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ORIGINAL ARTICLE
Vascular and cardiac imaging

A novel echocardiographic risk score for light-chain amyloidosis

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Aims

The prognosis of light-chain (AL) amyloidosis, a plasma cell dyscrasia, is largely determined by the presence of cardiac involvement. Conventional staging is achieved using cardiac biomarkers (high-sensitivity troponin, *N*-terminal pro-beta natriuretic peptide) and free light-chain difference (Mayo staging). We sought to evaluate the role of echocardiographic parameters as prognostic markers in AL amyloidosis and examine their utility compared with conventional staging.

Methods and results

Seventy-five consecutive patients with AL amyloidosis reviewed at a referral amyloid clinic who underwent comprehensive echocardiographic assessment were retrospectively identified. The evaluated echocardiographic parameters included left ventricular (LV) ejection fraction, mass, diastolic function parameters, global longitudinal strain (GLS), and left atrial (LA) volume. Mortality was assessed through a review of clinical records. During a median follow-up of 51 months, 29/75 (39%) patients died. Patients who died had a larger LA volume (47 ± 12 vs. 35 ± 10 mL/m^2, $P < 0.001$) and a higher E/e' (18 ± 10 vs. 14 ± 6, $P = 0.026$). Univariate clinical and echocardiographic predictors of survival included LA volume, E/e', e′, LVGLS, and Mayo stage (at significance of $P < 0.1$). Left atrial volume and LVGLS were significant determinants of mortality when examined using clinical cut-offs, although E/e' was not. A composite echocardiographic risk score comprising LA volume and LVGLS provided similar prognostic performance to Mayo stage [area under the curve (AUC) 0.75, 95% confidence interval (CI) 0.64–0.85 vs. AUC 0.75, 95% CI 0.65–0.858, $P = 0.91$].

Conclusion

Left atrial volume and LVGLS were independent predictors of mortality in AL amyloidosis. A composite echocardiographic score combining LA volume and LVGLS has similar prognostic power to Mayo stage for all-cause mortality.

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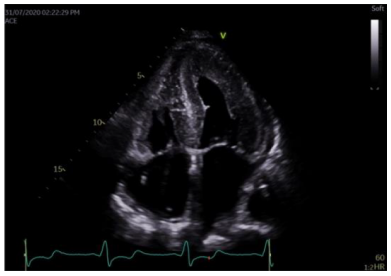
Graphical Abstract



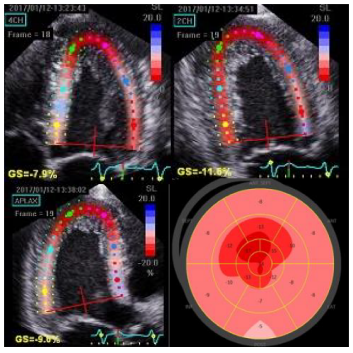
Left Atrial Dilatation

Mild: 34 - 41mL/m^2
Moderate: 42 - 48mL/m^2
Severe: >48mL/m^2

Left Atrial Volume

LAVI < 42mL/m^2
Normal or mildly dilated
+ 0 points

LAVI ≥ 42mL/m^2
Moderate or severely dilated
+1 point



LVGLS Impairment

Mild: -16% to -14%
Moderate: -14% to -12%
Severe: >-12%

LVGLS

LVGLS ≤ -12%
Normal to moderately impaired
+ 0 points

LVGLS > -12%
Severely impaired
+1 point

Echo Score 0 1 2

An echocardiographic risk score was derived using a cohort of 74 patients with light-chain amyloidosis from a single centre. A composite score using left atrial volume and global longitudinal strain, stratified patients into three distinct risk groups. Patients were allocated one point for left atrial dilatation (indexed left atrial volume >42 mL/m^2) and reduced left ventricular global longitudinal strain (>−12%). Prognostic power in predicting all-cause mortality was similar to the existing Mayo staging system [area under the curve (AUC) 0.75, 95% confidence interval (CI) 0.64–0.85 vs. AUC 0.75, 95% CI 0.65–0.858, $P = 0.91$].

Keywords Echocardiography • Infiltrative cardiomyopathy • Amyloidosis • Speckle tracking • Longitudinal strain

Introduction

Cardiac amyloidosis is the archetype of infiltrative cardiomyopathy and often presents with a clinical phenotype of heart failure with preserved ejection fraction. Systemic light-chain (AL) amyloidosis is a plasma cell dyscrasia with multisystem involvement; however, prognosis of AL amyloidosis is often related to cardiac involvement. This is reflected in the use of the 'Mayo score' in staging AL amyloidosis. This score comprises the cardiac biomarkers, high-sensitivity troponin (hs-Trop) and *N*-terminal pro-brain natriuretic peptide (NT-proBNP), and the free light-chain difference (dFLC).[1]

While the original and the revised Mayo score staging of AL amyloidosis have demonstrated prognostic utility, limitations to the use of

these biomarkers exist. The variation in troponin assays used between centres, for example hs-TropI and hs-TropT, each of which has its own defined ranges, makes temporal comparisons more difficult. Similarly, assays for NT-proBNP have changed over time, with similar implications as for troponin. Additionally, both troponin and NT-proBNP are affected by factors such as body mass index and coexistent renal failure, the latter being relatively common in systemic AL amyloidosis.

In contrast, traditional echocardiographic markers of cardiac structure and function are standardized with universally defined normal ranges. Moreover, a transthoracic echocardiogram (TTE) is routinely performed in patients with AL amyloidosis to evaluate cardiac involvement and is inexpensive and widely available. Novel echocardiographic indices such as left ventricular global longitudinal strain (LVGLS) have been validated across a broad range of disease processes and are increasingly being utilized in the clinical evaluation of AL amyloidosis.[2] In this study, we sought to examine the prognostic utility of echocardiographic parameters vs. the Mayo staging in patients with AL amyloidosis.

Methods

Seventy-five consecutive patients with AL amyloidosis reviewed at a single quaternary referral institution, in a multidisciplinary amyloidosis clinic between June 2008 and September 2018 who had undergone a TTE were included in this retrospective study. All patients underwent comprehensive TTE assessment, including two-dimensional, colour, Doppler and strain imaging by speckle tracking. All echocardiograms were performed using Vivid E9 or E95 ultrasound systems (GE Vingmed, Horten, Norway), with patients scanned in the left decubitus position.

Left ventricular (LV) systolic function was assessed by ejection fraction using Simpson's biplane method of discs, with LV end diastolic and end systolic volumes acquired from the apical four- and two-chamber view; LV ejection fraction (LVEF) was calculated.[3] Left ventricular diastolic function was assessed using a composite of parameters as in recent guidelines, including pulsed wave Doppler mitral inflow, tissue Doppler e′ velocity obtained from the septal and lateral mitral annulus, *E*/average e′, left atrial (LA) volume, and peak velocity of tricuspid regurgitation.[4] Maximum biplane LA volume was measured at end systole, immediately prior to mitral valve opening, from zoomed four- and two-chamber apical views that were optimized for the left atrium, and was indexed to body surface area (LAVI). Left ventricular mass was calculated using the Devereux method, and was also indexed to body surface area.[5]

Strain analysis by speckle tracking was performed offline (General Electric Horton, Norway, Viewpoint Ver 6.9.1) on focused LV views from the apical four-chamber, two-chamber, and long-axis views, acquired at high frame rates (>55 fps) to determine peak systolic LVGLS. The LV endocardial border was traced and region of interest adjusted to include the LV myocardium. Left ventricular global longitudinal strain values reported are midmyocardial global longitudinal strain (GLS) values. All echocardiographic measurements were repeated over three cardiac cycles and averaged for final analysis.

Outcome data were obtained through the review of patient medical records, with follow-up taken as time from the index echocardiogram. Mayo stage was calculated for each patient using biochemistry obtained contemporaneous with the TTE, including hs-TropI, NT-proBNP, and dFLC. Free light-chain difference was defined as the absolute difference between the involved and uninvolved serum-free light-chain levels. Mayo stage was determined by allocating one point for each biomarker that was elevated, stratifying patients into one of four possible stages.[1]

Interobserver variability for echocardiographic measurements was examined in 10 randomly selected patients, by the same investigator, with measurements performed 4 weeks apart. Similarly, interobserver variability was determined with a second observer performing measurements on the same 10 patients, blinded to the results obtained by the first observer.

Statistical analysis

Statistical analysis was performed using SPSS (IBM Corporation, Version 26, Armonk, NY, USA). Continuous variables were expressed as mean and standard deviation, or median and interquartile range if not normally distributed. Comparisons between groups for continuous variable analysis were performed using a Student's *t*-test or Mann–Whitney test if not normally distributed, while categorical variables were analysed using the χ^2 test. Parameters that predicted mortality were determined by univariate analysis. Parameters that were predictors of mortality on univariate analysis at significance of $P < 0.1$ were entered into a multivariate backwards stepwise linear regression model. Receiver-operating curves were utilized to determine the area under the curve (AUC) for univariate predictors. DeLong's test was performed to examine differences in AUC.[6]

Intra- and interobserver variability for LAVI, LVGLS, and LVEF were assessed by the intraclass correlation coefficient. Values of >0.75 and >0.9 were considered good and excellent reliability, respectively.[7]

Ethics approval was provided by the Western Sydney Local Health District ethics committee (HREC No. ETH13628).

Table 1 Baseline patient characteristics

Gender	24F, 51M
Age (years)	61.8 ± 10
Height (cm)	169 ± 10
Weight (kg)	80 ± 15
BMI (kg/m^2)	27.8 ± 4.9
eGFR (mL/min/1.73 m^2)	60 ± 27
Chemotherapy	71 (95%)
VCD	30 (40%)
CDT	21 (28%)
MD	14 (19%)
Other	6 (8%)
ASCT	11 (15%)
Hypertension	33 (45%)
Hypercholesterolaemia	27 (36%)
Diabetes mellitus	9 (12%)
Ischaemic heart disease	9 (12%)
Atrial fibrillation	11 (15%)
Mayo stage (*n*)	
I	25 (33%)
II	22 (30%)
III	15 (20%)
IV	13 (17%)

ASCT, autologous stem-cell transplantation; BMI, body mass index; CDT, cyclophosphamide, thalidomide, dexamethasone; eGFR, estimated glomerular filtration rate; VCD (CyBorD), cyclophosphamide, bortezomib, dexamethasone; MD, melphalan, dexamethasone.

Results

Baseline characteristics are shown in *Table 1*. The mean age was 61.8 ± 10 years, and 51/75 patients were males. Seventy-one of 75 patients received chemotherapy, the majority receiving bortezomib (Velcade), cyclophosphamide, and dexamethasone (VCD; 30/75); 11 patients underwent allogeneic stem-cell transplantation. Twenty-five patients were classified as Mayo Stage I, 22 were Stage II, while Stages III and IV had 15 and 13 patients, respectively.

During a median follow-up of 51 months, 29/75 (39%) patients died. Patients were divided into two subgroups based on mortality; they did not differ in age, gender, or body mass index, though systolic blood pressure approached statistical significance ($P = 0.051$). Eleven patients were in atrial fibrillation; the rate of atrial fibrillation was similar between the two groups, 6/46 (13%) in survivors vs. 5/29 (17%) in non-survivors ($P = 0.617$). Patients that died had significantly greater LA

Table 2 Patient characteristics and echocardiographic parameters in survivors and non-survivors

	Patient group that was alive ($n = 46$)	Patients who died during follow-up ($n = 29$)	*P*-value
Age (years)	61.7 ± 9	62.0 ± 12	0.88
Gender	17F, 29M (65%M)	7F, 22M (73%M)	0.246
Systolic BP (mmHg)	127 ± 17	118 ± 18	0.051
BMI (kg/m^2)	28.0 ± 4.8	27.3 ± 5.2	0.552
Heart rate (b.p.m.)	75 ± 14	74 ± 13	0.567
Atrial fibrillation	6/46 (13%)	5/29 (17%)	0.617
eGFR (mL/min/1.73 m^2)	62 ± 28	58 ± 24	0.588
NT-proBNP (ng/L)	1924 ± 4456	4226 ± 3996	0.030
dFLC (mg/L)	247 ± 448	402 ± 598	0.218
LVEF (%)	58 ± 7	55 ± 7	0.122
LA volume (mL/m^2)	35 ± 10	47 ± 12	<0.001
LVGLS (%)	−16.5 ± 4	−14.6 ± 5	0.090
LV mass (g/m^2)	115 ± 30	129 ± 45	0.097
e′ (cm/s)	6.1 ± 2	5.3 ± 2	0.087
E/e′	14 ± 6	18 ± 10	0.026
Mayo			0.001
Stage I	23/25 (92%)	2/25 (8%)	
Stage II	12/22 (55%)	10/22 (45%)	
Stage III	6/15 (40%	9/15 (60%)	
Stage IV	5/13 (38%)	8/13 (62%)	

BMI, body mass index; dFLC, free light-chain difference; eGFR, estimated glomerular filtration rate; LFEV, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3 Mayo stage and univariate echocardiographic predictors of survival

	Hazard ratio	*P*-value
LVEF	0.963	0.131
GLS	0.927	0.074
LV mass	1.005	0.209
LA volume	1.055	0.001
E′	0.822	0.069
E/*E*′	1.057	0.016
Mayo stage	1.810	0.001

GLS, global longitudinal strain; LVEF, left ventricular ejection fraction.

Table 4 Multivariate model of echocardiographic variables (left atrial volume, left ventricular global longitudinal strain, *E*/e′) as predictors of survival

	Hazard ratio	*P*-value
LA volume	1.049	0.002
E/e′	1.030	0.310
LVGLS	0.975	0.593

LA, left atrial; LVGLS, left ventricular global longitudinal strain.

volume (35 ± 10 vs. 47 ± 12 mL/m^2, $P < 0.001$), and higher *E*/e′ (14 ± 6 vs. 18 ± 10, $P = 0.026$); both LV mass and LVGLS approached statistical significance (*Table 2*). There was no difference between groups in LV systolic function evaluated by LVEF (*Table 2*). As expected, mortality increased with increasing Mayo stage and was 8, 45, 60, and 62% in patients in Mayo Stages I–IV, respectively.

On univariate analysis, echocardiographic parameters that were predictors of mortality at significance of $P < 0.1$ included LAVI, e′ velocity, *E*/e′, and LVGLS (*Table 3*). As expected, the Mayo stage was also an independent predictor of survival. Univariate echocardiographic predictors of mortality (significance of $P < 0.1$) were entered into a multivariable Cox proportional hazards model and included *E*/e′ and LA volume and LVGLS (e′ velocity was not entered into the model due to collinearity with *E*/e′; *Table 3*). In this multivariable model of echocardiographic parameters, LAVI was the only independent echocardiographic predictor of mortality (*Table 4*). Indexed left atrial volume correlated with Mayo stage (Spearman correlation coefficient 0.5, $P < 0.001$), and all patients in Mayo Stages III and IV had dilated left atria (LAVI ≥34 mL/m^2).

We evaluated LVGLS (LV systolic function), LAVI, and *E*/e′ (diastolic function) as categorical variables using clinically applicable cut-off values to evaluate their impact on mortality vs. the Mayo stage. Left ventricular global longitudinal strain was divided into three groups based on the previously reported clinical cut off of better than −16, −12 to −16%, and worse than −12% for normal, reduced, and severely reduced GLS, respectively.[8] Indexed left atrial volume was divided into three groups using a clinical cut off of ≤34, 34–42, and ≥42 mL/m^2, corresponding to normal, mild-to-moderate LAVI dilatation, or greater than moderate LAVI dilatation.[3] *E*/e′ was divided into three groups based on clinical values of <8, 8–15, and ≥15, corresponding to normal, likely abnormal, and increased LV filling pressure.[9] Stratification by clinical groups of LAVI ($P < 0.001$), LVGLS ($P = 0.031$), and Mayo stage ($P = 0.001$) were significant predictors of mortality, while *E*/e′ did not

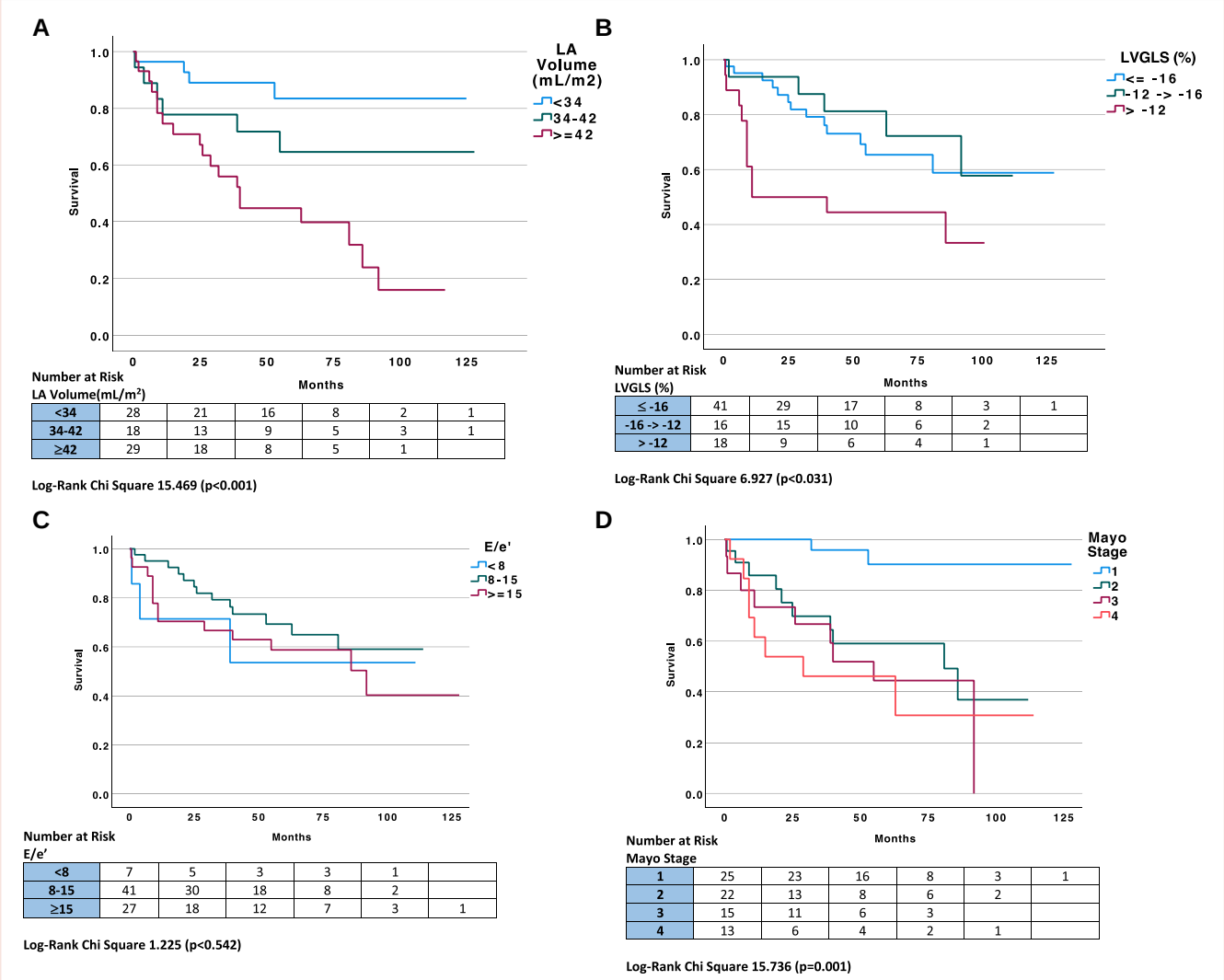


Figure 1 Kaplan–Meier curves for (*A*) left atrial volume, (*B*) left ventricular global longitudinal strain, (*C*) *E*/*e*′ (using standard clinically used cut offs), and (*D*) Mayo stage.

reach significance on Kaplan–Meier analysis (*Figure 1A–D*). Of note, patients with a normal LAVI <34 mL/m^2 had particularly good 'long-term' outcomes (median follow-up 60.5 ± 46 months) and conversely, patients with LVGLS worse than −12%, had poor outcomes.

Using the clinical cut offs for LVGLS and LAVI to construct a simple echocardiographic score, the highest risk group had both LVGLS (worse than −12%) and LAVI (>42 mL/m^2), intermediate risk group had LVGLS −12 to −16% and LAVI 34–42 mL/m^2, and the lowest risk group had LVGLS better than −16% and LAVI <34 mL/m^2, respectively. A risk score was then constructed by allocating one point each for LVGLS worse than −12% and LAVI >34 mL/m^2, thereby dividing patients into one of three groups, highest risk group had both LVGLS (worse than −12%) and LAVI (>42 mL/m^2), intermediate risk group had either LVGLS worse than −12% or LAVI >42 mL/m^2 and lowest risk group had LVGLS better than −12% and LAVI <42 mL/m^2 with 2, 1, and 0 points, respectively (see *Graphical Abstract*). Kaplan–Meier curves were constructed for the novel echocardiographic risk score (Echo score; *Figure 2*). The novel 'Echo score' had similar prognostic performance to Mayo stage [AUC 0.745, 95% confidence interval (CI) 0.638–0.853 vs. AUC 0.752, 95% CI 0.645–0.858, $P = 0.911$].

Intra- and interobserver variability of LAVI were both excellent, with an intraclass correlation coefficient of 0.987 (95% CI 0.946–0.997), while interobserver correlation coefficient was 0.935 (95% CI 0.731–0.984). Similarly, LVGLS was highly reproducible with an intraclass correlation coefficient of 0.989 (95% CI 0.864–0.998), while interobserver correlation coefficient was 0.980 (95% CI 0.924–0.995). Left ventricular ejection fraction showed good intra- and interobserver variability, with an intraclass correlation coefficient of 0.871 (95% CI 0.517–0.967) and an interobserver coefficient of 0.772 (95% CI 0.115–0.943).

Discussion

Cardiac involvement in AL amyloidosis portends a poor prognosis. A TTE is routinely performed for AL amyloidosis assessment. We demonstrated that cardiac imaging can identify patients with higher mortality, and therefore, such risk stratification could potentially guide the selection of optimal therapeutic regimens. The salient findings are that

(1) A simple echocardiographic parameter, LAVI, was an independent prognostic marker in patients with AL amyloidosis.

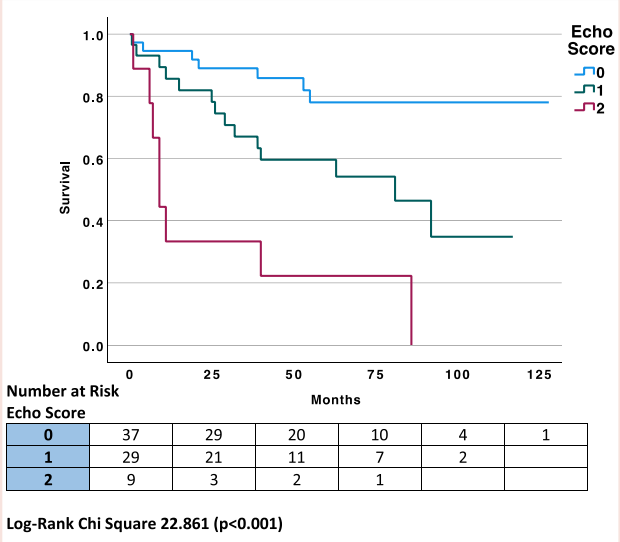


Figure 2 Kaplan–Meier curve for novel echocardiographic risk score. Patients were allocated one point for left atrial dilatation (indexed left atrial volume >42 mL/m^2) and reduced left ventricular global longitudinal strain (>−12%).

(2) Indexed left atrial volume and LVGLS, stratified using clinical cut-off values, demonstrated worse outcomes with worse LVGLS and increasing LAVI.
(3) A composite echocardiographic score derived from LAVI and LVGLS demonstrates similar predictive value as the Mayo staging.

Heart failure with preserved ejection fraction is the commonest cardiac presentation in AL amyloidosis, and survival in this disease is largely determined by cardiac involvement. The median survival after onset of heart failure symptoms is as low as 6 months.[10] About 60–90% of all patients with AL have cardiac involvement,[10] and its prognostic significance is reflected in the use of hs-Trop and NT-proBNP in the widely accepted Mayo stage.[11] Mayo staging has been validated for its ability to discriminate low-risk patients with favourable prognosis from those with advanced cardiac involvement and a higher Mayo stage, who progress rapidly. Median survival from diagnosis decreases dramatically with increasing Mayo stage, with survival rates of 94, 40, 14, and 5.8% months for Mayo Stages 1–4, respectively.[1] However, the limitation of the score includes variations in assays used and alterations in biomarker levels with renal dysfunction. Additionally, the Mayo score with inclusion of dFLC is less friendly for the cardiology community.

Cardiac involvement in AL amyloid is pivotal in determining prognosis, and hence, it is not surprising that direct cardiac evaluation using echocardiographic parameters provides prognostic information. Transthoracic echocardiogram is non-invasive, widely available and is routinely performed to evaluate patients with AL amyloid. The development of advanced echocardiographic techniques, including strain analysis, has reclassified evaluation and stratification of LV systolic function when compared with utilizing LVEF.[8] Both LAVI and LVGLS are well-standardized measures and are now routinely used in clinical practice.

Various echocardiographic parameters have previously attracted interest as possible prognostic tools in staging AL amyloidosis. These include LVEF, LAV, and LVGLS by speckle tracking echocardiography. There is a presumed correlation between LA enlargement and Mayo stage (through NT-proBNP), and prior studies have shown that LA enlargement and dysfunction have promise in the diagnosis and prognosis of cardiac AL amyloidosis.[12–14] While LA changes are a surrogate for LV diastolic dysfunction, a coexistent atrial myopathy consequent to cardiac AL amyloidosis could also contribute to the observed changes.[15] Fitzgerald *et al.*[16] demonstrated that LA dilatation was more suggestive of cardiac amyloidosis than patients with similar degrees of LV hypertrophy due to hypertension. Similarly, LAVI using three-dimensional echocardiography correlates with Mayo stage,[17] while Nochioka *et al.*[18] used a cut off of 48 mL/m^2, representing severe LA dilatation, when investigating LA structure and function in both light-chain and transthyretin cardiac amyloidosis. In our study, LA volume correlated with Mayo stage, and all patients in Mayo Stages III and IV demonstrated LA dilatation (LAVI >34 mL/m^2). Importantly, mortality among patients with normal LAVI (<34 mL/m^2) was significantly lower, demonstrating the negative predictive value of a normal LAVI.

In a study of 94 patients with advanced disease (Mayo Stages III and IV), LVGLS provided incremental value over BNP, troponin, LVEF, and Mayo stage.[19] Left ventricular global longitudinal strain worse than −12% defines severely decreased LVGLS[8] and in unselected patients, those with LVGLS worse than −12% had high all-cause mortality similar to LVEF <35%.[20] More specifically in AL amyloidosis, severely reduced LVGLS (−11.78 and −10.2%, respectively)[21,22] predicted adverse outcomes similar to our findings. Left ventricular global longitudinal strain has also shown incremental value in predicting mortality in AL amyloidosis compared with individual biomarkers[23,24] and earlier formulations of the Mayo stage.[21,25] Recently, Chuy *et al.*[19] demonstrated in patients with advanced AL amyloidosis (Mayo Stages III and IV) that LVGLS has incremental prognostic value to Mayo stage. Similarly, an alternative staging system, using NT-proBNP, troponin T, and LVGLS, was recently proposed[2] using quartiles of LVGLS with more complex LVGLS cut offs (−16.2, −12.2, and −9.1%) and two cut-off levels for NT-proBNP. This is, however, more complicated than the simple Echo score proposed in our paper, though the Echo score requires further validation.

We derived the Echo score using standard clinical cut offs representing moderate or greater LA dilatation (≥42 mL/m^2) and severely reduced LVGLS (worse than −12%) to facilitate uptake and use in routine clinical practice. The Echo score which combined LVGLS a marker of systolic function, and LAVI a measure of LV diastolic function, provided prognostic utility similar to the Mayo score. Left atrial volume is easy to measure and is reproducible. Left ventricular global longitudinal strain measurements have been standardized across vendor platforms[26] with good inter- and intraobserver reproducibility. Left ventricular global longitudinal strain using speckle tracking is also angle independent and increasingly being utilized in routine clinical practice. Given these attributes, we contend that the new score is particularly useful for cardiologists managing AL amyloidosis.

Limitations

The limitations of this study are that it is retrospective in nature, a relatively small number of patients is included in it, and it is a single-centre study. However, the study included AL patients across all the Mayo stages, although only a small number had advanced disease [35% (26/74) classified as Stage III or IV]. However, comprehensive TTEs were performed and our data were meticulously collected, with complete patient follow-up (median 51 months). Given the high level of mortality in AL amyloidosis, the study's finding that a significant proportion of patients died (39%) is not surprising, thus meeting the primary end point.

Conclusions

Indexed left atrial volume, a simple and reproducible parameter, is an independent echocardiographic predictor of overall mortality in AL amyloidosis. Patients with normal LAVI have relatively good outcomes.

When LAVI was combined with LVGLS, a composite echocardiographic risk score stratified patients with AL amyloidosis into three groups with distinct clinical trajectories, with similar efficacy to the Mayo stage. Further validation in a larger cohort is required to evaluate the incremental value of these echocardiographic parameters compared with conventional Mayo staging. Finally, serial echocardiograms could potentially be used for follow-up in patients with AL amyloidosis to monitor progress and response to therapy.

Lead author biography

Paul Geenty is a cardiologist and research fellow at Westmead Hospital in Sydney, Australia, and a PhD candidate at the University of Sydney. His research interests include multi-modality imaging and advanced echocardiography techniques, cardiopulmonary exercise testing, cardiomyopathies, and heart failure.

Data availability

The clinical data underlying this article will be made available on reasonable request to the corresponding author.

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