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Left atrial size predicts long-term outcome after balloon mitral valvuloplasty

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Abstract

Background: The treatment of choice for severe rheumatic mitral stenosis is balloon mitral valvuloplasty (BMV). Numerous predictors of immediate and long-term procedural success have been described. The aims of this study were to describe our experience with BMV over the last decade and to evaluate predictors of long-term event-free survival.

Methods: Medical records were retrospectively analyzed of patients who underwent BMV between 2009 and 2021. The primary outcome was a composite endpoint of all-cause mortality, mitral valve replacement (MVR), and repeat BMV. Long-term event-free survival was estimated using the Kaplan-Meier curves. Logistic regression was used to create a multivariate model to assess pre-procedural predictors of the primary outcome.

Results: A total of 96 patients underwent BMV during the study period. The primary outcome occurred in 36 patients during 12-year follow-up: 1 (1%) patient underwent re-BMV, 28 (29%) had MVR, and 8 (8%) died. Overall event-free survival was 62% at 12 years. On multivariate

analysis, pre-procedural left atrial volume index (LAVI) > 80 mL/m^2 had a significant independent influence on event-free survival, as did previous mitral valve procedure and systolic pulmonary arterial pressure above 50 mmHg.

Conclusion: Despite being a relatively low-volume center, excellent short and long-term results were demonstrated, with event-free survival rates consistent with previous studies from high-volume centers. LAVI independently predicted long-term event-free survival.

Key words: mitral valve, mitral stenosis, balloon mitral valvuloplasty, left atrial size, event-free survival

Introduction

Mitral stenosis (MS) is a common manifestation of rheumatic heart disease. While rare in developed countries, it is still prevalent in developing countries and in areas with migrant populations [1].

Since the introduction of the Inoue balloon four decades ago [2], balloon mitral valvuloplasty (BMV) has become the preferred treatment option for suitable patients. Indeed, the current American Heart Association and American College of Cardiology (AHA/ACC) guidelines advocate BMV for patients with symptomatic MS with a mitral valve area (MVA) ≤ 1.5 cm^2 who have favorable anatomical and clinical characteristics, and no procedural contra-indications (level of recommendation IA) [3].

Since proper patient selection is paramount to ensure short- and long-term success after BMV, much research has attempted to identify predictors of success. The Wilkins score describes anatomical characteristics of the mitral valve (MV) and sub-valvular apparatus which were predictive of acute procedural success [4–13]. The quality of the procedural result has been widely described as a major predictor of long-term event-free survival [5, 8]. A myriad of other factors has been reported as independently influencing either immediate or long-term results including among others: age; sex; atrial fibrillation; New York Heart Association (NYHA) class; previous surgical commissurotomy; valve calcification; concomitant mitral regurgitation (MR); MV gradient; and pulmonary arterial pressure [6–9, 12–25].

The aims of this study were to describe a single-center experience with BMV over the last decade, and to evaluate pre-procedural predictors of long-term event-free survival.

Methods

Patient population and data collection

clinical records of 96 patients who underwent BMV due to MS at the Sheba Medical Center Invasive Cardiology Unit between May 2009 to January 2021 were investigated. The research protocol was approved by our Institutional Review Board.

Baseline characteristics including age, gender, relevant medical history, NYHA functional class before and after the procedure, laboratory tests, echocardiographic measurements before and after the procedure, and invasive measurements were abstracted retrospectively from the electronic patient records. The information was documented in an electronic report form. A letter of consent was sent to patients with missing data and and were later called to collect the missing information.

Echocardiographic examination

Transthoracic echocardiography (TTE) was performed within 3 months prior to BMV. Transvalvular gradients were assessed using Doppler flow velocity analysis after optimization of gain settings and beam orientation. Maximal and mean gradients were obtained. Valve area was evaluated by planimetry, pressure half time, and by the continuity equation according to the current American Society of Echocardiography (ASE) guidelines [26]. Wilkins score was calculated by grading its components (grade 1–4); leaflet mobility, leaflet thickening, leaflet calcification, and sub-vavlvular thickening. Presence of commissural calcification was noted as well [4]. Each patient was assigned to one of three groups according to Cormier score [27]. Transesophageal echocardiography (TEE) was performed routinely before anesthesia. The diagnosis of significant MS was confirmed, and the presence of intra-cardiac thrombus was ruled out. All procedures were guided by continuous TEE imaging.

Left atrial volume index (LAVI) was calculated as left atrial volume (performed post-hoc by 2 experienced experts)/body surface area (BSA) [28].

Hemodynamic assessment and BMV technique

All patients underwent invasive hemodynamic assessment prior to induction of anesthesia. Pressures were recorded in the right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge using a 7 F Swan-Ganz flotation catheter. Simultaneous pressures in the pulmonary capillary wedge and left ventricle (LV) were recorded to assess the trans-mitral gradient. Cardiac output was calculated using measured Fick (O_2 consumption was measured with a Cosmed Fitmate PRO, Rome, Italy). Valve area was assessed using the Gorlin equation [28]. After a decision was made to proceed with BMV, patients underwent anesthesia induction and endotracheal intubation. If no contra-indication was noted, trans-septal puncture was performed using a standard technique under TEE guidance and BMV was performed using the Inoue balloon technique [2]. Post-valvuloplasty measurements were repeated after BMV.

Statistical analysis

Variables were described according to their properties. Categorical variables are reported in frequencies and percentages, and significance was assessed using the Chi-square test or the Fischer exact test. Continuous variables were reported as mean and standard deviation values, and significance was assessed using either independent sample or paired t-test. Data was stratified to primary outcome — all-cause mortality, mitral valve replacement (MVR), and second BMV. Long-term primary outcome event-free survival was estimated using the Kaplan-Meier curves, adjusted for age, Wilkins score, and LAVI, analyzed at 5 and 10 years for the primary outcome. Selected statistically significant variables from the univariate analysis and other clinically influential variables were included in the logistic regression to create a multivariate model demonstrating pre-procedural predictors for the primary outcome.

All statistical tests were 2-sided, and a p-value of less than 0.05 was considered significant.

Results

The study included 96 patients who underwent BMV due to severe MS at a single center from 2009 to 2021. Mean follow-up was 4.2 years and total follow-up of 402 patient-years. Mean follow-up for patients with an event was 2.76 ± 2.68 years and for patients without events 5.07 ± 2.79 years ($p < 0.01$).

Primary endpoint events, defined as death, re-BMV, or MVR, occurred in 36 patients. Sixty patients remained event-free at the end of follow-up. The baseline clinical characteristics, stratified according to whether a primary endpoint was recorded during follow-up, are shown in Table 1. Mean age was 52 ± 16 years. Patients with an event were older than event-free patients (58 ± 15 vs. 48 ± 15, p = 0.003). Most patients were women (81%). Among common comorbidities, hypertension (p = 0.022) and atrial fibrillation (p = 0.029) were significantly more common in the event group. Previous MV procedure had been performed in 19% of the patients and was numerically more prevalent in the group with subsequent events. Most patients suffered from NYHA class II–III heart failure.

The pre-procedure echocardiographic characteristics stratified according to primary outcome are shown in Table 2. Greater LA area, LA diameter, LAVI, LV mass, peak mitral gradient, and systolic pulmonary artery pressure (SPAP) measurements were demonstrated in the group with primary outcome event (p = 0.037, p = 0.028, p = 0.055, p = 0.023, p = 0.042, p = 0.011, respectively). Non-invasive assessment of valve area was performed by pressure half time or continuity, and in some cases by planimetry as well. No difference in non-invasively assessed valve area was noted between patients with and without an event. Similar findings were found on invasive assessment of valve area using the Gorlin formula [28].

The pre-procedure hemodynamic measurements stratified according to primary outcome are shown in Table 3. No significant differences were noted between groups.

Comparison of pre- and post-valvuloplasty hemodynamic measurements for the entire cohort are shown in Table 4. Following intervention, the trans-mitral gradient dropped from 11.86 ± 5.25 mmHg to 4.69 ± 2.12 mmHg (p < 0.001) and the MVA increased significantly from 1.21 ± 0.5 cm^2 to 2.58 ± 1.5 cm^2 (p < 0.001).

As shown in Table 5, the Wilkins score was > 8 in 28% of the cohort. However, Wilkins score > 8 was present in 50% of patients with the primary endpoint, and in only 15% of patients without an event (p < 0.001). Leaflet mobility and leaflet calcification scores were significantly greater in the event-positive group (p = 0.02, p = 0.002, respectively), as was the Cormier score (p = 0.001).

Post-procedural increase in MR to moderate or above was recorded in 13 (14%) patients. Of these, a total of 7 underwent MVR, 5 during the first year after BMV.

During long-term follow-up, 1 (1%) patient underwent re-BMV, 28 (29.2%) underwent MVR, and 8 (8.3%) died (1 patient underwent surgery and died during long-term follow-up). The primary outcome was noted in 31% at 5 years, and in 36% at 10 years. Overall event-free survival was 62% at 12-years.

Survival-free analysis at 5 and 10 years stratified according to age, Wilkins score, and LAVI are shown in Figure 1. Patients who were aged 60 years or more at the time of BMV had higher prevalence of the primary outcome. At 5 years, event-free survival was 75% in younger patients, in contrast to 50% in the older group ($p = 0.038$). At 10 years, corresponding frequencies were 60% for younger patients and 40% for the above 60 group ($p = 0.101$). When patients were stratified according to Wilkins score ≤ 8 and > 8, differences were even more remarkable with 5-year event-free survival of 75% for Wilkins score ≤ 8, and only 35% for Wilkins score > 8 ($p = 0.006$), corresponding frequencies at 10 years were 60% and 28% respectively ($p = 0.006$). In patients with LAVI > 80 mL/m^2, 5-year event-free survival was only 45% as compared to 75% for patients with LAVI ≤ 80 mL/m^2 ($p = 0.006$), corresponding frequencies at 10 years were 35% and 55% respectively ($p = 0.014$).

Using multivariate analysis, the following variables were independently associated with the primary endpoint: previous MV procedure (valvuloplasty or commissurotomy); pre-procedure LAVI > 80 mL/m^2; and SPAP > 50 mmHg. The model is shown in Table 6.

Discussion

In this paper long-term outcomes are described of a single-center cohort of patients with MS undergoing BMV. Over the past half-century, mitral stenosis has become a rare entity in the developed world and few centers have sufficient experience in the performance of BMV, the treatment of choice for suitable patients. We performed 96 BMV procedures over a 12-year period, an average of 8 procedures per year. Despite being a relatively low-volume center, excellent short and long-term results were demonstrated, which compares well with those reported from high-volume centers in the past [5, 14, 15, 29].

The primary outcomes were death, repeat BMV, or MVR. Patients were stratified according to occurrence of the primary outcome. Those with the primary outcome were 10 years older than the event-free group, were more likely to suffer from hypertension and atrial fibrillation, and were numerically twice as likely to have had a previous MV intervention (BMV

or surgical commissurotomy). They had significantly greater LA size, SPAP, LV mass, and peak but not mean mitral gradient. They had significantly more leaflet calcification and less leaflet mobility resulting in significantly higher Wilkins and Cormier scores. Despite this, acute hemodynamic improvement as assessed by reduction in gradient, calculated valve area, and pulmonary capillary wedge pressure was equivalent between the groups.

Long-term event-free survival in the present cohort was 69% at 5 years and 64% at 10 years. Previous studies have assessed various composite endpoints at different time points. While direct comparison between studies is difficult due to different patient populations, use of different end-point definitions and different duration of follow-up, outcomes in the current study seem comparable to these series. A similar primary endpoint was utilized in several studies. These demonstrate event-free survival ranging from 51% at 5 years [16] to 83.3% at 12 years [17], and even 81% at 24 year follow-up [6]. Other studies included post-procedure NYHA class in the primary outcome and demonstrated event-free survival ranging from 52% after 7.5 years [18] to 60% at 15 years [19].

To elucidate the significance of pre-procedural parameters on long-term outcome, multivariate analysis was performed using a number of regression models. It was found that the following parameters were independently associated with the occurrence of the primary endpoint: LAVI using a cut-off value of 80 mL/m^2; SPAP with a cut-off of 50 mmHg; and previous MV procedure. Several studies have demonstrated different factors associated with immediate procedural and long-term results. Vahanian et al. [7] described MV structure and calcification, and balloon size as independent predictors of immediate procedural results. An additional study from this group identified MV anatomy, pre-procedure MVA, and previous MV commissurotomy as relevant factors [8]. Cohen et al. [16] depicted Wilkins score ≤ 8 as an independent predictor for long-term event-free survival, along with pre-procedure lower LV end-diastolic pressure and NYHA class. In the current analysis, Wilkins score > 8 was associated with worse long-term outcomes on univariate analysis but was not an independent predictor of the primary outcome on multivariate analysis. Similar to our findings, higher SPAP on pre-procedural echocardiography has previously been described as an independent predictor for the same primary outcome as the present study [17]. Pre-procedural left atrial size has been associated with acute procedural success [9, 21], however, according to available research, it has not previously been identified as a predictor of long-term outcome, as shown in this cohort.

The present study demonstrates that relatively low-volume centers can obtain good results after BMV. This is important given the relative scarcity of this disease nowadays. Procedural success was obtained by careful patient selection based on pre-procedural clinical and echocardiographic assessment, maintaining two dedicated operators who were present in all procedures, and using a TEE guided approach using sequential inflations with increasing balloon volume and assessment of valve gradient and regurgitation after each inflation.

Conclusions

Described herein, a simple measure reported routinely on echocardiography, namely LAVI, adds to an ability to predict long-term outcomes in patients undergoing BMV.

Conflict of interest: None declared

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Table 1. Baseline clinical characteristics stratified by primary outcome.

	Total (n = 96)	**Event-positive (n = 36)**	**Event-free (n = 60)**	**P-value**
Age [years]	52 ± 16	58 ± 15	48 ± 15	**0.003**
Female	78 (81%)	28 (78%)	50 (83%)	0.5
Atrial fibrillation	44 (48%)	22 (63%)	22 (39%)	**0.029**
Hypertension	22 (24%)	13 (37%)	9 (16%)	**0.022**
Diabetes mellitus	11 (12%)	6 (17%)	5 (9%)	0.242
Dyslipidemia	25 (27%)	13 (37%)	12 (21%)	0.102
Previous MV procedure:	17 (19%)	10 (28%)	7 (12%)	0.073
Valvuloplasty	11 (12%)	5 (15%)	6 (11%)	
Commissurotomy	5 (6%)	4 (12%)	1 (2%)	
Both	1 (1%)	1 (3%)	0	
Pregnancy during the procedure	3 (4%)	0	3 (6%)	0.191
GFR < 60	6 (9%)	4 (16%)	2 (5%)	0.105
Creatinine	0.9 ± 0.5	1.03 ± 0.74	0.78 ± 0.29	0.126
Hemoglobin [mg/dL]	12.2 ± 1.3	11.84 ± 1.62	12.38 ± 1	0.159
NYHA class:				0.373
NYHA I	5 (7%)	0	5 (8%)	
NYHA II	30 (42%)	12 (33%)	18 (30%)	
NYHA III	33 (47%)	12 (33%)	21 (35%)	
NYHA IV	3 (4%)	2 (6%)	1 (2%)	

Data is presented as mean ± standard deviation for continuous variables, and number (%) for categorial variables.
GFR — glomerular filtration rate; MV — mitral valve; NYHA — New York Heart Association

Table 2. Pre-procedural echocardiographic characteristics stratified by primary outcome.

	Total (n = 96)	**Event-positive (n = 36)**	**Event-free (n = 60)**	**P-value**
LV ejection fraction [%]	59.5 ± 4.5	59 ± 2.7	59.7 ± 5.2	0.579
LA volume index [mL/m^2]	73.2 ± 43.9	89.1 ± 67	64.6 ± 19.4	**0.055**
LA diameter [cm]	4.7 ± 1	5 ± 1.2	4.5 ± 0.7	**0.028**
LA area [cm^2]	30.8 ± 9.8	34.3±13.3	28.6 ± 5.9	**0.037**
LV mass [g]	136.5 ± 31.5	148.5 ± 30	130.3 ± 30.7	**0.023**
Mean mitral gradient [mmHg]	9.7 ± 4	9.7 ± 3.5	9.7 ± 4.3	0.96
Peak mitral gradient [mmHg]	19 ± 6.78	20.9 ± 5.9	17.8 ± 7	**0.042**
Mitral valve area [cm^2]				
Planimetry (n = 35)	1.32 ± 0.46	1.21 ± 0.37	1.41 ± 0.52	0.213
Pressure half time (n = 65)	1.19 ± 0.31	1.15 ± 0.34	1.21 ± 0.29	0.5
Continuity (n = 34)	1.02 ± 0.38	1 ± 0.34	1.03 ± 0.41	0.806
Mitral regurgitation:				0.917
Non	48 (50%)	18 (50%)	30 (50%)	
Mild	30 (31%)	12 (33%)	18 (30%)	
Mild-moderate	13 (13.5%)	5 (14%)	8 (13%)	
Moderate	5 (5%)	1 (3%)	4 (7%)	
AV disease > mild:				
Aortic stenosis	2 (2%)	1 (3%)	1 (2%)	0.721
Aortic regurgitation	15 (19%)	7 (23%)	8 (16%)	0.434
Tricuspid regurgitation > mild	25 (31%)	12 (39%)	13 (26%)	0.229
SPAP [mmHg]	50 ± 18	57.4 ± 18.1	45.8 ± 16.8	**0.011**

Data is presented as mean ± standard deviation for continuous variables, and number (%) for categorial variables.
AV — aortic valve; LA — left atrium; LV — left ventricle; SPAP — systolic pulmonary artery pressure

Table 3. Pre-procedural hemodynamic measurements stratified by primary outcome.

	Total (n = 96)	**Event-positive (n = 36)**	**Event-free (n = 60)**	**P-value**
Cardiac output	4.66 ± 1.6	4.3 ± 1.4	4.9 ± 1.7	0.113
Cardiac index	2.67 ± 0.97	2.5 ± 0.9	2.82 ± 1	0.136
Aorta mean pressure	76.7 ± 18.93	76.55 ± 19.62	76.79 ± 18.72	0.955
Aorta systolic pressure	105.45 ± 26.15	106.71 ± 28.58	104.69 ± 24.85	0.736
Mean pulmonary artery pressure	29.33 ± 10.88	30.61 ± 10.51	28.51 ± 11.14	0.392
Mean wedge pressure	20.69 ± 6.92	22.42 ± 7.29	19.57 ± 6.49	0.064
Mean mitral valve gradient	11.96 ± 5.29	12.39 ± 5.62	11.7 ± 5.13	0.551
Mitral valve area	1.22 ± 0.48	1.14 ± 0.45	1.27 ± 0.5	0.206
Pulmonary vascular resistance	2.1 ± 1.73	2.53 ± 2.2	1.81 ± 1.32	0.108

Data is presented as mean ± standard deviation.

Table 4. Hemodynamic measurements pre- and post-procedure.

	Pre-procedure	**Post-procedure**	**P-value**
Cardiac output	4.58 ± 1.5	5.33 ± 1.78	**0.004**
Cardiac index	2.62 ± 0.86	3.06 ± 1.09	**0.003**
Aorta mean pressure	69.52 ± 17.15	65.76 ± 8.99	0.299
Aorta systolic pressure	94.96 ± 15.76	89.36 ± 14.09	0.120
Mean pulmonary artery pressure	27.91 ± 10.35	24 ± 10.37	**0.002**
Mean wedge pressure	19.79 ± 5.8	14.39 ± 6.98	< **0.001**
Mean mitral valve gradient	11.86 ± 5.25	4.69 ± 2.12	< **0.001**
Mitral valve area	1.21 ± 0.5	2.58 ± 1.5	< **0.001**
Pulmonary vascular resistance	2.02 ± 1.76	1.9 ± 1.35	0.634

All data presented as mean ± standard deviation.

Table 5. Pre-procedural Echocardiographic Scores Stratified by Primary Outcome.

	Total (n = 79)	Event-positive (n = 27)	Event-free (n = 52)	P-value
Wilkin's score > 8	22 (28%)	14 (50%)	8 (15%)	< **0.001**
Leaflet mobility:				**0.02**
1	36 (46%)	7 (26%)	29 (56%)	
2	37 (47%)	14 (52%)	23 (44%)	
3	5 (6%)	5 (18%)	0	
4	1 (1%)	1 (4%)	0	
Leaflet thickening:				0.149
1	28 (36%)	8 (30%)	20 (39%)	
2	46 (58%)	15 (55%)	31 (59%)	
3	4 (5%)	3 (11%)	1 (2%)	
4	1 (1%)	1 (4%)	0	
Leaflet calcification:				**0.002**
1	11 (14%)	5 (18%)	6 (12%)	
2	44 (56%)	8 (30%)	36 (69%)	
3	21 (26%)	11 (41%)	10 (19%)	
4	3 (4%)	3 (11%)	0	
Sub-valvular thickening:				0.343
1	18 (23%)	4 (15%)	14 (27%)	
2	45 (57%)	16 (59%)	29 (56%)	
3	15 (19%)	6 (22%)	9 (17%)	
4	1 (1%)	1 (4%)	0	
Commissural calcification:				0.256
Non	61 (77%)	19 (70%)	42 (81%)	
Antero-lateral	7 (9%)	3 (11%)	4 (8%)	
Antero-medial	2 (3%)	0	2 (3%)	
Postero-medial	9 (11%)	5 (19%)	4 (8%)	
Cormier score:				**0.001**
Group 1	32 (40%)	5 (18%)	27 (52%)	
Group 2	39 (49%)	16 (57%)	23 (44%)	
Group 3	9 (11%)	7 (25%)	2 (4%)	

Data is presented as number (%).

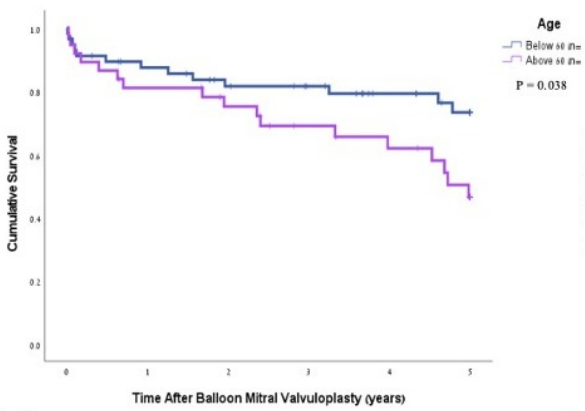
Table 6. Multivariate analysis of pre-procedural factors predicting primary outcome.

Variable	Odds ratio (95% confidence interval)	P-value
Age	1 (0.94–1.06)	0.99
Atrial fibrillation	0.491 (0.08–3)	0.441
Previous mitral valve intervention	13.91 (1.866–103.63)	**0.01**
Wilkins score > 8	3.32 (0.42–26.45)	0.258
Left atrial volume index > 80 mL/m^2	15.78 (1.47–169.16)	**0.023**
Systolic pulmonary artery pressure > 50 mmHg	9.33 (1.53–56.92)	**0.016**

Figure 1. The Kaplan-Meier curves of event-free survival at 5 and 10 years; **A.** Stratified according to age (below and above 60 years old); **B.** Stratified according to the Wilkins score (below and above 8); **C.** Stratified according to left atrial volume index (below and above 80 mL/m^2).

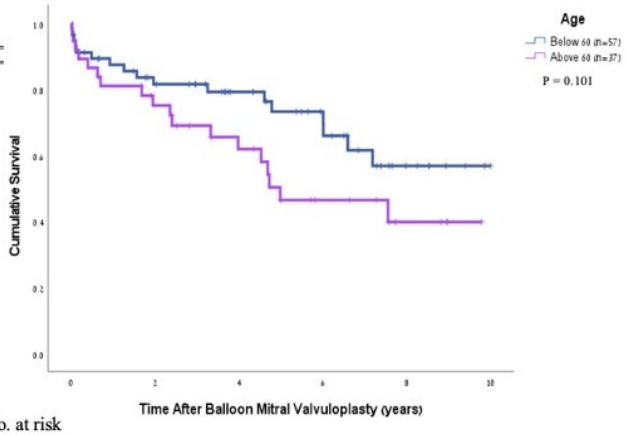
Figure 1

Figure 1A



No. at risk

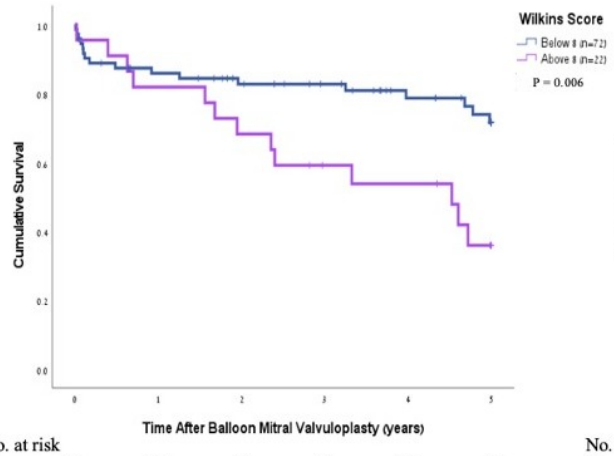
≤60	57	46	40	36	29	24
>60	37	29	25	20	17	11



No. at risk

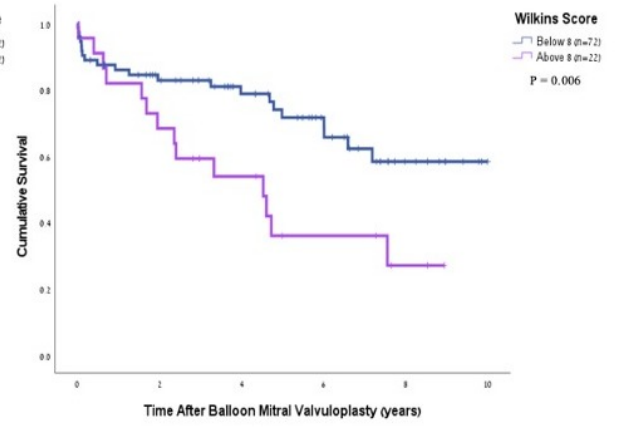
≤60	57	40	29	20	7	1
>60	37	25	17	9	4	0

Figure 1B



No. at risk

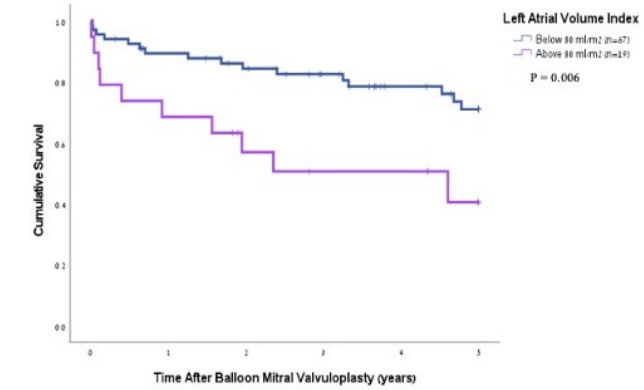
≤8	72	57	50	45	36	30
>8	22	18	15	11	10	5



No. at risk

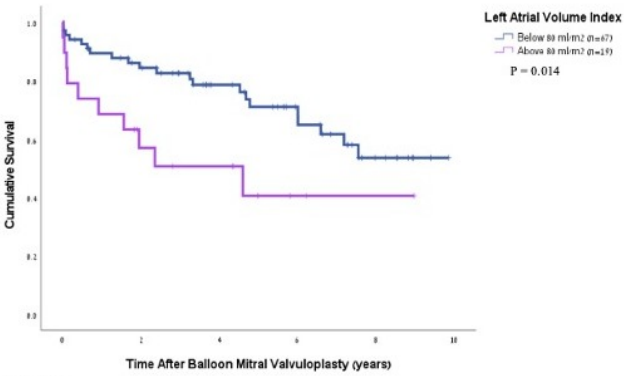
≤8	72	50	36	24	9	1
>8	22	15	10	5	2	0

Figure 1C



No. at risk

≤80	67	55	49	42	33	28
>80	22	16	9	7	7	3



No. at risk

≤80	67	49	33	23	8	0
>80	22	9	7	2	1	0