Synergistic Utility of Brain Natriuretic Peptide and Left Ventricular Global Longitudinal Strain in Asymptomatic Patients With Significant Primary Mitral Regurgitation and Preserved Systolic Function Undergoing Mitral Valve Surgery

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Background—In asymptomatic patients with ≥3+ mitral regurgitation and preserved left ventricular (LV) ejection fraction who underwent mitral valve surgery, we sought to discover whether baseline LV global longitudinal strain (LV-GLS) and brain natriuretic peptide provided incremental prognostic utility.

Methods and Results—Four hundred and forty-eight asymptomatic patients (61±12 years and 69% men) with ≥3+ primary mitral regurgitation and preserved left ventricular ejection fraction, who underwent mitral valve surgery (92% repair) at our center between 2005 and 2008, were studied. Baseline clinical and echocardiographic data (including LV-GLS using Velocity Vector Imaging, Siemens, PA) were recorded. The Society of Thoracic Surgeons score was calculated. The primary outcome was death. Mean Society of Thoracic Surgeons score, left ventricular ejection fraction, mitral effective regurgitant orifice, indexed LV end-diastolic volume, and right ventricular systolic pressure were 4±1%, 62±3%, 0.55±0.2 cm^2, 58±13 cc/m^2, and 37±15 mm Hg, respectively. Forty-five percent of patients had flail. Median log-transformed BNP and LV-GLS were 4.04 (absolute brain natriuretic peptide: 60 pg/dL) and −20.7%. At 7.7±2 years, death occurred in 41 patients (9%; 0% at 30 days). On Cox analysis, a higher Society of Thoracic Surgeons score (hazard ratio 1.55), higher baseline right ventricular systolic pressure (hazard ratio 1.11), more abnormal LV-GLS (hazard ratio 1.17), and higher median log-transformed BNP (hazard ratio 2.26) were associated with worse longer-term survival (all $P<0.01$). Addition of LV-GLS and median log-transformed BNP to a clinical model (Society of Thoracic Surgeons score and baseline right ventricular systolic pressure) provided incremental prognostic utility (χ^2 for longer-term mortality increased from 31–47 to 61; $P<0.001$).

Conclusions—In asymptomatic patients with significant primary mitral regurgitation and preserved left ventricular ejection fraction who underwent mitral valve surgery, brain natriuretic peptide and LV-GLS provided synergistic risk stratification, independent of established factors. **(*Circ Cardiovasc Imaging*. 2016;9:e004451. DOI: 10.1161/CIRCIMAGING.115.004451.)**

Key Words: echocardiography ■ hemodynamic ■ hypertension ■ mitral valve ■ sample size

In the developed world, myxomatous degeneration of the mitral valve (MV) is the most common cause of mitral regurgitation (MR).[1,2] Surgical correction remains the cornerstone of management in severe primary MR because medical management alone does not improve the hemodynamic consequences of the regurgitant valve and its impact on outcome.[3,4] According to the most recent guidelines, indications for surgical intervention in patients with severe primary MR are development of symptoms, asymptomatic left ventricular (LV) systolic dysfunction, new-onset AF, or pulmonary arterial hypertension.[5] However, appropriate timing of surgical intervention in asymptomatic severe primary MR is often challenging. Advances in MV repair have led to excellent long-term results with low morbidity and mortality at experienced centers[6,7] such that the threshold to recommend surgical intervention at these centers has been lowered by the guidelines when

See Clinical Perspective

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there is a high chance of repair.[5] However, many patients are unaware of the onset of symptoms because of their gradual onset and their unwitting ability to subtly reduce exercise to prevent symptoms from occurring.[8] Furthermore, LV dysfunction is difficult to assess in severe MR, and LV contractility may already be irreversibly impaired, even though left ventricular ejection fraction (LVEF) remains in the usual normal range. Previous reports have shown that outcome after MV surgery is impaired once preoperative LVEF is <60%, and, thus, an LVEF <60% is considered abnormal and a potential indication for surgery in severe MR.[3] Additionally, impaired LVEF postoperatively (<50%) has been shown to predict poorer long-term survival.[9]

All of these challenges in MR management have led to the recognition of a need for parameters other than LV size and LVEF that may assist in the detection of the approach or onset of LV dysfunction and help optimize surgical timing. Brain natriuretic peptide (BNP) is a hormone secreted from myocardial cells in response to either diastolic stretch indicating volume overload, or wall stress indicating pressure overload, and is a marker of LV dysfunction.[10–12] Multiple previous reports have demonstrated incremental utility of BNP in predicting outcomes in patients with primary MR.[13–16] However, most of these studies had relatively small sample sizes or short follow-up times with heterogeneous end points. Assessment of left ventricular global longitudinal strain (LV-GLS), using speckle-tracking echocardiography provides quantitative assessment of LV contractile function that may be more sensitive to early change than LVEF.[17] In patients with significant MR, abnormal baseline LV-GLS is associated with a reduction in postoperative LVEF.[18–23] However, prognostic data regarding the role of LV-GLS in MR patients is sparse.[24,25] Furthermore, to the best of our knowledge, the potential additive value of BNP and LV-GLS in risk stratification of patients with significant MR who underwent MV surgery has not been previously studied. In a contemporary population of asymptomatic patients with significant MR and preserved LVEF who underwent MV surgery, we sought to determine whether baseline LV-GLS and BNP (1) were associated with a reduction in postoperative LVEF and (2) provided incremental prognostic utility over conventional measures previously shown to affect outcome in this condition.

Methods

This was a retrospective observational cohort study of consecutive asymptomatic patients with ≥III+ primary MR and preserved LVEF (LVEF ≥60%) who underwent MV surgery at our institution between 2005 and 2008. In the original MV surgical database, there were 1130 patients who underwent MV surgery in the described time frame. To be included in the current study, the following were the inclusion criteria: asymptomatic status, a comprehensive baseline echocardiogram with adequate LV-GLS measurements and LVEF ≥60%, BNP levels measured within 30 days of the resting echocardiogram (>90% on the same day), and follow-up echocardiogram between 10 and 12 months postoperatively. The following were exclusion criteria: any degree of concomitant aortic or mitral stenosis (based on gradient and valve area, according to current guidelines[5]); moderate or greater level of aortic regurgitation; and history of hypertrophic obstructive cardiomyopathy, infective endocarditis, and MV surgery. In addition, 46 patients with suboptimal LV-GLS measurements were also excluded (including 12 patients who were in atrial fibrillation at the time of echocardiogram). The final study population consisted of 448 patients who met the study criteria. The relevant baseline characteristics of the final study population versus the original registry of 1130 patients were similar and shown in the Data Supplement. The current study was approved by the Institutional Review Board.

Baseline clinical parameters were electronically recorded prospectively at the time of the initial encounter. For the current study, all data were manually extracted from the electronic medical records. Presence of atrial fibrillation was recorded based on history and electrocardiographic data. We recorded type of MV surgery (repair versus replacement), along with concomitant procedure (coronary artery bypass grafting, MAZE, pulmonary vein isolation, or left atrial appendage ligation/excision). A Society of Thoracic Surgeons (STS) score was calculated in all patients.

For BNP assay, all blood samples were collected into EDTA Vacutainer tubes and analyzed according to standard clinical laboratory routine. Plasma BNP (pg/mL, not the newer proNT-BNP assay) was determined by chemiluminescence immunoassay on site (Biosite Diagnostics, San Diego, CA).

Echocardiography Data

All patients underwent comprehensive transthoracic echocardiogram (TTE) preoperatively at the time of initial clinical evaluation using commercial instruments (Philips Medical Systems, Bothell, WA; Siemens Medical Solution, Inc, Malvern, PA; and General Electric, Milwaukee, WA). LV ejection fraction, indexed LV volumes, and left atrial volumes were measured according to guidelines.[26] In patients with missing volumetric data, they were remeasured. Severity of MR was reascertained using multiple previously described techniques.[27] This included qualitative visual assessment (as a % of LA size) and measurement of effective regurgitant orifice area and vena contracta width. Because of the severity of MR, diastolic function was not reported. Presence of flail mitral leaflet was recorded. Right ventricular systolic function was measured as normal, mild, moderate, or severe. Right ventricular systolic pressure (RVSP) was measured at rest.[27]

Left Ventricular Global Longitudinal Strain

LV peak global systolic longitudinal strain (LV-GLS) measurements were obtained on baseline TTEs from gray-scale images recorded in the apical 2-, 3-, and 4-chamber views (Figure 1). All raw data were stored in Digital Imaging and Communications in Medicine format without compression. LV-GLS was analyzed off-line using Velocity Vector Imaging (Syngo VVI; Siemens Medical Solutions, Mountain View, CA), as previously described.[28] The frame rate was at least 30 frames/s. After manual definition of the LV endocardial border, the endocardium was automatically tracked throughout the cardiac cycle. Global LV strain was obtained by averaging all segmental strain values from all 3 apical views. Peak global strain was defined as the peak negative value on the strain curve during the entire cardiac cycle. All measurements were made off-line by an investigator blinded to all clinical and demographic information. Measurements were performed and averaged for 3 cardiac cycles. Because the reported LV-GLS values are negative, a lower absolute number represented a worse value than higher.

Postoperative Echocardiography

Similar to preoperative TTE, we recorded standard measurements on TTEs obtained during follow-up. These included chamber dimensions, LVEF, severity of MR, RVSP, and right ventricular systolic function.

Outcomes

The date of the patient's MV surgery at our institution was defined as the beginning of the observational period. Follow-up was ascertained by chart review. On the basis of results of postoperative TTE, abnormal LV systolic function was defined as LVEF <50%. In addition, we also recorded the date at which mortality occurred. Mortality data

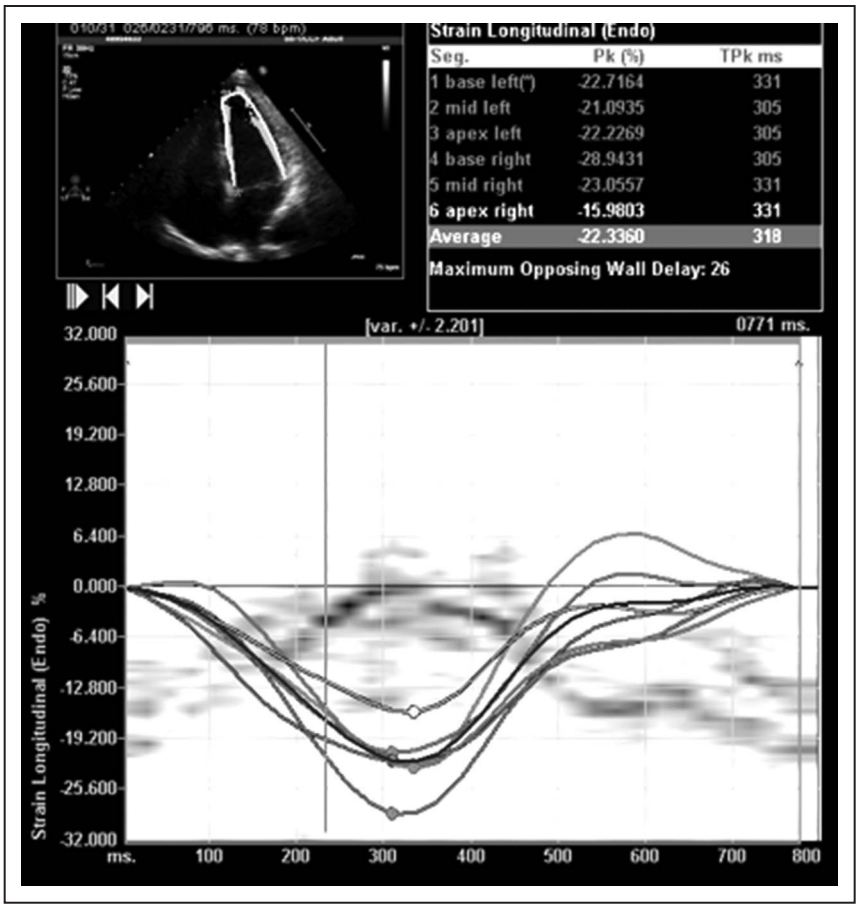

Figure 1. An illustrative example of left ventricular global longitudinal strain assessment in 4-chamber view, obtained from a patient in the study sample. Global strain values represent an average of values obtained from various left ventricular segments.

were obtained from review of medical records or state and nationally available databases. We further attempted to classify deaths as cardiac or noncardiac. The primary end point was all-cause mortality. For the secondary end point, we excluded 3 patients who died because of a documented malignancy that was diagnosed during follow-up. There were no patients with additional noncardiac causes of death (eg. renal/liver/neurological issues).

Statistical Analysis

Continuous variables are expressed as mean±SD, or median and interquartiles for skewed distributions, and compared using the Student *t* test or ANOVA (for normally distributed variables) or the Mann–Whitney test (for non-normally distributed variables). Categorical data are expressed as percentage and compared using χ^2 test or Fisher exact test, as appropriate. Because the distribution of BNP was skewed, values were logarithmically transformed for analysis. Correlation between continuous variables was assessed using Spearman correlation coefficient. Intra- and interobserver variability for LV-GLS measurements was assessed using intraclass correlation coefficients and coefficient of variation. To test the association between dependent variable (postoperative LVEF <50%) and various relevant preoperative predictors, univariable logistic regression analysis was performed. For multivariable logistic regression analysis, we created a model considering relevant characteristics including age, sex, medications, LVEF, indexed LV volumes, log-transformed BNP (lnBNP), LV-GLS, and coronary artery bypass grafting. To assess outcomes, Cox proportional hazards analysis was performed. We created a parsimonious model in which prespecified relevant variables, associated with adverse outcomes in patients with primary MR, were included. Even though the STS score has only been validated to predict 30-day postoperative mortality, similar to previous reports, we used it in the survival analysis because it is a composite of many factors that are known to be associated with adverse postoperative events in the longer term, while being aware that such a score does not necessarily represent the exact mortality at any particular year of follow-up.[29] Hazard ratios (HRs) with 95% confidence intervals were calculated and reported. To ensure that the proportional hazards assumption was not violated, graphical inspection of Schoenfeld residuals plotted against time was performed. Also, to test the linearity of the relationship between LV-GLS or BNP and survival in the Cox proportional hazards model, we performed polynomial transformations of LV-GLS and BNP. In addition, the cumulative proportion of events as a function over time was obtained by the Kaplan–Meier method, and event curves were compared using a log-rank test in which proportional hazards were not violated and a generalized Wilcoxon (Breslow) test in which the survival curves clearly cross and the proportional hazards were violated. In addition, the discriminative ability of various survival models were compared using the c-statistic,[30] and the classification of risk was assessed using integrated discrimination improvement. Statistical analysis was performed using SPSS version 11.5 (SPSS, Inc, Chicago, IL), Stata version 10.0 (StataCorp, College Station, TX), and R 3.0.3 (including survival version, R foundation for Statistical Computing, Vienna, Austria). A *P* value of <0.05 was considered significant.

Results

Baseline clinical and echocardiographic characteristics of the study sample are shown in Tables 1 and 2. The mean STS score was 4±1%, with an expected low prevalence of cardiovascular risk factors from this sample of patients with primary MR. The median lnBNP was 4.0 (interquartile range: 3.25–4.93), corresponding to an absolute BNP value of ≈60 pg/dL. Only 51 patients (11%) had an absolute BNP value >250 pg/mL, whereas 153 patients (34%) had values >100 pg/dL. The

Table 1. Baseline Characteristics of the Study Sample (n=448)

Variable	
Age, y	61±12, 61 (53–70)
Male sex	307 (69)
Body mass index, kg/m^2	27±4, 25 (22–28)
History of hypertension	111 (25)
History of diabetes mellitus	12 (3)
History of obstructive coronary artery disease	51 (11)
History of atrial fibrillation	94 (21)
History of hyperlipidemia	105 (23)
History of smoking	145 (32)
Society of Thoracic Surgeons score, %	4.1±1, 4.2 (4.06–4.5)
Angiotensin-converting enzyme inhibitor	157 (35)
β-Blockers	177 (40)
Oral anticoagulants	67 (15)
Serum creatinine, mg/dL	0.99±0.3, 1.0 (0.8–1.1)
Log-transformed brain natriuretic peptide	4.1±2, 4.04 (3.26–4.93)
Log-transformed brain natriuretic peptide	
<Median (4.04)	234 (52)
≥Median	214 (48)
Serum hemoglobin, mg/dL	14.3±2, 14.4 (13.5–15.3)
Low-density lipoprotein, mg/dL	109±33, 107 (84–127)
High-density lipoprotein, mg/dL	57±18, 56 (46–68)
Triglycerides, mg/dL	111±65, 90 (71–128)

Categorical variables listed as n (%). Continuous variables listed as mean±SD and median with interquartile range.

Table 2. Baseline Echocardiographic Variables of the Study Sample (n=448)

Variable	
Left ventricular ejection fraction, %	62±3, 62 (60–65)
Indexed left ventricular end-systolic volume, cc/m^2	23±12, 22 (19–31)
Indexed left ventricular end-diastolic volume, cc/m^2	58±13, 59 (51–68)
Indexed left atrial volume, cc/m^2	48±18, 47 (38–61)
Mitral effective regurgitant orifice, cm^2	0.55±0.2, 0.53 (0.47–0.64)
Mitral leaflet flail	200 (45)
Mitral valve prolapsed	
Anterior	57 (13)
Posterior	203 (45)
Bileaflet	188 (42)
Right ventricular systolic pressure, mm Hg	37±15, 34 (28–43)
Tricuspid regurgitation	
None–trivial	208 (46)
Mild	167 (37)
Moderate	47 (11)
Moderate–severe	2 (0.4)
Severe	23 (5)
Right ventricular function	
Normal	426 (95)
Mildly reduced	18 (4)
Moderately reduced	3 (0.7)
Severely reduced	1 (0.2)
Left ventricular global longitudinal strain, %	−20.6±2, −20.7 (−22.3 to −19.7)
% Left ventricular global longitudinal strain distribution	
Worse than median (−20.7%)	222 (50)
≥Better than median	226 (50)

Categorical variables listed as n (%). Continuous variables listed as mean±SD and median with interquartile range.

median LV-GLS was −20.7% (interquartile range: −22.2% to −19.2%). The reproducibility of GLS, expressed as the coefficient of variation, was 5.5% to 7.7% and 7.4% to 8.7% for intraobserver and interobserver variation (variation represents a % of LV-GLS). The intraclass correlation coefficients for intraobserver and interobserver reproducibility of LV-GLS measurements were 0.90 (0.81–0.97) and 0.86 (0.71–0.92), respectively (both $P<0.001$). In the study sample, 249 patients (56%) had dilated LV and 338 patients (75%) had a dilated left atrium, based on recommended indexed volume cutoffs.[26] There was a weak correlation between BNP and LV-GLS ($r=0.12$; $P=0.009$), whereas there was no correlation between BNP and baseline LVEF ($r=-0.01$; $P=0.8$). Similarly, there was a weak correlation between LV-GLS and LVEF ($r=-0.1$; $P=0.04$).

In the current study, the mean time from clinical evaluation to MV surgery was 62±45 days with a median of 32 (4–93) days. Each of these patients had at least a class IIa indication using American College of Cardiology/American Heart Association guidelines prevalent at the time of surgery. There was no correlation between time to surgery and LV-GLS ($r=-0.001$; $P=0.5$) or BNP ($r=0.03$; $P=0.5$). The type of surgery in 414 patients (92%) was MV repair and in 34 (8%) MV replacement (only 1 patient received a mechanical valve prosthesis). Additional procedures performed at the time of MV surgery were left atrial appendage ligation/excision in 121 patients (27%), Maze procedure/pulmonary vein isolation in 97 patients (22%), tricuspid valve repair in 42 patients (9%), and coronary artery bypass grafting in 51 patients (11%). In 48 out of 51 patients with coronary artery bypass grafting (94%), a single vessel coronary bypass was performed. During follow-up, 12 patients have required redo MV surgery, all MV replacements (none within 30 days postoperatively).

The median time for postoperative echocardiography was 11 (10–12) months. On postoperative echocardiography, mean LVEF, MV gradient, and RVSP were 52±8%, 4±2 mm Hg, and 32±8 mm Hg, respectively. Also, 94 patients (21%) had an abnormal LVEF (<50%), whereas 429 patients (96%) had <2+MR, 408 (91%) had <2+tricuspid regurgitation, and 359 (80%) had RVSP <35 mm Hg. Results of logistic regression

Table 3. Logistic Regression Analysis Demonstrating the Association Between Various Baseline Predictors and Postoperative Left Ventricular Systolic Dysfunction (LVEF<50%)

Variable	Wald Statistic	Odds Ratio With 95% CI	*P* Value	Wald Statistic	Odds Ratio With 95% CI	*P* Value
Age (for every 10-y increase)	5.2	1.23 (1.07–1.42)	0.02	4.7	1.20 (1.03–1.42)	0.04
Male sex	3.0	1.49 (0.97–2.53)	0.1	…	…	…
Hypertension	0.8	1.28 (0.73–2.24)	0.4	…	…	…
Coronary artery disease	0.01	1.21 (0.32–2.73)	0.9	…	…	…
Atrial fibrillation	1.5	1.39 (0.81–2.40)	0.2	…	…	…
Angiotensin-converting enzyme inhibitor	1.9	1.35 (0.84–2.18)	0.2	…	…	…
β-Blockers	2.3	1.40 (0.95–2.58)	0.1	…	…	…
Baseline left ventricular ejection fraction	0.3	0.98 (0.90–1.06)	0.6	…	…	…
Baseline LVEDVi (for every 1 cc/m^2 increase)*	12.3	1.41 (1.13–1.71)	<0.001	10.1	1.37 (1.08–1.66)	<0.001
Baseline LVESVi (for every 1 cc/m^2 increase)*	11.8	1.36 (1.12–1.67)	<0.001	…	…	…
Mitral ERO (for every unit increase)	1.3	1.72 (0.68–4.33)	0.3	…	…	…
Flail mitral leaflet	0.1	1.07 (0.68–1.70)	0.7	…	…	…
Baseline RVSP (for every 10 mm Hg increase)	0.6	1.41 (0.56–3.54)	0.5	…	…	…
lnBNP (for every unit increase)	15.8	1.49 (1.23–1.86)	<0.001	12.9	1.44 (1.20–1.74)	<0.001
LV-GLS (for every unit increase)	15.0	1.22 (1.11–1.34)	<0.001	12.3	1.19 (1.09–1.30)	<0.001
Type of mitral valve surgery (repair vs replacement)	1.8	1.32 (0.82–2.21)	0.4	…	…	…
Concomitant CABG	0.03	1.25 (0.36–2.69)	0.7	…	…	…

For multivariable logistic regression analysis, the following 9 variables were considered for analysis: age, sex, β-blockers, angiotensin blockers, baseline left ventricular ejection fraction, baseline LVEDVi (or LVESVi, as discussed above), lnBNP, LV-GLS, and CABG. CABG indicates coronary artery bypass grafting; CI, confidence interval; ERO, effective regurgitant orifice; LnBNP, log-transformed brain natriuretic peptide; LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; LV-GLS, left ventricular global longitudinal strain; and RVSP, right systolic ventricular pressure.

*Because of significant collinearity between left end-diastolic volume index and left end-systolic volume index, only left end-diastolic volume index was entered for multivariable analysis. Results were similar if left end-systolic volume index was considered.

analysis demonstrating the association between various relevant factors and postoperative abnormal LVEF are shown in Table 3. We demonstrate that age at the time of surgery, baseline LV-GLS, and lnBNP had an independent association with abnormal postoperative LVEF. Neither quadratic nor cubic transformations of lnBNP or LV-GLS had a significant association with LVEF when forced into the logistic regression model that already included these variables in a nontransformed form.

Outcomes

During a mean follow-up of 7.7±2 years (median 8.2 [6.7–8.9] years), death was observed in 41 patients (9%). There were no 30-day postoperative deaths, whereas 7 patients (1.5%) had transient ischemic attack and 2 patients (0.5%) had stroke. There were 94 patients (21%) who had transient atrial fibrillation during 30 days postoperatively, whereas 22 patients (5%) remained in permanent atrial fibrillation beyond 30 days. There were 6 patients (1%) who were admitted for management of congestive heart failure during long-term follow-up. There were 3 deaths because of malignancy during long-term follow-up (excluded from secondary outcome survival analysis, as reported below).

We subsequently performed survival analysis for the primary outcome of longer-term death using Cox proportional hazards method. The results of multivariable analysis are shown in Table 4. In the current study, a higher lnBNP (HR: 2.26), higher STS score (HR: 1.55), more abnormal LV-GLS (HR: 1.17), and higher baseline RVSP (HR: 1.11) were independently associated with higher mortality (all $P<0.01$). Of note, neither mitral effective regurgitant orifice area (HR: 1.05 [0.21–5.2]; $P=0.8$) nor flail mitral leaflet (HR: 1.24 [0.60–2.58]; $P=0.5$) was associated with mortality on univariable Cox survival analysis. Neither quadratic nor cubic transformations of lnBNP, LV-GLS, RVSP, or STS score were significant predictors of outcomes when forced into the Cox model that already included these variables in a nontransformed form.

As shown in Figure 2, the addition of lnBNP and LV-GLS to a standard clinical model (STS score and RVSP) provided incremental prognostic utility in these patients with significant increases in χ^2 for longer-term mortality at every stage (χ^2 increased from 31–47 to 61, P value for differences <0.01). Using integrated discrimination improvement, we subsequently tested whether addition of lnBNP and LV-GLS improved risk stratification for longer-term mortality, in addition to the clinical model, described above. The results are shown in Figure 3. Similarly, the addition of lnBNP to the clinical model increased the c-statistic for longer-term mortality from 0.59 (0.51–0.71) to 0.68 (0.53–0.83; $P<0.01$).

Table 4. Multivariable Cox Proportional Hazards Survival Analysis for Longer-Term Mortality in the Study Sample

	Hazard Ratio (95% Confidence Interval)	*P* Value
Log-transformed brain natriuretic peptide (for every unit increase)	2.26 (1.67–3.06)	<0.001
Left ventricular global longitudinal strain (for every unit worsening)	1.17 (1.08–1.27)	<0.001
Society of Thoracic Surgeons score (for every % increase)	1.55 (1.22–1.91)	<0.001
Baseline right ventricular systolic pressure (for every 10 mm Hg increase)	1.11 (1.02–1.35)	0.03

Further addition of LV-GLS increased the c-statistic to 0.75 (0.60–0.88; *P*<0.01).

During follow-up, the breakdown of longer-term mortality in the study sample, based on lnBNP median was as follows: lnBNP < median (lnBNP <4.04; absolute BNP <60 pg/dL; and number of events 4/234 or 1.7%) and lnBNP ≥ median (lnBNP ≥4.04; absolute BNP ≥60 pg/dL; and number of events 37/214 or 17%). Hence, in the current study, 90% of primary events occurred in patients with lnBNP >4.04 (absolute BNP value of 60 pg/dL). Similarly, 75% events occurred in patients with absolute BNP values >100 pg/dL. The Kaplan–Meier curves showing the longer-term outcomes in the study sample, separated on the basis of lnBNP level above or below the median value, are shown in Figure 4A. Similarly, the breakdown of longer-term mortality in the study sample, based on LV-GLS median, was as follows: LV-GLS worse than median (−20.7%) and number of events 33/222 or 15%, and LV-GLS ≥ better than median and number of events 8/226 or 3.5%. The Kaplan–Meier curves showing the longer-term outcomes in the study sample, separated on the basis of LV-GLS better or worse than median value, are shown in Figure 4B.

Subsequently, to understand the interplay between LV-GLS and lnBNP, we created 4 subgroups, based on medians. The proportion of deaths, based on these 4 subgroups, were as follows: (1) LV-GLS better than median and lnBNP < median (2/128 [2%]), (2) LV-GLS worse than median and lnBNP < median (3/106 [3%]), (3) LV-GLS better than median and lnBNP better than median (7/98 [7%]), and (4) both LV-GLS and lnBNP better than median (29/116 [25%]). Figure 5 illustrates the survival curves according to LV-GLS and BNP medians (*P*<0.001).

When patients with concomitant obstructive coronary artery disease were excluded from the multivariable Cox proportional hazards survival analysis (total n=397 and number of events=36), the results were similar. A higher lnBNP (HR: 1.82 [1.29–3.47]; *P*<0.01), higher STS score (HR: 1.37 [1.09–1.89]; *P*<0.01), and more abnormal LV-GLS (HR: 1.07 [1.02–1.24]; *P*=0.03) were associated with increased mortality.

We finally performed the secondary Cox survival analysis without documented malignancy-related deaths that occurred during follow-up (the patients were censored at the time of death but not included in survival analysis). The results of secondary Cox survival analysis were similar for the secondary end point of nonmalignancy deaths (n=38). A higher lnBNP (HR: 2.35 [1.63–3.25]; *P*<0.001), higher STS score (HR: 1.49 [1.20–2.29]; *P*=0.001), more abnormal LV-GLS (HR: 1.15 [1.07–1.31; *P*<0.001], and higher baseline RVSP (HR: 1.09 [1.01–1.37]; *P*=0.04) were significantly associated with increased mortality.

Discussion

In the current study of asymptomatic patients with significant MR and preserved LVEF who underwent MV surgery, we demonstrate that patients who experience postoperative reduction in LVEF have worse preoperative LV-GLS and BNP. Furthermore, we demonstrate that increasing BNP levels and worsening LV-GLS were independently associated with mortality, providing additive (rather than duplicative) prognostic utility to previously known predictors. BNP and LV-GLS sequentially improved risk classification in these patients, independently of known prognostic variables. Another observation was that the vast majority of patients had BNP values that would be considered in the normal or mildly elevated range. In fact, in the current sample, only 11% patients had an absolute BNP value >250 pg/mL, and 90% of deaths occurred in patients with an absolute BNP value of ≥60 pg/dL. Patients who had both BNP and LV-GLS values worse than median had significantly worse survival during longer-term follow-up. However, the study is potentially underpowered to make conclusive assertions about subgroup analyses, and a larger, prospective study is needed.

In symptomatic patients or those with overt LV dysfunction, the decision about MV surgical timing is already clear. As a result, for the current study, we only included asymptomatic patients with preserved LVEF because we intuited that this is the population where additional biomarker assay/strain analysis information may have the most clinical utility in determining long-term risk. The strain biomarker assay could also aid in helping determine the timing of surgery, especially in those patients who are risk averse and wish to postpone surgery for as long as possible. The vast majority of the patients in this study were referred for consideration of MV repair, and based on the American College of Cardiology/American Heart Association recommendations, 92% underwent MV repair,[5] with a 0% 30-day mortality. It seems that abnormal preoperative LV-GLS and BNP levels may reflect an intrinsic abnormality in LV function which at least in some patients is not eliminated by surgery because the prognostic impact of LV-GLS and BNP persists in spite of surgery. Furthermore, the significant association persisted even when only those patients who underwent surgery were studied and was also seen in that group without significant coronary artery disease.

Multiple previous reports have demonstrated incremental utility of BNP in patients with primary MR.[13–16] However, these had relatively small sample sizes, short follow-up durations (ranging from 2 to 5 years), and heterogeneous end points (eg development of symptoms, LV dysfunction, heart failure admissions, need for surgery, or mortality). However, BNP as a biomarker is nonspecific, with multiple clinical situations resulting in elevated values. Also, similar to the findings of the current study, BNP levels are lower in valvular heart disease than in other causes of heart failure.[31] As a result, different (lower) BNP

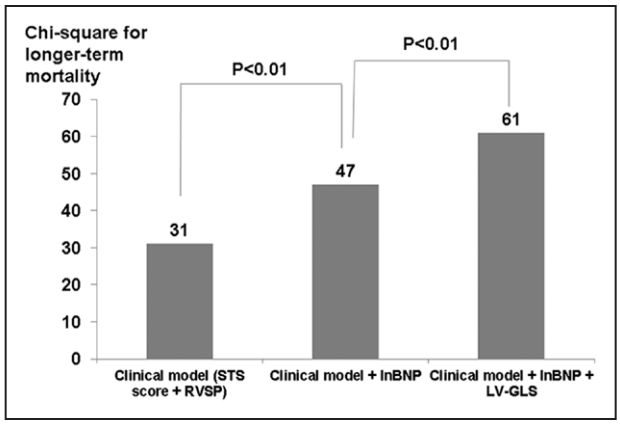

Figure 2. Prognostic utility of incrementally adding log-transformed brain natriuretic peptide (lnBNP) and left ventricular global longitudinal strain (LV-GLS) to a clinical model (Society of Thoracic Surgeons score [STS] and right ventricular systolic pressure [RVSP]).

thresholds may be needed in patients with valvular heart disease (including those based on age, sex, and the assay-manufacturing company[32]) to adequately predict outcomes.

Currently, the definition of what constitutes normal LV-GLS values remains controversial. The mean value of LV-GLS in the current study (−20.6%) was similar to what has been reported in current guidelines and is derived from a meta-analysis of healthy subjects, free of cardiovascular disease, where different strain analyses packages were used (−19.7%).[26,33] However, it is significantly higher than what was reported in a study of healthy individuals free of cardiovascular disease, where, similar to the current study, only VVI software was utilized (−17.3%).[34] That study also demonstrated that LV-GLS values obtained using VVI software were similar for different echocardiography vendors (similar to our study).[34] However, a recent study has demonstrated that although there is a very strong correlation between LV-GLS values obtained using different strain analysis packages in same individuals, the absolute mean values vary between −18% and −21.5% (with a mean of −20% for the Siemens strain software).[35] However, that study included patients with a wide spectrum of LV systolic function, rather than healthy individuals free of cardiovascular disease. Impaired LV-GLS in asymptomatic patients with severe MR and preserved ejection fraction have been shown in several previous reports to predict postoperative LV dysfunction after MV surgery.[18–23] However, these reports had relatively small sample sizes and short follow-up durations. In addition, no survival analysis was reported. A previous study reported an association between impaired LV-GLS and mortality; however, only 23% of these patients underwent MV surgery.[24] Another study using rest and stress echocardiography reported a higher event rate (death, MV surgery, and heart failure admissions) in patients with an abnormal GLS contractile reserve.[25] The current study had a significantly larger sample size and a much longer follow-up with a hard end point of mortality, along with studying the sequentially incremental impact of LV-GLS and BNP.

In the pathophysiologic cascade of MR, chronic volume overload results in increased LV end-diastolic volume and pressure. This results in increased wall stress, eventually followed by compensatory concentric remodeling and eventual overt LV systolic dysfunction. Elevated BNP, a marker of increased wall stress, and abnormal LV-GLS, a marker of early regional myocardial dysfunction, may help identify impaired LV myocardium earlier and at different stages of the pathophysiologic cascade, before the onset of overt LV systolic dysfunction. On the basis of the current study, it seems that BNP and LV-GLS

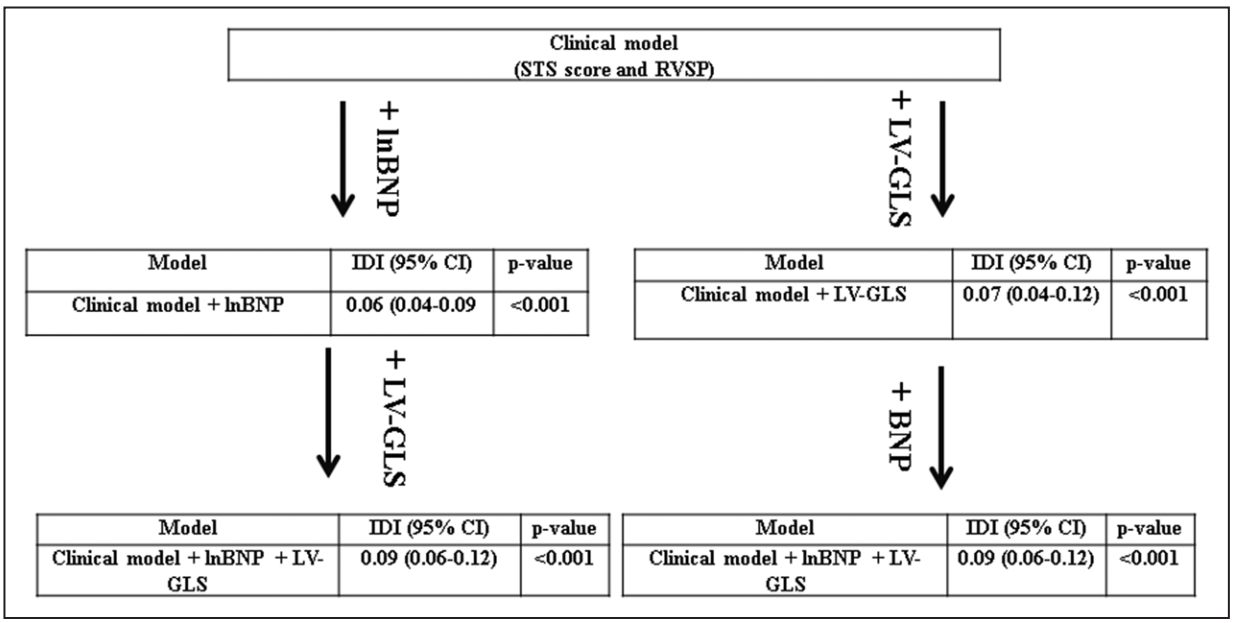

Figure 3. Incremental reclassification of longer-term mortality risk in the study sample, based on various models. Incremental comparison of log-transformed brain natriuretic peptide (lnBNP), followed by left ventricular global longitudinal strain (LV-GLS) to the clinical model is shown on the left side of the figure, whereas comparison of LV-GLS, followed by lnBNP is shown on the right side of the figure. CI indicates confidence interval; IDI, integrated discrimination index; RVSP, right systolic ventricular pressure; and STS, Society of Thoracic Surgeons.

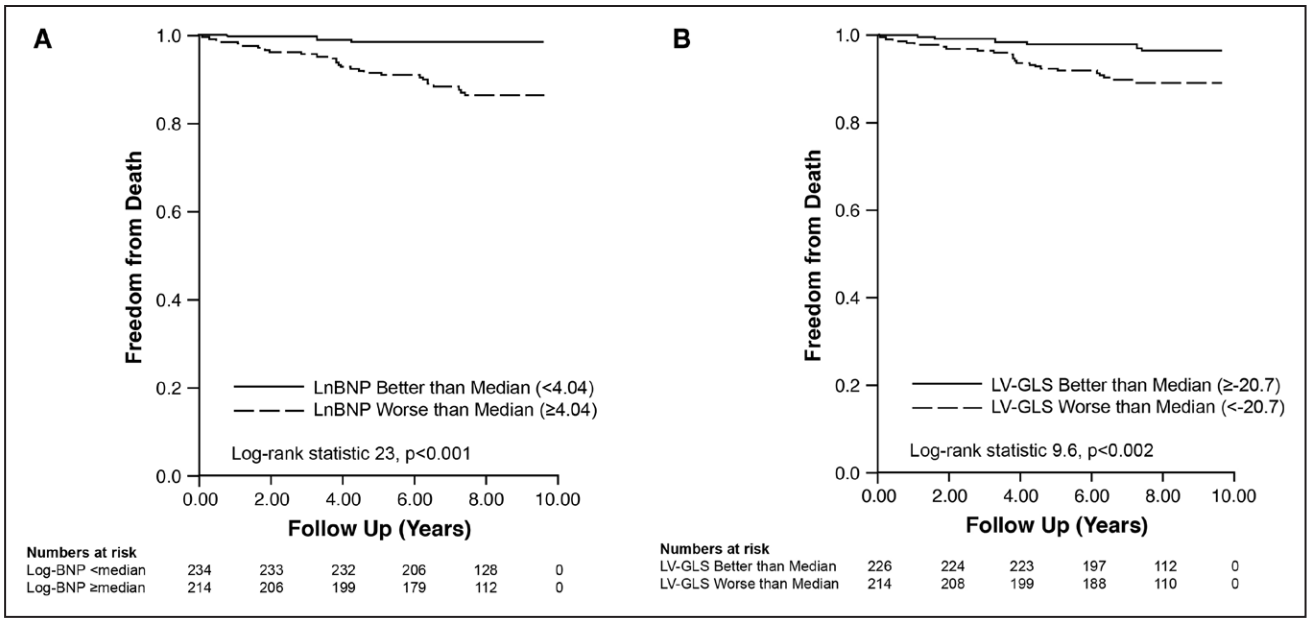

Figure 4. Kaplan–Meier survival curves for the study sample (**A**) separated based on log-transformed brain natriuretic peptide (lnBNP) higher or lower than median and (**B**) left ventricular global longitudinal strain (LV-GLS) better or worse than median. For LV-GLS, the higher the absolute value, the better it is. In contrast, for log BNP, the lower the value, the better it is.

provide incremental and additive prognostic value. Using these markers could potentially provide synergistic improvement in reclassification of risk in patients with significant MR before the onset of overt LV systolic dysfunction or symptoms. Furthermore, these markers could potentially aid in further optimization of surgical timing in asymptomatic patients before the onset of atrial fibrillation or pulmonary hypertension.

Limitations

This was a retrospective observational study from a tertiary referral center with its inherent biases, including selection bias. Not all patients had BNP levels measured; however, the baseline characteristics of those who did versus not were not significantly different (Data Supplement). A high proportion of patients underwent MV surgery, despite being asymptomatic, based on prevalent valve guidelines. As a result, we were not able to have a larger comparison group of patients without MV surgery to make valid statistical comparisons. The current study does not address the question whether even earlier MV surgery would be associated with improved outcomes. Our institution is well experienced in MV surgery with an extremely low rate of

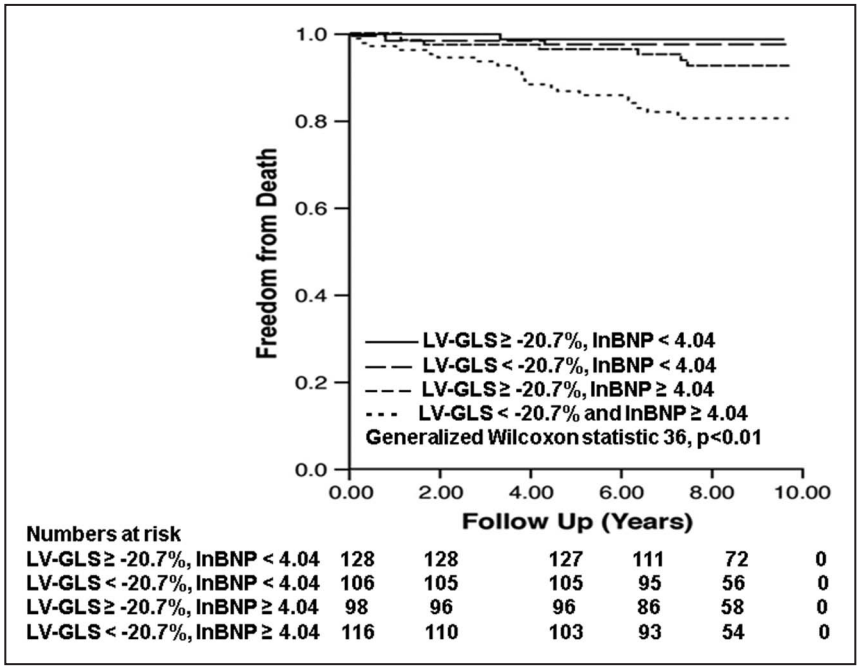

Figure 5. Kaplan–Meier survival curves for the study sample, separated into 4 subgroups created based on left ventricular global longitudinal strain (LV-GLS; median: –20.7%) and log-transformed brain natriuretic peptide (lnBNP; median: 4.04) better or worse than median. For LV-GLS, the higher the absolute value, the better it is. In contrast, for lnBNP, the lower the value, the better it is.

adverse events, and results from this cohort might not be generalizable across all other centers. We report unadjusted Kaplan–Meier survival curves; hence, they should be interpreted with caution. We report all-cause mortality as the primary end point, as opposed to cardiac mortality, because it has been demonstrated previously that all-cause mortality is more objective and unbiased than cardiac mortality.[36] However, on secondary outcomes analysis, where documented noncardiac deaths were censored but not included, the basic results were similar.

Conclusions

In asymptomatic patients with significant primary MR and preserved LVEF who underwent MV surgery, a combination of abnormal BNP and LV-GLS was associated with abnormal postoperative LVEF and increased longer-term mortality, providing improved risk reclassification, independent of clinical risk factors and echocardiographic variables. Future prospective studies are needed to confirm these observations.

Disclosures

Dr Gillinov reports the following conflicts: speaker's bureau for Atricure, Edwards, Medtronic, and St. Jude's Medical. He also reports equity stake in Pleuraflow. Dr Sabik is a consultant for Medtronic and Sorin. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

In 448 asymptomatic patients with ≥3+ mitral regurgitation and preserved left ventricular ejection fraction who underwent mitral valve surgery (92% repair), we sought to assess whether baseline left ventricular (LV) global longitudinal strain and brain natriuretic peptide provided incremental prognostic utility. On Cox analysis, a higher Society of Thoracic Surgeons (STS) score, higher baseline right ventricular systolic pressure, more abnormal LV global longitudinal strain, and higher log-transformed BNP were associated with worse survival. The addition of LV global longitudinal strain and log-transformed BNP to a clinical model (Society of Thoracic Surgeons score and baseline right ventricular systolic pressure) provided incremental prognostic utility. Similarly, the addition of log-transformed BNP to the clinical model increased the c-statistic for mortality from 0.59 to 0.68, whereas the addition of LV global longitudinal strain increased the c-statistic to 0.75. These markers could potentially aid in further optimization of surgical timing in asymptomatic patients before the onset of atrial fibrillation or pulmonary hypertension.

Synergistic Utility of Brain Natriuretic Peptide and Left Ventricular Global Longitudinal Strain in Asymptomatic Patients With Significant Primary Mitral Regurgitation and Preserved Systolic Function Undergoing Mitral Valve Surgery

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Supplemental Material

Supplemental Table. Relevant baseline characteristics of the current study sample (n=448) compared to the remaining patients from the original MV surgical database (n=682)

Variable	Current study sample (n=448)	Remaining patients from the original MV surgical sample (n=682)	p-value
Age (years)	61±12	62±12	0.5
Male gender	307 (69)	457 (67)	0.6
History of hypertension	111 (25)	184 (27)	0.4
History of obstructive coronary artery	51 (11)	89 (13)	0.4
History of atrial fibrillation	94 (21)	136 (20)	0.5
Society of Thoracic Surgeons Score (%)	4.1±1	4.2±1	0.8
Angiotensin converting enzyme inhibitor	157 (35)	252 (37)	0.5
Beta Blockers	177 (40)	259 (38)	0.6
Oral anticoagulants	67 (15)	89 (13)	0.4
LV ejection fraction (%)	62±3	62±2	0.8
Indexed LV end diastolic diameter (cm/m2)	1.6±0.2	1.6±0.3	0.8
Indexed left atrial diameter (cm/m2)	4.7± 0.9	4.5± 0.8	0.2
Mitral effective regurgitant orifice (cm2)	0.55±0.2	0.56±0.3	0.7
Mitral leaflet flail	200 (45)	300 (44)	0.5
Mitral valve prolapse **Anterior** **Posterior** **Bileaflet**	 57 (13) 203 (45) 188 (42)	 83 (12) 309 (45) 302 (44)	0.7
Right ventricular systolic pressure mm Hg	37±15 mmHg	35±14 mmHg	0.4

Categorical variables listed as n (%). Continuous variables listed as mean±SD