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The Echo Score Revisited

Impact of Incorporating Commissural Morphology and Leaflet Displacement to the Prediction of Outcome for Patients Undergoing Percutaneous Mitral Valvuloplasty

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***Background*—**Current echocardiographic scoring systems for percutaneous mitral valvuloplasty (PMV) have limitations. This study examined new, more quantitative methods for assessing valvular involvement and the combination of parameters that best predicts immediate and long-term outcome after PMV.

***Methods and Results*—**Two cohorts (derivation n=204 and validation n=121) of patients with symptomatic mitral stenosis undergoing PMV were studied. Mitral valve morphology was assessed by using both the conventional Wilkins qualitative parameters and novel quantitative parameters, including the ratio between the commissural areas and the maximal excursion of the leaflets from the annulus in diastole. Independent predictors of outcome were assigned a points value proportional to their regression coefficients: mitral valve area ≤1 cm^2 (2), maximum leaflets displacement ≤12 mm (3), commissural area ratio ≥1.25 (3), and subvalvular involvement (3). Three risk groups were defined: low (score of 0–3), intermediate (score of 5), and high (score of 6–11) with observed suboptimal PMV results of 16.9%, 56.3%, and 73.8%, respectively. The use of the same scoring system in the validation cohort yielded suboptimal PMV results of 11.8%, 72.7%, and 87.5% in the low-, intermediate-, and high-risk groups, respectively. The model improved risk classification in comparison with the Wilkins score (net reclassification improvement 45.2%; P<0.0001). Long-term outcome was predicted by age and postprocedural variables, including mitral regurgitation, mean gradient, and pulmonary pressure.

***Conclusions*—**A scoring system incorporating new quantitative echocardiographic parameters more accurately predicts outcome following PMV than existing models. Long-term post-PMV event-free survival was predicted by age, degree of mitral regurgitation, and postprocedural hemodynamic data. **(*Circulation*. 2014;129:886-895.)**

Key Words: balloon valvuloplasty ■ echocardiography ■ mitral valve stenosis

Rheumatic valvular disease continues to be a significant problem particularly in developing countries, with mitral stenosis (MS) being a frequent manifestation.[1] Definitive treatment of symptomatic MS is based on either surgical mitral valve replacement or percutaneous mitral valvuloplasty (PMV), with an echocardiographic assessment of valve morphology commonly used to determine the appropriate choice.[2] Currently, this assessment relies primarily on a semiquantitative scoring system that includes an assessment of leaflet mobility, valve thickening, subvalvular fibrosis, and valve calcification (Wilkins score).[3] Although this scoring method has been widely used because of its simplicity and reasonable success in separating patients with successful versus unsuccessful outcomes based on an increase in valve area, the grading of individual components remains semiquantitative, subject to observer variability, and less reliable in classifying patients with scores within the midrange. Furthermore, it does not include assessment of commissural morphology[4–7] and thus does not assess postprocedural mitral regurgitation (MR), which is an important predictor of long-term outcome.[8–15] Several subsequent models that seek to include a prediction of MR have been proposed; however, the best combination of parameters to predict both outcome variables remains to be defined.[4,16–20] Commissural morphology, in particular, asymmetrical commissural remodeling, and absolute leaflet displacement in diastole provide quantitative variables that are based on the fundamental mechanistic derangement of rheumatic mitral valve stenosis and can be reproducibly measured.

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This present study was designed to (1) explore more quantitative methods for assessing valvular involvement, in particular, to examine the impact of asymmetrical commissural remodeling and leaflet displacement on prediction of the results after PMV; (2) determine the combination of parameters that best predicts immediate procedural outcome and incorporate them into an appropriate scoring system; (3) validate the resulting model in a prospective cohort of patients undergoing PMV; and (4) identify the determinants of long-term event-free survival following the procedure.

Methods

Study Populations

Derivation Cohort

To define the potential of new more quantitative measure of mitral valve morphology to predict outcome following PMV, 204 consecutive patients who underwent PMV between January 2000 and October 2011 for symptomatic rheumatic MS, and had at least 1 comprehensive transthoracic echocardiogram before and within 24 hours after the PMV at our institution (Massachusetts General Hospital) were studied. The mean age was 57±16 years (range, 21–88), and 168 were women (82%). Most of the patients were in New York Heart Association functional class III/IV. Mitral valvuloplasty had previously been performed in 45 patients (22%). Atrial fibrillation was present in 96 patients (47%) at the time of the procedure. The study was approved by the institutional review committee, and the subjects gave informed consent.

Echocardiography

Comprehensive Doppler echocardiography was performed before and within 24 hours after PMV with the use of commercially available equipment (Sonos 5500, Sonos 7500, and iE33, Philips Medical Systems, Andover, MA; Vivid 7, GE Healthcare, Milwaukee, WI). Patients were examined in the left lateral recumbent position with the use of standard parasternal and apical views.[21,22] Mitral valve area (MVA) was measured by direct planimetry of the mitral valve orifice in the parasternal short-axis view and by the Doppler half-time method (preprocedure study only). Peak and mean transmitral diastolic pressure gradients were measured from Doppler profiles recorded in the apical 4-chamber view. The presence and severity of MR was evaluated by integrating data from the color flow image,[23] analysis of the vena contracta,[24] and study of the pulmonary venous systolic reflux. The continuous-wave Doppler tricuspid regurgitant velocity was used to determine systolic pulmonary artery pressure with the use of the simplified Bernoulli equation assigning a value of 10 mm Hg to account for right atrial pressure. Left atrial volume was assessed by the biplane area-length method from apical 2- and 4-chamber views. All results were based on the average of 3 measurements for patients in sinus rhythm and 5 measurements for patients in atrial fibrillation. Each echocardiogram was analyzed offline by 2 observers blinded to the procedural outcome.

Echocardiographic Assessment of Valve Suitability (Echo Score)

The morphology of the mitral valve was initially assessed as described by Wilkins et al,[3] (current score) based on a semiquantitative grading of mitral valve leaflet mobility, thickening, calcification, and subvalvular thickening, each on a scale of 0 to 4, with higher scores representing more abnormal structure. The total echocardiographic score was obtained by adding the scores of each of these individual components. According to this system, a score of 0 would be a totally normal valve, whereas a score of 16 would represent an immobile valve with fibrosis involving the entire leaflet and subvalvar apparatus and severe superimposed calcification.

Quantitative Measurement of Commissural Morphology

Assessment of commissural morphology was determined by the commissural area ratio as follows. The MVA was first outlined by tracing the inner margin of the leaflets from the parasternal short-axis view. Second, the ventricular (outer) surface of the leaflets was traced, and the area between the 2 tracings was recorded. The major diameter of the outer border was then measured, and its midpoint was determined. A line perpendicular to the major dimension passing through this point (the minor dimension) was then drawn, and the leaflet area on either side of the minor dimension was measured (Figure 1). The symmetry of commissural thickening was then quantified as the ratio between the leaflet areas on either side of the minor dimension. Because the ratio between the areas was used and not absolute values, variation in receiver gain settings should have limited influence on the ratio.

Leaflet Displacement

Apical displacement of the leaflets was measured in the apical 4-chamber view as the distance from the mitral annulus to the midportion of the leaflets at their point of maximal displacement from the annulus (doming height) in diastole (Figure 2). The midportion of the leaflet was taken as the end of the height measurement to account for variation in leaflet calcification.

Cardiac Catheterization/PMV

Standard hemodynamic measurements of the left ventricular, left atrial, right ventricular, and pulmonary artery pressures were recorded before and immediately after the procedure. Cardiac output was determined by the Fick method, and MVA was calculated by using the Gorlin formula.[25] The grade of mitral calcification was also assessed by fluoroscopic examination at catheterization. The grade was qualitatively scored from 0 (no calcification seen) to 4 (severe calcification). MR was assessed by left ventriculography after the procedure and graded by using the Sellers classification. PMV was performed with the use of an anterograde transseptal approach by using either the double-balloon or Inoue technique a previously described.[26]

Procedural Success and End Point Definitions

Procedural success was defined as an increase of ≥50% of MVA or a final area of ≥1.5 cm^2, with no more than 1 grade increment in MR severity assessed by echocardiography 24 hours after the procedure. The reference measurement for MVA was 2-dimensional echocardiography planimetry.[27,28]

The long-term outcome was a composite end point of death, mitral valve replacement, or repeat PMV. Outcome data were obtained from follow-up appointments in the clinic or by the review of medical records to obtain additional information.

Validation Cohort

A second set of patients who were referred for PMV between April 2010 and March 2013 at Hospital das Clinicas of the Federal University of Minas Gerais, Brazil, was enrolled as the validation cohort. The study was approved by the institutional review committee, and the subjects gave informed consent.

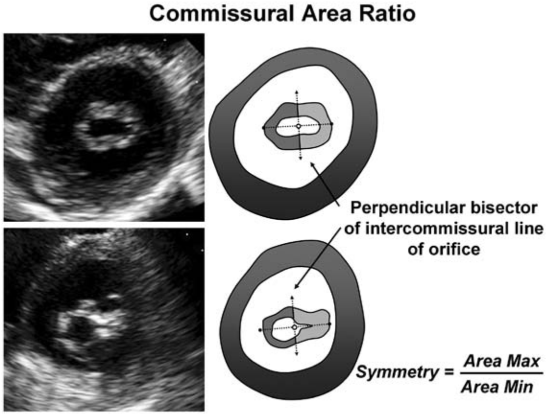

Figure 1. Echocardiographic parasternal short-axis view showing 2 traced areas to calculate the commissural area ratio. Asymmetry of commissural thickening was quantified by the ratio between the largest to the smallest area.

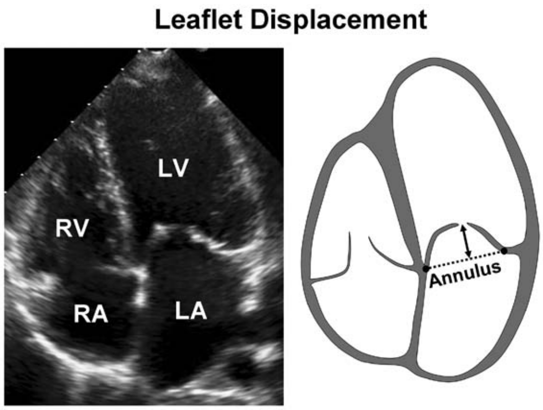

Figure 2. Echocardiographic apical 4-chamber view showing maximum apical displacement of the leaflets relative to the mitral annulus. LA indicates left atrium; LV, left ventricle; RA, right atrium; and RV, right ventricle.

The definition of procedural success was the same as used for the derivation cohort, and the same clinical and echocardiographic data were assessed in both cohorts.

Statistical Analysis

Categorical variables, expressed as numbers and percentages, were compared by χ^2 test, whereas continuous data, expressed as median and interquartile range, were compared by using the Student unpaired and paired *t* test or the Mann-Whitney U test, as appropriate. Logistic regression analysis was used to identify the predictors of postprocedural outcome.

Our strategy for the multivariable analysis included the 4 echocardiographic components of the Wilkins score in an initial model. In a second model, all clinically important variables that express different morphological features of MS were selected. We initially constructed this multivariate model with variables entered in a continuous format followed subsequently by categorizing the continuous variables to construct the score.

The performance of the models was assessed by using standard bootstrapping procedures, and the models were compared with the use of the Akaike information criterion. A shrinkage coefficient was used to quantify overfitting.[29–31] The discrimination and calibration of the final multivariable models in both derivation and validation data sets were measured to assess their performance in outcome prediction.[31–34] After correcting for overfitting, calibration was assessed by using the Hosmer-Lemeshow goodness-of-fit test[35]and a calibration plot.

Receiver-operating characteristic curves were used to identify the point that maximizes overall sensitivity and specificity in predicting suboptimal results after the procedure.

Risk Score

A point-based scoring system was developed from the final multivariable logistic regression model in which a number of points was assigned to each predictor in the model by rounding each β-coefficient to the nearest integer. The score, ranging from 0 to 11, was the sum of the points corresponding to each variable of the multivariable model, and 3 risk groups were defined.

Reclassification tables were constructed as a further measure to assess the incremental value of the modified score in improving the outcome prediction of PMV afforded by the current score.

Original risk categories and the resulting new classification were compared by computing the net reclassification improvement.[36] The integrated discrimination improvement was also estimated focusing on the differences between integrated sensitivities and 1-minus specificities for both models.[34,36,37]

The reproducibility of echocardiographic variables was assessed by the intraclass correlation coefficients for repeated measures in a random sample of 20 patients.

Long-Term Survival

Long-term event-free survival was estimated by using a Cox proportional hazards model. The association of the outcome with baseline and postprocedural factors was evaluated by using a stepwise variable selection technique. The selected variables for the multivariable model were age, New York Heart Association functional class, atrial fibrillation, and morphological echocardiographic variables, including MVA, leaflet displacement, commissural area ratio, subvalvular thickening, total of points of modified score, and Wilkins score. Subsequently, postprocedural variables were included in the model: left atrial volume, MR degree, mean pulmonary artery pressure, and mean transvalvular gradient. Long-term event-free survival rates were estimated by the Kaplan-Meier method and compared by the log-rank test.

Statistical analyses were performed with SAS (version 9.2, SAS Institute, Cary, NC) and R software, version 2.15.1 (R foundation for statistical computing, Vienna, Austria)

Results

Immediate Outcome

Derivation Cohort

PMV was successful in 133 patients (65%) with a mean MVA increase from 1.1±0.3 to 2.0±0.6 cm^2 (*P*<0.001), mean gradient decrease from 12.1±4.5 to 6.1±2.1 mm Hg (*P*<0.001), and mean pulmonary pressure decrease from 36.1±11.4 to 29.9±10.3 mm Hg (*P*<0.001). PMV was considered unsuccessful because of insufficient valve opening in 31 patients (15%) or >1 grade increase in MR grade in 40 patients (20%). In 26 of these patients, the resulting MR was moderate, whereas in 14 patients it was severe. Four patients (2%) required emergency surgery for MV replacement because of severe MR.

Predictors of Outcome Following PMV

Patients who had successful PMV were younger, had lower values for each of the individual predictors of structural abnormality, and the total echocardiographic score (Wilkins), as well, greater quantitative leaflet displacement, a lower commissural area ratio, smaller left atrium, and less fluoroscopic mitral calcification. Previous MV intervention was not a factor associated with outcome (95% confidence interval, 0.34–1.40). Age, sex, atrial fibrillation, and previous MV intervention were not associated with outcome. The clinical, echocardiographic, and hemodynamic data predictive of outcome by univariable analysis are compared in Table 1.

To identify those MV morphological parameters that were independently predictive of an optimal increase in MV area without an increase in the degree of MR, 2 multivariate analyses were performed. In the first multivariable model, the 4 echocardiographic components of the Wilkins score were included to determine whether the individual components were independently predictive of outcome or whether there was overlap between components. With the use of this model, only calcification and subvalvular thickening were independently predictive of outcome (Table 2).

In the second logistic model, we additionally included age, body surface area, fluoroscopic calcium grade, left atrial volume, MVA by planimetry, leaflet displacement (doming height), and commissural area ratio. Based on this model, the only significant independent predictors of immediate outcome

Table 1. Characteristics of the Study Population According to Immediate Outcome After PMV

Variables	Success (n=133)	Suboptimal (n=71)	Odds Ratio* (95% CI)	*P* Value
Age, y	55 (43–68)	65 (52–76)	2.014 (1.458–2.804)	<0.001
Body surface area, m^2	1.75 (1.61–1.96)	1.70 (1.58–1.84)	0.782 (0.581–1.053)	0.105
Female sex, n (%)	109 (82)	59 (83)	0.792 (0.371–1.693)	0.548
Atrial fibrillation, n (%)	62 (47)	34 (48)	1.260 (0.715–2.223)	0.424
Previous mitral valve procedure†	32 (24)	13 (18)	0.688 (0.339–1.395)	0.300
MV area, cm^2‡	1.1 (0.98–1.3)	0.98 (0.83–1.1)	0.429 (0.292–0.628)	<0.001
LAV index, mL/m^2	59 (46–78)	64 (49–94)	1.221 (0.852–1.742)	0.274
Fluoroscopic calcium grade ≥2	12 (9)	22 (31)	4.067 (1.433–11.537)	0.008
Echocardiographic score determinants				
Thickness	2 (1–2)	2 (2–3)	1.674 (1.227–2.286)	0.001
Calcium	2 (1–2)	2 (2–3)	1.896 (1.391–2.588)	<0.001
Mobility	2 (2–2)	2 (2–3)	1.860 (1.354–2.555)	<0.001
Subvalvular	2 (2–2)	2 (2–3)	1.670 (1.391–2.588)	0.002
Wilkins score (total of points)	8 (6–9)	9 (8–10)	2.264 (1.615–3.181)	<0.001
Wilkins score ≥10 points	24 (18)	32 (45)	3.726 (1.958–7.091)	<0.001
Maximum leaflet displacement, mm	15 (12–17)	12 (10–15)	0.451 (0.318- 0.641)	<0.001
Commissural area ratio	1.1 (1.0–1.2)	1.2 (1.1–1.4)	1.998 (1.257- 3.176)	0.003

Data are expressed as absolute number (percentage) or median and interquartile range. CI indicates confidence interval; LAV, left atrial volume, MV, mitral valve; PMV, percutaneous mitral valvuloplasty; and SD, standard deviation.

*Odds ratio per 1-SD increase.

†Surgical commissurotomy or percutaneous valvuloplasty.

‡Planimetry could not be performed in 9 patients because of very irregular and calcified mitral orifice, and MVA was calculated by PHT.

were baseline MVA, leaflet displacement, commissural area ratio, and subvalvular thickening (Table 2). Thus, when the new quantitative echocardiographic variables were included, neither total score (Wilkins) nor calcification, thickening, and mobility independently predicted outcome.

Table 2. Multivariable Predictors of Immediate Outcome After PMV

Models	Odds Ratio	95% CI	*P* Value
Model 1: Wilkins score			
Leaflets calcification	1.943	1.339–2.818	0.002
Subvalvular thickening	2.083	1.167–3.718	0.013
Leaflets mobility	1.487	0.799–2.767	0.211
Leaflets thickness	1.298	0.694–2.426	0.414
Wilkins score (total of points)*	1.484	1.260–1.747	<0.001
Model 2: new model with variables in continuous format†			
MV area, cm^2‡	0.113	0.021–0.622	0.012
Maximum displacement of leaflets, mm	0.842	0.748–0.948	0.004
Commissural area ratio	1.182	1.028–1.358	0.019
Subvalvular thickening‡	1.932	1.027–3.624	0.041

CI indicates confidence interval; MV, mitral valve; and PMV, percutaneous mitral valvuloplasty.

*This variable was not included in the model together with the individual components of the score.

†Shrinkage factor of 0.900.

‡Mitral valve area by planimetry.

§Subvalvular thickening was categorized in a binary fashion (absent or mild versus extensive thickening).

Predictors of a Suboptimal Increase in Valve Area Versus Increased MR

To explore the role of these morphological variables (MVA, leaflet displacement, commissural area ratio, and subvalvular thickening) in predicting procedural failure, we analyzed the determinants of postprocedural MVA and of the increase in MR separately. When valve area was evaluated as a continuous outcome, the variables that remained in the model were baseline MVA, the maximum leaflet displacement, and commissural area ratio, whereas commissural area ratio (odds ratio per 10% of increase ratio, 1.226; 95% confidence interval, 1.067–1.408; P=0.004) and subvalvular thickening (odds ratio, 2.705; 95% confidence interval, 1.310–5.584; P=0.007) were predictors of increased MR analyzed as a binary outcome.

Calculation of a Predictive Score

Multivariable analysis with independent variables (MVA, leaflet displacement, commissural area ratio, and subvalvular thickening) expressed in dichotomous format was performed. A shrinkage factor was estimated from the bootstrap procedure, and we shrunk the regression coefficients (Table 3). This final model was well calibrated (Figure 3). The model performance including continuous variables showed an Akaike information criterion of 200.064, whereas the use of the dichotomized variables showed an Akaike information criterion of 201.232.

A point-based scoring system was developed from the final multivariable logistic regression model (Table 3). This modified echocardiographic score included 4 echocardiographic variables (MVA, maximum leaflet displacement, commissural area ratio, and subvalvular involvement). Three risk groups

Table 3. Score for Immediate Outcome Prediction*

Variable	Prevalence n (%)	β-Coefficient	Odds Ratio	95% CI	*P* Value	Points
MV area ≤1cm^2	73 (36)	1.006	2.734	1.321–5.656	0.007	2
Maximum LD ≤12 mm	71 (35)	1.224	3.400	1.654–6.992	0.001	3
CA ratio ≥1.25	75 (37)	1.132	3.100	1.506–6.384	0.002	3
Subvalvular involvement†	37 (18)	1.173	3.231	1.355–7.709	0.008	3

Constant = −2.140. CA indicates commissural area; CI, confidence interval; LD, leaflet displacement; and MV, mitral valve.
*Shrinkage factor of 0.897.
†Absent or mild vs extensive thickening.

were defined: a low (score of 0–3), intermediate (score of 5), and high (score of 6–11) with observed suboptimal results of 16.9%, 56.3%, and 73.8%, respectively. (Scores of 1,4,7, and 10 cannot be calculated by using the values assigned to the individual variables.) The bounds were chosen based on the extent of structural damage to the mitral valve attributable to rheumatic disease. A patient is considered to be at low risk when only 1 morphological feature of rheumatic mitral stenosis was found. Intermediate risk was defined when 2 structural pathological changes were detected. High-risk patients are defined as patients with at least 2 structural changes in the commissures, cusps, and chordae tendinea combined, regardless of the orifice area.

The new score significantly improved reclassification of subjects with unfavorable results of PMV, with a net reclassification improvement of 45.2% (*P*<0.0001) in comparison with the Wilkins score. The integrated discrimination improvement was estimated as 13.2% in comparison of the Wilkins score with the modified score (*P*<0.0001). Reclassification of patients classified as intermediate risk based on the Wilkins score (9–11) yielded an net reclassification improvement of 76.8% (*P*<0.001; Table 4).

Although there was a high concordance between the Wilkins score and the new score in high-risk patients, 15 patients classified as low risk with the Wilkins score were reclassified as high risk with the new score. Because the rate of unsuccessful procedure was high in this subgroup of patients, especially because of worsening MR (6 of 8 with suboptimal results), we believe that these patients are not good candidates for the percutaneous intervention. This finding also confirms that the Wilkins score poorly predicts postprocedural MR.

Validation Cohort

To test the validity of our model, a separate validation cohort of 121 patients who met the same inclusion as the derivation cohort was studied. The mean age of the patients in this validation cohort was 41 years (range, 20–65); 107 (88%) were women. Most of the patients were in New York Heart Association functional class III or IV. At presentation, 19 (16%) were in atrial fibrillation. The characteristics of the validation cohort in comparison with the derivation cohort are shown in Table 5.

These patients were younger, had smaller MVAs, but less morphological deformity of their valves. PMV was successful in 95 patients (79%) with an increase in MR grade in 13 patients (11%). Similar to the derivation cohort, 3 patients (2.5%) developed severe MR owing to the disruption of the valve integrity, which was confirmed during surgery for MV replacement (a tear of the posterior mitral leaflet in 2 patients, and chordal rupture in 1 patient).

The majority of the patients (83%) were in the low-risk group by the use of the Wilkins score, 20 patients were in the

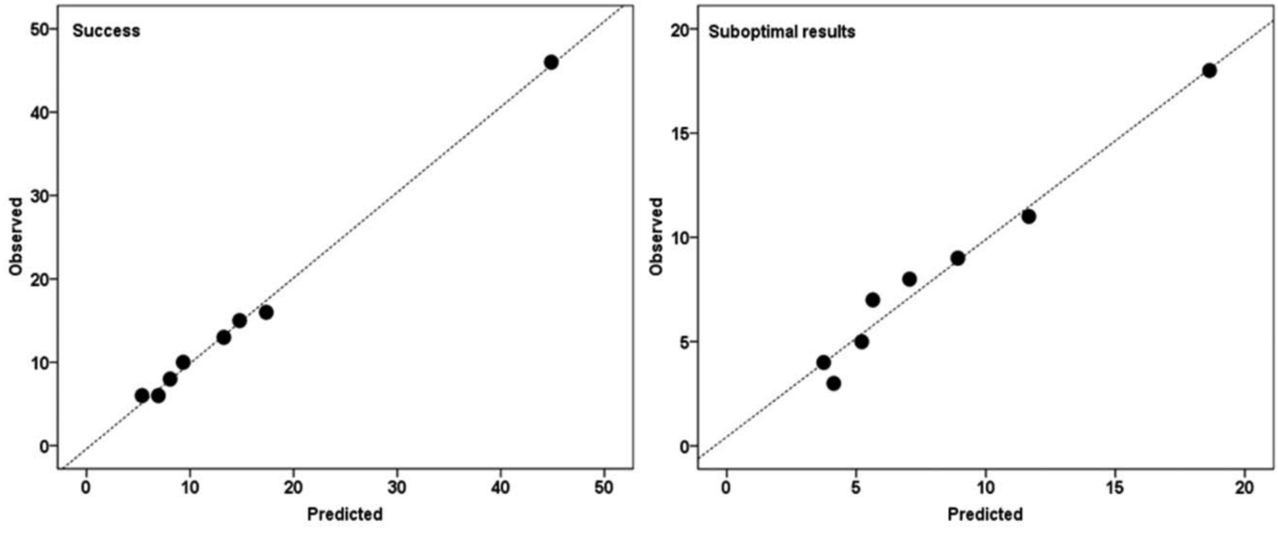

Figure 3. Observed vs predicted immediate outcome for success (**left**) and suboptimal results after percutaneous mitral valvuloplasty (**right**).

Table 4. Immediate Outcome After PMV as Predicted by Both Previous and Modified Echocardiographic Score

	Modified Echocardiographic Score			
Wilkins Score	Low	Intermediate	High	Total
Low				
Number of individuals	96	14	15	125
Suboptimal	13	8	8	29
Success	83	6	7	96
Proportion of suboptimal	13.5	57.1	53.3	23.2
Intermediate				
Number of individuals	34	18	20	72
Suboptimal	9	10	16	35
Success	25	8	4	37
Proportion of suboptimal	26.5	55.6	80.0	48.6
High				
Number of individuals	0	0	7	7
Suboptimal	0	0	7	7
Success	0	0	0	0
Proportion of suboptimal	…	…	100.0	100.0
Total				
Number of individuals	130	32	42	204
Suboptimal	22	18	31	71
Success	102	14	17	133
Proportion of suboptimal	16.9	56.3	73.8	34.8

PMV indicates percutaneous mitral valvuloplasty.

intermediate risk group, and only 1 was in the high-risk group. The total Wilkins score did not predict immediate adverse outcome after PMV in this population. However, by applying the new scoring system in the validation cohort, 102 patients were classified in the low-risk group, 11 were in the intermediate-risk group, and 8 were in the high-risk group; the suboptimal result rates for the low-, intermediate-, and high-risk groups were 11.8%, 72.7%, and 87.5%, respectively. The new score showed good discrimination and calibration. Figure 4 compares the predicted with observed suboptimal results for each increment in the risk score in the validation set.

Reproducibility of New Echocardiographic Variables

For the new echocardiographic parameters, the 2 independent observers achieved a high level of agreement. For the commissural area ratio, the intraclass correlation coefficient was 0.92 for interobserver and 0.95 for intraobserver variability. For the maximum leaflets displacement, the intraclass correlation coefficient was 0.92 for interobserver and 0.91 for intraobserver variability.

Long-Term Event-Free Survival

During a mean follow-up period of 29 months (range, 0–146), 70 adverse clinical events were observed, including 30 deaths, 32 MV replacements, and 8 repeat PMVs. The long-term event-free survival was strongly determined by the quality of immediate results (hazard ratio, 5.383; 95% confidence interval, 3.226–8.981; $P<0.001$; Figure 5). Event-free survival rate at 1-, 3-, and 5-year follow-up was 88%, 79%, and 71% in patients with good results in comparison with 49%, 32%, and 12% in those who had a suboptimal result after PMV.

Table 5. Characteristics of the Derivation Cohort in Comparison With the Validation Cohort

Variables	Main Cohort (n=204)	Validation Cohort (n=121)	*P* Value
Age, y	58 (45–70)	41 (33–49)	<0.001
Body surface area, m^2	1.72 (1.59–1.91)	1.6 (1.5–1.75)	0.001
Female sex, n (%)	168 (82)	107 (88)	0.142
Atrial fibrillation, n (%)	96 (47)	19 (16)	<0.001
MVA, cm^2*	1.1 (0.9–1.3)	1.0 (0.8–1.1)	<0.001
Peak gradient, mm Hg	21 (16–26)	19 (16–25)	0.182
Mean gradient, mm Hg	11 (8–14)	11 (8–15)	0.389
SPAP, mm Hg	48 (38–62)	46 (40–56)	0.506
Echocardiographic score determinants			
Thickness	2 (2–2)	2 (2–2)	<0.001
Calcium	2 (1–3)	1 (1–2)	<0.001
Mobility	2 (2–2)	2 (2–2)	0.742
Subvalvular	2 (2–2)	2 (2–2)	0.198
Wilkins score, total of points	8 (6–10)	7 (6–8)	<0.001
Maximum leaflet displacement, mm	14 (11–16)	15 (13–16)	0.006
Commissural area ratio	1.2 (1.1–1.4)	1.1 (1.0–1.1)	<0.001
Preprocedural data (cardiac catheterization)			
Mean PAP, mm Hg	33 (27–41)	35 (26–42)	0.689
LA pressure, mm Hg	23 (19–27)	23 (18–28)	0.404
Postprocedural data			
Increased in MR grade	40 (20)	13 (11)	0.037
MVA, cm^2	1.5 (1.3–1.8)	1.6 (1.4–1.8)	0.426
Mean gradient, mm Hg†	7 (5–8)	5 (4–7)	<0.001
Mean PAP, mm Hg	32 (24–38)	27 (23–36)	0.208
LA pressure, mm Hg	19 (14–24)	15 (12–19)	<0.001

Data are expressed as number (percentage) or median and interquartile range. LA indicates left atrium; MR, mitral regurgitation; MVA, mitral valve area; PAP, pulmonary artery pressure; and SPAP, systolic pulmonary artery pressure.
*MVA by planimetry.
†Gradient measured 24 hours after the procedure by echocardiogram.

Predictive factors of long-term event-free survival are shown in Table 6. The echocardiographic parameters for assessing MV morphology were also predictors of event-free survival. However, because the immediate outcome was a predictor of long-term survival, the multivariable analysis was performed again to include the hemodynamic variables recorded after the procedure.

By this multivariable analysis, only age and postprocedure invasive mean pulmonary artery pressure, mean transvalvular gradient, and MR were associated with event-free survival.

Discussion

In the present study, we observed that (1) although all of the components of the current echo score (Wilkins) were related to immediate outcome on individual analysis, only leaflet

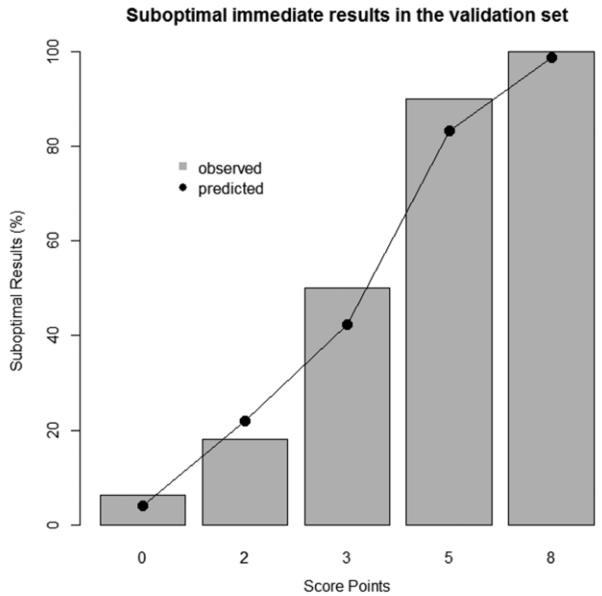

Figure 4. Predicted (●) vs observed (open bars) suboptimal immediate results after percutaneous mitral valvuloplasty for integer increments in the risk score in the validation cohort.

calcification and subvalvular thickening were independent predictors; (2) when all of the univariate predictors of outcome including the newly defined commissural area ratio and leaflet displacement were included in the multivariable model, the independent predictors were baseline MVA, leaflet displacement, commissural area ratio, and subvalvular thickening; (3) when these independent predictors were combined and scaled to create a new model, its predictive value was significantly greater than that of the Wilkins model and accounted for both an increase in valve area and MR; (4) the new model accurately predicts suboptimal results after PMV in an external validation cohort; and (5) following PMV, the predictors of long-term outcome were age and postprocedure mean pulmonary artery pressure, transvalvular gradient, and degree of MR.

Echocardiographic Parameters Predictors of Immediate Outcome

Since the onset of PMV, a number of parameters of mitral valve anatomy and function, and scores combining groups of variables, as well, have been proposed to predict procedural outcomes and thus guide patient selection. These can be broadly divided into those that relate to an optimal increase in valve area and those predicting MR.

Increase in Valve Area

The studies examining predictors of a successful increase in valve area have yielded varying results. The original model proposed by Wilkins et al[3] included an assessment of leaflet mobility, calcification, fibrosis, and mobility. They observed that a total score including a semiquantitative assessment of each parameter was predictive of outcome, whereas no single parameter was a significant determinant. Subsequently, Abascal et al[16] showed that, of the 4 components of the total echocardiographic score, valvular thickening was the only morphological predictor of the change in valve area after PMV.[16] Reid et al[38] analyzed 555 patients with MS and found that leaflet mobility was the only independent morphological feature for predicting MV area after PMV. More recently, Rifaie et al[18] showed that, among the individual parameters of the total echocardiographic score, both calcification and subvalvular disease were the only independent predictors of immediate postprocedural outcome. Similar to the results of Abascal and Rifaie, we also found that subvalvular involvement and valve calcification were predictive of outcome. These seemingly conflicting results likely reflect differences in the severity and duration of disease in the respective populations. In the current model, when the quantitative assessment of leaflets mobility expressed as the maximal leaflets displacement relative to the annulus (dome height) was included in

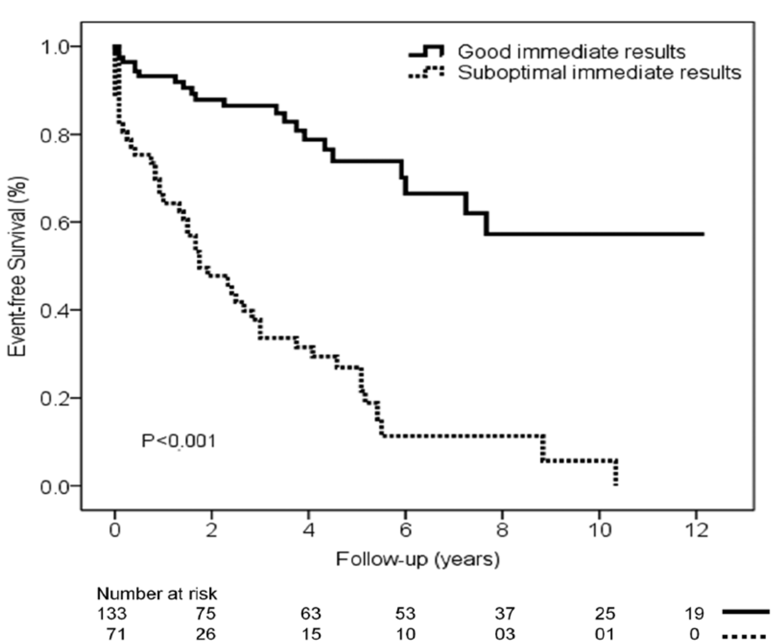

Figure 5. Kaplan-Meier survival curves comparing event-free survival rates according to the immediate results after percutaneous mitral valvuloplasty.

Table 6. Predictors of Long-Term Event-Free Survival

	Univariable Analysis		Multivariable Analysis	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Clinical data				
Age, y	1.036 (1.018–1.054)	<0.001	1.030 (1.008–1.053)	0.007
NYHA functional class	1.461 (1.047–2.038)	0.026	…	…
Atrial fibrillation	1.803 (1.108–2.934)	0.018	…	…
Morphological echocardiographic variables				
MV area, cm^2	0.169 (0.057–0.498)	0.001	…	…
Leaflets displacement, mm	0.864 (0.804–0.928)	<0.001	…	…
CA ratio ≥ 1.25	1.940 (1.196–3.149)	0.007	…	…
Subvalvular thickening	1.830 (1.245–2.689)	0.002	…	…
Modified score, total of points	1.215 (1.120–1.319)	<0.001	…	…
Wilkins score, total of points	1.394 (1.239–1.569)	<0.001	…	…
Postprocedural data				
LAV index, mL/m^2	1.009 (1.003–1.015)	0.002	…	…
Mitral regurgitation degree	2.147 (1.457–3.165)	<0.001	1.740 (1.092–2.774)	0.020
Mean gradient, mm Hg*	1.171 (1.095–1.251)	<0.001	1.138 (1.016–1.273)	0.025
Mean PAP, mm Hg†	1.053 (1.029–1.077)	<0.001	1.035 (1.008 - 1.062)	0.011

CA indicates commissural area; CI, confidence interval; HR, hazard ratio; LAV. left atrial volume; MV, mitral valve; NYHA, New York Heart Association; and PAP, pulmonary artery pressure.

*Gradient measured 24 hours after the procedure by echocardiogram.

†Pulmonary artery pressure invasively measured.

the model, it became the predictor of successful increase in valve area. Therefore, leaflets displacement appears to incorporate the effects of leaflet thickness and calcification and of commissural fusion into a single variable,[17,38] which can be accurately measured in a consistent reference imaging plane.

Predictors of MR

Models designed to predict an inappropriate increase in MR have focused primarily on the qualitative assessment of commissural morphology. Fatkin et al[5] demonstrated the influence of commissural calcification on the short-term outcome in a series of 30 patients. Subsequently, Padial et al[4] reported that the degree and symmetry of commissural disease was associated with the development of severe MR after PMV. Likewise, Cannan et al[6] found that commissural calcification assessed as a categorical variable by 2-dimensional echocardiography was a better predictor of significant MR than the echocardiographic score. Finally, in a study of patients with an echocardiographic score of 8 or less by using the current model, commissural calcification was associated with the development of MR after PMV.[7] In our study, an elevated commissural area ratio was an independent predictor of outcome supporting the importance of commissural morphology in determining immediate outcome of PMV. Commissural area ratio can be considered as a continuum in which the higher the value, the greater the risk of MR. However, for simplicity, we dichotomized this variable in our model. When an abnormal increase in MR occurs in patients with an asymmetrical commissural involvement, it appears to result from excessive splitting of the less calcified commissure.[39]

Although severe MR is accepted as a poor outcome of PMV, the effect of moderate MR has been less clear. We found that the event-free survival rate at 2 years was only 13% in patients with moderate MR in comparison with 62% in those with mild MR (*P*<0.001). Likewise, the rate of mitral valve replacement was significantly greater in patients with moderate MR than in those without significant MR (46% versus 9%, *P*<0.001).

Consistent with other series, we found that MVA and subvalvular thickening were also important predictors of procedural success.[40,41] These parameters also reflect the severity and chronicity of disease and are consistent with previous findings.[13,39,42] The main distinction between our study and previous studies is that we categorized subvalvular involvement in a binary fashion, because the quantification of the severity of the calcification and thickening of the chordae tendinea is difficult, and only severe and extensive subvalvular deformation was a predictor of poor outcome.

Long-Term Event-Free Survival

The prediction of long-term prognosis is primarily influenced by the immediate procedural outcome, the residual hemodynamic consequences of the MS, and the age of the population.[43–48] Our study enrolled a heterogeneous population including older patients with long-standing disease and less-favorable valve anatomy. Consistent with previous studies, long-term outcome was strongly determined by age and the quality of immediate results.[43–48] Age was the only predictor of adverse outcome among the preprocedural factors, whereas immediate post-PMV MR, pulmonary artery pressure, and transvalvular gradient were associated with event-free survival. The morphology of the mitral valve was not an independent predictor of long-term outcome when adjusted for age and postprocedural hemodynamic data. Previous studies that include mitral valve anatomy as a predictor of long-term outcome look at preprocedure variables and thus include poor immediate results of the procedure. However, once the procedure has occurred, these structural findings lose their significance.[49] Similar to our results, Bouleti et al,[43] studying 1024 patients with long-term follow-up after PMV, found that the contribution of valve anatomy with the prediction of late results was restricted to the presence of valve calcification in men. However, the influence of sex on the progression of MS remains unclear.[50] Therefore, late prognosis depends on multiple factors and should be interpreted according to the quality of immediate results.

When the new score was applied to the second validation cohort, results similar to those in the derivation cohort were obtained. However, in this younger group with less severe morphological deformity of the valve, the Wilkins score failed to provide significant risk discrimination.

Conclusions

This study describes a model and score for predicting procedural success based on a composite outcome of increase in valve area, and without worsening MR, in candidates for PMV. The score includes new quantitative parameters to assess leaflet displacement and asymmetry in commissural remodeling in addition to MVA and subvalvular thickening. The presented scoring system was significantly more predictive than the Wilkins score and was particularly valuable in predicting outcome in patients in the intermediate-risk group. The study further showed that, although the morphological features of the valve were useful in predicting procedure outcome once the procedure was performed, only age, degree of MR, mitral gradient, and pulmonary artery pressure were predictive of long-term outcome.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The management of symptomatic mitral stenosis is based on the echocardiographic assessment of valve morphology to determine appropriate therapy. Percutaneous mitral valvuloplasty is currently considered to be the procedure of choice in patients with suitable valve anatomy. In the past 2 decades, the indications of the procedure have been expanded to include patients with unfavorable valve anatomy as a consequence of changes in epidemiology and advances in invasive techniques. Current echocardiographic scoring systems for percutaneous mitral valvuloplasty have inherent limitations that raise the need of an alternate approach to assess valve morphology. Technical refinements in echocardiographic examinations enable a detailed analysis of global mitral valve anatomy affected by the rheumatic process, taking into account the fundamental mechanistic derangement of rheumatic mitral valve stenosis, to assist physicians in selecting the best management strategies for the patients.