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Ratio of interventricular septal thickness to global longitudinal strain accurately identifies cardiac amyloidosis

Louie Cao ,[1] Gloria J Hong,[1] Michael Abiragi,[1] Jonathan Le,[1] P Ryan Tacon,[1] I-Min Chiu,[1] Jignesh Patel ,[2] Lily K Stern,[1] Chathuri Daluwatte,[3] David Ouyang,[1] Piero Ricchiuto[3]

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[1]Cedars-Sinai Medical Center, Los Angeles, California, USA
[2]Cedars-Sinai Medical Center, Beverly Hills, California, USA
[3]Alexion Pharmaceuticals Inc, Boston, Massachusetts, USA

Correspondence to
Dr Piero Ricchiuto; piero.ricchiuto@alexion.com

ABSTRACT

Objectives Conventional transthoracic echocardiographic measurements like global longitudinal strain (GLS) have shown promise in distinguishing cardiac amyloidosis (CA), but with limited specificity. We investigated the performance of common echo measurements, GLS, and their combinations in discriminating CA from an undifferentiated cohort with increased left ventricular wall thickness.

Methods We conducted a retrospective single-centre case–control study of 876 echos from 232 patients with CA and 1325 echos from 279 patients who underwent pyrophosphate scintigraphy but had CA definitively ruled out. Common echo measurements were collected and additional GLS measurements were performed post hoc. We reported discrimination performance with the area under the receiver operating characteristic curve (AUC) and associated sensitivity, specificity and positive predictive value at the optimal threshold.

Results We found that the ratio of end-diastolic interventricular septal thickness (IVSd) to GLS had the highest performance in differentiating CA with an AUC of 0.812. At the optimal threshold of >0.15, IVSd/GLS had a sensitivity of 0.70 and specificity of 0.80 for CA. Other measurements and ratios, including the ratio of left ventricular ejection fraction to GLS (AUC 0.682), had lower performance when evaluated against a suspicious control cohort with increased left ventricular wall thickness.

Conclusion If validated in prospective multi-centre studies, the routine measurement of IVSd/GLS can assist with earlier diagnosis of CA, resulting in earlier initiation of treatment in this underserved population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Individual echo measurements, such as ejection fraction or global longitudinal strain (GLS), have limited ability to identify cardiac amyloidosis. Recent studies using combinations of measurements have shown more promise.

WHAT THIS STUDY ADDS

⇒ This is the first study to identify the ratio of interventricular septal thickness (IVSd) over GLS (IVSd/GLS) as a marker that distinguishes cardiac amyloidosis from mimickers in a high-suspicion population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ When evaluating a patient with suspected cardiac amyloidosis, the use of IVSd/GLS may result in earlier identification, referral and treatment.

INTRODUCTION

Cardiac amyloidosis (CA) is caused by the deposition of misfolded proteins in the myocardium, most prevalently transthyretin (ATTR) or immunoglobulin light chains (AL). Regardless of the aetiology, CA leads to increased left ventricular wall thickness and restrictive cardiomyopathy with heart failure symptoms. Common echocardiographic measurements fail to precisely discriminate CA from other aetiologies of increased left ventricular wall thickness, and additional testing is needed to confirm the diagnosis. CA is often diagnosed late or underdiagnosed, given its prevalence in well-evaluated select populations.[1–3] This limits the opportunity for patients to receive recently approved and developing therapies that can improve outcomes in CA.[4 5]

Recent research has focused on methods that can assist with the early identification of CA. Transthoracic echocardiography (TTE) is a common initial test when evaluating patients with cardiovascular symptoms. Typical TTE features that are signatures of CA include increased left ventricular wall thickness, normal or small left ventricular cavity, preserved left ventricular ejection fraction (LVEF) and diastolic dysfunction.[6] However, many of these features are also commonly found in hypertensive heart disease or hypertrophic cardiomyopathy (HCM).[7 8] Individually, these measurements have limited ability to identify CA with specificity, resulting in hesitation to highlight concern for CA by an interpreting cardiologist.

The use of speckle-tracking echocardiography to measure left ventricular global longitudinal strain (GLS) has been increasingly adopted as a tool for identifying CA. Compared with LVEF, it is typically thought to be more sensitive for left ventricular dysfunction, especially in settings such as CA in which LVEF is typically normal or mildly reduced.[9] CA is commonly said to have an apical sparing pattern, representing decreased basal strain but preserved apical strain. However, when used to distinguish CA from a population who had clinical suspicion for CA but negative testing, the diagnostic accuracy of apical sparing decreased significantly.[8] One study found the LVEF/GLS ratio to perform well when differentiating CA from a control group consisting of patients with HCM and hypertensive heart disease.[10] Another study used the ratio of left ventricular mass index/GLS to differentiate CA and Fabry's disease,[11] but both ratios had limited generalisability when used in an undifferentiated population.[8]

In this study, we evaluated the performance of common echocardiographic parameters, including GLS, and their combinations in distinguishing CA from an undifferentiated control group with high clinical suspicion for CA that received negative confirmatory testing. We sought to evaluate how common heuristics can help increase the clinical suspicion with enough conviction to perform more confirmatory testing.

METHODS

Study design

We conducted a retrospective single-centre case–control study at Cedars-Sinai Medical Center in Los Angeles, California. A total of 511 patients were identified as either having CA or were ruled out after having undergone a full work-up. 232 CA patients were identified via the Cardiac Amyloid Registry Study[12] and were diagnosed with ATTR or AL amyloidosis using pyrophosphate scintigraphy, monoclonal gammopathy testing, genetic testing and/or tissue biopsy. The negative control cohort consisted of 279 patients who underwent pyrophosphate scintigraphy but ultimately had ATTR CA ruled out with grade 0 pyrophosphate scintigraphy. AL CA was ruled out in this group with normal serum free light chains and negative serum and urine immunofixation electrophoresis or were ruled out by a haematologist. TTEs were excluded from analysis if patients were post-heart transplant, had a left ventricular assist device or were on extracorporeal membrane oxygenation. This study was approved by the Cedars-Sinai Institutional Review Board (Study 1049). Patients were not involved in the design and conduct of this study.

Data collection

Clinical variables and echocardiographic data were extracted from the electronic medical record (Epic Systems, Verona, Wisconsin, USA) as well as the echocardiography structured reporting software (ScImage Picom, Los Altos, California, USA). All available TTEs were performed between 20 January 2001 and 31 May 2022. A total of 876 pre-transplant TTEs from the CA cohort and 1325 pre-transplant TTEs from the negative cohort were identified for analysis. Common echo measurements that were collected included LVEF, end-diastolic interventricular septal thickness (IVSd), mitral A wave velocity and end-diastolic left ventricular internal dimension (LVIDd). All echo measurements were made in accordance with the guidelines of the American Society of Echocardiography.[13] None of the measurements were indexed to sex or body surface area. In addition, we also combined measurements by calculating the ratio between two measurements, including IVSd to GLS, IVSd to mitral A wave velocity, LVIDd to GLS, LVIDd to mitral A wave velocity and LVEF to GLS. Missing measurements were excluded from the analysis.

GLS was measured using Tomtec (TOMTEC Imaging Systems, Unterschleißheim, Germany) by five clinicians (LC, GJH, MA, JL, PT) blinded to the subject's study group. Using each patient's three most recent pre-transplant TTEs when available, an apical four-chamber, apical two-chamber and apical three-chamber view from each TTE was uploaded to Tomtec. Endocardial borders were automatically labelled by Tomtec and manually adjusted by the clinicians, after which automated GLS measurement was performed over one cardiac cycle. GLS measurement was not performed if one or more apical views were unavailable or foreshortened, the endocardial border was poorly visualised, or if GLS could not be measured by the software. GLS measurements were reported as absolute values.

Statistical analysis

Continuous variables were reported using median (IQR) and categorical variables were reported with number (percentage). Performance of TTE measurements, GLS measurements and ratios in discriminating CA was evaluated using area under the receiver operating characteristic curve (AUC). For clinical utility, we defined the optimal cut-off threshold for predicting CA using the Youden index and reported corresponding sensitivity, specificity, positive predictive value and negative predictive value. Statistical analysis was performed in Python (Python Software Foundation, Beaverton, Oregon, USA).

RESULTS

Demographics and clinical characteristics of the study cohort are shown in table 1. Compared with the control group, patients in the CA group were older (77 years vs 75 years, p=0.002), more likely to be male (82.3% vs 65.9%, p<0.001) and had a lower body mass index (25.8 vs 26.4, p=0.003). The CA group included 60 (25.9%) patients with AL amyloidosis and 170 (73.3%) patients with ATTR amyloidosis, which is consistent with the higher prevalence of ATTR in general.[14] The ATTR subjects included 110 (64.7%) with wild-type transthyretin and

Table 1 Demographics and clinical characteristics of study cohort

	Cardiac amyloidosis N=232 patients	Control N=279 patients	P value
Age, years, median (IQR)	77 (70–83)	75 (68–83)	0.002
Male sex, n (%)	191 (82.3%)	184 (65.9%)	<0.001
Ethnicity (%)			
White	156 (67.2%)	184 (65.9%)	0.76
Black	50 (21.6%)	66 (23.7%)	0.57
Asian	12 (5.2%)	11 (3.9%)	0.51
Other	14 (6.0%)	18 (6.5%)	0.77
BMI, kg/m^2, median (IQR)	25.8 (23.4–28.3)	26.4 (22.9–30.8)	0.003
Hypertension, n (%)	115 (49.6%)	197 (70.6%)	<0.001
Diabetes mellitus, n (%)	30 (12.9%)	89 (31.9%)	<0.001
Coronary artery disease, n (%)	88 (37.9%)	118 (42.3%)	0.38
Atrial fibrillation, n (%)	90 (38.8%)	96 (34.4%)	0.24
Chronic kidney disease, n (%)	93 (40.1%)	116 (41.6%)	0.73
Heart transplantation	50 (21.6%)	2 (0.7%)	<0.001
Amyloidosis type, n (%)			
AL	60 (25.9%)		
ATTR	170 (73.3%)		
Wild-type	110 (64.7%)		
Variant	29 (17.1%)		
Unknown	31 (18.2%)		
Unknown	2 (0.8%)		
	N=876 TTEs	N=1325 TTEs	
Aortic stenosis, n (%)			
Mild	19 (2.1%)	55 (4.1%)	0.006
Moderate	16 (1.8%)	42 (3.1%)	0.041
Severe	15 (1.7%)	42 (3.1%)	0.033
History of aortic valve replacement, n (%)	93 (10.6%)	193 (14.6%)	0.007

AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; BMI, body mass index; TTE, transthoracic echo.

29 (17.1%) with genetic mutations in transthyretin. The control group had a greater prevalence of hypertension (70.6% vs 49.6%, p<0.001), diabetes mellitus (31.9% vs 12.9%, p<0.001) and aortic stenosis at all severities, with a higher rate of aortic valve replacement (14.6% vs 10.6%, p=0.007). There were no differences between the CA and control groups in ethnicity or history of coronary artery disease, atrial fibrillation or chronic kidney disease.

We evaluated the performance of common echocardiographic measurements to discriminate between CA and patients ruled out for CA (table 2). On pre-transplant TTE, both groups had increased end-diastolic left ventricular posterior wall thickness, although this was more pronounced in the CA group (1.6 cm vs 1.2 cm, p<0.001). The CA group had lower LVEF (54.0% vs 58.0%, p<0.001), lower LVIDd (4.3 cm vs 4.6 cm, p<0.001), greater IVSd (1.6 cm vs 1.2 cm, p<0.001), lower mitral A wave velocity (42.0 cm/s vs 77.5 cm/s, p<0.001) and reduced GLS (8.7% vs 13.3%, p<0.001). There was no difference in the presence of atrial fibrillation during GLS measurements.

The ratio of IVSd/GLS had the highest performance with an AUC of 0.812 (see figure 1 for the receiver operating characteristic curve). Using a threshold of >0.15, it had a sensitivity of 0.70 and a specificity of 0.80 for the detection of CA. We found that IVSd/GLS was best at distinguishing variant ATTR (AUC of 0.888), followed by wild type ATTR (AUC of 0.833), followed by AL (AUC of 0.701) (figure 2). Another high-performing variable was the ratio of IVSd/mitral A wave velocity (AUC of 0.810), with sensitivity of 0.72 and specificity of 0.76 at cut-off threshold >0.03. IVSd (AUC of 0.781), mitral A wave velocity (AUC of 0.757) and GLS (AUC of 0.728) had moderate performance in discriminating CA from the negative cohort. Other measurements, such as LVEF/GLS ratio, did not perform as well in our study (table 3).

Table 2 Echocardiographic and global longitudinal strain measurements

	Cardiac amyloidosis	Control	P value
LVEF (%), median (IQR), N=2068	54.0 (40.0–62.0)	58.0 (46.0–65.0)	<0.001
LVIDd (cm), median (IQR), N=1988	4.3 (3.8–4.8)	4.6 (4.1–5.2)	<0.001
LVPWd (cm), median (IQR), N=1955	1.6 (1.3–1.8)	1.2 (1.0–1.4)	<0.001
IVSd (cm), median (IQR), N=1994	1.6 (1.4–1.9)	1.2 (1.0–1.4)	<0.001
Mitral A wave velocity (cm/s), median (IQR), N=1358	42.0 (32.4–64.0)	77.5 (50.1–104.0)	<0.001
GLS (%), median (IQR), N=817	8.7 (6.7–12.1)	13.3 (9.5–16.8)	<0.001
Presence of atrial fibrillation during GLS measurement, n (%)	162 (18.5%)	235 (17.7%)	0.65

GLS, global longitudinal strain; IVSd, end-diastolic interventricular septum thickness; LVEF, left ventricular ejection fraction; LVIDd, end-diastolic left ventricular internal diameter; LVPWd, end-diastolic left ventricular posterior wall thickness.

DISCUSSION

In this study, we compared a group of CA patients with a control group of patients who had echocardiographic features highly suspicious for CA but eventually were ruled out for the disease with negative pyrophosphate scintigraphy and monoclonal gammopathy workup. Our deliberate choice of control group stands in contrast to prior studies. By choosing patients with high enough clinical suspicion of CA to warrant further testing, this comparison best represents the clinical use case of patients in consideration for CA and hopefully results in the most representative performance metrics. We evaluated the ability of conventional TTE measurements, GLS and their combinations to distinguish CA in these conditions.

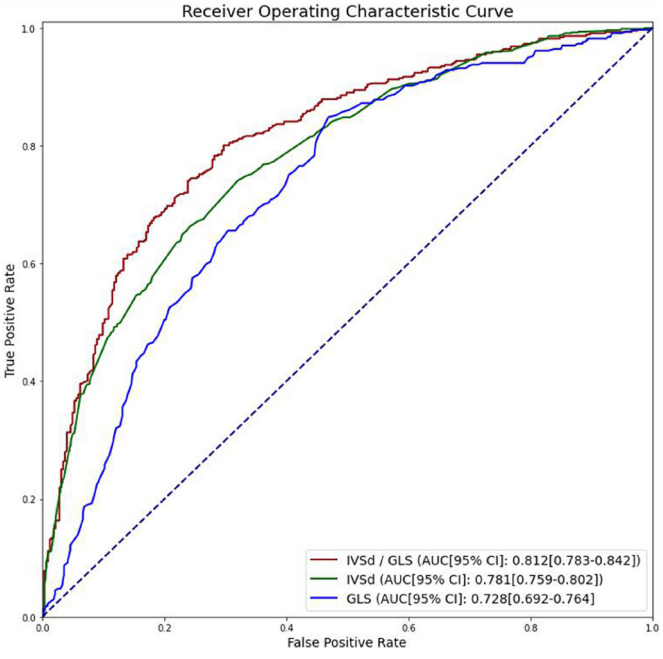

Figure 1 Performance of interventricular septal thickness over global longitudinal strain for identifying cardiac amyloidosis. Red: receiver operating characteristic curve for IVSd/GLS. Green: receiver operating characteristic curve for IVSd. Blue: receiver operating characteristic curve for GLS. AUC, area under the receiver operating characteristic curve; GLS, global longitudinal strain; IVSd, end-diastolic interventricular septal thickness.

Our study is the first to find IVSd/GLS to have high diagnostic accuracy with an AUC of 0.812 and optimal cut-off of >0.15. We additionally found that IVSd/GLS had an even stronger performance in the ATTR subtype, likely due to increased IVSd in ATTR hearts compared with AL.[15] IVSd performed well in general, with the top three analysed variables being IVSd/GLS, IVSd/mitral A wave velocity and IVSd alone. With an AUC of 0.810, the performance of IVSd/mitral A wave velocity is likely indistinguishable from IVSd/GLS in a real-world setting. LVEF/GLS, which has been previously found to perform well, was less able to distinguish CA in our study.

Increased wall thickness is a hallmark of CA, and our study confirms increased IVSd is enriched for CA; however, it alone might be insufficient to exclude confounders.[16] Increased IVSd was previously incorporated into guidelines for the diagnosis of CA,[17] as CA with normal IVSd is exceedingly rare.[18] However, our study demonstrates a significant overlap in IVSd measurements between CA patients and our control population of patients with negative pyrophosphate scintigraphy, as demonstrated by its sensitivity of 0.66 and specificity of 0.76. Decreased GLS is also a well-documented feature of CA;[19] however, our results, as well as other studies, suggest GLS is sensitive but not specific in identifying CA patients.[8] LVEF/GLS has been previously reported to distinguish CA from control groups consisting of HCM and hypertensive heart disease.[10] In our cohort, as well as other validation studies,[8 20] LVEF/GLS performed poorly, suggesting worse performance in a more general at-risk population. Because we used a suspicion-defined control group, abnormal IVSd and GLS were present in many patients around the time of pyrophosphate scintigraphy, and this study highlights their modest discriminatory performance.

Prior research has shown the effectiveness of specifically suggesting CA in TTE reports for increasing CA testing.[21] Thus, flagging patients with abnormal IVSd/GLS can result in earlier evaluation and higher suspicion for CA. Multiparametric scores have also been shown to be effective for diagnosing CA[22]; the incorporation of IVSd/GLS and similar combinations may enhance the performance of these scores. Furthermore, deep learning approaches have been suggested that combine visible measurement

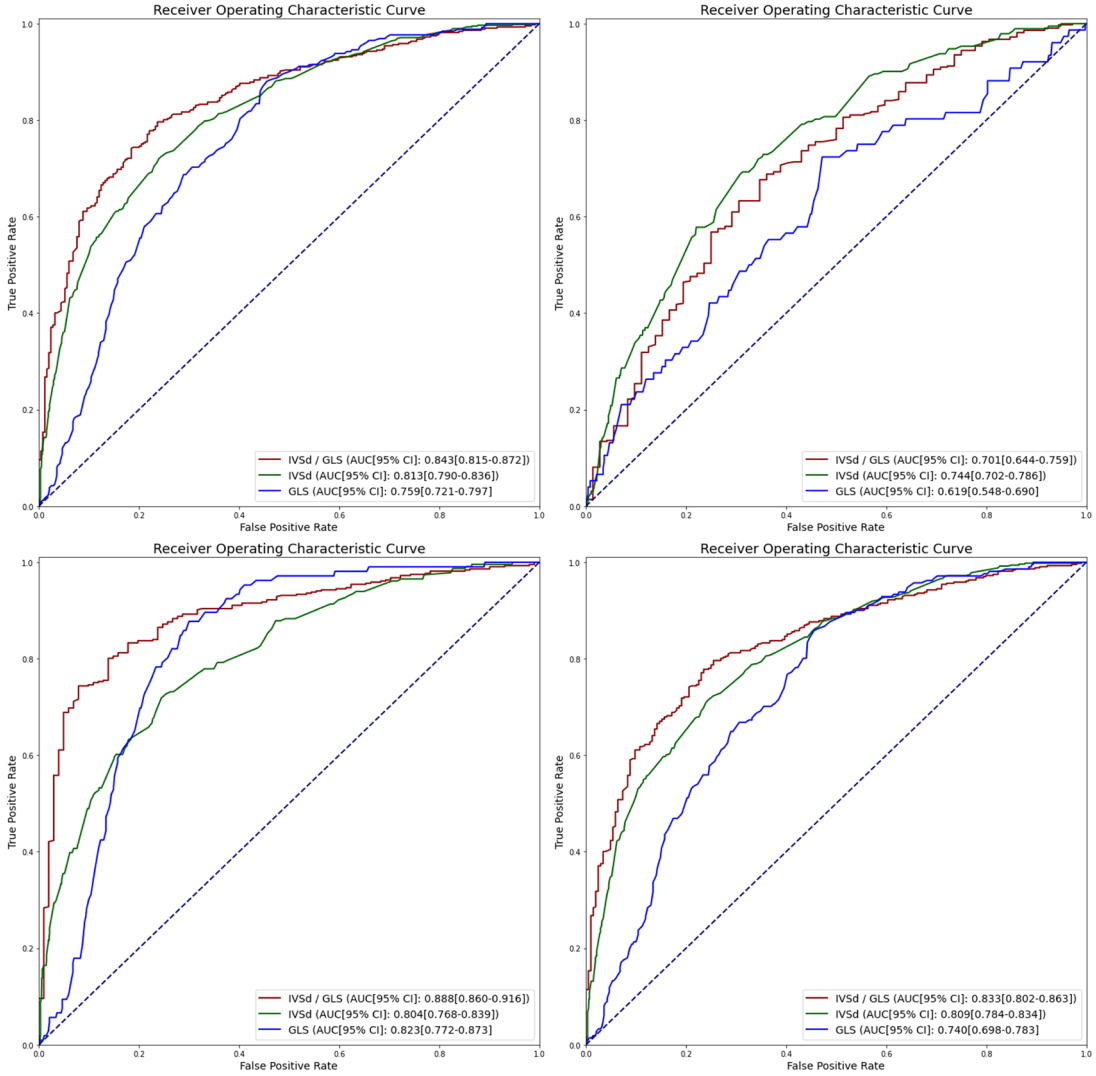

Figure 2 Performance of interventricular septal thickness over global longitudinal strain for identifying subtypes of cardiac amyloidosis. Red: receiver operating characteristic curve for IVSd/GLS. Green: receiver operating characteristic curve for IVSd. Blue: receiver operating characteristic curve for GLS. Top left: ATTR amyloidosis. Top right: AL amyloidosis. Bottom left: variant ATTR. Bottom right: wild-type ATTR. AL, light chain; ATTR, transthyretin; AUC, area under the receiver operating characteristic curve; GLS, global longitudinal strain; IVSd, end-diastolic interventricular septal thickness.

findings as well as features that are more difficult to quantify, such as texture and motion.[23] As artificial intelligence techniques for automated TTE interpretation and GLS measurement are increasingly adopted,[24] their use in these types of studies can significantly increase the number of TTEs analysed, thus providing more accurate results. Clinical use of automated GLS measurement would facilitate the incorporation of IVSd/GLS into pre-existing workflows in a wide range of practice settings.

Limitations

Our study has a few limitations worth discussing. This retrospective single-centre study warrants future prospective evaluation prior to clinical use. Studies should also assess the impact of other types of controls in evaluating metric performance. Intervendor variability exists in all measurements, including GLS,[25] so accurate assessment of IVSd/GLS is needed for the strongest performance. There is intraobserver variability in GLS[25] that we sought to minimise by repeated measures across different studies from the same patient. Interobserver variability in GLS measurements should be taken into account as well, although it is typically lower than in other TTE measurements.[26] Although GLS has been increasingly adopted, the portion of TTEs that undergo strain measurement remains small, which limits the applicability of IVSd/GLS.

CONCLUSION

In this study comparing CA patients with patients who were referred for pyrophosphate scintigraphy but had CA ruled out, we demonstrate that IVSd/GLS can be used to identify CA in a population with high clinical suspicion for CA. This ratio has superior performance compared with individual echocardiographic measurements as well as other ratios that are already abnormal in patients at

Table 3 Test characteristics of selected echocardiographic variables and ratios

	AUC (95% CI)	Optimal threshold	Sensitivity	Specificity	PPV	NPV
IVSd/GLS	0.812 (0.783 to 0.842)	>0.15	0.70	0.80	0.72	0.79
IVSd/mitral A wave velocity	0.810 (0.784 to 0.835)	>0.03	0.72	0.76	0.65	0.82
IVSd	0.781 (0.759 to 0.802)	>1.45	0.66	0.76	0.73	0.46
Mitral A wave velocity	0.757 (0.732 to 0.782)	< 62.2	0.74	0.65	0.55	0.81
GLS	0.728 (0.692 to 0.764)	< 13.0	0.85	0.53	0.56	0.83
LVIDd/Mitral A wave Velocity	0.708 (0.680 to 0.739)	>0.08	0.66	0.68	0.56	0.77
LVEF/GLS	0.682 (0.645 to 0.718)	>4.52	0.63	0.68	0.56	0.71
LVIDd/GLS	0.659 (0.621 to 0.697)	>0.38	0.69	0.59	0.55	0.73
LVIDd	0.633 (0.608 to 0.657)	< 4.60	0.70	0.50	0.49	0.71
LVEF	0.579 (0.554 to 0.604)	< 54.1	0.51	0.64	0.49	0.66

AUC, area under the receiver operating characteristic curve; GLS, global longitudinal strain; IVSd, end-diastolic interventricular septum thickness; LVEF, left ventricular ejection fraction; LVIDd, end-diastolic left ventricular internal diameter; LVPWd, end-diastolic left ventricular posterior wall thickness; NPV, negative predictive value; PPV, positive predictive value.

high suspicion for CA. If validated in future studies, the incorporation of this easily obtainable measurement can assist with earlier diagnosis of CA, resulting in reduced morbidity and mortality.

X Louie Cao @LouieCaoMD and Lily K Stern @LilySternMD

Contributors JP, LKS, CD, DO and PR were responsible for conception and study design. LC, GJH, MA, JL, PRT and IC were responsible for acquisition of data. LC, IC and DO were responsible for analysis and interpretation of the data and for drafting the manuscript. All authors revised the manuscript for content, gave final approval for publication and agreed to be accountable for all aspects of the work's accuracy and integrity. PR is the guarantor for the overall content.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Cedars-Sinai IRB (Study 1049). Participants gave informed consent to participate in the study before taking part.

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ORCID iDs
Louie Cao http://orcid.org/0000-0002-9680-5801
Jignesh Patel http://orcid.org/0000-0003-0618-6750

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