The Echo Score Revisited: Impact of Incorporating Commissural Morphology and Leaflet Displacement to the Prediction of Outcome for Patients Undergoing Percutaneous Mitral Valvuloplasty

**Running title:** Nunes et al.; *Prediction of outcome after percutaneous mitral valvuloplasty*

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Abstract

**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 MS undergoing PMV were studied. Mitral valve (MV) morphology was assessed using the 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: MV area ≤ 1cm² (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. Using 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 compared with the Wilkins score, (net reclassification improvement 45.2% (p<0.0001). Long-term outcome was predicted by age and post-procedural variables, including MR, mean gradient and pulmonary pressure.

**Conclusions**—A scoring system incorporating new quantitative echocardiographic parameters more accurately predicts outcome following PMV compared with existing models. Long-term post PMV event-free survival was predicted by age, degree of MR and post-procedural hemodynamic data.

**Key words:** echocardiography, mitral stenosis, percutaneous mitral valve repair
Introduction

Rheumatic valvular disease continues to be a significant problem particularly in developing countries, with mitral stenosis (MS) being a frequent manifestation.\textsuperscript{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.\textsuperscript{2} Currently, this assessment relies primarily on a semi-quantitative scoring system that includes an assessment of leaflet mobility, valve thickening, subvalvular fibrosis and valve calcification (Wilkins score).\textsuperscript{3} Although this scoring method has been widely employed due to 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 semi-quantitative, subject to observer variability and less reliable in classifying patients with scores within the mid-range. Furthermore, it does not include assessment of commissural morphology\textsuperscript{4-7} and thus does not assess postprocedural mitral regurgitation (MR), which is an important predictor of long-term outcome.\textsuperscript{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.\textsuperscript{4, 16-20} Commissural morphology, in particular, asymmetric commissural remodeling, and absolute leaflet displacement in diastole provide quantitative variables, which are based on the fundamental mechanistic derangement of rheumatic mitral valve stenosis and can be reproducibly measured. This present study was designed to: 1) explore more quantitative methods for assessing valvular involvement, in particular, to examine the impact of asymmetric 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 leaflet morphology to predict outcome following PMV a 204 consecutive patients who underwent PMV between January 2000 and October 2011 for symptomatic rheumatic MS, and had at least one comprehensive transthoracic echocardiogram before and within 24 hours after the PMV at our institution (MGH) were studied. The mean age was 57 ± 16 years (range 21 to 88) and 168 were women (82%). Most of the patients were in NYHA functional class III/IV. Mitral valvuloplasty had previously been performed in 45 patients (22%). Atrial fibrillation was present in 93 patients (46%) 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 prior to and within 24 hours after PMV using 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 using standard parasternal and apical views. Mitral valve area (MVA) was measured by direct planimetry of the mitral valve orifice in the paraesternal short-axis view and by the Doppler half-time method (pre-procedure study only).
Peak and mean trans-mitral diastolic pressure gradients were measured from Doppler profiles recorded in the apical four-chamber view. The presence and severity of MR was evaluated by integrating data from the color flow image,\(^2\) analysis of the vena contracta,\(^3\) and study of the pulmonary venous systolic reflux. The continuous-wave Doppler tricuspid regurgitant velocity was used to determine systolic pulmonary artery pressure (SPAP) using the simplified Bernoulli equation assigning a value of 10mmHg to account for right atrial pressure. Left atrial (LA) volume was assessed by the biplane area-length method from apical 2- and 4-chamber views. All results were based on the average of three measurements for patients in sinus rhythm and five measurements for patients in atrial fibrillation. Each echocardiogram was analyzed offline by two 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 semi-quantitative grading of mitral valve leaflet mobility, thickening, calcification and subvalvular thickening, each on a scale of 0-4, 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, while 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. Secondly, the ventricular (outer) surface of the leaflets was traced and the area between the two tracings recorded. The major diameter of the outer border was then
measured and its mid-point 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 measured (Figure 1). Symmetry of commissural thickening was then quantified as the ratio between the leaflet areas on either side of the minor dimension. Since 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 four chamber view as the distance from the mitral annulus to the mid portion of the leaflets at their point of maximal displacement from the annulus (doming height) in diastole (Figure 2). The mid-portion of the leaflet was taken as the end of the height measurement in order to account for variation in leaflet calcification.

**Cardiac catheterization/Percutaneous mitral valvuloplasty**

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 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). Mitral regurgitation was assessed by left ventriculography after the procedure and graded using Sellers classification. PMV was performed using an anterograde trans-septal approach using either the double-balloon or Inoue technique a previously described.\(^ {26}\)

**Procedural success and endpoint definitions**

Procedural success was defined as an increase $\geq 50\%$ of mitral valve area or a final area $\geq 1.5 \text{ cm}^2$, with no more than one grade increment in MR severity assessed by echocardiography 24
hours after the procedure. The reference measurement for MVA was two-dimensional echocardiography planimetry.\textsuperscript{27, 28}

The long-term outcome was a composite endpoint of death, mitral valve replacement or repeat PMV. Outcome data was obtained from follow up appointments in the clinic or by reviewing 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.

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 chi-square test, whereas continuous data, expressed as median and interquartile range, were compared using Student’s unpaired and paired t-test or the Mann–Whitney U test, as appropriate. Logistic regression analysis was used to identify predictors of post procedural outcome.

Our strategy for the multivariable analysis included the four echocardiographic components of 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 continuous format followed subsequently by categorizing the continuous variables to construct the score.

The performance of the models was assessed using standard bootstrapping procedures...
and the models were compared using Akaike information criterion (AIC). A shrinkage coefficient was used to quantify overfitting.\textsuperscript{29-31} The discrimination and calibration of the final multivariable models in both derivation and validation datasets were measured to assess their performance in outcome prediction.\textsuperscript{31-34} After correcting for overfitting, calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test\textsuperscript{35} and a calibration plot.

Receiver-operating characteristic (ROC) curves were used to identify 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 $\beta$ 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 three 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 (NRI).\textsuperscript{36} The integrated discrimination improvement (IDI) was also estimated focusing on the differences between integrated sensitivities and one minus specificities for both models.\textsuperscript{34, 36, 37}

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 using a Cox proportional hazards model. The
association of the outcome with baseline and post-procedural factors was evaluated using a stepwise variable selection technique. The selected variables for the multivariable model were age, NYHA functional class, atrial fibrillation, and morphological echocardiographic variables, including MVA, leaflet displacement, commissural area ratio, subvalvar thickening, total of points of modified score and Wilkins score. Subsequently, post-procedural 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, North Carolina), and R software, version 2.15.1 (R foundation for statistical computing, Vienna, Austria).

Results

Immediate Outcome

Derivation Cohort

Percutaneous mitral valvuloplasty was successful in 133 patients (65%) with a mean MVA increase from $1.1 \pm 0.3$ to $2.0 \pm 0.6 \text{ cm}^2$ ($p<0.001$), mean gradient decrease from $12.1 \pm 4.5$ to $6.1 \pm 2.1 \text{ mmHg}$ ($p<0.001$) and mean pulmonary pressure decrease from $36.1 \pm 11.4$ to $29.9 \pm 10.3 \text{ mmHg}$ ($p<0.001$). PMV was considered unsuccessful because of insufficient valve opening in 31 patients (15%) or greater than 1 grade increase in MR grade in 40 patients (20%). In 26 of these patients the resulting MR was moderate while in 14 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 as well as the total echocardiographic score (Wilkins),
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% CI 0.34 - 1.40). Age, gender, 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.

In order 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, two
multivariate analyses were performed. In the first multivariable model, the four
echocardiographic components of Wilkins score were included, to determine whether the
individual components were independently predictive of outcome or whether there was overlap
between components. Using 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 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.

**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 post-procedural mitral valve area and of increase in MR separately. When valve area was evaluated as a continuous outcome, the variables that remained in the model were baseline mitral valve area, the maximum leaflet displacement, and commissural area ratio, whereas commissural area ratio (odds ratio [OR] per 10% of increase ratio 1.226, 95% confidence interval [CI] 1.067 – 1.408, p=0.004) and subvalvular thickening (OR 2.705, 95% CI 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 AIC of 200.064 whereas using the dichotomized variables the AIC was 201.232.

A point-based scoring system was developed from the final multivariable logistic regression model (Table 3). This modified echocardiographic score included four echocardiographic variables (mitral valve area, maximum leaflet displacement, commissural area ratio, and subvalvular involvement). Three risk groups 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.* The bounds were chosen based on the extent of structural damage to the mitral valve due to rheumatic disease. A patient is considered to be at low risk when only one morphological feature of rheumatic mitral stenosis was found. Intermediate risk was defined when two structural pathological changes were detected. High risk patients are defined as patients with at least two structural changes in the commissures, cusps, and chordae.

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* The bounds were chosen based on the extent of structural damage to the mitral valve due to rheumatic disease. A patient is considered to be at low risk when only one morphological feature of rheumatic mitral stenosis was found. Intermediate risk was defined when two structural pathological changes were detected. High risk patients are defined as patients with at least two structural changes in the commissures, cusps, and chordae.
tendinea combined, regardless of the orifice area.

* Scores of 1, 4, 7, and 10 cannot be calculated using the values assigned to the individual variables.

The new score significantly improved reclassification of subjects with unfavorable results of PMV, with a net reclassification improvement (NRI) of 45.2% (p<0.0001) when compared to the Wilkins score. The integrated discrimination improvement (IDI) was estimated as 13.2% comparing 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 NRI of 76.8% (p<0.001) (Table 4).

Although there was a high concordance between Wilkins score and new score in high-risk patients, 15 patients in low-risk of Wilkins score were reclassified in high-risk with the new score. As the rate of unsuccessful procedure was high in this subgroup of patients, especially due to 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 to 65), 107 (88%) were women. Most of the patients were in NYHA functional class III or IV. At presentation, 19 (16%) was in atrial fibrillation. The characteristics of the validation cohort comparing with derivation cohort are shown in Table 5.

These patients were younger, had smaller MVA’s but less morphologic 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 due to disruption of the valve integrity, which was confirmed during surgery for MV replacement (a tear of the posterior mitral leaflet in 2 patients, and 1 patient had chordal rupture).

The majority of the patients (83%) were in low risk using the Wilkins score, 20 patients in the intermediate risk and only one in the high-risk group. The total Wilkins score did not predict immediate adverse outcome after PMV in this population. However, applying the new scoring system in the validation cohort, 102 patients were classified in low risk, 11 in the intermediate risk, and 8 in the high-risk group, with the suboptimal results 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 to 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 to 146), 70 adverse clinical events were observed, including 30 deaths, 32 MV replacements, and 8 repeat PMV. The long-term event-free survival was strongly determined by the quality of immediate results (hazard ratio 5.383; 95% CI 3.226 to 8.981, p<0.001) (Figure 5). Event-free survival rate at 1-, 3- and 5-years follow-up was 88%, 79% and 71% in patients with good results compared to 49%, 32% and 12% in those who had a suboptimal result after PMV.
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 post procedure 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) while all of the components of the current echo score (Wilkins) were related to immediate outcome on individual analysis, only leaflet 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 post procedure 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, as well scores combining groups of variables 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 semi-quantitative 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 four 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 analyzed 555 patients with MS and found that leaflet mobility was the only independent morphologic feature for predicting MV area after PMV.\(^{38}\) 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 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 Mitral Regurgitation**

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 mitral regurgitation after PMV. Likewise, Cannan et al \(^6\) found that commissural calcification assessed as a categorical variable by two-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 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. Comissural 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 asymmetric 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 event-free survival rate at 2 years was only 13% in patients with moderate MR compared 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 mitral valve area 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 since the quantification of the severity of the calcification and thickening of the chordae tendinae 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 old 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 pre-procedural factors, whereas immediate post-PMV mitral regurgitation, 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 pre-procedure 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 studying 1024 patients with long-term follow-up after PMV found that the contribution of valve anatomy to the prediction of late results was restricted to the presence of valve calcification in men.\(^{43}\) 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...
morphologic 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 mitral valve area 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 while morphologic 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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**Conflict of Interest Disclosures:** None.

**References:**


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Table 1. Characteristics of the study population according to immediate outcome after PMV

<table>
<thead>
<tr>
<th>Variables</th>
<th>Success (n=133)</th>
<th>Suboptimal (n=71)</th>
<th>Odds ratio* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 [43/68]</td>
<td>65 [52/76]</td>
<td>2.014 (1.458-2.804)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.75 [1.61/1.96]</td>
<td>1.70 [1.58/1.84]</td>
<td>0.782 (0.581-1.053)</td>
<td>0.105</td>
</tr>
<tr>
<td>Female gender (n/%)</td>
<td>109 (82)</td>
<td>59 (83)</td>
<td>0.792 (0.371-1.693)</td>
<td>0.548</td>
</tr>
<tr>
<td>Atrial fibrillation (n/%)</td>
<td>62 (47)</td>
<td>34 (48)</td>
<td>1.260 (0.715-2.223)</td>
<td>0.424</td>
</tr>
<tr>
<td>Previous mitral valve procedure †</td>
<td>32 (24)</td>
<td>13 (18)</td>
<td>0.688 (0.339-1.395)</td>
<td>0.300</td>
</tr>
<tr>
<td>MV area (cm²) ‡</td>
<td>1.1 [0.98/1.3]</td>
<td>0.98 [0.83/1.1]</td>
<td>0.429 (0.292-0.628)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAV index (mL/m²)</td>
<td>59 [46/78]</td>
<td>64 [49/94]</td>
<td>1.221 (0.852-1.742)</td>
<td>0.274</td>
</tr>
<tr>
<td>Fluoroscopic calcium grade ≥ 2</td>
<td>12 (9)</td>
<td>22 (31)</td>
<td>4.067 (1.433-11.537)</td>
<td>0.008</td>
</tr>
<tr>
<td>Echocardiographic score determinants</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thickness</td>
<td>2 [1/2]</td>
<td>2 [2/3]</td>
<td>1.674 (1.227-2.286)</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium</td>
<td>2 [1/2]</td>
<td>2 [2/3]</td>
<td>1.896 (1.391-2.588)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mobility</td>
<td>2 [2/2]</td>
<td>2 [2/3]</td>
<td>1.860 (1.354-2.555)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wilkins score (total of points)</td>
<td>8 [6/9]</td>
<td>9 [8/10]</td>
<td>2.264 (1.615-3.181)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wilkins score ≥ 10 points</td>
<td>24 (18)</td>
<td>32 (45)</td>
<td>3.726 (1.958-7.091)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum leaflet displacement (mm)</td>
<td>15 [12/17]</td>
<td>12 [10/15]</td>
<td>0.451 (0.318-0.641)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Commissural area ratio</td>
<td>1.1 [1.0/1.2]</td>
<td>1.2 [1.1/1.4]</td>
<td>1.998 (1.257-3.176)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are expressed as absolute number (percentage) or median and interquartile range

*: odds ratio per 1 SD increase.
†: Surgical commissurotomy or percutaneous valvuloplasty.
‡: Planimetry could not be performed in 9 patients due to very irregular and calcified mitral orifice and MVA was calculated by PHT.

LAV=left atrial volume, MV = mitral valve
Table 2. Multivariable predictors of immediate outcome after PMV

<table>
<thead>
<tr>
<th>Models</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1: Wilkins score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaflets calcification</td>
<td>1.943</td>
<td>1.339 – 2.818</td>
<td>0.002</td>
</tr>
<tr>
<td>Subvalvular thickening</td>
<td>2.083</td>
<td>1.167 – 3.718</td>
<td>0.013</td>
</tr>
<tr>
<td>Leaflets mobility</td>
<td>1.487</td>
<td>0.799 – 2.767</td>
<td>0.211</td>
</tr>
<tr>
<td>Leaflets thickness</td>
<td>1.298</td>
<td>0.694 – 2.426</td>
<td>0.414</td>
</tr>
<tr>
<td>Wilkins score (total of points)*</td>
<td>1.484</td>
<td>1.260-1.747</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Model 2: New model with variables in continuous format</strong> †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV area (cm²) ‡</td>
<td>0.113</td>
<td>0.021-0.622</td>
<td>0.012</td>
</tr>
<tr>
<td>Maximum displacement of leaflets (mm)</td>
<td>0.842</td>
<td>0.748-0.948</td>
<td>0.004</td>
</tr>
<tr>
<td>Commissural area ratio</td>
<td>1.182</td>
<td>1.028-1.358</td>
<td>0.019</td>
</tr>
<tr>
<td>Subvalvular thickening†</td>
<td>1.932</td>
<td>1.027-3.624</td>
<td>0.041</td>
</tr>
</tbody>
</table>

*: 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 (absente or mild versus extensive thickening)

Table 3. Score for Immediate Outcome Prediction*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence (n/%)</th>
<th>β coefficient</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV area ≤ 1cm²</td>
<td>73 (36)</td>
<td>1.006</td>
<td>2.734</td>
<td>1.321 – 5.656</td>
<td>0.007</td>
<td>2</td>
</tr>
<tr>
<td>Maximum LD ≤ 12 mm</td>
<td>71 (35)</td>
<td>1.224</td>
<td>3.400</td>
<td>1.654 – 6.992</td>
<td>0.001</td>
<td>3</td>
</tr>
<tr>
<td>CA ratio ≥ 1.25</td>
<td>75 (37)</td>
<td>1.132</td>
<td>3.100</td>
<td>1.506 – 6.384</td>
<td>0.002</td>
<td>3</td>
</tr>
<tr>
<td>Subvalvular involvement†</td>
<td>37 (18)</td>
<td>1.173</td>
<td>3.231</td>
<td>1.355 – 7.709</td>
<td>0.008</td>
<td>3</td>
</tr>
</tbody>
</table>

Constant = - 2.140
*: Shrinkage factor of 0.897
†: absente or mild versus extensive thickening
CA = Commissural area; MV = mitral valve; LD = Leaflet displacement
**Table 4.** Immediate outcome after PMV as predicted by both previous and modified echocardiographic score

<table>
<thead>
<tr>
<th>Wilkins score</th>
<th>Modified echocardiographic score</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Number of individuals</td>
<td>96</td>
<td>14</td>
<td>15</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>Suboptimal</td>
<td>13</td>
<td>8</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Success</td>
<td>83</td>
<td>6</td>
<td>7</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Proportion of suboptimal</td>
<td>13.5</td>
<td>57.1</td>
<td>53.3</td>
<td>23.2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Number of individuals</td>
<td>34</td>
<td>18</td>
<td>20</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Suboptimal</td>
<td>9</td>
<td>10</td>
<td>16</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Success</td>
<td>25</td>
<td>8</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Proportion of suboptimal</td>
<td>26.5</td>
<td>55.6</td>
<td>80.0</td>
<td>48.6</td>
</tr>
<tr>
<td>High</td>
<td>Number of individuals</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Suboptimal</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Success</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Proportion of suboptimal</td>
<td>…</td>
<td>…</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>Number of individuals</td>
<td>130</td>
<td>32</td>
<td>42</td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>Suboptimal</td>
<td>22</td>
<td>18</td>
<td>31</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Success</td>
<td>102</td>
<td>14</td>
<td>17</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>Proportion of suboptimal</td>
<td>16.9</td>
<td>56.3</td>
<td>73.8</td>
<td>34.8</td>
</tr>
</tbody>
</table>
Table 5. Characteristics of the derivation cohort compared with the validation cohort

<table>
<thead>
<tr>
<th>Variables</th>
<th>Main cohort (n=204)</th>
<th>Validation cohort (n=121)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 [45/70]</td>
<td>41 [33/49]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.72 [1.59/1.91]</td>
<td>1.6 [1.5/1.75]</td>
<td>0.001</td>
</tr>
<tr>
<td>Female gender (n/%)</td>
<td>168 (82)</td>
<td>107 (88)</td>
<td>0.142</td>
</tr>
<tr>
<td>Atrial fibrillation (n/%)</td>
<td>96 (47)</td>
<td>19 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MV area (cm²) *</td>
<td>1.1 [0.9/1.3]</td>
<td>1.0 [0.8/1.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak gradient (mmHg)</td>
<td>21 [16/26]</td>
<td>19 [16/25]</td>
<td>0.182</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>11 [8/14]</td>
<td>11 [8/15]</td>
<td>0.389</td>
</tr>
<tr>
<td>SPAP (mmHg)</td>
<td>48 [38/62]</td>
<td>46 [40/56]</td>
<td>0.506</td>
</tr>
<tr>
<td>Echocardiographic score determinants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickness</td>
<td>2 [2/2]</td>
<td>2 [2/2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium</td>
<td>2 [1/3]</td>
<td>1 [1/2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mobility</td>
<td>2 [2/2]</td>
<td>2 [2/2]</td>
<td>0.742</td>
</tr>
<tr>
<td>Subvalvular</td>
<td>2 [2/2]</td>
<td>2 [2/2]</td>
<td>0.198</td>
</tr>
<tr>
<td>Wilkins score (total of points)</td>
<td>8 [6/10]</td>
<td>7 [6/8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum leaflet displacement (mm)</td>
<td>14 [11/16]</td>
<td>15 [13/16]</td>
<td>0.006</td>
</tr>
<tr>
<td>Commissural area ratio</td>
<td>1.2 [1.1/1.4]</td>
<td>1.1 [1.0/1.1]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Pre-procedural data (Cardiac catheterization)**
- Mean PAP (mmHg) 33 [27/41] 35 [26/42] 0.689
- LA pressure (mmHg) 23 [19/27] 23 [18/28] 0.404

**Postprocedural data**
- Increased in MR grade 40 (20) 13 (11) 0.037
- MV area (cm²) 1.5 [1.3/1.8] 1.6 [1.4/1.8] 0.426
- Mean gradient (mmHg) † 7 [5/8] 5 [4/7] <0.001
- Mean PAP (mmHg) 32 [24/38] 27 [23/36] 0.208
- LA pressure (mmHg) 19 [14/24] 15 [12/19] <0.001

Data are expressed as number (percentage) or median and interquartile range
*: MVA by planimetry
†: Gradient measured 24 hours after the procedure by echocardiogram
LA= left atrium; MV= mitral valve; PAP = pulmonary artery pressure; SPAP = systolic pulmonary artery pressure
Table 6. Predictors of long-term event-free survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.036 (1.018-1.054)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1.461 (1.047-2.038)</td>
<td>0.026</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.803 (1.108-2.934)</td>
<td>0.018</td>
</tr>
<tr>
<td>Morphological echocardiographic variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV orifice area (cm²)</td>
<td>0.169 (0.057-0.498)</td>
<td>0.001</td>
</tr>
<tr>
<td>Leaflets displacement (mm)</td>
<td>0.864 (0.804-0.928)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CA ratio ≥ 1.25</td>
<td>1.940 (1.196-3.149)</td>
<td>0.007</td>
</tr>
<tr>
<td>Subvalvular thickening</td>
<td>1.830 (1.245-2.689)</td>
<td>0.002</td>
</tr>
<tr>
<td>Modified score (total of points)</td>
<td>1.215 (1.120-1.319)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wilkins score (total of points)</td>
<td>1.394 (1.239-1.569)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postprocedural data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAV index (mL/m²)</td>
<td>1.009 (1.003-1.015)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mitral regurgitation degree</td>
<td>2.147 (1.457-3.165)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean gradient (mmHg)*</td>
<td>1.171 (1.095-1.251)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean PAP (mmHg) †</td>
<td>1.053 (1.029-1.077)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*: Gradient measured 24 hours after the procedure by echocardiogram
†: Pulmonary artery pressure invasively measured

CA = Commissural area; HR = hazard ratio; LAV= left atrial volume; MV= mitral valve; PAP = pulmonary artery pressure

Figure Legends:

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

**Figure 2.** Echocardiographic apical four-chamber view showing maximum apical displacement of the leaflets relative to the mitral annulus.
**Figure 3.** Observed versus Predicted immediate outcome for success (left panel) and suboptimal results after percutaneous mitral valvuloplasty (right panel).

**Figure 4.** Predicted (closed circle) versus observed (open bars) suboptimal immediate results after percutaneous mitral valvuloplasty (PMV) for integer increments in the risk score in the validation cohort.

**Figure 5.** Kaplan–Meier survival curves comparing event-free survival rates according to the immediate results after percutaneous mitral valvuloplasty (PMV).
Commissural Area Ratio

Symmetry = \frac{\text{Area Max}}{\text{Area Min}}

Figure 1
Figure 2
Figure 3
Suboptimal immediate results in the validation set

- **Observed**
- **Predicted**

**Suboptimal Results (%) vs. Score Points**

- Score Points: 0, 2, 3, 5, 8
- Suboptimal Results: 0, 20, 40, 60, 80, 100

Figure 4
The Echo Score Revisited: Impact of Incorporating Commissural Morphology and Leaflet Displacement to the Prediction of Outcome for Patients Undergoing Percutaneous Mitral Valvuloplasty

Maria Carmo P. Nunes, Timothy C. Tan, Sammy Elmariah, Rodrigo do Lago, Ronan Margey, Ignacio Cruz-Gonzalez, Hui Zheng, Mark D. Handschumacher, Ignacio Inglessis, Igor F. Palacios, Arthur E. Weyman and Judy Hung

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