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The myocardial function index (MFI): An integrated measure of cardiac function in AL-cardiomyopathy

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ABSTRACT

Background: Amyloid light chain (AL) amyloidosis is a systemic disease that can cause restrictive cardiomyopathy (AL-CM). Current imaging techniques are not sensitive to detect myocardial dysfunction in AL-CM. We sought to evaluate role of a novel marker of myocardial dysfunction (myocardial function index, MFI) obtained using changes in left ventricular (LV) blood pool and myocardial volume in diastole and systole.

Methods: Consecutive patients diagnosed with AL-CM who had underwent cardiac MRI between 2001–2017 were identified and compared to healthy individuals. Two independent operators used cardiac MRI to perform epicardial and endocardial tracings in systole and diastole to obtain myocardial volume in diastole (MVd) and myocardial volume in systole (MVs). Changes in myocardial volumes during the cardiac cycle were measured to calculate the MFI by $\frac{(MVd-MVs)+Stroke\ volume}{MVd+LV\ end\ diastolic\ volume}$. Multivariable analysis was performed to evaluate predictors of all-cause mortality and survival was evaluated using Kaplan Meier analysis.

Results: Patients with AL-CM (n = 129, 61 ± 10 years, 32 % women) were older and more likely to be men compared to the normal cohort (n = 101, 39 ± 15 years, 61 % women). MFI was lower in patients with AL-CM (19 % [15; 23] vs 38 % [35; 41], $p < 0.001$) and MFI < 30 % discriminated between AL-CM with 92 % sensitivity and 100 % specificity (AUC 0.98, $p < 0.001$). Higher MFI was independently associated with survival even after adjusting for conventional prognostic biomarkers of AL-CM (HR 0.02, 95 % CI 2.23 *104 – 0.24, $p < 0.05$). Two independent operators demonstrated high intra and inter-rater correlation in measurements used to calculate MFI.

Conclusion: MFI is a novel metric for assessing LV function. It is abnormal in patients with AL-CM and may play a role in risk stratification.

1. Introduction

Amyloid light chain amyloidosis (AL) is a systemic disease where immunoglobulin light chains misfold in the circulation and infiltrate peripheral tissues [1,2]. In approximately half of the patients with systemic AL, toxic fibrils infiltrate myocardium and result in restrictive cardiomyopathy [3,4]. The progressive deposition of amyloid fibrils within myocardial interstitium expands extracellular volume and manifests as increased ventricular wall (LV) thickness. Moreover, the misfolded light chain aggregates induce myocyte destruction with associated edema, further contributing to extracellular expansion and increased ventricular wall thickness [5–7]. These changes result in diastolic dysfunction in earlier stages and both diastolic and systolic dysfunction in later stages, manifesting as heart failure.[8] AL cardiomyopathy is often diagnosed at later stages with a mean survival of < 1 year in patients with heart failure symptoms [9,10]. These changes result in diastolic dysfunction in earlier stages and both diastolic and systolic dysfunction in later stages, manifesting as heart failure [8]. AL cardiomyopathy is often diagnosed at later stages with a mean survival of < 1 year in patients with heart failure symptoms [9,10]. Therefore,

Abbreviations: AL, amyloid light chain; AL-CM, amyloid light chain cardiomyopathy; MFI, myocardial function index; LV, left ventricular.

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early detection and accurate prognostication may guide clinical decision-making.

Characterizing myocardial function in AL cardiomyopathy (AL-CM) is challenging. Commonly reliable surrogates of ventricular function, such as LV ejection fraction (LVEF), may be preserved early on despite reduced stroke volume and cardiac output [11,12]. Strain imaging is used to help characterize abnormal myocardial mechanical properties but remains dependent on image quality and operator experience [13,14]. Furthermore, current metrics of ventricular function are limited to isolated measures in either systole or diastole and fail to capture unique features of myocardium through the entirety of the cardiac cycle. A unifying, comprehensive measure of cardiac function accounting for the progressive dysfunction in AL cardiomyopathy remains elusive.

Therefore, we sought to apply and evaluate a novel MRI derived measure of LV function, myocardial function index (MFI), in patients with AL-CM. We aimed to 1) first assess reproducibility of MFI as a novel metric of cardiac function, 2) assess the potential association between MFI and AL-CM in comparison to a normal reference group, and 3) asses potential association between MFI and all-cause mortality may have in AL-CM.

2. Methods

2.1. Participants

This study was approved by the Mayo Clinic Institutional Review Board. All included participants had consented to the use of their clinical and imaging data for research purposes. A retrospective review was performed using a database of all patients at Mayo Clinic in Rochester, MN who underwent clinically indicated cardiac MRI (CMR) with a protocol appropriate for amyloid cardiomyopathy evaluation (n = 1752) between the years 2001 and 2017. Exclusion criteria included a history of congenital heart disease, acute coronary syndrome (ACS), valve replacement, cardiac transplant, transthyretin (TTR) amyloidosis, or participants having received chemotherapy or bone marrow transplant for AL-amyloidosis prior to CMR. Eligibility required a diagnosis of AL-CM was established by 1) documented tissue diagnosis of light chain amyloidosis, 2) documented plasma cell dyscrasia in a bone marrow biopsy demonstrating a predominance of lambda/kappa producing plasma cells OR by the presence of monoclonal light chain in serum or urine, and 3) echocardiographic evidence of cardiac involvement (increased LV wall thickness, LV diastolic dysfunction and abnormal LV longitudinal strain). A total of 129 participants met eligibility criteria. A previously described sample of 101 healthy volunteers with normal cardiac function served as controls.[15].

2.2. Imaging data

Demographic, CMR, and laboratory data were obtained within 30 days of tissue diagnosis of AL and extracted from the electronic medical records. Routine echocardiography was performed within two years of CMR. The echocardiographic data included LV size and ejection fraction, LV global longitudinal strain, diastolic function assessment – mitral annulus early diastolic velocity (e'), ratio of mitral inflow early to late diastolic velocity (E/A) ratio of mitral inflow to annulus early diastolic velocity (E/e') (a surrogate of LV filling pressures), deceleration time, estimated right ventricular filling systolic pressures, and doppler derived stroke volume and cardiac index.

2.3. Myocardial function index formula derivation

The standard metric of cardiac function to assess systolic function is the LVEF.

$$LVEF = \frac{LV\ end\ diastolic\ volume\ (EDV) - LV\ end\ systolic\ volume\ (ESV)}{LVEDV}$$

The LVEF accounts for chamber blood volume changes and does not capture cyclical volumetric changes.[15–17] The MFI was then derive to account for myocardial and blood pool volumes and excluded geometric assumptions.

$$MFI = \frac{(LVEDV + myocardial\ volume\ in\ diastole\ (MVd)) - (LVESV + myocardial\ volume\ in\ systole\ (MVs))}{(MVd + LVEDV)}$$

Given stroke volume (SV) = LVEDV – LVESV, the MFI formula may be mathematically simplified to:

$$MFI = \frac{(MVd - MVs) + SV}{MVd + LVEDV}$$

The novel myocardial function index incorporates changes in myocardial volume through the entirety of the cardiac cycle [16]. The derivation of myocardial volumes in systole and diastole were obtained in an operator-dependent manner by MRI.

2.4. MRI volumetric assessment

Volumetric measures of the left ventricle at systole and diastole (MVs and MVd respectively) were derived by CMR and obtained by one operator (Fig. 1). Myocardial tracings were performed at the epicardial border of the myocardium at end-systole and end-diastole and included the LV wall contributing to the interventricular septum. With respect to confluence of ventricular structures, tracings of end diastolic volumes included papillary muscle. Prior to this study, technical staff conducted tracings of the epicardium and endocardium at end diastole and endocardium at end systole at the time of CMR per routine protocol [15,16]. A single operator reviewed these tracings for uniformity and accuracy. MRI specifications are described in the protocol of a preliminary study [15].

2.5. Measurement agreement analysis

Measurement agreement of MVs and MVd were performed for 10 % of the study group by using tracings from two independent operators who were blinded from participant characteristics. Each operator referenced the study protocol to perform epicardial tracings. Operator tracings were repeated after a two-week period to assess intra-rater agreement.

2.6. Statistical methods

Summary characteristics were presented as mean and standard deviation for data with normal distribution and median with interquartile range for data with non-normal distributions. A Shapiro-Wilk test assessed normality of variable distribution. Normal and skewed data were compared by an unpaired *t*-test or Mann-Whitney *U* test respectively. Categorical variables were presented as percentages of the cohort compared using a chi-square analysis. Interrater and intra-rater

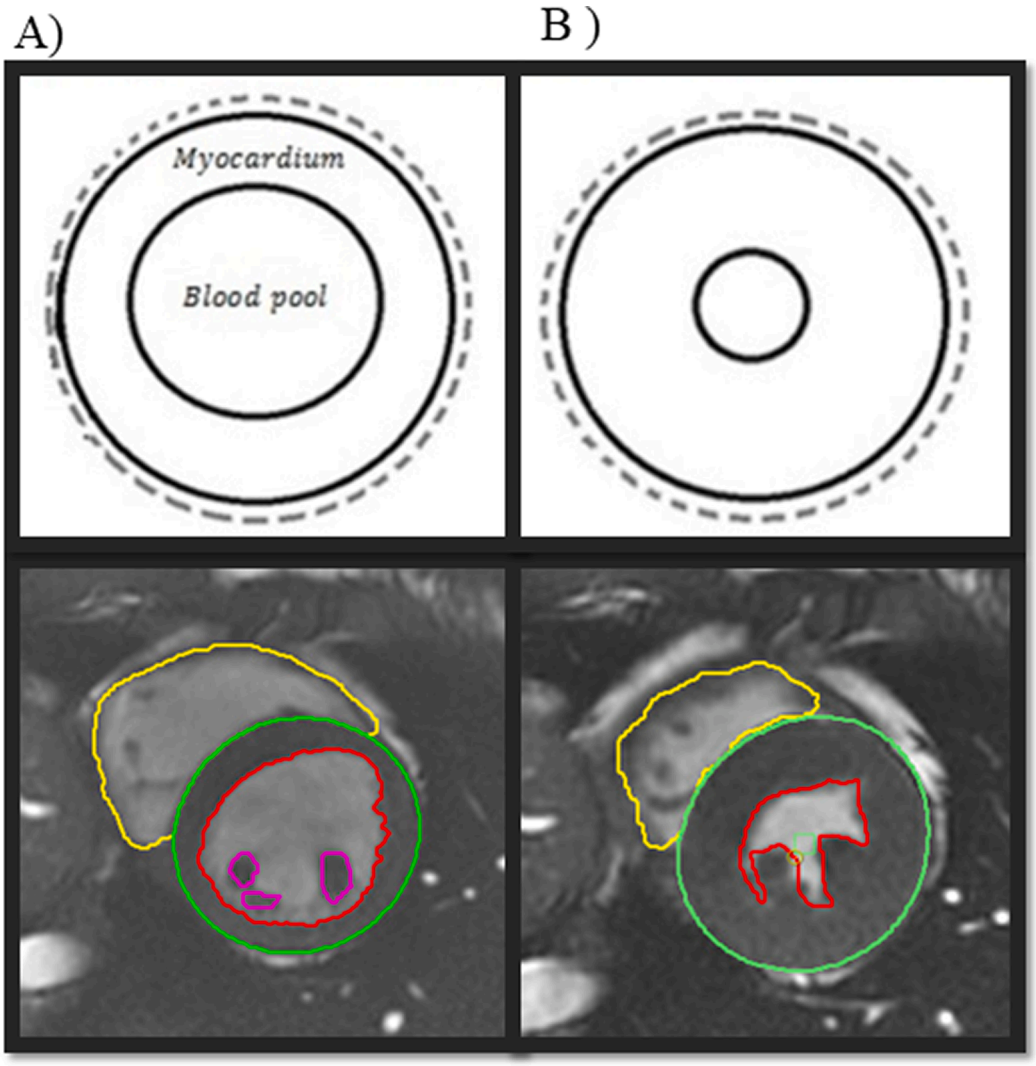

Fig. 1. Epicardial and endocardial contours at A) end systole and B) end diastole. A schematic illustrates cardiac MRI with overlaying tracings below. Colored lines represent operator tracings of endocardium of the right ventricle (yellow), epicardium of the left ventricle (green), endocardium of the left ventricle (red), and papillary muscle observed in diastole (purple).

reliability of operator-performed myocardial tracing (LVEDV, LVESV and SV) were assessed by two independent operators at two-week intervals. Interrater reliability was assessed using intraclass correlation coefficient (ICC) estimates calculated using a mean-rating (k = 2), consistency, two-way mixed-effects model. Intra-rater reliability was measured using two samples of single operator tracings at a two-week interval using a single-rater, absolute agreement, 2-way mixed-effect model. Receiver-operator curve and optimal cutoff value, based on equal weighting of sensitivity versus specificity, were determined to distinguish ventricular function between normal cohort and AL-CM patients. The association between MFI and survival was assessed using a Cox proportional hazard model controlled for age, sex and biomarkers clinically used to prognosticate AL-CM described by the Mayo Clinic 2012 staging system of AL-amyloidosis (elevated N-terminal pro hormone BNP (NT-pro BNP) > 1,800 pg/mL, free light chain difference (dFLC) greater than 18 mg/dL and cardiac troponin T or high sensitivity troponin T (TnT) > 0.025 ng/mL or 45 ng/L respectively). The incremental value of MFI to the Mayo Clinic 2012 staging system of AL-amyloidosis was assessed by examining a change of model fitting (ΔChi^2) when MFI was added as a covariate to a model with age, sex, NT-proBNP, difference in FLC, and TnT as previously described. Kaplan-Meier survival curves stratified by MFI were used to illustrate survival in patients with AL-CM patients; groups were compared using log-rank test. A subgroup analysis to assess MFI as a measure of ventricular function in patients with preserved ejection fraction was preformed after excluding participants with LVEF < 50 %. Analyses were preformed using STATA 16.1.

3. Results

Table 1 lists demographic, clinical, and imaging characteristics of patients studied. A total of 129 patients with AL-CM and 101 normal patients were included in the final analysis. Echocardiographic characteristics may be referenced in Supplemental Table 1. Among the included 129 AL-CM patients, 41 (32 %) were females with a mean age 61 ± 10 years. A total of 54 (42 %) patients had hypertension, 61 (47 %) had diabetes and 44 (34 %) had hyperlipidemia. The majority of patients had AL-CM categorized as Stage 3 (n = 43, 37 %) or stage 4 (n = 37, 32 %). The mean NT-pro BNP was 2883 ng/dl and echo LVEF of the AL-CM group was 55 ± 11 % [IQR 56–66]. The median follow-up for AL-CM participants was 2.33 [IQR 0.33; 6.41] years. A total of 107 patients had chemotherapy and 39 underwent bone marrow transplantation following by time of last follow-up. The normal participants were significantly younger (39 ± 15 years, p < 0.001), more likely to be female (61 %, p < 0.001), and less likely to have traditional cardiovascular comorbidities.

Table 1
Baseline characteristics.

Characteristics		AL-CM		Normal control	p-value
	n		n		
Clinical			101		
Age	129	61 ± 10		39 ± 15	< 0.001
Female sex, %	41	32	62	61	< 0.001
Body Mass Index, kg/m^2	126	27 [24; 29]		26 [22; 28]	0.033
Body surface area, m^2	128	1.94 ± 0.23		1.82 ± 0.23	< 0.001
Hypertension, %	54	42	18	18	< 0.001
Hyperlipidemia, %	44	34	32	32	0.698
Diabetes mellitus, %	61	47	18	18	< 0.001
Mayo Clinic Staging of AL-CM	115				
Stage 1, %	10	9			
Stage 2, %	25	22			
Stage 3, %	43	37			
Stage 4, %	37	32			
Laboratory					
Creatinine, mg/dL	119	1.1 [0.9; 1.3]			
NT-proBNP, pg/mL	113	2,883 [1,444; 5,400]			
Elevated troponin T, n (%)	121	75 (62)			
dFLC > 18 mg/dL, n (%)	70	60	47	40	
Bone marrow plasma cells, %	121	10 [5; 20]			
PCLI, %	81	0.2 [0; 0.6]			
β2- microglobulin, ug/mL	85	3.13 [2.42; 4.17]			
Serum albumin, g/dL	100	3.2 [2.7; 3.6]			
MRI	129		101		
MVd, cm^3		203 [162; 247]		127 [109 – 153]	< 0.001
MVs, cm^3		205 [172; 252]		108 [95; 130]	< 0.001
MVs/MVd		1.02 [0.98; 1.05]		0.87 [0.84; 0.89]	< 0.001
LV EDV,mL		124 [101; 158]		117 [96; 137]	0.102
LV ESV, mL		57 [41; 78]		39 [32; 52]	< 0.001
LV Stroke Volume, mL		65 [54; 80]		74 [62; 88]	< 0.001
LVEF, %		53 [45; 61]		66 [60; 69]	< 0.001
MFI, %		19 [15; 23]		38 [35; 41]	< 0.001

Data are expressed as median and interquartile range or mean ± SD for continuous variables and percentages for categorical variables.
Abbreviations: NT-proBNP: N-terminal pro hormone brain natriuretic peptide, dFLC: plasma free light chain difference, PCLI: Plasma cell labeling index, LVEF: left ventricular ejection fraction (by 2D echocardiography), GLS: global averaged left ventricular longitudinal peak systolic strain, E/e': ratio of the peak early mitral inflow velocity (E) over the early diastolic mitral annular velocity (e'), E/A: mitral inflow velocity to ventricular filling velocity ratio, E': mitral inflow velocity, LA:left atrial volume index, MVs: myocardial volume at end systole, MVd: myocardial volume at end diastole, LV EDV: left ventricular end diastolic volume, LV ESV: left ventricular end systolic volume, MFI: myocardial Function Index.
Elevated troponin considered cardiac troponin T > 0.025 ng/mL or high sensitivity troponin T > 45 ng/L.

The median MVd and MVs in AL-CM patients was 203 [IQR 162; 247] and 205 [IQR 172; 252] respectively. These were significantly greater than controls, with MVd and MVs in controls being 127 cm^3 [IQR 109 – 153] and 108 cm^3 [IQR 95; 130] respectively ($p < 0.001$). The median MVs/MVd ratio was also higher in the AL-CM group compared to the controls (1.02 [IQR 0.98; 1.05] vs 0.87 [IQR 0.84; 0.89], $p < 0.001$) but the median MFI was significantly lower (19 % [15; 23] vs 38 % [35; 41], $p < 0.001$) (Table 1). There was a moderate inverse correlation between MFI and global longitudinal strain (correlation coefficient −0.55); i.e. a lower MFI is correlated with more positive global longitudinal strain. A logistic regression suggested MFI was associated with all-cause death (OR 1.15* 10^3, 95 % CI 3.53–3.77* 10^5, $p = 0.017$). When either transplant or chemotherapy were included as covariates, MFI remained associated with all-cause death (OR 3.97* 10^2, 95 % CI 1.06–1.40* 10^5, $p = 0.048$; OR 3.69* 10^2, 95 % CI 1.04–1.31* 10^5, $p = 0.048$ respectively). These findings reduce the likelihood that treatment differences may have interfered with observed outcomes.

3.1. Measurement agreement

Inter-rater reliability in estimation of MFI was very good at baseline (ICC 0.88, 95 % CI 0.75–0.94, $p < 0.001$) and improved the second time after two-week period (ICC 0.99, 95 % CI 0.98 – 0.99, $p < 0.001$) (Table 2). Intra-rater variability was very low at both baseline and after a two-week period (ICC 1.00; 95 % CI 0.99 – 1.00) indicating excellent consistency in measurements between operators in reproducing the myocardial tracings used to calculate MFI.

3.2. Characteristics of MFI in AL-CM

For the purposes of determining a potential MFI threshold that may be sensitive or specific for AL-CM, a group of normal patients without cardiovascular disease was used. By using a normal reference cohort, an MFI < 30 % discriminated between AL-CM and normal myocardium with 92 % sensitivity and 100 % specificity (AUC 0.98, p-value < 0.001).

3.3. Association between MFI and survival

During a median follow up of 2.33 [IQR 0.33; 6.41] years, 96 (74 %) patients in the AL-CM group died. Higher MFI (HR 0.02, 95 % CI 2.23 *104 – 0.24, $p = 0.006$) was associated with survival a multivariable model adjusted for age, sex, and elevated Mayo 2012 Staging System prognostic biomarkers of AL (NT-proBNP > 1800 pg/mL, dFLC > 18 mg/dL, cTnT > 0.025 ng/mL or hsTnT > 45 ng/L) (Table 3, Fig. 2). There was incremental prognostic value in the addition of MFI to the Mayo 2012 Staging System, which is based upon age, sex, NT-proBNP, cTnT, and dFLC. The ΔChi^2 of a Cox regression model including age, sex, and the Mayo 2012 Staging System variables as covariates was ΔChi^2 11.44 ($p = 0.042$) and increased to ΔChi^2 19.26 ($p = 0.004$) when MFI was added as a covariate (Table 3, Supplemental Table 2). The addition of longitudinal strain did not improve the prediction of all-cause mortality.

3.4. MFI in patients in preserved LVEF (≥ 50 %)

A total of 87 out of 129 patients with AL-CM (67 %) had preserved LVEF by cardiac MRI (LVEF ≥ 50 %). When these patients were compared with the normal controls with LVEF ≥ 50 (n = 87), there were no differences in age, sex, cardiovascular comorbidities, and LVEF by echocardiography (Supplemental Table 2). There was a modest but significant difference in EF by MRI between the two groups (59 [IQR 50; 66] % in AL-CM vs 66 [IQR 61; 69] % in controls, $p < 0.001$). However, there were larger magnitude differences between MVs/MVd ratio (1.01 [IQR 0.97; 1.05] in AL-CM vs 0.87 [IQR 0.84; 0.89] in controls, $p < 0.001$) and MFI (20 % [IQR 16; 26] in AL-CM vs 38 % [IQR 35; 41] in controls, $p < 0.001$).

Similar to the entire cohort, MFI continued to be independently associated with mortality in AL-CM when LVEF was ≥ 50 %. In multivariate model, age (HR 1.04, 95 % CI 1.01– 1.07, $p = 0.004$), lower MFI (HR 3.36*10–3, 95 % CI 4.56*10–5 – 0.25, $p = 0.009$) and higher Tn T

Table 2
Inter- and Intra-rater Reliability.

	Intraclass Correlation[1]	95 % Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	F	df1	df2	*p*
Inter-rater reliability							
Baseline Tracing	0.88	0.75	0.94	8.43	29	29	< 0.001
Repeat Tracing[2]	0.99	0.98	0.99	114.69	29	29	< 0.001
Intra-rater reliability							
Operator 1	1.00	0.99	1.00	404.65	29	29	< 0.001
Operator 2	1.00	0.99	1.00	658.29	29	29	< 0.001

[1] ICC(3,k). Inter-rater reliability was assessed with a two operator interclass correlation utilizing mean-rating, consistency, 2-way mixed-effect model (ICC 3, k).
[2] ICC (3, 1). Intra-rater reliability was assessed with a single operator interclass correlation utilizing a single-rater, absolute agreement, 2-way mixed-effects model.

Table 3
Association between survival and traditional predictive variables for AL-CM with MFI.

				LVEF ≥ 50 % Subgroup		
Variable	Hazard Ratio	95 % Confidence Interval	p-Value	Hazard Ratio	95 % Confidence Interval	p-Value
Variables in Mayo 2012 Staging System for Amyloid Light Chain Cardiomyopathy						
Age	1.03	1.01 – 1.05	0.013	1.04	1.01 – 1.07	0.005
Sex	1.01	0.63 – 1.62	0.965	1.10	0.63 – 1.93	0.739
NT-proBNP, pg/mL*	1.03	0.61 – 1.75	0.910	0.89	0.49 – 1.59	0.688
TnT*	1.50	0.90 – 2.50	0.120	1.90	1.02 – 3.52	0.042
dFLC, mg/dL*	1.34	0.85 – 2.10	0.208	1.08	0.62 – 1.87	0.786
MFI and Variables in Mayo 2012 Staging System for Amyloid Light Chain Cardiomyopathy						
MFI	0.01	$2.23 *10^{4}$ – 0.24	0.006	$3.36*10^{-3}$	$4.56*10^{-5}$ – 0.25	0.009
Age	1.03	1.01 – 1.05	0.012	1.04	1.01 – 1.07	0.004
Sex	1.13	0.71 – 1.82	0.600	1.28	0.73 – 2.23	0.393
NT-proBNP, pg/mL*	0.78	0.44 – 1.38	0.394	0.64	0.34 – 1.21	0.166
TnT*	1.48	0.89 – 2.46	0.130	1.93	1.05 – 3.54	0.033
dFLC, mg/dL*	1.31	0.83 – 2.05	0.244	0.86	0.48 – 1.52	0.599

* NT-proBNP > 1800 pg/mL, dFLC > 18 mg/dL, cTnT > 0.025 ng/mL or hsTnT > 45 ng/L.
MFI: myocardial function index, NTproBNP: N-terminal pro hormone brain natriuretic peptide, TnT: troponin T, dFLC: free light chain difference.

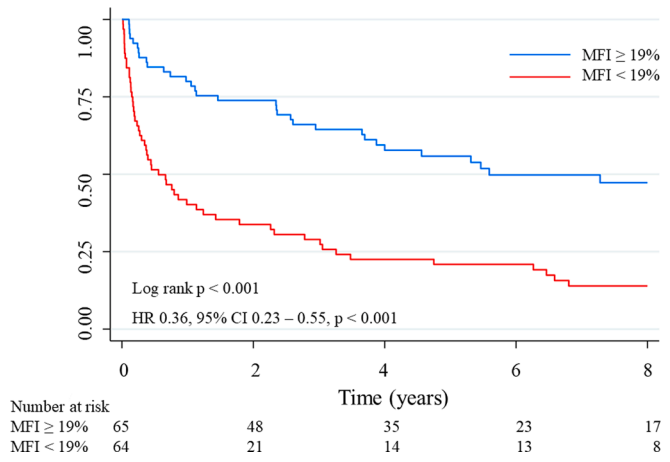

Fig. 2. Kaplan-Meier survival estimates in participants with AL-CM stratified by MFI above and below the median MFI in AL-CM. Length of follow-up was determined by one standard deviation beyond the mean time to last-follow-up or death. AL-CM participants with MFI below the median were significantly more likely to experience death in a cox regression model adjusted for age and sex (HR 0.36, 95 % CI 0.23 – 0.55, p < 0.001).

(HR 1.93, 95 % CI 1.05 – 3.54, p = 0.033) were associated with all-cause mortality after adjusting for sex, and other Mayo 2012 prognostic biomarkers of AL-CM (Table 3). When MFI was included as a covariate in a Cox regression model including age, sex, and the 2012 Mayo Staging System variables, we again observed an incremental increase in ΔChi^2 of the model from ΔChi^2 12.50 (p = 0.029) to ΔChi^2 19.21 (p = 0.004) (Supplemental Table 2).

4. Discussion

The current study demonstrates the feasibility and potential application of MFI as a novel index of cardiac function in AL-CM. Our findings support MFI as a feasible, reproducible measure of cardiac function with an association with all-cause mortality when applied to a group of patients with AL-CM.

4.1. Imaging assessment of cardiac function in AL-CM

Common imaging measures of cardiac function have limitations when applied to patients with infiltrative cardiomyopathies.[13,14,18] Global longitudinal strain (GLS) is a validated marker but carries significant operator-dependent and geometric considerations that decrease reproducibility of this measure in AL-CM [18,19]. Stroke volume or cardiac output/ index (SVi) relies on the blood pool as a functional surrogate of myocardium and appears to be less reproducible than GLS. [20] Mid-wall fractional shortening observed by M−mode echocardiography reflects a mismatch of the fractional shortening at the endocardium and LV end-systolic stress.[21] While mid-wall fractional shortening demonstrates diagnostic and prognostic value in AL-CM, it is limited by geometric assumptions, inherent limitations of M−mode echocardiography, and remains an isolated measure of systolic function alone and fails to capture a comprehensive evaluation of myocardial dysfunction [22–24].

Given significant challenges with respect to complex pathophysiologic remodeling in infiltrative cardiomyopathies, we hypothesized that capturing the dynamic anatomic and volumetric changes during the cardiac cycle may produce a comprehensive physiologic measure of cardiac function. One proposed model, the myocardial contraction fraction (MCF), measures a ratio of SV and myocardial volume [25,26]. MCF has demonstrated good predictive value in cohorts with AL-CM and

appears to distinguish pathologic and non-pathologic hypertrophy [27]. Given our previous observations that suggest changes in myocardial volume through the cardiac cycle may significantly influence myocardial geometry and conventional measures of myocardial function, we sought to develop a model of cardiac function inclusive of this assumption. Thus, MFI was developed to apply simple tracings of epicardium (Fig. 1) at any given level that capture changes to both blood pool and myocardium with disease progression in AL-CM.

4.2. MFI derivation

When first deriving MFI, we aimed to address two important limiting assumptions of myocardium: imaging-specific and physiologic. Longitudinal or radial direction variations may impair accurate assessments of cardiac function or reproducibility. Importantly, our previous works highlighted significant differences in myocardial compressibility between normal and heart failure myocardium. [28,29] Evidence suggests the confluence of blood between myocardium and blood pool contribute to a measurable difference in myocardial geometry.[15,16,30–32] To navigate this challenge and respect the extensive tissue remodeling unique to AL-CM, our approach was to utilize two epicardial tracings at any given level in both end-systole and end-diastole in the calculation of MFI.

4.3. Feasibility and reproducibility of MFI

The feasibility and reproducibility of most measures of cardiac function are limited by difficulties with geometric alignment, imaging quality, and operator variability.[18–20,33] In the current study, we analyzed two independent operator epicardial tracings at any level during end-systole and end-diastole. Measurements derived from epicardial tracings were similar among independent operators and consistently reproducible.

4.4. The use of MFI to characterize AL-CM

Characterization of AL-CM remains a challenge and may require accessibility to advanced imaging equipment, methods, or expertise in multimodal imaging to determine if patients with systemic amyloidosis have cardiac involvement.[10,34] Our data suggested MFI may be able to distinguish AL-CM from normal myocardium below an MFI cutoff of 30 %. We elected to use a normal reference group to test whether MFI may have potential to discriminate disease from a normal reference group; however, future studies are needed to best understand if specific reference values may be applied to all-comer patients who may not always present with normal myocardium.

4.5. Association between MFI and death

Finally, we assessed potential prognostic utility of MFI in patients with AL-CM. Cardiac involvement in AL amyloidosis portends a poor prognosis and thus characterization of AL-CM is a potential additive tool to prognostication. Kumar et. al proposed the revised 2012 Mayo Clinic prognostic staging system for light chain amyloidosis by incorporating circulating cardiac and free light chain biomarkers (NT-proBNP, TnT, dFL).[35] While circulating markers are clinically used to stage prognosis in AL-CM, there remain no reliable imaging prognostic tools in this patient group. Interestingly, the integration of MFI as a measure of cardiac function to the serologic biomarkers used to stage AL-CM appears to improve the predictive value in AL-CM. Higher MFI in AL-CM was associated with greater overall survival and support the value of integrating physiologic assessment tools with established clinical biomarkers to assess AL-CM. Future studies that validate MFI in larger groups of patients with diverse etiologies of infiltrative cardiomyopathies are needed to broaden our understanding of MFI's prognostic potential.

4.6. Limitations

The current retrospective, single center experience in a relatively small cohort poses limitations in study design. The MRI tracings used to calculate MFI were operator-dependent and may have introduced an element of operator-error. Future studies that use physiologically diverse groups of patients are needed to better our understanding of how sensitive and specific MFI may be in identifying AL-CM. Further validation in prospective cohorts at external centers would further establish the value of MFI. The sensitivity and specificity associated with an MFI value that discriminated AL-CM from normal myocardium in may have been related to fewer comorbidities in the normal group which served as control. Arterial hypertension may lead to lower cardiac stroke volumes between participants with AL cardiomyopathy and normal controls. Differences in MFI between a homogenous group of patients with and without hypertension require further investigation. Additional studies are needed to further examine MFI cutoff values that may suggest the presence of AL-CM using physiologically diverse control groups.

5. Conclusion

In summary, MFI is an easily derived and reproducible measure of LV function, appears able to distinguish AL-CM from normal myocardium, and may correlate with overall survival.

Disclosures

The authors have no disclosures to report.

Registration number of clinic studies

This study was reviewed and approved by the Mayo Clinic IRB (19-007779).

CRediT authorship contribution statement

Nadia Akhiyat: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Vidhu Anand:** Writing – review & editing, Methodology. **Vinayak Kumar:** Writing – review & editing. **Alexander Ryu:** Writing – review & editing, Conceptualization. **Raymond Gibbons:** . **Barry A. Borlaug:** . **Krishnaswamy Chandrasekaran:** Conceptualization. **Omar Abou Ezzeddine:** . **Nandan Anavekar:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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