


Echocardiographic and clinical predictors of cardiac amyloidosis: limitations of apical sparing

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Abstract

Aims The accuracy of an apical-sparing strain pattern on transthoracic echocardiography (TTE) for predicting cardiac amyloidosis (CA) has varied in prior studies depending on the underlying cohort. We sought to evaluate the performance of apical sparing and other TTE strain findings to screen for CA in an unselected population and determine the frequency that patients with echocardiographic concern for CA undergo evaluation for amyloidosis in clinical practice.

Methods and results As strain is routinely performed at our institution on all clinical TTEs, we identified all TTEs performed from 2016 through 2019 with reported concern for CA or apical sparing. We determined the performance characteristics for echocardiographic strain findings in discriminating CA including apical sparing, the ejection fraction to global longitudinal strain ratio (EF/GLS), and the septal apical–septal basal ratio (SA/SB); other clinical predictors of confirmed CA; and predictors of patients who underwent complete evaluation for CA. CA was confirmed by endomyocardial biopsy or diagnostic cardiac imaging. A total of 547 TTEs, representing 451 patients, reported concern for CA and had adequate strain for analysis. A total of 111 patients underwent complete evaluation for amyloidosis with 100 patients undergoing complete cardiac evaluation for CA. In those 100 patients, multivariable predictors of confirmed CA were age [odds ratio (OR) 3.37 per 5 years], a visual apical-sparing pattern (OR 10.85), and left ventricular ejection fraction (LVEF)/GLS > 4.1 (OR 35.37). CA was less likely in those with coronary artery disease (OR 0.04), hypertension (OR 0.18), and increased systolic blood pressure (OR 0.60 per 5 mm Hg increase). SA/SB [area under the curve (AUC) 0.72, 95% confidence interval (CI) 0.60–0.84] and LVEF/GLS (AUC 0.72, 95% CI 0.60–0.84) both had improved discrimination for CA compared with the apical-sparing ratio (AUC 0.66, 95% CI 0.54–0.79). Many patients with suggestive TTE findings did not receive an evaluation for amyloidosis. Complete evaluation was more likely with Caucasian race (OR 2.1), increased septal thickness (OR 1.4), increased body mass index (OR 1.2), and if the report specifically stated ‘amyloid’ (OR 1.9). Evaluations were less likely in patients with comorbidities. While hypertension reduced the likelihood of evaluating for CA, 34% of patients with CA had hypertension (>130/80 mm Hg) at time of diagnosis.

Conclusions In a broad population of patients undergoing TTE, apical sparing on strain imaging increased the likelihood of CA diagnosis but with modest sensitivity and specificity. GLS/EF ratio may be a more reliable tool to screen for CA. The low rate of complete evaluation in patients with concerning TTE findings indicates a strong need for practice improvement and enhanced disease awareness.

Keywords Amyloidosis; Echocardiography; Cardiac magnetic resonance imaging; Nuclear scintigraphy; Strain imaging; Apical sparing

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Introduction

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy caused by the deposition of misfolded protein aggregates in the heart, with light chain (AL) or transthyretin (ATTR) amyloidosis accounting for the substantial majority of cases. The diagnosis of CA remains a clinical challenge, and the disease remains underdiagnosed with up to 17% of patients with heart failure (HF) and left ventricular ejection fraction (LVEF) > 40% having evidence of CA at autopsy without prior clinical suspicion.¹ With therapies now available for both ATTR and AL amyloidosis that slow or halt progression of disease, it is imperative to identify patients who will benefit from further CA investigations and accurately diagnose CA as early as possible in the disease process.

Advances in multimodality imaging have greatly improved screening for and identification of CA with transthoracic echocardiography (TTE) often the primary initial imaging modality in evaluation. Patients with clinical and/or echocardiographic concerning features for CA are then referred for further evaluation and definitive testing using a dedicated cardiac magnetic resonance imaging, technetium pyrophosphate (PYP) scintigraphy, and/or endomyocardial biopsy (EMB) in addition to assessment for signs of a monoclonal gammopathy (to evaluate for AL amyloidosis). Historically, clues to the diagnosis on TTE have included such findings as a speckled myocardium, increased septal thickness, significantly reduced annular velocities (the 5–5–5 rule), and features of a restrictive cardiomyopathy (such as biatrial enlargement).² Unfortunately, all of these features, while helpful, have limitations in sensitivity and/or specificity. More recently, strain analysis on echocardiography has emerged as a potentially more powerful diagnostic tool.

Strain findings in CA include a markedly reduced global longitudinal strain (GLS) out of proportion to the LVEF (as measured by an increase in the LVEF/GLS ratio), an increase in the septal apical to basal segmental strain ratio (SA/SB), and findings of apical sparing on the bullseye strain map.^{3–5} To assess for the latter, strain analyses from echocardiogram images are translated into a bullseye plot to illustrate regional variability. Visually, an apical-sparing pattern is represented by preservation of the apical strain with reduction in the middle and basal strain, appearing as a red circle or 'cherry' on top of a background of lighter red or blue. Mathematically, an apical-sparing ratio is calculated as the apical longitudinal strain divided by the sum of the average basal strain and the average middle longitudinal strain.

An apical-sparing pattern ratio ≥ 1 (ApSpar_Ratio ≥ 1) on TTE was initially found to have high diagnostic accuracy (93% sensitivity, 82% specificity) in discriminating patients with known CA ($n = 30$) compared with a small, preselected comparator group of patients with hypertrophic obstructive cardiomyopathy (HOCM, $n = 15$) and severe aortic stenosis (AS, $n = 15$).³ Notably, none of the patients with HOCM or

AS underwent any reported evaluation for CA, while it is now established that a significant percentage of patients with HOCM and AS may actually have CA when thoroughly investigated.^{6,7}

In a larger and more diverse cohort of 1187 patients referred to amyloid specialty centres in Europe, the accuracy of ApSpar_Ratio for detecting CA was more modest with sensitivity of 58% in patients with systemic AL and 71% in patients with septal or posterior wall thickness ≥ 1.2 cm.⁴ The performance characteristics of all of the LV strain findings (EF/GLS, SA/SB, and ApSpar_Ratio) in an unselected population have not yet been adequately described. From a practical clinical perspective, it is very important to understand how useful apical sparing can be as a signal for CA in patients undergoing TTE for any indication. Additionally, it has not been reported how effective TTE findings of potential amyloidosis, including apical sparing, are at stimulating clinicians to pursue the diagnosis of CA.

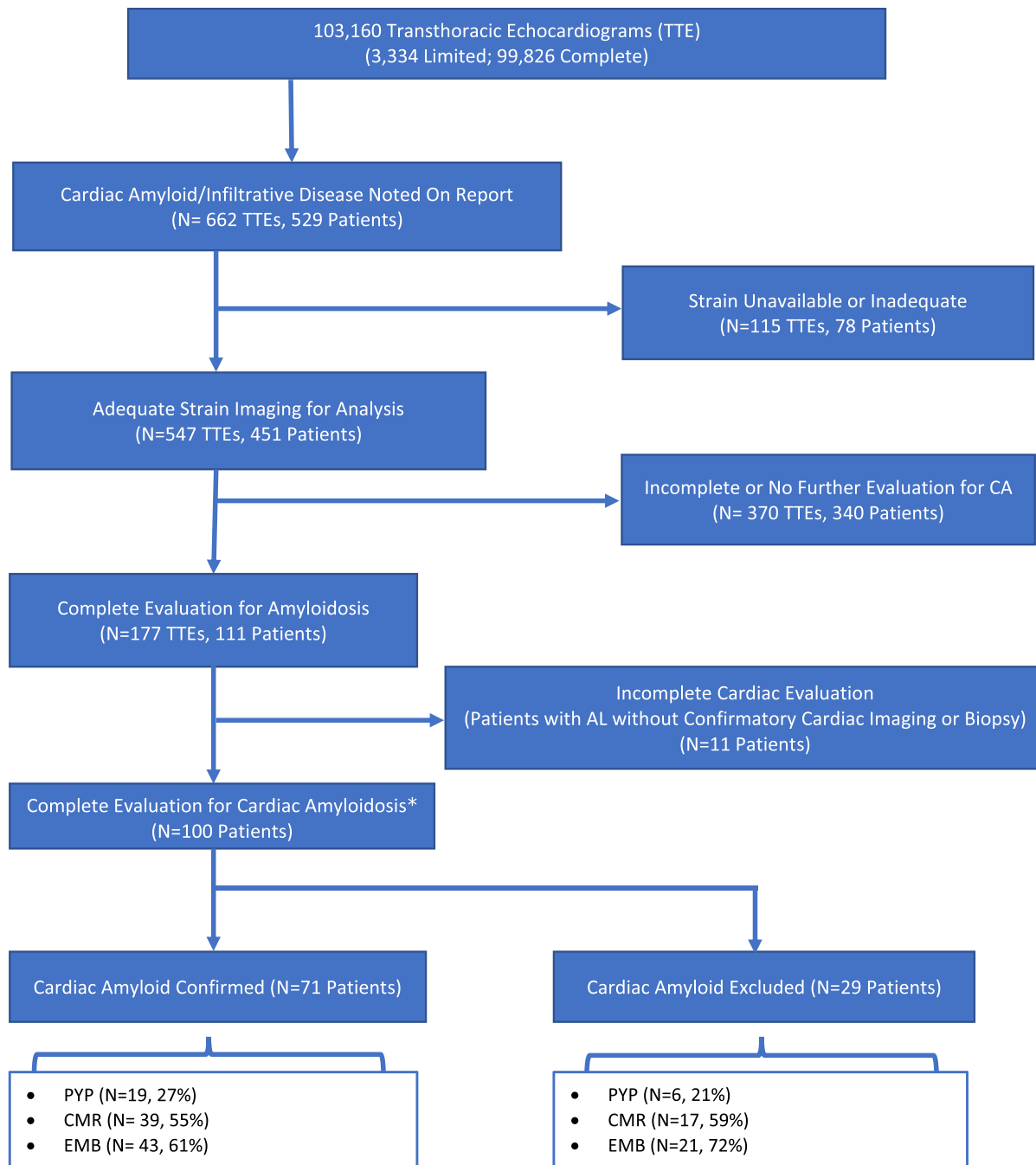
The Washington University in St. Louis serves a large and diverse patient population with HF and obtains LV strain analysis as standard procedure on all patients who undergo complete TTE. By examining a broad population undergoing TTE for any indication, we sought to determine the frequency that CA evaluation is pursued in clinical practice when TTE findings are suggestive of CA and to examine the associations of TTE strain characteristics with confirmed CA.

Methods

We retrospectively identified all TTEs performed at the Washington University Medical Center between 1 January 2016 and 4 October 2019 where the echocardiographer noted concern for CA in the summary report via text queries for 'amyloid', 'infiltrative', 'speckled', 'apical sparing', or 'bulls' (short for bullseye) with subsequent manual verification and exclusion of reports that did not include any noted concerns for amyloidosis (i.e. 'no *apical sparing*' and 'no echo hallmarks of *amyloid*'). In addition to other amyloid findings, the echocardiographers at our centre routinely annotate the presence of apical sparing on subjective evaluation of the bullseye peak segmental strain plot (ApSpar_Visual). Longitudinal strain values were subsequently extracted from clinical echocardiographic images, and exams lacking segmental longitudinal strain values for more than two segments were discarded. A total of 451 patients were included in the study after applying inclusion and exclusion criteria (*Figure 1*). The investigation conformed to the principles outlined in the *Declaration of Helsinki*⁸ and was approved by the Washington University in St. Louis Institutional Review Board with waiver of consent.

Additional echocardiographic characteristics were extracted from the TTE report including vital signs, interven-

Figure 1 Study flowchart. Out of 103 160 transthoracic echocardiograms (TTEs), 547 TTEs, representing 451 patients, reported concern for cardiac amyloidosis (CA) and had adequate strain for analysis. A total of 111 patients underwent complete evaluation for amyloidosis, while 100 patients underwent complete cardiac evaluation for CA.



tricular septal thickness (IVSd), and LVEF. We manually extracted from the electronic health record patients’ base-line demographics, creatinine, comorbidities, and any subsequent evaluation for amyloidosis, including cardiac magnetic resonance imaging with late gadolinium enhance-

ment (CMR), technetium PYP nuclear scintigraphy, EMB, and evaluation for monoclonal proteins with serum free light chains and either protein electrophoresis or immunofixation. Evaluations for amyloidosis were included through 2/14/2020.

Detailed echocardiographic review

Left ventricular ejection fraction was determined with contrast enhancement using the biplane Simpson's rule.⁹ Myocardial strain imaging was obtained from the apical four-chamber, two-chamber, and long-axis views as part of the original clinical echocardiogram by the performing sonographer. Notably, GLS has been shown to have good reproducibility even among various skill levels with an intra-class coefficient of 0.89 comparing trainees to experts.¹⁰ In our study, all sonographers had extensive training and clinical experience. TTEs were performed on the Vivid E95 by General Electric or the Philips Epiq7 machine. A total of 97.3% of the studies utilized the 17-segment model of LV segmentation, while the remainder utilized the 18-segment model.⁹

Apical sparing was objectively evaluated by calculating the ratio of apical strain to the basal and middle segments (ApSpar_Ratio) similarly to other published studies^{3,5} by the formula:

$$\text{ApSpar_Ratio} = \frac{\text{Average apical LS}}{\text{Average basal LS} + \text{Average middle LS}}$$

Calculated apical sparing was defined as the absolute value of the ApSpar_Ratio ≥ 1 . Additional strain measurements associated with CA were also computed (LVEF/GLS and SA/SB).^{5,11,12}

Amyloidosis evaluations (complete, incomplete, and not performed)

Two independent CA experts (J. M. and D. L.) reviewed all amyloidosis evaluations and categorized them as complete, incomplete, or absent. Similar to prior studies, a diagnosis of amyloidosis required a confirmatory biopsy, a Grade 2 or 3 PYP scan without evidence of a monoclonal protein, or a positive hereditary ATTR test with classic TTE or magnetic resonance imaging findings and clinical scenario.^{3,13} Exclusion of amyloidosis required an appropriate evaluation to rule out AL and negative cardiac imaging (negative CMR or Grade 0 PYP scan) or negative EMB. A Grade 1 PYP scan was considered an incomplete evaluation in the absence of further testing.¹³ Patients with a positive extracardiac biopsy for AL without further cardiac imaging were considered complete evaluations for amyloidosis but were incomplete for CA evaluation, as the TTE strain findings could not be confirmed.

A complete evaluation for AL amyloidosis required quantification of serum free light chains, as well as serum protein electrophoresis and/or immunofixation assay. Patients with evidence of a monoclonal protein including abnormal free light chain ratio (<0.26 or >1.65)¹³ were considered incomplete evaluations without tissue biopsy regardless of further imaging, because CMR and bone scintigraphy cannot fully exclude CA.^{13,14} Complete evaluations for CA were overall consistent with the recent European Society of Cardiology (ESC) position statement.¹⁵

Among patients with complete evaluation for CA, we identified patients that did or did not meet a minimal threshold for CA evaluation according to a recent expert statement for ATTR screening (IVSd ≥ 14 mm in men >65 and women >70 with either HF or 'red flag' signs or symptoms, such as apical sparing or signs of infiltration)¹⁶ as well as the ESC position statement for CA screening (IVSd ≥ 12 mm + red flag or clinical scenario).¹⁵

Statistical analyses

Baseline characteristics were compared between patients with a complete, incomplete, or absent evaluation; patients with and without ApSpar_Ratio ≥ 1 ; and patients with and without CA after further cardiac imaging and/or EMB. For patients with multiple TTEs in the study period, the first TTE meeting inclusion criteria were used.

Categorical variables were compared using the χ^2 or Fisher's exact test for 2×2 comparisons. Continuous variables with approximate normal distributions were compared using Student's *t*-test for two groups or one-way analysis of variance accounting for unequal variances for three groups, using the Tukey–Kramer adjustment for between-group comparisons. Non-parametric variables were analysed with the Kruskal–Wallis test for three groups or the Wilcoxon test for two groups and between-group comparisons. Approximate normality was assessed through histograms, Q–Q plots, and the Shapiro–Wilk test.

Harrell's C-statistic and receiver-operating characteristic (ROC) analysis were used to determine the discriminative ability of ApSpar_Ratio, LVEF/GLS, and SA/SB in predicting CA in patients undergoing complete evaluation. The performance characteristics of prior described cut-offs (ApSpar_Ratio ≥ 1 , LVEF/GLS > 4.1 , and SA/SB > 2.1) were also explored.^{3,11,12} Optimal cut-offs for the study cohort were computed using the Youden index. Stepwise, multivariable logistic regression evaluated the association of covariates with ApSpar_Ratio ≥ 1 , those undergoing a complete evaluation for amyloidosis, and those with confirmed CA. A *P*-value of 0.25 was used for entry, with a *P*-value of 0.15 required to stay in the model. Additionally, sensitivity analyses were performed in patients who underwent EMB and in those with left ventricular hypertrophy (LVH) (IVSd ≥ 1.2 cm).

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) using a two-sided alpha set to 0.05.

Results

Out of 103 160 TTEs from 2016 to 2019, there were 451 patients (mean age 62.5 years, 64% male) with reported findings for CA by our initial text search with manual confirmation (Figure 1, Table 1). Of these, 229 patients (50.8%) were found

to have ApSpar_Ratio ≥ 1 . Echocardiographers reported a visual apical-sparing pattern (ApSpar_Visual) in 308 of the 451 patients based on their assessment of the bullseye peak segmental strain plot. Of those with ApSpar_Visual, 185 (60%) had calculated ApSpar_Ratio ≥ 1 .

Characteristics and predictors of ApSpar_Ratio ≥ 1

In univariate analysis, patients with ApSpar_Ratio ≥ 1 were more likely to have baseline HF, a greater median IVSd (1.6 vs. 1.5 cm), a lower median LVEF (51% vs. 55%), higher LVEF/GLS, and higher SA/SB. Hypertension (HTN), end-stage renal disease (ESRD), and other cardiovascular comorbidities

were not associated with ApSpar_Ratio ≥ 1 . In multivariable analysis, significant predictors of ApSpar_Ratio ≥ 1 were increased IVSd, female sex, and HF (Table 1). ApSpar_Ratio ≥ 1 was less likely with increased LVEF, increased body mass index, and hyperlipidaemia at baseline.

Characteristics and predictors of evaluation for amyloidosis

Among all the patients with echocardiographic concerns for CA (with or without apical sparing), patients who underwent complete evaluation for amyloidosis were more likely to be Caucasian, have increased IVSd, and have lower systolic blood pressure (BP) in multivariable analysis (Table 2). They were

Table 1 Demographics, comorbidities, and echocardiographic findings associated with apical sparing (ApSpar_Ratio ≥ 1) in the complete cohort

	Apical sparing N = 229	No apical sparing N = 222	Univariate P-value	Multivariable odds ratio	Multivariable P-value
Demographics and comorbidities					
Age (years), mean (SD)	63.5 (16.0)	61.4 (14.3)	0.16		
Female, N (%)	92 (40.2)	70 (31.5)	0.06	1.93 (1.26–2.94)	<0.01
Race			0.64		
Caucasian, N (%)	79 (34.5)	86 (38.7)			
Black, N (%)	143 (62.5)	130 (58.6)			
Other/unknown, N (%)	7 (3.1)	6 (2.7)			
Hypertension, N (%)	192 (83.8)	187 (84.2)	1.00		
Systolic blood pressure	138 (120, 154)	138 (122, 152)	0.94		
Diastolic blood pressure	75 (66, 88)	77 (66, 87)	0.72		
Hyperlipidaemia, N (%)	148 (64.6)	158 (71.2)	0.16	0.57 (0.37–0.89)	0.012
Diabetes mellitus, N (%)	76 (33.2)	84 (37.8)	0.33		
ESRD, N (%)	48 (21.0)	53 (23.9)	0.50		
eGFR, median (IQR)	54.5 (21.5, 80.0)	55.0 (24.8, 78.1)	0.76		
Documented OSA, N (%)	27 (11.8)	28 (12.6)	0.89		
Coronary artery disease, N (%)	68 (29.7)	74 (33.3)	0.42		
Atrial fibrillation/flutter, N (%)	57 (24.9)	48 (21.6)	0.44		
Heart failure, N (%)	164 (71.6)	130 (58.6)	<0.01	1.77 (1.12–2.79)	0.015
HOCM, N (%)	1 (0.44)	0 (0)	1.0		
BMI, median (IQR)	25.8 (21.9, 29.5)	26.8 (23.5, 31.5)	0.01	0.82 (0.70–0.96)	0.012
Echocardiographic findings					
IVSd (cm), median (IQR)	1.6 (1.3, 1.9)	1.5 (1.2, 1.7)	<0.001	1.33 (1.19–1.49)	<0.001
LVEF, median (IQR)	51 (40, 60)	55 (44, 63)	0.02	0.91 (0.84–0.98)	0.013
Severe AS, N (%)	5 (2.2)	6 (2.7)	0.77		
GLS, median (IQR)	−9.2 (−11.2, −7.5)	−11.1 (−13.7, −9.1)	<0.001	-	-
GLS ≤ -17	3 (1.3)	10 (4.5)	0.051	-	-
ApSpar_Visual, N (%)	185 (80.8)	123 (55.4)	<0.001	-	-
LVEF/GLS, median (IQR)	5.3 (4.3, 6.6)	4.6 (3.8, 5.6)	<0.001	-	-
LVEF/GLS > 4.1 , N (%)	183 (79.9)	152 (68.5)	<0.01	-	-
SA/SB ^a , median (IQR)	4.0 (2.8, 8.8)	2.1 (1.6, 2.9)	<0.001	-	-
SA/SB $> 2.1^a$, N (%)	205 (89.9)	106 (48.2)	<0.001	-	-

ApSpar_Ratio, apical sparing assessed through the formula; ApSpar_Visual, apical sparing annotated by the echocardiographer after visual assessment of the bullseye peak segmental strain pattern; AS, aortic stenosis; BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLS, global longitudinal strain; HOCM, hypertrophic obstructive cardiomyopathy; IQR, interquartile range; IVSd, interventricular septal thickness at end diastole; LVEF, left ventricular ejection fraction; LVEF/GLS, ratio of left ventricular ejection fraction to global longitudinal strain; OSA, obstructive sleep apnoea; SA/SB, ratio of septal apical strain to septal basal strain; SD, standard deviation.

Apical sparing defined as patients with ApSpar_Ratio ≥ 1 . Multivariable odds ratio and P-value generated from stepwise multivariable logistic regression. An odds ratio above 1 represents a greater likelihood, while an odds ratio < 1 represents a reduced likelihood. Odds ratio presented for absolute increase in 5% for LVEF, 0.2 cm for IVSd, and 5 units for BMI. Other echocardiographic strain characteristics (ApSpar_Visual, LVEF/GLS, GLS, and SA/SB) were statistically and clinically correlated with ApSpar_Ratio ≥ 1 and not entered into the multivariable model.

^aSeptal apical or basal strain segment missing from three patients.

We bolded the values that were significant at a $p < 0.05$ level.

Table 2 Demographics, comorbidities, and echocardiographic findings associated with complete, incomplete, or absent evaluation for amyloidosis

	Complete N = 111	Complete Incomplete N = 139	Complete Absent N = 201	Univariate P-value	Multivariable OR	Multivariable P-value
Demographics and comorbidities						
Age (years), mean (SD)	63.4 (14.2)	62.4 (13.8)	62.0 (16.6)	0.72		
Female, N (%)	34 (30.6)	45 (32.4)	83 (41.3)	0.10		
Race				<0.001	2.1 (1.2–3.7)	<0.01
Caucasian, N (%)	62 (55.9)	39 (28.1)	64 (31.8)	-		
Black, N (%)	48 (43.2)	97 (69.8)	128 (63.7)	-		
Other/unknown, N (%)	1 (0.9)	3 (2.2)	9 (4.5)	-		
Hypertension, N (%)	69 (62.2)	128 (92.1) ^a	182 (90.6) ^a	<0.001	0.3 (0.1–0.5)	<0.001
Systolic blood pressure	123 (110, 141)	141 (125, 157) ^a	142 (125, 158) ^a	<0.001	0.9 (0.8–0.9)	<0.001
Diastolic blood pressure	73 (63, 81)	77 (67, 90) ^a	78 (68, 91) ^a	0.01		
Hyperlipidaemia, N (%)	66 (59.5)	103 (74.1) ^a	137 (68.2)	0.048		
Diabetes mellitus, N (%)	18 (16.2)	64 (46.0) ^a	78 (38.8) ^a	<0.001	0.4 (0.2–0.7)	<0.01
ESRD, N (%)	16 (14.4)	39 (28.1) ^a	46 (22.9)	0.04		
eGFR, median (IQR)	58.0 (37.6, 75.6)	38.6 (15.0, 70.4) ^a	58.0 (24.0, 82.9)	<0.001		
Documented OSA, N (%)	17 (15.3)	22 (15.8)	16 (8.0)	0.048		
Coronary artery disease, N (%)	22 (19.8)	52 (37.4) ^a	68 (33.8) ^a	<0.01	0.5 (0.3–1.0)	0.045
Atrial fibrillation/flutter, N (%)	31 (27.9)	34 (24.5)	40 (19.9)	0.25		
Heart failure, N (%)	75 (67.6)	104 (74.8)	115 (57.2)	<0.01		
HOCM, N (%)	1 (0.9)	0 (0)	0 (0)	^b		
BMI, median (IQR)	27.0 (23.3, 31.4)	26.3 (21.9, 30.6)	25.7 (22.2, 30.0)	0.17	1.2 (1.0–1.5)	0.037
Echocardiographic findings						
IVSd (cm), median (IQR)	1.7 (1.4, 1.9)	1.5 (1.2, 1.7) ^a	1.5 (1.2, 1.7) ^a	<0.001	1.4 (1.3–1.7)	<0.001
LVEF, median (IQR)	53 (40, 63)	51 (40, 63)	55 (42, 63)	0.45	0.9 (0.8–1.0)	0.11
Severe AS, N (%)	2 (1.8)	1 (0.7)	8 (4.0)	^b		
GLS, median (IQR)	-9.6 (-11.6, -7.5)	-10.1 (-12.4, -8.4)	-10.1 (-12.9, -8.4)	0.13		
GLS ≤ -17, N (%)	5 (4.5)	2 (1.4)	6 (3.0)	0.35		
ApSpar Visual, N (%)	82 (73.9)	99 (71.2)	127 (63.2)	0.10		
ApSpar_Ratio, median (IQR)	1.04 (0.81, 1.49)	1.01 (0.85, 1.29)	0.96 (0.79, 1.27)	0.22		
ApSpar_Ratio ≥ 1, N (%)	62 (55.9)	73 (52.5)	94 (46.8)	0.27		
LVEF/GLS, median (IQR)	5.2 (4.3, 6.4)	4.8 (4.1, 5.8)	4.74 (4.0, 6.1)	0.05		
LVEF/GLS > 4.1, N (%)	90 (81.1)	103 (74.1)	142 (70.7)	0.13		
SASB, median (IQR) ^c	3.0 (1.9, 5.3)	3.0 (2.0, 4.2)	2.8 (1.9, 4.5)	0.63		
Echo report text						
'Speckled', N (%)	1 (0.5)	1 (0.7)	0	^b		
'Bulls', N (%)	4 (3.6)	1 (0.7)	4 (2.0)	^b		
'Infiltrative', N (%)	32 (28.8)	37 (26.6)	39 (44.3)	0.0010		
'Amyloid', N (%)	86 (77.5)	103 (74.1)	107 (56.2)	<0.001	1.9 (1.1–3.3)	0.032

ApSpar_Ratio, apical sparing assessed through the formula: ApSpar_Visual, apical sparing annotated by the echocardiographer after visual assessment of the bullseye peak segmental strain pattern; AS, aortic stenosis; BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLS, global longitudinal strain; HOCM, hypertrophic obstructive cardiomyopathy; IQR, interquartile range; IVSd, interventricular septal thickness at end diastole; LVEF, left ventricular ejection fraction; LVEF/GLS, ratio of left ventricular ejection fraction to global longitudinal strain; OR, odds ratio; OSA, obstructive sleep apnoea; SASB, ratio of septal apical strain to septal basal strain; SD, standard deviation. Multivariable OR with 95% confidence interval and P-value generated from stepwise multivariable logistic regression for association with complete evaluation. An OR above 1 represents a greater likelihood, while an OR < 1 represents a reduced likelihood. OR presented for an increase in 0.2 cm for IVSd, 5 units for BML, 5 mm Hg for blood pressure, and absolute increase of 5% for LVEF.

^aSignificantly different from complete evaluation at $P < 0.05$.

^bGiven infrequency of covariate, no accurate P-value can be generated.

^cCreatinine missing for four patients with absent evaluation.

We bolded the values that were significant at a $p < 0.05$ level.

90% more likely to undergo evaluation if ‘amyloid’ was specifically mentioned on the TTE report rather than less specific terms such as ‘infiltrative’ cardiomyopathy. Patients with other cardiovascular comorbidities [HTN, diabetes mellitus, coronary artery disease (CAD)] were less likely to undergo evaluation. The multivariable model provided very good discrimination for patients who underwent complete evaluation with a C-statistic of 0.838.

Evaluations were considered incomplete due to presence of a monoclonal protein without appropriate follow-up

(71%), incomplete AL labs (9%), lack of evaluation for ATTR CA in a patient without monoclonal protein (12%), a competing diagnosis (e.g. sarcoid) needing further testing (3%), or Grade 1 PYP scan without further evaluation (5%).

Characteristics and predictors of confirmed cardiac amyloidosis

Of the 111 patients with complete evaluation for amyloidosis, 100 patients had a complete cardiac evaluation. Eleven pa-

Table 3 Demographics, comorbidities, and echocardiographic findings associated with confirmed cardiac amyloidosis after complete evaluation

	CA N = 71	No CA N = 29	Univariate P-value	Multivariable odds ratio	Multivariable P-value
Demographics and comorbidities					
Age (years), mean (SD)	67.9 (11.7)	53.2 (14.2)	<0.001	3.37 (1.69–6.71)	<0.001
Male, N (%)	50 (74)	22 (75.9)	0.63		
Race			0.17		
Caucasian, N (%)	41 (57.8)	13 (44.8)			
Black, N (%)	30 (42.3)	15 (51.7)			
Other/unknown, N (%)	0 (0)	1 (3.5)			
Hypertension, N (%)	38 (53.5)	24 (82.8)	<0.01	0.18 (0.03–1.20)	0.076
Systolic blood pressure	118 (103, 132)	143 (124, 154)	<0.001	0.60 (0.45–0.82)	<0.01
Diastolic blood pressure	71 (62, 78)	81 (71, 92)	<0.001		
Hyperlipidaemia, N (%)	43 (60.6)	18 (62.1)	1.00		
Diabetes mellitus, N (%)	8 (11.3)	8 (27.6)	0.07		
ESRD, N (%)	5 (7.0)	7 (24.1)	0.04		
eGFR, median (IQR)	65.6 (42.5, 80.0)	55.3 (23.9, 72.0)	0.07		
Documented OSA, N (%)	10 (14.1)	4 (13.8)	1.00		
Coronary artery disease, N (%)	12 (16.9)	8 (27.6)	0.27	0.04 (0.003–0.62)	0.021
Atrial fibrillation/flutter, N (%)	20 (28.2)	9 (31.0)	0.81		
Heart failure, N (%)	51 (71.8)	21 (72.4)	1.00		
HOCM, N (%)	1 (1.4)	0 (0)	1.00		
BMI, median (IQR)	28.3 (24.1, 30.9)	26.5 (23.2, 31.5)	0.72		
Echocardiographic findings					
IVSd (cm), median (IQR)	1.8 (1.5, 1.9)	1.4 (1.3, 2.0)	0.04		
LVEF, median (IQR)	52 (40, 61)	53 (35, 63)	0.87		
Severe AS, N (%)	2 (2.8)	0 (0)	1.00		
GLS, median (IQR)	-8.9 (-10.7, -6.5)	-10.4 (-11.7, -8.1)	0.04		
GLS ≤ -17, N (%)	1 (1.4)	2 (6.9)	0.20		
ApSpar_Visual, N (%)	57 (80.3)	19 (65.5)	0.13	10.85 (1.40–83.89)	0.022
ApSpar_Ratio, median (IQR)	1.2 (0.9, 1.5)	0.9 (0.6, 1.2)	0.01		
ApSpar_Ratio ≥ 1, N (%)	47 (66.2)	12 (41.4)	0.03		
LVEF/GLS, median (IQR)	5.6 (6.6, 4.9)	4.5 (3.6, 5.3)	0.001		
LVEF/GLS > 4.1, N (%)	66 (93.0)	18 (62.1)	<0.001	35.37 (3.05–409.61)	<0.01
SA/SB, median (IQR)	4.0 (2.4, 6.0)	2.0 (1.6, 3.4)	0.001		
SA/SB > 2.1, N (%)	57 (80.3)	13 (44.8)	<0.001		
Endomyocardial biopsy, N (%)	43 (60.6)	21 (72.4)	-	-	-
CMR, positive/total (%)	39/44 (88.6)	5/17 (29.4)	-	-	-
PYP scan, positive/total (%)	19/20 (95.0)	0/6 (0)	-	-	-
Amyloid type					
ATTR	35 (49.3)	-	-	-	-
AL	35 (49.3)	-	-	-	-
AA	1 (1.4)	-	-	-	-

AA, amyloid A protein amyloidosis; AL, light chain amyloidosis; ApSpar_Ratio, apical sparing assessed through the formula; ApSpar_Visual, apical sparing annotated by the echocardiographer after visual assessment of the bullseye peak segmental strain pattern; AS, aortic stenosis; ATTR, transthyretin amyloidosis; BMI, body mass index; CA, cardiac amyloidosis; CMR, cardiac magnetic resonance imaging; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLS, global longitudinal strain; HOCM, hypertrophic obstructive cardiomyopathy; IQR, interquartile range; IVSd, interventricular septal thickness at end diastole; LVEF, left ventricular ejection fraction; LVEF/GLS, ratio of left ventricular ejection fraction to global longitudinal strain; OSA, obstructive sleep apnoea; PYP, technetium pyrophosphate scan; SA/SB, ratio of septal apical strain to septal basal strain; SD, standard deviation.

Cardiac amyloidosis confirmation by non-invasive imaging (CMR or PYP) or endomyocardial biopsy. Data presented as odds ratio with 95% confidence interval. Multivariable analysis performed using stepwise multivariable logistic regression. Odds ratios presented per 5 years age interval and 5 mm Hg blood pressure interval.

We bolded the values that were significant at a p<0.05 level.

tients with AL did not undergo any further confirmatory cardiac imaging or EMB that could confirm TTE findings (Figure 1, Table 3). Of the 100 patients with a complete CA evaluation, 71 patients were confirmed positive, 43 by EMB. Of the 28 patients with confirmed CA without EMB, 1 had hereditary ATTR with classic TTE findings and a positive muscle biopsy, 1 had hereditary ATTR and a positive CMR, 12 had positive PYP for ATTR after ruling out AL, and 14 had a positive extracardiac biopsy for AL with confirmatory CMRs. There were 29 patients with complete evaluations in which CA was excluded: 21 by EMB, 7 by negative AL evaluation and negative CMR, and 1 by negative AL evaluation and Grade 0 PYP scan. All but six patients had IVSd \geq 1.2 cm; interestingly, of those six, three were diagnosed with CA.

In univariate analyses, those with confirmed CA had a lower incidence of cardiovascular comorbidities, were older, had greater median IVSd (1.8 vs. 1.4 cm), had increased LVEF/GLS, and had an increased SA/SB on univariate analysis (Table 3). ApSpar_Visual was not significantly different between the two groups ($P = 0.13$), while ApSpar_Ratio \geq 1 was more likely in patients with CA ($P = 0.03$).

In multivariable regression, increased age, absence of CAD, lower systolic BP, ApSpar_Visual, and LVEF/GLS > 4.1 were independent predictors of CA (Table 3). Patients with confirmed CA tended to be marginally less likely to have baseline HTN, with a non-significant P -value ($P = 0.08$). However, in patients with confirmed CA, 24 (34%) met criteria for HTN (\geq 130/80 mm Hg) at the time of their TTE.

Patients with cardiac amyloidosis meeting proposed threshold criteria

We subsequently evaluated the number of patients with confirmed CA that met the proposed threshold for ATTR CA screening in a recent expert statement (IVSd \geq 14 mm in men >65 and women >70).¹⁶ Thirty-seven patients (52%) with confirmed CA (9 ATTR, 27 AL, and 1 AA) in our cohort did not meet these criteria. Eight patients had IVSd $<$ 14 mm (3 ATTR and 5 AL), 21 men were <65 years (range 48–64 years; 6 ATTR, 14 AL, and 1 AA), and 13 women were <70 years (range 34–69 years; 1 ATTR and 12 AL). The ESC criteria (IVSd \geq 12 mm + red flag)¹⁵ would have only missed three patients with CA: two patients with AL and 0.9 cm IVSd and one patient with hereditary ATTR and 1.1 cm IVSd.

Receiver-operating characteristic analysis of transthoracic echocardiography strain findings

In ROC analysis of the 100 patients with complete cardiac evaluation, SA/SB [area under the curve (AUC) 0.72, 95% confidence interval (CI) 0.60–0.84] and LVEF/GLS (AUC 0.72, 95% CI 0.60–0.84) both had improved discrimination for CA com-

pared with the continuous ApSpar_Ratio (AUC 0.66, 95% CI 0.54–0.79) (Figure 2, Table 4). In a sensitivity analysis of patients who underwent EMB ($n = 64$, 43 positive for CA), ApSpar_Ratio \geq 1 was present in 30 patients with CA (70%) and 7 patients without CA (33%), yielding an AUC of 0.68 (95% CI 0.56–0.81; Supporting Information, Table S1). In the 94 patients with LVH (IVSd \geq 1.2 cm) and complete CA evaluation, ApSpar_Ratio \geq 1 yielded an AUC of 0.62 (95% CI 0.51–0.73).

Discussion

Among all the patients at our centre with reported TTE concern for CA or infiltrative cardiomyopathy, including a visual apical-sparing pattern (ApSpar_Visual), 51% had a calculated ApSpar_Ratio \geq 1. In patients with a subsequent complete evaluation for CA, ApSpar_Ratio \geq 1 was associated with diagnosis of CA, though with more modest sensitivity and specificity than originally reported. In patients who underwent EMB, 30% of patients with +CA did not have ApSpar_Ratio \geq 1, while 33% of those with (–)EMB did have ApSpar_Ratio \geq 1 (Figure 3). No particular comorbidity was predictive of ApSpar_Ratio \geq 1 outside of CA, however. As ApSpar_Ratio \geq 1 correlated with lower LVEF, lower strain, and a diagnosis of HF, ApSpar_Ratio \geq 1 may be more broadly indicative of a cardiomyopathy, of which CA is a significant cause.

Barriers to evaluation for cardiac amyloidosis

Despite annotated TTE concern for CA, only a fraction of patients underwent complete evaluation, representing a critical area for future quality improvement. Notably, mentioning ‘amyloid’, specifically, in the TTE report, as opposed to less specific terms, increased the likelihood of evaluation by nearly 90%. Patients with other comorbidities were also less likely to be evaluated, which can miss many patients with CA. Over half (54%) of our patients with confirmed CA had a history of HTN, 24 had hypertensive BP at time of the echocardiogram, and 17% had CAD. HTN and other CV comorbidities would be expected at a similar prevalence in patients with amyloidosis until a patient reaches later stage disease and develops hypotension.

Caucasians were twice as likely to be evaluated as other patients, a finding that deserves further study and is consistent with prior reports. Others have noted that African-Americans with CA often present with more severe HF, and CA may be missed in this cohort due to similarities in presentation with hypertensive heart disease.¹⁷

The number of incomplete or absent AL evaluations also shows a critical need to improve education of general practitioners or non-specializing cardiologists who are often front-

Figure 2 Receiver-operating characteristic curves for echocardiographic strain parameters and cardiac amyloidosis in patients following a complete evaluation. Receiver-operating characteristic curves are presented for ApSpar_Ratio (continuous), LVEF/GLS (continuous), and SA/SB (continuous) along with the sensitivity and specificity for specified cut-offs. Data presented are cut-off value, sensitivity, and specificity. A cut-off of 1 for ApSpar_Ratio yielded a sensitivity of 66% and specificity of 55%, while the optimal cut-off by the Youden method was 1.1 (55% sensitivity, 72% specificity). A cut-off of 2.1 for SA/SB yielded a sensitivity of 80% and specificity of 55%, while the optimal cut-off by the Youden method was 2.4 (76% sensitivity, 66% specificity). Finally, a cut-off of 4.1 for LVEF/GLS yielded a sensitivity of 93% and specificity of 35%, while the optimal cut-off by the Youden method was 4.9 (79% sensitivity, 55% specificity). ApSpar_Ratio, relative apical-sparing ratio calculated by the formula; LVEF/GLS, left ventricular ejection fraction to global longitudinal strain ratio; SA/SB, ratio of septal apical strain to septal basal strain.

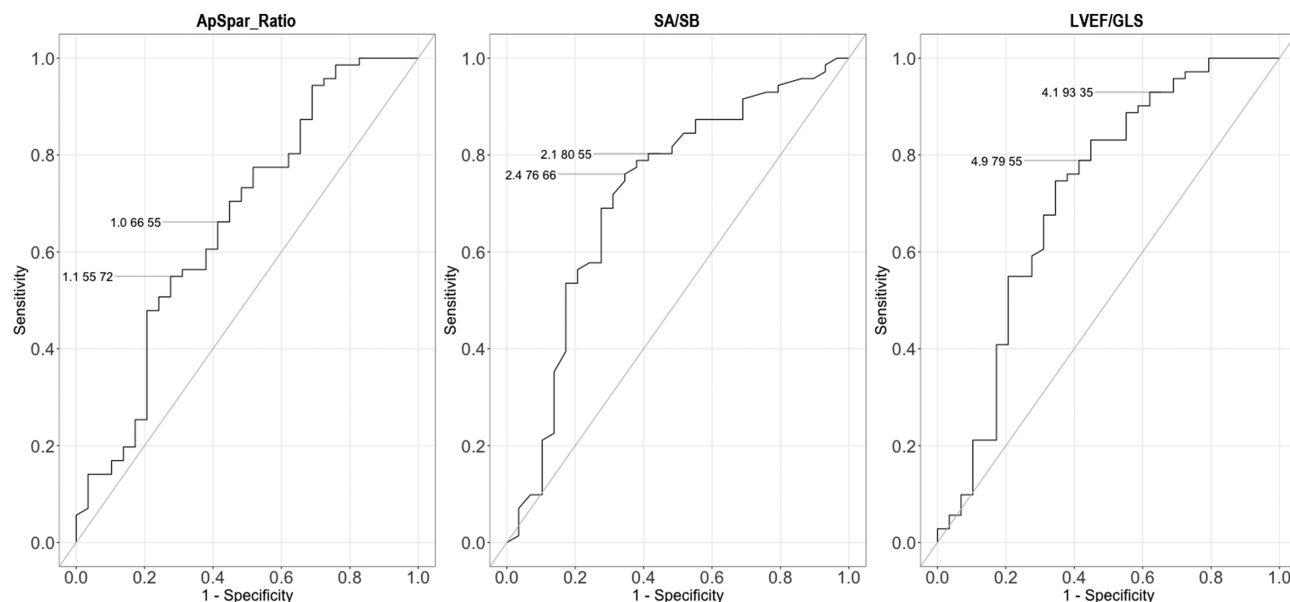


Table 4 Performance characteristics of strain parameters for discriminating patients with confirmed cardiac amyloidosis by cardiac imaging and/or endomyocardial biopsy

	Optimal cut-off ^a	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value	AUC (95% CI)	P-value
ApSpar_Ratio	1.13	-	-	-	-	0.66 (0.54–0.79)	0.011
ApSpar_Ratio > 1.00	-	66 (54–77)	59 (39–76)	80 (71–86)	41 (31–53)	0.62 (0.52–0.73)	0.023
ApSpar_Ratio > 1.13	-	55 (43–67)	72 (53–87)	83 (72–90)	40 (32–48)	0.64 (0.54–0.74)	<0.01
LVEF/GLS	4.95	-	-	-	-	0.72 (0.59–0.84)	<0.001
LVEF/GLS > 4.10	-	93 (84–98)	38 (21–58)	79 (73–83)	69 (46–85)	0.65 (0.56–0.75)	0.001
LVEF/GLS > 4.95	-	75 (62–84)	66 (46–82)	84 (76–90)	50 (39–61)	0.69 (0.59–0.80)	<0.001
SA/SB	2.40	-	-	-	-	0.72 (0.60–0.84)	<0.001
SA/SB > 2.10	-	80 (69–89)	55 (36–74)	81 (74–87)	53 (39–67)	0.68 (0.57–0.78)	<0.001
SA/SB > 2.40	-	76 (65–85)	66 (46–82)	84 (76–90)	53 (41–65)	0.71 (0.61–0.81)	<0.001
ApSpar_Visual	-	80 (69–89)	34 (18–54)	75 (69–80)	42 (26–59)	0.57 (0.47–0.67)	0.15

ApSpar_Ratio, apical sparing assessed through the formula; ApSpar_Visual, apical sparing annotated by the echocardiographer after visual assessment of the bullseye peak segmental strain pattern; AUC, area under the curve; CI, confidence interval; LVEF/GLS, ratio of left ventricular ejection fraction to global longitudinal strain; SA/SB, ratio of septal apical strain to septal basal strain.

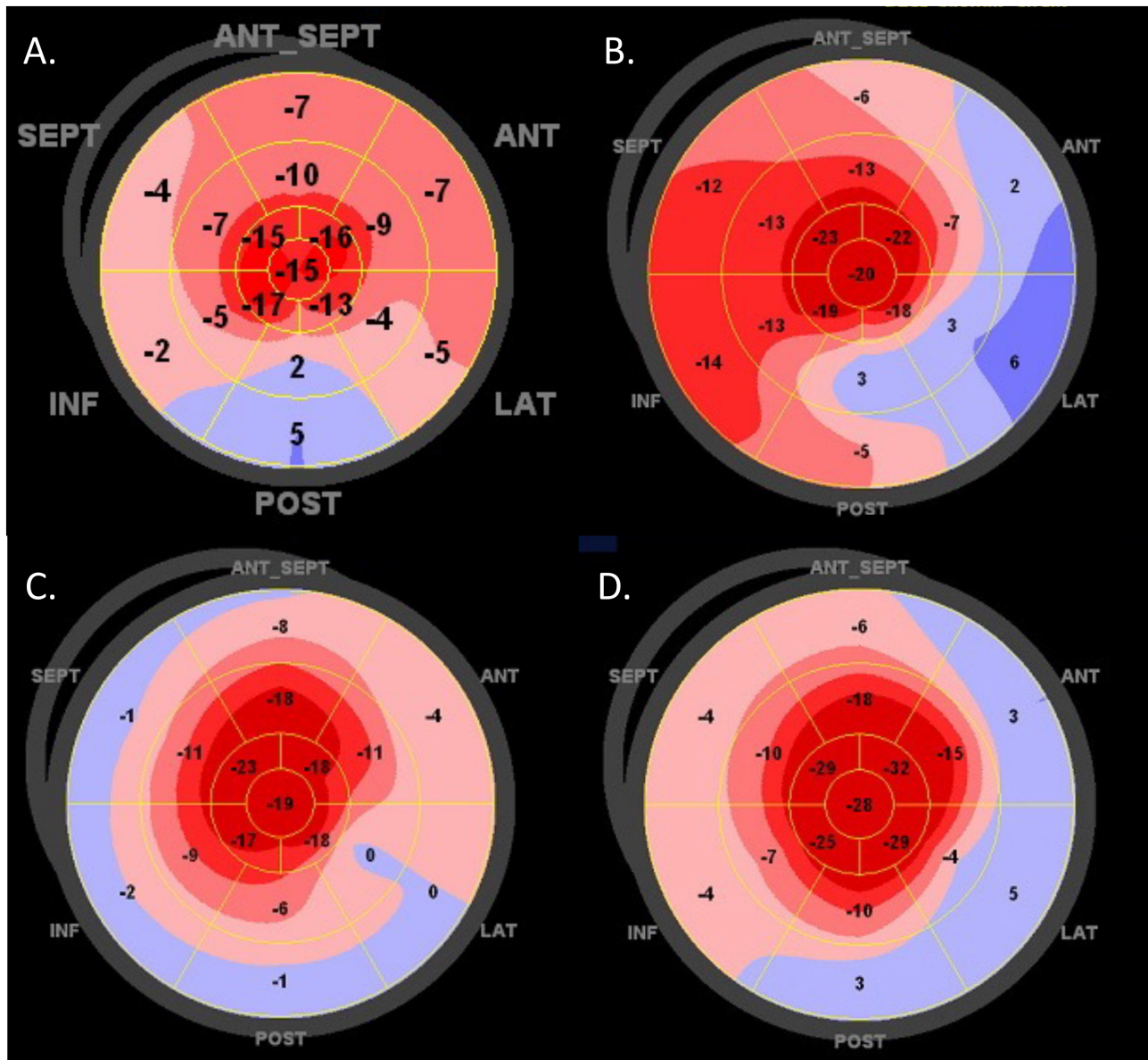
Results of receiver-operating characteristic analysis for the discrimination of cardiac amyloidosis by echocardiographic strain parameters (ApSpar_Ratio, LVEF/GLS, and SA/SB) evaluated as continuous variables and using cut-off values. Cut-off values used were those that were data driven determined by the Youden method and those from prior literature (ApSpar_Ratio ≥ 1, LVEF/GLS > 4.1, and SA/SB > 2.4). LVEF/GLS and SA/SB showed better discriminating capability than ApSpar_Ratio. ApSpar_Visual did not improve discrimination for cardiac amyloidosis in the univariable model (P = 0.15).

^aOptimal cut-off by the Youden method (data driven).

line in seeing a patient with concern for CA. As non-invasive methods are increasingly being used to screen for and diagnose CA,^{18,19} it is imperative that treating providers recognize

the limitations of each test, the need for complete AL evaluation, and that EMB remains the gold standard in times of diagnostic uncertainty.

Figure 3 Apical-sparing pattern in patients with and without cardiac amyloidosis after complete evaluation including endomyocardial biopsy. Examples of patients with both left ventricular hypertrophy and apical sparing as noted both by the echocardiographer (ApSpar_Visual) and the formula (ApSpar_Ratio ≥ 1). ApSpar_Ratio ranged from 1.6 to 1.7 for the four cases. After complete evaluation including endomyocardial biopsy, only Patient D was positive for cardiac amyloidosis.



Echocardiographic findings and cardiac amyloidosis

In all patients who underwent a complete CA evaluation, ApSpar_Ratio ≥ 1 had modest discriminating ability for CA (66% sensitivity, 59% specificity), in line with similar findings in patients with chronic kidney disease²⁰ as well as a large cohort of patients referred to amyloid specialty centres.⁴ Sensitivity analyses also showed no significant difference in performance of ApSpar_Ratio ≥ 1 after confining our cohort to those who underwent EMB or had LVH. While negative pre-

dictive value and positive predictive value are certainly related to the population being tested, the sensitivity and specificity of a test can also change with major differences between populations.²¹ Our sample provides the best reference to date for these parameters in a general screening population, which will be useful as LV strain becomes more widely used. The diagnosis of CA was in line with expert consensus statements including the ESC position statement,¹⁵ and all evaluations were reviewed by two CA specialists (J. M. and D. L.) according to established criteria. The difference between a negative and incomplete evaluation for CA was also more specifically

delineated in order to more appropriately evaluate the performance characteristics of apical sparing.

It is unclear what impact the use of two different ultrasound machines (General Electric and Philips) may or may not have had on the findings of the study. Current recommendations for the use of apical sparing in detecting CA do not account for the ultrasound machine type and are thought to be generalizable across all machines. In the European Association of Cardiovascular Imaging/American Society of Echocardiography Inter-Vendor Comparison Study, the average GLS correlated well between GE and Philips (Pearson correlation coefficient 0.869),²² but there have been concerns that variations in regional or segmental measurement could have a greater impact on the reproducibility of apical sparing across software packages. In a small study of 18 patients with amyloidosis, EchoPAC (GE) had the best discrimination ability for detecting CA using regional strain values compared with two other software packages (Velocity Vector Imaging and Qlab).²³ This regional variability across software packages may decrease the fidelity of using apical sparing as the sole screening test for CA in clinical practice and lend more utility to alternative measurements that utilize averages, such as the LVEF/GLS ratio. Importantly, though, in one study of 100 patients with CA, hypertrophic cardiomyopathy, or hypertensive cardiomyopathy solely using EchoPAC, LVEF/GLS ratio had superior accuracy in detecting CA than the finding of apical sparing.⁵

Despite the reduced performance in our cohort, ApSpar_Ratio ≥ 1 did remain an important predictor of CA. Apical sparing also presents an easy form of visual identification of patients with its hallmark bullseye pattern (ApSpar_Visual), although clinicians should be cognizant that the subjective evaluation of apical sparing (ApSpar_Visual) does not fully correlate with the calculated ApSpar_Ratio ≥ 1 . In our study, ApSpar_Ratio ≥ 1 was better at discriminating CA than ApSpar_Visual on univariate analysis, while ApSpar_Visual became more important after accounting for LVEF/GLS and other covariates. In line with previous studies, LVEF/GLS and SA/SB were more accurate univariate discriminators for CA overall than ApSpar_Ratio,^{4,5} with greater sensitivity but less specificity than ApSpar_Ratio. The combination of increased LVEF/GLS and an apical-sparing pattern may prove to be a powerful tool in helping identify patients at significantly increased risk for CA.

How sensitive are proposed screening criteria for cardiac amyloidosis?

The age cut-offs and IVSd cut-offs proposed by one expert group for ATTR CA evaluation¹⁶ would have missed 26% of the patients in our study with confirmed ATTR CA and 77% of the patients with confirmed AL CA. While these thresholds were designed for ATTR as opposed to AL, there is reasonable concern that such cut-offs would reduce the number of pa-

tients evaluated for all forms of CA. The broader ESC criteria are likely preferable as they were more likely to capture patients in our cohort with CA, only missing three patients. Until our screening algorithms for CA improve, clinicians should continue to consider CA more broadly, especially while ruling out AL.

Improving cardiac amyloidosis identification in the future

Given the limitations of selection criteria and imaging findings to date, recent advances in echocardiographic amyloid risk scores⁴ show promise, although optimal risk scores should likely include a mix of clinical and echocardiographic parameters. The most important intervention will be improving awareness and education as well as increasing frequency of appropriate evaluation for CA. While accuracy was more modest in our more generalized cohort, strain imaging still helped identify patients with concern for CA in this study and could have significant impact if more broadly used. TTE reports should also use exact wording to prompt appropriate evaluations. In patients of concern, electronic medical record alerts with specific recommended follow-up may also be beneficial, whether alerting the treating provider or an appropriate specialist. Certainly, cardiovascular comorbidities such as HTN or CAD should not dissuade evaluation in patients with concerning clinical history and TTE findings.

Strengths and limitations

Because our institution routinely acquires LV strain imaging on all patients who undergo TTE, the study results are an indicator of the utility of ApSpar in a broad clinical context. Patients with a wide range of comorbidities were included, including those with other causes of LVH.

This study was limited to a single centre, retrospective evaluation of patients with concern for amyloidosis on TTE, and the cohort comprised patients with heterogeneous forms of CA. The sample size prevented a determination if specific TTE parameters correlated with a particular type of CA. Patients were not captured if there was no concern for CA in the summary report, and the search terms may not have encompassed everyone with CA. However, the presence of apical sparing is commonly reported at our centre when visually apparent, the search terms still represent a broad search of an otherwise unselected population undergoing TTE, and our study remains generalizable to the search terms used.

There were also noted differences in patients who underwent complete evaluation, and the accuracy of apical sparing will likely be further reduced when applied to the entire cohort. However, there was no substantial difference in TTE strain characteristics or LVEF between patients who did

or did not undergo complete evaluation, and it is reasonable to believe a significant portion of patients with CA were missed in the group of patients who did not undergo complete evaluation. Certainly, all patients had potential 'red flag' signs on echocardiography.

Conclusions

While it remains a helpful tool for identifying patients with potential CA, apical sparing on TTE has modest sensitivity and specificity in a real-world cohort and other cardiomyopathies can mimic CA. Ultimately, there is a crucial need for improved CA education and awareness, as a significant number of patients with signs of CA on echocardiography do not undergo complete CA evaluation. Clear communication and specific follow-up recommendations alone could have a large impact. Clinicians should also consider CA more broadly, especially because recent proposed cut-offs advanced for the evaluation of ATTR CA would have missed more than half of patients with confirmed ATTR and AL CA in our cohort. More sensitive criteria, such as the recent ESC position statement, appear preferable as a screening tool to prompt further evaluation.

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Conflict of interest

Dr. Zhang has received consulting fees from Eidos Therapeutics. Dr. Gorcsan has received research support from GE Healthcare, TomTec, Hitachi, V-wave Ltd, EBR systems, and Canon. Dr. Lenihan is a consultant for Lilly, Roche, Pfizer, Prothena, and Acorda and has received research support from Myocardial Solutions. Dr. Mitchell has received research support from Pfizer, the Longer Life Foundation, and Children's Discovery Institute as well as modest consulting fees from Pfizer.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Performance Characteristics of Strain Parameters for Discriminating Cardiac Amyloidosis in Patients Undergoing Endomyocardial Biopsy.

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