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ORIGINAL RESEARCH

Echocardiographic Markers of Early Left Ventricular Dysfunction in Asymptomatic Aortic Regurgitation

Is It Time to Change the Guidelines?

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ABSTRACT

BACKGROUND The ideal timing for surgery in asymptomatic chronic aortic regurgitation (AR) remains unclear. New thresholds for left ventricular ejection fraction (LVEF), left ventricular (LV) indexed end-systolic volume (iESV), and global longitudinal strain (GLS) have been associated with mortality in these patients. These represent markers of early LV dysfunction.

OBJECTIVES The authors sought to assess the relationship between these markers (LVEF <60%, iESV ≥45 mL/m^2, and GLS worse than −15%) and mortality, comparing them to Class I/IIa American College of Cardiology/American Heart Association guideline recommendations and absence of any of these.

METHODS A total of 673 asymptomatic patients with chronic clinically significant (≥ moderate-severe) AR between 2004 and 2019 at a single referral center were retrospectively analyzed. The primary study outcome was all-cause mortality.

RESULTS Mean age was 57 ± 17 years, 97 (14%) were female, 293 (45%) had hypertension, and 273 (41%) had an abnormal number of valve cusps. Aortic valve replacement was performed in 281 (48%) patients, and 69 (10%) died while under surveillance (without aortic valve replacement). LVEF <60% was present in 296 (44%) patients, 122 (25%) of 482 had GLS worse than −15%, and 261 (39%) had iESV ≥45 mL/m^2. Mortality under surveillance was highest when Class I/IIa recommendations were present (HR: 4.22; 95% CI: 2.15-8.29), followed by the presence of 1 or more markers of early LV dysfunction (HR: 2.18; 95% CI: 1.21-3.92); no markers was used as the reference (all, $P < 0.05$). LVEF showed the strongest association with mortality, statistically slightly better than GLS and iESV. In the absence of Class I/IIa recommendations, 1 marker of early LV dysfunction was associated with higher, although not statistically significant, mortality compared with no markers ($P = 0.063$), followed by 2 markers; highest mortality was when all 3 markers were present (HR: 5.46 [95% CI: 2.51-11.90]; $P < 0.001$).

CONCLUSIONS Patients with asymptomatic clinically significant chronic AR incur a survival penalty when Class I/IIa guideline recommendations are attained. In patients without these recommendations, at least 2 markers of early LV dysfunction identify those with higher mortality risk who may benefit from early surgery.
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Aortic regurgitation (AR) is associated with left ventricular (LV) pressure and volume overload, which is typically well tolerated for years, sometimes decades, before onset of myocardial dysfunction.[1] The current ACC (American College of Cardiology)/AHA (American Heart Association) valve practice guideline recommends aortic valve surgery when symptoms appear, when there is onset of LV systolic dysfunction (left ventricular ejection fraction [LVEF] <55%), or significant LV dilation (end-diastolic dimension >65 mm, or end-systolic dimension [ESD] >50 mm) (>25 mm/m^2).[2] These thresholds or surgical recommendations are based on studies from the 1990s to the early 2000s.[1,3-6] During that time, surgical mortality was higher, the available replacement valves were of older generation, and primary surgical repair was in its infancy. With advancements in surgical techniques, including the option for valve repair in selected patients, newer generation valve prostheses, and novel ways to assess LV size and function, it is fundamental to reevaluate these guideline recommendations.[7] Recent studies have shown that LV size assessment by volumes, rather than linear dimensions, more accurately captures LV remodeling, which is not symmetrical in AR.[8-12] Moreover, recent studies have revealed that mortality begins to increase at a lower threshold of ESD (>20 mm/m^2) compared with the currently recommended threshold of 25 mm/m^2.[13,14] Similarly, echocardiographically derived global longitudinal strain (GLS) can detect subclinical myocardial dysfunction, which is associated with worse outcomes in patients with chronic severe AR.[15] A higher ejection fraction (EF) threshold of 60% has also shown a stronger association with outcomes compared with the current threshold of 55% in the guidelines.[10,16,17] The prevalence of these novel markers for the onset of LV myocardial dysfunction and their relative importance is not known. Therefore, we aimed to evaluate the prevalence of these potential markers of early LV dysfunction, their relative importance in association with outcomes, and the prognostic significance of the presence of >1 of these markers in a large contemporary cohort of patients with asymptomatic chronic severe AR.

METHODS

PATIENT POPULATION. This study received approval from the local institutional review board, and only patients who had given prior consent to participate in research were included. We enrolled asymptomatic consecutive patients with moderate to severe AR and severe AR identified retrospectively, diagnosed through comprehensive transthoracic echocardiography between January 2004 and April 2019, including patients from our previous work.[10,15] Patients with acute AR due to active endocarditis or dissection, moderate or more left-sided valve diseases (aortic stenosis, mitral stenosis, and mitral regurgitation), prior aortic or mitral valve surgery, ischemic cardiomyopathy, prior myocardial infarction, prior coronary artery bypass grafting, hypertrophic cardiomyopathy, LV assist devices, or cardiac amyloidosis were excluded from the study. Detailed information about the cohort has been previously described.[8,10,15]

Patients underwent comprehensive cardiology and/or cardiothoracic surgical evaluations within 30 days of the echocardiogram. If multiple echocardiograms were available, we included the first one that showed greater than moderate AR. The decision for aortic valve replacement (AVR) was made based on available guideline recommendations and involved shared decision-making among the patient, primary cardiologist, and/or cardiac surgeon. Baseline characteristics at the time of the echocardiogram, including demographic data, clinical information such as comorbidities, Charlson Comorbidity Index, NYHA functional class, and recent laboratory results, were extracted from the electronic medical records.

ECHOCARDIOGRAPHY. Data obtained from echocardiograms included measurements of LV dimensions and LVEF, as well as assessments of AR severity (vena contracta, effective regurgitant orifice area, and regurgitant volume using the proximal isovelocity surface area method or continuity equation).[18] Other data collected included assessment of diastolic flow reversal in the descending thoracic/abdominal aorta, aorta dimensions, LV early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, and measurements of right ventricular size and systolic function. The severity of AR was assessed by using regurgitant volume and regurgitant orifice area when available (85%). In cases when quantification was not feasible, the severity was determined using a combination of semi-quantitative (eg, vena contracta, jet area, descending thoracic aorta velocity time integral), and qualitative (holodiastolic reversals in the abdominal aorta) parameters. Moderate to severe AR was defined by regurgitant volume 45 to 60 mL, and severe AR was defined by regurgitant volume ≥60 mL.

ABBREVIATIONS AND ACRONYMS

AIC = Akaike information criterion

AR = aortic regurgitation

AVR = aortic valve replacement

EF = ejection fraction

ESD = end-systolic dimension

GLS = global longitudinal strain

iESV = indexed end-systolic volume

LV = left ventricular

LVEF = left ventricular ejection fraction

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TABLE 1 Baseline characteristics

	No Markers (n = 252)	Class I/IIa Guideline Recommendations (n = 137)	Markers of Early LV Dysfunction (n = 284)	Total (N = 673)	*P* Value
Age, y	59.6 ± 16.4	58.3 ± 17.5	54.8 ± 17.8	57.3 ± 17.4	0.0044[a]
Female	40 (15.9%)	19 (13.9%)	38 (13.4%)	97 (14.4%)	0.6998[b]
Body mass index, kg/m^2	27.4 ± 8.5	26.8 ± 4.7	27.6 ± 4.8	27.4 ± 6.4	0.3612[a]
Body surface area, m^2	2.0 ± 0.2	2.0 ± 0.3	2.0 ± 0.2	2.0 ± 0.2	0.4293[a]
Systolic blood pressure, mm Hg	129 ± 19	134 ± 20	130 ± 19	131 ± 19	0.0345[a]
Diastolic blood pressure, mm Hg	65 ± 11	65 ± 14	65 ± 13	65 ± 13	0.9112[a]
Diabetes	23 (9.5)	12 (8.9)	29 (10.4)	64 (9.8)	0.8798[b]
Hypertension	116 (48.1)	59 (43.7)	118 (42.3)	293 (44.7)	0.3953[b]
Chronic kidney disease	7 (2.8)	10 (7.3)	12 (4.2)	29 (4.3)	0.1103[b]
Lung disease	19 (7.9)	10 (7.4)	26 (9.3)	55 (8.4)	0.7548[b]
Hyperlipidemia	111 (46.1)	55 (40.7)	88 (31.5)	254 (38.8)	0.0028[b]
Severity weighted sum of diseases	1.6 ± 2.2	1.4 ± 2.0	1.3 ± 2.0	1.4 ± 2.1	0.1892[a]
Abnormal number of cusps	98 (39.2)	49 (36.0)	126 (44.4)	273 (40.7)	0.2185[b]
Ejection fraction, %	65 ± 4	49 ± 6	60 ± 4	60 ± 7	<0.0001[a]
Biplane ejection fraction, %	63 ± 5	51 ± 8	58 ± 5	58 ± 7	<0.0001[a]
End-diastolic dimension, mm	58 ± 5	63 ± 7	61 ± 6	60 ± 6	<0.0001[a]
Indexed end-diastolic dimension, mm/m^2	29 ± 3	32 ± 5	30 ± 3	30 ± 4	<0.0001[a]
End systolic dimension, mm	36 ± 4	46 ± 6	40 ± 4	40 ± 6	<0.0001[a]
Indexed end-systolic dimension, mm/m^2	18 ± 2	24 ± 4	20 ± 2	20 ± 3	<0.0001[a]
End diastolic volume, mL	180 ± 44	234 ± 73	225 ± 67	210 ± 65	<0.0001[a]
Indexed end-diastolic volume, mL/m^2	89 ± 18	118 ± 33	111 ± 31	104 ± 30	<0.0001[a]
End-systolic volume, mL	66 ± 18	115 ± 39	96 ± 31	89 ± 34	<0.0001[a]
iESV, mL/m^2	33 ± 7	57 ± 19	47 ± 15	44 ± 16	<0.0001[a]
AR severity					0.0002[b]
Moderate to severe	137 (54.4)	48 (35.0)	113 (39.8)	298 (44.3)	
Severe	115 (45.6)	89 (65.0)	171 (60.2)	375 (55.7)	
AR regurgitant volume, mL (n = 571)	69 ± 25	71.8 ± 23.87	74.5 ± 29.53	71.8 ± 26.84	0.0927[a]
E/e′ (n = 616)	11 ± 4	17 ± 67	10 ± 4	12 ± 30	0.4973[a]
RVSP, mm Hg (n = 500)	30 ± 8	32 ± 11	30 ± 8	30 ± 9	0.1022[a]
Mid ascending aorta dimension, mm (n = 603)	41 ± 7	41 ± 7	41 ± 7	41 ± 7	0.8434[a]
Sinus of Valsalva dimension, mm (n = 627)	40 ± 6	42 ± 6	41 ± 6	41 ± 6	0.0337[a]
LVEF <60%	0 (0.0)	135 (98.5)	161 (56.7)	296 (44.0)	<.0001[b]
Biplane LVEF <60%	67 (26.6)	125 (91.2)	189 (66.5)	381 (56.6)	<.0001[b]
GLS ≤15% (n = 482)	0 (0.0)	51 (56.7)	71 (35.3)	122 (25.3)	<.0001[b]
iESV ≥45 mL/m^2	0 (0.0)	101 (73.7)	160 (56.3)	261 (38.8)	<.0001[b]
iESD ≥20 mm/m^2	54 (22.0)	113 (84.3)	130 (46.6)	297 (45.1)	<.0001[b]
E/e′ ≥15 (n = 616)	33 (13.8)	22 (18.5)	33 (12.8)	88 (14.3)	0.3277[b]

Values are mean ± SD or n (%). [a]Kruskal-Wallis *P* value. [b]The chi-square *P* value.

AR = aortic regurgitation; E/e′ = early diastolic mitral inflow to tissue Doppler velocity; GLS = global longitudinal strain; iESD = indexed end-systolic dimension; iESV = indexed end-systolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; RVSP = right ventricular systolic pressure.

The LV biplane volumes were manually traced in all the studies by a Level III staff echocardiographer blinded to patient outcomes (V.A.). GLS in all patients was analyzed offline by using vendor-independent analytic software (AutoStrain LV Analysis, LOT 31.0, TomTec Imaging Systems) as previously described in a publication from our group.[15] Visual verification ensured reliable tracking of all myocardial segments throughout the cardiac cycle; however, limited manual adjustments were made only in cases in which the automatically generated region of interest, particularly at the mitral annular plane, was suboptimal.

OUTCOMES. The primary outcome was survival under medical surveillance (without AVR) and, among the patients with chronic severe asymptomatic AR, those with echocardiographic markers of early LV dysfunction were compared with those with ACC/AHA Class I and IIa guideline recommendations for surgery. Current Class I guideline recommendation in asymptomatic patients is LVEF <55%, and Class IIa

guideline recommendations are LV end-systolic diameter >50 mm or indexed LV ESD >25 mm/m^2. The following echocardiographic markers of early LV dysfunction were evaluated: LVEF <60%, indexed LV end-systolic volume ≥45 mL/m^2, and GLS worse than −15%; these were chosen based on recent data showing risk of mortality when these markers were present.[8-12,15-17] The endpoint studied was all-cause mortality. The relative importance of different markers of early LV dysfunction and the impact of multiple markers were also evaluated.

Vital status information was retrieved by using the Mayo Clinic records and Accurint (LexisNexis Risk Solutions), a Web-based resource combining multiple national sources (queried on May 31, 2019). Patients not known to be deceased were censored at the date of last follow-up.

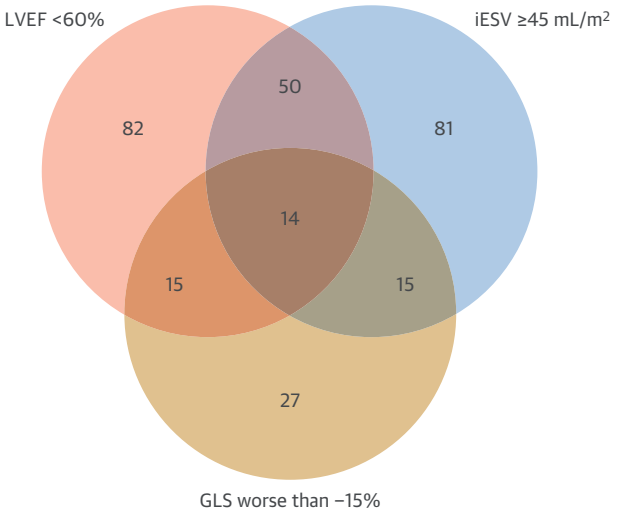
STATISTICAL ANALYSIS. Baseline characteristics are presented as mean ± SD or median (IQR) for continuous variables and frequencies and percentages for categoric variables. Normality was not formally tested but was instead assessed based on visual inspection of histograms and quantile-quantile plots. Comparisons between groups were made by using the chi-square test for categorical variables and analysis of variance or Kruskal-Wallis test for continuous variables. The survival curves were constructed by using the Kaplan-Meier method in which patients were censored at AVR or last follow-up in the absence of death or AVR. Survival curves were adjusted for age and sex using a direct adjustment method. Cox proportional hazards models were used to estimate HRs and 95% CIs attached to surgical indication groups. Multivariable Cox regression adjusting for age and sex was used to evaluate the impact of Class I and IIa guideline recommendations and markers of early LV dysfunction on mortality under medical surveillance. The Akaike information criterion (AIC) was calculated to evaluate the relative importance of these different markers. In addition, survival C-statistics of different multivariable models were calculated to assess the discriminatory ability of different surgical triggers (guideline recommendations and markers of early LV dysfunction).

All analyses were performed by using SAS version 9.4 (SAS Institute, Inc), and 2-sided values of $P < 0.05$ were considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. The study included 673 asymptomatic patients with chronic ≥moderate to severe AR who met the inclusion criteria and were part of previous publications.[8,10,15] Baseline characteristics are described in Table 1. The mean age of the cohort was 57.3 ± 17.4 years, 97 (14.4%) were female, 293 (44.7%) had hypertension, and 273 (40.7%) had an abnormal number of aortic valve cusps. The LVEF was <60% in 296 (44%) patients, GLS was worse than −15% in 122 (25.3%) patients, indexed end-systolic volume (iESV) was ≥45 mL/m^2 in 261 (38.8%) patients, and indexed ESD was ≥20 mm/m^2 in 297 (45.1%) patients. One of these markers of early LV dysfunction (LVEF <60%, GLS worse than −15%, or iESV ≥45 mL/m^2) was present in 170 (25.3%) patients, 2 (22.0%) in 148 patients, and 3 (16.9%) in 114 patients. A total of 188 (27.9%) patients had none of these markers of early LV dysfunction.

FIGURE 1 Prevalence of Echocardiographic Markers of Early Left Ventricular Dysfunction in AR



Venn diagram showing the 3 markers of early left ventricular dysfunction: left ventricular ejection fraction (LVEF) <60%, indexed end-systolic volume (iESV) >45 mL/m^2, and global longitudinal strain (GLS) worse than −15% and their overlap. AR = aortic regurgitation.

ASSOCIATION OF CLASS I AND IIa GUIDELINE RECOMMENDATIONS AND MARKERS OF EARLY LV DYSFUNCTION WITH ALL-CAUSE MORTALITY. During a median follow up of 2.5 years (IQR: 0.28-6.7 years), 69 patients died and 281 underwent AVR. Class I or IIa guideline recommendations for surgery were present in only 137 (20.4%) patients, whereas 284 (42.2%) patients exhibited at least 1 of the 3 markers of early LV dysfunction. The most common markers of early LV dysfunction were reduced LVEF <60%, observed in 161 (56.7%) patients, followed by iESV ≥45 mL/m^2 in 160 (56.3%) patients and GLS worse than −15% in 71 (35.3%) patients. When

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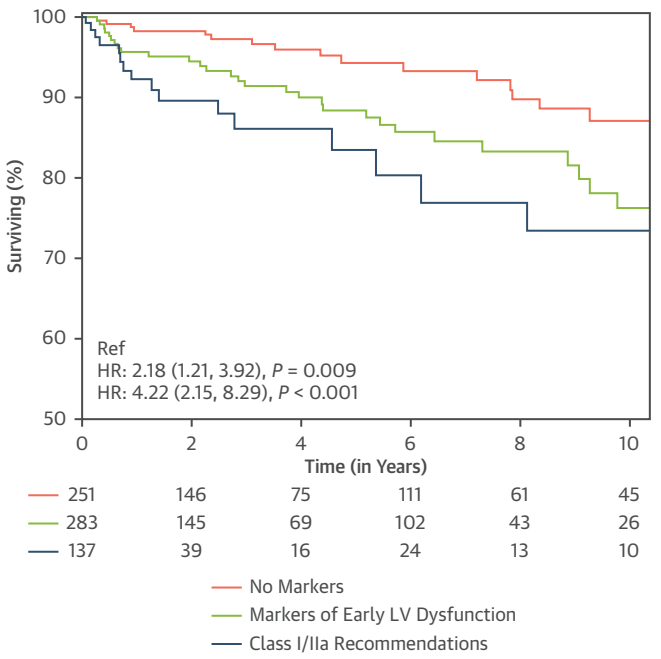
FIGURE 2 Kaplan-Meier Curves for All-Cause Mortality Stratified by Markers of Early LV Dysfunction and Guideline-Based Recommendations



Kaplan-Meier survival curves for all-cause mortality under medical management by presence of surgical triggers in adjusted models (adjusted for age, sex, and comorbidities [Charlson Comorbidity Index]). Patients with markers of early left ventricular (LV) dysfunction had higher all-cause mortality, compared with no markers, but the mortality was highest when Class I/IIa guideline recommendations for surgery were present. HRs were 12.18 (95% CI: 1.21-3.92; $P = 0.009$) and 4.22 (95% CI: 2.15-8.29; $P < 0.001$), respectively.

plotted in a Venn diagram, the overlap between these markers of early LV dysfunction shows that 14 (4.9%) patients had all 3 markers present and 80 (28.2%) had 2 markers present (Figure 1).

Kaplan-Meier curves adjusted for age, sex, and comorbidities (Charlson Comorbidity Index) revealed increased mortality in patients with Class I or IIa guideline recommendations (HR: 4.22 [95% CI: 2.15-8.29]; $P < 0.001$) and patients with markers of early LV dysfunction (HR: 2.18 [95% CI: 1.21-3.92]; $P = 0.009$) compared with patients free of any of these (Figure 2, Central Illustration). When the 3 markers of early LV dysfunction (LVEF <60%, iESV ≥45 mL/m^2, and GLS worse than −15%) were assessed, the presence of any 1 marker was associated with higher mortality, although not statistically significant, compared with no markers (HR: 1.84 [95% CI: 0.97-3.50]; $P = 0.063$), followed by presence of 2 markers (HR: 3.39 [95% CI: 1.72-6.68]; $P < 0.001$); highest mortality was noted when all 3 markers were present (HR: 5.46 [95% CI: 2.51-11.90]; $P < 0.001$) (Figure 3). The 5-year Kaplan-Meier estimates for AVR were 33% (27%-39%) in the group with no triggers, 59% (47%-68%) in the group with Class I/IIa guideline recommendations, and 44% (37%-50%) in the group with markers of early LV dysfunction ($P < 0.001$) (Supplemental Figure 1).

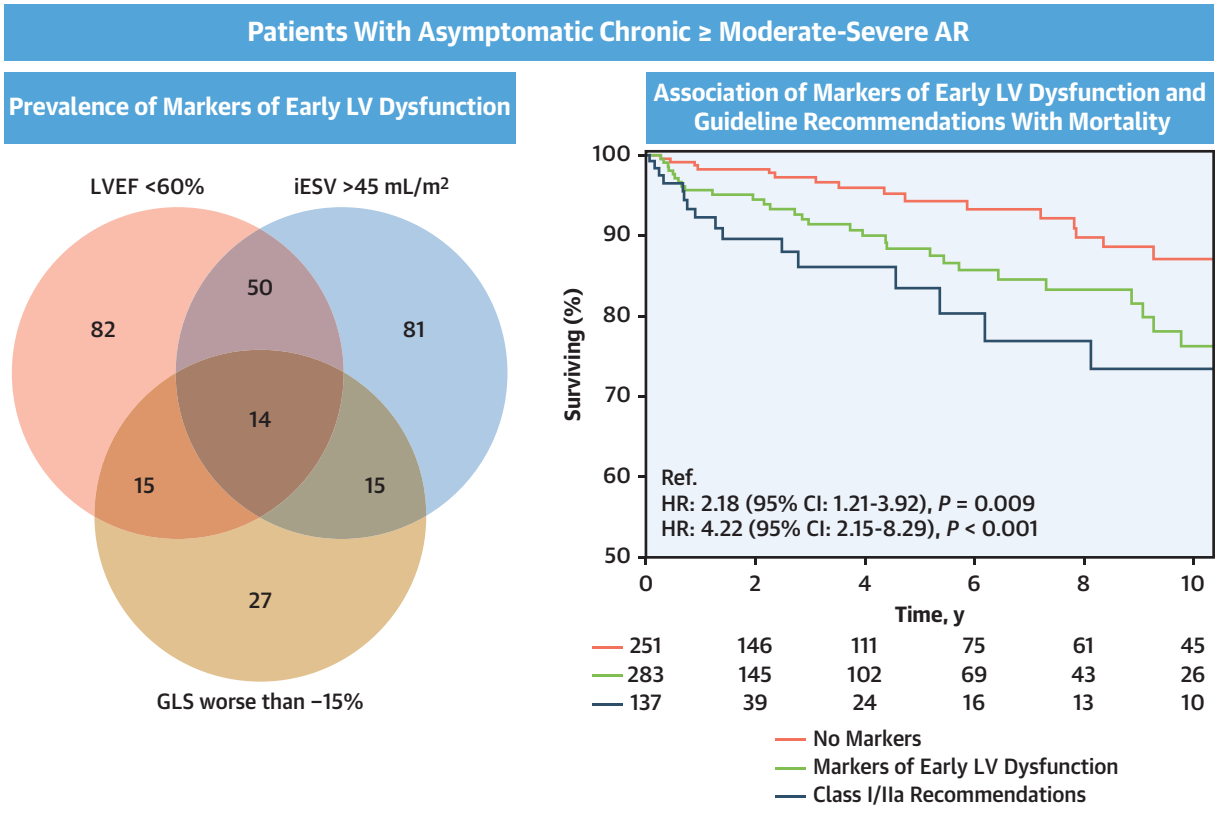
The age, sex, and comorbidities-adjusted models (Table 2) censored to AVR and adjusted for AVR as a time-dependent variable evaluated the various markers of early LV dysfunction to assess their incremental role against the baseline clinical model. The C-statistic of the baseline model censored to AVR was 0.796 (95% CI: 0.741-0.850) and increased with the addition of LVEF <60% to 0.833 (95% CI: 0.785-0.880) (HR: 2.54 [95% CI: 1.55-4.17]; $P < 0.001$). LVEF <60% had the lowest AIC, suggesting that it provided the best fitting model for association with mortality compared with other markers of early LV dysfunction. Similarly, iESV ≥45 mL/m^2 (HR: 2.27 [95% CI: 1.34-3.84]; $P = 0.002$) and GLS worse than −15% (HR: 2.25 [95% CI: 1.36-3.73]; $P = 0.009$) increased the C-statistic and had a lower AIC. Similar results were obtained for the model adjusted for age, sex, comorbidities, and time-dependent AVR.

DISCUSSION

The current study, which included 673 asymptomatic patients with chronic asymptomatic clinically significant AR, yielded several important findings. First, the presence of Class I/IIa guideline recommendations for AVR was associated with higher all-cause mortality compared with age and sex-matched echocardiographic markers of early LV dysfunction. Second, mortality rates increased significantly with the number of markers of early LV dysfunction present. Third, 3 markers of early LV dysfunction were identified that showed the strongest association and incremental value for predicting mortality: LVEF <60%, iESV ≥45 mL/m^2, and GLS worse than −15%. Lastly, only 137 (20.4%) patients had Class I or IIa guideline recommendations for surgery, whereas 284 (42.2%) patients exhibited 1 of the 3 markers of early LV dysfunction. This finding suggests that early LV dysfunction, not captured by the current Class I and IIa guideline recommendations, is often present in asymptomatic patients with chronic severe AR.

ECHOCARDIOGRAPHIC MARKERS OF ONSET OF MYOCARDIAL DYSFUNCTION. LV size assessment. The recommended thresholds for LV size are based on linear dimensions (performed using M-mode

CENTRAL ILLUSTRATION **Prevalence and Impact of Echocardiographic Markers of Early LV Dysfunction in AR**



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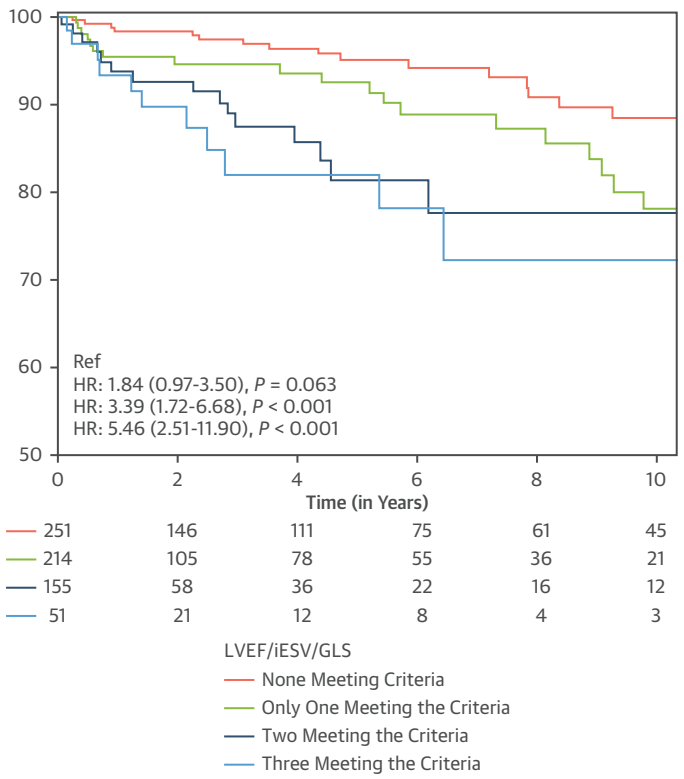
The figure shows the prevalence of echocardiographic markers of early left ventricular dysfunction, left ventricular ejection fraction (LVEF) <60%, indexed end-systolic volume (iESV) ≥45 mL/m^2, and global longitudinal strain (GLS) worse than −15%, and their overlap (left panel) and association of these markers with all-cause mortality compared with Class I and IIa guideline recommendations for aortic valve replacement and no triggers (right panel). The most common markers of early LV dysfunction were reduced LVEF <60%, observed in 161 (56.7%) patients, followed by iESV ≥45 mL/m^2 in 160 (56.3%) patients and GLS worse than −15% in 71 (35.3%) patients. When plotted in a Venn diagram, the overlap between these markers of early LV dysfunction is shown in Figure 1; 14 (4.9%) patients had all 3 markers present and 80 (28.2%) had 2 markers present (left panel). Patients with markers of early LV dysfunction had higher all-cause mortality, compared with no markers, but the mortality was highest when Class I/IIa guideline recommendations for surgery were present. HRs were 2.18 (95% CI: 1.21-3.92; $P = 0.009$) and 4.22 (95% CI: 2.15-8.29, $P < 0.001$), respectively. AR = aortic regurgitation; LV = left ventricular; Ref. = Reference.

echocardiography in the initial studies including patients with severe AR[1,4-6]), which are no longer recommended for assessing LV size according to American Society of Echocardiography chamber quantification guidelines.[19] Recent studies in patients with chronic severe AR have shown that LV enlargement is better assessed by LV volumes indexed to body surface area, and these measurements have a stronger association with outcomes such as symptoms and mortality.[8,11,20,21] Approximately one-third of patients may have enlarged LV volumes while having linear dimensions below the surgery threshold set by guideline cutoffs.[8]

LV function assessment. The guideline-recommended LV function or EF cutoffs, which were recently increased from 50% to 55%, are based on smaller, older studies. Recent data suggest that the onset of myocardial dysfunction occurs at a lower threshold of 60%, which is a better predictor of outcomes.[10,16,17] GLS, which evaluates speckle tracking and can detect early myocardial dysfunction, has also been studied recently and shown to be associated with mortality at a threshold below −15%.[15,22]

Other markers, such as late gadolinium enhancement by cardiac magnetic resonance imaging (which assesses myocardial fibrosis), have been shown to be

FIGURE 3 Kaplan-Meier Curves for All-Cause Mortality by Presence of Markers of Early LV Dysfunction



Kaplan-Meier survival curves for all-cause mortality under medical management by presence of 1 or more markers of early LV dysfunction (ejection fraction [EF] <60%, indexed ESV >45 mL/m^2, and GLS worse than −15%) in adjusted models (adjusted for age, sex, and comorbidities [Charlson Comorbidity Index]). Patients with 1 marker of early LV dysfunction present had higher (but not statistically significant) all-cause mortality, compared with no markers, but the mortality was higher and statistically significant when 2 or all 3 markers were present. There was an increase in mortality with increasing numbers of markers of early LV dysfunction. HRs were 1.84 (95% CI: 0.97-3.50; $P = 0.063$), for 1 marker of early LV dysfunction present, 3.39 (95% CI: 1.72-6.68; $P < 0.001$) for 2 markers present, and 5.46 (95% CI: 2.51-11.90; $P < 0.001$) when all 3 markers were present. Abbreviations as in Figures 1 and 2.

associated with all-cause mortality in patients without other indications for aortic valve surgery.[23]

In the current study, we observed that among asymptomatic patients with chronic severe AR, the Class I or IIa guideline recommendations were present in 20% of patients, whereas 42% of patients exhibited 1 of the 3 markers of early LV dysfunction that showed a significant association with mortality. This finding suggests that a substantial proportion of patients who may be suitable candidates for early surgery, particularly at valve centers with surgical expertise, are likely not being identified. Recent studies reported that nearly one-third of patients may have enlarged volumes (iESV ≥45 mL/m^2) despite having dimensions below the intervention threshold.[8] However, our study encompassed all echocardiographic markers of early LV dysfunction that exhibit a statistically significant association with mortality, resulting in a higher percentage of 42%.

To our knowledge, the current study is the first to show the relative importance of these variables and the impact of presence of >1 marker of early LV dysfunction on all-cause mortality. LVEF <60% exhibited the most statistically significant association with mortality, slightly stronger than iESV ≥45 mL/m^2 and GLS worse than −15%, which showed a similar level of association. GLS has the ability to identify subclinical myocardial dysfunction before a decline in EF. The statistical superiority of LVEF over GLS in this study is likely due to missing GLS data in 28% of patients and not related to the threshold, as both GLS worse than −15% and −19% had similar AIC values. The measurement of EF is readily obtainable in the majority of patients, and our findings emphasize the importance of accurately estimating EF using the biplane volumetric method whenever feasible. The biplane method of disc summation also allows for the calculation of ESV, which, when indexed to body surface area, serves as another marker of early LV dysfunction that can be estimated using this method.[19] The estimation of GLS may require a learning curve and may be challenging or impossible to assess if the LV endocardium is poorly visualized, if an ultrasound enhancing agent is used, or in cases of rhythm abnormalities.[24] We also observed a similar limitation in our cohort, in which the GLS data were unavailable in a significant number of patients.

The current study also found that mortality rises significantly with increases in the number of markers of early LV dysfunction present; when all 3 of these markers are present, the mortality is higher than the presence of Class I guideline recommendation or presence of symptoms.[14] Therefore, the evaluation of these markers of early LV dysfunction should be carefully performed (particularly EF by volumetric analysis), and the presence of >1 marker should be noted carefully.

With advancements in surgical aortic valve repair techniques, the renaissance of the Ross procedure,[25] and the availability of newer generation prostheses, there has been significant improvement in both

TABLE 2 Association of Markers of Early LV Dysfunction With All-Cause Mortality, Adjusted for Age, Sex, and Comorbidities (Charlson Comorbidity Index)

	Censored for AVR				Adjusted for Time-Dependent AVR			
	HR (95% CI)	*P* Value	C-Statistic (95% CI)	AIC	HR (95% CI)	*P* Value	C-Statistic (95% CI)	AIC
LVEF	0.95 (0.93-0.98)	<0.001	0.832 (0.781-0.882)	641.5	0.96 (0.94-0.98)	<0.001	0.811 (0.760-0.863)	1010.2
LVEF <60%	2.54 (1.55-4.17)	<0.001	0.833 (0.785-0.880)	640.0	2.25 (1.49-3.39)	<0.001	0.814 (0.764-0.864)	1007.6
GLS ≤15%	2.25 (1.36-3.73)	0.002	0.830 (0.782-0.878)	644.6	2.39 (1.53-3.72)	<0.001	0.818 (0.772-0.865)	1009.7
iESV ≥45 mL/m^2	2.27 (1.34-3.84)	0.002	0.832 (0.783-0.880)	644.6	1.61 (1.04-2.50)	0.034	0.811 (0.761-0.861)	1017.8
iESD ≥20 mm/m^2	1.40 (0.86-2.28)	0.180	0.826 (0.778-0.875)	650.0	1.18 (0.78-1.79)	0.427	0.811 (0.762-0.861)	1016.7
Markers of early LV dysfunction			0.836 (0.789-0.882)	637.6			0.812 (0.762-0.862)	1005.2
No markers	1.00 (Ref.)				1.00 (Ref.)			
Markers of early LV dysfunction	2.18 (1.21-3.92)	0.009			1.88 (1.16-3.03)	0.010		
Class I/IIa guideline recommendations	4.22 (2.15-8.29)	<0.001			3.38 (1.96-5.83)	<0.001		
LVEF/iESV/GLS			0.842 (0.796-0.889)	635.7			0.817 (0.768-0.866)	1004.9
None meeting criteria	1.00 (Ref.)				1.00 (Ref.)			
1 meeting criteria	1.84 (0.97-3.50)	0.063			1.73 (1.04-2.88)	0.035		
2 meeting criteria	3.39 (1.72-6.68)	<0.001			2.67 (1.51-4.74)	<0.001		
3 meeting criteria	5.46 (2.51-11.90)	<0.001			4.23 (2.21-8.11)	<0.001		

C-statistic of baseline age and sex model = 0.796 (95% CI: 0.741-0.850). C-statistics and AICs are on models without missing data.
AIC = Akaike information criterion; Ref. = reference; other abbreviations as in Table 1.

operative and long-term survival, necessitating a reevaluation of the timing of surgery. Given the development of better methods to assess LV size (2- and 3-dimensional volumes) and novel indicators of LV dysfunction (GLS), there is an urgent need to prospectively evaluate their association with mortality and determine their role as triggers for surgery.

STUDY LIMITATIONS. The limitations of the current study include its retrospective design, which only allows for the evaluation of risk associations rather than predictors and limits the ability to assess if these markers of early LV dysfunction may be responsive to AVR. Because the study was conducted at a single referral center, the racial and ethnic diversity is limited. The small proportion of female subjects in this study likely reflects the lower prevalence of AR in the female population and possible referral biases, with more male subjects being referred for evaluation than female subjects.[26] In addition, due to the study's retrospective nature, data on GLS were unavailable in 28% of patients. The data on GLS are in the early stages, and the ideal cutoff needs to be established and validated in prospective studies. Lastly, the study solely focused on echocardiographic markers of early LV dysfunction, and the role of late gadolinium enhancement and increased extracellular volume from cardiac magnetic resonance imaging could not be evaluated because it is not routinely performed clinically. However, considering that an echocardiogram is frequently the first and often the only available test, our results indicate broader applicability.

CONCLUSIONS

The current study including 673 asymptomatic patients with chronic severe AR identified 3 important markers of early LV dysfunction associated with all-cause mortality: LVEF <60%, iESV ≥45 mL/m^2, and GLS worse than −15%. Compared with no markers, the all-cause mortality was higher when >1 of these markers of early LV dysfunction was present and highest when Class I or IIa guideline recommendations were present, suggesting that there remains a survival penalty with current guideline indications. Among these markers of early LV dysfunction, reduced LVEF was the most common, followed by enlarged LV ESV and abnormal GLS. The mortality increased with the increase in the numbers of markers present. Prospective studies are needed to determine if intervention at the time of development of markers of early LV dysfunction improves long-term outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with asymptomatic clinically significant chronic AR have a higher mortality when ACC/AHA Class I/IIa guideline recommendations are attained (HR: 4.22; 95% CI: 2.15-8.29), compared with markers of early LV dysfunction (LVEF <60%, iESV ≥45 mL/m^2, and GLS worse than −15%) (HR: 2.18; 95% CI: 1.21-3.92) and no markers (reference). In patients without these recommendations, presence of at least 2 markers of early LV dysfunction can identify patients with higher mortality risk who may benefit from early surgery.

TRANSLATIONAL OUTLOOK: Prospective multicenter studies are urgently needed to determine whether intervening at the time markers of early LV dysfunction develop can improve long-term outcomes and consequently assess the role of these markers as indicators for surgery.

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KEY WORDS aortic regurgitation, aortic valve, echocardiography, ejection fraction, end-systolic volume, global longitudinal strain

APPENDIX For a supplemental figure, please see the online version of this paper.

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