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ORIGINAL RESEARCH

Prognostic Value of E/E′ Ratio in Patients With Unoperated Severe Aortic Stenosis

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OBJECTIVES The aim of this study was to evaluate the value of clinical and echo-Doppler parameters for the prognosis of unoperated severe aortic stenosis (AS).

BACKGROUND Approximately one-third of severe, symptomatic AS patients are denied surgery. Risk stratification of unoperated AS is important to determine eligibility for percutaneous aortic valve replacement, an evolving treatment option for AS patients deemed suboptimal for surgical aortic valve replacement.

METHODS We retrospectively compared clinical and echo-Doppler parameters between survivors and nonsurvivors of 125 patients with unoperated severe AS.

RESULTS The 1-year survival rate was 62.4%. In univariate analysis, survivors compared with nonsurvivors were younger (80.0 $\pm$ 10.9 years vs. 84.9 $\pm$ 11.1 years, $p = 0.02$), had a greater left ventricular ejection fraction (LVEF) (55 $\pm$ 15% vs. 50 $\pm$ 16%, $p = 0.042$), a higher left ventricular stroke volume (63 $\pm$ 19 ml vs. 56 $\pm$ 13 ml, $p = 0.015$), a lower E/E′ ratio (12.19 $\pm$ 5.7 vs. 16.87 $\pm$ 7.43, $p < 0.001$), and a lower prevalence of E/E′ $>$15 (20% vs. 55%, $p < 0.001$). Symptomatic status was nonsignificantly different between survivors and nonsurvivors. In patients with an LVEF $\geq$50%, the subgroup with E/E′ $\leq$15 and with E/E′ $>$15 had a 73.8% and 47.8% 1-year survival rate, respectively ($p = 0.027$). In the patients with an LVEF $<$50%, the patients with E/E′ $\leq$15 and those with E/E′ $>$15 demonstrated a 70.6% and 22.3% 1-year survival rate, respectively ($p = 0.003$). In multivariate analysis, significant predictors of mortality were E/E′ $>$15 and a combination of E/E′ $>$15 and B-type natriuretic peptide $>$300 ng/ml: adjusted mortality risk 2.34 (95% confidence interval (CI) 1.27 to 4.33, $p = 0.0072$) and 2.59 (95% CI 1.21 to 5.55, $p = 0.014$), respectively.

CONCLUSIONS The E/E′ ratio is the single most predictive clinical and echo-Doppler parameter in the assessment of overall prognosis in patients with unoperated severe AS. LVEF was a significant predictor of survival only in the univariate analysis. B-type natriuretic peptide alone was not a predictor of prognosis in the study population. However, the combination of E/E′ and B-type natriuretic peptide is even more predictive of the 1-year prognosis. (J Am Coll Cardiol Img 2010;3:899–907) © 2010 by the American College of Cardiology Foundation

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Aortic stenosis (AS) is the most common valvular heart disease in the Western world, and its prevalence is increasing as the population ages (1). Surgical aortic valve replacement (AVR) is the only effective treatment for severe AS in patients with symptoms or left ventricular (LV) systolic dysfunction. However, in asymptomatic patients with severe AS, the timing of surgery is controversial (2). Although a number of centers perform AVR in selected asymptomatic patients (3–5), the EuroHeart survey found that one third of symptomatic elderly patients with severe AS were denied surgery (6). Advanced age, comorbidities, and a reduced LV ejection fraction (LVEF) are important factors in decision making because they are associated with an increased operative risk (7–13). As a result, symptomatic, mostly elderly and debilitated AS patients receive only medical treatment, and the prognosis of patients with unoperated symptomatic AS is very poor (14–21). There is likely to be a patient selection bias for surgery among both symptomatic and asymptomatic patients with severe AS, with patients having the most significant comorbidities not being offered surgery (4,22).

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AUC = area under the curve

AVR = aortic valve replacement

BNP = B-type natriuretic peptide

LV = left ventricular

LVEF = left ventricular ejection fraction

Risk assessment in unoperated AS patients, both symptomatic and asymptomatic, may be challenging. In elderly AS patients with comorbidities, symptoms may not be identified due to limited physical activity (23–28). Furthermore, the clinical manifestations of other noncardiac disorders (e.g., pulmonary disease, obesity, deconditioning) may overlap with symptoms of AS (29), thus making it complicated to identify the primary cause of symptoms. Risk stratification is becoming more important as percutaneous AVR is evolving as a treatment option for patients with severe AS with comorbidities that may preclude surgical AVR.

The objective of our study was to evaluate retrospectively the impact of a spectrum of clinical and echo-Doppler parameters on the outcomes of unoperated patients with severe aortic valve stenosis in the absence other significant valvular heart disease.

METHODS

Patient selection. This was a retrospective, observational cohort study from a large community-based medical center. The study was approved by the institutional review board. Waiver for patient consent was granted because of the retrospective nature of the study.

The Cedars-Sinai Medical Center echocardiography database was searched for patients with severe AS for the period September 2003 to May 2008. Severe AS was defined as a maximal transaortic velocity of ≥4 m/s, mean transaortic pressure gradient of ≥40 mm Hg, or aortic valve area of <1.0 cm^2. By reviewing medical records, we identified 146 consecutive patients with symptomatic severe AS, severe AS with LV systolic dysfunction (LVEF ≤50%), or asymptomatic severe AS with preserved LV systolic function (LVEF >50%) with available follow-up information confirming that these patients did not receive surgery. To have a study population in which aortic valve stenosis was the primary valve lesion, 12 patients with severe mitral regurgitation were excluded. In addition, to be able to accurately assess LV diastolic function, 2 patients with mitral stenosis and 3 patients with a history of mitral valve surgery were excluded. Finally, 4 participants were excluded due to active malignancy with an estimated survival of <1 year. The remaining 125 patients were included in the final analysis.

Clinical data. Clinical data included age, sex, symptomatic status (dyspnea, chest pain, and syncope), history of smoking, diabetes mellitus (patients taking antihyperglycemic medications or with a fasting blood glucose level ≥125 mg/dl), hypertension (patients taking antihypertensive medications or with known hypertension regardless of treatment), hypercholesterolemia (participants taking lipid-lowering medications or with a plasma low-density lipoprotein cholesterol level >160 mg/dl), congestive heart failure, atrial fibrillation, history of coronary heart disease (old myocardial infarction, coronary artery stenosis on coronary angiography, wall motion abnormality on echocardiogram), previous cardiac surgery (coronary artery bypass grafting or heart valve replacement), chronic pulmonary disease, peripheral vascular disease, chronic renal failure (serum creatinine ≥2.0 mg/dl), plasma B-type natriuretic peptide (BNP) level, if it was obtained within a month of echocardiography, history of a cerebrovascular accident, and physical activity level (activity level was classified as active if the patient lived independently and limited if the patient required assisted care).

We also collected data concerning medical treatment with aspirin, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, peripheral vasodilators, and statins.

Echocardiography. LV GEOMETRY AND SYSTOLIC FUNCTION. LV dimensions were acquired in the parasternal long-axis view. LV internal dimension and posterior wall and septal thickness were measured at end-diastole and at end-systole (30). LV mass was calculated with the corrected formula of the American Society of Echocardiography and indexed for body surface area (30). LV end-diastolic volume, end-systolic volume, and ejection fraction were calculated by Simpson's method (30).

AORTIC STENOSIS SEVERITY. The Doppler echocardiographic indexes of AS severity included the peak Doppler velocity across the aortic valve, the peak and mean transvalvular pressure gradient obtained with the use of the modified Bernoulli equation, and the aortic valve area obtained with the use of the standard continuity equation (2).

LV FILLING HEMODYNAMICS. Early transmitral filling peak velocity, early deceleration time, and transmitral atrial wave velocity were obtained with a pulsed-wave sample at the tip of the mitral valve (31). Early diastolic velocity of the lateral aspect of the mitral annulus (E′) was measured by Doppler tissue imaging (32). Pulmonary vein flow was obtained on apical 4-chamber view. Abnormal pulmonary vein flow was determined as blunting or reversal of the systolic component of the pulsed Doppler flow signal (31). As E/E′ >15 and E/E′ <8 usually indicate an elevated and normal LV filling pressure respectively (31), we performed a separate analysis using these cutoff values.

PULMONARY ARTERY SYSTOLIC PRESSURE. Pulmonary artery systolic pressure was estimated as the sum of the right ventricular to right atrial pressure gradient during systole and the right atrial pressure. The right ventricular to right atrial peak systolic pressure gradient was calculated by the modified Bernoulli equation. Right atrial pressure was estimated based on echocardiographic characteristics of the inferior vena cava (33).

Clinical outcome. The end point for the present study was death within 1 year of follow-up. The last evaluation of patient survival status was performed in May 2009.

Statistical analysis. All analyses were performed with the statistical software program SPSS V.13.0 (SPSS Inc., Chicago, Illinois). Continuous data were presented as mean ± SD. Categorical data were presented as an absolute number or percentages. The significance level was set at $p = 0.05$.

Table 1. Comparison of Echocardiographic Variables Between Nonsurvivors and Survivors

	N	Nonsurvivors (n = 47)	Survivors (n = 78)	p Value
LV geometry and systolic function				
LVEF (%)*	121	50 ± 16	55 ± 15	0.042
Stroke volume (ml)*	109	56 ± 13	63 ± 19	0.015
LVID, diastolic (mm)	116	47 ± 9	47.0 ± 12	0.836
LVID, systolic (mm)	117	34 ± 10	33 ± 12	0.727
LV mass index	116	123 ± 38	128 ± 62	0.674
Aortic stenosis severity				
V_{max} (m/s)	124	3.8 ± 1.0	3.7 ± 0.9	0.68
Mean pressure gradient (mm Hg)	120	35 ± 19	32 ± 16	0.362
Aortic valve area (cm^2)	120	0.7 ± 0.2	0.8 ± 0.2	0.126
Diastolic parameters				
E (cm/s)*	117	111 ± 33.86	94.5 ± 33.62	0.009
A (cm/s)	97	96 ± 45	96 ± 39	0.932
E/A	101	1.14 ± 0.7	1.13 ± 0.8	0.956
Deceleration time (ms)	115	237 ± 114	247 ± 100	0.602
E′ (cm/s)	122	7.7 ± 3.2	8.4 ± 3.2	0.299
E/E′*	122	16.9 ± 7.4	12.2 ± 5.7	<0.001
E/E′ <8	122	6%	19%	0.057
E/E′ >15*	122	55%	20%	<0.001
Abnormal pulmonary vein flow	53	50%	42%	0.548
Systolic pulmonary artery pressure (mm Hg)	98	48 ± 14	45 ± 14	0.353

*$p < 0.05$.
A = atrial; E = early; LV = left ventricular; LVEF = left ventricular ejection fraction; LVID = left ventricular internal dimension.

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Between-groups comparisons of baseline data were performed using the independent-samples *t* test. All categorical variables were compared between the 2 groups using the Pearson chi-square test. Test of homogeneity of variances was performed for each individual variable with the Levene statistic.

Clinical and statistical variables were entered into Cox regression models to evaluate the independent predictors of 1-year survival. Hazard ratios were estimated using Cox proportional hazards models. Hazard ratios with 95% confidence intervals were provided when appropriate. Kaplan-Meier analysis was used to estimate survival. The log-rank test was used to compare survival across 2 groups. Data are presented as mean ± SD. A p value <0.05 was considered statistically significant.

Table 2. Comparison of Clinical Variables Between Nonsurvivors and Survivors

Parameter	N	Nonsurvivors (n = 78)	Survivors (n = 47)	p Value
Age (yrs)*	125	85 ± 11	80 ± 11	0.02
Male sex	125	63%	61%	0.87
Height (cm)	125	66 ± 4	66 ± 5	0.484
Weight (lbs)	125	152 ± 33	160 ± 41	0.313
Symptoms				
Dyspnea	120	60%	53%	0.44
Angina	120	19%	22%	0.63
Syncope	120	10%	12%	0.807
Any symptoms	120	71%	63%	0.379
Cardiovascular risk factors				
Smoking history	119	35%	36%	0.948
Hypertension	119	69%	76%	0.376
Diabetes mellitus*	118	19%	40%	0.016
Hyperlipidemia	119	52%	51%	0.878
Cardiovascular comorbidities				
Congestive heart failure	120	60%	43%	0.056
Atrial fibrillation	119	40%	27%	0.133
Coronary heart disease	119	54%	47%	0.417
Old myocardial infarction	118	13%	16%	0.624
Previous heart surgery	124	17%	13%	0.61
Peripheral vascular disease	119	21%	12%	0.186
History of cerebrovascular accident	119	21%	12%	0.186
Noncardiac comorbidities				
Chronic renal failure	119	21%	19%	0.767
Chronic obstructive pulmonary disease	120	21%	15%	0.358
Inactive	119	17%	11%	0.556
Malignancy	118	17%	19%	0.818
Medications				
Aspirin	119	33%	36%	0.762
ACE inhibitors/ARBs	119	44%	51%	0.459
Beta-blockers	119	40%	43%	0.735
Calcium channel blockers	119	19%	23%	0.604
Diuretics	119	42%	41%	0.971
Vasodilators	119	25%	25%	0.967
Statins	119	52%	44%	0.381
Laboratory				
Serum creatinine	114	1.45 ± 0.85	1.38 ± 1.04	0.715
Serum BNP (pg/ml)	85	1,345 ± 1,550	950 ± 1,140	0.198
BNP >300 (pg/ml)*	85	84%	65%	0.048

*p < 0.05.
ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; BNP = B-type natriuretic peptide.

RESULTS

There were 54 (43%) men and 71 (57%) women with a mean age of 81.6 ± 11 years. Clinical variables were available for all patients. The LVEF was calculated using Simpson's rule in 74% of cases. In all other cases, LVEF was estimated visually by 2 experienced echocardiographers (S.B. and R.J.S). A reliable continuous waveform signal of TR for estimation of systolic pulmonary artery pressure was present in 98 (78%) patients. The atrial wave of mitral inflow pulsed-wave Doppler signal was recorded in 117 (94%) of cases. Mitral annulus tissue Doppler imaging was available for 122 (98%), and pulmonary vein flow was interpretable in 53 (42%) patients (Table 1). The BNP level was measured in 85 (68%) of patients (Table 2).

The mean aortic valve area was 0.72 ± 0.12 cm^2, the peak velocity across the aortic valve was 3.8 ± 0.9 m/s, and the mean pressure gradient was 33 ± 17 mm Hg. The reasons that AVR was not performed are shown in Table 3.

Comparison of clinical and echocardiographic parameters between survivors and nonsurvivors. The overall 1-year rate survival was 62.4%. As shown in Table 2, univariate analysis demonstrated that survivors compared with nonsurvivors were younger (80.0 ± 10.9 years vs. 84.9 ± 11.1 years, p = 0.02), and a history of diabetes was more prevalent in survivors compared with nonsurvivors (40% vs. 19%, p = 0.016). There was no significant difference in the prevalence of any of the symptoms attributable to AS between the 2 study groups (71% vs. 63%, p = 0.379). In addition, there was no difference with regard to the distribution of other cardiovascular diseases, noncardiac comorbidities, and medical treatment. Although the mean plasma BNP levels were higher in nonsurvivors compared with survivors, this difference did not reach statistical significance (1,345 ± 1,550 vs. 950 ± 1,140, p = 0.198). However, the BNP cutoff value of >300 pg/ml was significantly more prevalent in nonsurvivors compared with survivors (84% vs. 65%, p = 0.048).

Table 3. Reasons That Aortic Valve Replacement Was Not Performed

Asymptomatic patients (no.)	41
Noncardiac comorbidities	17 (41%)
Asymptomatic status	15 (36%)
Advanced age	6 (15%)
Patient declined intervention	3 (8%)
Symptomatic patients (no.)	79
Cardiac comorbidities	12 (15%)
Noncardiac comorbidities	28 (36%)
Advanced age	11 (14%)
Symptoms thought due to another etiology	8 (10%)
Patient declined intervention	5 (6%)
Referred to percutaneous aortic valve replacement	4 (5%)
Died before surgery	10 (13%)
No data regarding symptoms	5

Most prevalent reason for nonreferral to surgical aortic valve replacement was comorbidities in both asymptomatic and symptomatic cohorts.

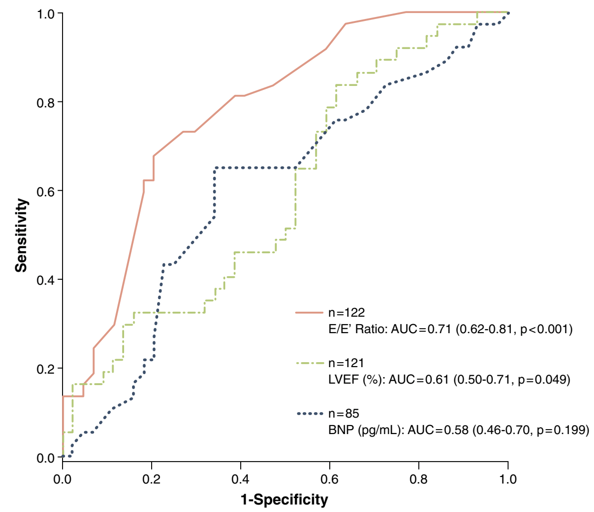

Figure 1. Receiver-Operator Characteristic Curve for the Prediction of Prognosis in Unoperated Severe Aortic Stenosis

The area under the curve (AUC) and corresponding p values for the 1-year mortality rate are shown for E/E′, left ventricular ejection fraction (LVEF), and B-type natriuretic peptide (BNP).

As shown in Table 1, survivors compared with nonsurvivors had a greater LVEF (55 ± 15 vs. 50 ± 16, p = 0.042), a higher LV stroke volume (63 ± 19 ml vs. 56 ± 13 ml, p = 0.015), a lower E/E′ ratio (12.19 ± 5.7 vs. 16.87 ± 7.43, p = 0.001), and a lower prevalence of E/E′ >15 (20% vs. 55%, p < 0.001). The rest of the echocardiographic variables of LV geometry, AS severity, and diastolic parameters were also similar between the 2 study groups. Figure 1 shows the receiver-operator characteristic curve for the prediction of prognosis in unoperated severe AS. The areas under curve (AUC) and corresponding p values for the 1-year mortality rate are shown for E/E′, LVEF, and BNP level. E/E′ was a significant predictor of outcome (AUC = 0.71 [0.62–0.81], p < 0.001). The baseline LVEF was significant for predicting 1-year morality (AUC = 0.61 [0.50−0.71], p = 0.049), whereas the serum BNP level alone was an insignificant predictor (AUC = 0.58 [0.46−0.70], p = 0.20).

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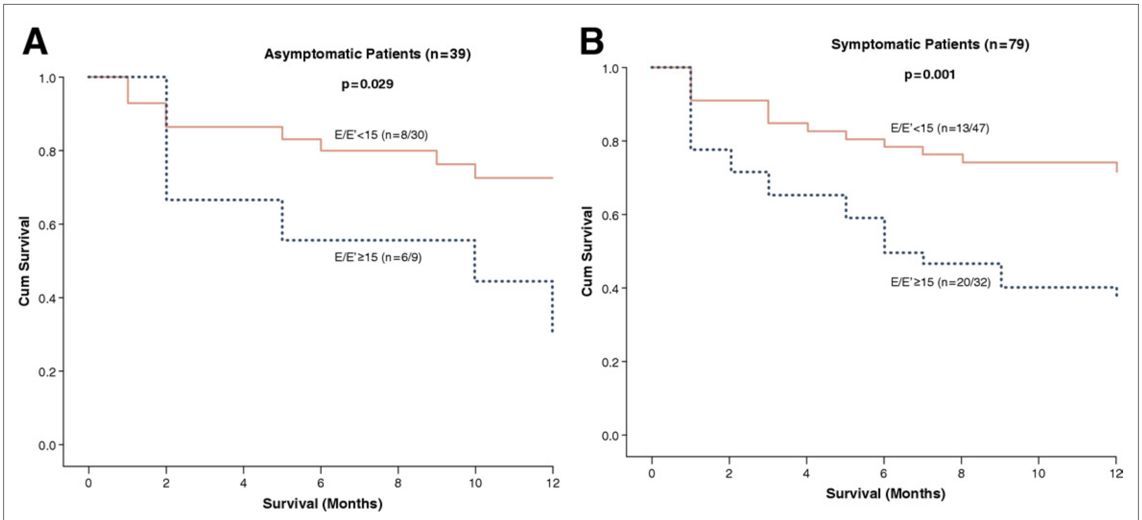

Figure 2. One-Year Survival in Unoperated Severe Aortic Stenosis Patients With and Without Symptoms as Stratified by E/E′ Cutoff of 15

There was significantly higher 1-year survival rate in patients with E/E′ <15 compared with patients with E/E′ ≥15 among both asymptomatic (n = 39) **(A)** and symptomatic (n = 79) **(B)** subjects (p = 0.029). Cum = cumulative.

As shown in Figure 2, in patients with E/E′ >15 (n = 41), the 1-year survival rate was 40%, whereas patients with E/E′ ≤15 (n = 78) had a significantly higher survival rate in the same time period (73.3%, p < 0.0001). In symptomatic patients, the subgroup of subjects with E/E′ ≤15 (n = 47), the 1-year survival rate was 72.3%, whereas in those with E/E′ >15 (n = 32) the 1-year survival rate was 37.5% (p = 0.001). In asymptomatic patients with E/E′ ≤15 (n = 30) and E/E′ >15 (n = 9), the 1-year survival rate was 73.3% and 33.3%, respectively (p = 0.029). Although E/E′ <8 is usually a marker of low ventricular filling pressure, there was no significant difference in our study using this cutoff.

To determine whether this effect was due to abnormal LV systolic function, we analyzed patients with preserved (LVEF ≥50%) and those with reduced (LVEF <50%) LV systolic function separately (Fig. 3). In patients with LVEF ≥50%, the subgroup with E/E′ ≤15 (n = 61) compared with subgroup with E/E′ >15 (n = 23) had a significantly better 1-year survival rate (73.8% vs. 47.8%, p = 0.027). The benefit was even more prominent in patients with LVEF <50%. The patients with E/E′ ≤15 (n = 17) and patients with E/E′ >15 (n = 18) demonstrated a 70.6% and 22.3% 1-year survival rate, respectively (p = 0.003).

As the plasma BNP level >300 pg/ml emerged as a significant univariate predictor of 1-year mortality, we further stratified the study population using a combination of E/E′ and BNP level. In patients with both E/E′ >15 and BNP ≥300 ng/ml, there was a 75% (21 of 28) 1-year mortality rate compared with a rate of 29% (16 of 56) in those without this combination (p < 0.0001). In contrast, there was a 21% (4 of 21) 1-year mortality rate in patients with E/E′ ≤15 and BNP ≤300 ng/ml compared with a 50% (33 of 65) mortality rate in patients without this combination (p = 0.02).

To account for multiple confounders, we created Cox regression models. Adjustments were made for all significant univariate variables as well as all clinical variables that had potential impact on 1-year survival. As shown in Table 4, the significant predictors of mortality in these models were E/E′ >15 with a relative risk of 2.34 (1.27–4.33, p = 0.0072) and a combination of E/E′ >15 and BNP ≥300 ng/ml with a relative risk of 2.59 (1.21–5.55, p = 0.014).

DISCUSSION

LV systolic function is a major prognostic marker for valvular heart disease. Currently, an LVEF <50% is used as an American Heart Association/American College of Cardiology guideline for recommending AVR in asymptomatic patients (2). However, in our study we found that E/E′ was more prognostic than LVEF. The findings of our study are not completely unexpected. In patients with severe AS, obstruction of LV outflow results in systolic pressure overload and LV wall hypertrophy. As a result of increased wall thickness and diminished compliance of the chamber, LV end-diastolic

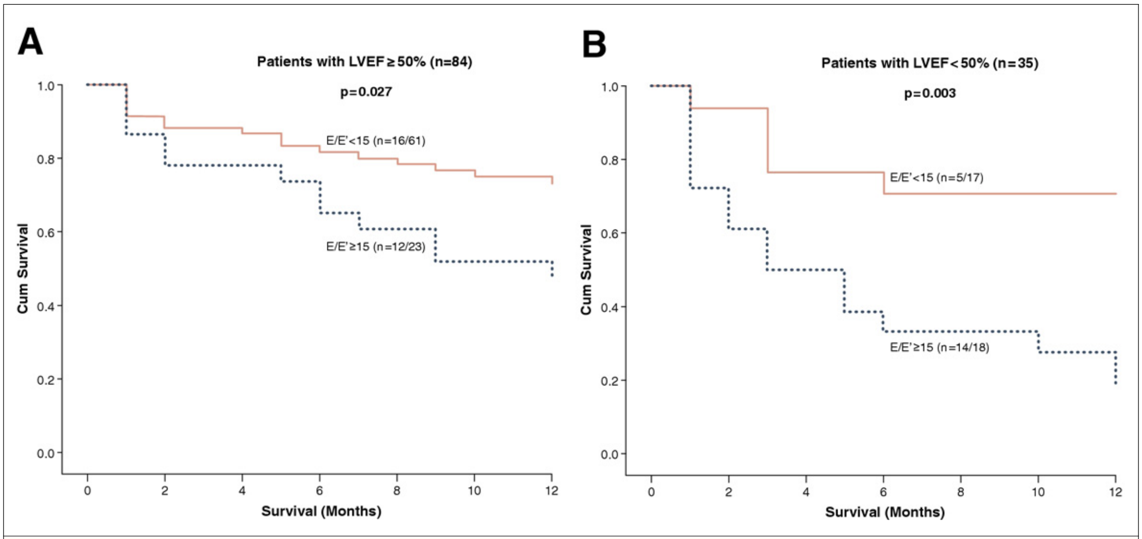

Figure 3. One-Year Survival in Unoperated Severe Aortic Stenosis Patients With LVEF ≥50% and LVEF <50% as Stratified by E/E′ Cutoff of 15

One-year survival in unoperated severe AS patients with LVEF <50% (n = 35) and LVEF >50% (n = 84) as stratified by E/E′ cutoff of 15. There was significantly higher 1-year survival rate in patients with E/E′ <15 compared with patients with E/E′ ≥15 among both subjects with LVEF ≥50% (n = 84) **(A)** and subjects with LVEF ejection fraction <50% **(B)**. Abbreviations as in Figures 1 and 2.

pressure increases without chamber dilation (34–36). Thus, increased end-diastolic pressure usually reflects diastolic rather than systolic dysfunction (37). Diastolic dysfunction is prevalent in patients with preserved systolic ejection performance and is very frequent in patients with depressed systolic function (38,39). The Doppler-derived E/E′ ratio has been found to be a reliable estimate of LV filling pressure in patients with AS (40). Our study demonstrates that an elevated E/E′ ratio is a marker for a subset of patients with AS at a very high risk of 1-year mortality.

Assessment of symptoms is subjective and is often difficult in the elderly, particularly in inactive subjects. Symptoms develop in 10% to 40% of asymptomatic AS patients on an exercise stress test at a relatively low workload (22–27). In our series, an asymptomatic status was not associated with better survival. The absence of symptoms was also an unreliable indicator of marked echocardiographic changes, such as a low LVEF and pulmonary hypertension associated with severe AS. Of note, we found that 12% of asymptomatic patients had both an LVEF <40% and pulmonary artery hypertension (estimated pulmonary artery pressure ≥35 mm Hg). In patients with severe AS and uncertainty with regard to asymptomatic status, exercise stress testing is useful to identify occult symptoms as well as for risk stratification (41). However, given the advanced age and clinical characteristics of our study population, stress testing may not have been feasible in the majority of participants. For patients who are unable to exercise, E/E′ seems to be a valuable echo-Doppler parameter for risk stratification.

In patients with AS, plasma BNP levels have been demonstrated to be correlated with LV end-systolic wall stress and to predict the onset of symptoms (42–44). The mean plasma BNP level in our cohort was considerably higher compared with

Table 4. Cox Regression Model Using Variables Significant in Univariate Analysis and Clinically Significant Variables

Parameter	Relative Risk	95% Confidence Interval	p Value
Model 1 (N = 110)			
Age	1.02	0.98–1.05	0.328
LVEF >50%	0.56	0.31–1.02	0.057
E/E′ ≥15*	2.34	1.27–4.33	0.007
Presence of symptoms	1.01	0.54–1.91	0.966
Model 2 (N = 78)			
Age	1.02	0.97–1.07	0.521
LVEF >50%	0.68	0.32–1.44	0.313
E/E′ ≥15*	2.48	1.15–5.38	0.021
BNP ≥300 ng/ml	1.48	0.57–3.87	0.424
Presence of symptoms	0.93	0.46–1.92	0.852
Model 3 (N = 79)			
Age	1.02	0.98–1.08	0.325
LVEF >50%	0.67	0.32–1.39	0.278
E/E′ ≥15 and BNP ≥300 ng/ml*	2.59	1.21–5.55	0.014

*$p < 0.05$.
Abbreviations as in Tables 1 and 2.

values observed in asymptomatic AS (43,44). This difference is probably due to different characteristics of our study population. Our cohort primarily consisted of symptomatic AS patients or patients with an unclear symptomatic status due to physical limitations. The predictive value of plasma BNP level cutoffs, useful in truly asymptomatic AS, had a limited role in risk stratification in our cohort. However, the combined use of plasma BNP >300 ng/ml and E/E′ >15 was the most accurate predictor for identifying a subset of patients with an extremely poor outcome and a high 1-year mortality rate of 75%.

Recently, Mullens et al. (45) failed to demonstrate a correlation between filling pressures and E/E′ ratio in patients with primary LV systolic dysfunction and considerable LV dilation. Our study cohort consisted mostly of patients with severe AS and concentric LV hypertrophy, but LV dimensions and LVEF were normal or slightly abnormal in the majority of cases. In patients with a depressed LVEF, the first-line evidence of elevated LV filling pressure is derived from the Doppler mitral inflow pattern. However, in patients with a normal LVEF, E/E′ >15 is considered to be a reliable marker of high left-sided filling pressures (31).

Unoperated AS patients are subject to both cardiac and noncardiac mortality. Subjects with a high perioperative risk are increasingly being considered for percutaneous AVR. Patients with a high cardiac risk and a relatively favorable noncardiac comorbidity profile are likely to benefit most from this new endovascular approach to AVR. In this regard, we found that elevated E/E′ may serve as a useful echo-Doppler parameter to identify patients with increased cardiac risk.

Study limitations. The retrospective nature of this study and the modest number of patients evaluated are limitations of the study. In addition to the small number of patients, hemodynamic and laboratory variables were obtained at different times; hence, it is possible that there were different loading conditions and filling pressures at the time of echocardiography and during measurement of the BNP.

CONCLUSIONS

The overall prognosis of unoperated severe AS is poor. In patients with severe AS, E/E′ has independent prognostic value. Among multiple clinical and echocardiographic parameters, we found that E/E′ >15 is the single most accurate parameter for risk stratification. In patients with unoperated severe AS, E/E′ >15 is superior to age, reduced LVEF, or plasma BNP levels in identifying subjects at very high risk of dying within 1 year. However, the combination of E/E′ and BNP is even more predictive of the 1-year prognosis.

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REFERENCES

1. Lindroos M, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. J Am Coll Cardiol 1993;21:1220–5.
2. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1–142.
3. Pellikka PA, Sundt TM. Management of asymptomatic severe aortic stenosis: is aortic valve replacement indicated? Nat Clin Pract Cardiovasc Med 2008;5:608–9.
4. Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. Ann Thorac Surg 2006;6:2116–22.
5. Carabello BA, Paulus WJ. Aortic stenosis. Lancet 2009;373:956–66.
6. Iung B, Cachier A, Baron G et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J 2005;26:2714–20.
7. Bouma BJ, van Den Brink RB, et al. To operate or not on elderly patients with aortic stenosis: the decision and its consequences. Heart 1999;82:43–8.
8. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
9. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15:816–23.
10. Edwards FH, Peterson ED, Coombs LP, et al. Prediction of operative mortality after valve replacement surgery. J Am Coll Cardiol 2001;37:885–92.
11. Hannan EL, Racz MJ, Jones RH, et al. Predictors of mortality for patients undergoing cardiac valve replacement in New York State. Ann Thorac Surg 2000;70:1212–8.
12. Ambler G, Omar RZ, Royston P, et al. Generic, simple risk stratification model for heart valve surgery. Circulation 2005;112:224–31.

13. Lee SJ, Lindquist K, Segal MR, et al. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006;295: 801–8.
14. Ross J Jr., Braunwald E. Aortic stenosis. Circulation 1968;38:61–7.
15. Frank S, Johnson A, Ross J Jr. Natural history of valvular aortic stenosis. Br Heart J 1973;35:41–6.
16. Chizner MA, Pearle DL, deLeon AC Jr. The natural history of aortic stenosis in adults. Am Heart J 1980;99: 419–24.
17. O'Keefe JH Jr., Vliestra RE, Bailey KR, Holmes DR Jr. Natural history of candidates for balloon aortic valvuloplasty. Mayo Clin Proc 1987;62: 986–91.
18. Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. Circulation 1982;6: 1105–10.
19. Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. Eur Heart J 1987;8: 471–83.
20. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. Eur Heart J 1988;9 Suppl E:57–64.
21. Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. Am J Cardiol 1988;61:123–30.
22. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005; 21:111–24.
23. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. Eur Heart J 2005;26: 1309–13.
24. Lancellotti P, Lebois F, Simon M, et al. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation 2005;112:I377–82.
25. Alborino D, Hoffmann JL, Fournet PC, Bloch A. Value of exercise testing to evaluate the indication for surgery in asymptomatic patients with valvular aortic stenosis. J Heart Valve Dis 2002;11:204–9.
26. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in symptomatic aortic valve stenosis: role of exercise testing. Heart 2001;86: 381–6.
27. Peidro R, Brion G, Angelino A. Exercise testing in asymptomatic aortic stenosis. Cardiology 2007;108:258–64.
28. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. Am J Cardiol 2009;194:972–7.
29. Bach DS, Cimino N, Deeb GM. Unoperated patients with severe aortic stenosis. J Am Coll Cardiol 2007;50: 2018–9.
30. Lang RM, Bierig M, Devereux RB, et al., Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
31. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165–93.
32. Park HS, Naik SD, Aronow WS, et al. Differences of lateral and septal mitral annulus velocity by tissue Doppler imaging in the evaluation of left ventricular diastolic function. Am J Cardiol 2006;98:970–2.
33. Ommen SR, Nishimura RA, Hurrell DG, Klarich KW. Assessment of right atrial pressure with 2-dimensional and Doppler echocardiography: a simultaneous catheterization and echocardiographic study. Mayo Clin Proc 2000; 75:24–9.
34. Gaasch WH, Levine HJ, Quinones MA, Alexander JK. Left ventricular compliance: mechanisms and clinical implications. Am J Cardiol 1976;38: 645–53.
35. Hess OM, Ritter M, Schneider J, Grimm J, Turina M, Krayenbuehl HP. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. Circulation 1984;69:855–65.
36. Murakami T, Hess OM, Gage JE, Grimm J, Krayenbuehl HP. Diastolic filling dynamics in patients with aortic stenosis. Circulation 1986;73:1162–74.
37. Gaasch WH. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. JAMA 1994;271:1276–80.
38. Hess OM, Villari B, Krayenbuehl HP. Diastolic dysfunction in aortic stenosis. Circulation 1993;87 Suppl IV:73–6.
39. Villari B, Hess OM, Kaufmann P, et al. Effect of aortic valve stenosis (pressure overload) and regurgitation (volume overload) on left ventricular systolic and diastolic function. Am J Cardiol 1992;69:927–34.
40. Bruch C, Stypmann J, Grude M, Gradaus R, Breithardt G, Wichter T. Tissue Doppler imaging in patients with moderate to severe aortic valve stenosis: clinical usefulness and diagnostic accuracy. Am Heart J 2004;148: 696–702.
41. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. Am J Cardiol. 2009;104:972–7.
42. Ikeda T, Matsuda K, Itoh H, et al. Plasma levels of brain and atrial natriuretic peptides elevate in proportion to left ventricular end-systolic wall stress in patients with aortic stenosis Am. Heart J 1997;133:307–14.
43. Gerber I, Stewart R, Legget M, et al. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis Circulation 2003;107:1884–90.
44. Monin J-L, Lancellotti P, Monchi M, et al. Risk score for predicting outcome in patients with asymptomatic aortic stenosis. Circulation 2009;120: 69–75.
45. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. Circulation 2009; 119:62–70.

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