthy controls (0.55 ± 0.10 vs 0.63 ± 0.09 vs 0.35 ± 0.09, p < 0.05) • Higher ECV was associated with worse survival in both univariable and multivariable analysis ($p <$ 0.01)
Agha 2021	ECV	44	11	• Patients with AL cardiac amyloidosis had higher ECV values compared with healthy controls [0.48 (0.27–0.88) vs 0.32 (0.22–0.52), $p = 0.008$] • ECV > 0.50 was associated with worse survival ($p = 0.0098$)

Table 3c
Characteristics of studies that examined association between T2 and mortality.

Article	Variable(s) examined	Patients (n)	Death (n)	Outcomes
Wassmuth 2011	T2 to skeletal muscle ratio	36	23	• Patients with cardiac amyloid had lower T2 ratio compared with healthy volunteers (1.5 ± 0.4 vs 1.7 ± 0.2, p < 0.05) • T2 ratio < 1.5 was associated with worse survival ($p < 0.005$)
Legou 2017	T2 to skeletal muscle ratio	73	8	• Patients with cardiac amyloid had lower T2 ratio compared with healthy controls (1.16 ± 0.30 vs 1.37 ± 0.34, p < 0.05) • T2 ratio < 1.36 was associated with worse survival ($p = 0.01$)
Ridouani 2018	Native T2 values (ms) T2 to skeletal muscle ratio	42	18	• Native T2 values were higher for patients with AL and ATTR amyloid compared with healthy controls (63.2 ± 4.7, 56.2 ± 3.1, 51.1 ± 3.1 respectively, p = 0.001) • Native T2 value not significant associated with overall survival in patients with cardiac amyloid [HR 1.03 (95% CI 0.94, 1.12), $p = 0.53$] • T2 ratio was not significantly different for patients with AL and ATTR amyloid compared with healthy controls (1.31 ± 0.4, 1.41 ± 0.2, 1.44 ± 0.3 respectively, $p = 0.2$). Did not examine relationship between T2 ratio and mortality.
Kotecha 2018	Native T2 values (ms)	274	75	• Native T2 values were higher for patients with AL and ATTR compared with healthy controls (56.6 ± 5.1, 54.2 ± 4.1, 48.9 ± 2.0 respectively, p < 0.01) • Native T2 < 55 ms was associated with higher survival in patients with AL amyloid but not ATTR amyloid (p = 0.01 and 0.126, respectively) • Native T2 values predicted mortality in AL amyloid after adjusting for ECV and NT-proBNP in multivariate analysis [HR 1.32 (95% CI 1.05, 1.67), p < 0.05] • Native T2 values predicted mortality in AL amyloid after adjusting for NYHA functional class and E/e' in multivariate analysis [HR 1.34 (95% CI 1.09, 1.64), p < 0.01] • Native T2 values predicted mortality in AL amyloid after adjusting for LVEF and LV mass in multivariate analysis [HR 1.41 (95% CI 1.13, 1.76), p < 0.01] • Native T2 value was not significant associated with overall survival in patients with ATTR amyloid [HR 0.84 (95% CI 0.68, 1.04), $p = 0.104$]
Agha 2021	Native T2 values (ms) T2 to ECV ratio	44	11	• Native T2 values were higher for patients with cardiac amyloid compared with healthy controls [53.30 (41.00–60.00), 48.70 (44.00–53.00) respectively, $p = 0.016$] • Patients with cardiac amyloid had lower T2/ECV ratio compared with healthy volunteers [121.42 (56.80–132.19) vs 164.73 (101.61–198.69), $p = 0.017$] • T2/ECV ratio ≤100 was associated with worse survival ($p = 0.0001$)

4. Discussion

In this systematic review and meta-analysis of 9 studies examining the relationship between CMR-derived myocardial tissue mapping characteristics and mortality in patients with cardiac amyloidosis, we found that higher ECV and T1 times, as well as lower T2 to skeletal muscle ratio, were associated with higher mortality. Overall, there was a high mortality rate in patients with cardiac amyloidosis. This meta-analysis adds to the growing body of literature showing that use of non-invasive imaging, such as tissue mapping parameters from CMR, may be useful in prognostication of patients with cardiac amyloidosis.

Native T1 relaxation values are affected by a combination of tissue edema such as in myocardial inflammation or infarction, and interstitial volume expansion such as myocardial fibrosis [16]. Disease states such as Takatsubo cardiomyopathy, cardiac amyloidosis, myocarditis have been demonstrated to have elevated native T1 values, while cardiac hemochromatosis has been shown to have lower native T1 values [17]. In this meta-analysis, we demonstrated that, in patients with cardiac amyloidosis, higher native T1 time confers a worse prognosis in a continuous relationship. It is plausible that since cardiac amyloidosis is a disease of myocardial interstitium, higher T1 values represent a surrogate marker of interstitial volume expansion from fibril deposition and therefore greater overall burden of disease. Although native T1 value is not dependent on the use of gadolinium, it is dependent on other technical parameters including pulse sequences, timing during the cardiac cycle, and CMR field strength [18]. Therefore, an important challenge in using T1 values for prognostication is that reference values of native T1 times may be different between centres. In addition, there are three MRI sequences routinely used in clinical practice for native T1 mapping, which can generate different T1 values from the same patient. Inversion recovery sequences based on Look-Locker protocol such as Modified Look-Locker inversion recovery (MOLLI) and Shortened Modified Look-Locker inversion recovery (ShMOLLI) result in similar native T1 values, while Saturation Recovery Sequences (SASHA) leads to a higher native T1 values [19]. The studies that examined native T1 values in this meta-analysis used MOLLI and ShMOLLI. Therefore, the findings in this meta-analysis may not be directly applicable to T1 measurements using SASHA. However, the relationship between higher T1 values and mortality is likely preserved regardless of T1 mapping sequences.

In comparison to native T1 times, ECV is a relative measurement of interstitial and extracellular matrix expansion. It can be estimated based on patient's hematocrit, T1 values of myocardium and blood before and after gadolinium administration. Disease states that cause cardiac

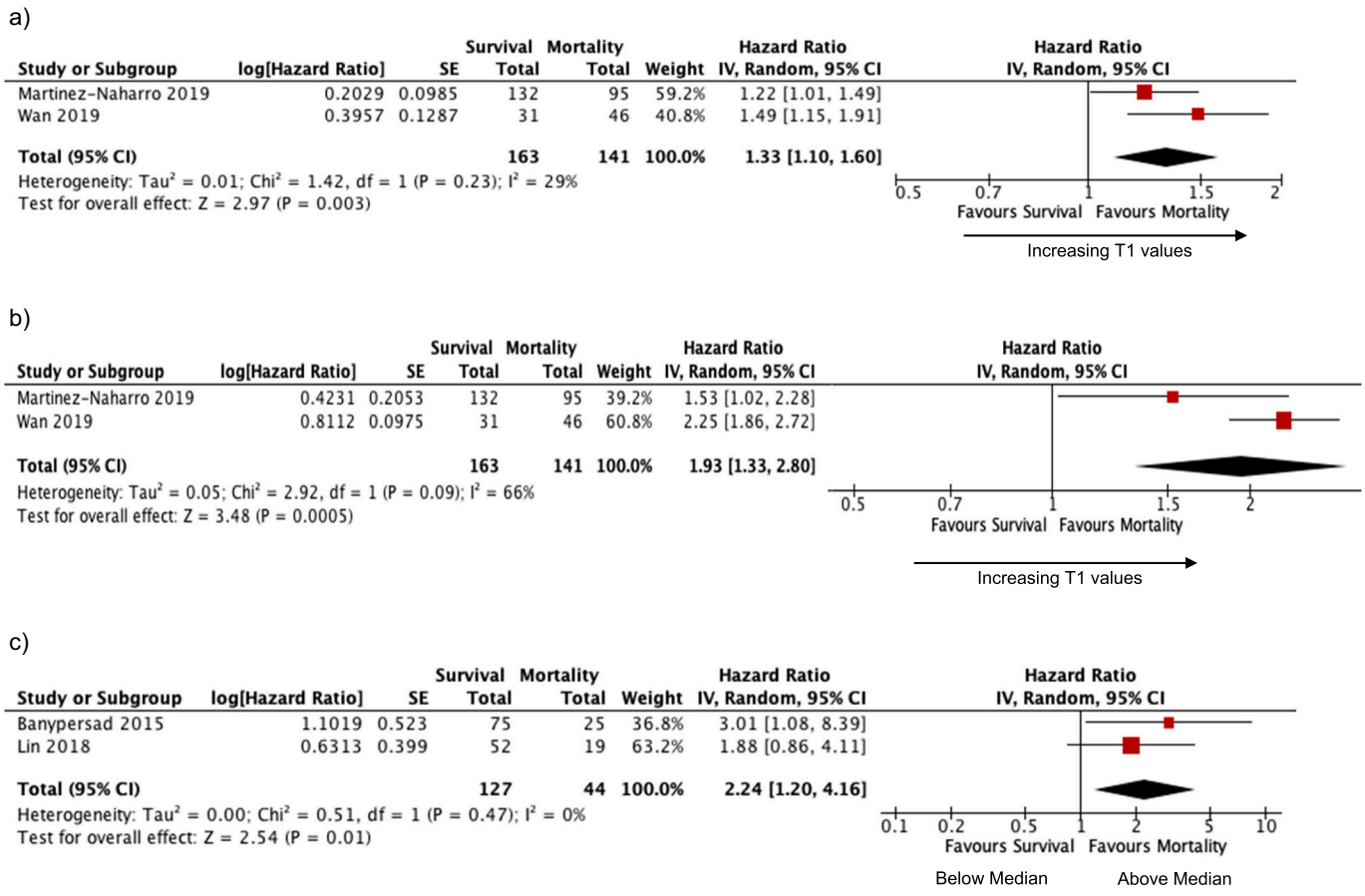


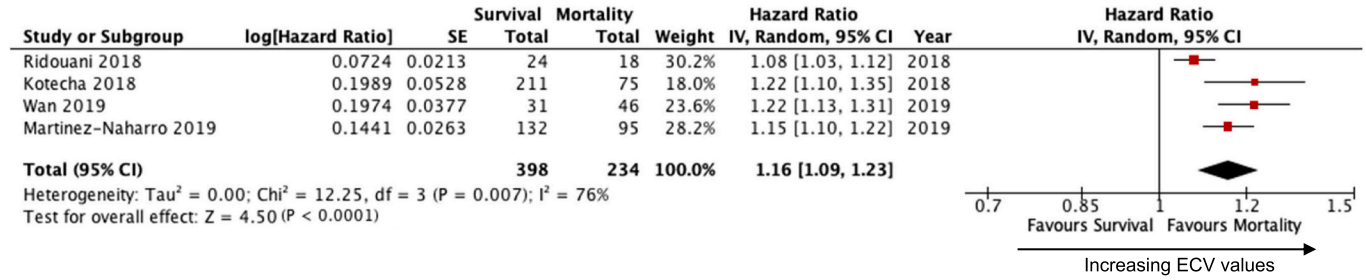
Fig. 2. a Forest plots of Hazard Ratios per 60 ms higher native T1 values.
b. Forest plots of Hazard Ratios per 1 standard deviation higher native T1 values.
c. Forest plots of Hazard Ratios comparing above vs below (reference) median native T1 values.

fibrosis such as aortic stenosis and hypertrophic cardiomyopathy can cause elevated ECV values compared to healthy individuals due to extracellular collagen deposition. In cardiac amyloidosis, extracellular matrix expansion is due to widespread and substantial amyloid protein accumulation, and the resultant ECV is higher than any other cardiomyopathy [20]. It is therefore physiologically plausible that higher ECV values, like native T1 times, correlate with disease severity and therefore higher consequent mortality. In this current meta-analysis, we demonstrated that this relationship is continuous, with incremental increases in ECV correlating with worse survival. Therefore, this study adds further validity to the recently proposed notion that ECV can be employed as an initial non-invasive modality for assessment of disease progression, and potentially treatment response [21]. In comparison to native T1 times, ECV is less prone to variation between centres or due to magnet field strength. However, it requires the administration of gadolinium, which has been associated with nephrogenic systemic fibrosis in patients with kidney dysfunction, which frequently complicates systemic amyloidosis. Therefore, ECV assessment may not always be feasible for patients with cardiac amyloidosis who may have renal impairment due to amyloid deposition.

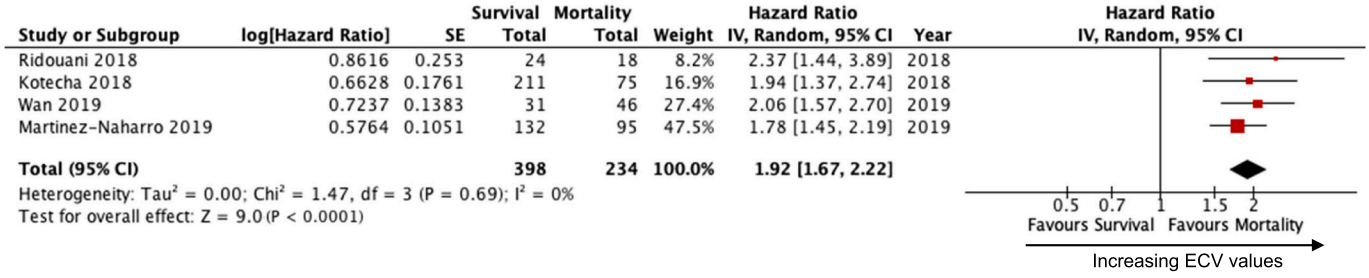
Recently, there has been an increasing interest in utilizing T2 mapping in cardiac amyloidosis. Though highly reproducible when using standardized imaging protocols, T2 values are affected by MRI field strength, image post-processing software, and sex [22]. There is also significant variation within the same heart between different segments, levels and even axes [22]. However, indexing T2 values to skeletal muscle reduces the effects of MRI field strengths and sequences, making it more attractive for clinical use. Despite this, there is significant heterogeneity in T2 ratio values across different studies (1.5 ± 0.4 in Wassmuth 2011, 1.16 ± 0.30 in Legou 2017) [14,15]. Overall, studies examining T2 to skeletal ratio in cardiac amyloidosis have yielded conflicting results. Results of this meta-analysis suggest that lower T2 ratio confers worse prognosis, while others suggesting it is no different from controls [8,12]. The reasons for this difference remain to be elucidated. One hypothesis is that amyloidosis proteins contain hydrophobic beta-pleated sheets which interact and limit movement in local water protons and decrease T2 values [23]. Given the heterogeneity of findings regarding T2 times in cardiac amyloidosis, further studies are required.

Over the last few years, there has been increasing awareness and understanding of the high morbidity and mortality associated with cardiac amyloidosis which has spurred the need for non-invasive methods of diagnosis and monitoring of disease progression. However, studies on prognostic value of CMR parameters in cardiac amyloidosis endorse significant amount of heterogeneity between studies, limiting applications of individual study findings to the general population. To our knowledge, our study is the most up to date meta-analysis that incorporated three commonly used CMR tissue mapping parameters. Despite heterogeneity in individual study populations and methods, we found consistent trends in the prognostic value of native T1 time, T2 times and ECV. Therefore, our study help strengthen the generalizability of using CMR for cardiac amyloidosis prognostication in a heterogenous, real-world patient population. Previously, meta-analysis by Pan et al. demonstrated that ECV is better than LGE and T1 at diagnosing and prognosticating cardiac amyloidosis [4]. Elevated ECV values and T1 portend worse cardiac prognosis [4]. Our study corroborates the findings by Pan et al. but with a few notable differences. First, our study grouped prognostic studies on ECV and T1 and determined hazard ratios

a)



b)



c)

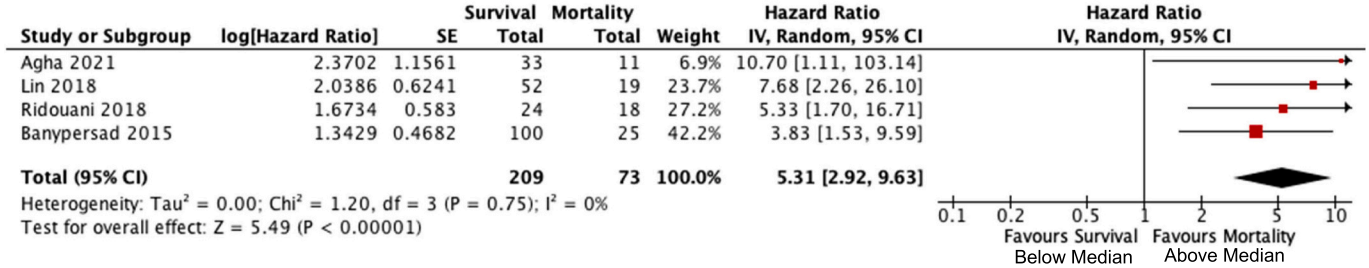


Fig. 3. a Forest plots of Hazard Ratios per 3% higher ECV.
b. Forest plots of Hazard Ratios per 1 standard deviation higher ECV.
c. Forest plots of Hazard Ratios comparing above vs below (reference) median ECV.

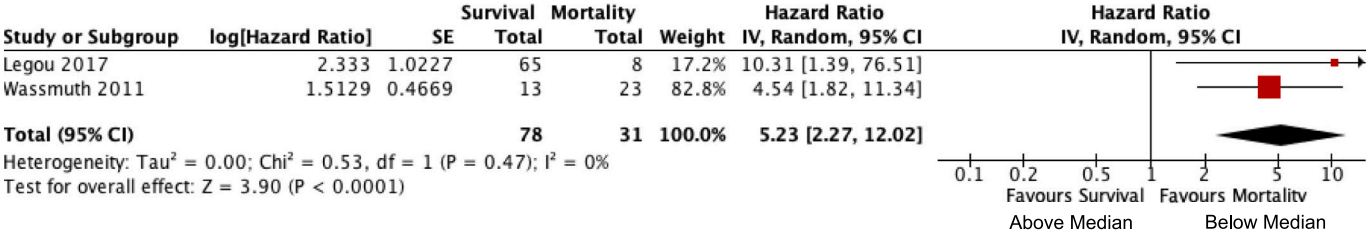


Fig. 4. Forest plots of Hazard Ratios comparing below mean vs above mean (reference) T2 ratio.

based on either an incremental increase or categorical comparison based on the median value. This choice was guided by the variables used in the studies. Compared with Pan et al. where hazard ratios were pooled together despite differences in the units of variables reported, our study preserves the integrity of the data. Accordingly, not all the studies could be pooled, thereby limiting the power of the meta-analysis. Second, our meta-analysis was done two years later than Pan et al. with an up-to-date literature search and inclusion of recently published studies. Third, our study also examined T2 in cardiac amyloidosis which was not examined in Pan et al.

This systematic review has several limitations. First, although prior studies demonstrated that baseline ECV and T1 values may differ between different amyloid subtypes, our meta-analysis did not differentiate ATTR from AL amyloid. The small number of included studies was insufficient to make direct comparison between ATTR and AL amyloid. In addition, not all studies included both subtypes of cardiac amyloidosis, or categorize mortality based on amyloid subtypes. With that said, in the overall meta-analysis, there is a roughly similar number of ATTR and AL subtypes among included participants and the findings that higher ECV and T1 values confer worse survival is consistent across all studies examined in this meta-analysis. Therefore, the relationships between ECV, T1 and mortality may be similar in both types of cardiac amyloidosis. Few patients were diagnosed with other subtypes of amyloidosis, such as AA amyloidosis from systemic inflammatory conditions, and the findings of this systematic review therefore may not extend to patients diagnosed with these variants of cardiac

amyloidosis. Given that various subtypes of cardiac amyloidosis may differ in prognosis and treatment options, the prognostic value of CMR parameters in specific amyloid subtypes remains an area of interest for future study. Second, our meta-analyses did not use multivariable analyses to account for heterogeneity at the between-study level in the patient populations (such as age, sex, LVEF and NYHA functional class, time from diagnosis), method of diagnosis of amyloidosis, and technical parameters related to CMR image acquisition (such as MRI vendors, magnet strengths, types of sequences) due to study sample sizes. Therefore, even though a correlation was observed between CMR parameters and mortality, we cannot exclude underlying confounding variables. In addition, the incremental and comparative prognostic value of CMR beyond LVEF and biomarkers will need to be determined in future studies. Third, for native T1 and T2, only a small number of studies utilizing different magnet strengths could be pooled together based on how the data were presented. Our meta-analysis performed separate pooling based on differing units at the cost of reducing study numbers in each analysis. Though more confirmatory data from different centers would be helpful, we believe this meta-analysis provides the best summary of available published prognostic data to date. Lastly, we noted there were differences in method of diagnosis used to confirm cardiac amyloidosis (ranging from biopsy to non-invasive imaging) between studies, a likely major source of between study heterogeneity. Although most of the studies used imaging-based techniques to confirm the diagnosis, this may reflect the recent development and clinical adoption of more advanced imaging techniques such as technetium pyrophosphate nuclear imaging and tissue mapping techniques on CMR, as well as the increasing utilization of non-invasive imaging over biopsies to minimize procedure-related risks.

5. Conclusion

In this systematic review and meta-analysis of nine studies examining tissue mapping parameters using CMR and prognosis in patients with cardiac amyloidosis, higher ECV, T1 values and lower T2 to skeletal muscle ratio were associated with heightened risk of mortality. Overall, tissue mapping using CMR may offer a useful non-invasive technique to monitor disease progression and determine prognosis in patients with cardiac amyloidosis.

Authors statement

The authors declare that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

The authors declare that no generative AI and AI-assisted technologies has been used in the writing process.

CRediT authorship contribution statement

Sean Cai: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Hourmazd Haghbayan:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Kelvin K.W. Chan:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Djeven P. Deva:** Writing – review & editing, Methodology, Formal analysis. **Laura Jimenez-Juan:** Writing – review & editing, Methodology, Formal analysis. **Kim A. Connelly:** Writing – review & editing, Methodology, Formal analysis. **Ming-Yen Ng:** Writing – review & editing, Investigation, Formal analysis. **Raymond T. Yan:** Writing – review & editing, Methodology, Formal analysis. **Andrew T. Yan:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.131892.

References

[1] AbouEzzeddine OF, D.R. Davies, C.G. Scott, et al., Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction, JAMA Cardiol. 6 (11) (Nov 1 2021) 1267–1274, https://doi.org/10.1001/jamacardio.2021.3070.
[2] F.L. Ruberg, M. Grogan, M. Hanna, J.W. Kelly, M.S. Maurer, Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review, J. Am. Coll. Cardiol. 73 (22) (Jun 11 2019) 2872–2891, https://doi.org/10.1016/j.jacc.2019.04.003.
[3] R.H. Falk, K.M. Alexander, R. Liao, S. Dorbala, AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy, J. Am. Coll. Cardiol. 68 (12) (Sep 20 2016) 1323–1341, https://doi.org/10.1016/j.jacc.2016.06.053.
[4] J.A. Pan, M.J. Kerwin, M. Salerno, Native T1 mapping, extracellular volume mapping, and late gadolinium enhancement in cardiac amyloidosis: a meta-analysis, JACC Cardiovasc. Imaging 13 (6) (Jun 2020) 1299–1310, https://doi.org/10.1016/j.jcmg.2020.03.010.
[5] P. Guyot, A.E. Ades, M.J. Ouwens, N.J. Welton, Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves, BMC Med. Res. Methodol. 12 (Feb 1 2012) 9, https://doi.org/10.1186/1471-2288-12-9.
[6] L. Everest, S. Blommaert, D. Tu, et al., Validating restricted mean survival time estimates from reconstructed Kaplan-Meier data against original trial individual patient data from trials conducted by the Canadian cancer trials group, Value Health 25 (7) (Jul 2022) 1157–1164, https://doi.org/10.1016/j.jval.2021.12.004.
[7] S.M. Banypersad, M. Fontana, V. Maestrini, et al., T1 mapping and survival in systemic light-chain amyloidosis, Eur. Heart J. 36 (4) (Jan 21 2015) 244–251, https://doi.org/10.1093/eurheartj/ehu444.
[8] F. Ridouani, T. Damy, V. Tacher, et al., Myocardial native T2 measurement to differentiate light-chain and transthyretin cardiac amyloidosis and assess prognosis, J. Cardiovasc. Magn. Reson. 20 (1) (Aug 16 2018) 58, https://doi.org/10.1186/s12968-018-0478-3.
[9] K. Wan, W. Li, J. Sun, et al., Regional amyloid distribution and impact on mortality in light-chain amyloidosis: a T1 mapping cardiac magnetic resonance study, Amyloid. 26 (1) (Mar 2019) 45–51, https://doi.org/10.1080/13506129.2019.1578742.
[10] A. Martinez-Naharro, T. Kotecha, K. Norrington, et al., Native T1 and extracellular volume in transthyretin amyloidosis, JACC Cardiovasc. Imaging 12 (5) (May 2019) 810–819, https://doi.org/10.1016/j.jcmg.2018.02.006.
[11] L. Lin, X. Li, J. Feng, et al., The prognostic value of T1 mapping and late gadolinium enhancement cardiovascular magnetic resonance imaging in patients with light chain amyloidosis, J. Cardiovasc. Magn. Reson. 20 (1) (Jan 3 2018) 2, https://doi.org/10.1186/s12968-017-0419-6.
[12] T. Kotecha, A. Martinez-Naharro, T.A. Treibel, et al., Myocardial edema and prognosis in amyloidosis, J. Am. Coll. Cardiol. 71 (25) (Jun 26 2018) 2919–2931, https://doi.org/10.1016/j.jacc.2018.03.536.
[13] A.M. Agha, N. Palaskas, A.R. Patel, et al., Cardiac magnetic resonance predicting outcomes among patients at risk for cardiac AL amyloidosis, Front. Cardiovasc. Med. 8 (2021) 626414, https://doi.org/10.3389/fcvm.2021.626414.
[14] R. Wassmuth, H. Abdel-Aty, S. Bohl, J. Schulz-Menger, Prognostic impact of T2-weighted CMR imaging for cardiac amyloidosis, Eur. Radiol. 21 (8) (Aug 2011) 1643–1650, https://doi.org/10.1007/s00330-011-2109-3.
[15] F. Legou, V. Tacher, T. Damy, et al., Usefulness of T2 ratio in the diagnosis and prognosis of cardiac amyloidosis using cardiac MR imaging, Diagn. Interv. Imaging 98 (2) (Feb 2017) 125–132, https://doi.org/10.1016/j.diii.2016.08.007.
[16] P. Haaf, P. Garg, D.R. Messroghli, D.A. Broadbent, J.P. Greenwood, S. Plein, Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: a comprehensive review, J. Cardiovasc. Magn. Reson. 18 (1) (Nov 30 2016) 89, https://doi.org/10.1186/s12968-016-0308-4.
[17] J.M. Liu, A. Liu, J. Leal, et al., Measurement of myocardial native T1 in cardiovascular diseases and norm in 1291 subjects, J. Cardiovasc. Magn. Reson. 19 (1) (Sep 28 2017) 74, https://doi.org/10.1186/s12968-017-0386-y.
[18] N. Kawel, M. Nacif, A. Zavodni, et al., T1 mapping of the myocardium: intra-individual assessment of the effect of field strength, cardiac cycle and variation by myocardial region, J. Cardiovasc. Magn. Reson. 14 (May 1 2012) 27, https://doi.org/10.1186/1532-429X-14-27.
[19] T. Teixeira, T. Hafyane, N. Stikov, C. Akdeniz, A. Greiser, M.G. Friedrich, Comparison of different cardiovascular magnetic resonance sequences for native myocardial T1 mapping at 3T, J. Cardiovasc. Magn. Reson. 18 (1) (Oct 4 2016) 65, https://doi.org/10.1186/s12968-016-0286-6.
[20] D.M. Sado, A.S. Flett, S.M. Banypersad, et al., Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease, Heart. 98 (19) (Oct 2012) 1436–1441, https://doi.org/10.1136/heartjnl-2012-302346.
[21] S.M. Banypersad, D.M. Sado, A.S. Flett, et al., Quantification of myocardial extracellular volume fraction in systemic AL amyloidosis: an equilibrium contrast

cardiovascular magnetic resonance study, Circ. Cardiovasc. Imaging 6 (1) (Jan 1 2013) 34–39, https://doi.org/10.1161/CIRCIMAGING.112.978627.
[22] M. Wiesmueller, W. Wuest, R. Heiss, C. Treutlein, M. Uder, M.S. May, Cardiac T2 mapping: robustness and homogeneity of standardized in-line analysis, J. Cardiovasc. Magn. Reson. 22 (1) (May 28 2020) 39, https://doi.org/10.1186/s12968-020-00619-x.
[23] A.D. Gean-Marton, C.F. Kirsch, L.G. Vezina, A.L. Weber, Focal amyloidosis of the head and neck: evaluation with CT and MR imaging, Radiology. 181 (2) (Nov 1991) 521–525, https://doi.org/10.1148/radiology.181.2.1924798.