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Authors: Adam R Kowalówka[1, 2], Wojciech Wańha[3], Marcin Malinowski[1, 2], Paulina Kania-Olejnik[2], Marek A Deja

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Results of aortic valve replacement for aortic stenosis and moderate functional mitral regurgitation

Short title: Aortic stenosis with moderate FMR

Adam R Kowalówka[1, 2], Wojciech Wańha[3], Marcin Malinowski[1, 2], Paulina Kania-Olejnik[2], Marek A Deja[1, 2]

[1]Department of Cardiac Surgery, Medical University of Silesia, Faculty of Medical Sciences, Katowice, Poland
[2]Department of Cardiac Surgery, Upper-Silesian Heart Center, Katowice, Poland
[3]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland

Correspondence to:
Marek A Deja, MD, PhD,
Department of Cardiac Surgery,
Medical University of Silesia,
Ziołowa 45/47, 40–635 Katowice, Poland,
phone: +48 32 359 86 44,
e-mail: mdeja@sum.edu.pl

WHAT'S NEW?

Moderate functional mitral regurgitation in patients scheduled for aortic valve replacement with aortic stenosis is generally treated conservatively because there is no strong evidence of survival affect. Routine assessment based one just one echocardiography imaging prior to surgery may miss truly moderate, affecting survival functional mitral regurgitation, which is variable in nature. To our knowledge it is the first study considering in time moderate functional mitral regurgitation in patients with aortic stenosis. To diagnose the permanent moderate mitral regurgitation which truly affects survival one needs to confirm it on two separate occasions at different time points. The incidental finding of functional mitral regurgitation in patients with aortic stenosis is not per se a predictor of decreased survival but the permanent moderate functional mitral regurgitation in patients with aortic stenosis is a strong predictor of impaired survival.

ABSTRACT

Background: Referral and admission echocardiography (ECHO) in patients scheduled for aortic valve replacement (AVR) with aortic stenosis (AS) may differ in the assessment of moderate functional mitral regurgitation (FMR).

Aims: Our study was to determine the truly moderate-FMR and evaluate its impact on survival.

Methods: We conducted an observational study of patients referred for AVR with AS and up to moderate FMR, between 2014 and 2019. Patients were divided into three groups: (1) no/mild (N-FMR); (2) moderate-FMR on one ECHO (either at referral or admission) termed incidental (I-FMR); (3) moderate FMR in two studies (both at referral and admission) termed permanent (PM-FMR).

Results: The referral and admission assessment were performed median 35 days apart. Of the 679 elective patients who underwent elective isolated AVR, 516 patients had N-FMR, 102 patients had I-FMR, and 61 patients had PM-FMR. Median follow-up was 46 months (22.5–58.5); max 73.3. 30-day mortality was 2.5% vs. 1% vs. 8.2% (N-FMR vs. I-FMR vs. PM-FMR, respectively; $P = 0.01$). Five-year survival was 84.1% in N-FMR vs. 88.5% in I-FMR vs. 60.6% in PM-FMR group, where was the lowest ($P < 0.001$). In multivariable modeling PM-FMR increased mortality (hazard ratio [HR], 1.88 [1.05–3.37]; $P = 0.03$). The I-FMR had no effect on mortality (HR, 0.67 [0.32–1.37]; $P = 0.28$). Five-year survival after excluding 30-day mortality was 86.3% vs. 89.4% vs. 66.0%; (N-FMR vs. I-FMR vs. PM-FMR, respectively; $P = 0.02$). The PM-FMR increased late mortality (HR, 2.17 [1.14–4.15]; $P = 0.01$).

Conclusions: In patients undergoing isolated AVR for AS, the presence of permanent moderate FMR significantly impacts 30-day and mid-term survival.

Key words: aortic stenosis, aortic valve replacement, mitral regurgitation,

Abbreviation list:

AS, aortic stenosis; AVR, aortic valve replacement; BAV, bicuspid aortic valve; CPB; cardiopulmonary bypass; FMR, functional (secondary) mitral regurgitation, I-FMR incidental moderate functional mitral regurgitation; N-FMR, without or mild functional mitral regurgitation; PM-FMR, permanent moderate functional mitral regurgitation; SAVR, surgical aortic valve replacement. TAVI, transcatheter aortic valve implantation;

INTRODUCTION

Aortic stenosis (AS) is the most common acquired valve disorder in Europe and North America affecting almost 5% of elderly population. Mitral regurgitation (MR) has an estimated prevalence of 3% in the general population. Both diseases separately affect more than 176 million people worldwide [1, 2]. This is a growing trend, and it is partly due to increased life expectancy and better access to medical care. Simultaneous replacement of both aortic and mitral valves significantly increases morbidity and mortality [3–6]. Moderate functional MR during aortic valve replacement (AVR) is often treated conservatively, as the trend toward MR improvement or non-progression was observed. However, the optimal treatment in this cohort with moderate functional mitral regurgitation is still debatable and the outcome is unknown [7]. To operate or not on moderate FMR during AVR for AS is still mostly the surgeon's decision. To facilitate this process additional evidence is required. Echocardiographic (ECHO) assessment of the moderate functional mitral regurgitation (FMR) may provide various results related to patient's clinical condition and volume overload status [8, 9]. Routine assessment prior to surgery may miss truly moderate functional mitral regurgitation which is variable in nature. FMR, which diagnosis is usually based on just one ECHO imaging, may not affect survival after AVR [10].

To precisely identify patients with truly moderate FMR we evaluated patients referred to our department with AS for AVR with and without moderate FMR. Then on admission we checked ones again if they had moderate FMR and create by this way three groups: without FMR, with moderate MR in one assessment (incidental FMR) and moderate MR seen in both evaluations (permanent FMR). Our study aimed to assess the influence of incidental, moderate and permanent moderate FMR on the outcome of AVR for AS.

METHODS

Study population and clinical variables

We retrospectively analyzed the cardiac surgical database of patients operated between 2014 and 2019 in the Department of Cardiac Surgery at the Medical University of Silesia in Katowice, Poland. Institutional Review Board was consulted, and patient consent was waived (PCN/CBN/0052/KB/118/22, 2022-06-15). Baseline clinical and procedural data, and outcomes at follow-up were entered into prespecified electronic case report forms. Follow-up status was assessed by personal contact or from National Registry of Cardiac Surgical Procedures (www.krok.csioz.gov.pl.), which contains the mortality data acquired from the National Health Fund.

The study included 679 elective patients referred for surgical AVR for severe AS, with no or up to moderate FMR from our satellite cardiology centers. On admission ECHO assessment was performed to confirm the status of FMR. Both studies were conducted by experienced echocardiographists at satellite centers and on admission to our center. Assessment of the degree of functional mitral regurgitation was based on integrative criteria in accordance with the guidelines current at the time patient's assessment [2, 11, 12]. Patients were retrospectively divided into three cohorts based on the presence of moderate FMR:

(1) no/mild FMR (N-FMR) — the patients without moderate FMR;

(2) incidental moderate FMR (I-FMR) — the patients with moderate FMR observed in **one** transthoracic echo only, either the referral or admission study;

(3) permanent moderate FMR (PM-FMR) — the patients with moderate FMR present in **two** echocardiographic studies i.e referral and admission TTE.

Endpoints

The primary endpoint was mid-term survival after AVR for AS in relation to the presence of preoperative incidental or permanent FMR. PM-FMR was defined as a moderate MR occurring in both referral and admission ECHO studies. I-FMR was identified when moderate FMR was noticed only in one ECHO study — either referral or admission. The 30-day mortality was also reported. The other clinical and echocardiographic patient characteristics were included in survival analysis.

Statistical analysis

Data are presented as median with interquartile range (IQR) or number with proportion as appropriate. Quantitative data were compared using the Kruskal-Wallis one-way analysis of variance on ranks with post-hoc Dunn's method for non-normally distributed data and one-way analysis of variance with post-hoc Holm-Sidak method for normal distribution. The frequencies were compared with chi-square test or Fisher exact test when feasible. The Kaplan-Meier curves were used to depict estimated long-term survival. The influence of various factors on survival was assessed with log rank test. To adjust for other confounders, parsimonious multivariable modeling with Cox regression was performed for overall mortality and mortality of postoperative 30-day survivors. Cox regression was used to seek for univariable predictors of survival and all patients' characteristics presented in the Table 1 were tested. The multivariable

model was built with Cox regression with the stepwise backward conditional method of variable inclusion using the factors with score statistics <0.1 on univariable testing. The 30-day and 5-year survival following AVR with PM-FMR are presented. *P* <0.05 was considered significant. Statistical analysis was performed with SPSS version 22 (IBM, Armonk, NY, US).

RESULTS

Baseline and surgical characteristics

Of initial 2626 patients with aortic valve intervention, we excluded patients with urgent, emergency and salvage surgery (n = 53), patients treated by transcatheter aortic valve implantation (n = 246), reoperations (n = 166), and endocarditis (n = 68). Patients with concomitant procedures: coronary artery bypass grafting (n = 532), aorta surgery (n = 296), mitral surgery (n = 194), tricuspid surgery (n = 20), and other procedures (n = 10) were excluded too. Moreover, patients with severe aortic insufficiency (n = 133), severe mitral regurgitation (n = 42) or with any other than functional mitral valve pathology (n = 170) were also not considered (Figure 1).

Six hundred seventy-nine elective patients who underwent isolated AVR for aortic stenosis with up to moderate functional mitral regurgitation in our institution between 2014 and 2019 were include in the analysis. Moderate FMR was present in 93 patients at referral ECHO imaging, 131 patients at admission ECHO and in 61 patients in both ECHO studies. By cohorts, 516 patients were in N-FMR group (297 men), 102 patients I-FMR group (53 men) and 61 patients in PM-FMR group (25 men) (Figure 2). Median time between the referral and admission TTE studies was 35 days (interquartile range [IQR], 25–49).

Patient with N-FMR (66 [60–73]) were younger than patients with I-FMR (70 [65–74]) and PM-FMR (75 [69–77]); *P* <0.01. On admission echocardiography patients with N-FMR had smaller ventricles with end systolic volume (ESD) (50 [38–65] ml) than those with I-FMR (59 [44–73] ml) and PM-FMR (66 [45–91] ml); *P*<0.01. They also had smaller end diastolic volume (EDV) in N-FMR (118 [97–145] ml) than in I-FMR (126 [111–154] ml) and in PM-FMR (134 [111–163] ml, respectively; *P* <0.01). The highest prevalence of atrial fibrillation (AF) was in in PM-FMR (23%) vs. N-FMR (10.7%) and I-FMR (19.6%), respectively (*P* = 0.01). The prevalence of pulmonary hypertension defined as systolic PAP above 30 mm Hg was highest also in PM-FMR group (31.1%) than N-FMR (9.7%) and I-FMR (16.7%); *P* <0.01.

The aortic valve gradients, and the prevalence of concomitant moderate aortic regurgitation did not differ between the groups. Patients did not differ in Canadian Cardiovascular Society Scale (CCS) and New York Heart Association (NYHA) Functional Classification. The prevalence of

hypertension diabetes, chronic obstructive pulmonary disease (COPD), extracardiac atherosclerosis, and smoking were similar between the groups. The presence of coronary artery disease had no influence on survival in our cohort (P = 0.57 by log rank test) and the need for concomitant coronary artery bypass grafting (CABG) was an exclusion criterion.

The baseline demographic data and clinical characteristics of the study population are summarized in Table 1.

After analyzing operative data, we find no difference in prothesis size implanted, cardiopulmonary bypass time (CPB) or cross clamp time (x-clamp) was found. Mechanical aortic valves were mostly implanted in N-FMR followed by I-FMR and PM-FMR (32% vs. 20% vs. 15%) opposite to biological which were implanted mostly in PM-FMR (66% vs. 77% vs. 85%); P <0.01 (Table 2). The incidence of postoperative bleeding was similar between groups.

Clinical outcomes

Follow up was 100% complete with median of 46 (22.5–58.5) months, max. 73.3. 30-day mortality was significantly highest in PM-FMR 8.2% (5 patients) vs. N-FMR 2.5% (13 patients) and I-FMR (1 patient), respectively (P = 0.02).

Five-year survival was 84.1% vs. 88.5% vs. 60.6% for N-FMR vs. I-FMR vs. PM-FMR (P <0.01) (Figure 3). After adjusting for other confounders multivariable analysis revealed PM-FMR as an independent risk factor impacting survival (HR, 1.88 [1.05–3.37]; P = 0.03), (Table 3). I-FMR did not affect survival (HR, 0.67 [0.32 months 1.37]; P =0.67). Other predictors of mortality included pulmonary hypertension (estimated systolic PAP >30 mm Hg) (HR, 1.82 [1.07–3.08]; P = 0.02), preoperative troponin T (HR 1.29 [1.02–1.64]; P = 0.03) and diabetes on insulin (HR, 2.38 [1.22–4.65]; P = 0.01).

After excluding 30-day mortality, the five-year survival was still inferior in PM-FMR group 86.3% vs. 89.4% vs. 66.0%; P = 0.02 (Figure 4). In multivariable modeling, PM-FMR remained a strong predictor of mortality (HR, 2.17 [1.14–4.15]; P = 0.02), together with preoperative troponin T (HR, 1.40 [1.09–1.80]; P <0.01) and pulmonary hypertension (HR, 1.85 [1.03–3.35]; P = 0.04), (Table 4).

DISCUSSION

The current guidelines on valvular heart diseases help to decide when to operate in secondary mitral regurgitation caused by coronary artery disease or related with atrial fibrillation [1], but there is paucity of data when to intervene in secondary mitral regurgitation related to aortic

stenosis [2, 13]. The problem is important, as concomitant mitral regurgitation concurrent with aortic stenosis is common [14]. Recently, Japan multicenter registry CURRENT showed that relatively high proportion (80%) of patients in whom moderate to severe MR was left untreated had lower degree of MR after AVR. Moreover, additional mitral valve repair did not improved survival in this group [15]. To assess precisely whether FMR can influence symptoms severity, risk of LV failure and most importantly survival is very difficult. Literature findings are inconsistent [5, 16]. Variability of secondary MR makes clinical assessment based on one ECHO imaging insufficient [17]. The FMR mechanism is heterogenous and there is no single strong parameter to predict precisely the severity of FMR [10], for instance the increase in preload deteriorates FMR and can induce congestive heart failure [17–19]. Such conditions are not permanent and the decision about the type of valve surgery is usually based just on one ECHO report.

We have shown that moderate FMR found in one echocardiographic study but not confirmed on another occasion did not affect survival of patients subjected to AVR (HR, 0.67 [0.32–1.37]; $P = 0.67$). However, patients who were referred with moderate FMR and the same moderate grade was confirmed on admission strongly and adversely affected the survival (HR, 1.88 [1.05–3.37]; $P = 0.03$). To our best knowledge, it is the first study when moderate FMR evaluation over time was assessed to precisely define patient population with permanent moderate FMR prior to AVR.

The worse survival in our PM-FMR cohort is consistent with the results found by Caballero-Borrego and colleagues in patients with moderate MR vs. no/mild MR [20].

Interestingly, there are studies where the early operative results were excellent with no mortality [16, 21]. In one of these, Jeong and colleagues did not find differences in cumulative survival at 10-year follow up (95.1% no-MR vs. 83.6% MR group; $P = 0.10$), although found some in cardiac related mortality events [16]. On the other hand, Absil and colleagues noticed increased operative mortality and mid-term survival but differences between MR 0–1 vs. MR 2–3 grade were not significant (60.9% vs. 55%) [5]. Also, no difference was reported by Barreiro with perioperative mortality of 3.8% vs. 7.1% ($P = 0.21$) and late survival of 40.8% vs. 41.4%; ($P = 1.0$). But the prevalence of functional etiology in that population was only 21.4% [6]. Early mortality reported by Takeda in the group with no/trivial MR (1.7%) vs. group with mild/moderate MR (2.9%) did not differ but was lower than in the current study [22]. Most authors citied above relied on only one FMR ECHO assessment and our data may explain the discrepancy between previous results.

Moreover, effective regurgitant orifice area (EROA) >10 mm^2 was previously associated with severe symptoms and higher pulmonary arterial pressure after mixed surgical AVR (SAVR) and transcatheter AVR (TAVI) [23]. TAVI and SAVR patient population differ much in severity of comorbidities but reports after TAVI in FMR corresponds with SAVR results up to 24 months of follow-up [24–27].

Our permanent FMR patient population had more often left atrium and ventricle enlarged, and more prevalent AF and pulmonary hypertension. Also, the patients with PM-FMR were significantly older than the other groups. In fact, the FMR presence related to higher age as the N-FMR group was the youngest. It may suggest that longer standing disease (AS) may more likely lead to FMR. The same may relate to LV volumes as the higher LV volumes correlated with FMR.

To avoid studying the ischemic mitral regurgitation we excluded the patients who required myocardial revascularization from the study and the presence of coronary artery disease had no influence on survival in our cohort ($P = 0.57$ by log-rank test).

Current guidelines in FMR related to AS suggest a conservative approach if no predictors of deterioration like atrial fibrillation, enlarged left atrium, increased left ventricular mass indexed, pulmonary hypertension or preoperative peak aortic valve gradient <60 mm Hg are present [15, 28–30]. Similar improvement or non-progression of FMR degree was also documented after TAVI [25, 31–33]. Even though, moderate FMR can improve after isolated AVR poor clinical outcomes were noticed in this cohort [16, 28, 22]. Moreover, persistent FMR at discharge can worsen survival after AVR [34].

Certain limitations of our study must be acknowledged. This was a retrospective analysis. In the current study we focused on overall survival and the cause of deaths were unavailable. We did not assess the other clinical endpoints (e.g. late reoperations) nor analyzed the postoperative follow-up ECHOs. Therefore, we cannot comment on the postoperative course of FMR.

The usual practice is that the decision on the treatment of FMR is based on one echocardiography [35]. Meanwhile, our results show that only the permanent FMR that was present on two TTEs, affected the outcome. The incidental appearance of FMR on echocardiography that was not confirmed in another study had no influence on survival. Thus, bearing in mind the dynamic nature of FMR one should not make therapeutic decisions based on single echocardiographic finding. We consider permanent moderate FMR in patients with AS scheduled for AVR a strong life-shortening predictor. The existence of PM-FMR in this patient population may indicate the need for additional mitral valve surgery, but this requires further studies.

Article information

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Table 1. Baseline characteristics

Variable	**N-FMR (n = 516)**	**I-FMR (n = 102)**	**PM-FMR (n = 61)**		***P*-value**
Clinical characteristics					
Age, years, median (IQR)	66.00 (60.00–73.00)[a,b]	70.00 (64.75–74.00)[c]	75.00 (69.00–77.00)		<0.001
Male sex, n (%)	297 (42.4)	53 (52.0)	25 (41.0)		0.02
BSA, m^2, median (IQR)	1.87 (1.72–2.02)	1.87 (1.74–2.02)	1.83 (1.69–1.94)		0.21
NYHA, n (%)					0.35
NYHA I	44 (8.5)	5 (4.9)	2 (3.3)		–
NYHA II	327 (63.4)	73 (71.6)	38 (62.3)		–
NYHA III	138 (26.7)	24 (23.5)	20 (32.8)		–
NYHA IV	7 (1.4)	0 (0)	1 (1.6)		–
Hypertension, n (%)	424 (82.2)	85 (83.3)	55 (90.2)		0.29
Diabetes mellitus, n (%)					0.13
With insulin	37 (7.2)	10 (9.8)	5 (8.2)		–
With oral agents	109 (21.1)	20 (19.6)	21 (34.4)		–
COPD, n (%)	31 (6.0)	7 (6.9)	2 (3.3)		0.63
Renal failure, n (%)	22 (4.5)	13 (13.8)	4 (7.3)		<0.01

Creatinine level mg/dl, median (IQR)	0.88 (0.76–1.02)[a]	0.93 (0.78–1.11)	0.91 (0.80–1.08)		0.04
GFR preop (ml/min/1.73 m^2), median (IQR)	81.00 (68.00–90.00) n = 516[a,b]	73.50 (60.00–84.25) n = 102	73.00 (56.50–84.00) n = 61		<0.001
Troponin T, ng/ml, median (IQR)	0.012 (0.008–0.020) n = 516[a, b]	0.015 (0.009–0.024) n = 102	0.016 (0.009–0.026) n = 61		0.04
Current smoke, n (%)	70 (13.6)	5 (4.9)	4 (6.6)		0.09
Hyperlipidemia, n (%)	341 (66.1)	78 (76.5)	42 (68.9)		0.12
Atrial fibrillation, n (%)	55 (10.7)	20 (19.6)	14 (23.0)		0.01
Euroscore II, %, median (IQR)	1.24 (0.85–1.88)[a, b]	1.62 (1.05–2.50)[c]	2.35 (1.28–4.14)		<0.001
Coronary angiography results, n (%)					0.51
No lesions	452 (88)	90 (88)	48 (79)		
Single vessel disease	47 (9.1)	7 (6.9)	9 (15)		
Double vessel disease	12 (2.3)	4 (3.9)	3 (4.9)		
Triple vessel disease	5 (1.0)	1 (1.0)	1 (1.6)		
PCI in the past, n (%)	57 (11)	19 (19)	5 (8.2)		0.06
CAD (PCI or angio-result), n (%)	101 (20)	26 (26)	15 (25)		0.31
Previous MI, n (%)	32 (6.2)	11 (11)	7 (12)		0.12
	Admission echocardiography				
Bicuspid aortic valve, n (%)	171 (33.1)	25 (24.5)	10 (16.4)		0.01
Aortic insufficiency (AI), n (%)					0.15
No	244 (47.3)	49 (48.0)	25 (41.0)		–
Mild	168 (32.6)	24 (23.5)	24 (39.3)		–

Moderate	104 (20.2)	29 (28.4)	12 (19.7)		–
Mitral regurgitation (MR), n (%)					<0.001
No	266 (51.6)	20 (19.6)	0 (0)		–
Mild	250 (48.4)	50 (49.0)	0 (0)		–
Moderate	0 (0)	32 (31.4)	61 (100)		–
LA, mm, median (IQR)	40.00 (36.00–44.00) n = 396	43.00 (40.00–47.00) n = 74	44.00 (40.00–47.75) n = 44		<0.001
LVESV, ml, median (IQR)	50.8 (38.12–64.90) n = 461[a, b]	58.9 (44.13–73.15) n = 97	66.0 (45.35–91.26) n = 56		<0.001
LVEDV, ml, median (IQR)	118.2 (97.33–145.00) n = 462[a, b]	126.0 (111.00–153.66) n = 97	134.50 (111.25–163.01) n = 56		<0.01
Ejection fraction, %, median (IQR)	55.0 (50.00–60.00)[a, b]	55.0 (49.50–60.00)	55.0 (41.00–60.00) n = 61		<0.001
Mean aortic gradient, mm Hg, median (IQR)	47.0 (39.00–58.00) n = 514	48.0 (38.00–60.00)	46.0 (42.00–62.00) n = 61		0.49
Peak aortic gradient, mm Hg, median (IQR)	81.0 (69.00–95.75)	87.0 (68.00–101.50) n = 101	83.0 (71.50–102.5) n = 61		0.28
Pulmonary hypertension, n (%)	50 (9.7)	17 (16.7)	19 (31.1)		<0.001
LF, %	212 (49.6) n = 427	41 (44.6) n = 92	23 (46.9) n = 49		0.66

[a](N-FMR vs. I-FMR) <0.05; [b](N-FMR vs. PM-FMR) <0.05; [c](I-FMR vs. PM-FMR) <0.05

Abbreviations: AS, aortic stenosis; BSA, body surface area; COPD, chronic obstructive pulmonary disease (long term use of bronchodilators or steroids for lung disease); ESV, end-systolic volume; EDV, end-diastolic volume; GFR, glomerular filtration rate (ml/min/1.73 m^2); I-FMR incidental moderate functional mitral regurgitation; N-FMR, without or mild functional

mitral regurgitation; LA, left atrium; LF, low flow (stroke volume <35 ml/m^2); LV, left ventricle; NYHA, New York Heart Association; PM-FMR, permanent moderate functional mitral regurgitation

Table 2. Operative data

Variable	**N-FMR (n = 516)**	**I-FMR (n = 102)**	**PM-FMR (n = 61)**	***P*-value**
CBP time, min, median (IQE)	65.00 (55.00–80.00)	62.00 (51.00–76.25)	62.00 (53.50–70.00)	0.17
X-clamp time, min, median (IQE)	51.00 (42.25–62.00)	48.00 (41.00–61.00)	48.00 (41.00–55.50)	0.06
Stentless valve, n (%)	15 (3)	4 (3)	0 (0)	<0.01
Biological valve, n (%)	338 (65)	78 (77)	52 (85.0)	
Mechanical valve, n (%)	163 (32)	20 (20)	9 (15)	
Prothesis size, mm, median (IQE)	23.00 (21.00–23.00)	23.00 (21.00–23.00)	23.00 (21.00–23.00)	0.12
Bleeding, ml, median (IQE)	550.00 (400.00–750.00), n = 512	550.00 (350.00–700.00), n = 99	507.50 (378.75–686.25), n = 58	0.39

Abbreviations: CPB time, cardiopulmonary bypass time; X-clamp time, cross-clamp time; other — see Table 1

Table 3. Univariable and multivariable analysis of mortality predictors after aortic valve replacement

Univariable analysis				**Multivariable analysis**		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
LF	1.59	0.97–2.62	0.06			
COPD	1.96	0.94–4.08	0.07			
Diabetes mellitus (vs. no diabetes)						
Oral agents	1.40	0.84–2.34	0.19	1.20	0.71–2.02	0.49
Insulin	2.54	1.31–4.89	<0.01	2.38	1.22–4.65	0.01
Atrial fibrillation	1.89	1.10–3.23	0.02			
Bicuspid aortic valve	0.57	0.32–1.00	0.05			
Pulmonary hypertension	2.06	1.24–3.41	<0.01	1.82	1.07–3.08	0.03
Age, years	1.02	0.99–1.04	0.06			
Log (pre-op troponin T), ng/ml	1.40	1.12–1.74	<0.01	1.29	1.02–1.64	0.03
GFR pre-operation, ml/min/1.73 m^2	0.98	0.97–0.99	0.001	0.98	0.97–1.00	0.07
FMR (vs. N-FMR)						
I-FMR	0.80	0.39–1.63	0.56	0.67	0.32–1.37	0.28
PM-FMR	2.75	1.61–4.70	<0.001	1.88	1.05–3.37	0.03

Abbreviations: COPD, chronic obstructive pulmonary disease; other — see Table 1

Table 4. Univariable and multivariable analysis of mortality predictors after aortic valve replacement excluding 30-day mortality

Univariable analysis				**Multivariable analysis**		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age, years	1.02	0.99–1.05	0.10			
EuroSCORE II	1.14	1.02–1.27	0.02			
GFR pre-operation, ml/min/1.73 m^2	0.98	0.97–0.99	<0.01			
Bicuspid aortic valve	1.33	0.96–1.84	0.08			
Pulmonary hypertension	2.12	1.20–3.75	0.01	1.86	1.03–3.35	0.04
Log (pre-op troponin T), ng/ml	1.40	1.09–1.79	<0.01	1.41	1.10–1.80	<0.01
FMR (vs. N-FMR)						
I-FMR	0.94	0.44–2.00	0.87	0.83	0.38–1.78	0.64
PM-FMR	2.59	1.39–4.84	<0.01	2.17	1.14–4.15	0.02

Abbreviations: see Tables 1 and 3

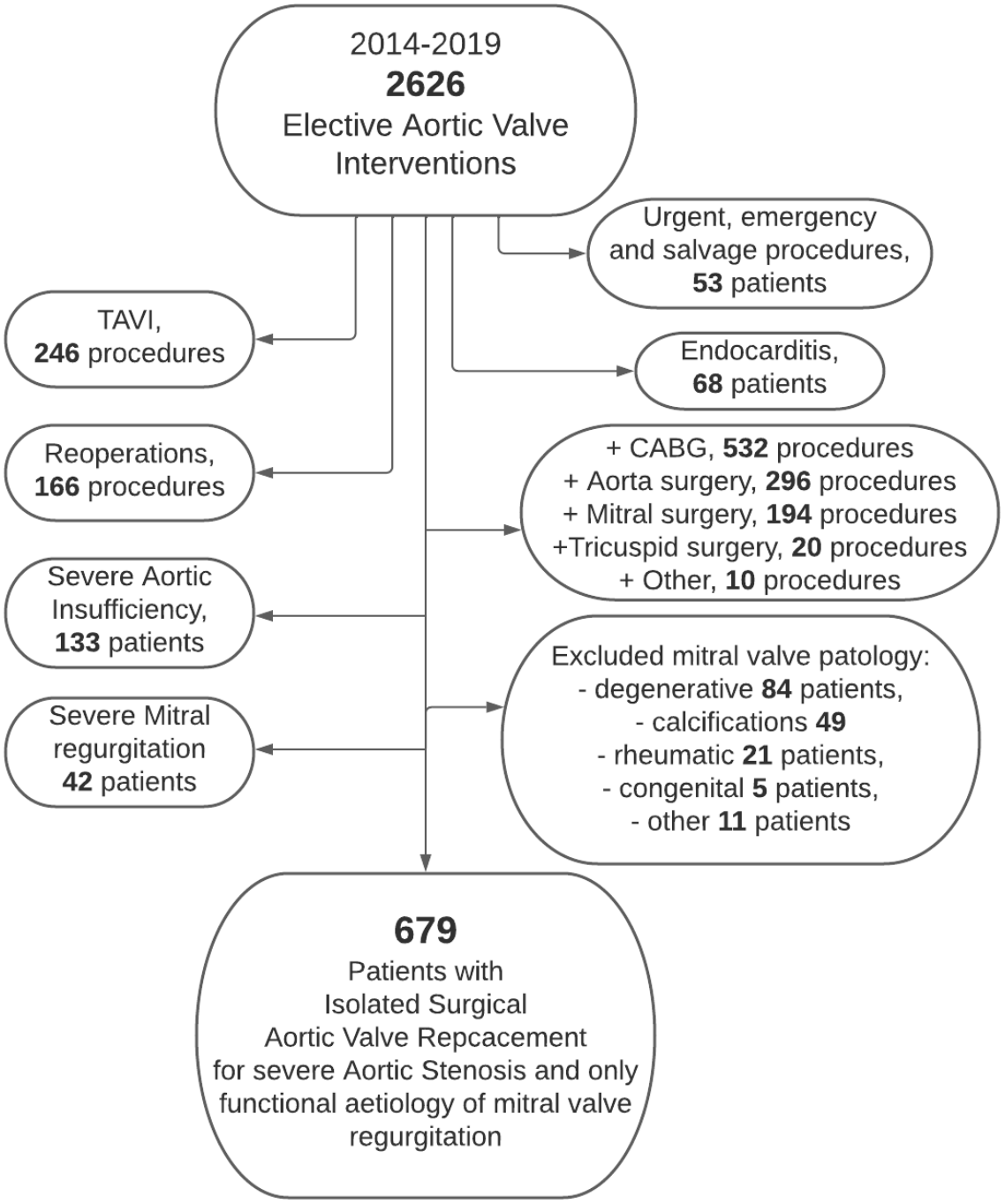

Figure 1. Selection flowchart

Abbreviations: CABG, coronary artery bypass grafting; TAVI, transcatheter aortic valve implantation

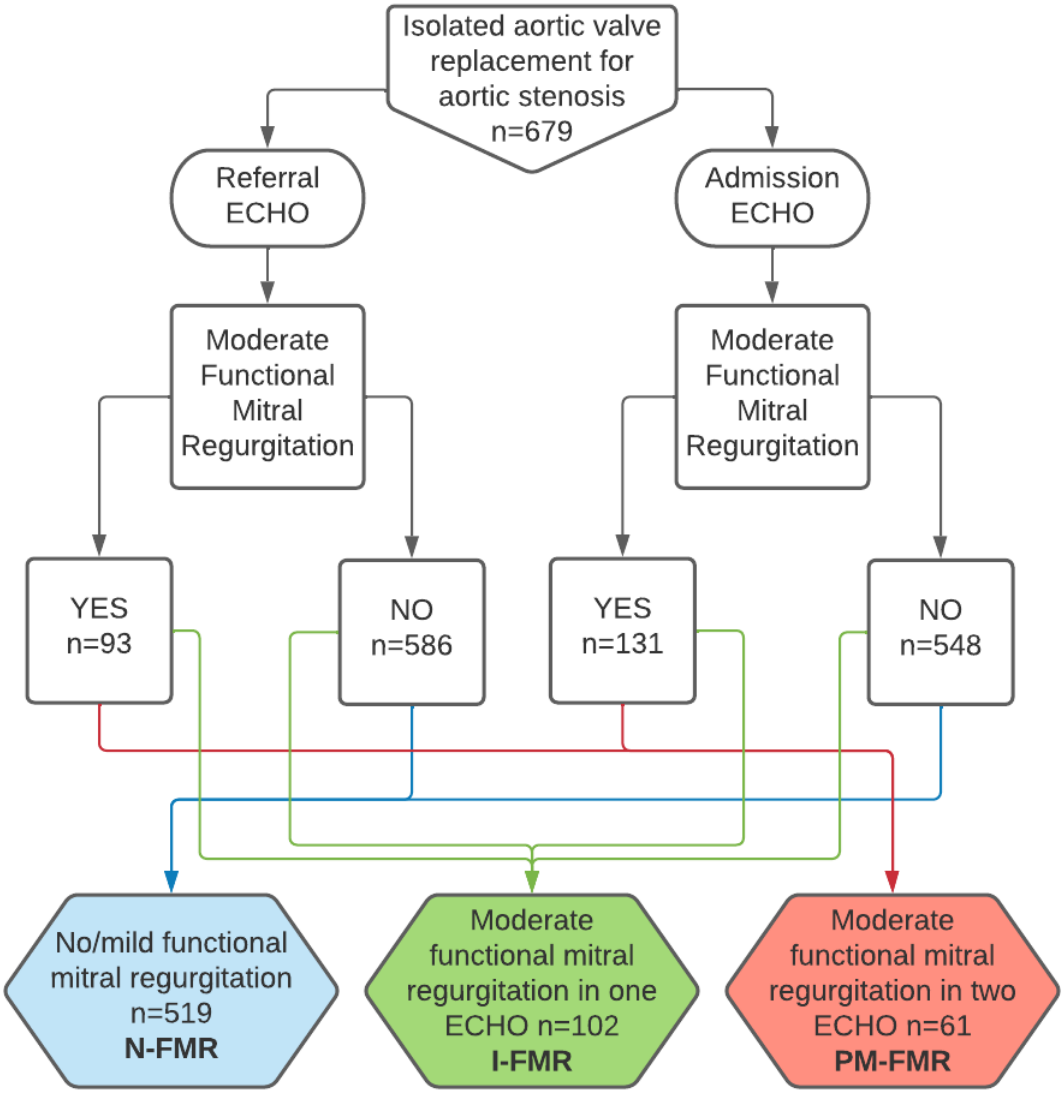

Figure 2. Flowchart of patients with functional mitral regurgitation

Abbreviations: ECHO, echocardiography; other — see Table 1

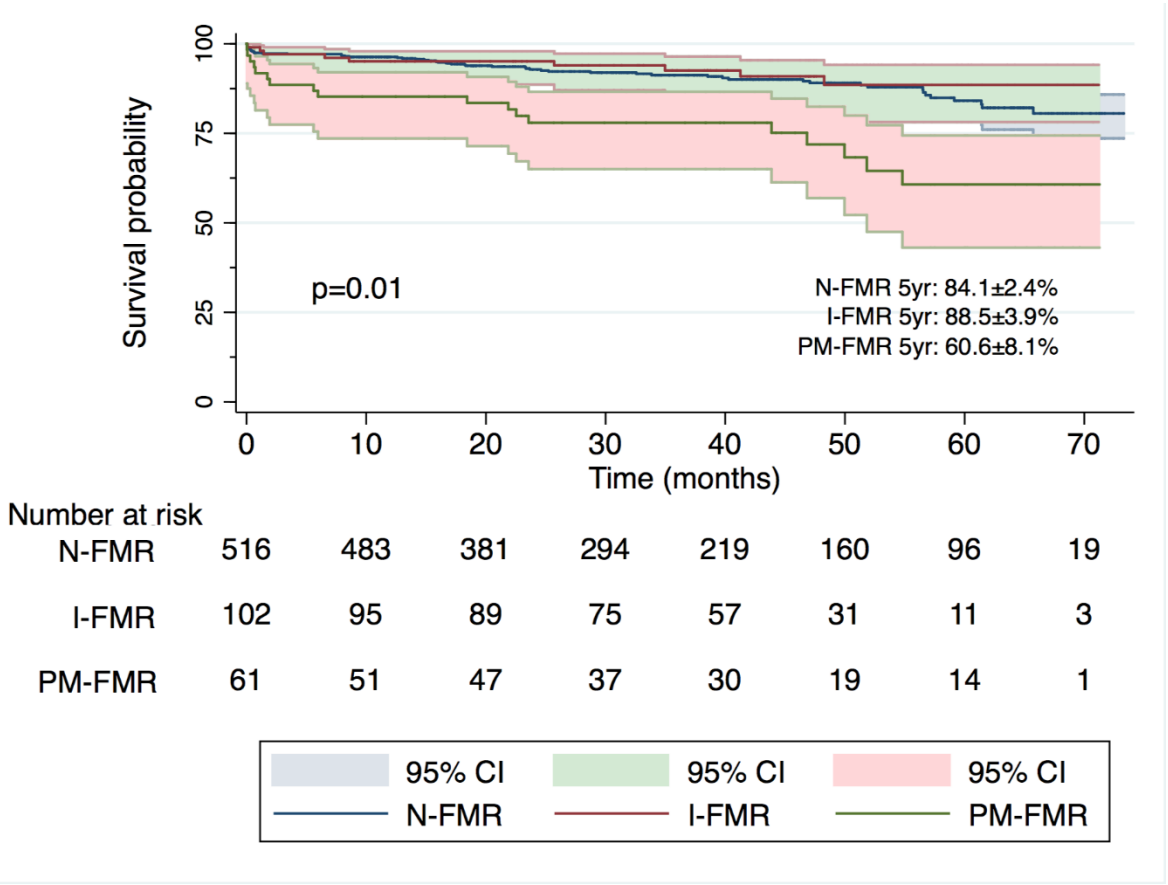

Figure 3. Kaplan-Meier survival estimates for patients after AVR for AS with no-moderate functional mitral regurgitation (N-FMR) vs. incidental moderate FMR (I-FMR) vs. permanent FMR (PM-FMR)

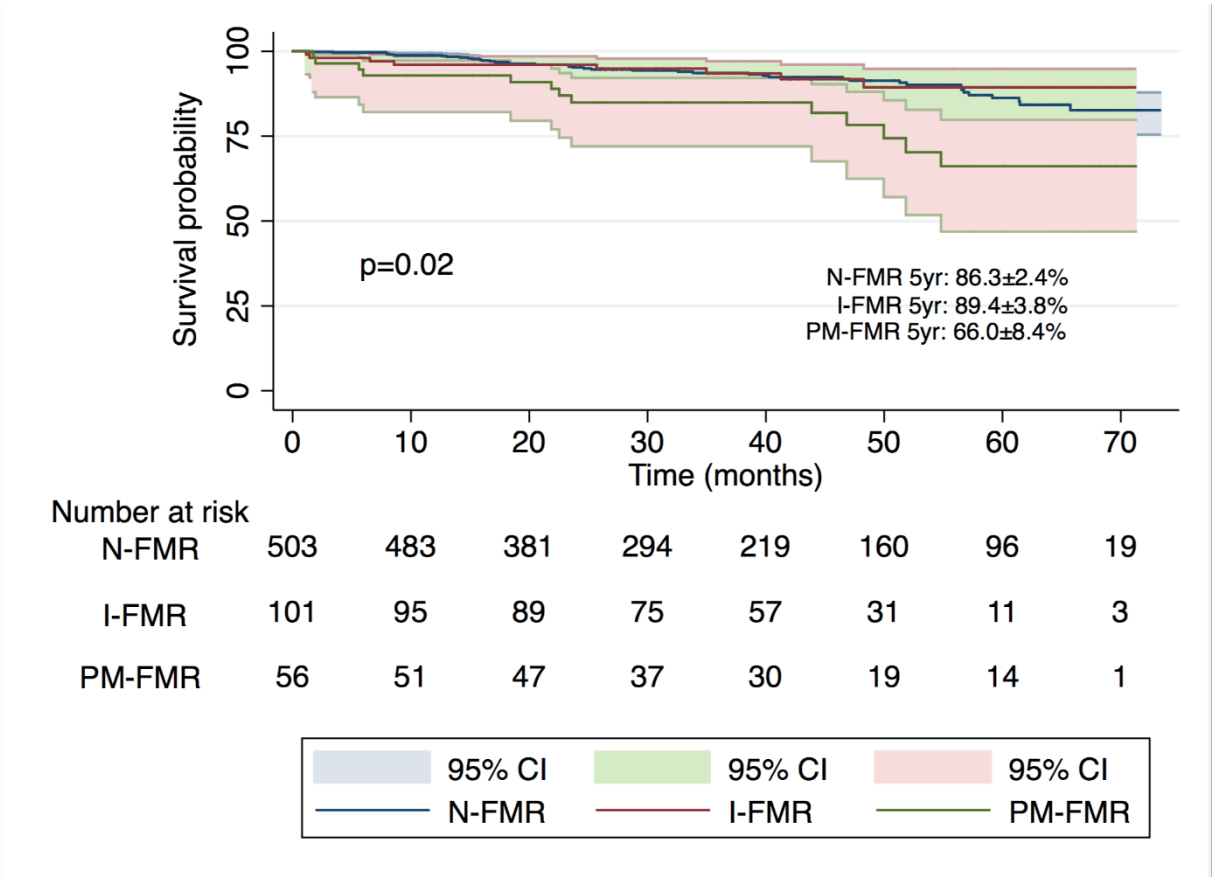

Figure 4. Kaplan-Meier 30-day landmark analysis for patients after AVR for AS with no-moderate functional mitral regurgitation (N-FMR) vs. incidental moderate FMR (I-FMR) vs. permanent FMR (PM-FMR)