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20-year follow-up of rheumatic mitral stenosis patients after percutaneous mitral commissurotomy: invasive transmitral gradient differential as a predictor of events

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Abstract

Percutaneous mitral valve commissurotomy (PMC) is a viable alternative to mitral valve (MV) surgery in the treatment of patients with rheumatic mitral stenosis (RMS).

In this single-center retrospective study of consecutive patients with RMS submitted to PMC from 1991 to 2008, we analyzed clinical, echocardiographic, and hemodynamic data and events during follow-up (FUP) until December 2021. Major adverse cardiovascular events (MACE) were a combined endpoint of all-cause death, cardiovascular hospitalization, and MV re-intervention. A total of 124 patients were enrolled: 108 (87.1%) were female, with a mean age at PMC of 46 [standard deviation (SD) 11] years. PMC was successful in 91.1%, with a mean reduction in invasive transmitral pressure gradient (TMPG) of 8 (SD 7) mmHg at PMC time. During the mean FUP of 20 (SD 6) years, 51 (41.1%) patients had MV re-intervention (86.3% surgery and 13.7% redo-PMC), 37 (29.8%) were hospitalized, and 30 (24.2%) died. Approximately 75% of patients remained MACE-free after 10 years, and this percentage decreased to around 40% after 20 years; at this time mark, about 8 in 10 patients were alive.

A reduction of <5 mmHg in TMPG at PMC time was associated with a 2.7-fold greater rate of MACE compared to a reduction of 5 mmHg, independent of MV regurgitation after PMC and moderate disease of other valves (adjusted hazard ratio 2,7; 95% confidence interval 1.395-5.298, p=0.003). In this cohort with favorable long-term results after PMC, a reduction of <5 mmHg in TMPG at PMC time was associated with MACE during FUP. More studies are needed to validate this independent predictor.

Key words: rheumatic mitral stenosis, cardiac catheterization, percutaneous mitral commissurotomy, long-term follow-up, predictor of events.

Introduction

Rheumatic heart disease (RHD) has decreased worldwide, but continues to be a major medical concern in developing countries, remaining the most common cause of cardiovascular morbidity and early mortality in young people worldwide [1].

Mitral valve stenosis (MVS), the most common manifestation of RHD, is a progressive disease of leaflet thickening, commissural fusion, and chordal shortening and fusion, potentially leading to atrial fibrillation (AF), ischemic stroke, pulmonary hypertension, and heart failure. The contemporary treatment strategies for clinically significant rheumatic MVS are percutaneous mitral balloon commissurotomy (PMC) and mitral valve replacement (MVR) [2]. In symptomatic patients with severe rheumatic MVS and suitable anatomical features, guided by the Wilkins Score, the PMC is considered the treatment of choice. On the other hand, patients with contraindication to PMC should undergo MVR. Contraindications to PMC include presence of left atrium thrombus, concomitant mitral valve (MV) regurgitation and excessive MV calcification [3].

Immediate, mid and long term results of the procedures are variable depending on many factors, including patient and mitral valve characteristics, as are the local expertise of interventionists and surgeons. A recent meta-analysis of randomized controlled trials concluded that, despite the current insufficient evidence to assert the superiority of either PMC or MVR, considering the higher morbidity associated with cardiac surgery, PMC should be the preferred procedure for young patients with favourable valve morphology [4].

As the era of PMC began in 1984 [5], there is limited data on very long-term outcomes for patients with severe rheumatic MVS who have undergone PMC. Moreover, information about predictors of events remains limited.

The objective of this study is to assess long-term events of rheumatic MVS patients following PMC and to identify potential predictors of such events.

Materials and Methods

Study population

This is an observational retrospective single-centre study performed in the Cardiology Department of Centro Hospitalar Universitário de São João, Porto, Portugal. We included all consecutive patients aged 18 years old with clinically significant rheumatic MVS, with mitral valve area (MVA) <1.5 cm2 and grade 2 mitral regurgitation (MR), who underwent PMC between 1st January of 1991 and 31th December of 2008. All patients with asymptomatic MVS, MVA 1.5 CM2, grade 3-4 MR, or with intra-cardiac thrombus were excluded. Patient´s information was reviewed from medical records.

Procedure and data collection

After right and left catheterization, PMC was performed with the Inoue commissurotomy technique using Inoue single balloon (Toray Industries, Inc., NY, United State); atrial septostomy and commissurotomy were X-ray fluoroscopy guided. The balloon diameter and catheter size were chosen based on the patient´s height [6].

At procedure time, before and after PMC, simultaneous direct left atrium (LA) and left ventricle (LV) pressures were assessed. Direct LA pressure was obtained after transseptal technique, while direct LV pressure was acquired by retrogradely introducing a pigtail catheter from the aorta into the LV.

Transmitral pressure gradient (TMPG) was determined by planimetry of the area bounded by the LV and LA pressures tracings in diastole. After PMC, a left ventriculography was done for evaluation of mitral regurgitation.

All patients underwent echocardiography at baseline (within six months before PMC), within 72h after PMC and 6 months post procedure. Also, an echocardiogram was performed immediately after PMC to access success of procedure, which was defined as MVA 1.5 cm2, along with grade 2 mitral regurgitation and no major cardiac complication requiring emergent surgery.

Clinical and other echocardiographic data were collected at baseline and within 6 months post the procedure. Various echocardiographic parameters, namely MVA, transmitral mean pressure gradient (TMPG), Wilkins' score, mitral regurgitation (MR) grading and pulmonary systolic artery pressure (PSAP) were recorded.

Long term follow-up was accessed until 31th December of 2021, checking for considered outcomes, through medical records and phone interview. Several possible clinical, echocardiographic and haemodynamic parameters were checked for prognostic value.

Outcomes

Primary outcome consisted of a composite of major adverse cardiovascular events (MACE) including all-cause mortality, mitral valve re-intervention (either re-do PMC or surgery, including valvuloplasty and replacement of mitral valve with biological or mechanical prosthesis) and cardiovascular hospitalization. The later comprised hospitalizations due to heart failure, stroke or systemic embolism, myocardial infarction and arrhythmias.

Other accessed outcomes were PMC success, peri-procedural complications, valvular infection and serious bleeding (The Bleeding Academic Research Consortium (BARC) definition type 3 or more) [7].

Statistical analysis

Categorical variables were presented as frequency and percentage and analysed using a Chi-square test or Fisher's exact test as appropriate. Continuous variables are presented as the mean with standard deviation (SD) or median with interquartile range (IQR) and analysed using a t-test or Mann-Whitney test as appropriate. To test for independent predictors of the composite clinical endpoint we used cox survival models. Kaplan–Meier curves for the survival time free from the composite clinical endpoint were constructed with strata; a two-tailed p-value <0.05 as statically significant was considered. All statistical analyses were performed using SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characterization

A total of 124 patients were enrolled, the majority were women (108 (87,1%)), with mean age of 46 (SD 11) years old at PMC time. At baseline, 42 (33,9%) patients were in NYHA class III and 100 (80,6%) had a Wilkins score 8; all patients had preserved biventricular systolic function and 103 (83,1%) had PSAP greater than 40 mmHg. Table 1 describes the population baseline characterization.

Data related to percutaneous mitral commissurotomy

Using a mean balloon size of 28 (SD 1) mm, PMC was successful in the majority of cases (113 patients,91,1%), with a mean reduction of invasive TMPG of 8 (SD 7) mmHg and median reduction of PSAP of 8 (IQR 10) mmHg. Table 2 displays hemodynamic data pre- and post-PMC.

The procedure was unsuccessful in 11 (8,9%) patients, due to MVA<1.5 cm2, echocardiographic grade of 3-4 MR or left atrium rupture with cardiac tamponade in 6 (4,3%), 4 (3,2%) and 1 (0,8%) patients, respectively.

No in-hospital deaths were registered. Major complications related to PMC were observed in 5 (4,0%) patients, with 4 required emergent surgery. Two patients developed grade-4 MR and required mitral valve replacement. Additionally, one patient experienced a left atrium rupture with cardiac tamponade, compelling surgical cardiac repair; and another patient had a major bleeding at femoral arterial access, which was managed surgically (both BARC 3b). One patient had a stroke after the procedure and was treated conservatively.

At first echocardiogram within 72 hours post-PMC, it was documented a median improvement in MVA of 0,9 (IQR 0,5) cm2. Additionally, median reductions in TMPG of 6 (IQR 6) mmHg and in PSAP of 10 (IQR 14) mmHg were observed. Excluding the 2 patients submitted to MV

replacement, mitral regurgitation was absent, grade 1, grade 2 and grade 3 in 38 (31,1%), 65(53,3%), 17 (13,9%) and 2 (1,6%) patients, respectively.
Minor complications occurred in 35 (28,2%) patients: 20 (16,1%) had residual inter-auricular communication, 12 (9,7%) had grade 2 or 2+ MR, 1 (0,8%) patient was diagnosed with femoral aneurysm, other with moderate pericardial effusion and another with deep vein thrombosis, all treated conservatively.

Follow-up

At 6-months appointment, most patients were at NYHA class I (70; 56,5%), followed by class II (50;40,2%) and only 4 patients were at class III. Regarding mitral regurgitation, it was absent, grade 1, grade 2 and grade 3 in 56 (45,9%), 50 (41,0%), 14 (11,5%) and 2 (1,6%) patients, respectively. Sixteen patients developed *de novo* atrial fibrillation (about one third of the pool of patients at sinus rhythm at PMC time). No deaths were registered in the first 6 months after-PMC.
During the mean follow-up time of 21 (SD 6) years (minimum of 1 and maximum of 31 years), 30 (24,2%) patients died, 37 (29,8%) were hospitalized due to cardiovascular causes and 51 (41,1%) patients had at least one MV re-intervention.
The deceased patients were mainly women (27; 90,0%) with mean age of 71 (SD 11) at time of death, and mean time to death after PMC was 18 (SD 6) years. Four, 2 and 2 patients died in context of heart failure, stroke and septic shock (of intra-abdominal and respiratory origins), respectively; the remaining causes of death are unknown due to inaccessible medical records.
Regarding admissions, the majority was due to decompensated heart failure (19; 51,4%), followed by stroke (7; 18,9%), rapid atrial fibrillation with hemodynamic compromise (3; 8,1%), myocardial infarction (3; 8,1%), tachy-brady syndrome requiring pacemaker implantation (3; 8,1%) and digitalis intoxication (2; 5,4%). Patients with at least one admission were mostly women (88,2%), with mean age of 64 (SD 12) years, with a mean time to first admission since PMC of 15 (SD 6) years.
In parallel, patients at first re-intervention had mean age of 58 (SD 11) years, and 11 (SD 6) years had pass since PMC. Of the 51 patients who underwent at least one re-intervention, 7 (13,7%) had re-PMC and 44 (86,3%) had surgery. Implantation of a mechanical or biological MV prosthesis occurred in 30 (68,2%) and 12 (27,3%) of the surgical re-intervened patients, respectively; the remaining 2 (4,5%) were submitted to valvuloplasty. At the same procedure, 13 (29,5%) patients underwent concomitant other valve intervention: 10 had tricuspid annuloplasty and 4 aortic valve replacement with biological prothesis. Later, 6 (4,8%) patients required second re-intervention: 2 patients with two previous PMC and one patient with previous PMC and surgical valvuloplasty had substitution of MV with mechanical prosthesis;

one patient had a third PMC; another patient with biological MV prosthesis underwent PMC. The remained patient had a mechanical MV prosthesis and underwent substitution of aortic valve with a biological prosthesis in context of a native aortic valve endocarditis. No other cases of endocarditis were documented.

Concerning time-to-event analysis, 74,9%, 40,4% and 25,0% of patients kept MACE-free after 10, 20 and 30 years, respectively; as for mortality of all causes, the probability of survival for PMC intervened patients was 95,7%, 81,4% and 50,2% at 10, 20 and 30 years, correspondingly – see Figure 1 for Kaplan Meier curves. Regarding re-intervention, 79,8%, 56,3% and 48,8% of patients kept free from re-intervention after 10, 20 and 30 years, respectively.

Using Cox regression, uni- and multianalysis of eventual predictors of MACE are displayed at Table 3. We found that a reduction <5 mmHg in invasive TMPG at PMC time was associated with a 2,2-fold greater rate of MACE compared to patients with a reduction 5 mmHg (HR_{crude} 2,2; 95% CI 1,319-3,813 p=0,003). After adjusting for the presence of mitral regurgitation after PMC (HR_{crude} 1,7; 95% CI 1,020-2,950, p=0,042) and for moderate disease of other valves ((HR_{crude} 1,9; 95% CI 1,070-3,267, p=0,028), the observed effect remained significant and was even greater ($HR_{adjusted}$ = 2,7; 95% CI 1,395-5,298, p=0,003).

Discussion

The majority of studies addressing follow-up after PMC does not exceed 10 years [8-10]. This study adds some extra insights regarding very long term follow up of patients who performed PMC - even after 30 years, the probability of being alive was about 50%.

When comparing to other studies with long term FUP, the documented overall survival at 20 years of 81,4% is similar to that of Fawzy, Bouleti and Kubota et al cohorts – 70,5%, 73,3% and 75%, respectively. Also, Braiteh et al reported a 90,5% survival at 15 years [11-14].

In our cohort, the deceased patients were elder (mean age 71 years), about 10 years younger than the mean age of death in general population in Portugal (in 2021, of 82 years old) [15]. Also, an average of 17 years had passed since the PMC, which combined with no in-hospital deaths, and successfully treated periprocedural complications, denotes the safety and good short to long-term results of the procedure.

About one third of the patients were at least one time hospitalized due to CV causes; also, about 40% of patients required at least one mitral re-intervention, underscoring the chronicity of the RHD, manifested by a natural history of mitral valve restenosis, left atrium dilatation, with higher risk of atrial fibrillation and stroke [16]. The majority was submitted to surgery, which could be in part explained by the significant proportion of patients that required concomitant surgery for other valve.

The search for outcomes predictors after PMC has captured the attention of numerous authors, aiming to enhance patient selection and procedural techniques. Generally, the identified independent predictors predominantly revolve around baseline clinical factors (such as age, body surface area, NYHA classification, and atrial fibrillation) and anatomical characteristics (including echocardiographic valve area, mean gradient, mitral valve calcification, and left atrium diameter). Immediate procedural outcomes, such as echocardiographic final mean gradient, final mitral valve area, and final mitral valve regurgitation, also play a pivotal role in outcome prediction. Morever, in the work of Bouleti et al it is demonstrated and validated a 13-point scoring system for "late results", but it lacked hemodynamic variables. Interestingly, there is conflicting data regarding Wilkins Score as a predictor of events. Furthermore, in our cohort, Wilkins Score greater than 8 did not predict events, probably denoting the PMC efficacy even in the grey zone of 9 to 11 [11-14,17-19].

When analysing such studies, we have to take into account the heterogeneous FUP times as well as different composites of MACE considered. For example, Bouletti et al. considered "late functional results" as a composite of cardiovascular death, MV re-intervention and NYHA III-IV; Fawzy et al considered a similar composite but with death from all causes, Kubota et al MACE was composed by death and re-intervention, while Braiteh et al just look for mortality predictors [11-14]. In our cohort, we decided to also add the hospitalizations of CV cause to MACE composite, due to its clinical and health care burden relevance. Other studies also have determined predictors of mitral valve restenosis, but because we did perform a standardized echocardiographic follow-up, this type of analysis could not be done [18].

To our knowledge, this is the first study to document a reduction < 5 mmHg in invasive transmitral pressure gradient at the PMC procedure, as an independent predictor for events. This effect was further magnified after adjusting for mitral regurgitation and moderate disease in other valves, possibly indicating a more accurate reflection of the actual hemodynamic improvement. We believe this could have clinical implications, as a practical and objective "cutoff" to help the interventional cardiologist during the procedure, besides the MVA and mitral regurgitation. Of course, further multicentric with standardized MACE definition will be needed to validate this predictor.

Limitations

This study had several limitations. First, given its retrospective nature, outcomes were prone to review bias and subject to confounding from other factors. There was no data regarding quality of life nor rates of mitral re-stenosis. As PMC was performed in a single tertiary referral centre study, results may not reflect the practices in other populations worldwide.

Conclusions

PMC was safe and effective in clinically significant rheumatic MS. Most of the patients were free from adverse events after 10 years and 80% was alive after 20 years; still, about 40% required re-intervention. A reduction <5 mmHg of invasive transmitral pressure gradient post PMC during the procedure was associated with more events during follow up, indicating a possible target to guide interventional cardiologists during PMC procedure; more studies are needed to validate this independent predictor.

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Table 1. Baseline patients' clinical and echocardiographic characteristics.

VARIABLE, units	Expressed as	Value
Age, years	Mean (SD)	46 (11)
Female sex	N (%)	108 (87,1%)
Weight, Kg	Median (IQR)	60 (13)
Height, cm	Mean (SD)	158 (7)
IMC, Kg/m^2	Median (IQR)	24 (4)
NYHA class:	N (%)	
Class I		10 (8,1%)
Class II		72 (58,1%)
Class III		41 (33,1%)
Class IV		1 (0,8%)
Atrial fibrillation	N (%)	72 (41,9%)
Previous mitral valve surgical comissurotomy	N (%)	7 (5,6%)
Wilkins Score	Median (IQR)	7 (2)
Wilkins Score 8	N (%)	100 (80,6%)
Wilkins Score 9-11	N (%)	24 (19,7%)
Associated other valve disease, any degree	N (%)	85 (68,5%)
Moderate to severe disease of other valve	N (%)	20 (16,3%)
Tricuspide regurgitation of any grade	N (%)	65 (52,4%)
Pulmonary systolic artery pressure > 40 mmHg	N (%)	103 (83,0%)
Mitral regurgitation severity	N (%)	
Grade 0		69 (55,6%)
Grade 1		53 (42,7%)
Grade 2		2 (1,6%)

IQR, interquartile range; SD, standard deviation.

Table 2. Hemodynamic evaluation pre- and post-PMC, by invasive catheterization and by echocardiography. All continuous variables are expressed as medians (interquartile range).

Invasive and Echocardiographic Parameters		**Pre-PMC**	**Post-PMC**	**Differential pre- and post-PMC ǂ**
Cath *	Pulmonary systolic artery pressure, mmHg	44 (20)	37 (15)	8 (10)
	Pulmonary diastolic artery pressure, mmHg	20 (9)	15 (6)	5 (8)
	Pulmonary mean artery pressure, mmHg	29 (16)	22 (12)	5 (8)
	Direct left atrium pressure, mmHg	22 (10)	14 (8)	7 (8)
	Transmitral mean pressure gradient, mmHg	12 (5)	4 (4)	8 (7)
Echo **	Pulmonary systolic artery pressure, mmHg	48 (17)	38 (15)	10 (14)
	Transmitral mean pressure gradient, mmHg	10 (8)	4 (4)	6 (6)
	Left atrium diameter, mm	47 (7)	46 (10)	1 (7)
	Left ventricle end-diastolic diameter, mm	49 (6)	50 (23)	0 (4)
	Mitral valve area by planimetry, cm^2	1,0 (1,1)	1,9 (2,4)	- 0,9 (0,5)
	Mitral valve area by pressure half time, cm^2	1,0 (0,2)	1,9 (0,3)	- 0,9 (0,5)

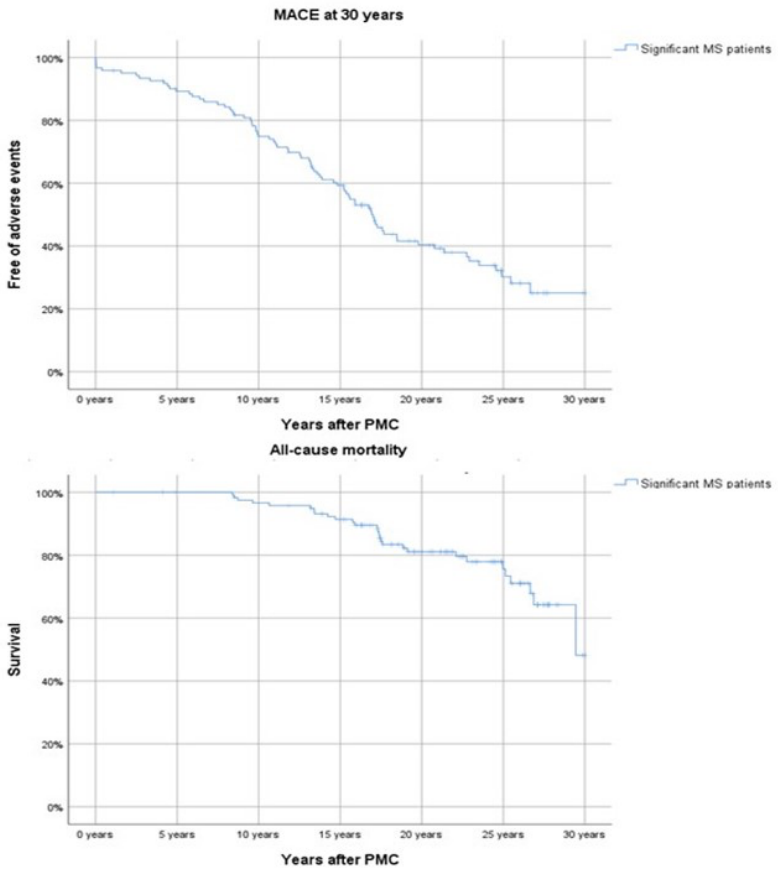
*Cath, during catheterization, invasive haemodynamic parameters were measured before and immediately after PMC; **Echo, echocardiographic parameters were measured at baseline and within 72h after PMC; ǂDifferential pre- and post-PMC expressed for each parameter as the difference between the value before PMC and the value after PMC.

Table 3. Univariate and multivariate analysis of predictors of primary outcome.

Variable	Univariate analysis			Multivariate analysis		
	Crude Hazard Ratio	**95% CI**	**p value**	**Adjusted Hazard Ratio**	**95% CI**	**p value**
Differential of invasive TMPG pre and after PMC < 5 mmHg 5 mmHg	2,114 1	1,033-4,324	**0,040**	2,719 1	1,395-5,598	**0,003**
Fluoroscopic MR immediately after PMC, any degree Yes No	1,735 1	1,020-2,950	**0,042**	2,251 1	1,157-4,383	**0,017**
Associated moderate to severe disease of other valves Yes No	1,870 1	1,070-3,267	**0,028**	2,189 1	1,018-4,707	**0,045**
Age, years	1,036	1,014-1,058	**0,001**	1,040	0,999-1,082	0,057
Sex Male Female	0,892 1	0,470-1,691	0,726	Not included		
Atrial Fibrillation at PMC time Yes No	0,693 1	0,441-1,088	0,111	Not included		
NYHA class III at baseline Yes				Not included		

No	1,209 1	0,457- 3,197	0,702	
Wilkins Score > 8 Yes No	 1,141 1	 0,949- 1,33	 0,161	 Not included
Invasive PSAP at baseline, mmHg	0,996	0,980- 1,012	0,616	Not included
Differential of invasive PSAP pre and after PMC, mmHg	0,971	0,941- 1,002	0,069	Not included
Echocardiographic PSAP at baseline, mmHg	1,007	0,996- 1,109	0,240	Not included
Differential of echocardiographic PSAP pre and after PMC, mmHg	0,990	0,971- 1,010	0,324	Not included
Differential of echocardiographic TMPG pre and after PMC, mmHg	1,052	1,002- 1,104	0,531	Not included

95% CI, 95% confidence interval; TMPG, transmitral mean pressure gradient; PMC, percutaneous mitral commissurotomy; MR, mitral regurgitation; NYHA, New York Heart Association. PSAP: pulmonary systolic arterial pressure. Note: The variable "Differential of invasive TMPG pre and after PMC" was associated with the primary outcome (Hazard ratio of 0,901; 95% CI 0,849-0,957 and p<0,001). To perform a more practical analysis of this variable, we discretized it into a binary format using the 25th percentile as the threshold (5 mmHg).



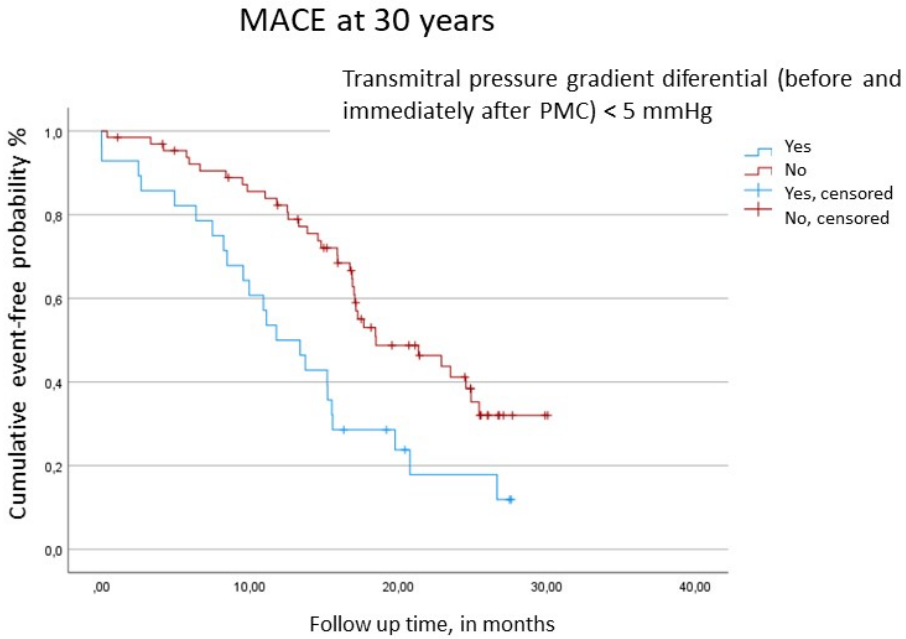


Figure 1. On the left, Kaplan Meier curves regarding major adverse cardiovascular events (MACE) and mortyality during follow-up of patients submitted to percutaneous mitral valve commissurotomy (PMC). On the right, also displayed MACE subdivided accordingly to presence ore absence of reduction <5 mmHg in transmitral pressure gradient at PMC time.