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TESI DI LAUREA

Prognostic role of the invasive right heart catheterization assessment in patients undergoing transcatheter mitral valve edge-to-edge repair.

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1. ABBREVIATIONS AND ACRONYMUS

AF= atrial fibrillation

aFMR= atrial functional mitral regurgitation

CVD= cardio-vascular death

DMR= degenerative mitral regurgitation

EROA= effective regurgitant orifice area

HF= heart failure

iFMR= ischemic functional mitral regurgitation

LA= left atrial

LAD= left atrial diameter

LV= left ventricular

LVEF= left ventricular ejection fraction

LVEDV= left ventricle end-diastolic volume

mPAP= mean pulmonary arterial pressure

MA= mitral annulus

MV= mitral valve

MVARC= Mitral Valve Academic Research Consortium

MR= mitral valve regurgitation

niFMR= non-ischemic functional mitral regurgitation

NYHA= New York Heart association

PAC= pulmonary arterial compliance

PAWP= pulmonary arterial wedge pressure

PH= pulmonary hypertension

RA= right atrium

RV= right ventricle

RVol = regurgitant volume

sPAP= systolic pulmonary arterial pressure

TEER= transcatheter edge-to-edge repair

TEE= transesophageal echocardiography

TTE= transthoracic echocardiography

vFMR= ventricular functional mitral regurgitation

VHD= valvular heart disease

2. ABSTRACT

Background: Mitral regurgitation (MR) is a highly prevalent valvular heart disease (VHD), affecting 10% of the population, representing the second most frequent VHD in high-income countries. Beside echocardiographic assessment, right heart catheterization (RHC) is a common step in mitral valve transcatheter edge to edge repair (M-TEER) work-up. Several right ventricle hemodynamic parameters have been identified as predictors of adverse outcome in patient undergoing M-TEER.

Aim of the study: evaluate the prognostic impact of RV invasive hemodynamic parameters as predictors of adverse outcomes in patients with significant MR treated with TEER. Furthermore, investigate the diagnostic accuracy and the prognostic impact of the new threshold values for mPAP, PVR e PCWP introduced by the new Guidelines for the diagnosis and treatment of pulmonary hypertension published in 2022.

Methods: A total of 152 patient with symptomatic severe MR, both degenerative and functional, treated with M-TEER between December 2014 and May 2023 at the Padua University Hospital were enrolled. All patients underwent complete diagnostical assessment through transthoracic and transesophageal echocardiography (TTE and TEE). Among all patients, 71 underwent elective invasive RHC before M-TEER and invasive hemodynamic parameters were recorded. The M-TEER procedure was performed according to current clinical practice. Follow-up was performed through outpatient visit including clinical and echocardiographic examination. Main outcomes of interest were all cause mortality and hospitalization for heart failure (HFH), and the composite death-HFH.

Results: RV FAC, TAPSE, RAVi, RV disfunction were significantly associated to the composite outcomes and death at longest follow up. Only invasive, and not, echocardiographic sPAP or TAPSE/sPAP showed significant association with the outcomes. PCWP, PAPm, RVSWi were the RHC parameters that showed significant association with death at longest follow up with PCWP and PAPm being independent predictors of worse outcomes at the multivariate analysis. ROC curve analysis showed high sensitivity of the new ESC cut-offs for one year mortality. A significant association with long-term mortality for mPAP greater than 20 mmHg ($p=0.003$) and PCWP greater than 15 mmHg ($p=0.04$), as well as a trend towards significance for PVR greater than 2 WU ($p=0.06$) was noted.

Conclusion: RHC catheterization has an important prognostic role of in patients undergoing mitral valve edge to edge repair. The new proposed ESC cut-offs for predict all-cause mortality in this subset of patients. mPAP and PCWP are independent predictors of worst prognosis at long term follow up.

3. INTRODUCTION

Mitral regurgitation (MR) is a highly prevalent valvular heart disease (VHD), affecting 10% of the population (1), representing the second most frequent VHD in high-income countries (2). The mitral valve (MV) apparatus is complex in function and anatomy. Its role involves facilitating the filling of the left ventricle (LV) during diastole and effectively preventing backflow during the high-pressure phase of systole. This effectiveness is attributed to the precise coordination among various components such as the mitral annulus (MA), leaflets (anterior and posterior), chordae, and papillary muscles, along with the optimal anatomy and function of the left atrium (LA) and ventricle (3). The disruption of any component of this dynamic structure and its complex interactions with the surrounding anatomy may cause the failure of the MV leaflets to coapt during systole, when the valve should be closed, resulting in blood regurgitation from the LV to the LA with significant clinical implications (4). MR incidence is constantly increasing in high-income countries, despite a decline in rheumatic etiology which still predominate in developing countries (2). Prevalence of moderate to severe MR significantly increases with age, impacting over 10% of individuals over 75 years old, especially men (5). This implicates a rising public health problem, as a growing number of patients with MR are referred to valve centers for treatment requiring hospitalization or intervention (6). Additionally, MR is frequently associated with other heart disease such as chronic heart failure (HF) (50%) and myocardial infarction (20-25%). This association worsens patients' prognosis increasing morbidity and mortality rates leading to a various complications, including arrythmias, endocarditis and sudden cardiac death as well (5,7). Notwithstanding this, significant progress has been achieved in the diagnosis, quantification and timing of treatment for MR with the potential to reduce mortality and HF in these patients (8).

3.1. Etiology

From an etiological standpoint, two types of MR are distinguished: primary MR, also known as degenerative MR (DMR), and secondary MR or functional MR (FMR) (4). These two entities exhibit substantial variations in comorbidities, prognosis and therapeutic approaches. Differentiate between them is hence paramount to ensure the appropriate therapeutic course to each patient (9). DMR

patients should be classified according to the Carpentier classification system (*Figure 1*) which serves as a valuable tool for understanding the underlying causes of the MV disease, evaluating the feasibility of valve repair and selecting appropriate therapeutic interventions. Carpentier type I primary MR is characterized by normal leaflet size and motion, resulting in regurgitation attributed to either leaflet perforation or congenital clefts. Carpentier type II MR is characterized by excessive leaflet motion, manifesting as prolapse or flail leaflets. Carpentier type III is characterized by restrictive leaflets motion. It's further distinguished in type IIIa, with resticted leaflets motion during systole and diastole, and type IIIb with restriction during systole only. Carpentier type IIIa is frequently observed in DMR cases of rheumatic disease and MA calcification (6,10). Carpentier type IIIb is commonly observed in FMR, both ischemic FMR (iFMR) and non-ischemic FMR (niFMR). Inferior wall and posterior papillary muscle motion abnormalities, with tethering of posterior leaflet, or severe left ventricle enlargment and remodelling, with tethering of both leaflets, are the causal mechanisms of type IIIB FMR (11). In addition, left ventricular enlargement can potentially lead to MV annulus dilation further aggravating MR with a Carpetier type I pattern. The Carpentier type I MR pattern is also typical of atrial FMR (aFMR),where atrial enlargement promotes the aforementioned annulus dilation (12).

3.1.1 Primary Mitral Regurgitation

Primary MR is defined as a primary abnormality of the MV apparatus. Today the most common cause of primary MR is myxomatous degeneration of the MV leaflets leading to MV prolapse (13), affecting 2-3% of global population (14). The severity spectrum of myxomatous degeneration spans from fibroelastic deficiency, characterized by thin leaflets and focal prolapse, to Barlow's disease, characterized by diffusely thickened and redundant leaflets (15). Additionally, primary MR may arise from leaflet perforation or cleft leaflets, the latter characterized by deep indentations extending to the MA. Leaflet motion restriction can result from various factors. Rheumatic disease, which was the primary cause of primary MR in the past, remains the most frequent etiology of DMR in developing countries (4). Also medication effects, radiation, and connective tissue disorders can lead to thickening of leaflet edges and subvalvular apparatus. In elderly patients, MA calcifications are emerging as a significant cause of MR: this degenerative process typically

initiates in the posterior annulus and progresses into the base of the leaflets and subvalvular apparatus, impairing both annular and leaflet function (10).

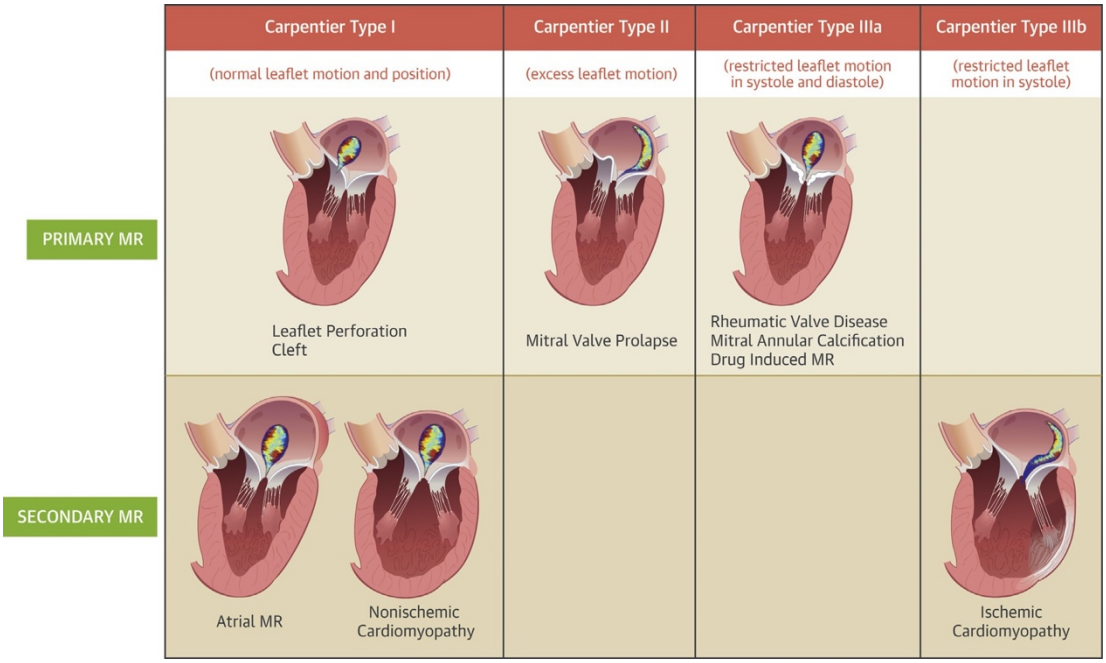


Figure 1: Carpentier classification of the etiology of MR (6)

3.1.2 Secondary Mitral Regurgitation

In contrast to primary MR, vFMR occurs due to an imbalance between increased leaflets tethering (caused by global and/or focal LV dilation, papillary muscle displacement and/or dysfunction) and decreased closure forces (caused by reduced LV contractility and/or synchronicity). This leads to poor coaptation during systole without intrinsic structural valve changes (6,10,16). The traditional causes of FMR typically involve non-ischemic cardiomyopathy and ischemic remodeling (most frequent etiology). LV dilatation with apical and lateral papillary muscles displacement, systolic dysfunction, and global/regional LV abnormalities are the causes of ventricular functional MR (vFMR) (17). FMR in the context of LV dysfunction occurs in 20% to 25% of patients after myocardial infarction and in up to 50% of HF patients (7). IFMR can result from regional wall motion abnormalities, most commonly leading to posterior leaflet tethering and posteriorly directed regurgitation. The abnormal motion of the cardiac wall in iFMR may coincide with myocardial hibernation or scarring. Additionally, iFMR may induce central MR when there are widespread abnormalities in wall motion due to multivessel coronary disease or severe ventricular remodeling, resulting in a similar

equal lateral displacement of both papillary muscles as observed in nonischemic cardiomyopathy (12). Inadequate coaptation due to the mismatch between the dilated annulus, following ventricular enlargement and the leaflet length may also occurs (6,18). The etiology of MR in nonischemic cardiomyopathy is multifactorial most commonly due to long standing hypertension or idiopathic dilatated cardiomyopathy (11). A less frequent but increasingly acknowledged scenario is when MR is secondary to LA enlargement, most often from persistent atrial fibrillation (AF) and/or heart failure with preserved ejection fraction (HFpEF) associated with severe LA dilation, referred to as aFMR (19,20). The anulus dilatation caused by long-term AF and changes in the atrium seem to be crucial, showing a Carpentier type I pattern (12). In patients with FA, MR severity improves after restoration of sinus rhythm, suggesting a causal relationship (21).

3.2. Pathophysiology

The mechanisms depend on the etiology (organic or functional MR) and the onset mode (acute or chronic).

In the early stages of primary MR, the disruption in closure of the MV, lead to retrograde blood flow from the LV to the LA during ventricular systole. Retrograde blood flow through the MV is promoted by the lower pressure during systole in LA compared to LV. The chronic volumetric overload of the LV leads to remodeling of both the LA and LV with eccentric hypertrophy that results in an increase in left ventricular end-diastolic volume (LVEDV) without any increase in wall thickness. Consequently, there will be no increase in left ventricular end-diastolic pressure (LVEDP). (4). Furthermore, considering the low afterload to outflow offered by the low pressure atrium, patients with MR often present an overestimated ejection fraction (LVEF) despite decreased myocardial contractility (22). LV dysfunction may be masked by a borderline LVEF, between 50% and 60%, and revealed only in the postoperative echocardiography when MR correction results in an immediate LVEF drop (2). However, with prolonged and worsening MR, ongoing chamber enlargement occurs beyond the compensatory limits. Progressive LV enlargement contributes to escalating MR due to alterations in ventricular geometry and annular dilation. Additionally, the volume-overload regurgitated in LA during each systole, results in LA dilatation with possible onset of AF. As the disease advances, LVEDP increases, leading to a decline in contractile function, reduced myofiber content,

and interstitial fibrosis (23). This deterioration culminates in irreversible LV pump dysfunction and failure in maintaining forward stroke volume, progressing to the decompensated stage of MR characterized by congestive HF symptoms and a poor prognosis (24). Notably, irreversible ventricular dysfunction may precede the onset of symptoms (6).

In acute MR, the adaptive mechanism described earlier fails due to acute valve dysfunction. Thus, sympathetic stimulation is the only possible response, leading to increased contractility and heart rate. Given the small size of the LA and its reduced compliance during acute dysfunction, the increased regurgitant volume (RVol) results in elevated LA pressure, causing pulmonary edema and reduced forward outflow (4).

In the context of iFMR, LV dilatation and remodeling lead to lateral and apical displacement of one or both papillary muscles resulting in systolic tenting of MV with leaflet tethering and MA dilation and flattening. In addition, systolic LV disfunction reduces valve closing forces. Moreover, regional wall motion abnormalities alone can cause leaflet tethering, resulting in severe MR despite preserved LVEF (25). All these variables are volume-loading dependent, explaining the dynamic nature of FMR (11). In case of global remodeling, with increased LV sphericity, leaflets tethering is symmetrical resulting in a central regurgitant jet. In contrast, if remodeling is localized, the involvement of the posterior papillary muscle causing posterior tenting of both leaflets (more pronounced at P2 or P3) leads to asymmetrical leaflets tethering and posteriorly directed regurgitant jet (11,12). MA dilatation usually occurs in the later stages of FMR pathophysiology, and it is often asymmetric, affecting commonly the posterior annulus (26). Conversely in niFMR, global LV dilatation and increased sphericity result in symmetric MA dilatation (more pronounced in the septal-lateral direction) and a central regurgitant jet (27). Moreover, the mitral leaflets elongate as an adaptive process due to increased tethering, leading to leaflet area increasing by up to 35% to reduce the MR grade. Inadequate remodeling of the leaflet may contribute to severe MR (28,29). Despite this, papillary muscle displacement can still result in significant MR (28). Also the normal saddle-shaped annulus is critical for maintaining normal stress and function of the leaflets. Losing this shape and the flattening of the MA with remodeling of the LV result in increased stress on the leaflets in FMR (11,30).

In patients with significant chronic MR, when the compensatory mechanism fails, the reduced compliance of the atrium leads to increased LA filling pressures with retrograde repercussions on the pulmonary vascular system, endothelial dysfunction of the pulmonary arteries, arteriolar and venular vascular remodeling, right ventricle (RV) dysfunction, and secondary tricuspid regurgitation (TR) which further exacerbates RV dysfunction. This lead to symptoms onset, representing a pivotal point in the natural history of MR (9,31,32). The increase in pulmonary pressure results in pulmonary hypertension (PH), defined as an invasive mean pulmonary artery pressure (mPAP) > 20 mmHg according with the new 2022 ESC Guidelines for the diagnosis and treatment of pulmonary hypertension. Pulmonary hypertension is further classified in pre-capillary, post capillary and combined pulmonary hypertension. Post capillary hypertension arise left side heart disease and it's defined by an increase in pulmonary capillary wedge pressure (PCWP), surrogate of LA pressure, over 15 mmHg. Precapillary hypertension involve directly pulmonary vasculature and it distinguished by pulmonary vascular resistance (PVR) >2 WU. Some patients exhibit both high PCWP and high PVR; those cases are defined combined PH (33). On echocardiography, pulmonary hypertension (PH) is defined as systolic PAP (sPAP) >50 mmHg and can be observed 15%-32% of patients with moderate or severe MR undergoing valve surgery (34). Usually, patients with MR exhibited isolated post-capillary PH. However, as PH progresses, pulmonary atrial compliance (PAC) decreases and PVR rises because of proliferative changes in small pulmonary arteries shifting the phenotype towards a combined PH. The RV and pulmonary artery (PA) constitute a cardio-pulmonary unit (RV-PA coupling) whose functionality is determined by RV contractility and afterload. With the increase in afterload (i.e., PA pressure), RV develops compensatory concentric hypertrophy. Eventually, the RV can't cope with the increasing afterload and RV dilation is the only means to maintain stroke volume according to the Frank-Starling law (35). At this point, the RV-PA unit decouples (36). PH can develop even before the onset of symptoms and the LV dysfunction. PH and RV dysfunction are associated with a worsening prognosis in these patients, correlating with increased mortality in patients hospitalized for HF (37) and it is a predictor of postoperative survival (38,39). In detail, a retrospective cohort study using the Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Therapy national registry demonstrated that severe PH is associated with an increased risk of all-cause mortality and hospitalization

for HF. Additionally, it has been demonstrated that even a mild increase of PAP is associated with adverse clinical outcomes, emerging concerns that the current European guidelines for MR treatment may recommend intervention for DMR too late in the course of the disease, as they set the threshold sPAP > 50 mmHg (40).

3.3. Clinical presentation

In case of acute MR, the small size of LA results in retrograde increase in pressures, leading to significant dyspnea and reduced forward flow, culminating in cardiogenic shock with acute pulmonary edema. In chronic settings, the clinical presentation may be more nuanced. As long as LA dilatation occurs and LVEF and filling pressures remain normal, patients may be asymptomatic, occasionally experiencing exertional dyspnea. The clinical presentation may deteriorate when hemodynamic compensation mechanisms fail with a reduction in systolic function and significant rise in filling pressures, especially in pulmonary circulation. This is the time when dyspnea worsens and exercise tolerance declines. When patients report new-onset symptoms or worsening symptomatology, repeat transthoracic echocardiography (TTE) is indicated to verify their attribution to MR or its effect on the LV, supporting the indication for correction. TTE should also be repeated when new-onset AF occurs to identify any changes in the severity of MR and LV status with implications for the LA (31,32). However, there is not always a direct correspondence between patient-reported symptoms and ventricular dysfunction, therefore the role of echocardiographic monitoring even in asymptomatic patients is essential. During physical examination of MR, a systolic murmur is typically detected best heard at the cardiac apex radiating to the left axilla if the posterior leaflet is affected or towards the base if the anterior leaflet is affected. S1 is often weak while S2 may be accentuated in presence of PH; occasionally S3 may be heard due to rapid proto-diastolic filling (2,4,9).

3.4. Diagnosis

TTE is the imaging technique of choice for the initial assessment of MR, providing detailed information on MV morphology, MR grade, LV status, and identifying the etiology of MR. This evaluation has prognostic implications and is crucial in determining the timing and feasibility of surgical or transcatheter intervention. If TTE results are inconclusive or inconsistent, it can be supplemented with transesophageal echocardiography (TEE), cardiac magnetic resonance (CMR) and heart catheterization (RHC) (4,9,16).

	Mild	Moderate	Severe
Structural parameters			
LA size	Normal*	Normal or dilated	Usually dilated**
LV size	Normal*	Normal or dilated	Usually dilated**
Mitral leaflets or support apparatus	Normal or abnormal	Normal or abnormal	Abnormal/ Flail leaflet/ Ruptured papillary muscle
Doppler parameters			
Color flow jet area[ζ]	Small, central jet (usually < 4 cm^2 or < 20% of LA area)	Variable	Large central jet (usually > 10 cm^2 or > 40% of LA area) or variable size wall-impinging jet swirling in LA
Mitral inflow –PW	A wave dominant[ϕ]	Variable	E wave dominant[ϕ] (E usually 1.2 m/s)
Jet density –CW	Incomplete or faint	Dense	Dense
Jet contour –CW	Parabolic	Usually parabolic	Early peaking–triangular
Pulmonary vein flow	Systolic dominance[§]	Systolic blunting[§]	Systolic flow reversal†
Quantitative parameters[ψ]			
VC width (cm)	< 0.3	0.3-0.69	≥ 0.7
R Vol (ml/beat)	< 30	30-44 45-59	≥ 60
RF (%)	< 30	30-39 40-49	≥ 50
EROA (cm^2)	< 0.20	0.20-0.29 0.30-0.39	≥ 0.40

Table 1: Qualitative and quantitative parameters useful in grading MR severity (41)

3.4.1. Echocardiography

It is recommended an echocardiographic integrated approach for the assessment of MR severity, including qualitative, semiqualitative and quantitative parameters (*Table 2*) (41,42). The qualitative assessment evaluates morphology and correct functioning of the MV, direction and extent of regurgitant jet via color Doppler, and flow's characteristics in relation to the cardiac cycle phase using continuous Doppler (9,16). When using color Doppler to evaluate the regurgitant jet extension, it must be considered that if the jet is eccentric (typical of DMR), the extent of regurgitation may be underestimated, while it is overestimated if the jet is concentric, due to the color setting mode (4). Quantitative analysis, which considers effective regurgitant orifice area (EROA), RVol, and regurgitant fraction, should be also employed when evaluating patient with MR. The first two can be measured using the continuity method or the proximal isovelocity surface area (PISA)

method, the latter being easier and more reproducible than the continuity method (4,10). However, the PISA method has significant limitations due to the assumption of a round orifice, which often does not reflect reality, particularly in FMR forms where the regurgitant orifice is more elliptical. Moreover, the assumption that EROA is nearly static throughout systole and does not change dynamically contributes to underestimating the severity of MR (6,43). These phenomena are particularly common in FMR. For this reason, two different cut-offs, ≥ 40 mm^2 for DMR and ≥ 30 mm for FMR, have been established to diagnose severe MR. Using the PISA method, it is also possible to derive the RVol. As mentioned before, the threshold applied to patients with FMR is reduced (RVol ≥ 45 ml) compared to patients with DMR (RVol ≥ 60 ml) (16,44). In cases where these quantitative parameters are discordant, a semi-quantitative evaluation can be implemented to assess MR severity, by measuring the vena contracta, systolic flow reversal in pulmonary veins, and trans-mitral flow velocity (E wave >1.2 m/s) (4). Current recommendations include LV evaluation ((LVESD ≥ 40 mm) and LA evaluation (LA diameter ≥ 55 mm or LA volume ≥ 60 ml/m^2) for a more complete assessment of MR severity (16). RV size and function should be assessed with the RV focused apical 4-chamber view rather than the conventional 4-chamber view (RVf4C), due to the complex structure and retrosternal position of the RV, which make its visualization more challenging (45). The measurements obtained in RVf4C projection suggest if RV dilation occurs with a lower variability than in the conventional view: a basal RV diameter >43 mm in women and >47 mm in men, and an RV:LV ratio >1 indicate RV dilation (36). One of the most used parameters for evaluating RV dysfunction is Tricuspid Annular Plane Systolic Excursion (TAPSE), measured in M-mode echocardiography. TAPSE <17 mm indicates RV systolic dysfunction and is a prognostic factor for PH (45). However, TAPSE is a parameter that deteriorates late in PH. By calculating the TAPSE:sPAP ratio (derived parameter evaluating RV-PA coupling), an independent prognostic factor regardless of LV dysfunction severity can be obtained. This ratio is recommended by the 2022 ESC/ERS PH guidelines for risk assessment (45,46).

In presence of significant MR, TEE should always be performed: it provides superior-quality images compared to TTE due to the proximity of the esophagus to the LA and MV. 3D TEE provides a frontal view of mitral leaflets resembling the “surgical view” of MV, facilitating discussions within the Heart Team. It is used for

intraprocedural assessment during transcatheter interventions and preoperative evaluation of pathogenetic mechanism of MR and feasibility of repair procedure (4,9,16).

Patients with discordant symptoms and MR grade at rest, may be evaluate with exercise echocardiography, identifying changes in mitral RVol and pulmonary pressures during maximal exercise (16,47,48)

	Primary mitral regurgitation	Secondary mitral regurgitation
Qualitative		
Mitral valve morphology	Flail leaflet, ruptured papillary muscle, severe retraction, large perforation	Normal leaflets but with severe tenting, poor leaflet coaptation
Colour flow jet area	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size
Flow convergence	Large throughout systole	Large throughout systole
Continuous wave Doppler jet	Holosystolic/dense/triangular	Holosystolic/dense/triangular
Semiquantitative		
Vena contracta width (mm)	≥7 (≥8 mm for biplane)	≥7 (≥8 mm for biplane)
Pulmonary vein flow	Systolic flow reversal	Systolic flow reversal
Mitral inflow	E-wave dominant (>1.2 m/s)	E-wave dominant (>1.2 m/s)
TVI mitral/TVI aortic	>1.4	>1.4
Quantitative		
EROA (2D PISA, mm^2)	≥40 mm^2	≥40 mm^2 (may be ≥30 mm^2 if elliptical regurgitant orifice area)
Regurgitant volume (mL/beat)	≥60 mL	≥60 mL (may be ≥45 mL if low flow conditions)
Regurgitant fraction (%)	≥50%	≥50%
Structural		
Left ventricle	Dilated (ESD ≥40 mm)	Dilated
Left atrium	Dilated (diameter ≥55 mm or volume ≥60 mL/m^2)	Dilated

Table 2: Severe MR criteria based on 2D echocardiography (16).

3.4.2. Cardiac magnetic resonance

CMR serves as a valid alternative for quantifying MR when echocardiographic data are incongruent. Moreover, it provides insights into the potential presence of myocardial fibrosis, frequent in DMR, and associated with the risk of sudden cardiac death and ventricular arrhythmias (16,49). Additionally, CMR aids in prognostic assessment of FMR patients by evaluating the extent of myocardial scar, which is associated with poor prognosis (16,50). However, it remains uncertain whether CMR data can be interchangeable with echocardiographic data in predicting outcomes (9).

3.4.3. Right heart catheterization

RHC is an invasive hemodynamic procedure used to evaluate the RH chambers and the PA via percutaneous vascular access, most commonly via femoral vein, but the

internal jugular, brachial, or subclavian veins may also be employed. It's the gold standard for measuring the pressure in right heart and pulmonary circulation and the only reliable methods in discriminating among the various forms of PH. In accordance with the currently used Seldinger technique, a guiding wire enters into the vessel lumen through a hallow needle (4,51). The procedure is performed with a Swan-Ganz (S-G) catheter, which enables the assessment of preload, afterload, and RV function by directly measuring four hemodynamic parameters: right atrial pressure (RAP), pulmonary arterial pressure (PAP), PCWP, and cardiac output (CO) (36,52) measured by the Fick method or thermodilution (36). RAP reflects central venous pressure but increases in cases of compromised compliance of the right atrium (RA) and RV, as seen in PH. PCWP indirectly measures LA pressure and, in the early stages of PH, will be higher than RAP (RAP/PAWP < 1). This ratio changes only when RV dysfunction occurs (RAP/PAWP > 1), making RAP:PAWP ratio a promising prognostic indicator, outperforming isolated RAP in some studies. (53). From these direct parameters, other indirect parameters can be derived, including stroke volume indexed to body surface area (SVi); right ventricle stroke work indexed (RVSWi), which reflects the effective work performed by the RV during each cardiac cycle; pulmonary artery pulsatility index (PAPi), a parameter with prognostic value for survival in patients with advanced HF; and PAC. Last but not least, PVR can be derived, which accounts for approximately 75% of the RV afterload (36). According to ESC guidelines on PH, RHC may be considered in patient with suspected PH associated to left heart disease to aid diagnosis and treatment.

Parameter	Definition
RAP/PAWP ratio	$\frac{RAP}{PAWP}$
Pulmonary vascular resistance (PVR)	$\frac{mPAP-PAWP}{CO}$
Total pulmonary resistance (TPR)	$\frac{mPAP}{CO}$
Stroke volume (SV)	$\frac{CO}{HR}$
Stroke volume index (SVi)	$\frac{CI}{HR}$
PA compliance	$\frac{SV}{PASP-PADP}$
RV stroke work index (RVSWi)	$\frac{(mPAP-RAP) \times CI \times 0.0136}{HR}$
PA pulsatility index (PAPi)	$\frac{PASP-PADP}{RAP}$

Table 3: Hemodynamic parameters derived from standard RHC

3.5. Management and prognosis

3.5.1. Medical therapy

In acute forms of MR, vasodilators, whenever possible, are recommended in addition to acute HF therapy for reducing filling pressures and increase forward flow. In chronic DMR vasodilators has not shown evident benefits because the LV afterload is already low due to LV eccentric hypertrophy and low LA pressure (4,16). When MR is associated with arterial hypertension, antihypertensive therapy is indicated in order to reduce LV afterload and MR in favor of increased forward outflow. In patients with MR associated with HFrEF, medical therapy in accordance with guidelines for the management of HF is recommended (16). Optimal medical therapy (OMT) included beta-blockers, mineralocorticoid receptors antagonists (MRAs), diuretics, sodium-glucose transporter 2 (SGLT2) inhibitors, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) or Sacubitril/Valsartan (ARNI) (16,54). Therapeutic options are limited in patients with MR associated HFpEF since no drug has been significantly shown to reduce mortality and morbidity in this setting (54). However, a targeted update to the 2021 ESC Heart Failure Guidelines recommends SGLT2 inhibitors as class IA therapy to primarily reduce the risk of HF hospitalizations and to a lesser extent CV death in patients with HFpEF (55).

If patients experience persistent symptoms despite OMT, indication for MV intervention should be considered to prevent further deterioration of LV function, MR grade and/or cardiac remodeling (16).

3.5.2. Indications for intervention

Given the differences between DMR and FRM in pathophysiology, natural history and prognosis, there are different recommendations for the management of these two diseases.

In patients with DMR, surgical intervention is recommended in presence of severe symptomatic (dyspnea on exertion, orthopnea and reduced exercise tolerance) MR associated with an acceptable surgical risk (16). Indeed, it has been demonstrated that the onset of symptoms, even mild symptoms, worsens the prognosis and thus surgical intervention has a strong indication (class IB) in symptomatic patients with an acceptable surgical risk (16,32).

Surgery is also recommended in presence of factors associated with worse outcomes regardless of symptomatic status. Surgery should be considered in patients with LV dysfunction (defined as LVEF ≤ 60% and/or LVESD ≥ 40 mm), or in patients with preserved LV function (LVEF > 60% or LVESD < 40 m) and new-onset AF due to MR, or sPAP at rest >50 mmHg or in presence of significant LA dilatation (LA volume index ≥ 60 ml/m² or LA diameter ≥ 50 mm). If none of these criteria are met, there is no indication for intervention and patient should be monitored with periodic clinical and echocardiographic follow-up, preferably in Heart Valve Centers. Follow-up includes measurement of BNP levels, TTE (including exercise test) and ECG-Holter monitoring, every 6 months if severe MR is associate with preserved LVEF (>60%); follow-up can be extended to 12-24 months for patients with moderate MR and preserved LVEF (16). MV repair is the first-choice surgical technique due to better survival rates compared to valve replacement (56). If repair is not feasible, a conservative approach is recommended performing MV replacement preserving sub-valvular apparatus. In patients with contraindications to surgery or high surgical risk, transcatheter edge-to-edge repair (TEER) is safely indicated (class IIb, level B recommendation), after carefully evaluating echocardiography criteria and intervention feasibility and futility in Heart Team (16,57).

In case of FMR, LV abnormalities play a pivotal role in guiding therapeutic approach. Surgical intervention, after a careful Heart Team evaluation, is recommended only in presence of severe MR and symptoms that persist despite OMT (including cardiac resynchronization – CRT -) (16,54,55). Surgery is the first choice intervention in patients requiring coronary bypass artery graft or other cardiac surgery. However, surgery in these patients leads to limited outcomes due to the underlying LV dilatation, dysfunction and cardiac remodeling. Indeed, indications for isolated MV surgery are restrictive due to the high surgical risk or contraindications to surgery in these patients. In patients with concomitant CAD or other cardiac disease requiring treatment but judged not appropriate for surgery by the Hart Team, TEER is recommended after PCI and/or TAVI (if severe FMR persists) (16). Similarly, TEER is recommended in symptomatic patients without these comorbidities, not eligible for surgery and fulfilling the criteria of a suggested increased chance of responding to the treatment. In high-risk symptomatic patients not eligible for surgery and not fulfilling the criteria suggesting an increased

response to treatment, the Heart Team may consider TEER procedure after careful evaluation of heart transplant and ventricular assist device (VAD). In contrast to DMR where surgery has a stronger recommendation, in FMR valve surgery is indicated in patients judged appropriate for surgery by the Heart Team in class IIb (16).

3.5.3. Transcatheter edge-to-edge repair of mitral valve

The edge-to-edge MV surgical repair technique, also known as "Alfieri's stitch", was introduced in 1991. This technique is based on a "functional" rather than "anatomical" repair: a surgical suture is applied between the anterior and posterior leaflets of MV along their free margin, at the site of the regurgitant jet, thereby creating a "double orifice" valve (58). The great success of the Alfieri's stitch is mainly due to its simplicity and reproducibility, as well as the percutaneous replication of this technique (59). The first device approved for the transcatheter treatment of patients with severe MR who are not candidates for traditional surgery was the MitraClip system (Abbott, Chicago, IL, USA). It was implanted for the first time in 2003 and was subsequently approved by the European Commission in 2008 and by the FDA in 2013 for the treatment of severe primary MR (58). Since its introduction in 2020, the fourth-generation MitraClip has been available in four sizes: NT and XT size with clips width of 4 mm and arm lengths of 9 mm or 12 mm respectively, and the wide platforms, NTW and XTW, that offer a wider implantation base (6 mm) while maintaining the same arm lengths as their non extended counterparts (9 mm for NTW and 12 mm for XTW). The efficacy and safety of M-TEER using the MitraClip device were analyzed in the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study Trial) randomized trial. The study compared MitraClip to surgery in a 2:1 ratio, including patients with MR grade moderate and severe, both DMR and FMR. Surgery showed more efficacy in reducing MR grade compared to percutaneous repair. Furthermore, despite similar rates of high residual grade of mitral regurgitation (MR grade ≥3+), surgery for MV dysfunction was more common in patient underwent percutaneous repair (20%) compared to those who had initially undergone MV surgery (2.2%) However, patients undergoing TEER experienced better improvement in NYHA class and quality of life at 12-months due to a reduction in LVED dimensions, compared to surgery. The safety endpoint favored the MitraClip cohort with a significant reduction in adverse events within 30 days (major adverse events: 15% clip *vs*. 48%

surgery) (57). At 5 years follow up surgery was superior to percutaneous repair in the composite endpoint of freedom from death, surgery for MV dysfunction and MR ≥ 3+ (64.3% for surgery versus 44.2% for percutaneous repair). However no significant difference in mortality between the two procedures was noted. (57,60). Subsequently two randomized trials, the French MITRA-FR and the COAPT (Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation), published in 2018, investigated the role of M-TEER in patients with FMR compared to OMT, reporting contrasting results (58). The MITRA-FR trial found no significant reduction in mortality or rehospitalization rates at 12 months in patients treated with MitraClip compared to OMT (respectively 55% *vs*. 51%) (61). Conversely, the COAPT trial demonstrated a significant reduction in mortality (29.1% *vs.* 46.1%) and rehospitalization rates at 24 months in the MitraClip-treated group compared to the medical control group (35.8% *vs.* 67.9%). Moreover, the safety endpoint, assessed as freedom from major adverse events at 12 months, was significantly better in the MitraClip-treated group compared to the controls (58,62). These contrasting results can be explained by the inclusion in the COAPT study of patients with disproportionate MR (more severe MR but less dilatated LV), witch responded better to treatment than MITRA-FR proportionated patients with MR severity proportionate to LV dilatation; differences in adherence to medical therapy may also have influenced the outcomes (58,63).

More recently the PASCAL system (Edwards Lifesciences, CA, USA) has obtained CE mark. First implanted in 2016, it was developed to replicate the edge-to-edge technique (58). The efficacy and safety of this device were reported in the CLASP study, published in 2019, demonstrating a significant reduction of MR grade (MR ≤2+ in 98% of patients) and an improvement in NYHA class and quality of life 30 days post-procedure (64). The main differences between the two available system for TEER, MitraClip and PASCAL, are illustrated in the following figure (Figure 2).

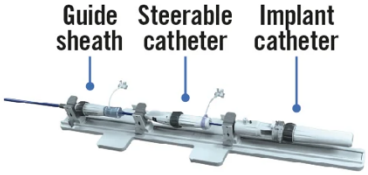
	MitraClip (4th-generation)	PASCAL Precision (2nd-generation)
Delivery catheter		
Available implants		
Device material	Rigid arms of cobalt-chromium alloy	Flexible arms of nitinol
Central spacer	No	Yes
Optional independent grasping	Yes	Yes
Closure mechanism	Active (locking element)	Passive (nitinol shape memory)
Number of working catheters	2	3
Orientation of hooks/friction elements	Longitudinal	Horizontal
Continuous LA pressure	Yes	Yes
Overall system stability	High	Improved with PASCAL Precision

Figure 2: Technical differences between two available device and implants for M-TEER (65).

3.5.4. Prognosis

The prognosis of patients with MR varies significantly depending on the underlying etiology. However, untreated severe MR is associated with symptoms of heart failure, reduced quality of life, and decreased survival due to LV dysfunction, reduced cardiac output, and pulmonary congestion (65). Goel et al (66) reported that, in non-operated patients, the overall 1-year and 5-year mortality is 20% and 50% respectively and the hospitalization rate for HF significantly increases, going from 40% at 1-year to 90% after 5 years (Figure 3). In patients treated with medical therapy alone, NYHA III or IV dyspnea, reduced LVEF, severe MR and EROA ≥40 mm^2 are all factors associated with poor outcomes.

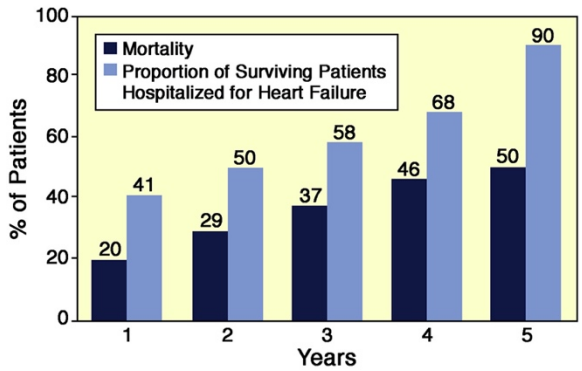


Figure 3: Outcomes of unoperated patients with severe symptomatic MR and HF (66).

Most patients with DMR undergoing surgical MV repair achieve long-term event-free survival similar to an age-matched population, provided that the correction is performed before significant deterioration of LV geometry and function occurs. In contrast, while OMT has been shown to impact LV function, symptomatology, and the severity of FMR, there is no data showing that surgical treatment of FMR is associated with a lower incidence of death or hospitalization. Indeed, patients with FMR have varying degrees of cardiac remodeling and myocardial dilation and usually have significant LV dysfunction, making the correction of the mitral defect alone insufficient to restore a good prognosis, although reduction or correction of MR may provide symptomatic relief (67,68).

The results of a subgroup analysis from the EVEREST II trial at both 12-months and 5-years follow-up showed significant differences ($p = 0.02$) in the treatment effect between patients with DMR and FMR: it demonstrated the superiority of surgery over percutaneous repair in patients with DMR, in addition to showing better surgical performance in patients who were <70 years of age, evaluating the composite endpoint of freedom from death, MV surgery, or 3+ or 4+ MR grade (57,60).

The COAPT study, investigating the role of M-TEER in patients with FMR associated with HF, reported that two-thirds of non-operated patients died or were hospitalized for HF within two years despite optimal medical therapy. As these patients often have a risk too high to be candidates for traditional surgery, percutaneous repair represents a valid and safe alternative. The COAPT study demonstrated that M-TEER reduces HFH and mortality rates, and improves quality of life and functional capacity at 24-month follow-up, compared to medical therapy alone (69).

Nonetheless, the results from these historical studies, such as EVEREST and COAPT, do not reflect the current landscape because advances in the diagnosis and quantification of MR, percutaneous technique, and the percutaneous TEER device, along with better patient selection, have improved M-TEER outcomes (Figure 4). Indeed, the use of the fourth-generation of MitraClip system was investigated in the EXPAND study published in 2023: at 1-year follow-up, 95.5% of patients achieved MR no greater than moderate, and MR no more than mild in 83.5% of patients

(79.2% in patients with DMR and 89.5% in patients with FMR). HFH occurred in 18.9% of patients, more frequently in those with FMR compared to DMR.

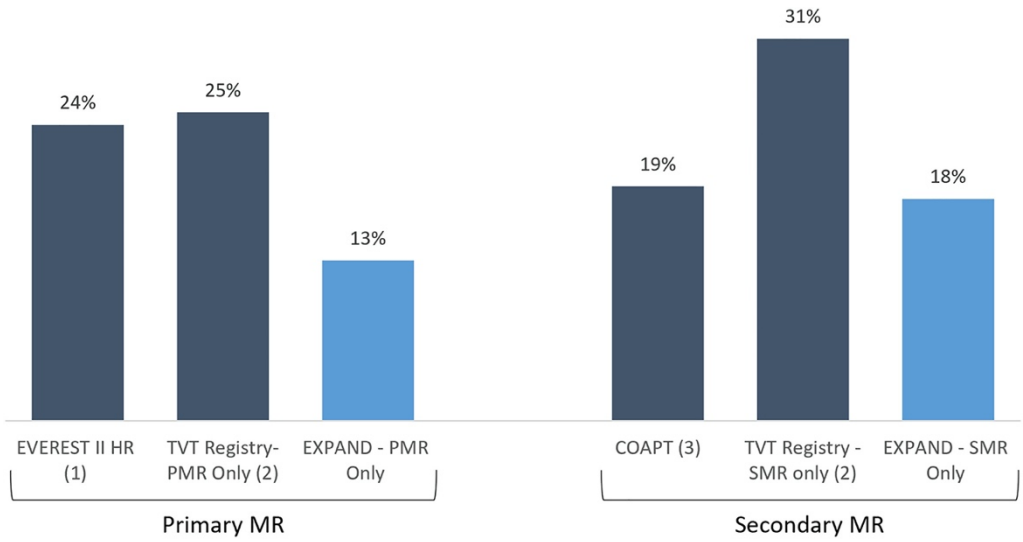


Figure 4: 1-year all-cause mortality rates (70).

4. AIM OF THE STUDY

Given the above-exposed background, we aimed to evaluate the prognostic impact of RV invasive hemodynamic parameters as predictors of adverse outcomes in patients with significant MR treated with TEER. Furthermore, we investigated the diagnostic accuracy and the prognostic impact of the new threshold values for mPAP, PVR e PCWP introduced by the new Guidelines for the diagnosis and treatment of pulmonary hypertension published in 2022.

5. MATERIALS AND METHODS

5.1. Patient population and study design

The study population consists of 152 patients diagnosed with significant and symptomatic MR deemed suitable to transcatheter edge-to-edge MV repair and evaluated by the local Heart-Team. The procedure was performed at the Hemodynamics and Interventional Cardiology Unit of the Padua University Hospital, between September 2014 and May 2024 after a complete diagnostical assessment through TTE, TEE, RHC.

Inclusion criteria were: symptomatic significative MR, both DMR, FMR and mixed etiology, in high-risk patients unsuitable for surgery according to the current standard of care (16), and suitable MV anatomy according to the instruction for use of the device. All patients included in the study were deemed ineligible for surgical intervention according to the decision of the Heart Team and underwent TEER according to current guideline recommendations (16). Available TEER devices were Mitraclip first generation MitraClip, NTR and XTR, NT and NTW, XT and XTW, Pascal P10 and Pascal ACE.

For each patient, anamnestic data were collected: age, gender, body mass index (BMI), and body surface area (BSA), diagnosis of MR, differentiating between DMR and FMR, degree of MR, NYHA functional class, any comorbidities such as arterial hypertension, diabetes, dyslipidemia, cancer, COPD.

All patients underwent TTE before the procedure and at discharge to evaluate the procedural instrumental outcomes, at 1-3 months, at 1 year, and then annually during follow-up. TEE was performed for pre-procedural assessment and during the procedure for procedural guidance. RHC was also recommended for pre-procedural assessment. Follow-up data, both clinical and echocardiographic, were obtained through outpatient or inpatient visits.

5.3. Echocardiographic assessment

Both TTE and TEE examinations were conducted and interpreted by experienced echocardiographic cardiologists according to European Association of Cardiovascular Imaging guidelines (8,19,71). LV dimensions were assessed from the parasternal long-axis view, meanwhile LVEDV and LVESV were assessed from the apical 2-chamber and apical 4-chamber views, calculating LVEF according to

the Simpson biplane method. LV parameters, both dimensions and volumes, were indexed to body surface area (LV diameter index and LV volume index). For the assessment of LA, its volume was measured at end-systole in the apical 2-chamber and 4-chamber views using the biplane method of disks, and then indexed to body surface area (LA volume index). LA dimension was measured at end-systole as the anteroposterior linear diameter from the parasternal long-axis view and then indexed to body surface area (LA diameter index). An echocardiographic integrated approach was applied for the assessment of MR severity, including calculating the EROA, as recommended (42). MR severity was classified as none/trivial, mild, moderate, and severe. The same approach was applied for the assessment and grading of TR.

5.4. Right heart catheterization assessment

RHC was an invasive hemodynamic procedure used to evaluate the right heart chambers and the PA via percutaneous vascular access. During the procedure, the femoral vein was punctured with a hollow needle to allow the insertion of a guidewire into the vessel through the needle, which was then removed; subsequently, an introducer was advanced along the venous axis to the right heart, allowing for the insertion of the Swan-Ganz (S-G) balloon flotation catheter. The S-G catheter enabled the assessment of preload, afterload, and RV function. Parameters measured directly by catheterization were: PCWP, mPAP, PVR, and mean RAP. Meanwhile, others have been derived: SVi, PAC, PAPi, RVSWi and PCWP/RAP ratio.

5.5. Heart team

Each patient was evaluated by a multidisciplinary team, known as Heart Team, composed of interventional cardiologists, clinical cardiologists, cardiac surgeons with MV surgery expertise, and interventional imaging cardiologist. The purpose of the Heart Team evaluation was planning an optimal therapeutic strategy for each patient, integrating data from diagnostic tests, patient's age and clinical conditions, and informed patients and/or family expectations regarding therapeutic chances, as recommended in current guidelines for management of VHD (16). A crucial step in the decision-making process was the risk stratification using validated scores to assess post-operative mortality, i.e. the STS-PROM (Society of Thoracic Surgeons

predicted risk of mortality) score for the 30-days mortality after cardiac procedure and the EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) for the peri-operative mortality (during and shortly after surgery).
Moreover, Heart Team sessions included evaluation of MV morphology and definition of the specific pathogenic mechanism causing MR for appropriate planning of the selected transcatheter procedure.

5.5. M-TEER procedure

The procedure was performed under general anesthesia or deep sedation, with fluoroscopic and TEE guidance. Several iterations of the devices were available during the enrolling period. The MitraClip procedure involved a percutaneous access via femoral vein, using a 24F steerable guiding catheter that was advanced along the main venous vascular axis to the RA and the clip delivery system (CDS) was introduced through the guide catheter. The procedure is performed under fluoroscopic and echocardiographic guidance (TTE and TEE). To allow passage of the device from the RA to the LA, a transseptal puncture was performed posteriorly and superiorly at a height relative to the coaptation point of the leaflets, depending on etiology of MR (4-5 cm above the annulus for DMR, while 3.5 cm in FMR); the guide catheter and dilator were advanced into the LA. Once in the LV, a series of steps were performed to correctly position the clip opened below valve leaflets, perpendicularly to the valve orifice. With 3D echocardiography in long-axis view, the correct position of the clip was verified, in order to grasp the leaflet edges. At this point, the clip was gradually closed and retracted until the leaflets were captured within the clip's arms to reduce the severity of the regurgitation. This closure phase was not definitive because, if necessary, the clip could be reopened and repositioned. If the result obtained with a single clip was not satisfactory, more than one clip could be applied and repeat echocardiographic assessments were performed after each clip placement to evaluate MV regurgitation and stenosis and the morphological result. Once the correct positioning and anchoring of the clip were confirmed and the efficacy and the risk of mitral stenosis evaluated, the device was definitively locked in position and the guiding catheter was retracted.
In patients undergoing M-TEER using the PASCAL system similar procedural steps were performed. However, there were differences due to different design features of PASCAL system. The device had flexible arms of nitinol, a shape memory

material that allowed the PASCAL paddles to passively secure the MV leaflets between the arms and the central spacer. Conversely, MitraClip consisted of one-piece device (no central spacer) made of cobalt-chromium core and polyester outer covering, resulting in more rigid arms compared to the nitinol arms, and it actively locked its clips in close position. Additionally, the PASCAL system incorporated 3 catheters (a 22 Fr steerable guide sheath, a steerable catheter, and an implant catheter with the device pre-attached at the distal end) differently from the 2 catheters of the MitraClip system (a steerable guide catheter and a clip delivery system).

5.6. Outcomes

All outcomes were defined according to the Mitral Valve Academic Research Consortium (MVARC) criteria including:

- Technical success (evaluated upon exiting the hemodynamics room): it includes successful access, delivery, and retrieval of the device delivery system and successful device deployment and correct positioning without procedural death or emergent surgery or reintervention.
- Device success (measured at 30 days): it includes proper device placement and positioning in absence of procedural death or stroke or device or access related complications requiring surgery or reintervention. Additionally, it is defined as post-procedural MR reduction at least acceptable without significant mitral stenosis and without evidence of structural or functional failure. MR reduction is acceptable when reduced by at least 1 grade from baseline and to no more than moderate; it is optimal when MR is reduced to trace or absent.
- Procedural success (measured at 30 days): it is defined as device success and major device or procedure related serious adverse events, such as death, stroke, significant bleeding, major vascular or cardiac structural complications, acute kidney injury, coronary artery disease requiring PCI/CABG. (72)

For the purpose of the study the main outcome of interest was the composite of all-cause death and hospitalization for HF (HFH) up to the longest available follow-up. The composite and the single-digit outcomes of death and HFH represent primary outcomes of effectiveness and safety. According to MVARC endpoint

definitions, all-cause mortality is an objective outcome and should be assessed consulting administrative registry database to minimize the number of patients lost to follow-up; factors contributing to the cause of death may be difficult to establish, however the cause of death should be categorized into cardiovascular and non-cardiovascular death. Similarly, hospitalization is defined as admission to hospital for ≥24 h, excluding planned hospitalization for pre-existing conditions; in particularly HFH is defined as the presence of symptoms, signs and/or laboratory evidence of worsening HF, and intravenous/mechanical HF therapies administration.

5.7. Statistical analysis

Descriptive statistics were reported as median [I quartile-III quartile] or media ± [std. dev.] for continuous variables and as absolute numbers (percentages) for categorical variables. The survival distribution at follow-up was evaluated using the Kaplan-Meier method, and the statistical significance (p-value) was assessed using the log-rank test.

The univariate analysis of the predictors of the outcomes of interest (death, HFH and the composite outcome) at 1-year follow-up and at the longest available follow-up was evaluated using univariable Cox Proportional Hazard model. Results were reported as Hazard Ratio (HR), 95% Confidence Interval (CI), and p-value. The correlation between echocardiographic and invasive sPAP was evaluated using Spearman's rank correlation coefficient. Furthermore, a multivariable Cox Proportional Hazard model was estimated for the composite endpoint. Clinical, echocardiographic, procedural characteristics and invasive parameters were evaluated as potential predictors of outcomes. Clinical variables of interest included STS-score PROM, EuroScore II, arterial hypertension, AF, CAD, peripheral artery disease (PAD), estimated glomerular filtration rate (eGFR) and MVARC technical, device and procedural success. LVEF, LVEDV indexed (LVEDVi), left atrium volume indexed (LAVi) type of MR, MR grade, MV gradient (at the end of procedure, pre discharge and at follow-up,) and as well parameters evaluating RH function and morphology as right atrium volume indexed (RAVi), right ventricle fractional area change (RV FAC), TR greater than moderate (TR ≥ 2+), TAPSE, sPAP and TAPSE/sPAP ratio were evaluated as echocardiographic predicting variables. RV disfunction was defined as TAPSE <15 mm and/or RV FAC < 35%,

and normal coupling as TAPSE/sPAP ratio > 0.35mm/mmHg. Patient were further stratified according to the combination of RV dysfunction and uncoupling in: 1) patient with both normal RV function and coupling, 2) patient with normal RV function and RV uncoupling, 3) patients with RV dysfunction and uncoupling and lastly 4) patients with RV disfunction and abnormal uncoupling. RHC variable of interest included: PCWP, sPAP and mPAP, PAC, PAPi, RWSWi, RAP, and PVR.

Receiver-operating characteristic (ROC) curves were constructed to establish optimal sensitivity and specificity threshold for mPAP, PCWP and PVR. These ROC-derived cut-off values were subsequently used in Kaplan-Meier analyses to examine associations with long-term mortality. For all statistical analyses, a p-value of less than 0.05 was considered significant. Analyses were performed using R software.

6. RESULTS

Between December 2014 and February 2024, a total of 152 patients with severe symptomatic MR (*Figure 1*), deemed inoperable for the heart team, underwent M-TEER in our center.

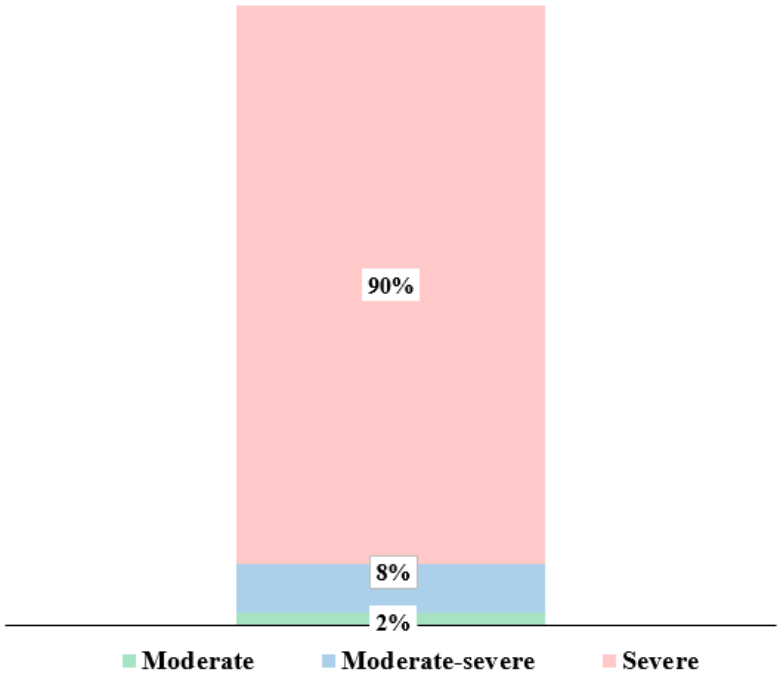


***Figure 1*: Pre-procedural mitral regurgitation grade**.

6.1. Baseline characteristics

The baseline demographic, clinical, and echocardiographic characteristics of the study population are shown in *Table 1*. The majority of patients were male (64%), with a median age of 79 years [71-83 years]. The median STS score was 3.6, and the median EuroSCORE II was 4.7. A considerable proportion of the patients (72%) were highly symptomatic for dyspnea, classified as NYHA class III or higher. DMR and vFMR etiologies accounting for 47% and 41% of cases respectively, while aFMR comprised 12% of the population. Overall, the left ventricle systolic function was mildly impaired with a median LVEF of 44% [33%-57%] and LV cavity moderately enlarged as indicated by a median VTDi of 89 ml/m^2 [71 ml/m^2 – 112 ml/m^2]. The 47% of population showed RV disfunction (defined as TAPSE ≤ 15mm and RV FAC ≤35%) with more than one third of the patient having more than moderate TR (36%). RV uncoupling was noted in 34% of the patients (*Figure 2*).

The presence of normal RV function and normal coupling was the most common scenario in our population (49%) followed by the presence of RV dysfunction and RV uncoupling (30%). The other iterations, normal RV plus RV uncoupling and RV dysfunction plus RV coupling were relatively rarer (*Figure 3*). Other relevant clinical and echocardiographic characteristics are shown in *Table 1*. Out of 152, 71 (46%) patients underwent RHC before M-TEER. PH was frequent in the population with 74% of patients showing mPAP higher than 20 mmHg. Median and IQR for each invasive derived-variable are shown in *Table 2*.

Clinical characteristics	Overall (n= 152)
Age (years)	79 [71, 83]
Male sex	98 (64%)
Arterial hypertension	126 (83%)
Dyslipidemia	87 (57%)
Diabetes mellitus type II	33 (22%)
Previous CAD	89 (59%)
Chronic lung disease	23 (15%)
NYHA class	
I	7 (5%)
II	35 (23%)
III	88 (58%)
IV	22 (14%)
AF/Flutter	90 (59%)
eGFR (mL/min)	54 [37, 70]
STS-score PROM (%)	3.6 [2.3, 5.9]
Euroscore II (%)	4.7 [2.9, 8.8]
Echocardiographic characteristics	
LVEF (%)	44 [33, 57]
LVEDVi (mL/m^2)	89 [71, 112]
LAVi (mL/m^2)	69 [53, 87]
RAVi (mL/m^2)	42 [29, 63]
RV FAC (%)	36 [29, 42]
TAPSE (cm)	1.78 [1.52, 2.15]
sPAP (mmHg)	43 [36, 52]
TAPSE/sPAP (mm/mmHg)	0.39 [0.31, 0.53]
RV dysfunction*	71 (47%)

***Table 1*: Clinical and baseline characteristics**. Values with ( ) are expressed as absolute number (percentage). Values with [ ] are expressed as media [interquartile range]. *RV dysfunction defined as TAPSE ≤ 15mm and/or RV FAC ≤ 35%.

CAD: coronary artery disease; NYHA: New York Heart Association; AF: atrial fibrillation; eGFR: estimated glomerular filtration rate; STS: Society of Thoracic Surgeons; PROM: predicted risk of mortality; LVEF: left ventricle ejection fraction; LVEDVi: left ventricle end-diastolic volume indexed; LAVi: left atrium volume indexed; RAVi: right atrium volume indexed; RV: right ventricle; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure.

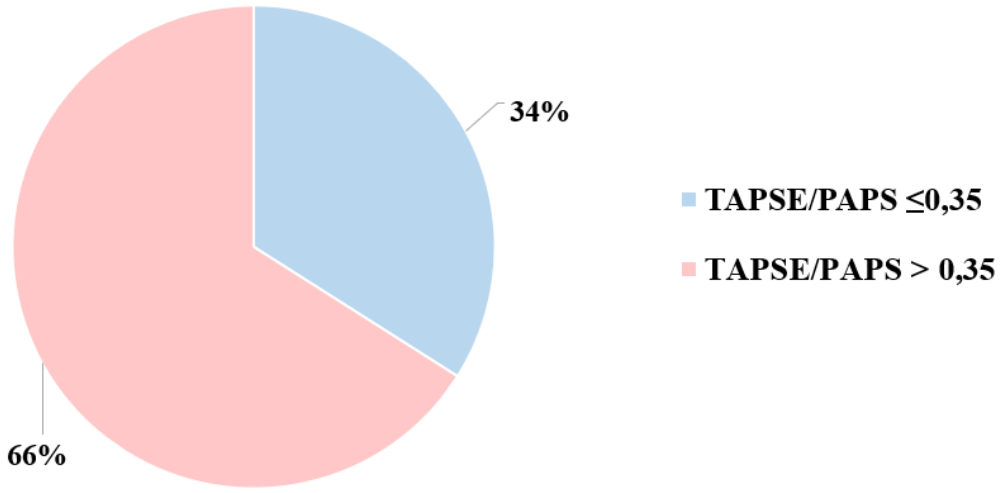


***Figure 2*: Right ventricle (RV) uncoupling**. RV uncoupling defined as TAPSE/sPAP ≤ 0.35 mm/mmHg.

TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure.

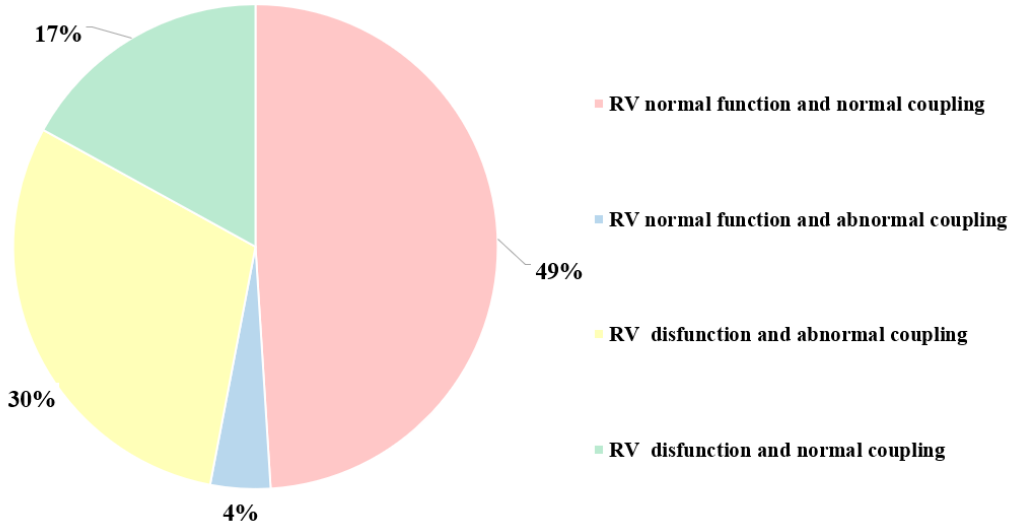


***Figure 3*: Interaction right ventricle function - coupling**. RV normal function defined as TAPSE >15 mm and/or RV FAC >35%; normal coupling defined as TAPSE/sPAP ratio > 0.35mm/mmHg.

RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; FAC: fractional area change; sPAP: systolic pulmonary artery pressure.

Right heart catheterization characteristics	Overall (n=71)
PCWP (mmHg)	18.0 [12.5, 22.5]
sPAP (mmHg)	40 [30, 50]
mPAP (mmHg)	27 [19, 32]
PVR (UW)	1.73 [1.09, 2.51]
RAP (mmHg)	6.5 [4.0, 10.0]
RAP/PCWP ratio	0.39 [0.29, 0.49]
PA compliance (ml/mmHg)	2.55 [1.96, 3.40]
PAPi	3.38 [2.53, 6.33]
RVSWi (g/m^2/beat)	7.7 [6.0, 12.5]
TAPSE/PAPS invasive	0.45 [0.33, 0.61]
mPAP >20 mmHg	52 (74%)
PCWP > 15 mmHg	51 (71%)
PVR >2 WU	28 (40%)

***Table 2*: Right heart catheterization baseline characteristics**. Values with ( ) are expressed as absolute number (percentage). Values with [ ] are expressed as media [interquartile range]. *PCWP: pulmonary capillary wedge pressure; sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure PVR: pulmonary vascular resistance; RAP: right atrial pressure; PA: pulmonary artery, PAPi: pulmonary artery pulsatility index; RVSWi: right ventricle stroke volume indexed; TAPSE: tricuspid annular plane systolic excursion; WU: Wood Unit.*

6.2. Procedural details and post-procedural outcomes

Procedural ad early outcomes are shown in *Table 3*. A median of 2 (IQR 1; 2) device were employed for each patient and technical, device and procedural success were achieved in 97%, 88% and 84% of procedure respectively. 94% of patient were discharged with residual MR ≤ 2+ (*Figure 4*). Post procedural echocardiography was performed after a media of 191 (74-307) days after the procedure and data are available for 99 patients. MR worsening after the discharge was seen in 37 (38%) of the patients with 87% of them showing MR ≤ 2+ at six months follow-up (*Figure 4*). Comprehensive echocardiographic evaluation at 6-months follow-up is shown in Table 4.

Procedural details	
Number of devices	
1	55 (36%)
2	80 (53%)
3	15 (9.9%)
4	1 (0.7%)
Number of devices for patient	2 [1.0, 2.0]
Type of device for patients	
At least one Wide or P10	53 (35%)
At least one Extended or Ace	74 (49%)
Both wide and extended	43 (28%)
MR grade intraprocedural at end procedure TEE	
None/trivial	14 (9.2%)
Mild	100 (66%)
Mild-moderate	8 (5.3%)
Moderate	23 (15%)
Severe	7 (4.5%)
MV gradient at end procedure TEE (mmHg)	3.15 [2.20, 4.00]
Post procedural outcomes	
MVARC technical success	147 (97%)
MVARC device success	133 (88%)
MVARC procedural success	128 (84%)
MR grade pre-discharge	
None/trivial	10 (6.6%)
Mild	81 (53%)
Mild-moderate	15 (9.8%)
Moderate	36 (24%)
Severe	10 (6.6%)
MV mean gradient pre-discharge (mmHg)	4.00 [3.00, 4.90]
LVEF pre-discharge (%)	44 [32, 56]
LVEDVi pre-discharge (mL/m^2)	84 [58, 104]
sPAP pre-discharge (mmHg)	39 [32, 46.75]
RV FAC pre-discharge (%)	38 [33, 44.75]
TAPSE pre-discharge (mm)	18.2 [15.4, 23.9]

***Table 3*: Procedural and short-term outcomes**. Values with ( ) are expressed as absolute number (percentage). Values with [ ] are expressed as media [interquartile range]. *MR: mitral regurgitation; MV: mitral valve; TEE: transesophageal echocardiography; MVARC: Mitral Valve Academic Research Consortium; LVEF: left ventricle ejection fraction; LVEDVi: left ventricle end-diastolic volume indexed; sPAP: systolic pulmonary artery pressure; RV: right ventricle; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion.*

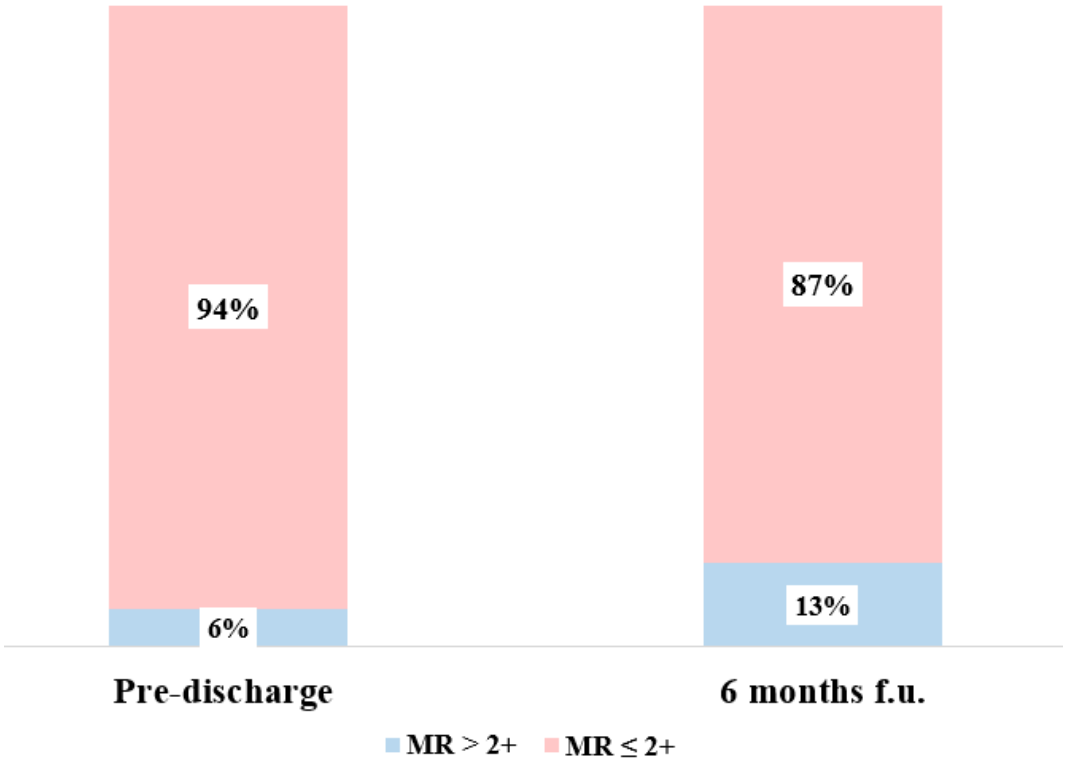


***Figure 4*: Post-procedural mitral regurgitation grade.**

Echocardiographic outcomes at mid-term follow-up

		Absolute value	Change from baseline
LVEF (%)		43 [32, 58]	-1 [-4, 3]
LVEDVi (mL/m^2)		86 [67, 109]	-6 [-16, 9]
LAVi (mL/m^2)		69 [55, 88]	1 [-13, 8]
RAVi (mL/m^2)		47 [37, 67]	5 [-5, 16]
RV FAC (%)		38 [33, 44]	3 [-3, 8]
TAPSE (mm)		18.4 [14.8, 21.7]	-0.4 [-3.5, 3.8]
TAPSE/sPAP (mm/mmHg)		0.43 [0.34, 0.61]	0.00 [-0.15, 0.18]
sPAP (mmHg)		40 [32, 48]	-3 [-13, 7]
MV gradient (mmHg)		4.00 [3.00, 5.00]	0.00 [-1.00, 1.00]
MR grade			
	None/trivial	4 (4.0%)	
	Mild	35 (35%)	
	Mild-moderate	18 (18%)	
	Moderate	30 (30%)	
	Moderate-Severe	3 (3.0%)	
	Severe	10 (10%)	
MR worsening from discharge		38 (38%)	

***Table 4*: Echocardiographic values and longitudinal changes.** Values with [ ] are expressed as media [interquartile range]. *LVEF: left ventricle ejection fraction; LVEDVi: left ventricle end-diastolic volume indexed; LAVi: left atrium volume indexed; RAVi: right atrium volume indexed; RV: right ventricle; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; MV: mitral valve; MR: mitral regurgitation.*

6.3. Outcomes at longest available follow-up

During a median follow up of 681 days (IQR 217, 1500), the primary outcomes of death, HF or a composite occurred in 76 (50%), 54 (36%) and 94 (61%) of patient respectively (*Figure 5, 6, 7*). At the univariate analysis, baseline STS score and eGFR were predictors of death and the composite outcome. Among echocardiographic baseline parameters, RV FAC (HR 0.95; CI 95% 0.92, 0.98; p <0.001 for death and HR 0.96; CI 95% 0.94, 0.99; p=0.003 for composite outcome), TAPSE (HR 0.52; CI 95% 0.30, 0.92; p= 0.023 only for death), RAVi, (HR 1.01; CI 95% 1.00, 1.02; p=0.013 for death and HR 1.01; CI 95% 1.00, 1.02; p=0.002 for composite endpoint), RV disfunction (HR 2.30; CI 95% 1.40, 3.79; p=0.001 for death and HR 1.84; CI 95% 1.18, 2.87; p=0.007 for composite endpoint) were significantly associated to the composite outcomes and death at longest follow up. Interestingly, echocardiographic sPAP did not show any significant association with

death at longest follow up whereases invasive sPAP did (HR 1.04; CI 95% 1.02, 1.07; p=0.003). This pattern was also observed for echocardiographic TAPSE/sPAP which exhibited just a trend toward higher rates of death at follow up (HR 0.24; CI 95% 0.06, 1.01; p=0.06), with invasive TAPSE/sPAP showing significant association with the composite outcome and death at longest follow up (HR 0.01; CI 95% 0.00, 0.15; p=0.002 for death and HR 0.1; CI 95% 0.01, 0.59; p=0.014 for composite endpoint). No significant correlation (p=0.31) was found between echocardiographic and invasive sPAP, even after excluding patient with moderate or more TR (p=0.76). Beside PAPs, also PCWP (HR 1.05; CI 95% 1.00, 1.10; p=0.038), PAPm (HR 1.06; CI 95% 1.02, 1.11; p=0.003), RAP (HR 1.14; CI 95% 1.04, 1.25; p=0.006), RVSWi (HR 1.08; CI 95% 1.00, 1.17; p=0.042) were the other RHC parameters that showed significant association with death at longest follow up. sPAP (HR 1.04; CI 95% 1.02, 1.06; p=0.001), mPAP (HR 1.04; CI 95% 1.01, 1.08; p=0.009), PA compliance (HR 0.74; CI 95% 0.55, 1.0; p=0.046), RVSVi (HR 1.06; CI 95% 1.00, 1.13; p=0.049) were predictors also for the composite outcomes. PVR > 2 WU display only a trend towards worse outcomes both for death (HR 2.04; CI 95% 0.95, 4.36; p=0.06) and the composite outcomes (HR 1.78; CI 95% 0.93, 3.42; p=0.08). Regarding HFH, significant predictors were RAVi (HR 1.01; CI 95% 1.01, 1.02; p=0.02), sPAP (HR 1.03; CI 95% 1.00, 1.06; p=0.036) and PA compliance (HR 0.58 CI 95% 0.38, 0.89; p=0.013). Procedural factors as MR residual grade and MVARC successes were strongly linked to better outcomes as shown in *Table 5*. Lastly, TR more than moderate at follow up has shown a significant more than 2-fold risk of HFH and composite outcomes. Other relevant association at univariate analysis are shown in *Table 5*. After adjusting for confounding variables, PVR (p= 0.04) and mPAP (p=0.04) remained independently associated with an increased risk of mortality at longest follow up, as shown in *Table 7*. Baseline eGFR, PAD, LVEF, TR grade ≥2 +, and MVARC procedural success were also identified as independent predictors (*Table 7*). Only eGFR (HR 0.98 95% CI 0.96-0.98, p=0.04) and MVARC (HR 0.20 95% CI 0.05-0.77, p=0.02) device success remained independently associated to the composite outcomes. No variables have shown independent association with HFH.

ROC curve analysis identified the following cut-off values with the highest sensitivity for predicting one-year mortality: 20.5 mmHg for mPAP (AUC 0.64, sensitivity 93%, specificity 39%), 14.5 mmHg for PCWP (AUC 0.63, sensitivity

93%, specificity 37%) and 1.31 Wood units (WU) for PVR (AUC 0.63, sensitivity 86%, specificity 37%) (*Figure 8*:). Utilizing these cut-off values, Kaplan-Meier analysis demonstrated a significant association with long-term mortality for mPAP greater than 20 mmHg (p=0.003) and PCWP greater than 15 mmHg (p=0.04), as well as a trend towards significance for PVR greater than 2 WU (p=0.06) (*Figure 9*).

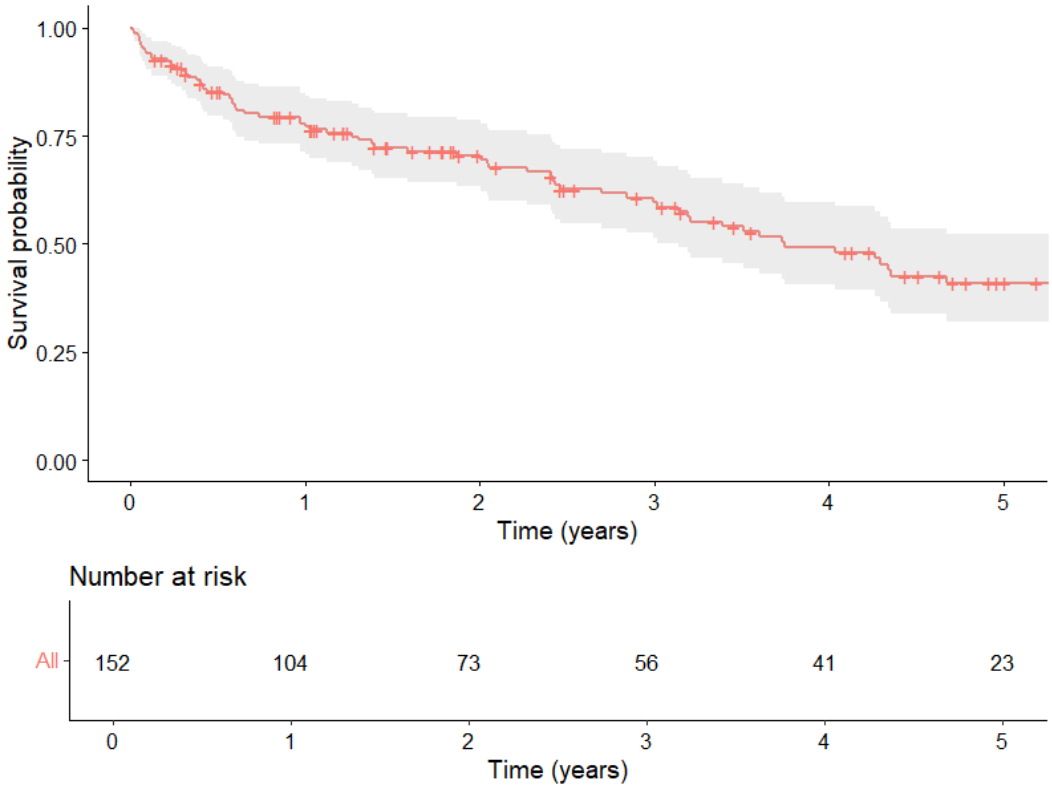


***Figure 5*: Kaplan-Meier analysis of overall population for death outcome.**

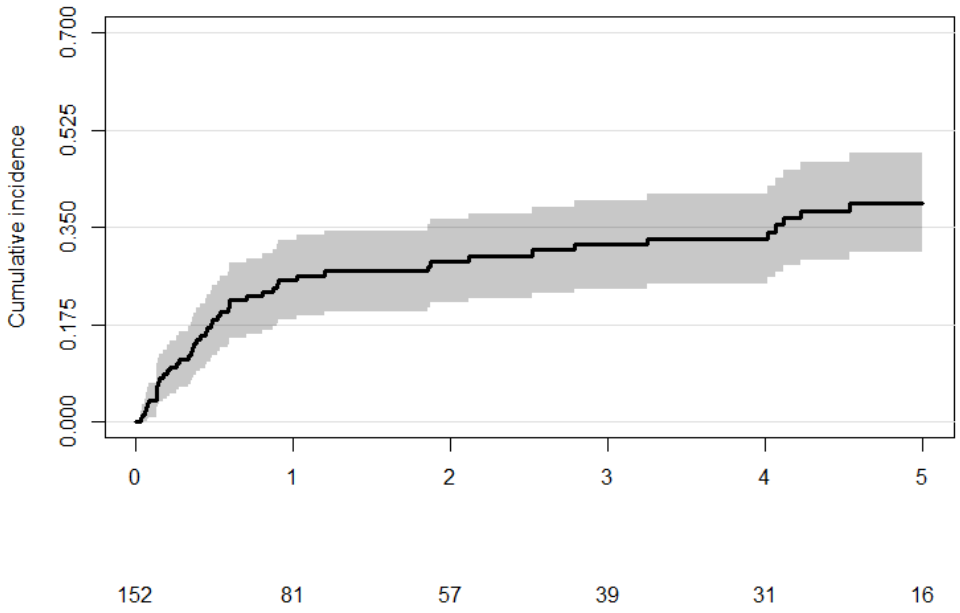


***Figure 6*: Kaplan-Meier analysis of overall population for HFH outcome.**

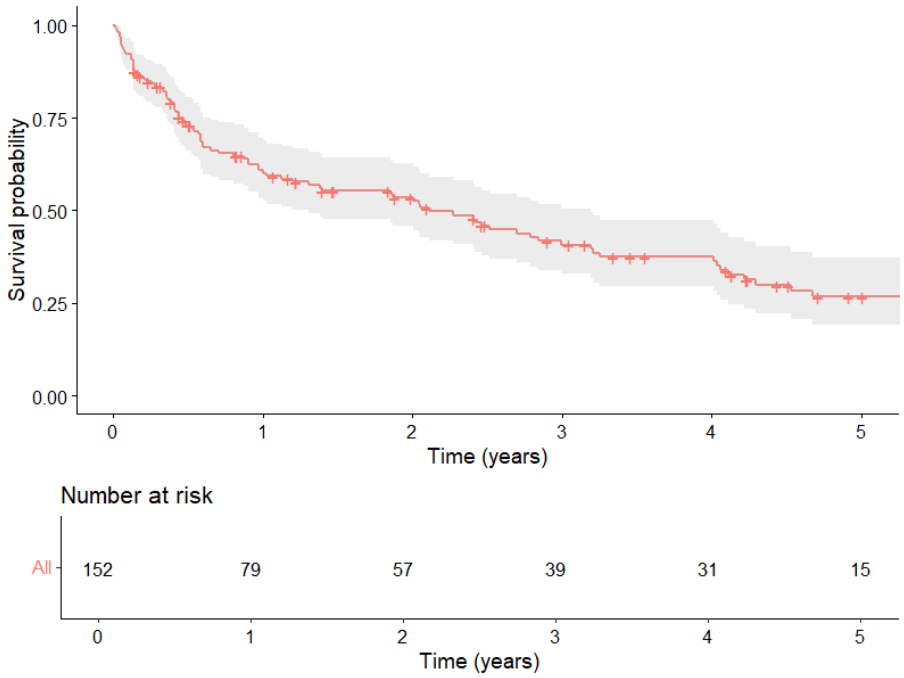


***Figure 7*: Kaplan-Meier analysis of overall population for composite death-HFH outcome.**

Univariate analysis at longest follow-up

		Death			Heart failure			Composite death-hf		
		HR	*95% CI*	*p*	*HR*	*95% CI*	*p*	*HR*	*95% CI*	*p*
STS-score		**1.06**	**1.02, 1.10**	**<0.001**	1.02	0.96. 1.07	0.5	**1.04**	**1.01, 1.08**	**0.007**
Euroscore II		1.01	0.98, 1.05	0.4	1.01	0.97, 1.05	0.7	1.01	0.98, 1.04	0.4
Hypertension		1.13	0.56, 2.28	0.7	1.26	0.54, 2.96	0.6	1.05	0.57, 1.93	0.9
AF		1.18	0.74, 1.89	0.5	0.84	0.49, 1.45	0.5	1.06	0.70, 1.61	0.8
CAD		1.42	0.88, 2.29	0.15	1.54	0.87, 2.72	0.13	**1.51**	**0.98, 2.31**	**0.060**
Peripheral disease		1.41	0.84, 2.37	0.2	1.58	0.84, 2.98	0.2	**1.72**	**1.07, 2.76**	**0.026**
eGFR (ml/min)		**0.99**	**0.98, 1.00**	**0.012**	**0.99**	**0.97, 1.00**	**0.014**	**0.99**	**0.98, 1.00**	**0.003**
LVEF (%) - ECHO-		0.99	0.97, 1.00	0.2	0.99	0.97, 1.01	0.6	0.99	0.98, 1.01	0.4
LVEDVi (ml/m^2) - ECHO-		1.00	1.00, 1.01	0.5	1.00	1.0, 1.01	0.5	1.00	1.00, 1.01	0.3
Type of MR	DMR	-	-	-	-	-	-	-	-	-
	vFMR	1.19	0.72, 1.97	0.5	1.26	0.71, 2.23	0.4	1.11	0.71, 1.72	0.6
	aFMR	1.04	0.48, 2.23	>0.9	0.85	0.32, 2.29	0.8	1.04	0.53, 2.05	>0.9
RV FAC (%) -ECHO-		**0.95**	**0.92, 0.98**	**<0.001**	**0.97**	**0.94, 1.00**	**0.065**	**0.96**	**0.94, 0.99**	**0.003**
TAPSE (mm) -ECHO-		**0.52**	**0.30, 0.92**	**0.023**	0.77	0.42, 1.38	0.4	0.70	0.43, 1.13	0.14
LAVi (ml/m^2) -ECHO-		1.00	1.00, 1.01	0.5	1.00	0.99, 1.01	>0.9	1.00	1.00, 1.01	0.5
RAVi (ml/m^2) -ECHO-		**1.01**	**1.00, 1.02**	**0.013**	**1.01**	**1.00, 1.02**	**0.023**	**1.01**	**1.00, 1.02**	**0.002**
TR ≥ 2+ -ECHO-		1.43	0.90, 2.28	0.13	1.30	0.75, 2.26	0.3	1.42	0.93, 2.16	0.10
sPAP (mmHg) -ECHO-		1.00	0.99, 1.02	0.7	1.01	0.99, 1.03	0.4	1.00	0.99, 1.02	0.7
TAPSE/sPAP (mm/mmHg) -ECHO-		**0.24**	**0.06, 1.00**	**0.050**	0.56	0.17, 1.87	0.3	0.50	0.18, 1.42	0.2
RV function*	1	-	-	-	-	-	-	-	-	-
	2	0.25	0.03, 1.86	0.2	0.22	0.03, 1.64	0.14	0.29	0.07, 1.24	0.095
	3	**1.96**	**1.06, 3.64**	**0.033**	1.48	0.76, 2.88	0.3	1.62	0.94, 2.79	0.082
	4	2.03	0.96, 4.30	0.065	0.94	0.37, 2.37	0.9	1.43	0.73, 2.78	0.3
PCWP (mmHg) - RHC -		1.05	1.00, 1.10	0.038	1.00	0.95, 1.06	>0.9	1.03	0.99, 1.07	0.14
sPAP (mmHg) - RHC -		**1.04**	**1.02, 1.07**	**0.003**	**1.03**	**1.00, 1.06**	**0.036**	1.04	**1.02, 1.06**	**0.001**
mPAP (mmHg) - RHC -		**1.06**	**1.02, 1.11**	**0.003**	1.02	0.98, 1.07	0.3	1.04	**1.01, 1.08**	**0.009**
RAP (mmHg) - RHC -		**1.14**	**1.04, 1.25**	**0.006**	0.97	0.86, 1.09	0.6	1.06	0.98, 1.15	0.14
PA compliance (ml/mmHg) - RHC -		0.83	0.59, 1.15	0.3	**0.58**	**0.38, 0.89**	**0.013**	0.74	**0.55, 1.0**	**0.046**
RVSWi (g/m^2/beat) - RHC -		**1.08**	**1.00, 1.17**	**0.042**	1.04	0.96, 1.13	0.3	1.06	**1.00, 1.13**	**0.049**
TAPSE/sPAP (mm/mmHg) - RHC -		**0.00**	**0.00, 0.15**	**0.002**	0.23	0.03, 2.13	0.2	0.08	**0.01, 0.59**	**0.014**
mPAP >20 mmHg - RHC -		**6.80**	**1.61, 28.8**	**0.009**	**3.78**	**1.11, 12.8**	**0.033**	5.43	**1.91, 15.5**	**0.002**
PCWP > 15 mmHg - RHC -		2.52	0.96, 6.58	0.059	1.56	0.62, 3.94	0.3	2.01	0.96, 4.22	0.065
PVR > 2 WU - RHC -		2.04	0.95, 4.36	0.066	1.37	0.60, 3.15	0.5	1.78	0.93, 3.42	0.083
MR ≥ 2 at end of procedure		**2.58**	**1.11, 5.99**	**0.028**	**3.66**	**1.45, 9.29**	**0.006**	2.93	**1.35, 6.36**	**0.007**
MR ≥ 2 pre discharge		**4.11**	**2.02, 8.37**	**<0.001**	**5.43**	**2.42, 12.2**	**<0.001**	3.74	**1.86, 7.50**	**<0.001**
MV grad. at end of procedure (mmHg)		0.97	0.81, 1.17	0.8	1.00	0.80, 1.25	>0.9	1.00	0.85, 1.18	<0.9
MV grad. pre discharge (mmHg)		1.03	0.91, 1.17	0.6	1.00	0.86, 1.16	>0.9	1.01	0.90, 1.13	0.8
MVARC										
Technical		0.55	0.17, 1.77	0.3	**0.32**	**0.10, 1.04**	**0.058**	0.62	0.20, 1.96	0.4
Device		**0.36**	**0.19, 0.68**	**0.002**	**0.29**	**0.15, 0.60**	**<0.001**	**0.37**	**0.21, 0.67**	**<0.001**
Procedural		**0.21**	**0.12, 0.37**	**<0.001**	**0.26**	**0.13, 0.53**	**<0.001**	**0.24**	**0.15, 0.41**	**<0.001**
LVEF (%) change from baseline		1.00	0.97, 1.04	0.8	0.99	0.95, 1.03	0.6	0.99	0.95, 1.02	0.4
LVEDVi (ml/m^2) change from baseline		0.99	0.98, 1.01	0.3	1.00	0.99, 1.02	0.6	1.00	0.99, 1.01	0.8
LAVi (ml/m^2) change from baseline		1.00	0.99, 1.02	0.7	1.00	0.98, 1.01	0.5	0.99	0.98, 1.00	0.3
RAVi (ml/m^2) change from baseline		1.00	0.98, 1.02	>0.9	1.00	0.98, 1.03	0.8	1.01	0.99, 1.03	0.4
TAPSE (mm) change from baseline		0.84	0.39, 1.85	0.7	0.83	0.41, 1.67	0.6	0.70	0.38, 1.29	0.3
TAPSE/sPAP (mm/mmHg) change from baseline		0.23	0.03, 1.52	0.13	1.50	0.41, 5.43	0.5	0.50	0.11, 2.19	0.4
TR ≥ 2 +		1.06	0.56, 2.04	0.8	**2.21**	**1.15, 4.23**	**0.017**	**2.04**	**1.19, 3.50**	**0.010**
TR change from baseline		0.98	0.60, 1.58	>0.9	1.53	0.93, 2.51	0.092	1.37	0.90, 2.08	0.14
TR worsening from baseline		0.81	0.37, 1.77	0.6	1.74	0.88, 3.44	0.11	1.26	0.69, 2.30	0.4
MR grade at f.u										
Mild		0.95	0.22, 4.11	>0.9	1.43	0.19, 10.9	0.7	1.44	0.34, 6.12	0.6
Mild-moderate		1.28	0.24, 6.69	0.8	2.51	0.31, 20.6	0.4	2.05	0.44, 9.63	0.4
Moderate		1.00	0.23, 4.43	>0.9	1.32	0.17, 10.3	0.8	1.33	0.31, 5.74	0.7
Moderate-severe		2.20	0.19, 25.1	0.5	4.73	0.42, 52.8	0.2	3.17	0.44, 22.9	0,3
Severe		**5.86**	**1.20, 28.5**	**0.029**	**12.0**	**1.46, 99.3**	**0.021**	**7.96**	**1.67, 37.9**	**0.009**
MR change from discharge		1.08	0.70, 1.66	0.7	0.89	0.57, 1.40	0.6	0.98	0.68, 1.42	>0.9
MV grad med worsening from discharge (mmHg)		0.97	0.44, 2.12	>0.9	0.66	0.39, 1.46	0.4	0.95	0.56, 1.61	0.8
sPAP worsening from baseline (mmHg)		1.03	0.58, 1.84	>0.9	0.96	0.52, 1.79	>0.9	1.05	0.63, 1.75	0.8

Table 5: **Outcomes at longest follow-up: univariate analysis**. *Interaction RV function/coupling: RV normal function + normal coupling (1), RV normal function + abnormal coupling (2); RV

disfunction + abnormal coupling (3); RV disfunction + normal coupling (4); RV normal function defined as TAPSE >15 mm and/or RV FAC >35%; normal coupling defined as TAPSE/sPAP ratio > 0.35mm/mmHg.

STS: Society of Thoracic Surgeons; AF: atrial fibrillation; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricle ejection fraction; LVEDVi: left ventricle end-diastolic volume indexed; MR: mitral regurgitation; DMR: degenerative mitral regurgitation; vFMR: ventricular functional mitral regurgitation; aFMR: atrial functional mitral regurgitation; RV: right ventricle; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; LAVi: left atrium volume indexed; RAVi: right atrium volume indexed; TR: tricuspid regurgitation; sPAP: systolic pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; mPAP: mean pulmonary artery pressure; RAP: right atrial pressure; PA: pulmonary artery; RVSWi: right ventricle stroke volume indexed; PVR: pulmonary vascular resistance; MV: mitral valve; MVARC: Mitral Valve Academic Research Consortium; RHC: right hear catheterization; WU: Wood Unit.

Multivariate analysis for death at longest follow-up

	p-value
CAD	0.49
eGFR (ml/min)	**0.02**
PAD	**0.04**
RAVi (ml/m2) - ECHO -	0.67
PA compliance (ml/mmHg) - RHC -	0.20
RVSWi (g/m2/beat) - RHC -	0.07
TR ≥ 2+	**0.04**
LVEF (%)	**0.04**
Type of MR -DMR	-
vFMR	0.07
aFMR	0.77
RAP (mmHg) - RHC -	0.17
RV dysfunction*	0.81
TAPSE/sPAP (mm/mmHg) - RHC -	0.21
PVR UW - RHC -	**0.04**
PCWP (mmHg) - RHC -	0.18
mPAP (mmHg) - RHC -	**0.04**
MVARC procedural success	**0.001**

***Table 7*: Multivariate analysis for death at long term follow up.** * RV dysfunction defined as TAPSE ≤ 15mm and/or RV FAC ≤ 35%.

CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; PAD: peripheral artery disease; RAVi: right atrium volume indexed; PA: pulmonary artery; RVSWi: right ventricle stroke volume indexed; TR≥2: tricuspid regurgitation moderate or greater; LVEF: left ventricle ejection fraction; MR: mitral regurgitation; DMR: degenerative mitral regurgitation; vFMR: ventricular functional mitral regurgitation; aFMR: atrial functional mitral regurgitation; RAP: right atrial pressure; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; mPAP: mean pulmonary artery pressure; MVARC: Mitral Valve Academic Research Consortium; RHC: right hear catheterization; WU: Wood Unit.

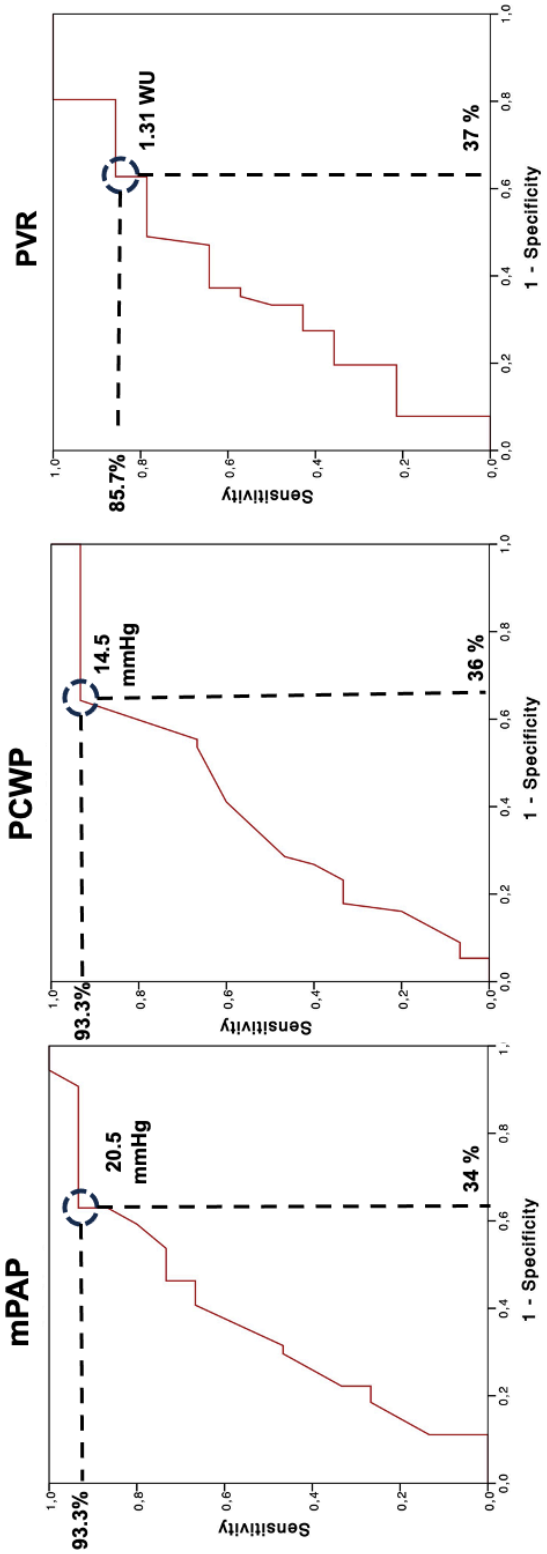


***Figure 8*: ROC analysis for 1-year all-cause mortality.**

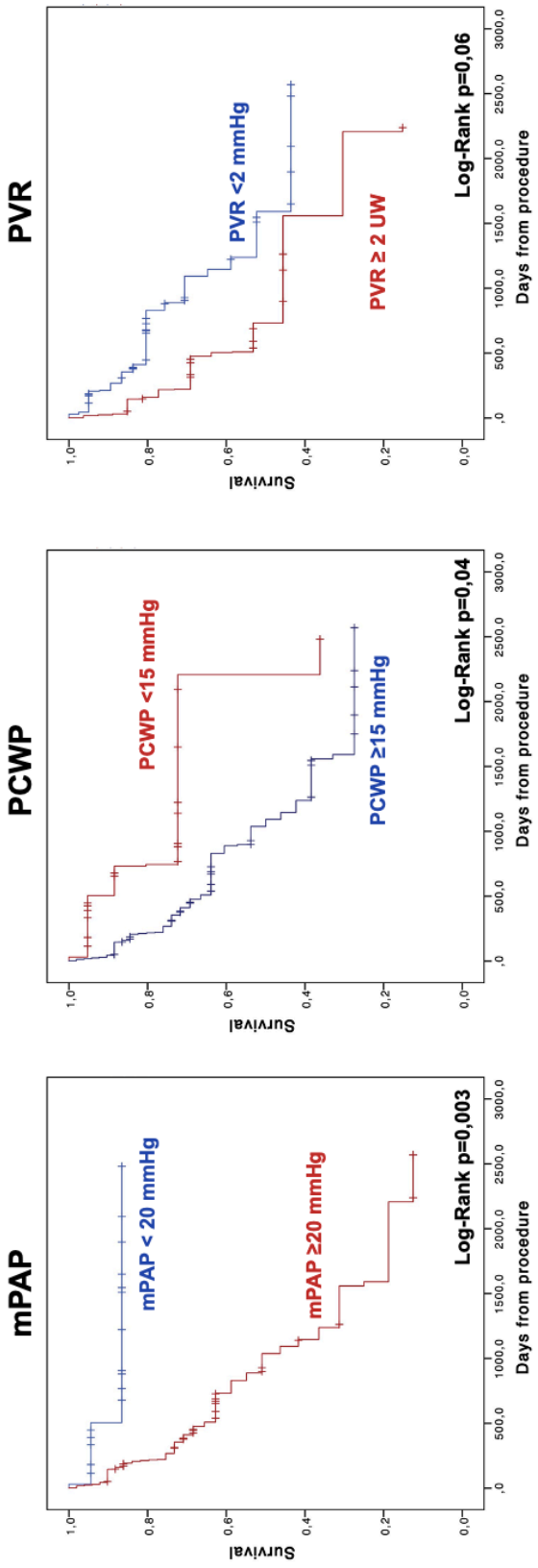


***Figure 9*: Kaplan-Meier analysis for death at longest follow-up.**

7. DISCUSSION

Our study reports a comprehensive analysis of the impact of invasive cardiopulmonary hemodynamic parameters on outcomes after M-TEER. The main findings of our study are as follows: 1) PH was present in the majority of patients with severe MR undergoing M-TEER (74%), and significant pre-capillary component was present in 40% of patients; 2) several echocardiographic parameters exploring right heart function and morphology are linked to worse outcomes; 3) invasive derived hemodynamic right ventricle parameters are important predictors of adverse event at follow up, sometimes outperforming the non-invasive counterparts; 4) the new threshold set by ESC guidelines are valuable in this settings, with an increased risk of events when used as predictive factors; 5) achieving MVARC successes and as little residual MR as possible is associated with better outcomes.

Overall, M-TEER showed to be a safe and effective, able to reduce MR grade without any excessive increase in MV mean gradient or procedural complication as demonstrated by the high rates of MVARC outcomes achieved. In the literature, data on the pre-procedural prognostic impact of PH on M-TEER are limited, and most of these are derived from retrospective analyses assessing the impact of PH in outcomes using different cut-offs for defining PH. Several studies have shown that the finding of sPAP $\geq$ 50 mmHg at pre-procedural echocardiographic evaluation is associated with an increased risk of all-cause mortality and HFH at 2 years (73). However, it is important to emphasize that the sPAP obtained at echocardiography is only an estimate of the real value, which in contrast can be measured directly with RHC. Our work demonstrates that, in this subset of patient, only invasive sPAP showed a meaningful impact on hard outcomes and no significant correlation exists between echocardiographic and invasive sPAP. While RHC directly measures sPAP, the echocardiographic measurement is only an estimate of the true value using continuous color Doppler to detect regurgitant blood flow through the tricuspid valve; as a result, the correlation between sPAP estimated by echocardiography and measured by RHC has been found to be modest (74), due to potential limitations such as the presence of elevated pulmonary pressures, the inability to acquire an estimate of sPAP in certain patient populations (e.g., COPD), and underestimation when the TR jet is not of good quality. This may explain why only invasive TAPSE/sPAP, and not echocardiographic one, is associated to worse outcomes.

Further studies are warranted in this regard, considering that echocardiographic TAPSE/sPAP has shown, in previous literature, to be an important predicting variables in patient undergoing TEER (75,76). However, it must be noted that those papers only involved FMR. It cannot be excluded that TAPSE/sPAP ratio exhibit substantial difference across different MR etiology and our results are driven by a lack of differentiation and small sample size. Since their publishing in 2018, the difference in hard endpoints between COAPT and MITRA-FR has divided the scientific community (61,62). Several factors have been cited as potential factors that have driven this difference. Among others, the exclusion from COAPT trial of patients with RV dysfunction and severe PH has been advocate as one of the key factors for the positive results of this trial. Even though including both DMR and FMR, the results of our univariate analysis foster this theory and further corroborate the pivotal role of right heart and right ventricle disfunction in the heart failure landscape. In addition, it highlights the importance of invasive evaluation as more accurate in evaluating predictors of worse outcomes. In this regard, our results are aligned to last ESC guidelines on PH (33) that advise performing RHC in patients with pulmonary hypertension and known left heart disease if RV dysfunction is present. We also provided external validation to the new threshold for the diagnosis and classification of pulmonary hypertension. In our population, the current 20 mmHg for mPAP and 15 mmHg for PCWP represent the best trade off in terms of sensitivity. For PVR, we found a lower value than stated by ESC Guidelines. We further proved that the use of mPAP and PCWP new thresholds is linked to a higher risk of death at longest follow up. Only a trend was noted when using PVR > 2 WU as predictor of all-cause mortality. However, a role played by the small sample size cannot be excluded for ROC an KM analysis regarding PVR.

Notably, after checking for confounding variables, mPAP and PCWP remained independently associated to all-cause mortality at longest follow up. Consistent with what has been reported in the literature, the MVARC endpoints of technical, device, and procedural success are strongly associated with better outcomes (72). Similarly, a residual MR grade no more than moderate appeared to be linked to a lower rate of adverse event at follow up. This emphasizes the importance of good patient selection and referral to high-volume centers for this procedure (77).

8. STUDY LIMITATIONS

Firstly, as retrospective registry, all the results are subject to potential selection bias. This is true especially for patients undergoing RHC, which has been performed according to referring hospital. As aforementioned, DMR and FMR carry inherited different risk of adverse events at follow up. However, no further analysis on different MR subsets was possible due to the small sample size. The small sample size and the limited number of RHC-related data could also have affected the ability to detect statistically significant differences in the outcomes of interest.

9. CONCLUSIONS

RHC catheterization has an important prognostic role of in patients undergoing mitral valve edge to edge repair. The right ventricle, in the MR landscape, is not only a bystander but an active player, acting as a key factor in shaping patients' prognosis. The new proposed ESC cut-offs for PH offer yeild valuable sensitivity and predictiveness for all-cause mortality in this subset of patients. mPAP and PCWP are independent predictors of worst prognosis at long term follow up.

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