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Research

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Biomarkers Score for Patients with Mitral Stenosis: A useful conjunction with Wilkins's Score for Early Intervention

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ABSTRACT

Objective: We proposed a novel new insight independent score of Mitral Stenosis (MS) based on elevated biomarkers.
Subjects and Methods: One hundred sixty-eight patients with MS candidate for Percutanous balloon valvuloplasty (PBMV) were included in the study. Brain Natriurectic Peptide (BNP), Tenascin-C (TN-C), copeptin and high-sensitive C-reactive protein (hs-CRP) were measured before PBMV. The cut-off value of each biomarker for prediction of systolic pulmonary artery pressure >50 mm Hg was calculated. Two points were given to a value ≥cut-off value and one point if less. Summation of points gave the biomarkers score.
Results: A biomarker score cut-off value ≥5.2 had a sensitivity of 83.6%, a specificity of 82.9% (AUC=0.85), in predicting cardiac events after successful PBMV. The Wilkins's score of ≥6.5 had a sensitivity of 73.5%, a specificity of 79.2% (AUC=0.80). The conjunction of Wilkins's score with biomarker score have higher predicting power (AUC=97%). The correlation co-efficient of biomarker score was (r=0.755), greater than that of the Wilkin's score (r=0.613). The combined biomarkers and Wilkins's score showed the strongest correlation with cardiac events (r=0.911). In multiple regression analysis, the regression co-efficient of biomarker score versus Wilkin's score was (0.595 *versus* 0.364), and the combined scores had the strongest powerful independent predictor of cardiac events (r=0.825).
Conclusions: In patients with MS especially asymptomatic patients, biomarker risk score that included BNP, tenacin-c, copeptin and hs-CRP and, had a good correlation with clinical outcomes after successful PBMV, and the conjunction of the biomarkers score and Wilkin's score provided higher prognostic value.

KEYWORDS: Wilkins's score; Biomarkers score; Mitral stenosis; Valvuloplasty.

ABBREVIATIONS: MS: Mitral Stenosis; PBMV: Percutanous balloon valvuloplasty; BNP: B-type natriuretic peptide; BMV: Balloon Mitral Valvuloplasty; MV: Mitral Valve; TN-C: Tenascin C; hs-CRP: High sensitive C-reactive protein; LA: Left Atrial; SPAP: Systolic Pulmonary Artery Pressure; PMV: Percutaneous mitral balloon valvuloplasty; EDTA: Ethylenediaminetetraacetic acid; ROC: Receivers Operating Characteristic.

INTRODUCTION

Rheumatic valvular heart diseases continue to be a major health problem in developing countries. Mitral stenosis is one of the most frequently encountered rheumatic valvular heart disease affections.[1,2] Mitral stenosis is a progressive disease, characterized by hemodynamic abnormalities as well as a rheumatic process,[3,4] causing progressive obstruction of left ventricular inflow. When the valve area decreases to <2 cm^2, subjects usually develop dyspnea with exertion as an initial symptom. Once this area falls to below 1.5 cm^2, intervention is of-

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ten necessary because of the intolerable symptoms, arrhythmia or pulmonary hypertension, especially in patients with a valve morphology suitable for PMBV.

Regular follow up for patients with significant mitral stenosis is crucial to take the proper decision of intervention in the proper time (either surgical replacement or alternatively balloon valvuloplasty if the valve morphology is suitable). It is frequently encountered that rheumatic MS patients describe equivocal symptoms. Due to the long latent period between onset of the initial rheumatic valvular affection and development of significant mitral stenosis, it is difficult for the treating physician to truly identify patients with symptoms that could be attributed to either hemodynamically significant stenosis or non cardiac dyspnea. Some patients who are considered asymptomatic adapt their level of exertion and thereby do not get symptoms. Symptomatic status is mainly subjective, and hence a better risk stratification objective tool is required to be implemented in regular follow up of rheumatic MS patients.[5]

The safety and success of Balloon Mitral Valvuloplasty (BMV) techniques is mostly dependent on the selection of patients. There are multiple predictors of the outcome, including age, functional class, previous commissurotomy, pre-procedure Mitral Valve (MV) area, valve anatomy, and balloon size used.[6] Brain natriuretic peptide (BNP) a useful biomarker would reflect disease severity, increase with progression of disease, reflect subclinical myocardial dysfunction, discriminate between patients in whom symptoms do and do not develop in the short to medium term, and be easily and reliably measured.[7]

Fibrotic changes in the heart and lung tissue are controlled by the activity of proteolytic enzymes, such as extracellular matrix-degrading metalloproteinases.[8] Matrix metalloproteinases can stimulate the secretion of TN-C, which acts as a strong mitogenic cofactor, leading to smooth muscle cell proliferation.[9] High sensitive C-reactive protein (hs-CRP) predicts morbidity and mortality in various clinical conditions. The effect of hs-CRP on progression of chronic rheumatic mitral stenosis may have a role, especially in developing atrial fibrillation and left atrial thrombi.

We hypothesize that biomarkers may be responsible for the progression of pulmonary hypertension and may be the cause beyond recurrence of symptoms or restenosis after successful PBMV. So we aimed to introduce a new insight of scoring regarding selection of patients with mitral stenosis for PBMV early, even in asymptomatic patients named (Biomarker score for PBMV).

PATIENTS AND METHODS

One hundred and sixty-eight patients with moderate to severe rheumatic mitral stenosis (MS) [MVA≤1.5 cm^2], were included in this study. All patients had suitable mitral valve scores for percutaneous dilation (mitral valve scores of ≤8).[10] Exclusion criteria were poor echocardiography window, significant renal impairment, presence of ischemic heart disease by history or resting wall motion abnormality on echo-Doppler study, previous cardiac surgery or valve intervention, coexistent heart muscle disease or other valvular lesion (if graded more than mild) or more, presence of Left Atrial (LA) thrombi. The study was approved by the local ethics committee, and written informed consent was obtained from all patients enrolled in the study.

ECHOCARDIOGRAPHIC EVALUATION

Comprehensive two-dimensional and color Doppler transthoracic echocardiogram was performed before PMV, using Vivid 7 instruments (GE Medical Systems, Milwaukee, Wisc., USA). The morphologic features of the mitral valve were categorized using the Wilkins echo score and the total echocardiographic score was obtained by adding the scores for leaflet mobility, thickness, calcification, and subvalvular lesions. Mitral Valve Area (MVA) was measured by direct planimetry in parasternal short-axis view, and continuous wave Doppler was used to calculate peak pressure gradient of tricuspid regurgitation. Mitral and tricuspid regurgitation were graded from 0 to 4+, depending on the spatial extent of the color flow jet area expressed as a percentage of the left or right atrial area. Systolic Pulmonary Artery Pressure (SPAP) was derived from the tricuspid regurgitant jet velocity (v) with the modified Bernoulli equation (4v2) and assuming a right atrial pressure of 10 mm Hg.[11] Patients were screened for left atrial thrombus with a two-dimensional transesophageal echocardiogram in the 24 h preceding the procedure. If thrombus was detected, the patient was not a candidate for PBMV. Transthoracic echocardiographic measurement of MVA and quantification of MR were repeated one day after Percutaneous mitral balloon valvuloplasty (PMV).

BIOCHEMICAL ANALYSIS

Brain Natriuretic Peptide Measurement

All samples were collected by veni-puncture into Ethylenediaminetetraacetic acid (EDTA) tubes within 2 hours of obtaining the baseline echocardiogram and one week after PMC (for group I). The blood samples were kept at room temperature and analyzed within 4 hours of sampling using the Triage BNP assay (Biosite diagnostics). Before analysis, each tube was inverted several times to ensure homogeneity. The BNP assay was a sandwich immuno-assay that consisted of a disposable device to which EDTA anticoagulated whole blood or plasma was added.

Serum Tenascin-C Measurement

Blood samples for TN-C were obtained before and 1 month after PMBV in the mitral stenosis group and obtained once in the control group. The blood samples for TN-C (ELISA kit for Human Tenascin, Uscn Life Science Inc., Wuhan, China) were obtained and centrifuged, then stored at -70 ºC until analy-

sis in all study subjects. Serum TN-C levels were measured with the large subunit containing the C dominant of FN III repeats level using one-step sandwich enzyme immunoassay kits.

Serum copeptin Measurement

Blood samples for copeptin (ELISA kit for Human Copeptin, Uscn Life Science Inc., Wuhan, China) were obtained immediately before and 24 h after PBMV, centrifuged, then stored at -70 ºC until assayed. The detection limit of the assay was 7.4 pg/ml.

High Sensitive C-reactive Protein Analysis

Blood samples were centrifuged and the serum was stored at -70 ºC until analysis. High sensitivity C-reactive protein (hs-CRP) levels were measured using high sensitivity assay (N Latex CRP Mono; Dade Behring, Marburg, Germany) by means of particle-enhanced immunonephelometry using the Behring Nephlometer System that allows detection of levels as low as 0.175 mg/L.

Percutaneous mitral balloon valvuloplasty: All patients underwent complete diagnostic right and left heart catheterization before MBV. All patients were given intravenous heparin (100 U/kg) immediately after we achieved LA access by means of transseptal left heart catheterization. Mitral balloon valvuloplasty was performed via a transatrial approach using multitrack double balloon technique. Procedural success was defined as MVA≥1.5 cm^2 and MR≤2/4, as used by Song, et al.[12]

Clinical and Echocardiographic Follow-up

A detailed clinical and echocardiographic (2D, continuous-wave Doppler and color-flow imaging) assessment were conducted at every 3 months for the first year and at 6-month intervals thereafter, with a median duration of 31 (range 19-54) months. The predefined study endpoints were assessed: a composite clinical events endpoint including cardiovascular death, mitral valve re-intervention, newly developed atrial fibrillation (AF), progressive re-elevation of pulmonary artery pressure, and hospital readmission due to decompensated heart failure. The patients were divided into two groups (favorable and unfavorable) according to clinical events and the need for post-PBMV mitral re-intervention or surgery.

Statistical Analysis

All continuous variables are reported as mean±SD or as percentages. Analysis was done with SPSS 16.0 (SPSS, an IBM company; Chicago, Ill, USA). Receivers Operating Characteristic (ROC) curves were calculated to determine the best cut-off values of studied biomarkers for predicting sPAP ≥50 mm Hg. Receivers operating characteristic (ROC) curves were calculated to determine the best cut-off values of biomarker score and Wilkins's score in predicting cardiac events after PBMV. Associations of biomarker score and echocardiographic parameters with outcomes were evaluated by use of the Spearman correlation coefficient. Independent predictors of biomarker score were determined by means of multiple regression analysis. Standardized *B* regression coefficients and their significance as determined by multilinear regression analysis were reported.

RESULTS

The demographic, echocardiographic and biochemical variables are presented in Table 1.

Variable	
Age (years)	39.6±1.5
Male/Females	75/93
BSA (m^2)	1.67±0.85
Atrial fibrillation rhythm	25/168
NYHA Class	2.1±0.7
Systolic blood pressure (mmHg)	117±10
Diastolic blood pressure (mmHg)	70±5
Echo-score	5.6±1.9
MVA–2D planimetry (cm^2)	0.97±0.2
Mean transmitral gradient (mmHg)	15.9±5.6
LA antero-posterior diameter (mm)	50.1±0.55
LVEDD (mm)	43.2±0.5
LVESD (mm)	26.5±0.3
LVEF (%)	69.9±11.8
RV diastolic diameter (mm)	32.5±1.1
PAPs (mmHg)	67.5±24.2
Mitral regurgitation grade	0.81±0.63
Brain natriuretic peptide (pg/ml)	112.5±41.3
Tenascin-C (ng/ml)	18.0±4.1
Copetin (pg/ml)	69.5±31.8
hs-CRP (mg/l)	4.9±2.7

BSA: Body Surface Area; MVA: Mitral Valve Area; 2D: Two dimensional; LVEDD: Left Ventricular End Diastolic; LVESD: Left Ventricular End Systolic; PAPs: Pulmonary artery systolic pressure; hs-CRP: high sensitive C-reactive protein.

Table 1: Baseline demographic, echocardiograpic and biomarkers data of patients with mitral stenosis Included in the study.

Calculation of the Biomarker Score

ROC curve analysis demonstrates overall, the cut off value of BNP, tenacin-C, copeptin and hs-CRP were 75.0 pg/ml, 12.5 ng/ml, 70.0 ng/ml and 5.8 mg/l respectably showed the best sensitivity and specificity for predicting sPAP>50 mm Hg (Table 2). Then we gave two points for each marker for a value equal or more than the demonstrated cut-off value and one point for the value less than the cut-off value [the total score was 4-8 point], (Table 3). The echocardiographic variables in patients with MS were significantly improved after PBMV (Table 4). All patients had an echo score under 8, reflecting the selected nature of this population. Procedural success was achieved in 161of 168(96%)

Biomarker	Cut-off	Sensitivity (%)	Specificity (%)	AUC	95% CI	P value
BNP (pg/ml)	≥75.0	80	73	0.72	0.63-0.82	<0.002
Tenacin-c (ng/ml)	≥12.5	82	50	0.73	0.64-0.82	<0.002
Copeptin (pg/ml)	≥70.0	76	64	0.69	0.58-0.80	<0.003
Hs-CRP (mg/l)	≥5.8	73	82	0.71	0.58-0.83	<0.002

BNP: Brain Natriuretic Peptide; Hs-CRP: high sensitive C-reactive protein.

Table 2: Validity of biomarkers cut-off values in predicting systolic pulmonary artery pressure ≥50 mm Hg in patients with mitral stenosis.

Biomarker	Cut-off value	Points
BNP level (pg/ml)	<75.0	1
	≥75.0	2
Tenascin-C (ng/ml)	<12.5	1
	≥12.5	2
Copeptin (pg/ml)	<70.0	1
	≥70.0	2
Hs-C-reactive protein (mg/l)	<5.8	1
	≥5.8	2
Total score		4-8

Table 3: Biomarker score for PBMV in patients with mitral stenosis.

Variable	Before PBMV	After PBMV	P-value
MVA–2D planimetry (cm^2)	0.97±0.2	2.2±0. 3	<0.001
Mean transmitral gradient (mmHg)	15.9±5.6	3.5±3.1	<0.0001
LA antero-posterior diameter (mm)	50.1±0.55	43.3±0.22	<0.02
LVEDD (mm)	43.2±0.5	43.5±0.7	>0.05
LVESD (mm)	26.5±0.3	26.3±0.6	>0.05
LVEF (%)	69.9±11.8	68.2±10.1	>0.05
RV diastolic diameter (mm)	32.5±1.1	24.7±0.6	<0.02
PAPs (mmHg)	67.5±24.2	33.7±15.2	<0.001

MVA: Mitral valve area; 2D: Two dimensional; LVEDD: Left ventricular end diastolic; LVESD: Left ventricular end systolic; PAPs: Pulmonary artery systolic pressure.

Table 4: Echocardiographic variables before and one day after percutaneous mitral valvuloplasty (PBMV).

patients, using the above-mentioned definition. The 7 inadequate immediate results were related to suboptimal valve opening (valve area <1.5 cm^2) in 6 cases and severe MR (grade≥3) in one cases.

During follow-up 67 patients developed unfavorable outcomes, (4 patients showed worsening of MR, 23 patients showed newly developed AF, 29 patients showed progressive re-elevation of pulmonary artery pressure and, 5 underwent repeat PBMV, and 6 hospital admissions due to decompensated heart failure). No valve replacement or death was recorded. Table 5 shows a comparison between patients with favorable *vs.* those with unfavorable outcomes after PBMV. The mean Wilkin's score was comparable between both groups (P>0.05), while the biomarker score was significantly elevated in those with unfavorable outcome (P<0.001).

The ability of biomarker score to predict patients with cardiac events was evaluated by means of ROC analysis (Figure 1). A biomarker score cut-off value ≥5.2 had a sensitivity of 83.6%, a specificity of 82.9% (AUC=0.85), in predicting cardiac events after successful PBMV. On the other hand the Wilkins's score of ≥6.5 had a sensitivity of 73.5%, a specificity of 79.2% (AUC=0.80), in predicting cardiac events. The conjunction of Wilkins's score with biomarker score have higher predicting power (AUC=97%) with a sensitivity of 92.4% and a specificity of 92.7%), (Table 6 and Figure 2) Table (7) shows the univariate and multivariate relationships of biomarker score and echocardiographic parameters to cardiac events during follow-up. In Spearman analysis, statistically significant correlations were found between biomarker score and other echocardiographic parameters. The correlation co-efficient of biomarker score was 0.755 (p<0.0001), greater than that of the Wilkins score (r=0.613,

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Variable	Favorable outcome group (N=94)	Unfavorable outcome group (N=67)	*P* value
Age	39.2±11	39.5±10	>0.05
LAD	49.8±1.2	5.2±1.2	<0.05
MVA	0.99±0.05	0.98±0.07	>0.05
Transmitral Mean PG	17.5±2.1	18.9±2.2	>0.05
RVD	3.1±0.4	3.2±0.2	>0.05
Pre- procedure MR	0.8±0.6	0.9±0.3	>0.05
PAPs (mmHg)	46.6±19.2	78.5+21.9	<0.01
Wilkin's score	5.4.2±1.2	5.8±1.1	>0.05
Biomarkers score	5.0±0.9	8.9±1.3	<0.001

MVA: Mitral Valve Area; RVD: Right Ventricular Diameter; MR: Mitral Regurgitation; PAPs: Systolic pulmonary artery pressure.

Table 5: Comparison between patients with favorable versus those with unfavorable outcomes after percutanous balloon mitral valvuloplasty.

Score	Cut-off	Sensitivity (%)	Specificity (%)	AUC	95% CI	*P* value
Wilkin's score	≥6.5	73.5	79.2	0.80	0.69-0.92	<0.002
Biomarkers score	≥5.2	83.6	82.9	0.85	0.74-0.96	<0.001
(Wilkin's +biomarker) scores		92.4	92.7	0.97	0.96-1.00	<0.000

PBMV: Percutaneous balloon mitral valvuloplasty.

Table 6: Validity of Wilkins score, biomarkers score cut-off values as well as the compunction of both scores in predicting outcomes after PBMV.

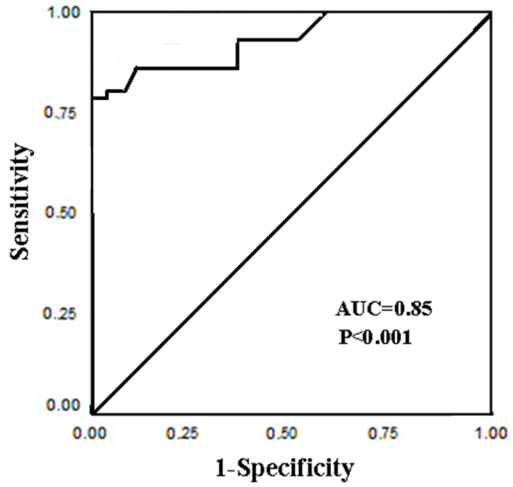

Figure 1: ROC curve for biomarker score showing sensitivity of 83.6% and specificity of 82.9% in predicting outcome after PBMV, at a cut off value of ≥5.2 mg/l (AUC at 95% CI=0.85(0.58-0.83).

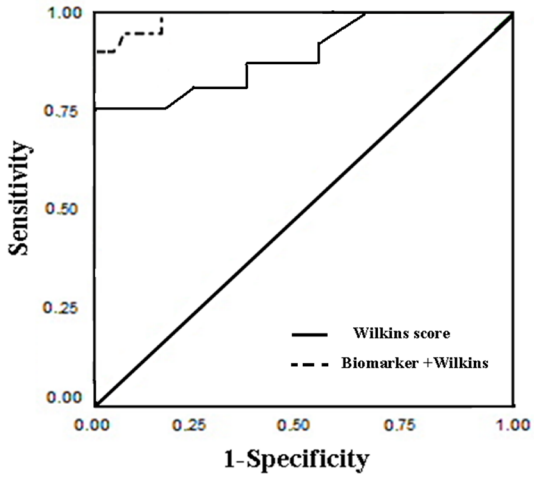

Figure 2: ROC curves for Wilkins score (AUC=0.80; 95% CI[0.74-0.96]) alone and the combined (Wilkins+biomarker scores) showing sensitivity of 92.4% and specificity of 92.7% for the combined scores in predicting outcome after PBMV (AUC at 95% CI=0.97(0.96-1.00).

Variable	Spearman coefficient	*P* value	standardized regression coefficient	*P* value
Wilkins score	0.613	<0.002	0.364	<0.01
Mitral valve area (cm²)	0.315	<0.004	--	
PAPs (mmHg)	0.460	<0.002	0.242	<0.04
Brain natriuretic peptide	0.495	<0.004	--	
Tenasin-c	0.583	<0.002	--	
Copeptin	0.492	<0.004	--	
High sensitive C-reactive protein	0.385	<0.003		
Biomarker score	0.755	<0.001	0.595	<0.001
Wilkins plus biomarker scores	0.911	<0.0001	0.825	<0.0001

Table 7: Univariate and Multivariate relationships of studied variables to cardiac events.

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p<0.002); MVA(r=0.312, p<0.02); sPAP(r=0.499, p<0.002). On the other hand the combined biomarkers and Wilkins's score showed the strongest correlation with cardiac events (r=0.911). In multiple linear regression analysis, the standardized regression coefficient (r=0.595) of biomarker score was much higher than those of Wilkin's score r=0.364), and the combined scores had the strongest powerful independent predictor of cardiac events after PBMV.

DISCUSSION

The present results showed that the efficacy of our biomarker risk score was superior to that of Wilkins score for prediction of cardiac events after successful PBMV for patients with moderate-severe MS. Moreover, a combination of both the risk scores provided higher prognostic value than the Wilkins score alone, for prediction of follow-up outcome after PBMV.

PBMV, is unique in that it provides dramatic hemodynamic and symptomatic relief as soon as it is carried out with success. Due to these sudden changes in hemodynamic and metabolic parameters in MS after PBMV, it has seemed to be highly attractive to investigate some characteristics of MS before and after the procedure.[13]

Compared to the Wilkins score, the biomarker score had several main advantages. (1) It provided complementary prognostic information to the Wilkins score for predicting follow-up outcome after PBMV, (2) The biomarker risk score could stratify risk among patients without symptoms and relatively low levels of Wilkins score. Precise prognostic information is important for tailoring treatment to individual patients and/or for facilitating the allocation of limited health care resources, (3) It could be argued that the biomarker risk score may be less influenced than Wilkins score by analytical and intra-individual variations, which might compromise the accuracy of prognostic assessments mild-moderate MS especially asymptomatic patients. (4) The risk score takes into account Natriuretic peptides, tenasin-C, copeptin and hs-CRP.

BNP seem to be very promising candidates, as there is great consistency on their ability to reflect the activity and progression, as well as to predict the prognosis.[14] Increased levels of TN-C have been found in rheumatic aortic valves and has a significant role in progression and severity of pulmonary hypertension.[15] The C-terminal part of the vasopressin prohormone (Copeptin) is measured easily and reliably.[16] As in chronic obstructive pulmonary disease, pulmonary hypertension is usually present in MS because of the increased left atrial pressure, pulmonary arteriolar constriction and obliterative changes in the pulmonary vascular bed.[13] hs-CRP is an important marker of chronic inflammatory process.

On the other hand, it was previously reported that TN-C had an increase in pulmonary hypertension.[17,18] Smooth muscle cell proliferation is one of the pathophysiologic roles of TN-C in pulmonary hypertension.[19,20] Higher TN-C levels were seen in patients with severe rheumatic mitral stenosis than in healthy subjects and TN-C was an independent predictor for mitral stenosis. After successful PBMV, there was a dramatic decrease not only in sPAP levels but also in TN-C levels.[21]

The present study found that the biomarker score was the strongest independent predictor of post PBMV outcome, with a best cut-off value being ≥5.2 mm Hg. The most commonly reported independent predictors of post-PMV clinical events (cardiovascular death, mitral valve surgery and repeat PMV) and restenosis are echo score and post-PBMV mitral valve area, both related to mitral valve anatomy.[22-25]

In mitral stenosis, pulmonary hypertension is due to three components: (1) passive, due to left atrial hypertension; (2) vasoreactive, due to pulmonary arteriolar constriction; and (3) due to structural changes in pulmonary vascular disease.[26,27] The first two are reversible, the first immediately after PMV and the second later, within a few months of intervention, while the third factor is permanent and does not usually regress.[28] Higher levels of CRP and others biomarkers may be responsible for atrial fibrosis. Such atrial fibrosis is supposed to be responsible for atrial fibrillation found in rheumatic mitral stenosis [29]

BNP and hs-CRP are important and may be sufficient, in assessment of activity and functional status. On the other hand TN-C and copeptin are largely associated with the progress of f pathologic changes and may give an idea about the early fibrotic changes in the pulmonary vasculature that may progress to irreversible pattern of pulmonary hypertension. Neuhold, et al.[30] reported that copeptin in chronic heart failure patients was superior to BNP and NT-proBNP for the prediction of all-cause mortality

For a proper selection of therapeutic strategy in patients with MS, clinical evaluation and assessment of MV anatomy are essential.[31-33] Transthoracic 2D echocardiography allows classification of patients into anatomic groups to predict immediate and long-term outcome.[34,35] Although most cardiologists use the Wilkin's score, several echocardiographic scoring systems have been suggested for evaluation of MV anatomy.[36-39] None of the available scores has been shown to be superior to any of the others.[40]

CLINICAL IMPLICATION

Our ability of doing biomarkers score will enhance the current evaluation of patients with MS and could be used in conjunction with Wilkins's score for proper selection and early intervention especially for asymptomatic moderate mitral stenosis Our proposed risk score is simpler to apply in asymptomatic patients with moderate MS. This facility might encourage broader implementation, because busy clinicians must typically priori-

tize multiple tasks. Therefore, we anticipate that our suggested risk score may be a valuable tool in clinical practice in the future.

CONCLUSION

In patients with mild-moderate mitral stenosis especially asymptomatic patients, biomarker risk score that included BNP, tenacin-c, copeptin and hs-CRP and, had a higher accuracy to that of Wilkins's score for predicting clinical outcomes after successful PBMV. A combination of the biomarkers score and Wilkins's score provided higher prognostic value for predicting clinical outcomes after successful PBMV.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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