JACC: CARDIOVASCULAR IMAGING VOL. 10, NO. 4, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.04.008

Prognosis of Light Chain Amyloidosis With Preserved LVEF

Added Value of 2D Speckle-Tracking Echocardiography to the Current Prognostic Staging System

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CME Editor Disclosure: *JACC: Cardiovascular Imaging* CME Editor Ragavendra R. Baliga, MD, has reported that he has no relationships to disclose.

Author Disclosures: This work was supported in part by the Robert A. Kyle Hematologic Malignancies Program and the Henry J. Predolin Foundation. The Mayo Clinic does not endorse the products mentioned in this article. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval

Issue Date: April 2017
Expiration Date: March 31, 2018

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Manuscript received November 23, 2015; revised manuscript received March 16, 2016, accepted April 21, 2016.

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ABSTRACT

OBJECTIVES This study evaluated whether 2-dimensional speckle-tracking echocardiography (2D-STE) has incremental value for prognosis over traditional clinical, echocardiographic, and serological markers—with main focus on the current prognostic staging system—in light-chain (AL) amyloidosis patients with preserved left ventricular ejection fraction.

BACKGROUND Cardiac amyloidosis (CA) is the major determinant of outcome in AL amyloidosis. The current prognostic staging system is based primarily on serum levels of cardiac troponin T (cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and free light chain differential (FLC-diff).

METHODS Consecutive patients with biopsy-proven AL amyloidosis and left ventricular ejection fraction ≥55% were divided into group 1 with CA (n = 63) and group 2 without CA (n = 87). Global longitudinal strain (GLS) by 2D-STE was performed with Vivid E9 (GE Healthcare Co., Milwaukee, Wisconsin) and *syngo* Velocity Vector Imaging (VVI) software (Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania) (GLS_{GE} and GLS_{VVI}, respectively).

RESULTS Thirty-two deaths (51%) occurred in group 1 and 13 (15%) in group 2 ($p \leq 0.001$). Group 1 had thicker walls, lower early diastolic tissue Doppler velocity at septal mitral annulus, and greater left ventricular mass, left atrial volume, glomerular filtration rate, FLC-diff, cTnT, and NT-proBNP ($p < 0.001$). For the entire cohort, $GLS_{GE} \geq -14.81$, $GLS_{VVI} \geq -15.02$, cTnT, NT-proBNP, FLC-diff, age, left ventricular wall thickness, early diastolic tissue Doppler velocity at septal mitral annulus, diastolic dysfunction grade, glomerular filtration rate, deceleration time, and left atrial volume were univariate predictors of death. In a multivariate Cox model, $GLS_{GE} \geq -14.81$ (hazard ratio [HR]: 2.68; 95% confidence interval [CI]: 1.07 to 7.13; $p = 0.03$), FLC-diff, NT-proBNP, and age were independent predictors of survival. There was also a strong trend for $GLS_{VVI} \geq -15.02$ (HR: 2.44; 95% CI: 0.98 to 6.33; $p = 0.055$). Using a nested logistic regression model, GLS_{GE} ($p = 0.03$) and GLS_{VVI} ($p = 0.05$) provided incremental prognostic value over cTnT, NT-proBNP, and FLC-diff. For survival analysis limited to group 2 (non-CA), GLS_{GE} and GLS_{VVI} both predicted all-cause mortality (GLS_{GE} HR: 1.23; 95% CI: 1.03 to 1.47 [$p = 0.02$]; GLS_{VVI} HR: 1.22; 95% CI: 1.01 to 1.49 [$p = 0.04$], respectively).

CONCLUSIONS 2D-STE predicted outcome and provided incremental prognostic information over the current prognostic staging system, especially in the group without CA. (J Am Coll Cardiol Img 2017;10:398–407)

Primary light chain (AL) amyloidosis is a plasma cell dyscrasia characterized by the extracellular deposition of insoluble fibrillary amyloid proteins in multiple organs. In the heart, it is characterized by amyloid deposition in the interstitium, resulting in marked increases in wall thickness and nondilated ventricles; it confers a poor prognosis (1,2).

Previous studies in AL amyloidosis have shown that 2-dimensional (2D) and Doppler echocardiographic abnormalities are associated with a poor outcome (3,4). According to recent reports, newer imaging techniques are independent predictors of survival, mainly due to the early detection of cardiac involvement. These techniques are tissue Doppler imaging (5,6) and 2D speckle-tracking echocardiography (2D-STE)-derived strain (7,8). 2D-STE is a novel angle-independent, noninvasive method that can assess global and regional myocardial mechanics (9). This method has been shown to be a robust, accurate, and sensitive tool for evaluating myocardial function (10). However, it uses different platform systems and software algorithms across vendors,

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

2D-STE = 2-dimensional speckle tracking echocardiography

AL = primary light chain

CA = cardiac amyloidosis

CCC = concordance correlation coefficient

CI = confidence interval

cTnT = cardiac troponin T

EF = ejection fraction

FLC-diff = free light chain differential

GLS = global longitudinal strain

HR = hazard ratio

LV = left ventricular

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

leading to practical concerns regarding reproducibility (11,12). This reproducibility has been studied in healthy individuals but has not been addressed in adults with cardiomyopathies.

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In a population with AL amyloidosis and mixed low and normal ejection fraction (EF), 2D-STE has been used as a tool to predict outcome, but no previous investigation has focused on AL amyloidosis with preserved EF (7,8). Traditionally, serum cardiac troponin T (cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and free light chain difference (FLC-diff) have been used for staging and prognosis (13–16).

The goal of the present study, therefore, was to evaluate the incremental prognostic information provided by 2D-STE-derived global longitudinal strain (GLS) over established clinical, echocardiographic, and serological markers, with the main focus on the current prognostic staging system (comprising serum cTnT, NT-proBNP, and FLC-diff measurements) in patients with primary AL amyloidosis and preserved left ventricular ejection fraction (LVEF), with or without cardiac amyloidosis (CA). As a secondary aim, we sought to evaluate whether prognostication was software-independent, with 2 methods of assessing left ventricular (LV) GLS: EchoPAC software (General Electric [GE] Healthcare Co., Milwaukee, Wisconsin) and *syngo* Velocity Vector Imaging (VVI) (Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania).

METHODS

STUDY POPULATION. The study population comprised 150 consecutive patients with biopsy-proven immunoglobulin AL amyloidosis referred to our institution for echocardiographic study from January 1, 2009, through December 30, 2012. The diagnosis of amyloidosis was made by either subcutaneous fat biopsy or any tissue biopsy of an involved organ, with positive Congo red staining specimens viewed under polarized light. AL amyloidosis was also confirmed by using tandem mass spectrometry and shotgun proteomics. Patients with EF <55% were identified before enrollment and excluded from the study. The Mayo Clinic Institutional Review Board approved this study, and all patients provided written consent.

Cardiac involvement has been defined by a hematology working group on amyloidosis as evidence of echocardiographic signs in absence of high voltages on electrocardiography (17) in conjunction with 3 serological biomarkers (cTnT, NT-proBNP, and FLC-diff) and respective cutpoints of ≥0.025 μg/l, ≥1,800 pg/l, and ≥18 mg/dl (13–15,18). Echocardiographic criteria suggesting CA were the presence of a granular "sparkling" appearance of the myocardium; increased LV wall thickness (i.e., mean of the septal and posterior walls) >12 mm; and thickening of the interatrial septum, valves, and right ventricle free wall and pericardial effusion (8,17,18). On the basis of these parameters, the cohort was divided into 2 groups in accordance with the presence of CA: group 1 had CA and group 2 did not have CA.

Patient electronic medical records were reviewed for demographic characteristics and clinical and echocardiographic data. Vital status information was obtained from hospital records and also ascertained through the Social Security Death Index. Echocardiography, cTnT, NT-proBNP, and FLC-diff were performed at diagnosis for all patients, with no time difference between echocardiography, serological biomarkers, and diagnosis date. Patients were monitored until December 31, 2014; the timing from performance of the index echocardiography to death was taken into account for survival calculations. The primary endpoint was defined as all-cause mortality.

ECHOCARDIOGRAPHY. As part of a routine clinical evaluation, all patients underwent a comprehensive 2D echocardiography and strain analysis. Sonographers with experience in obtaining 2D-STE performed the echocardiographic studies using a Vivid E9 GE Medical System with a 2.5- to 4.0-MHz transducer in accordance with the guidelines of the American Society of Echocardiography (19). Quantitative assessment of LVEF was performed using the modified Quinones equation or volumetric biplane Simpson method, or both, as appropriate. Apical 4-, 3-, and 2-chamber views were obtained with 3 consecutive heart cycles during a breath hold (average frame rate 52.0 frames/s) for GLS analysis.

All echocardiographic images were digitally stored in a Digital Imaging and Communications in Medicine format on the echo management information system and retrieved later for off-line GLS analysis (VVI).

SPECKLE-TRACKING ECHOCARDIOGRAPHY. GLS measurements were performed during the echocardiographic examination with dedicated vendor-specific software (EchoPAC PC version 6.0, GE Healthcare Co.). For off-line analysis, images were imported into vendor-independent software (*syngo* VVI), and 2 observers for whom GE findings were blinded (S.B.-G. and B.W.) analyzed the images. The left ventricle was divided into 16 segments, and

tracing was performed using a 1- to 3-beat cycle starting at mid- or end-systole. Beginning at the mitral annulus, the LV myocardium was traced using 8 to 15 points. Visual endocardial tracking was first analyzed and, if necessary, manually adjusted. No segments were excluded for 2D-STE analyses.

LABORATORY METHODS. cTnT testing was performed with sensitive fourth-generation assay reagents (Roche Diagnostics Corp., Indianapolis, Indiana) with a detection limit at <0.01 μg/l (reference <0.01 μg/l); NT-proBNP was measured with an automated double-incubation sandwich assay (Roche Diagnostics Corp.) (reference <171 pg/ml); and FLC was determined using the Freelite assay (The Binding Site Group Ltd., Birmingham, United Kingdom). The mean difference of kappa (reference 0.33 to 1.94 mg/dl) and lambda (reference, 0.57 to 2.63 mg/dl) FLC was reported as FLC-diff.

STATISTICAL ANALYSIS. Data are presented as mean ± SD or median (interquartile range) for continuous variables and as percentage of total for categorical variables. Continuous data were compared with Student *t* tests and Wilcoxon rank sum tests when assumptions were not met. Paired *t* tests were used to compare the means of GLS and segmental longitudinal strain between platform systems. For categorical variables, either Pearson chi-square or Fisher exact tests were used. Agreement was measured using the concordance correlation coefficient (CCC) and Bland-Altman analysis. Correlation was performed with the Spearman rank correlation coefficient.

For the entire cohort, survival analysis was based on the Kaplan-Meier method with the use of the log-rank test and univariate and multivariate Cox proportional hazards regression analyses. Multivariate Cox regression analysis was performed by incorporating into the model a set of variables that were most statistically significant according to univariate analysis or on the basis of their potential clinical relevance. This method included the parameters currently used in the prognostic staging system (cTnT, log NT-proBNP, and FLC-diff). For survival analysis limited to groups, these biomarkers (cTnT, log NT-proBNP, and FLC-diff) were not included in the model.

The incremental value of $GLS_{GE\text{-}VVI}$ over serological markers was assessed according to the overall difference between models with the log-likelihood chi-square model. Receiver-operating characteristic curves were created to determine the optimal cutoff values for GLS and death, and these values were reported along predetermined cTnT, NT-proBNP, and FLC-diff cutpoints of ≥0.025 μg/l, ≥1,800 pg/l, and ≥18 mg/dl, respectively, as previously reported (13,15). Receiver-operating characteristic curves were also created for prediction of CA. Because of non-Gaussian distribution, NT-proBNP concentrations were log-transformed.

Intraobserver and interobserver variability was assessed in 15 randomly selected patients for whom GLS analysis was independently performed by 2 investigators (S.B.-G. and L.F.N.) who were blinded to the initial results. Statistical analysis was performed using 2 commercially available software packages: JMP 10.0 (SAS Institute, Inc., Cary, North Carolina) and MedCalc statistical software version 12 (MedCalc Software, Ostend, Belgium). All probability values were 2-sided; p values <0.05 were considered statistically significant.

TABLE 1 Patient Characteristics

	Patients			
	Total (N = 150)	Group 1 (n = 63)	Group 2 (n = 87)	p Value
Age, yrs	64 ± 9	65 ± 9	64 ± 9	0.27
Male	97 (65)	39 (61)	58 (66)	0.54
Height, cm	172.6 ± 10.0	170.7 ± 10.0	173.9 ± 10.0	0.04
Weight, kg	81.5 ± 17.3	78.8 ± 19.6	83.5 ± 15.2	0.10
BMI, kg/m^2	27.2 ± 4.6	26.8 ± 4.8	27.6 ± 4.5	0.31
NYHA functional class I–II/III–IV	142 (95)/8 (5)	57 (90)/6 (10)	85 (98)/2 (2)	0.05
Hypertension	36 (24)	9 (14)	27 (31)	0.02
Hyperlipidemia	54 (36)	17 (27)	37 (42)	0.05
Diabetes mellitus	16 (11)	8 (13)	8 (9)	0.49
Systolic blood pressure, mm Hg	118 ± 20	120 ± 22	117 ± 19	0.35
Diastolic blood pressure, mm Hg	70 ± 11	68 ± 12	71 ± 10	0.12
Heart rate, beats/min	71 ± 11	73 ± 11	70 ± 12	0.06
cTnT, μg/l	<0.01 (<0.01–0.04)	0.04 (0.02–0.11)	<0.01 (<0.01–<0.01)	<0.001
NT-proBNP, pg/l	727 (171–3,659)	4,318 (2,193–9,496)	233 (97–680)	<0.001
FLC-diff, mg/Dl	3 (0.6–8.0) (n = 149)	6 (2–31) (n = 62)	1 (0.4–5.0) (n = 87)	<0.001
Serum creatinine, mg/dl	1.2 (0.9–1.7)	1.6 (1.1–3.2)	1.1 (0.7–1.4)	<0.001
GFR, ml/min	60 ± 33	49 ± 32	76 ± 29	<0.001

Values are mean ± SD, n (%), or median (interquartile range).

cTnT = cardiac troponin T; BMI = body mass index; FLC-diff = free-light chain differential; GFR = glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

RESULTS

BASELINE CHARACTERISTICS, SEROLOGICAL BIOMARKERS, AND BASIC ECHOCARDIOGRAPHIC EVALUATION. A total of 150 patients were included in this study; 63 (42%) were in group 1 (with CA) and 87 (58%) were in group 2 (without CA). Compared with patients in group 2, patients in group 1 were more likely to be more symptomatic (total New York Heart Association functional class III/IV, 6 [10%] vs. 2 [2%]; p = 0.05) and have renal dysfunction

TABLE 2 Strain Data of Study Participants

	Patients		
	Total (N = 150)	Group 1 (n = 63)	Group 2 (n = 87)
GE software, %			
GLS	−15.23 ± 3.87	−12.85 ± 3.65	−16.95 ± 3.03
GLS basal segments	−12.69 ± 4.67	−9.72 ± 4.26	−14.85 ± 3.67
GLS mid-segments	−15.24 ± 3.90	−12.88 ± 3.75	−16.95 ± 3.02
GLS apical segments	−17.11 ± 4.39	−15.86 ± 5.08	−18.02 ± 3.59
VVI software, %			
GLS	−14.70 ± 3.33	−12.83 ± 3.33	−16.05 ± 2.61
GLS basal segments	−13.77 ± 4.00	−11.52 ± 3.69	−15.37 ± 3.43
GLS mid-segments	−14.43 ± 3.56	−12.51 ± 3.67	−15.81 ± 2.76
GLS apical segments	−16.50 ± 4.03	−15.27 ± 4.57	−17.40 ± 3.34

Values are mean ± SD. The p value for every row comparison is <0.001, except the apical segments of global longitudinal strain (GLS) General Electric (GE) and Velocity Vector Imaging (VVI) (p = 0.003 and p = 0.001, respectively).

(mean ± SD glomerular filtration rate, 49 ± 32 ml/min vs. 76 ± 29 ml/min; p < 0.001). As expected, they had higher cTnT, NT-proBNP, and FLC-diff levels. Table 1 summarizes baseline clinical data of the groups.

All patients had normal LVEF, with no difference between groups (mean ± SD LVEF, 64 ± 5% in group 1 vs. 65 ± 5% in group 2; p = 0.17). As expected, patients in group 1 had thicker walls (mean LV wall thickness, 15.0 ± 3.0 mm vs. 12.0 ± 2.2 mm in group 2; p < 0.001) and greater LV mass index (mean 147 ± 45 g/m^2 vs. 108 ± 31 g/m^2; p < 0.001). Compared with group 2, group 1 had lower mean early diastolic tissue Doppler velocity at septal mitral annulus (4.6 ± 1.9 vs. 5.7 ± 1.6; p < 0.001), an increased ratio of early wave of mitral inflow and early septal diastolic velocity of tissue Doppler ratio (21 ± 10 vs. 14 ± 6; p < 0.001), and larger left atrial volume index (43 ± 11 ml/m^2 vs. 33 ± 8 ml/m^2; p < 0.001). Online Table 1 displays additional data regarding echocardiographic findings.

STRAIN ANALYSIS AND REPRODUCIBILITY. Strain results are detailed in Table 2. Groups 1 and 2 displayed statistically significant differences regardless of the software used (p < 0.001). As wall thickness increased, GLS decreased (i.e., was less negative) according to both methods (p < 0.001). This response was observed for all segments, with relative apical sparing. A similar pattern was observed for both software platforms, with a remarkably strong basal-apical gradient (p < 0.001).

From global and segmental perspectives (base, mid-, and apical regions), similar longitudinal strain values were seen in each specific group comparison across vendor systems (strain GE group 1 vs. strain VVI group 1; strain GE group 2 vs. strain VVI group 2) (Table 2).

As the walls became thicker (group 1), similar values with no statistically significant difference between GLS_{GE} compared with GLS_{VVI} was seen (−12.83 ± 3.85 vs. −12.85 ± 3.33; p = 0.94). Group 1 yielded a stronger correlation than group 2 (R = 0.83 vs. R = 0.47; p < 0.001), as well as better agreement in CCC (0.83 [95% confidence interval (CI): 0.73 to 0.89] vs. 0.67

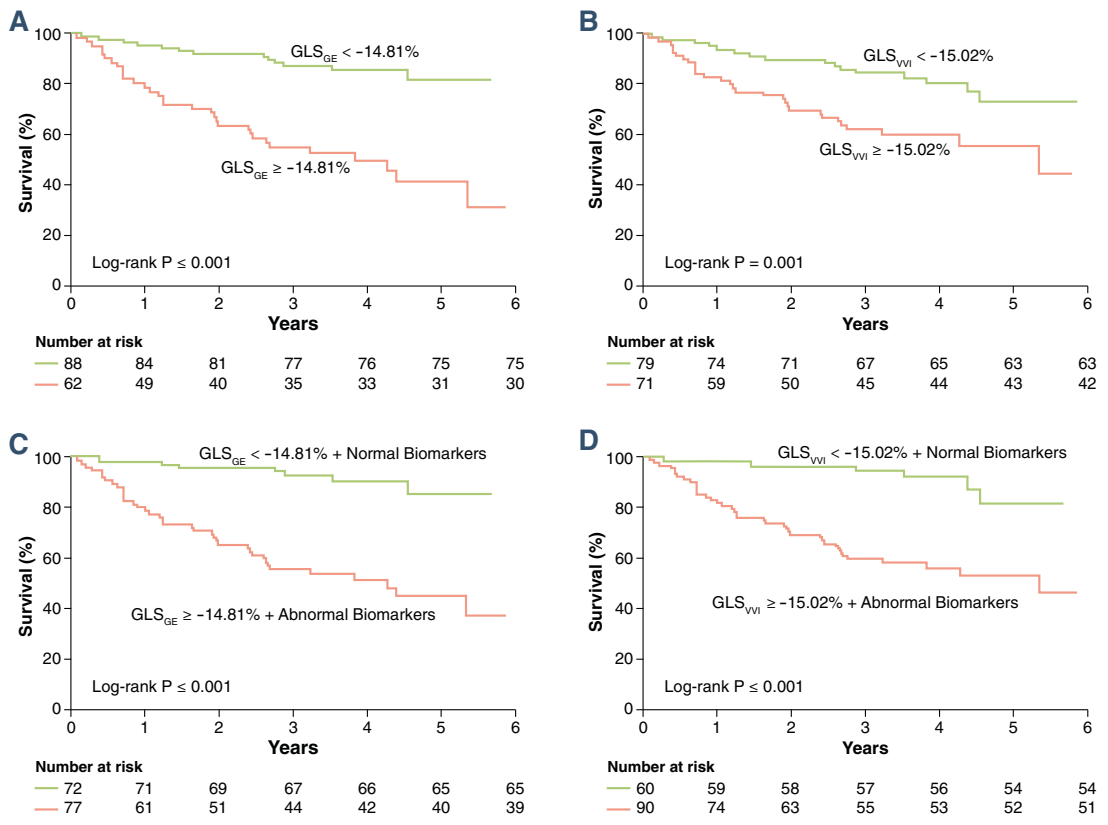
TABLE 3 Univariate and Multivariate Predictors of All-Cause Mortality Rate

	Univariate, HR (95% CI)	p Value	Multivariate HR (95% CI)*†‡	p Value†	Multivariate HR (95% CI)*†§	p Value†
Age, yrs	1.04 (1.01–1.08)	0.009	1.05 (1.01–1.10)	0.01	1.04 (1.01–1.09)	0.03
NYHA functional class I-II/III-IV	2.40 (0.83–5.57)	0.09	–	–	–	–
EF, %	0.97 (0.91–1.03)	0.36	–	–	–	–
DD grade	1.87 (1.31–2.73)	<0.001	1.12 (0.73–1.74)	0.59	1.11 (0.72–1.72)	0.63
Mean LVWT, mm	1.11 (1.01–1.20)	0.02	0.84 (0.69–1.01)	0.057	0.82 (0.66–1.01)	0.051
E/A ratio	1.23 (0.99–1.45)	0.05	–	–	–	–
DT, ms	0.99 (0.98–0.99)	0.04	–	–	–	–
e'_{sep}, cm/s	0.80 (0.67–0.96)	0.01	–	–	–	–
E/e'_{sep} ratio	1.02 (0.99–1.05)	0.22	–	–	–	–
LAVI, ml/m^2	1.03 (1.01–1.06)	0.01	–	–	–	–
GFR, ml/min	0.99 (0.98–0.99)	0.03	–	–	–	–
cTnT, µg/l‖	1.07 (1.04–1.10)	<0.001	1.05 (0.99–1.11)	0.053	1.04 (0.99–1.09)	0.10
Log NT-proBNP, pg/l	1.01 (1.01–1.02)	<0.001	1.22 (0.94–1.56)	0.12	1.38 (1.08–1.75)	0.01
FLC-diff, mg/dl	1.03 (1.01–1.04)	<0.001	1.02 (1.01–1.04)	<0.001	1.02 (1.01–1.04)	<0.001
$GLS_{GE} \geq -14.81$, %	4.71 (2.52–9.32)	<0.001	2.68 (1.07–7.13)	0.03	–	–
$GLS_{VVI} \geq -15.02$, %	2.57 (1.41–4.84)	0.001	–	–	2.44 (0.98–6.33)	0.055

*Adjusted for age, diastolic dysfunction (DD) grade, mean left ventricular wall thickness (LVWT), FLC-diff, cTnT, and Log NT-proBNP. †The dashes indicate data not applicable. ‡The main variable was GLS performed with Vivid E9 (GLS_{GE}) ≥ −14.81. §The main variable was GLS performed with VVI (GLS_{VVI}) ≥ −15.02. ‖Each incremental 0.01 µg/l in the all-cause mortality rate.

CI = confidence interval; DD = diastolic dysfunction; DT = deceleration time of mitral inflow; E/A = ratio of early and late diastolic waves of mitral inflow; E/e'_{sep} = ratio of early wave of mitral inflow and early septal diastolic velocity of tissue Doppler; EF = ejection fraction; e'_{sep} = early diastolic tissue Doppler velocity at septal mitral annulus; HR = hazard ratio; LAVI = left atrial volume index; NYHA = New York Heart Association; other abbreviations as in Tables 1 and 2.

FIGURE 1 Kaplan-Meier Plots of Time to All-Cause Mortality From the Overall Patient Population



(A) Global longitudinal strain performed by using GE software (GLS_{GE}). **(B)** Global longitudinal strain performed by using Velocity Vector Imaging software (GLS_{VVI}). **(C)** GLS_{GE} with normal and abnormal biomarkers. **(D)** GLS_{VVI} with normal and abnormal biomarkers. Normal biomarkers indicate N-terminal pro–B-type natriuretic peptide (NT-proBNP) <1,800 pg/l plus cardiac troponin T (cTnT) <0.025 μg/l plus free light chain differential (FLC-diff) <18 mg/dl; abnormal biomarkers indicate NT-proBNP ≥1,800 pg/l plus cTnT ≥0.025 μg/l plus FLC-diff ≥18 mg/dl.

[95% CI: 0.54 to 0.76]). Bland-Altman analysis revealed no bias in group 1 (group 1 mean, −0.02 ± 2.0 [p = 0.94]; group 2 mean, −0.8 ± 2.1 [p = 0.005]), and both groups had similar limits of agreement (−4.0 to 3.9 in group 1 vs. −4.9 to 3.3 in group 2; SD = 1.96).

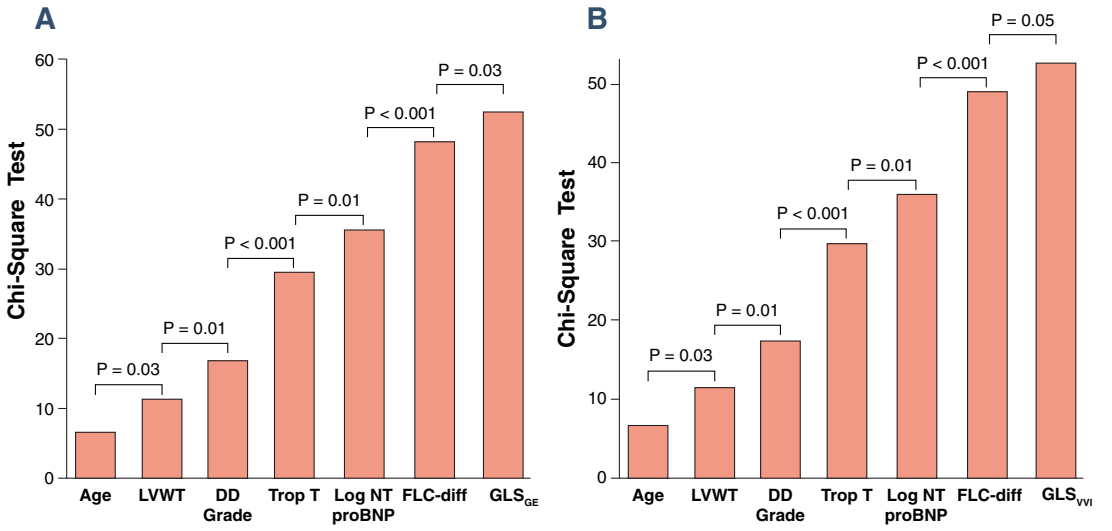
On comparison of GLS_{GE} and GLS_{VVI}, each software yielded similar results for prediction of CA (areas under the curve 0.82 and 0.77, respectively; p < 0.001 for both). For GLS_{GE}, the odds ratio was 1.45 (95% CI: 1.29 to 1.67; p < 0.001) and for GLS_{VVI}, the odds ratio was 1.44 (95% CI: 1.27 to 1.67; p < 0.001).

OUTCOME. Mean ± SD follow-up was 3.3 ± 1.5 years (median [interquartile range]: 3.4 [2.6 to 4.3] years) and was complete in 123 (82%) patients. Overall, there were 45 deaths (32 [51%] in group 1 and 13 [15%] in group 2; p < 0.001).

In univariate Cox regression analysis (Table 3), age, GLS_{GE} ≥−14.81, GLS_{VVI} ≥−15.02, diastolic dysfunction grade, mean LV wall thickness, early diastolic tissue Doppler velocity at septal mitral annulus, deceleration time, left atrial volume index, FLC-diff, log NT-proBNP, and cTnT were the univariate predictors of all-cause mortality. In the first multivariate model with GLS_{GE} ≥ −14.81 and after adjustment for age, diastolic dysfunction grade, LV wall thickness, FLC-diff, cTnT, and log NT-proBNP, GLS_{GE} ≥−14.81 (hazard ratio [HR]: 2.68; 95% CI: 1.07 to 7.13; p = 0.03), FLC-diff, and age were independent predictors of survival. In the second model with GLS_{VVI} ≥−15.02 and after the same adjustments, FLC-diff, log NT-proBNP, and age were associated with all-cause mortality. There was also a strong trend for GLS_{VVI} (HR: 2.44; 95% CI: 0.98 to 6.33; p = 0.055).

GLS_{GE} of −14.81% and GLS_{VVI} of −15.02% provided the best cutoff values to predict death (p < 0.001 and p = 0.001, respectively). As expected, patients with the most impaired GLS had the worst survival. By adding GLS, FLC-diff, NT-proBNP, and cTnT, powerful discriminatory segregation curves were seen for

FIGURE 2 Chi-Square Models Showing Incremental Predictive Information of GLS to Age, LVWT, DD Grade, cTnT, Log NT-proBNP, and FLC-diff



(A) GLS_{GE}. **(B)** GLS_{VVI}. Each model represents the sum of variables from the previous model. The final model contains age, left ventricular wall thickness (LVWT), diastolic dysfunction (DD) grade, cTnT, log NT-proBNP, FLC-diff, and GLS. Abbreviations as in Figure 1.

estimating survival ($p < 0.001$) (Figure 1). Comparing the nested log likelihood chi-square model to obtain a definite predictive power for the multivariate analysis, we found that the model containing GLS_{GE} and GLS_{VVI} added significant incremental value to age, LV wall thickness, diastolic dysfunction grade, cTnT, Log NT-proBNP, and FLC-diff (Figure 2).

For survival analysis limited to the group without cardiac involvement according to previously established criteria, GLS_{GE} and GLS_{VVI} both predicted overall mortality (GLS_{GE} HR: 1.23, 95% CI: 1.03 to 1.47 [$p = 0.02$]; GLS_{VVI} HR: 1.22, 95% CI: 1.01 to 1.49 [$p = 0.04$]). However, for survival analysis limited to those patients with suggestive CA, GLS_{GE} and GLS_{VVI} did not predict overall mortality (GLS_{GE} HR: 1.02, 95% CI: 0.93 to 1.13 [$p = 0.62$]; GLS_{VVI} HR: 1.03, 95% CI: 0.92 to 1.14 [$p = 0.59$]). Survival curves according to groups are shown in Figure 3.

FEASIBILITY AND VARIABILITY. The 2D-STE analyses with GE and VVI were feasible in all 2,700 segments evaluated. For intraobserver variability, Bland-Altman plots showed strong agreement with no bias (mean ± SD difference, -0.3 ± 1.3; $p = 0.35$) and narrower limits (2.2 to −2.9; 1.96 × SD). The CCC was 0.94 (95% CI: 0.83 to 0.98). For the interobserver variability, Bland-Altman analysis showed strong agreement and minimal bias (mean difference, -1.0 ± 1.0; $p = 0.002$) and narrower limits (1.0 to −3.0; SD, 1.96). The CCC was 0.92 (95% CI: 0.81 to 0.97).

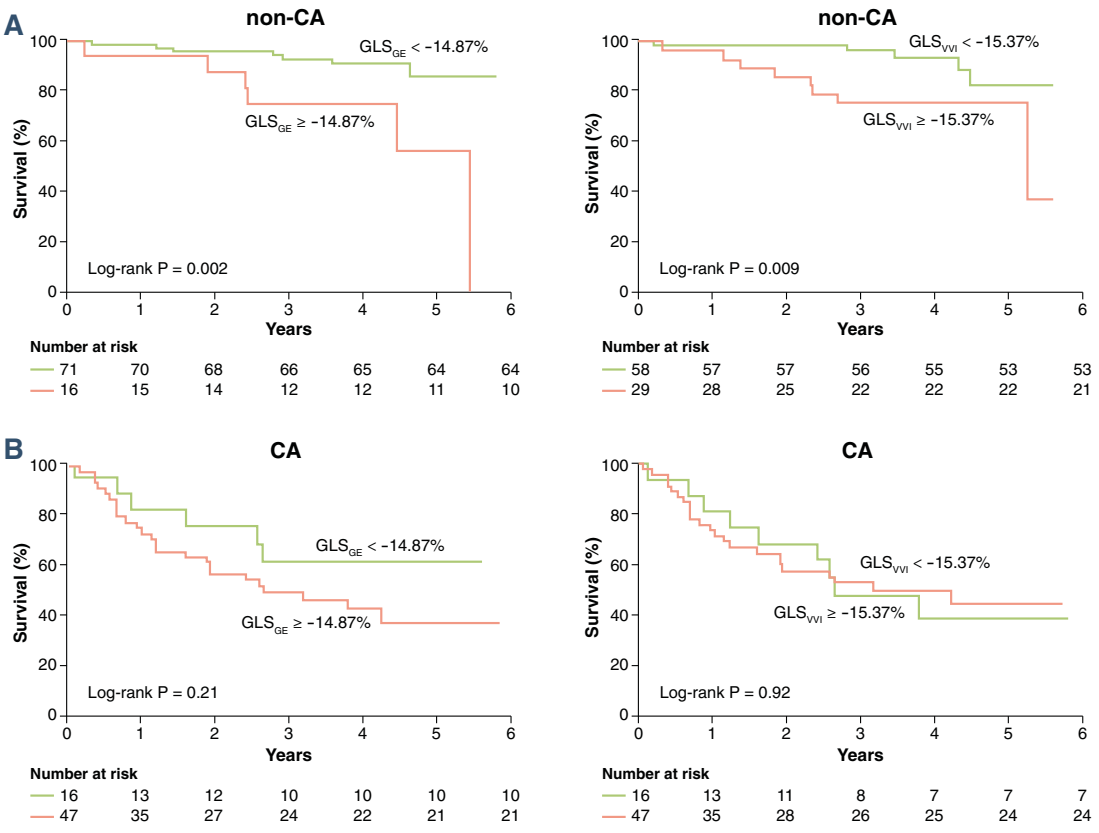
DISCUSSION

To our knowledge, this study is the largest that includes patients with CA and preserved EF and compares established serological biomarkers and two 2D-STE tracking software systems for outcome. Our main findings were as follows: 1) GLS_{GE} and GLS_{VVI} predicted all-cause mortality and provide additional prognostic information for all-cause mortality over established clinical, echocardiographic, and serological markers; 2) GLS_{GE} and GLS_{VVI} have prognostic value in patients with no evidence of CA according to previously established criteria; 3) a high degree of agreement exists between the 2 software methods in AL amyloidosis; and 4) the best correlation and agreement between the software methods were recorded in patients with clinical and echocardiographic findings suggestive of CA.

AL AMYLOIDOSIS OUTCOME. Cardiac involvement is a critical finding for patients with AL (17,20,21). In the present study, 2D-STE values were lower in AL amyloidosis patients with preserved EF and suggestive CA and were related to a poor outcome (Figure 1). Importantly, the technique provided greater prognostic information in patients without CA at the early stages of disease compared with the subset of patients with suggestive signs of cardiac involvement (Figure 3).

Preliminary studies have suggested the additional value of strain imaging for predicting outcome in

FIGURE 3 Kaplan-Meier Plots of Time to All-Cause Mortality



(A) GLS$_{GE}$ and GLS$_{VVI}$ obtained from patients without cardiac involvement. **(B)** GLS$_{GE}$ and GLS$_{VVI}$ obtained from patients with cardiac involvement. CA = cardiac amyloidosis; other abbreviations as in Figure 1.

patients with AL. Koyama and Falk (6) reported strain differences between cardiac and noncardiac involvement with tissue Doppler imaging-derived strain, but this cohort had patients with reduced EF. Similar to our finding, the investigators reported poorer outcome in patients with cardiac involvement (with or without heart failure); however, the poorest prognosis was in patients with CA, low EF, and evidence of congestive heart failure. Our study, by comparison, is characterized only by patients with normal EF. Similarly, Buss et al. (7) used 2D-STE in a mixed cohort of EF subjects and showed that this technique was an independent predictor of all-cause mortality. In their study, 2D-STE provided incremental value beyond the standard clinical, serological, and echocardiographic parameters. Recently, Quarta et al. (8) observed by using 2D-STE the prognostic significance of strain in patients with AL and familial amyloidosis. These observations underscore the potential benefit of strain for predicting outcome.

The emphasis of the present study was to show the incremental value of 2D-STE strain imaging in conjunction with the current prognostic staging system in patients with AL amyloidosis and preserved EF in early stages of the disease. This study found that in a population with preserved EF of AL amyloidosis, strain was compromised despite preserved EF. GLS was comparable between the 2 vendors utilized and provided incremental value when used with established prognostic methods (13-16). We believe that in addition to providing cutoff values for 2 commercially available systems, we recorded 2 different patient profiles. First, patients with AL amyloidosis who had normal EF and no evidence suggestive of cardiac involvement displayed less attenuated strain values and better outcomes. Second, patients with AL amyloidosis who had normal EF, increased LV wall thickness, serological markers, and other signs suggestive of CA had lower GLS values and worse survival. Importantly, GLS demonstrated predictive value in patients without CA according to previously established criteria. This observation suggests that the technique may be more valuable for those with early

stages of disease (i.e., without cardiac involvement), thereby having potentially important clinical implications due to detection of early cardiac involvement. Incorporation of GLS into the current staging system for patients at diagnosis may improve risk stratification and aid clinical decision-making.

2D-STE TECHNIQUES. 2D-STE was able to detect subclinical systolic dysfunction not apparent through conventional echocardiographic indexes. As the walls became thicker, strain decreased with both software methods. Patients with amyloidosis usually present with greater impairment in strain values compared with other cardiomyopathies with the same degree of increased wall thickness, such as hypertensive heart disease (22,23) and hypertrophic cardiomyopathy (24). In addition, the apical strain values were preserved in patients in whom cardiac involvement was suggested, which has been reported previously (8,25). Interestingly, this basal-to-apical gradient was observed with both software packages in our study and was more pronounced in patients with increased wall thickness.

SOFTWARE VARIABILITY. Comparing platforms by using a neutral imaging format, Bansal et al. (26) obtained images of patients with known or suspected ischemic heart disease using the Vivid 7 GE ultrasound system and validated GLS using GE and VVI software packages with harmonic magnetic resonance imaging. Similar to our findings, GLS was less negative according to VVI than GE. These findings were also reported by Biaggi et al. (11), who compared EchoPAC with VVI software in healthy patients.

In the present study, we confirmed that 2 commercially available systems are comparable. Agreement improved as wall thickness increased, with no bias. Even though we found good agreement, there is a lack of cross-platform standardization and absence of vendor neutrality that may lead to the inter-manufacturer variability (27). We therefore advise that once strain analysis is performed in a patient, the same software should to be used for that patient's follow-up.

STUDY LIMITATIONS. The sample size was small, with relatively few events, and larger studies are required to confirm our observations. Criteria for cardiac involvement may be considered present when there is echocardiographic evidence of amyloidosis in a patient with positive noncardiac biopsy results, according to the consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis (17). However, we also added biomarkers to further define CA diagnosis. We suggest that adding 2D-STE may improve the noninvasive diagnostic yield, although future studies in amyloid patients with documented cardiac involvement according to results of endomyocardial biopsy will be required for confirmation. Some patients in the CA group also had coexisting hypertension, which may be a potential confounder of increased wall thickness, but this characteristic corrected in the multivariate model, and GLS remained a significant predictor of outcome.

CONCLUSIONS

GLS with 2D-STE is reproducible and can be used as a prognostic marker in patients with AL amyloidosis and preserved LVEF. GLS has shown predictive value in AL amyloidosis patients without other evidence to support the diagnosis of CA. This finding suggests that the technique may be most valuable for patients with early stages of cardiac involvement. Incorporation of GLS into the echocardiographic examination of patients with AL amyloidosis improves the risk stratification for survival.

ACKNOWLEDGMENT The authors thank Dr. Lyle J. Olson for his contribution and suggestions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study underscores the potential benefit of strain imaging for predicting outcome in patients with AL. GLS predicted all-cause mortality in patients with AL amyloidosis and preserved LVEF with additional prognostic information compared with established clinical, echocardiographic, and serological methods. Importantly, this technique demonstrated predictive value in patients without CA according to previously established criteria. Incorporation of GLS into the current staging system for AL amyloidosis may improve risk stratification and aid in clinical decision-making.

TRANSLATIONAL OUTLOOK: Traditionally, LVEF has been the method of choice to evaluate systolic dysfunction. Newer imaging techniques, such as 2D-STE–derived strain, can better assess myocardial mechanics. This technique may play an important role in AL patients without CA at early stages of the disease. The documentation of cardiac involvement by using endomyocardial biopsy results remains a limitation, and additional studies using GLS for patients with AL and biopsy-proven CA should address this issue.

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KEY WORDS amyloid, cardiac amyloidosis, cardiomyopathy, echocardiography, mortality

APPENDIX For a supplemental table, please see the online version of this article.

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