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Transcatheter mitral and tricuspid valve therapies

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Transcatheter mitral and tricuspid valve therapies

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Editorial: Transcatheter mitral and tricuspid valve therapies

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Editorial on the Research Topic
Transcatheter mitral and tricuspid valve therapies

Transcatheter valve therapies have emerged as a viable treatments option for patients deemed high risk for conventional surgery. Whilst transcatheter aortic valve implantation (TAVI) is now established as the standard of care in high and intermediate risk aortic stenosis patients (1, 2), the mitral and tricuspid frontiers have proved to be more challenging. Anatomical heterogeneity, device development, refining patient selection and until recently the absence of randomised data have all been contributing factors. For mitral regurgitation transcatheter edge to edge repair (TEER) now benefits from positive randomised control trial (RCT) data (3) along with significant advancements in device technology. Transcatheter mitral valve replacement (TMVR) options are also making steady progress. More recently, having previously been referred to as the "forgotten valve", the vast unmet clinical need associated with tricuspid regurgitation has become the central focus of the structural heart community. There were positive signals of benefit in the only RCT of TEER (4) and tricuspid transcatheter valve replacement (TTVR) has shown great promise so far with randomised data coming soon (5). This research topic aims to explore a broad range of areas within mitral and tricuspid intervention with a particular focus on optimising outcomes, identification of favourable responders and challenging patient cohorts.

In degenerative mitral regurgitation (DMR), a significant proportion of patients do not derive symptomatic benefit or reverse remodel following TEER. Selecting the right patient for the right intervention to maximise benefit and potential for a durable result is vital. Central to procedural success and minimising residual regurgitation is detailed prior anatomical assessment and skilled interventional imaging using transoesophageal echocardiography (TOE). In their mini review, Hirasawa and Izumo outline the role of three-dimensional (3D) TOE in assessing mitral valve (MV) geometry and dimensions with the use multiplanar reconstruction. Intraprocedural 3D TOE imaging also aids in the improved visualisation and quantification of residual MR jets following device deployment.

MR is one of the commonest abnormalities associated with rheumatic heart disease (RHD) along with mitral stenosis. Gomes et al. looked at predictors of MR severity progression In their study of 539 patients with RHD. They found that age and LA volume were the most predictive factors with patients exhibiting features of both degenerative and functional MR (FMR). Mitral annular calcification (MAC) associated

with MV dysfunction also continues to pose a significant challenge to cardiologists and surgeons alike. The patients tend to more comorbid, and both percutaneous and surgical treatments are not without significant procedural risk. Where possible hybrid procedures that involve minimal decalcification or transcatheter approaches are used although patients continue to have poor longer-term outcomes (6). In their mini review, Ascione and Denti et al. outline the growing role of transcatheter mitral valve replacement with the Tendyne™ valve (Abbott, MN, United States), along with the various approaches to mitigating the risk of left ventricular outflow obstruction.

Great progress has been made in the management of secondary MR with the COAPT study paving the way for TEER in carefully selected patients. Despite this, these patients still have a poor prognosis and a significant proportion do not derive benefit from MR reduction. Further emphasising the need to better understand the disease itself and how we go about patient selection (7). In their systematic review and meta-regression analysis Shi et al. sought to assess clinical predictors following percutaneous MV repair using both annuloplasty and TEER in patients with FMR. Their findings once again linking LV volumes to mortality emphasise the importance of intervening early before excessive eccentric remodelling occurs. Greater focus has been placed on the right ventricle given its prognostic importance more broadly. The review article by Stolz et al. highlights the challenges of RV assessment using 2D echocardiography, and the added value of RV to pulmonary artery coupling in predicting outcomes in both mitral and tricuspid TEER patients. Finally, acute MR is a new frontier for mitral TEER. Papillary muscle rupture in the context of myocardial infarction is potentially a life-threatening complication and the management of such patients is very challenging. Both medical therapy and emergent surgery are associated with high rates of morbidity and mortality, paving the way for TEER as a less invasive alternative. Estevez-Loureiro et al. in their review of the topic outline the current role of transcatheter interventions in this setting with a summary of the latest registry data.

Finally, moving onto the previously neglected area of tricuspid regurgitation, we have seen a major effort by the structural heart community to focus attention on this vastly undertreated patient population. Recently in the first and only RCT, TV TEER demonstrated an improvement in quality of life in line with the degree of TR reduction (4). Tricuspid patients tend to have multiple comorbidities, advanced left heart disease or both, making them less than ideal surgical candidates. Fortunately, TTVR is showing promise with highly efficacious TR reduction and fewer anatomical obstacles compared to TMVR. That said, there is some hesitation regarding the RV's susceptibility to the abrupt surge in RV afterload that may follow TR elimination. Sala et al. discuss this in detail in their review highlighting the inadequacy of longitudinal 2D markers of contractility when compared to 3D volumetric RV assessment. They also emphasise the value to assessing RV ejection fraction, and its relationship to the pulmonary circulation as potential discriminators of patients that may suffer from afterload mismatch and RV failure.

Mitral and tricuspid valve disease are increasingly common as society ages and are directly associated with significant morbidity and mortality. Guideline directed medical therapy has an important role in some instances and limited in others (8), leaving transcatheter therapies with an important part to play. This research topic seeks to explore the important role of advanced imaging in refining procedural outcomes and patient selection. It also reviews the management of more challenging patient populations and new indications for TEER. Finally, the right heart is now firmly in focus as an important indicator of prognosis and tricuspid therapies rapidly coming to the aid of a previously underserved patient population.

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MINI REVIEW
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Role of 3D Transesophageal Echocardiography for Transcatheter Mitral Valve Repair—A Mini Review

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Edge-to-edge transcatheter mitral valve repair (TMVr) using MitraClip has been evolving rapidly in patients with severe mitral regurgitation (MR) at high surgical risk or having contraindications for surgery. Three-dimensional (3D) echocardiography plays an important role in the management of severe MR. In particular, 3D transesophageal echocardiography (TEE) imaging allows the evaluation of MV geometry and quantification of MR severity with dedicated software. Real-time 3D TEE is also commonly used to guide TMVr and facilitate the procedure. Further development of 3D echocardiography may help achieve safer and more beneficial results. The following article summarizes the current knowledge and the future perspectives of 3D TEE in TMVr.

Keywords: mitral regurgitation, transesophageal echocardiography, transcatheter mitral valve repair, MitraClip, 3D

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INTRODUCTION

Mitral regurgitation (MR) is one of the most common valvular heart diseases in developed countries. In the Framingham Heart Study, MR was observed in 19% of the participants (1) and the clinical burden is getting increased with age (2). Thus, patients with severe MR have been associated with a higher surgical risk, and the need for less invasive therapies has been increased.

In the last few decades, transcatheter mitral valve repair (TMVr) has developed rapidly as a treatment option for patients with severe MR at higher surgical risk or having contraindications for surgical mitral valve (MV) intervention. MitraClip (Abbott Vascular, Santa Clara, CA) is the most commonly used edge-to-edge TMVr device in the world that mimics the surgical Alfieri stitch. Several randomized control studies have demonstrated the benefits of the device in various clinical settings. The Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II trial (3) demonstrated a lower prevalence of major adverse events at 30-days after an MV procedure in patients treated with MitraClip compared to open-heart surgery. Subsequently, the Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk Patients (COAPT) trial (4) showed clinical benefits using the MitraClip system in patients with severe secondary MR. Based on these results, the current ACC/AHA guidelines recommended transcatheter MV repair for symptomatic primary MR with high or prohibitive surgical risk and symptomatic secondary MR (grade $\geq$3+) with a left ventricular ejection fraction (LVEF) of 20–50% and LV end-systolic diameter $\leq$70 mm despite maximally tolerated guideline-directed optimal medical therapy (5).

Echocardiography has long been a key imaging modality for the evaluation of valvular heart diseases. The identification of detailed anatomical characteristics of the MV is essential to understand the mechanisms of the diseases and to select an optimal timing and treatment, however, conventional two-dimensional (2D) echocardiography has substantial limitations in assessing the

complex anatomy of the MV apparatus inherent to the technical methodology. One of the main limitations is that 2D echocardiography can only show one acquisition plane which sometimes leads to misunderstanding of the MV geometry. Recent developments in ultrasound devices allow the characterization of the complex anatomy of cardiac structures with great accuracy using three-dimensional (3D) echocardiographic images with great accuracy (6, 7). In particular, real-time 3D transesophageal echocardiography (TEE) plays an indispensable role in the assessment and management of TMVr (8, 9). Herein, we summarize the current knowledge about the utility of 3D TEE for the management of edge-to-edge TMVr using MitraClip.

PRE-PROCEDURAL EVALUATION OF MITRAL REGURGITATION

MR is generally classified into two phenotypes; primary (organic) MR and secondary (functional) MR.

Primary MR is characterized by degenerative alterations of the MV leaflet such as prolapse and/or frailty. Three-dimensional TEE allows to visualize the comprehensive anatomy of the MV and is helpful for easy understanding of the diseased lesion resulting from the degeneration. Moreover, a quantitative evaluation of MV anatomy must be performed to identify patients who will benefit from the procedure. In the EVEREST trials, several anatomical criteria for primary MR were used as follows; a frail gap $<$10 mm and a frail width $<$15 mm (10). In addition, several exclusion criteria, such as severe leaflet calcification in the grasping zone, leaflet perforation, significant cleft, and MV opening area $<$4 cm^2, were defined. However, these measurements are sometimes difficult to assess using only conventional 2D images. Using 3D TEE with multiplanar reconstruction, a more accurate measurement of these dimensions can be obtained (**Figure 1A**).

Color Doppler 3D echocardiographic image is also informative for understanding the characteristics of MR. In many cases of primary MR, the eccentric direction of the regurgitant jet is commonly observed. Thus, it may be difficult to plan an optimal clip position. Color Doppler 3D TEE images depict the accurate location of the regurgitant orifice and the jet direction, which may help in planning the ideal positioning of the MitraClip.

In contrast, secondary MR is defined as MR due to LV and/or LA dysfunction without abnormalities in the MV leaflet and chordae tendineae (11). Although severe secondary MR is associated with adverse prognosis (12–14), the optimal treatment remains controversial. A recently published COAPT trial showed an incremental benefit of MitraClip implantation in addition to guideline-directed medical therapy in patients with symptomatic severe secondary MR at high surgical risk. In contrast, the Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation (MITRA-FR) trial showed no significant improvement in outcomes in patients treated with MitraClip. (15) The discrepancy in the results of these two randomized controlled trials may be due to the baseline characteristics of patients. Thus, the indications for TMVr therapy should be carefully evaluated (**Figure 1B**).

Quantitative assessment of MR severity is crucial for determining the indications for TMVr. However, quantitative assessment of secondary MR using 2D echocardiography has several limitations. In many cases with secondary MR, the flow convergence zone is not hemispherical and the regurgitant orifice has an oval or a crescent shape (16). Thus, the calculation derived by the proximal isovelocity surface area (PISA) method using 2D echocardiography can easily underestimate the MR severity (17, 18). Color Doppler 3D TEE and the multiplanar reconstruction provide a direct measurement of the regurgitant orifice area (3D VCA) which may improve the accuracy of MR grading (**Figure 1C**).

The MV geometry is also an important factor for considering the durability of TMVr. The COAPT trial used two anatomical inclusion criteria for secondary MR; coaptation length $\geq$2 mm and coaptation depth $<$11 mm. Several semi-automated echocardiographic software dedicated to 3D MV geometry have been introduced and applied for pre-procedural evaluation in clinical practice. MV area, perimeter, and leaflet area derived from 3D images can be measured using the software and may provide further incremental information about the degree of tenting and/or leaflet remodeling (19, 20) (**Figure 1D**).

Accordingly, the use of 3D TEE for selecting patients and evaluating the eligibility for TMVr is strongly recommended if available.

PROCEDURAL GUIDANCE OF MITRACLIP USING 3D TEE

During the TMVr procedure, TEE is generally used for guidance because interventionists require accurate geometrical information of the disease without direct inspection, unlike open-heart surgery. Clear visualization of the MV using 3D TEE images leads to better communication between imaging specialists and interventionists compared with 2D TEE. The utility of 3D TEE for procedural guidance has been demonstrated by a previous study that reported that 3D TEE reduced the procedural time compared to conventional 2D guidance alone (9). Thus, now the 3D TEE is mandatory for successful and safe TMVr therapy.

Transseptal Puncture

Determining the optimal transseptal puncture site is an initial crucial role of the 3D TEE guide for TMVr because it fixes the position of the steerable guide catheter (SGC) and influences the mobility of the clip delivery system (CDS) (21). However, clear visualization of the targeted puncture site is sometimes difficult using only 2D images when the site is very posterior (22). Thus, a precise understanding of the interatrial septum and surrounding structures is required for a successful puncture, and the puncture site should be posterosuperior of the interatrial septum. The superior-inferior and the anterior-posterior coordinates of

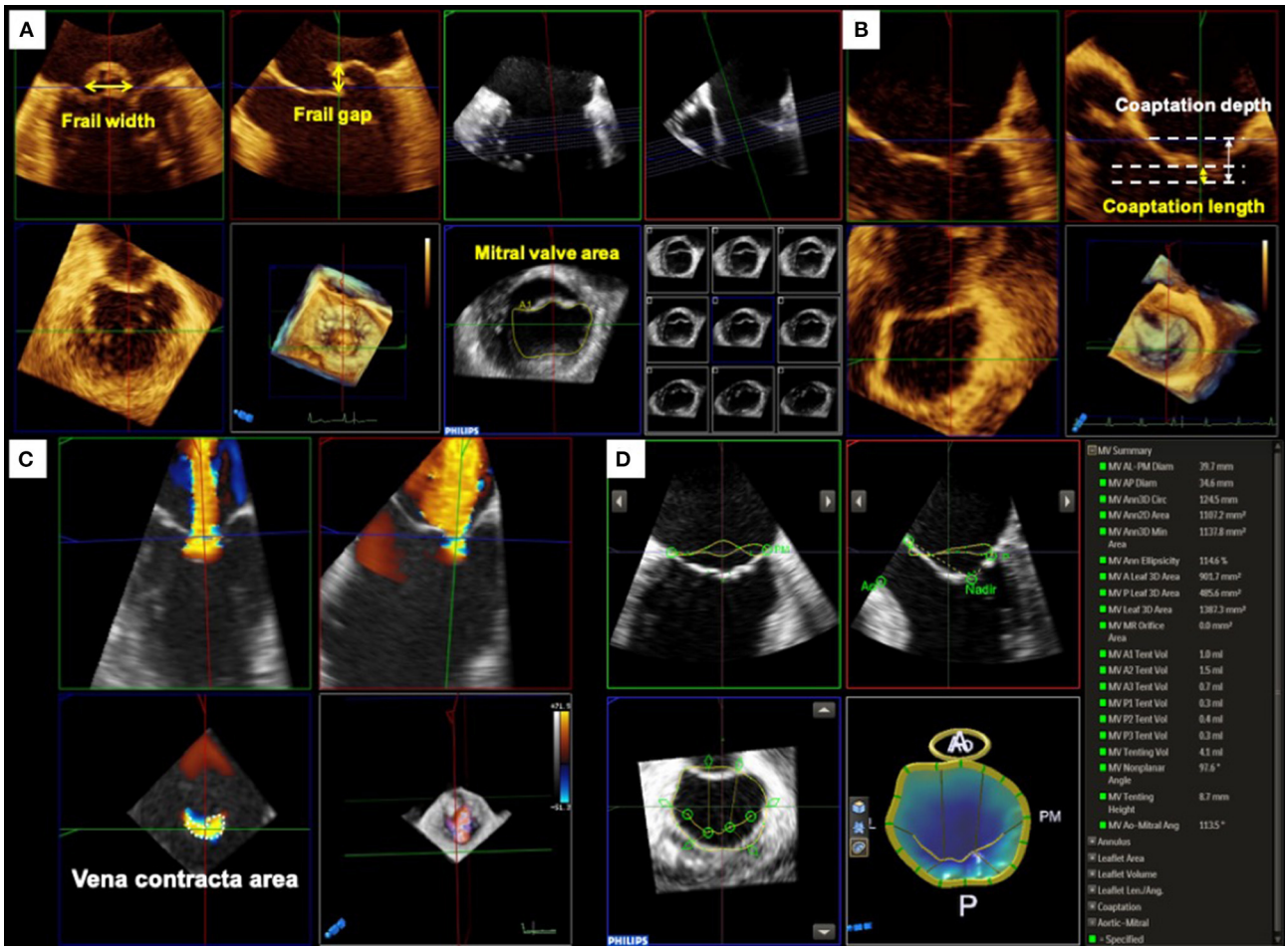

FIGURE 1 | Pre-procedural assessment and quantification of mitral valve geometry. **(A)** Primary mitral regurgitation. For treating primary MR with MitraClip, the frail gap and width of the lesion and mitral valve opening area are used for assessing the procedural durability. **(B)** Secondary mitral regurgitation. Whereas, the coaptation depth and length should be evaluated for secondary MR. **(C)** Quantification of mitral regurgitation by three-dimensional (3D) color Doppler. Three-dimensional vena contracta area allows to evaluate regurgitant orifice area directly and may improve the assessment of regurgitant severity. **(D)** MV geometrical assessment using Mitral Valve Navigator$^{A.I.}$. Semi-automated software dedicated to MV quantification provides useful information on the MV geometry from 3D TEE images.

optimal puncture site are commonly confirmed using mid-esophageal bi-caval and short-axis views, respectively. Real-time 3D TEE can provide two planes simultaneously with the x-plane function and will facilitate the identification of the optimal position to be punctured (**Figure 2A**). However, the ideal puncture site was slightly different between the MR morphologies (23, 24). In patients with primary MR, the height of the puncture site has to be 4–5 cm from the mitral annulus. In contrast, in patients with secondary MR due to leaflet tethering, the height can be reduced because the leaflet coaptation plane shifts to the left ventricle. However, a height from the leaflet coaptation of $<$3.5 cm should be avoided because it may make the procedure difficult (24, 25).

Guidance for Clip Deployment

After the CDS was inserted into the left atrium through the SGC, the clip was advanced into the LV. Two orthogonal echocardiographic views are normally used for the procedural guidance; an inter-commissural view and an LV outflow tract (LVOT) view from the mid-esophagus. The X-plane view provides these two planes simultaneously and enables the observation of the device. After the device was advanced to the LV using these X-plane views, the clip was slowly opened. Subsequently, the leaflets were grasped guided by TEE. Real-time 3D en-face MV view helps to assess the alignment of the clip which should be perpendicular to the line of the leaflet coaptation. After an initial grasp of the leaflets, the clip orientation must be evaluated (**Figure 2B**). Subsequently assessing the adequate insertion of both anterior/posterior leaflets, the MV geometry, which usually has a double-orifice, should be confirmed with the 3D en-face view. Before releasing the clip, the presence of residual MR has to be assessed carefully. Because patients treated with MitraClip had a higher prevalence of cardiac surgery during the first year after the procedure if significant residual MR exists in the EVEREST II trial (26). Moreover, significant residual MR has been shown as a strong determinant of poor outcomes after TMVr in several studies (27–30). Pulmonary venous flow patterns may provide

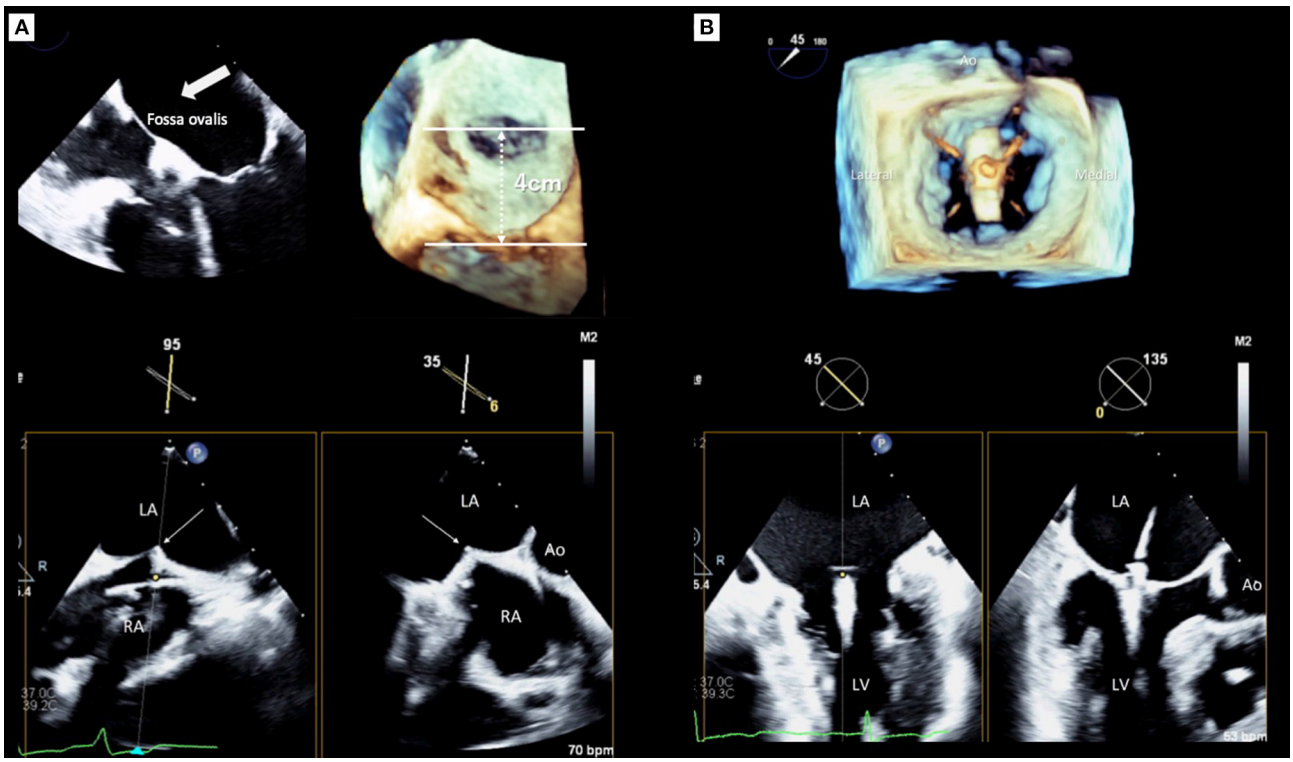

FIGURE 2 | Real-time guidance for MitraClip implantation using three-dimensional transesophageal echocardiography. **(A)** Transseptal puncture guidance, **(B)** Clip deployment. LA, left atrium; LV, left ventricle; Ao, aorta.

useful information for determining the severity of residual MR indirectly (31). However, quantification of residual MR after MitraClip implantation has been challenging using 2D TEE. The proximal isovelocity surface area method, which is commonly used for evaluating native MR, is not feasible for residual MR after MitraClip implantation since the residual jet may have multiple and eccentric orifices. Color Doppler 3D TEE images help find and visualize the jet if it exists. In addition, 3D VCA may be a feasible and reliable method for quantification of residual MR after TMVr (32). If these results were acceptable, the clip was released. Finally, all evaluations must be performed again to compare the pre- and post-procedural results using both 2D and 3D TEE. If the clip location and the reduction of MR are not appropriate, a new attempt should be made to adjust the clip location.

FUTURE PERSPECTIVES AND DISCUSSION

Recent technological development will be clinically applied for the management of TMVr.

Dedicated applications of 3D echocardiography provide better visualization and more accurate quantification of MV anatomy than before.

Real-time fusion imaging of 3D echocardiography and fluoroscopy provides useful information for understanding the positional relationship between MV and the surrounding structures. It facilitates that both echocardiographers and interventionists share the same recognition of MV geometry, which may lead to a better post-procedural result.

In summary, physicians have required a better understanding and more accurate quantification of the MV geometry as TMVr has rapidly developed for patients with severe MR at high surgical risk. Real-time 3D TEE has become an indispensable and essential modality for the diagnosis and management of MR, and guidance during the TMVr procedure. With the appropriate use of 3D TEE, a more accurate assessment can be achieved in both primary and secondary MR. It also allows echocardiographers to share recognition of the MV geometry with interventionists and facilitates the procedure. Furthermore, the technological development of echocardiographic devices will allow a better illustration of complex anatomical MV morphology and may result in risk reduction after TMVr.

AUTHOR CONTRIBUTIONS

KH and MI drafted the manuscript. MI prepared the figures. All authors read and approved the final manuscript.

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Progression of Mitral Regurgitation in Rheumatic Valve Disease: Role of Left Atrial Remodeling

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Introduction: Mitral regurgitation (MR) is the most common valve abnormality in rheumatic heart disease (RHD) often associated with stenosis. Although the mechanism by which MR develops in RHD is primary, longstanding volume overload with left atrial (LA) remodeling may trigger the development of secondary MR, which can impact on the overall progression of MR. This study is aimed to assess the incidence and predictors of MR progression in patients with RHD.

Methods: Consecutive RHD patients with non-severe MR associated with any degree of mitral stenosis were selected. The primary endpoint was a progression of MR, which was defined as an increase of one grade in MR severity from baseline to the last follow-up echocardiogram. The risk of MR progression was estimated accounting for competing risks.

Results: The study included 539 patients, age of 46.2 ± 12 years and 83% were women. At a mean follow-up time of 4.2 years (interquartile range [IQR]: 1.2–6.9 years), 54 patients (10%) displayed MR progression with an overall incidence of 2.4 per 100 patient-years. Predictors of MR progression by the Cox model were age (adjusted hazard ratio [HR] 1.541, 95% CI 1.222–1.944), and LA volume (HR 1.137, 95% CI 1.054–1.226). By considering competing risk analysis, the direction of the association was similar for the rate (Cox model) and incidence (Fine-Gray model) of MR progression. In the model with LA volume, atrial fibrillation (AF) was no longer a predictor of MR progression. In the subgroup of patients in sinus rhythm, 59 had an onset of AF during follow-up, which was associated with progression of MR (HR 2.682; 95% CI 1.133–6.350).

Conclusions: In RHD patients with a full spectrum of MR severity, progression of MR occurs over time is predicted by age and LA volume. LA enlargement may play a role in the link between primary MR and secondary MR in patients with RHD.

Keywords: progression, atrial fibrillation, mitral stenosis, left atrial, mitral regurgitation, rheumatic heart disease

INTRODUCTION

Rheumatic heart disease (RHD) remains a serious global health concern as the leading cause of cardiovascular death in children and young adults (1, 2). The prevalence of RHD has been rising steadily since 1990, reaching 40.5 million in 2019, and accounting for 306,000 deaths annually as a consequence of severe valvular disease (3). Mitral regurgitation (MR) is the most common valvular abnormality at the early RHD stages, usually associated with ongoing inflammatory rheumatic activity in children (4–7). This pure MR may resolve with effective treatment of the acute carditis and continued prophylactic therapy. In the late time course, MR is often associated with stenosis owing to intrinsic valvular lesions that include fibrosis with retracted leaflets, restricted mobility, and commissural fusion (8).

Although the mechanism by which MR develops in RHD is primarily related to the structural impairment of the mitral valve (MV) apparatus (8), longstanding volume overload with left-sided chamber alterations may trigger the development of secondary MR (9). Moreover, in the presence of atrial fibrillation (AF), which often occurs in patients with rheumatic MV disease, MR may also arise as a consequence of left atrial (LA) enlargement and mitral annular dilatation. Functional MR in patients with AF has been increasingly recognized (10–12). However, whether mitral annular dilatation causes MR in patients without left ventricular dysfunction remains controversial.

There is a growing awareness that MR continues to progress over time as the increased volume load on the left ventricle and LA results in geometric changes that lead to a further increase in the severity of MR (13, 14). Additionally, the most common pattern of MV pathology in middle-aged adults with RHD is mixed MV disease, which begets LA enlargement (8, 15). Taken together, both primary MR and secondary MR may coexist in the setting of RHD, which may have an impact on MR progression. However, because of the paucity of data available on the progression of rheumatic MR, the underlying mechanisms are not certain.

Previous studies addressing the progression of MR in adult patients with RHD have focused mainly on MR following valvuloplasty (16–20). In this context, the progression and prognosis are variables depending on the mechanism by which MR develops. We previously showed that MR originated at the site of commissural split or at the central orifice of the valve and remains stable over time. On the other hand, MR due to leaflet tearing at central scallop location or subvalvular damage results in severe adverse hemodynamics that require immediate surgery (20). However, there is a lack of studies on the natural history of rheumatic MR without intervention, as it requires large cohorts of patients with repeated echocardiograms and long-term follow-up. To fill these gaps of knowledge, we sought to investigate the incidence and predictors of MR progression in a substantial population of patients with RHD.

METHODS

Study Population

Patients were recruited prospectively from a tertiary center for heart valve disease among those routinely referred for management of RHD from 2011 to 2021. Patients with rheumatic MV disease with trivial, mild, or moderate MR associated with any degree of mitral stenosis based on the presence of typical rheumatic features by echocardiography criteria (21) were initially eligible for the study (Study flow is shown in **Figure 1**). Exclusion criteria included severe MR at baseline or following percutaneous mitral valvuloplasty, associated significant aortic valve disease, and no echocardiographic assessment of MR at last follow-up. Among 694 patients initially eligible for the study, 539 fulfilled the inclusion criteria and were enrolled.

Information on demographic data, functional capacity, right-sided heart failure, and current medications was obtained at baseline. AF was diagnosed based on a history of permanent AF, supported by a past 12-lead ECG. A diagnosis of new-onset AF in patients with sinus rhythm at the time of enrollment in the study was confirmed by a 12-lead ECG. All patients gave written informed consent, and the study protocol was approved by the UFMG institutional ethics committee.

Echocardiography

Comprehensive two-dimensional (2D) and Doppler echocardiographic examinations were performed in all patients at baseline and at follow-up using commercially available echocardiography machines. Measures of left ventricular dimensions and function were assessed as recommended (22). MR was graded as none/trace, mild, moderate, or severe by using an integrative approach (23). Parameters used to grade MR included the *vena contracta* width, regurgitant volume, and effective orifice area, qualitative assessment of the color flow jet, and, when available, the pulmonary venous flow signal. MV area was measured using direct planimetry. Peak and mean transmitral diastolic pressure gradients were measured from Doppler profiles recorded in the apical four-chamber view. The presence and severity of tricuspid regurgitation and systolic pulmonary artery pressure were evaluated according to the guidelines (20). LA volume was assessed by the biplane area-length method from apical 2- and 4-chamber views.

Definition of MR Progression

Progression of MR was defined as an increase of one grade in MR severity from baseline to the last follow-up echocardiogram. Patients in whom MR did not progress but died or underwent MV replacement were censored at the time of the events and also analyzed considering these events as competing risks (24). Patients who underwent percutaneous mitral valvuloplasty were censored at the time of the procedure and post-procedural MR was not considered as progression.

Statistical Analysis

Categorical variables were expressed as numbers and percentages and were compared by using chi-square or Fisher exact tests

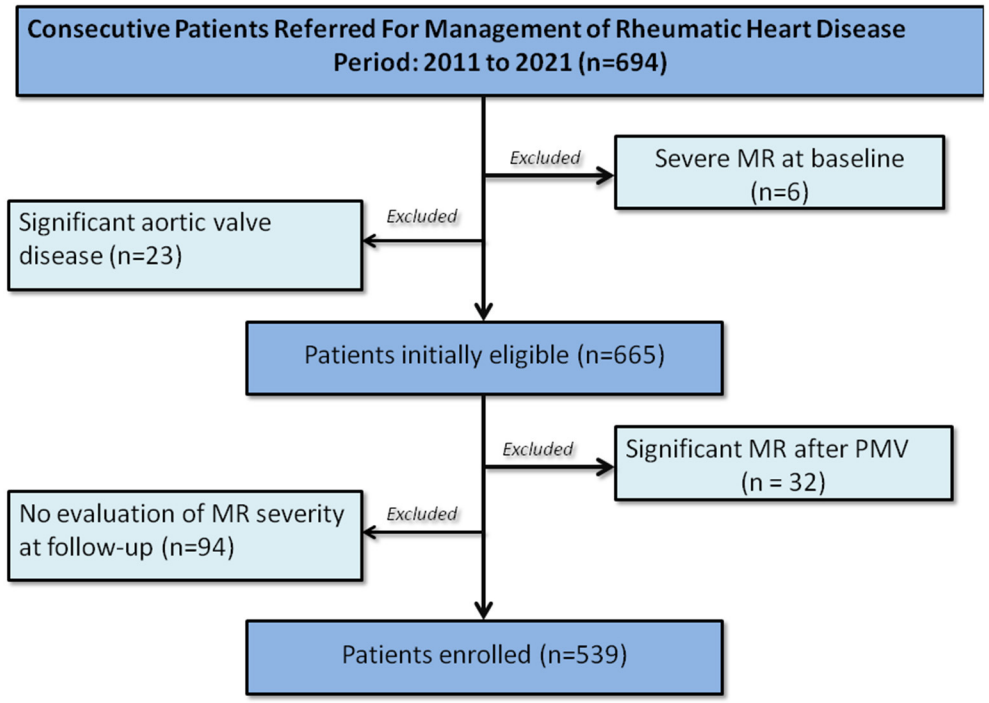

FIGURE 1 | Study population.

as appropriate. Continuous data were expressed as mean ± SD and were compared by using unpaired Student's t-test or Mann-Whitney test as appropriate.

The incidence rate of MR progression was calculated by dividing the number of progression by the person-years of follow-up calculated from the baseline until either the date of death or MV replacement or last follow-up echocardiogram.

Predictors of MR progression were assessed using two regression models. The first was the Cox proportional hazards model in which patients were censored at the time of death or MV replacement if it was not preceded by MR progression. The second model was the Fine-Gray competing risk model in which MR progression was the primary event and death or MV replacement was the competing risk (24) that may prevent progression of the valve regurgitation. The estimated regression coefficients for each variable were compared between the two models to assess differences in the direction of their association with the rate of MR progression (derived from the Cox model) vs. its incidence (derived from the Fine-Gray model) (24). Schoenfeld residuals were used to check the proportional hazards assumption.

Long-term MR progression according to cardiac rhythm was estimated by the Kaplan-Meier method and compared by the log-rank test. Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA) and R for Statistical Computing version 3.6.3 (R Foundation, Vienna, Austria).

RESULTS

Patient Characteristics

Our final cohort consisted of 539 patients, age of 46.2 ± 12 years, and 454 patients were women (83%). Baseline demographic and clinical characteristics according to MR progression are summarized in **Table 1**. At baseline, trivial MR was detected in 80 patients (15%), mild MR in 416 (77%), and moderate in 43 (8%). Most of the patients were in the New York Heart Association (NYHA) classes I and II (64%), whereas 194 (36%) patients were in NYHA classes III and IV at presentation. One hundred and sixteen patients (22%) were presented with right-sided heart failure. The medications most frequently used were beta-blockers (74% of cases) followed by diuretics (69% of cases).

In the overall population, the left atrium was severely dilated, with a mean volume of 54 ml/m^2 in the patients in sinus rhythm compared with 74 ml/m^2 in AF ($p < 0.001$). One hundred and thirty-five patients (25%) had a history of hypertension and 3% of diabetes. The majority of patients had no comorbidities.

Regarding baseline echocardiographic characteristics, patients who progressed had larger left ventricular chamber dimensions, LA volume, and lower ejection fraction. Of note, the severity of the associated mitral stenosis was similar between the patients with a mean valve area of 1.1 cm^2 in those patients who progressed or did not. Baseline echocardiographic features according to MR progression are summarized in **Table 2**.

TABLE 1 | Demographic and clinical characteristics of the study population stratified by mitral regurgitation (MR) progression.

Clinical data*	No progression ($n = 485$)	MR progression ($n = 54$)	*p* value
Age (years)	45.7 ± 12.1	50.0 ± 13.1	**0.016**
Female gender (%)	400 (83)	47 (87)	0.398
NYHA class III-IV (n/%)	179 (37)	19 (36)	0.919
Right-sided heart failure	106 (22)	14 (27)	0.399
Atrial fibrillation (n/%)	149 (31)	24 (44)	**0.039**
Previous valvuloplasty†	170 (35)	15 (28)	0.293
Ischemic cerebrovascular events‡	97 (20)	6 (11)	0.131
Diuretics use	339 (70)	39 (75)	0.439
Anticoagulation therapy	90 (32)	23 (36)	0.535
Heart rate (bpm)	70.1 ± 13.8	71.1 ± 12.7	0.576
Systolic blood pressure (mmHg)	117.8 ± 15.8	115.5 ± 14.5	0.332
Diastolic blood pressure (mmHg)	75.5 ± 10.9	74.7 ± 10.7	0.637

**Data are expressed as the mean value ± SD, or absolute numbers (percentage).*
† Surgical commissurotomy or percutaneous valvuloplasty.
‡ Stroke or transient ischemic attack at baseline.
Bold numbers mean a p-value <0.05%.

TABLE 2 | Baseline echocardiographic characteristics of the study population stratified by MR progression.

Echocardiographic data	No progression ($n = 485$)	MR progression ($n = 54$)	*p* value
LVDd (mm)	48.4 ± 6.0	50.5 ± 6.7	**0.017**
LVSd (mm)	31.6 ± 5.2	33.7 ± 6.7	**0.005**
LVEF (%)	58.5 ± 6.8	55.7 ± 6.9	**0.009**
LAV index (mL/m^2)	59.6 ± 23.9	67.9 ± 32.3	**0.027**
RA area (cm^2)	17.5 ± 6.9	17.0 ± 5.4	0.620
Peak gradient (mmHg)	18.3 ± 7.2	16.6 ± 6.0	0.083
Mean gradient (mmHg)	10.1 ± 4.9	9.3 ± 4.0	0.227
Mitral valve area (cm^2)*	1.14 ± 0.40	1.14 ± 0.36	0.996
SPAP (mmHg)	44.7 ± 17.0	40.3 ± 11.3	**0.025**
Systolic annular velocity (cm/s)†	10.5 ± 2.2	9.9 ± 2.1	**0.048**
Right ventricular FAC (%)	46.2 ± 10.1	48.7 ± 11.0	0.119
Moderate or severe TR (n/%)	77 (16)	6 (11)	0.384
C_n (mL/mmHg)	5.1 ± 1.9	5.6 ± 1.8	0.089

Data are expressed as the mean value ± SD, or absolute numbers (percentage).
**Mitral valve area by planimetry.*
† Peak systolic velocity at the tricuspid annulus.
C_n, net atrioventricular compliance; LA, left atrium; LAV, left atrial volume; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVSd= left ventricular end-systolic diameter; MR, mitral regurgitation; RA, right atrium; FAC, fractional area change; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.
Bold numbers mean a p-value <0.05%.

At a mean follow-up time of 4.2 years (interquartile range [IQR]: 1.2–6.9 years), 54 patients (10%) displayed MR progression. The majority of the patients progressed from mild-to-moderate MR ($n = 42$, 77.8%), mild-to-severe ($n = 6$, 11.1%), trivial MR-to-moderate ($n = 3$, 5.5%), and the other 3 patients (5.5%) from moderate-to-severe MR. Patients who progressed MR were older compared with those who did not progress. Permanent AF at baseline was found in 173 patients, more frequent in patients who had MR progression.

Predictors of MR Progression

The overall incidence of MR progression was 2.4 per 100 patient-years. During the follow-up, 120 patients underwent cardiac surgery for MV replacement and 27 patients died, being 23 cardiovascular-related and four non-cardiovascular-related deaths (**Figure 2**). In the Cox proportional hazard regression model, older age, the presence of AF, and larger LA volume were univariately associated with MR progression. Interestingly, prior mitral valvuloplasty, i.e., either percutaneous or surgical intervention, was inversely associated with MR progression. The severity of tricuspid regurgitation was not associated with MR progression (**Table 3**).

As death and MV replacement constitute a competing risk that may preclude the natural progression of MR, time-to-event analyses were performed considering competing risks. In the Cox proportional hazard regression model, MR progression was the primary outcome, and patients who underwent MV replacement or died were censored. In the Fine-Gray model, MV replacement and death were analyzed as competing events (**Table 4**). In the multivariable models, age and LA volume were independent predictors of MR progression during the follow-up (**Tables 3**, **4**). In the model with LA volume, AF was no longer a predictor of MR progression. The severity of TR regurgitation was included in the model as this entity is also associated with AF and right atrial dilation. For all variables included, the direction of the association was similar for the rate (Cox model) and incidence (Fine-Gray model) of MR progression. The hazard ratios of each predictor comparing Cox and Fine-Gray models are shown in **Figure 3**.

We performed a subgroup analysis stratifying according to the MR grade at the follow-up. To do so, we categorized MR progression in moderate ($n = 45$) and severe ($n = 9$), irrespective of the MR grade at baseline. By considering only severe MR in the Cox model, age was the most important predictor of progression (hazard ratio [HR] 2.592; 95% 1.357–4.952), and the effect of LA volume was attenuated (HR 1.121; 95% CI 0.807–1.557). However, the small number of patients in the severe MR category limits this analysis.

In the subset of patients in sinus rhythm, 59 patients showed an onset of AF during the course of the follow-up, which was associated with MR progression (HR 2.682; 95% CI 1.133–6.350). Of note, the risk of MR progression was higher in patients with permanent AF at enrollment (HR 4.549; 95% CI 2.148–9.631) compared with those who had new-onset of AF during the follow-up (HR 2.447; 95% CI 1.035–5.788; **Figure 4**). As expected, patients with new-onset of AF displayed larger LA volume compared with the patients who remained in sinus rhythm (61 and 54 ml/m^2, respectively).

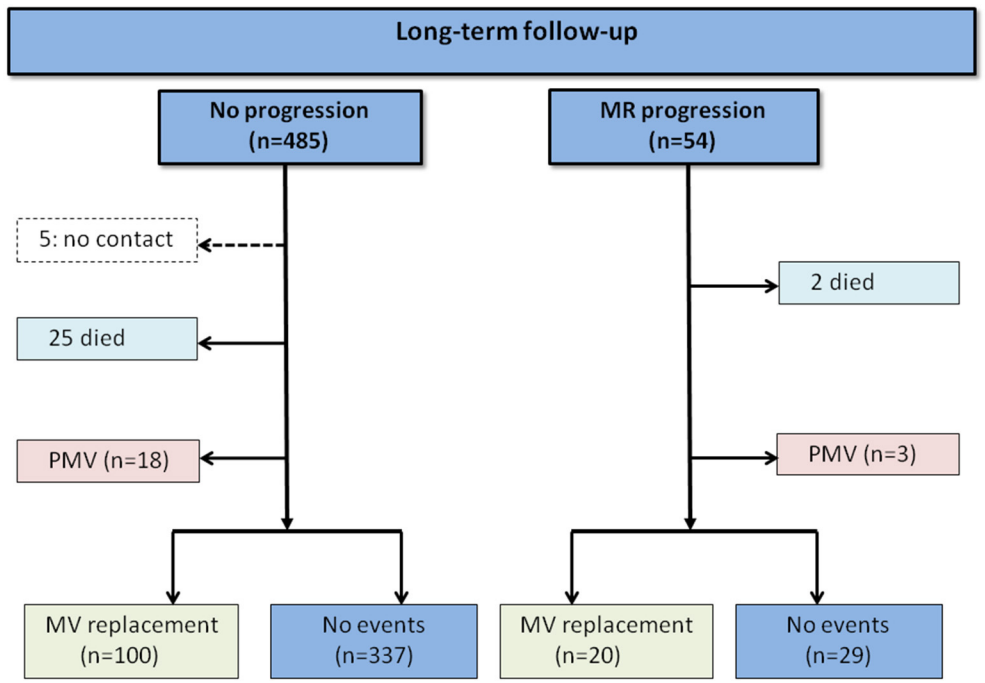

FIGURE 2 | Long-term follow-up of patients with rheumatic heart disease (RHD).

TABLE 3 | Clinical and echocardiographic characteristics associated with MR progression in patients with RHD: Cox regression model.

At baseline	Unadjusted		Multivariable model		Final model	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age*	1.563 (1.245–1.962)	0.000	1.486 (1.156–1.909)	0.002	1.541 (1.222 - 1.944)	**0.000**
Permanent AF	2.527 (1.467–4.354)	0.001	1.555 (0.781–3.095)	0.209		
LA volume index*	1.152 (1.069–1.241)	0.000	1.108 (1.014–1.211)	0.023	1.137 (1.054 - 1.226)	**0.001**
Prior PMV	0.453 (0.230–0.895)	0.023	0.493 (0.245–0.992)	0.047	0.479 (0.239 - 0.961)	**0.038**
Mild TR†	0.980 (0.291–3.302)	0.974	0.803 (0.235–2.752)	0.728		
Moderate TR	1.356 (0.310–5.938)	0.686	0.764 (0.160–3.647)	0.736		
Severe TR	0.465 (0.047–4.602)	0.512	0.253 (0.025–2.609)	0.249		

**Hazard ratio: x10.*
† Reference category was absence of tricuspid regurgitation.
LA, left atrium; AF, atrial fibrillation; PMV, percutaneous mitral valvuloplasty; TR, tricuspid regurgitation.
Bold numbers mean a p-value <0.05%.

DISCUSSION

The natural history of MR varies according to the time course of RHD. While MR in acute carditis may resolve with the control of inflammatory changes, MR at the late disease stages tends to progress over time, which in turn leads to clinical complications (25, 26). The present study showed that in RHD, progression of MR occurs over time with the overall incidence of 2.4 events of progression per 100 patient-years. Age and LA enlargement were major independent determinants of the progression of MR. New-onset AF during the course of the follow-up was associated with MR progression. The study accounts for competing risks to conduct time-to-event analyses appropriately of MR incidence in RHD patients with mixed MV disease.

Primary MR Progression

The severity of primary MR may increase over time as a consequence of the adverse remodeling of the left atrium and ventricle (27). The degree of regurgitation is an essential determinant of the hemodynamic changes, remodeling of left-sided chambers, and poor outcome. A previous study that includes primary MR, mainly valve prolapse, showed that progression of MR is variable and determined by the progression of lesions or mitral annulus size (28). The most important determinant of marked aggravation of MR is the occurrence of a new flail leaflet followed by an increase in annular diameter, which results in reduced leaflet coaptation. Another study evaluating patients with MV prolapse demonstrated that only mitral

TABLE 4 | Clinical and echocardiographic characteristics associated with MR progression in patients with RHD: Fine-Gray model.

At baseline	Unadjusted		Multivariable model		Final model	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.340 (1.072–1.675)	0.010	1.327 (1.012–1.740)	0.041	1.327 (1.055 - 1.669)	**0.016**
Permanent AF	1.928 (1.138–3.266)	0.015	1.460 (0.720–2.961)	0.290		
LA volume index	1.130 (1.060–1.205)	0.000	1.101 (1.018–1.191)	0.016	1.130 (1.060 - 1.203)	**0.000**
Prior PMV	0.567 (0.291–1.102)	0.094	0.656 (0.335–1.285)	0.220		
Mild TR*	0.859 (0.291–2.539)	0.780	0.690 (0.228–2.087)	0.510		
Moderate TR	0.885 (0.233–3.352)	0.860	0.485 (0.109–2.169)	0.340		
Severe TR	0.194 (0.021–1.788)	0.150	0.104 (0.011–1.005)	0.051		

LA, left atrium; AF, atrial fibrillation; PMV, percutaneous mitral valvuloplasty; TR, tricuspid regurgitation.
**Reference category was absence of tricuspid regurgitation.*
Bold numbers mean a p-value <0.05%.

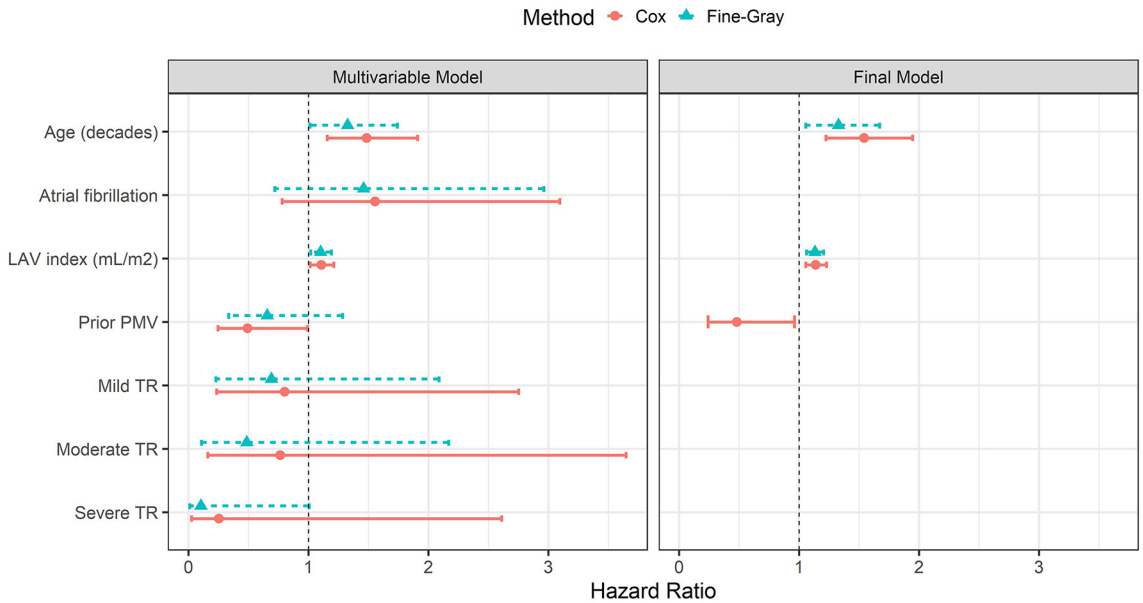

FIGURE 3 | Multivariable predictive models for prediction of mitral regurgitation (MR) progression in patients with rheumatic heart disease (RHD). Cox proportional hazards model considering mitral regurgitation (MR) progression as the primary event and the Fine-Gray model analyzing death and mitral valve replacement as a competing event.

annular diameter is a predictor of progression to severe MR (29).

Data on MR progression in patients with RHD are scarce and limited to acute carditis or MR related to percutaneous valve intervention (8, 16–18, 20, 25). In the setting of RHD, given the presence of mixed MV disease, mitral annular enlargement may be induced by both left ventricular and atrial enlargement, which contribute to aggravate the MR severity over time. However, as we included only non-severe MR, the impact of volume overload on the adverse remodeling of the left ventricle might be lower than in severe MR. Additionally, combined valve disease often occurs in RHD and patients may undergo valve replacement for stenosis as the predominant lesion, which influences the natural history of MR progression in the native valve. To address this issue, MV replacement was considered a competing risk that may preclude the occurrence of progression, avoiding biased estimates of progression risk with traditional time-to-event methods (30). The Fine-Gray model constitutes a tool that determines a sub-distribution in a correct way of the role of risk factors, thus taking into account the competition between pairs of events (31).

The significant regurgitant lesion in rheumatic MV has long been considered merely an anatomic variant of its stenotic counterpart, in which retraction of scarred valve leaflets has disrupted the integrity of the mitral seal (8, 32, 33). As the chronic rheumatic process is usually accompanied by at least some fusion of mitral commissures, the relative prevalence of pure regurgitation among hemodynamically severe MV lesions has consistently been reported to be low (8, 34). In agreement with the literature, our population with mixed MV disease, characteristics of pure regurgitation, and pure stenosis were

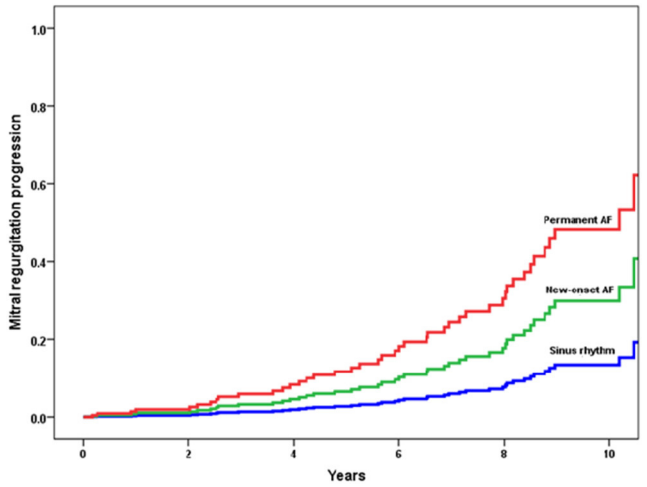

FIGURE 4 | Incidence of mitral regurgitation (MR) progression according to cardiac rhythm. Patients who had sinus rhythm at baseline but with a new-onset of atrial fibrillation during the follow-up were at risk for progression with a hazard ratio of 2.447 (95% CI 1.035–5.788). Patients with permanent atrial fibrillation were at the highest risk for progression with a hazard ratio of 4.459 (95% CI 2.148–9.631) when compared with patients in sinus rhythm.

overlapped, which makes it difficult to analyze the progression of the regurgitant lesion alone (13).

LA Enlargement in MR: The Link Between Primary and Secondary MR

In patients with primary MR, secondary MR can also develop because LA dilation leads to mitral enlargement of the MV annulus. In this context, the overlapping of secondary MR may contribute to further overall progression of the regurgitation. Indeed, there are instances in which both primary MR and secondary MR are present (13).

Left atrial enlargement in MR has been reported either as a compensatory mechanism with the aim to reduce atrial and pulmonary pressure or, conversely, as a marker of poor prognosis (35). Atrial enlargement is accompanied by chronic inflammatory changes, cellular hypertrophy, and wall fibrosis, which leads to reduced compliance and increased LA pressure and risk of AF (36). This association supports the poor prognosis of patients with LA enlargement due to primary MR (36–38).

Although the value of LA enlargement in predicting heart failure and death in the general population has been reported, in primary MR, there are limited data on its prognostic implications (35). A multicenter study showed that LA diameter is an independent predictor of survival in patients with chronic MR due to flail leaflets in sinus rhythm under medical treatment. The association between LA diameter $\geq$55 mm and the outcome is independent of symptoms or left ventricular dysfunction (37). Another study included 305 patients with MV prolapse and sinus rhythm who underwent MV repair. After a mean follow-up period of 8 years, patients with an area of >30 cm^2 presented a 2-fold increase in the risk of mortality when compared with those with an area of <25 cm^2. LA enlargement was a predictor of long-term mortality after surgery for valve repair in sinus rhythm patients (39).

In patients with rheumatic MV disease, a chronic pressure-volume overload on the left atrium leads to a range of adaptive processes that include LA remodeling (40), which encompasses changes in atrial size, function, and shape. LA enlargement also reflects the intrinsic compliance of the left atrium, risk of subsequent AF, and overall disease severity. In the presence of mixed MV disease, LA is affected by both stenosis and regurgitation, which aggravates its remodeling over time with the progression of MR as a consequence of the mitral annulus size. Subsequent progression of primary rheumatic lesions should also be considered. Turbulent flow drives valvular tissue injury, continuously stimulating inflammatory processes and mechanical trauma, which contribute to perpetuate the valvular damage (8). Additionally, patients with RHD often have associated AF, which may contribute to the progression of LA and annular dilation thus increasing the severity of MR. Indeed, there are cumulative pieces of evidence using three-dimensional (3D) echocardiography showing that significant secondary MR can sometimes occurs in AF patients with dilatation of mitral annulus and left atrium. In the present study, 32% of the patients had permanent AF at enrollment and 11% developed AF during the follow-up. Regardless of the cardiac rhythm, LA enlargement was an important predictor of MR progression.

Study Limitation

Despite providing relevant clinical information on LA remodeling and MV involvement in RHD, this study has some limitations. First, 3D analysis of MV accurately assesses morphology and regurgitation mechanisms. Leaflet remodeling, rather than crude annular dilatation, is associated with the severity of functional MR in patients with AF (41). In our study, mitral annulus by 3D was not assessed and LA dilation was considered a surrogate for mitral annulus enlargement. However, the previous study with 3D-transesophageal echocardiography showed that LA volume is the main predictor of mitral annulus enlargement (42). Moreover, large patient population is required to determine MR progression and 3D analysis of MV in all patients is a challenge. Second, assessment of LA function using novel parameters that include LA strain may be able to detect the onset of decreasing LA compliance and contractile dysfunction that is known to occur in more advanced diseases. In our study, LA function was not assessed. Indeed, atrial disease and remodeling form the basis of the atrial cardiopathy, which plays a critical role in the pathogenesis of AF (43). Third, LV volume and pressure were not measured directly in our study, which influence the amount of MR for a given lesion under different hemodynamic conditions (44).

Finally, the majority of our patients was progressed to moderate MR, which may not have an impact on clinical outcomes. However, the complex nature of mixed MV disease in the setting of RHD makes it necessary to consider all available data to reach a final management decision (13).

CONCLUSIONS

In patients with RHD with a full spectrum of MR severity, progression of MR occurs over time predicted by age and LA volume, corrected by competing risks. LA enlargement may play a role in the link between primary MR and secondary MR in patients with RHD. Assessment of MR progression may provide important insight into the long-term consequences of the disease and the rationale for patient management.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UFMG Institutional Ethics Committee (No. 3.586.751). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NG, VS, and MN: conception and design of the research. WE, MC, LP, and AP: acquisition of data. JS and MN: analysis and interpretation of data and statistical analysis. RL and WD: obtaining financing. NG and MN: writing of the manuscript and responsible for the overall content as guarantors. RL, JD-B, EA, TT, and JH: critical revision of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Transcatheter Mitral Valve-in-Valve Implantations Using Inverted J-Valve

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Background: As bioprosthetic valves are being widely used, the incidence of structural valve deterioration increases, as well as the need for reoperation. Transcatheter mitral valve-in-valve implantations are being increasingly adopted as an alternative to redo-surgical mitral replacement for patients with high surgical risks. This study reports a series of transcatheter mitral valve-in-valve implantations using inverted J-valves.

Methods: From April 2019 to September 2021, 17 symptomatic high-risk patients with mitral bioprosthetic valve dysfunction underwent transapical transcatheter mitral valve-in-valve implantations using inverted J-valves at our institution.

Results: The median age was 70 years, with 76.5% being female. The median Society of Thoracic Surgeons predicted risk of mortality (STS PROM) was 17.2% (8.7–82.24%). All patients had successful transapical transcatheter mitral valve-in-valve implantations except for one intraoperative death due to left ventricle rupture. Four patients underwent simultaneous transcatheter aortic valve implantation, two of which had valve-in-valve transcatheter aortic valve implantation. There was no major complication except one case of bleeding. Thirty-day mortality was 11.8% (2/17), and 90-days mortality was 23.5% (4/17). Percentages of patients with New York Heart Association class III/IV symptoms decreased from 100 (17/17) to 20% (3/15) at 30-days. Median mitral inflow velocity was 1.95 mm/s at 30 days, compared to 2.7 mm/s at baseline. Median mitral valve effective orifice area increases from 1.5 mm at baseline to 1.85 mm at 30 days.

Conclusion: Transcatheter transapical valve-in-valve implantations with J-valve can be a plausible solution to failed mitral bioprosthesis with acceptable results for high-risk patients.

Keywords: transcatheter mitral valve implantation, valve-in-valve, J-valve, structural valve deterioration, transapical

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INTRODUCTION

As bioprosthetic valves are being increasingly adopted, structural valve deterioration becomes a challenge for long-term prognosis. The introduction of valve-in-valve TAVI marks the beginning of a new era for failed bioprosthetic valves (1–4). Three-year follow-up results from PARTNER 2 registry (5) demonstrate favorable survival, sustained improved hemodynamic status, and excellent functional and quality-of-life outcomes using valve-in-valve TAVR for patients with structural valve deterioration.

However, the use of valve-in-valve transcatheter mitral valve replacement (TMVIV) remains controversial compared to repeat surgical interventions (6, 7), especially in patients with

small-sized failed surgical bioprostheses. Current guidelines (8, 9) acknowledge TMVIV as an alternative to surgical re-implantation in Comprehensive Valve Centers for patients with high surgical risks. Kamioka et al. (10) find similar clinical and echocardiographic outcomes after surgical redo mitral valve replacement and transcatheter mitral valve-in-valve therapy.

Usage of inverted TAVR prosthesis in TMVIV has been widely reported (11, 12). Mid-term reports from multiple cohorts have shown acceptable results using SAPIEN 3 [(Edwards Lifesciences), Melody (Medtronic, Minneapolis, MN), Lotus (Boston Scientific, Natick, MA, USA) and Direct Flow (Direct Flow Medical Inc., Santa Rosa, CA, USA)] (13–17). Most procedures are performed *via* a transapical or transseptal approach. The transapical route provides coaxial alignment and therefore reduces the risk of malposition and migration, along with left ventricular outflow tract obstruction. In addition, the transapical access offers an intergrated solution for patients in need of additional aortic valve intervention.

J-valve (Jie Cheng Medical Technologies, Suzhou, China) is a second-generation self-expanding bioprosthetic valve designed for transapical TAVR. It has been approved by the China National Medical Products Administration for both aortic valve stenosis and regurgitation after proved effective and safe in the multicentered study. Lu et al. (18) and Wei et al. (19) reported their experience with TMVIV using J-valve in 26 and 21 patients, respectively. In this study, we report 17 cases of TMVIV using inverted J-valves.

METHODS

Ethics Statement

The study protocol was approved by the West China Hospital Ethics Committees and Institutional Review Board, Sichuan, China. Written informed consent was obtained from all patients.

Patients

Our retrospective cohort included 17 consecutive patients with mitral bioprosthetic valve dysfunction (regurgitation and/or stenosis) who underwent transapical transcatheter mitral valve-in-valve implantations using inverted J-valves at our institution between April 2019 and September 2021. Indications for redo mitral valve replacement were based on the 2014 American College of Cardiology/American Heart Association Guideline for the Management of Patients with Valvular Heart Disease (20). Patients were deemed unsuitable for re-operative mitral valve surgery because of excessive surgical risk after heart team discussion. Inclusion criteria for the procedure were the following: presence of a dysfunctional bioprosthesis in mitral position; STS score >8% or logistic EuroSCORE >10; Exclusion criteria for the procedure included left ventricular thrombus; cardiac tumors; presence of periprosthetic leak; prosthesis label size <25 or >31; active endocarditis; myocardial infarction or stroke within 1 month; severe coronary artery disease that requires revascularization; presence of contraindications for anticoagulation. Notably, patients with left atrial thrombosis were not excluded from the cohort, as the transapical device would have little impact on the thrombosis comparing to transeptal devices.

Preprocedural Planning

All patients underwent clinical examinations, laboratory tests, echocardiography, and cardiac computed tomography before the procedure. The sizing of the J-valve was based on the label size of the previous bioprosthesis and the ring measurement on cardiac CT. Data on baseline characteristics, procedural details, and outcomes were retrospectively collected from the hospital information system. Transthoracic echocardiographic analysis was performed preoperatively, postoperatively, after implantation at 1 week and 1 month. Clinical follow-up was performed by the heart team at 1 month and 3months.

Device and Procedure

J-Valve^{TM} prosthetic valve (**Figure 1**) is originally a self-expanding TAVR device approved for both aortic stenosis and aortic regurgitation. Features of the J-Valve^{TM} system include a trifoliate porcine aortic valve, a self-expanding nitinol stent,

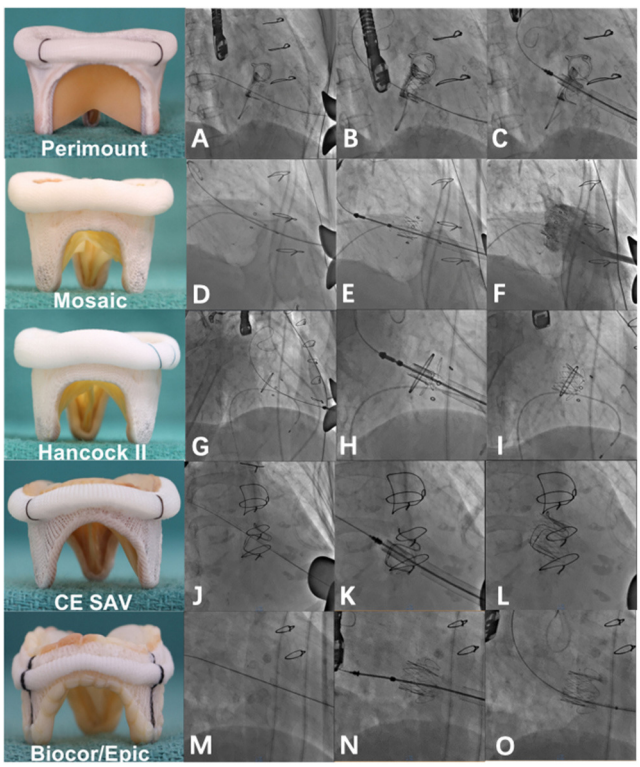

FIGURE 1 | Valve-in-valve implantation of a J-valve into different degenerated bioprosthetic valves. **(A)** A degenerated EDW Perimount mitral valve prosthesis under fluoroscopy. **(B)** J-valve deployment into a degenerated EDW Perimount mitral valve prosthesis. **(C)** Post-implantation. **(D–F)** Valve-in-valve implantation of a J-valve into a degenerated Mosaic prosthesis. **(G–I)** Valve-in-valve implantation of a J-valve into a degenerated Hancock II prosthesis. **(J–L)** Valve-in-valve implantation of a J-valve into a degenerated CE SAV prosthesis. **(M–O)** Valve-in-valve implantation of a J-valve into a degenerated Epic prosthesis. Note that there is no radiolucent marker on the Epic prosthesis.

three U-shaped anatomically oriented "graspers" for optimal positioning, and a polyester skirt covering the outer surface of the valve stent to minimize the risk of paravalvular leakage (21). The available sizes of the J-Valve were as follows: 21, 23, 25, 27, and 29 mm.

Transapical implantation of the J-Valve prosthesis was performed under general anesthesia by an interdisciplinary heart team in a hybrid operating room. The technique of the TMVIV procedure was similar to that of Lu et al. (18) and Wei et al. (19). All patients were kept on warfarin therapy with an INR goal of 2–3 for 3–6 months. Patients with atrial fibrillation received long-term warfarin for anticoagulation.

Definitions

We used standardized endpoint criteria according to the Mitral Valve Academic Research Consortium (MVARC) for the data collection (22).

Statistical Analysis

Statistical analysis was performed using the SPSS 20 (IBM, Armonk, NY, USA). After the normality test, continuous variables with normal distribution were described as mean (± standard deviation of the mean), and continuous variables without normal distribution were described as median (interquartile range, IQR). Categorical data were described as numbers (percentage). A value of $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

From April 2019 to September 2021, 17 patients underwent transapical TMVIV procedures in our institution (**Table 1**). The median age of the patients was 70 years (IQR 9), with 76.5% (13/17 being female. All patients were symptomatic with New York Heart Association (NYHA) class III (17.6%)/IV (82.4%) heart failure. All patients were deemed unsuitable for conventional redo mitral valve replacement surgery by our heart team due to extreme surgical risk, with a median Society of Thoracic Surgeons predicted risk of mortality (STS PROM) of 17.2% (IQR 27.4, range 8.7–82.2%.) and median Euroscore II of 24.7 (IQR 31.6). Our patient cohort even included some critical patients. Seven patients (41.2%) were hospitalized in the Intensive Care Unit (ICU) before the procedure, and 4 of those (23.6%) were intubated. One patient had a cardiac arrest 2 days before the procedure, and she was on Extracorporeal Membrane Oxygenation (ECMO) and Continuous Renal Replacement Therapy (CRRT) support. Compassionate emergency surgery was performed on these 7 critical patients in ICU, while the other 10 patients received elective surgery.

A variety of mitral bioprosthesis failed in our patient cohort 5–15 years after implantation, with a median time from the previous procedure of 10 years (IQR 5). The mechanism of bioprosthetic valvular dysfunction was secondary to severe mitral regurgitation in 64.7% ($n = 11$) and stenosis in 23.5% ($n = 4$) patients. Two patients had combined regurgitation and stenosis. The median left ventricular ejection fraction (LVEF) was 70% (IQR 7). Median mitral inflow velocity was 2.7 mm/s (IQR 0.5), and median

TABLE 1 | Baseline characteristics and procedural outcomes.

		***N* = 17**
Demographics	Age (years)	70 (9)
	Female (%)	13 (76.5%)
Medical history	Hypertension	4 (23.4%)
	Diabetes mellitus	10 (58.8%)
	Coronary artery disease	4 (23.5%)
	Pulmonary hypertension	13 (76.5%)
	History of heart failure	11 (64.7%)
	Atrial fibrillation	14 (82.4%)
	Pre-operation intubation	4 (23.5%)
	ICU hospitalization	7 (41.2%)
	Tricuspid regurgitation moderate or higher	12 (70.6%)
NYHA class	III	3 (17.6%)
	IV	14 (82.4%)
Risk score	Euroscore II	24.7 (31.6)
	STS	17.2 (27.4)
Mechanism of mitral valve failure	Regurgitation	11 (64.7%)
	Stenosis	4 (23.5%)
	Combined	2 (11.8%)
Previous procedure	Previous MVR (%)	10 (58.8%)
	Previous DVR (%)	7 (41.2%)
	Time from previous procedure (years)	10 (5)
	Previous mitral bioprosthesis size (mm)	25 (2)
Previous Device type	Hancock II	6 (35.2%)
	Epic	4 (23.6%)
	CE SAV	1 (5.9%)
	Mosaic	4 (23.6%)
	EDW Perimount	2 (11.8%)
Procedural details	Transapical access	17 (100%)
	TMVIV	13 (76.5%)
	TMVIV+TAVR	2 (11.8%)
	TMVIV+TAVIV	2 (11.8%)
	Replacing J-valve size (mm)	23 (2)
	Balloon pre-dilatation	4 (23.5%)
	Balloon post-dilatation	14 (82.4%)
	Device success	17 (100%)
	Procedural Success	16 (94.1%)
	Total procedure time (min)	82 (27)
	Fluoroscopy time	10.9 (6.4)
	Contrast dose (ml)	0 (34)
Procedural outcomes	Device success	17 (100%)
	Procedural Success	16 (94.1%)
	Prolonged ventilation, >24 h	6 (35.3%)
	Reintubation	2 (11.8%)
	Tracheotomy	3 (17.6%)
	Conversion to conventional surgery	0 (0%)
	LVOT obstruction	0 (0%)
	Valve embolization	0 (0%)
	Need for second valve implantation	0 (0%)
	Left ventricular perforation	1 (5.9%)
	Re-intervention	0 (0%)

(Continued)

TABLE 1 | Continued

		N = 17
30-day outcomes ($n = 15$)	Mitral inflow velocity (mm/s)	2.7 (0.5)
	Mitral valve EOA (cm^2)	1.5 (1.2)
	Bleeding complication	1 (5.9%)
	NYHA class ≥ III	3 (20%)
	Stroke	0 (0%)
	New complete heart block	0 (0%)
	Procedure-related death	1 (5.9%)

ICU, intensive care unit; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; MVR, mitral valve replacement; DVR, aortic and mitral valve replacement; TAVR, transcatheter aortic valve implantation; TAVIV, transcatheter aortic valve-in-valve implantation; TMVIV, transcatheter mitral valve-in-valve implantation; LVOT, left ventricle outflow tract; EOA, effective orifice area.

mitral valve EOA was 1.5 cm^2 (IQR 1.2). Twelve patients (71.6%) had moderate or severe tricuspid regurgitation. Seven patients (41.2%) had previous DVR (double valve replacement, i.e., aortic and mitral valve replacement). Six patients (35.2%) implanted Hancock II bioprosthesis, 4 patients (23.6%) implanted Epic, 4 patients (23.6%) implanted Mosaic, 2 patients (11.8%) implanted Edwards Perimount, and 1 patient (5.9%) implanted CE SAV. The median size of the previous mitral bioprosthesis was 25 mm (IQR 2).

Procedural Outcomes

All 17 patients had transapical TMVIV using J-valve, among which 2 patients (11.8%) had combined TAVR and 2 patients (11.8%) had combined valve-in-valve TAVR using J-valve. The median size of the J-valve was 23 mm (IQR 2). Balloon pre-dilatation was performed in 4 patients (23.5%), and balloon post-dilatation was performed in 14 patients (82.4%). One patient died immediately after balloon post-dilation due to left ventricular perforation. We presumed that the long stent of the Hancock II prosthesis was pushed to the left ventricle posterior wall during balloon post-dilation, leading to ventricular rupture. However, this presumption was not confirmed because the family refused an autopsy. Procedural success was achieved in the other 16 patients (94.1%). The median procedural time was 82 min (IQR 27). All patients are free from stroke, new complete heart block, LVOT obstruction, or valve embolization after the procedure. One patient had a bleeding complication. Six patients (35.3%) had prolonged ventilation over 24 h.

The first patient in our cohort was admitted to ICU before the procedure, and he had poor ventilation requiring intubation. After the procedure, the patient had reintubation with a tracheotomy. The patient had a prolonged intensive care unit stay of 16 days and died on day 25 due to in-hospital pneumonia. There was no other in-hospital mortality except for one intraoperative mortality described above. No patient was lost to follow-up at 90 days. Overall, 30-day mortality was 11.8% (2/17). One patient died 75 days after the procedure due to sudden cardiac death. Another patient died 90 days post-procedure due to cerebral hemorrhage. Overall, 90 days mortality was 23.5% (4/17). There was no other mortality at the last follow-up. No reintervention, conversion to conventional surgery, second valve implantation, or IABP was required.

Hemodynamic Performance

Median mitral inflow velocity decreases from 2.7 mm/s (IQR 0.5) at baseline to 1.8 mm/s (IQR 0.5) 1-week post-procedure. At 30-days follow-up, the median mitral inflow velocity was 1.95 mm/s (IQR 0.5). Median mitral valve EOA increases to 2.1 cm^2 (IQR 0.6) 1 week post-procedure, compared to a baseline level of 1.5 cm^2 (IQR 1.2). The percentage of patients with NYHA functional class III and IV decreased from 100% before the procedure to 31.3% at 1 week and 20% 1 month after the procedure.

DISCUSSION

In this study, we report 17 cases of TMVIV using J-valve at West China Hospital, Chengdu, China. Our cohort included patients with higher risks (mean STS-PROM of 28.58 ± 19.96%) compared to the study from Lu et al. (18) (12.3 ± 8.3%) and Wei et al. (19) (12.03 ± 10.5%). More patients underwent concomitant TAVR or TAVIV (23.5%) in our cohort. The 30-day mortality (11.8%) was higher than what was reported in the above cohorts (0–3.8%), but it was still acceptable considering that 41.2% of our patients were hospitalized in ICU, and 23.5% were intubated, and one was on ECMO before the procedure. Our patients had a high burden of comorbidities at baseline (58.8% with diabetes mellitus, 64.7% with a history of heart failure, 82.4% with atrial fibrillation, 76.5% with pulmonary hypertension, and 52.9% with renal insufficiency), and yet the median post-operative hospitalization days (8 days) were comparable to the results in the above studies.

Mitral inflow velocity (mm/s) decreased from 2.7 (0.5) to 1.95 (0.5) mm/s at 30-days, and the mitral valve EOA (cm^2) increased from 1.5 (1.2) to 1.85 (0.6) cm^2. Improvement in clinical symptoms has been shown in our cohort, as the percentage of patients with NYHA functional class III and IV decreased from 100% before the procedure to 31.3% at 1 week and 20% at 1 month after the procedure, indicating that the left ventricular ejection may have appeared to be better than it was before MR correction, which is consistent with the report of previous studies (23–25). A significant and immediate reduction in pulmonary artery pressure following TMVIV implantation was observed 1 week following implantation, and the effect was continuing at a 1-month follow-up. Considering the high incidence of chronic lung disease (94.1%) in our cohort, correction of MR plays an important role in relieving pulmonary hypertension. We also observed a decrease in the percentage of patients with moderated or severe tricuspid regurgitation, from 12 (70.6%) to 5(33%) at 30 days, which may be the consequence of reduced pulmonary arterial pressure. Medvedofsky et al. (26) reported tricuspid regurgitation regression in patients with pulmonary hypertension in association with a remarkable right ventricular reverse remodeling. Sadeghi et al. (27) reported TR regression in patients undergoing successful pulmonary endarterectomy, frequently occurring despite persistent TA dilation and no change in valve coaptation. Our finding was consistent with

their conclusion that functional tricuspid regurgitation may be reversed after pulmonary arterial pressure reduction. Therefore, indications for concomitant tricuspid valve intervention should be reconsidered in our cohort with 76.5% (13/17) of the patient being pulmonary hypertensive.

Importantly, significant paravalvular regurgitation was not observed following valve-in-valve implantation into mitral surgical bioprosthesis. 88.2 and 76.5% of our high-risk elderly patients were alive and well at 30-days and 90-days, respectively. One patient died intraoperatively due to left ventricular rupture during post-dilation. One patient was frail at baseline, and he died 25 days post-procedure due to a pulmonary infection. Another two patients died of sudden cardiac death and cerebrovascular hemorrhage at 75 and 90 days, respectively. Our experience with these mortality cases highlights the importance of careful decision-making when selecting very high-risk patients, and that balloon valvuloplasty should be adopted with discretion. In addition, we presumed that the long stent of the Hancock II prosthesis was pushed to the left ventricle posterior wall during balloon post-dilation, leading to ventricular rupture. This reminds cardiac surgeons not to implant the surgical bioprosthesis stent in proximity to the left ventricle posterior wall. The adverse event rate was low, and most patients have discharged within 14 days post-procedure. No structural failure of transcatheter valves or valve reoperation was observed in our relatively short follow-up. However, studies in a larger cohort with a longer follow-up are needed in the future.

We adopted transapical access in all procedures, which allows a short, direct, and coaxial route for TMVIV. Nevertheless, studies from Yoon et al. (17) showed that the procedural and clinical outcomes of the transseptal approach were comparable to those of the transapical approach, except for the more frequent requirement of closure of the iatrogenic atrial septal defect. The transapical route also allows an integrated solution to concomitant TAVR or valve-in-valve TAVR, which was performed in 4 (23.5%) patients. Also, the price and reimbursement policies make J-valve a more affordable choice compared to Sapien 3 in China. J-valve was the only commercially available device for transcatheter mitral valve replacement in China until Sapien 3 (Edwards Lifesciences) was approved by China National Medical Products Administration in June 2021. Besides a lack of experience in transseptal TMVR, the presence of a thickened fibrotic septum due to previous surgical intervention was another reason why the author favored the transapical route over the transeptal approach after reviewing the surgical records, which documented septum incision and sutures in most cases. In addition, a few patients in our cohort had left atrial thrombus identified before or during the procedure, which mandates transapical access.

CONCLUSION

Transapical TMVIV is a feasible and reproducible procedure. Our early experience with this strategy using J-valve is encouraging.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by West China Hospital Ethics Committees and Institutional Review Board, Sichuan, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL and BX: conception and design, data analysis, and interpretation. YG: administrative support. LL, BX, and BW: collection and assembly of data. All authors wrote the manuscript and approved the final manuscript.

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Mortality and Clinical Predictors After Percutaneous Mitral Valve Repair for Secondary Mitral Regurgitation: A Systematic Review and Meta-Regression Analysis

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Background: Percutaneous mitral valve repair (PMVR) provides an available choice for patients suffering from secondary mitral regurgitation (SMR), especially those whose symptoms persist after optimal, conventional, heart-failure therapy. However, conflicting results from clinical trials have created a problem in identifying patients who will benefit the most from PMVR.

Objective: To pool mortality data and assess clinical predictors after PMVR among patients with SMR. To this end, subgroup and meta-regression analyses were additionally performed.

Methods: We searched PubMed, EMBASE, and Cochrane databases, and 13 studies were finally included for meta-analysis. Estimated mortality and 95% confidence intervals (CIs) were obtained using a random-effects proportional meta-analysis. We also carried out a meta-regression analysis to clarify the potential influence of important covariates on mortality.

Results: A total of 1,259 patients with SMR who had undergone PMVR were enrolled in our meta-analysis. The long-term estimated pooled mortality of PMVR was 19.3% (95% CI: 13.6–25.1). Meta-regression analysis showed that mortality was directly proportional to cardiac resynchronization therapy (CRT) ($\beta = 0.009$; 95% CI: 0.002–0.016; $p = 0.009$), an effective regurgitant orifice (ERO) ($\beta = 0.009$; 95% CI: 0.000–0.018; $p = 0.047$), and a mineralocorticoid receptor antagonist (MRA) use ($\beta = -0.015$; 95% CI: −0.023–−0.006; $p < 0.001$). Subgroup analysis indicated that patients with preexisting AF ($\beta = -0.002$; 95% CI: −0.005– −0.000; $p = 0.018$) were associated with decreased mortality if they received a mitral annuloplasty device. Among the edge-to-edge repair device group, a higher left ventricular (LV) ejection fraction, or lower LV end-systolic diameter, LV end-systolic volume, and LV end-diastolic volume were proportional to lower mortality.

Conclusion and Relevance: The pooled mortality of PMVR was 19.3% (95% CI: 13.6–25.1). Further meta-regression indicated that AF was associated with a better outcome in conjunction with the use of a mitral annuloplasty device, while better LV functioning predicted a better outcome after the implantation of an edge-to-edge repair device.

Keywords: secondary mitral regurgitation, percutaneous mitral valve repair, atrial fibrillation, left ventricular function, predictor

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INTRODUCTION

Secondary mitral regurgitation (SMR), which is most commonly seen in dilated or ischaemic cardiomyopathies, is associated with significantly poor clinical outcomes and quality of life (1, 2). Although optimal medical therapy may be prescribed, symptoms of heart failure cannot be relieved in certain patients. Surgical mitral valve intervention is still recommended for patients at low surgical risk or for those without advanced left ventricular remodeling (3, 4). However, few therapeutic alternatives have been shown to lower the rate of hospitalization or death in the high-risk group.

The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial (5) and its 3-year follow-up results (6) confirm that percutaneous mitral valve repair (PMVR) is a feasible treatment for moderate-to-severe or severe SMR. Conflicting conclusions from the MITRA-FR (The Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trials (7, 8) render the benefit of PMVR debatable. It appears that a select population fulfilling COAPT inclusion criteria may benefit from PMVR (9, 10).

Long-term follow-up outcomes from the COAPT and MITRA-FR trials, and other recent research, including those providing extra data or using new transcatheter systems, provided us with a tremendous opportunity to pool all the evidence of PMVR for patients with SMR. As it is necessary to recognize patients who might benefit from PMVR the most, a meta-analysis and meta-regression were performed to identify these clinical predictors.

METHODS

We registered our meta-analysis in the International Prospective Register of Systematic Review (CRD42022321423), and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was used to design our manuscript (**Supplementary Material 1**).

Study Selection Criteria

Clinical research evaluating the safety and efficacy of PMVR for patients with SMR was considered for our meta-analysis. The inclusion criteria for our study included (1) patients who had severe SMR still suffered heart failure symptoms when optimal medical therapy was prescribed, (2) provided mortality and available baseline characteristic data, and (3) at least one transcatheter device was studied. We excluded review articles, duplicate studies or data, human *in vivo* experiments, and echocardiographic studies were not reviewed for inclusion (detailed information can be found in **Figure 1**). No language, publication date, or publication status restrictions were applied. References of prior systematic reviews and meta-analyses for related studies were also screened.

Search Strategy and Information Sources

We used keywords related to *secondary or functional mitral regurgitation*, *transcatheter mitral valve repair*, *MitraClip*, and *mitral annuloplasty device* to search PubMed, EMBASE, and Cochrane databases through the final search date of 30 December 2021 (detailed information for search strategy can be found in **Supplementary Material 2**).

Two reviewers performed a systematic review, and disagreements were resolved in a panel discussion by 3 reviewers. Study selection involved screening of titles and abstracts followed by a full-text evaluation of possible eligible studies.

Assessment of the Risk of Bias

Two independent reviewers performed the qualitative assessment and bias (low, intermediate, or high) using the Cochrane Collaboration tool (in **Supplementary Material 3**). Given that part of the enrolled studies were single-arm designs, the risk of publication bias was not assessed.

Endpoint and Data Collection Process

Mortality was the only endpoint in our meta-analysis. Two reviewers independently extracted data on the study design and PMVR device (**Table 1**), and baseline characteristics are summarized in **Supplementary Material 4**. Any discrepancies between the 2 reviewers were resolved through discussion.

Statistical Analysis

We directly performed a binary random-effects proportional meta-analysis to obtain the pooled estimates of mortality and 95% confidence intervals (CIs) of included studies. Statistical heterogeneity among studies was examined using the Cochran Q statistic and the I2 statistic, with I2 being considered substantial when it was >50% (22). Leave-one-out sensitivity analysis was conducted to evaluate the key studies with substantial influence on heterogeneity (23). Meta-regression analysis was carried out to assess the potential influence of important covariates on between-study heterogeneity (significance at $P \leq 0.05$), (24) and these models were applied to clarify whether the coexistence of these covariates explained the variability in effect estimates across all included studies for mortality. We also performed an additional sensitivity analysis to demonstrate the difference between edge-to-edge mitral valve repair devices and mitral annuloplasty devices. All data analyses were performed using statistical software. OpenMetaAnalyst (version 10.12) and RevMan (version 5.4) were used.

RESULTS

Characteristics of Included Studies

Finally, 1,259 patients with SMR from 13 studies, including 3 randomized trials [COAPT (6), MITRA-FR (8), and REDUCE FMR (13)], 6 single-arm studies [CLASP (11), MAVERIC (12), David Messika-Zeitou (14), Georg Nickenig (18), PTOLEMY-2 (19), and EVOLUTION (21)], and 4 prospective trials [Cristinia Giannini (15), Asgar (16), Patrizio Armeni (17), and TITAN (20)] were involved in our meta-analysis. Among these studies,

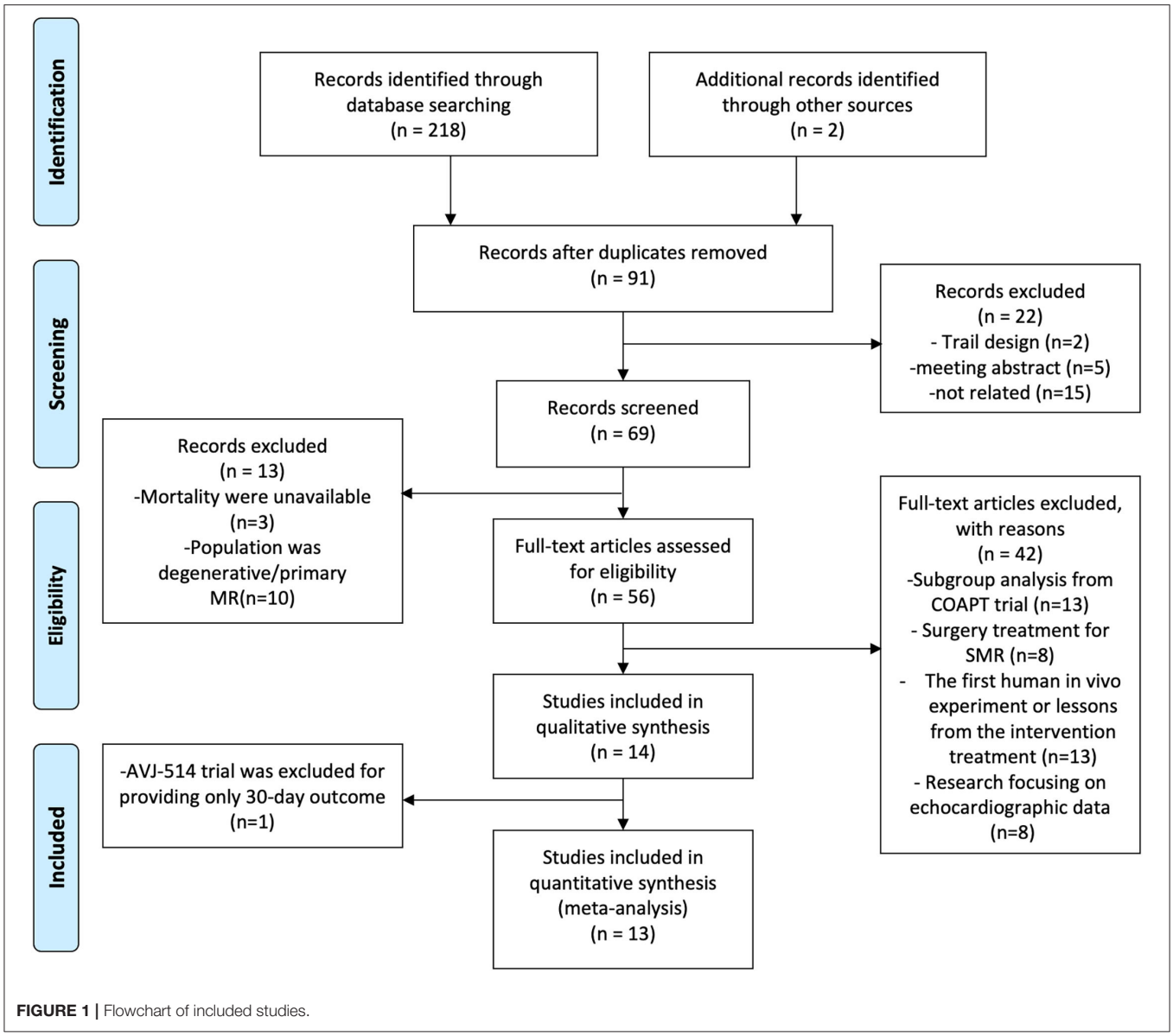

FIGURE 1 | Flowchart of included studies.

edge-to-edge repair devices were analyzed in 6 studies (CLASP, COAPT, MITRA-FR, Cristinia Giannini, Asgar, and Patrizio Armeni), while mitral annuloplasty devices were used in the other 7 studies. Detailed information on the characteristics of included studies is shown in **Table 1**.

Baseline Characteristics of Included Cohorts

Demographic data, functional characteristics, history, echocardiography parameters, and medication history are summarized in **Supplementary Material 4**. The mean age of the enrolled population was 71.02, and 68.45% of them were men. As to the pathogenesis of SMR, ischemic diseases accounted for 59.37%.

Pooled Mortality

The long-term estimated pooled mortality of PMVR was 19.3% (95% CI: 13.6–25.1) (**Figure 2**). A subgroup analysis was conducted to obtain the mortality associated with edge-to-edge mitral valve repair devices (23.9% [95% CI: 14.2–33.7]) and mitral annuloplasty devices (14.0% [95% CI: 10.5–17.4]), respectively (**Figure 3**). Leave-one-out sensitivity analysis is shown in **Supplementary Material 5**.

Meta-Regression Analysis

A meta-regression analysis was performed to assess the impact of potential baseline characteristics on pooled mortality. As shown in **Table 2** and **Figure 4**, mortality is directly proportional to CRT therapy, ERO, and MRA use. There was a significant increase in mortality in patients with CRT therapy ($\beta = 0.009$; 95% CI: 0.002–0.016; $p = 0.009$) and larger ERO ($\beta = 0.009$; 95% CI:

TABLE 1 | Information of included studies.

Study	Year	Clinical trial number	Study design	Device	Follow-up
CLASP (11)	2021	NCT03170349	Multicenter, multinational, prospective, single-arm study	PASCAL repair system	2-Year
MAVERIC (12)	2021	NCT03311295	International multicenter, prospective, single arm	ARTO system	2-Year
COAPT (6)	2021	NCT01626079	Randomized, parallel-controlled, open-label multicenter trial	MitraClip device	3-Year
MITRA-FR (8)	2019	NCT01920698	Randomized, open-label multicenter trial	MitraClip device	2-Year
REDUCE FMR (13)	2019	NCT02325830	Blinded, randomized, proof-of-concept, sham-controlled trial	Carillon mitral contour system	1-Year
Messika-Zeitou et al. (14)	2018	NCT01841554	Single-arm, prospective multicentre trial	Cardioband mitral system	1-Year
Giannini et al. (15)	2016		Propensity-matched cohort trial	MitraClip	3-Year
Asgar et al. (16)	2016		Two phases, propensity matched observational study	MitraClip	1-Year
Armeni et al. (17)	2016		Retrospective, nonrandomized, propensity matched observational study	MitraClip	1-Year
Nickenig et al. (18)	2016	NCT01841554	Single-arm, multicenter, prospective trial	Cardioband system	6-Month
PTOLEMY-2 (19)	2013	NCT00787293	Prospective multicenter phase I single-arm feasibility trial	Second-generation permanent percutaneous transvenous mitral annuloplasty (PTMA) device	1-Year
TITAN (20)	2012		Prospective, non-randomized, non-blinded, multicenter trial	Carillon Mitral Contour System	1-Year
EVOLUTION (21)	2011		Multicenter, phase I single-arm trial	MONARC device	1-Year

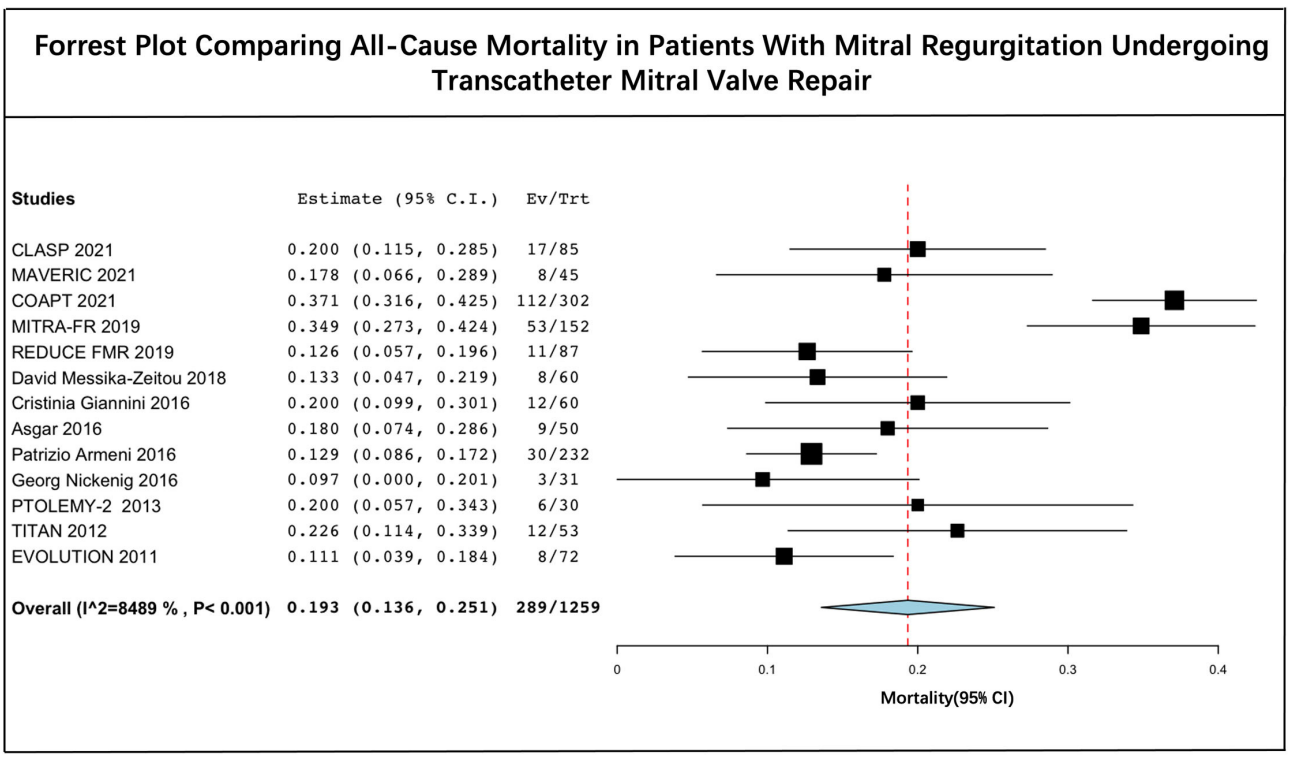

FIGURE 2 | Forrest plot comparing all-cause mortality in patients with mitral regurgitation undergoing transcatheter mitral valve repair.

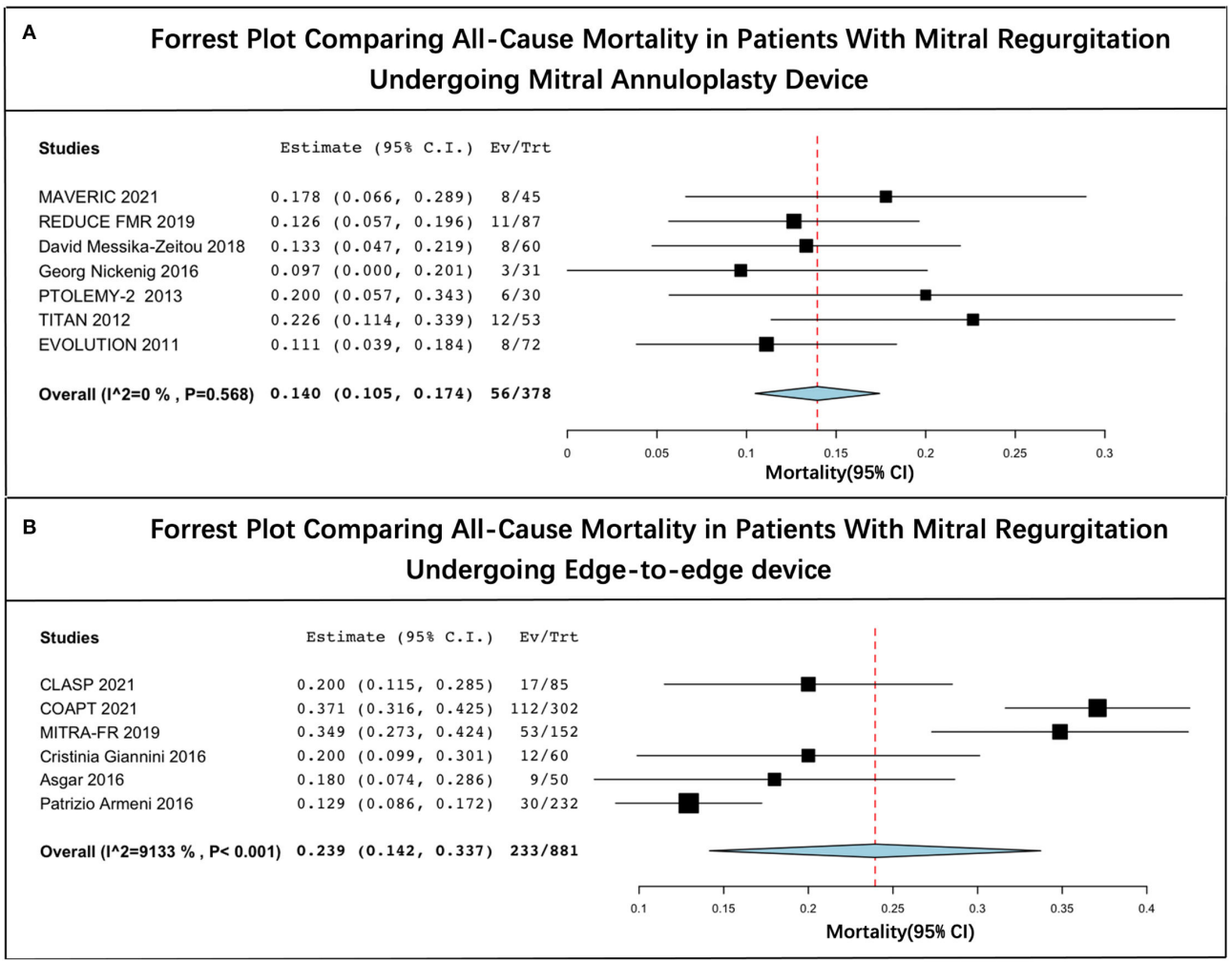

FIGURE 3 | Forrest plot of subgroup analysis. **(A)** Forrest plot comparing all-cause mortality in patients with mitral regurgitation undergoing mitral annuloplasty device and **(B)** forrest plot comparing all-cause mortality in patients with mitral regurgitation undergoing edge-to-edge device.

TABLE 2 | Meta-regression analysis for all-cause mortality in all patients.

Variable	No. of estimates	Univariate			Multivariate
		β Coefficient (95% CI)	*P*-value	Figure	
CRT (%)	8/13	0.009 (0.002–0.016)	0.009	**Figure 4A**	NE
ERO (mm^2)	7/13	0.009 (0.000–0.018)	0.047	**Figure 4B**	NE
MRA (%)	6/13	−0.015 (−0.023– −0.006)	<0.001	**Figure 4C**	NE

CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice area; MRA, mineralocorticoid receptor antagonist; NE, not entered into multivariate meta-regression analysis.

0.000–0.018; $p = 0.047$), while a decrease in patients prescribed MRA ($\beta = -0.015$; 95% CI: −0.023– −0.006; $p < 0.001$).

The subgroup analysis indicated that patients with preexisting AF ($\beta = -0.002$; 95% CI: −0.005– −0.000; $p = 0.018$) were associated with lower mortality if they had been subjected to a mitral annuloplasty device (**Table 3A**). Among those treated with an edge-to-edge repair device, the results were similar to CRT therapy and MRA. Further baseline characteristics revealing statistical significance were also identified (**Table 3B**).

DISCUSSION

Former meta-analyses demonstrated that, with regard to optimal medical treatment, PMVR is likely to be an efficacious and safe option (25, 26). Recently, new concepts and devices have, however, provided disparate evidence on this topic, rendering it necessary to reevaluate the effect of PMVR.

To the best of our knowledge, this is the largest and most advanced meta-analysis to date. Follow-up mortality among

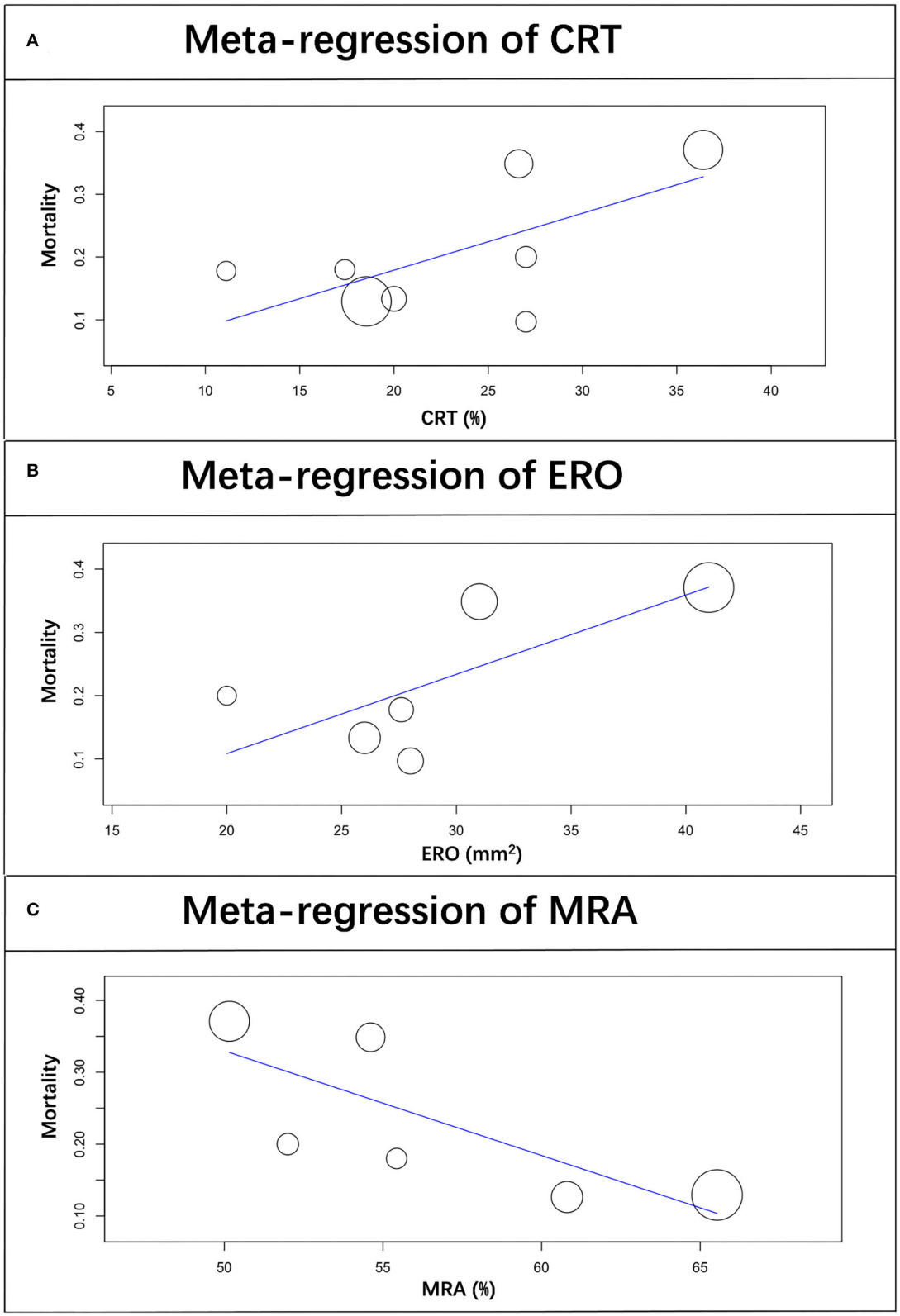

FIGURE 4 | Scatterplot showing the relationship between mortality and CRT therapy **(A)**, ERO **(B)**, and MRA prescription **(C)** in patients with SMR undergoing PMVR. The size of each point correlates with the number of patients in each included study.

TABLE 3 | Subgroup meta-regression analysis for all-cause mortality in mitral annuloplasty device **(A)** and edge-to-edge repair device **(B)**.

Variable	No. of estimates	Univariate			Multivariate
		β Coefficient (95% CI)	*P*-value	Figure	
(A): Results for mitral annuloplasty device					
AF (%)	5/7	−0.002 (−0.005 to −0.000)	0.018	**Supplementary Material 6A**	NE
(B): Results for edge-to-edge repair device					
CRT (%)	5/6	0.013 (0.007–0.018)	<0.001	**Supplementary Material 6B**	NE
MRA (%)	5/6	−0.013 (−0.022– −0.005)	0.003	**Supplementary Material 6C**	NE
BMI(kg/m2)	3/6	0.114 (0.042–0.186)	0.002	**Supplementary Material 6D**	NE
LVEF (%)	6/6	−0.050 (−0.101– −0.001)	0.046	**Supplementary Material 6E**	NE
LVESD (cm)	3/6	0.457 (0.229–0.686)	<0.001	**Supplementary Material 6F**	NE
LVESV (ml)	3/6	0.007 (0.003–0.010)	<0.001	**Supplementary Material 6G**	NE
LVEDV(ml)	3/6	0.013 (0.007–0.020)	<0.001	**Supplementary Material 6H**	NE

AF, atrial fibrillation; CRT, cardiac resynchronization therapy; MRA, mineralocorticoid receptor antagonist; BMI, body mass index; LVESD, LV end-systolic diameter; LVESV, LV end-systolic volume; LVEDV, LV end-diastolic volume; NE, not entered into multivariate meta-regression analysis.

patients with SMR after PMVR has been evaluated, and the estimated pooled mortality is 19.3%, with a 95% CI ranging from 13.0 to 25.5%. However, the I^2 statistic showed significant heterogeneity among studies. Further leave-one-out analysis and subgroup analysis indicated that the COAPT and MITRA-FR trials were the main sources of heterogeneity. COAPT and MITRA-FR trials were the first two randomized trials to evaluate the efficacy of PMVR in symptomatic patients with severe secondary mitral regurgitation using optimal medical therapy in accordance with guidelines. Their contradictory conclusions generated additional thought with regard to the selection of specific patients who could benefit the most from PMVR. We, therefore, conducted this meta-analysis to detect potential clinical factors associated with mortality by meta-regression.

In the past, EROA has been recognized as a strong predictor of mortality in mitral regurgitation (27). PMVR changes this conclusion. An echocardiographic analysis (28) from a COAPT trial indicated that greater ERO led to adverse outcomes during follow-up, as observed in optimal medical therapy patients, and showed no significant prognostic value among patients undergoing PMVR. Similarly, Nicole's research (29) affirmed that groups with different baseline EROs exhibited relevant clinical improvements after TMVR. We found, however, that ERO was positively associated with mortality after PMVR, a finding which contradicts the results of individual studies. A meta-regression is an efficient way of detecting potential variates with heterogeneity. Unfortunately, we failed to perform multivariate regression analyses for a limited number of baseline characteristics. This may have affected our conclusions as a result of unadjusted bias. Further research should, therefore, be conducted to clarify the association between ERO and mortality after PMVR.

Each article claims that all enrolled patients had undergone the optimal medical therapy. We noticed that guideline-recommended drugs for heart failure (30) were not fully prescribed. Hyperkalaemia is a major concern for cessation of MRA and our meta-regression analysis indicated that MRA was associated with better outcomes. Patiromer, a novel potassium binder, has been proven to improve adherence to MRA (31). It is hoped that this clinical trial increases the use of guideline-recommended drugs for heart failure.

Although subgroup analysis of a COAPT trial (32) suggested that MitraClip could decrease the 2-year mortality rate, regardless of prior CRT implantations, our meta-regression results from pooled data showed that CRT might be associated with poor prognosis. CRT and maximally tolerated guideline-directed medical therapy were preferential to PMVR, and CRT was especially recommended in patients with LVEF $\leq$35% (4, 30). However, HF symptoms and moderate-severe or severe SMRs persist or worsen in 30–40% of patients after CRT implantation, which means a poor long-term prognosis (33). This indicates that among patients with worsening cardiac functions, rigid adherence to guidelines may lead them to miss the optimal timing of PMVR, resulting in a reduced benefit. Therefore, further research is necessary to prove that PMVR should be prioritized over CRT, especially in patients with better cardiac function.

Subgroup analysis according to different treatment strategies provides us with a perspective to better understand the underlying factors affecting prognosis and the mechanism of SMR. The concept of atrial functional MR (AFMR) is becoming well-accepted with reference to patients with AF suffering significant mitral regurgitation without LV systolic dysfunction (34). Although the underlying mechanism is not well-clarified, impaired mitral annulus dynamics seem to contribute more than LA remodeling (35, 36). AF is an independent negative predictor of long-term mortality among patients with MitraClip implantations (26, 37, 38). Our sub-analysis of patients who were treated with a mitral annuloplasty device demonstrated that patients with AF benefited the most. To the best of our knowledge, this finding was first reported in our study. This also emphasizes that the pathogenesis of AFMR is related to the mitral annulus, and ring annuloplasty can improve the prognosis of these patients (39).

We identified LVEF as a positive variate associated with lower mortality among patients who had undergone the use of an edge-to-edge repair device. LVESD, LVESV, and LVEDV were identified as negative variates, suggesting that patients with poor

cardiac function might not benefit from PMVR. A former meta-analysis (40) of RCTs and propensity score-matched observation studies to assess the role of percutaneous mitral valve repair also indicated that a patient with a greater LVEDV at baseline was less likely to benefit from PMVR. Moreover, a *post-hoc* analysis from a COAPT trial also revealed that a higher baseline NYHA functional class was strongly associated with a greater risk for adverse events (41). Therefore, valve intervention is generally not recommended as an option when LVEF is <15% (30) in order to decrease the possibility of the reverse of LV remodeling.

LIMITATIONS

There are some limitations requiring attention. First, only 3 randomized data were enrolled, and the limitations of a retrospective study design could not be avoided. Second, because of the limited number of studies reporting the vital baseline characteristics, we were unable to conduct a meta-regression for these variates. We also failed to perform a multivariate regression analysis for the same reason, and confounding bias for the conclusion cannot be ignored. Third, although we discarded the data from the control group in controlled trials, data from single-arm designs may have resulted in bias in our meta-analysis. Nevertheless, meta-regression analysis is helpful in understanding heterogeneity and providing a perspective according to which patients may be stratified in terms of who may be best able to benefit from PMVR.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

WS: drafting of the manuscript, had full access to all of the data in the study, takes responsibility for the integrity of the data, and the accuracy of the data analysis. WS and CD: concept and design, statistical analysis, administrative, and technical or material support. WZ, DZ, and GY: acquisition and analysis or interpretation of data. WZ and CD: supervision. All authors: critical revision of the manuscript for important intellectual content.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.918712/full#supplementary-material

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Percutaneous mitral valve repair in patients developing severe mitral regurgitation early after an acute myocardial infarction: A review

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Acute mitral regurgitation (MR) may develop in the setting of an acute myocardial infarction (AMI) because of papillary muscle dysfunction or rupture. Severe acute MR in this scenario is a life-threatening complication associated with hemodynamic instability and pulmonary edema, and has been linked to a worse prognosis even after reperfusion. Patients treated solely with medical therapy have the highest mortality rates. Surgery has been the only treatment strategy until recently, but the results of the technique are hindered by high rates of morbidity and mortality. Therefore, the development of less invasive interventions for correcting MR would be ideal. We aimed to review the current role of transcatheter interventions in this clinical setting.

KEYWORDS

mitral regurgitation, myocardial infarction, transcatheter mitral valve (MV) repair, cardiogenic shock (CS), MitraClip®

Introduction

Acute mitral regurgitation (MR) may develop in the setting of an acute myocardial infarction (AMI) because of papillary muscle dysfunction or subvalvular apparatus rupture. This is a high-risk complication with a prevalence up to 3% of AMI patients. This condition is more common in patients presenting with hemodynamic instability or pulmonary edema, and is associated with an impaired prognosis even in the era of primary angioplasty (1–4). Anatomically, there are various types of lesions that may end up in the development of MR. Complete papillary muscle rupture is uncommon but is often fatal without rapid correction, leading the patient to cardiogenic shock (5). Acute MR without complete papillary muscular rupture may induce as well severe MR due to the combination of leaflet tethering and left ventricular dilation produced by an adverse remodeling pattern or partial papillary muscle rupture and can lead to recurrent heart

failure or cardiogenic shock (CS) during early after the event (6). The prevalence of the latter that may account for 35–55% of the cases, which means that severe MR without complete rupture is not so uncommon and may deteriorate patients' condition enough to require an intervention (4, 7). Surgery has been the standard of care until recently, but is associated with high rates of morbidity and mortality (up to 20–25%, in-hospital). Additionally, patients under isolated medical management present a dismal prognosis (8, 9). Therefore, the development of less invasive interventions for correcting MR in this scenario are appealing.

Scope of the problem: Prevalence and prognostic impact

In the setting of AMI, MR is a common finding, but the prevalence varies in different studies. Early angiographic studies report a prevalence of 12–19% with ventriculography performed within the first 16 days after the MI (10–12). In echocardiographic studies MR was observed in up to 50% of patients with AMI (4, 13–16). However, these prevalence studies have some limitations that must be pointed out. While some registries were performed in the era of fibrinolysis, in others PCI was the treatment of choice. Also, MR could be assessed in the first hours of the acute MI or echocardiography performed even 16 days after MI. Moreover, MR could be previously present and not be related to the acute coronary syndrome. Nevertheless, the prevalence reported is higher than the prevalence of MR in general population and therefore it can be assumed MR as a common complication of acute MI. The proportion of different degrees of ischemic MR is similar in patients with and without ST-segment elevation myocardial infarction submitted to PCI (4, 13). In the majority of studies, mild MR is by far more frequent and in a recent retrospective single-center study which included a thousand patients with AMI, mild MR was more frequent (76%), followed by moderate MR (21%) and severe (in 3% of patients) (13). Those elderly patients, female patients and with clinical evidence of heart failure present more frequently with greater MR grades (17–19). More severe MR also correlates with the presence of multivessel disease and lower left ventricular ejection fraction (LVEF) (11, 16, 19).

As previously mentioned, there are two mechanisms that may lead to development of MR early after MI. Papillary muscle rupture (partial or complete) is a life-threatening complication of AMI with a prevalence estimated of 1–3% (20, 21). This mechanical complication causes acute severe MR with acute volume overload, pulmonary edema and cardiogenic shock, with in-hospital mortality rate up to 80% in patients managed conservatively (22–24).

But MR may develop as well because of LV dilation and remodeling and leaflet tethering, resulting in an acute/subacute form of functional ischemic MR. This entity has also an impact on prognosis. Any degree of MR is independently associated with mortality in patients undergoing PCI for acute MI with a relationship between the MR severity and outcomes (3, 11). There is a correlation between ischemic MR severity and myocardial viability, with viable myocardial reducing LV remodeling and preventing development or worsening of MR. Importantly, early reperfusion with PCI in STEMI patients is associated with lower incidence of this type of ischemic MR (4, 25).

Imaging techniques

The diagnostic workup for patients developing MR after MI requires firstly a high index of suspicion, and, therefore echocardiography is paramount in the differentiation of the mechanism for the MR and excluding other causes for a new systolic murmur in patients developing heart failure postMI. In the acute MR setting left atrium is usually of normal size, and the sudden increase in left atrial pressure is transferred backwards into the pulmonary veins, causing a rapid developing pulmonary edema. This event may result as well in a poor transthoracic imaging window, and, subsequently requiring transesophageal echocardiography to confirm the presence and severity of MR.

Echocardiographic assessment should include careful assessment of LV (ejection fraction, dimensions and wall motion abnormalities), mitral valve structure (annulus, leaflets, chordae and papillary muscles), and quantitation of the degree of MR. An integrative approach to the evaluation of MR should be performed including qualitative, semi-quantitative and quantitative parameters according to imaging guidelines (26). Overall MR severity assessment, integrates LV size and function, left atrial size, impact on Doppler flows and predicted systolic pulmonary artery pressure. MR may also be a dynamic entity related to the occurrence of myocardial ischemia and may diminish or even disappear after it is corrected by PCI, so a re-assessment should be advisable after the revascularization.

Acute MR due to LV remodeling is a consequence of the loss in the normal spatial relationship between LV and the mitral valve complex. With adverse LV remodeling (dilatation and shape modification), one or both mitral leaflets are apically displaced into the LV and away from the center of the cavity due to the outward displacement of the papillary muscles. This pattern is best seen in the apical 3 and 4 chamber views. In this sub-entity, the leaflets are essentially normal and the mitral annulus may be dilated (primarily septal-lateral and to a lesser degree inter-commissural), although this is more frequent in non-acute MR setting. MR can develop both due to global or regional remodeling, but the specific remodeling site might be of relevance since inferior MIs are more likely to be associated with significant MR compared to anterior MIs. This is probably related to different tethering patterns. Most of the patients with

symmetric tethering have central jets, whereas patients with asymmetric tethering have posteriorly directed jets.

The most severe form of acute MR is papillary muscle rupture. Common two-dimensional echocardiographic features include a mitral leaflet flailing into left atrium together with severed chordae or a papillary muscle head bouncing within the left heart chambers. Complete avulsion of the papillary muscle is quite unfrequent in the primary PCI era, whereas a partial rupture or a tip rupture are more common. Posteromedial papillary muscle is more commonly affected than the anterolateral and this is related to the blood supply pattern. LV is frequently supranormal because of an abrupt decrease in afterload, and wall motion abnormalities can be undetected. Underestimation of the degree of MR by color Doppler is common due to the eccentricity of the jet. A summary of the types of MR after MI are shown in Figure 1.

In an acute setting, other imaging techniques such as cardiac computed tomography or cardiac magnetic resonance are less commonly performed. In a non-acute scenario, LV fibrosis location and extension, assessed by late gadolinium enhancement in cardiac magnetic resonance, have been related reverse remodeling or clinical outcomes in patients undergoing surgical or transcatheter mitral correction (27, 28).

Surgical treatment

Surgery has been the standard approach and the only option for patients who develop MR early after MI and who remain symptomatic despite revascularization until last years. The optimal surgical approach to this entity must take into consideration the mechanism underlying regurgitation. Papillary muscle rupture or ruptured chordae, causing severe acute MR is a very poorly tolerated condition, where prompt mitral valve surgery could be lifesaving. Even though urgent surgery with mechanical assistance after MI is supported due to the risk of abrupt decompensation, deferring intervention provides time for the development of fibrotic tissue and is associated with lower surgical mortality, especially in patients without initial hemodynamic instability neither fulfill criteria for shock (29, 30). One study identified a median time to surgery of seven days (7). Ultimately in patients with cardiogenic shock emergent surgery is linked to increased survival when is promptly performed (29). The 2020 ACC/AHA Guidelines for Valvular Heart Disease, recommend, if possible, mitral valve repair, especially if papillary muscle rupture is not complete and the tissue quality is suitable for repair (31). However, mitral valve replacement is more commonly performed because of greater reproducibility, and established durability in patients with a high adverse event rate (32). Surgical revascularization at the time of valve intervention does not seem to influence the acute postoperative course (33).

Although surgical interventions are associated with better outcomes than conservative management (8, 9), the results of the technique are blunted by a still high early mortality due to the performance of a significant aggressive procedure in patients with poor clinical condition and an ongoing ischemic/scarred myocardium. In a recent review of surgical series in acute MR, 8 series of cases reporting results on surgery vs. conservative management were analyzed (8). Overall early surgical mortality was 19.2%. Of course, is lower than the 51.4% reported in the medical arm, but it is still very high, taking into consideration that those patients included in these retrospective registries (since there is no randomized trial in this setting) are those who were selected to be operated and therefore, probably biased to have a better survival chance. Taking these facts into consideration, the development of new less aggressive interventional techniques to correct acute MR is really appealing.

Role of transcatheter interventions

The transcatheter options for MR treatment have grown exponentially during the last years. From all devices available, the edge-to-edge technique with the MitraClip system (Abbot Vascular, Santa Clara, USA) represents by far the most used and accumulates the larger clinical experience. The edge-to-edge repair (TEER) with MitraClip has been shown to be an efficacious device for correcting MR and it has been linked to clinical improvement both in primary and secondary MR (34–38). However, most MR cases are performed on patients in chronic and stable clinical situation, and, therefore, patients with acute MR are barely included in registries or randomized trials. Therefore, since acute MR represents a large unmet need in the development of less invasive treatments, the experience with TEER in this scenario has grown significantly in the last years.

The first experiences with MitraClip were case reports and small series of cases showing the feasibility of treating this complex scenario with a percutaneous device in both cases of subvalvular apparatus rupture or those more functional (39–44). In that series of extreme risk patients TEER was associated with significant clinical and hemodynamic improvement, setting the field for larger registries to come (Figure 2).

Subsequently, the IREMMI group published the larger series on the topic. The first paper was published in 2020 showing the European experience with MitraClip in this setting (45). Forty-four patients with a mean age of 70 ± 10.8 years were included between 2016 and 2018. Interestingly, median time between MI diagnosis and treatment was 18 days and between development of MR and treatment 12.5 days. Patients were highly symptomatic with 63.6% in NYHA IV at the moment of the procedure and 68.2% received acute mechanical reperfusion due to MI. Median EuroScore II was 15.1%, thus representing the high-risk of the cohort and 16 patients received mechanical

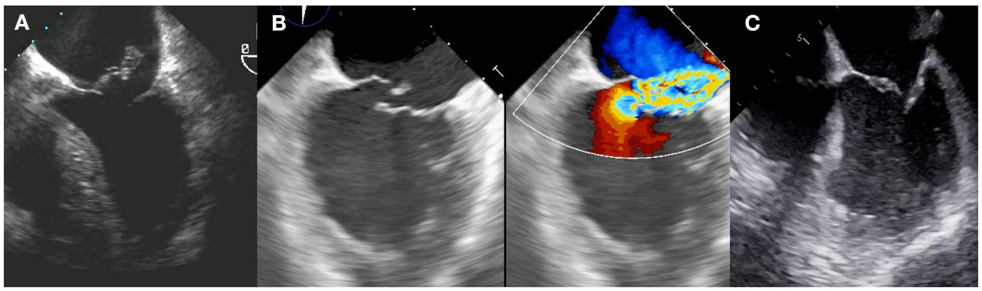

FIGURE 1
Types of postMI MR. **(A)** Complete papillary muscle rupture, with the papillary head flailing into left atrium. **(B)** Partial papillary muscle rupture. **(C)** Functional mechanism.

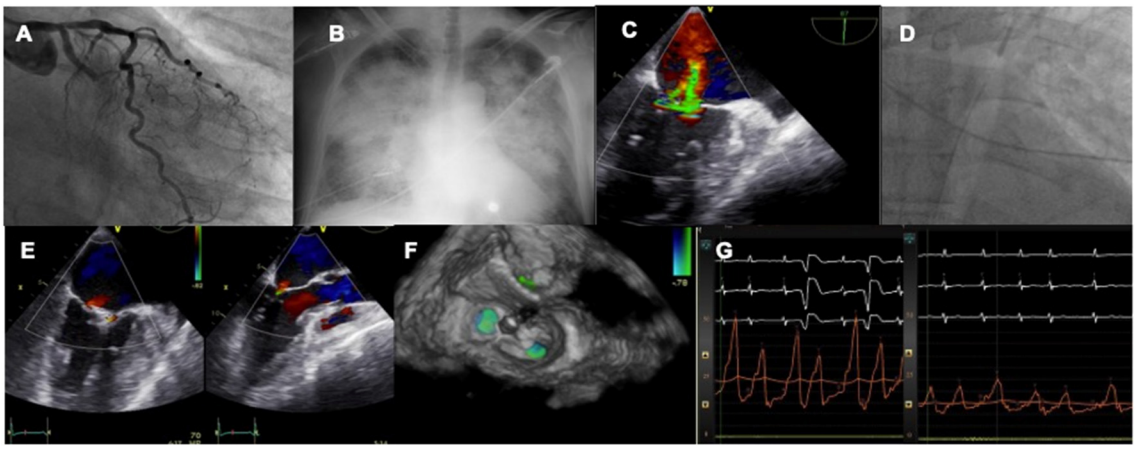

FIGURE 2
Case of acute MR after MI treated by TEER. A patient with LCX myocardial infarction **(A)** develops rapid pulmonary edema **(B)** and severe MR is diagnosed with echo **(C)**. An IABP is inserted to stabilize the clinical condition **(D)**. The valve is repaired with two MitraClip **(E,F)** leading to an acute drop in left atrial pressures **(G)**.

cardiac support (14 intraortic balloon pump, IABP, and 2 VA ECMO). In this series technical success was 86.6%. During follow-up, mortality at 30 days was 9.1%, representing a more than acceptable figure for such a high-risk cohort without surgical options. At 6-month MR $\leq 2+$ was noted in 72.5% and NYHA I–II was observed in 75.9% of surviving patients.

In the next registry authors investigated the role of cardiogenic shock (CS) in the outcomes of a cohort of 93 patients with TEER after acute MR due to MI (46). Ninety-three patients in this scenario were included in this investigation, mean age 70.3 $\pm$ 10.2 years, and with 53.8% deemed to be in CS at the time of MitraClip implantation. 66% of the patients in CS were under support with IABP/Impella and 12% under VA ECMO. Technical success was high and did not differ between groups. Interestingly, 30-day mortality, although higher in CS group, was not statistically significant between groups (10% CS vs. 2.3% non-CS; $p = 0.212$). It is relevant to point out that the mortality rate in those patients non in CS was extremely low, even for such a high-risk population. Likewise, the combined event mortality/re-hospitalization was comparable (28% CS vs. 25.6% non-CS; $p = 0.793$) and the MR reduction at 3-months was as well similar (Figure 3) after 7 months of follow-up.

Of interest, the only variable associated with clinical outcomes was the procedural success. Therefore, authors claimed that CS should not preclude a treatment with MitraClip in this group and the essential point is to have enough experience in the team to ensure an adequate result.

In another paper from the group, authors analyzed the effect of the left ventricular ejection fraction (LVEF) on outcomes of 105 patients receiving MitraClip for MR early after MI (47). Authors divided the cohort in a LVEF cut-off of 35%. Up to 1 year, mortality rates were comparable between groups (11 vs. 7%, $p = 0.51$ and 19 vs. 12%, $p = 0.49$) and neither was re-hospitalization rate at 3-month follow-up. Therefore, the positive effect of percutaneous treatment is sustained in those patients with lower ejection fractions.

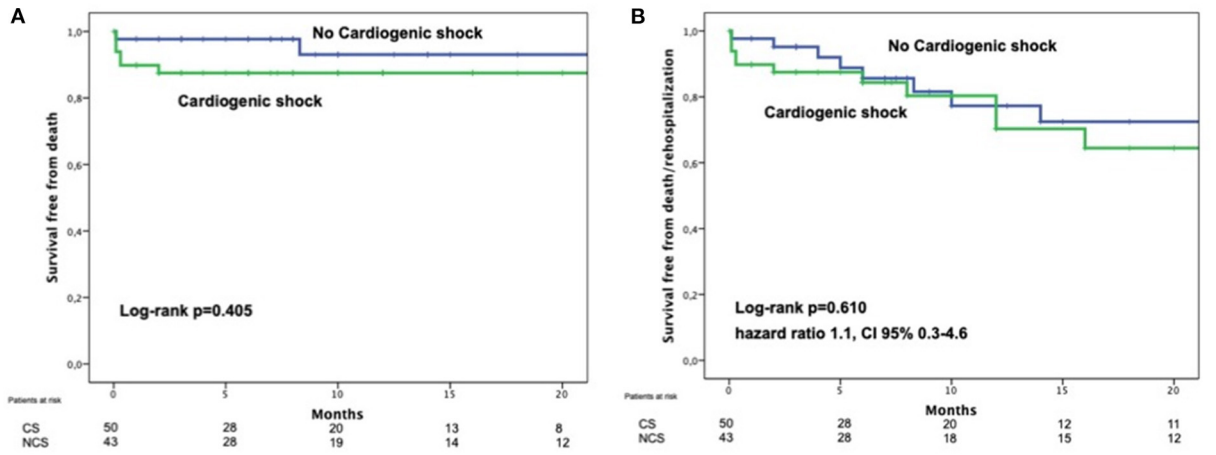

FIGURE 3
Comparison of survival free from death **(A)** or death and heart failure **(B)** of patients with postMI MR treated by TEER comparing those on cardiogenic shock with those who were not in cardiogenic shock. With permission from Haberman et al. (44).

Finally, the most comprehensive paper from the group compared three strategies of management of MR early after MI, conservative, surgical and TEER (9). A total of 471 patients were included in this registry (43% female, age 73 ± 11 years):266 were managed conservatively and 205 underwent interventions, of whom 106 were surgical management and 99 TEER. In line with previous surgical literature, those patients managed medically presented the worst outcomes with two-times more mortality than those who received an intervention. However, more interesting is the comparison of both interventional strategies. The article shows that those patients undergoing surgical correction presented worse outcomes than those receiving MitraClip, with a more than two-fold increase of mortality at 1 year. This difference was mainly driven by the mortality during hospitalization phase (16 vs. 6%, $p = 0.03$). And this finding was independent of the risk score profile of the patients (Figure 4).

Interestingly, this result was maintained even after propensity score adjustment and considering that patients in the TEER arm were older and had higher morbidity burden. However, only functional type MR was included in this investigation and therefore, results are limited to this subgroup.

Taking into consideration the positive results of this therapy in all the available literature we can conclude that there are several potential advantages on this treatment. First, the rapid hemodynamic improvement induced by the relief of MR with decrease in left chambers and pulmonary artery pressures and the increase of cardiac output, which may lead to a faster recovery (48). Second, the avoidance of the inflammatory reaction induced by the extracorporeal circulation necessary for surgical correction that can induce further LV damage (49). Moreover, MitraClip can avoid the restriction in the annular motion caused induced by prosthesis or surgical rings and the development of abnormal septal motion that can affect LV contractility and efficiency. In addition, this entity usually develops in a normal leaflet mitral valve, which usually present optimal leaflet tissue and anatomy for the device. Of relevance, TEER does not interfere with a delayed cardiac surgery in case the device fails or recurrent MR is present. And finally, TEER is associated with lower bleeding complications, a fact that can negatively affect an open-heart surgery, in patients usually at high bleeding risk due to the antithrombotic therapy related to post MI management.

However, we face some challenges and limitations as well when opting for this strategy. MitraClip in acute MR is a technically demanding procedure. Valve anatomy, a non-dilated atrium that complicates a precise transeptal puncture, the clinical status and the risk of entanglement in the subvalvular apparatus make these cases challenging. Nonetheless, and after taking these considerations into account, the procedure itself does not differentiate from the ones preformed in other clinical condition: increase coaptation surface or control flailing segments, decrease MR and obtain a drop in left atrium and pulmonary pressures.

Another question to consider is that procedures were performed in centers that had high levels of experience using MitraClip. Thus, TEER strategy cannot be generalized to less experienced teams. Likewise, clinical deterioration of some patients may be very fast, and this raises the question of whether specialized mitral teams should be prepared to deliver the therapy in emergent situations or whether they should even go to centers that do not offer it and whose patients are too unstable to be transferred.

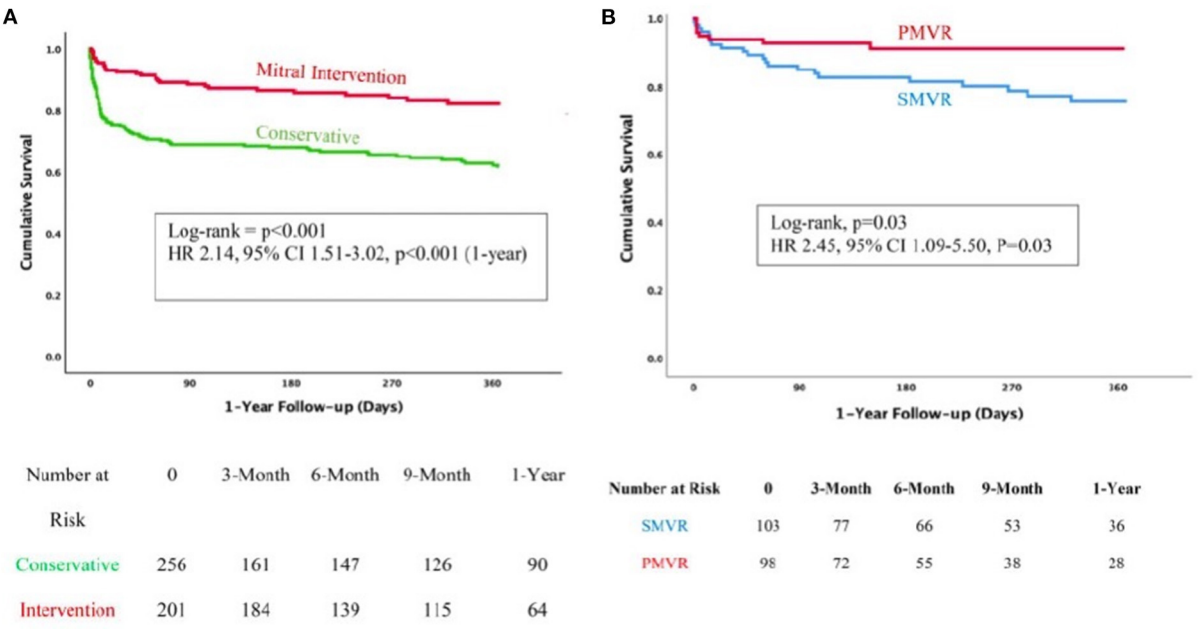

FIGURE 4
Comparison of patients with post MI MR under medical management vs. intervention **(A)** or surgery vs. TEER **(B)**. With permission from Haberman et al. (9).

Regarding limitations, several should be pointed out. Although results with TEER in this setting are promising, literature is limited to retrospective analysis of a small sample size. Therefore, we cannot exclude the presence of a selection bias in patients undergoing TEER, in the sense that only those who responded to the medical therapy and cardiac support were those who received the therapy. This population can represent a better prognostic category and therefore our conclusions may not be applicable to all patients. In addition, long-term clinical and echocardiographic follow-up is limited. Ideally, the implementation of a properly designed and executed randomized trial should provide more reliable information. However, as in surgical literature, this trial is still lacking. Further research must be warranted to elucidate the best management options for this condition.

A proposed algorithm for MR management including all available information is presented in Figure 5. Patients with subvalvular apparatus rupture should probably be first referred to conventional surgery unless the surgical risk is high and the valve anatomy is suitable for TEER (taking into account team experience). Conversely, patients with more "functional-type" MR seems to perform better with TEER as a first strategy and only patients with suboptimal valve anatomy can be first considered for open-heart surgery, if the risk is acceptable.

Future developments

As long as this is a novel therapy in the interventional field, there are still multiple unsolved issues. First, the time elapsing from MI or MR to TEER is very long in most of cases. This fact is due to the belief that MR will improve after revascularization in most cases or that patients are too sick to receive treatment. Data shows that the procedure is associated with a high technical success, and this translates in rapid recovery of clinical condition and therefore it should not be delayed. Likewise, it is likely that with earlier treatment the clinical result could be potentially better. Therefore, if MR is severe, associated with regional LV remodeling and the patient is symptomatic, is unlikely that the valve disease will resolve under medical management and the treatment should not be delayed. In our opinion, in those cases where heart team is prone to percutaneous treatment, the concept of Primary TEER (similar to primary PCI) should be implemented to avoid delays. Second, the role of mechanical cardiac support in patients with hemodynamic instability depends on the moment of development of MR. If MR is present at the time of coronary angiography and revascularization VA ECMO is not advisable since it increases the afterload and this can worsen the pulmonary edema. IABP/Impella and prompt MR correction are more advisable. However, those patients initially

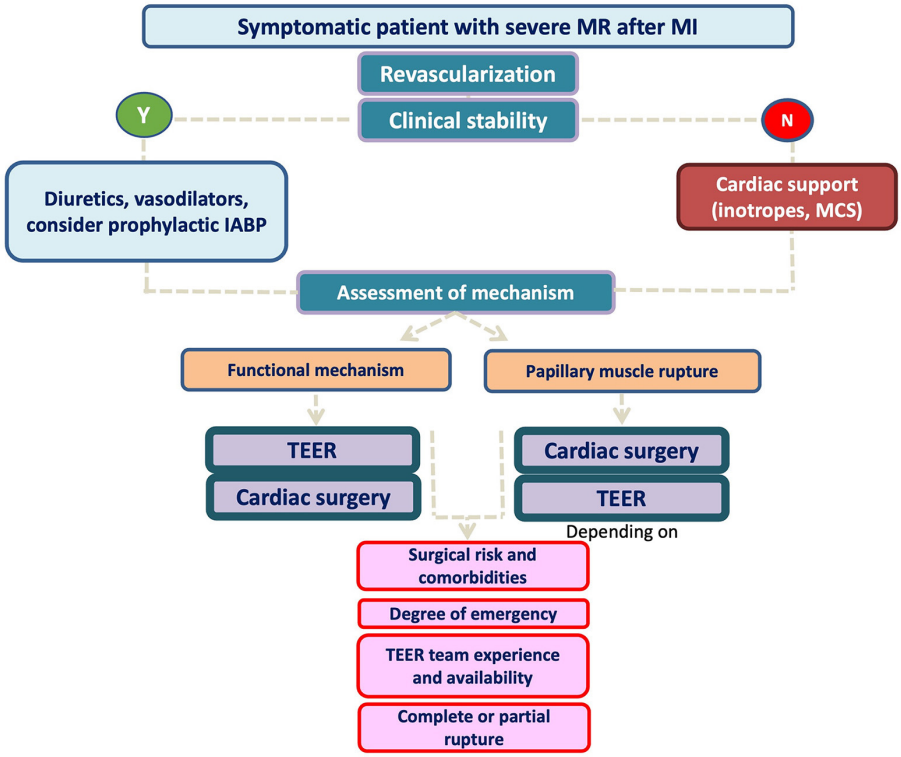

FIGURE 5
Proposed algorithm for post MI MR management.

in shock and under ECMO can develop MR during follow-up. In those cases, ECMO weaning is advisable to ensure the severity of MR. In cases that this cannot be done, TEER under ECMO is safe and feasible. In such cases, LV may be unloaded with a Impella combination (ECPELLA strategy), with potential benefits to TEER treatment (lower LV dimension, coaptation gap and less severe MR). And third, we only have information with the MitraClip device. In the last years different devices have gained space in the field both from repair, where PASCAL is showing promising results (50, 51), and from replacement (52, 53). The role of PASCAL should be similar to MitraClip but the role of replacement still needs further development.

Conclusion

TEER with MitraClip has shown to be an efficacious treatment for early MR after MI, in a selected group of patients. The possibility of a transcatheter correction in this scenario should be present in all algorithms of management of post MI mitral insufficiency, together with surgical option, for the heart team to have all available options of treatment.

Author contributions

RE-L, JB-A, FC-I, and MT conceived the idea. RE-L, BC-Q, and MB-P drafted the manuscript. RG-F and LP corrected the manuscript and assisted in the figures. MP and AÍ-R gave critical review. All authors gave final approval.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Transcatheter and surgical treatment of tricuspid regurgitation: Predicting right ventricular decompensation and favorable responders

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Isolated tricuspid regurgitation (TR) has gained increasing recognition in recent years both in the surgical and in the cardiological community. Left untreated, isolated TR significantly worsens survival. Despite being a strong predictor of negative prognosis, interventions to correct TR are rarely performed due to increased surgical risk and late patient presentation. Recently, the ultimate focus has been on patient selection, surgical or transcatheter indication, and correct timing. Furthermore, of paramount importance is the identification of predictors of outcome following treatment, in order to discriminate between favorable and unfavorable responders and guide the decision-making process of the most adequate treatment for every patient.

KEYWORDS

tricuspid regurgitation, transcatheter interventions, surgical treatment, patient selection, outcomes

Introduction

Isolated tricuspid regurgitation (TR) has gained increasing recognition in recent years both in the surgical and in the cardiological community. Initially considered benign, isolated severe TR has been found to be a strong predictor of prognosis (1, 2). Furthermore, when left untreated, TR significantly worsens survival, with a mortality rate at 5 years of ∼50% (3–5). Despite such strong evidence in the literature, management of patients with severe isolated TR remains controversial. Current guidelines (6, 7) provide specific indications for treatment of TR; while surgical correction of TR concomitantly to left-sided heart diseases has been accepted and is commonly performed, reluctancy remains regarding treatment of isolated TR. This is mainly related to the fact that even if severe, TR can be clinically well-tolerated for many years. Patients, in fact, tend to be asymptomatic, with a good quality of life, and whenever minor symptoms arise, they can be initially easily managed with an adequate medical therapy (8). However, following many years of tolerating TR, patients tend to develop organ failure difficult to manage with medical therapy, requiring a structural intervention on the valve which becomes

high risk for the multimorbid status of the patient (9–11). For this reason, for years, an extremely high in-hospital mortality following surgery has been reported in the literature, together with great uncertainty regarding long-term outcomes (12–14).

Therefore, despite being a disabling condition, a very low percentage of patients affected by isolated TR (∼5%) are currently receiving treatment, resulting in significant undertreatment of the disease (5, 15). This large unmet clinical need has favored the development and exponential growth of transcatheter devices for the treatment of TR. However, regardless the treatment strategy, whether surgical or transcatheter, patient selection and correct timing play the most important role in determining a favorable outcome following TR treatment (16). Recently, the ultimate focus has been trying to identify predictors of outcome following tricuspid valve (TV) treatment.

In the present article we aim at reviewing the currently available results in the literature regarding isolated TR treatment, both surgical and transcatheter, with particular attention to outcomes and predictors of a favorable vs. an unfavorable response.

Surgical treatment

The majority of tricuspid valve operations are performed concomitantly to left-sided valve surgeries, while only a minority, ∼14%, are performed in isolation (17–19). This likely occurs in response to the historically reported high in-hospital mortality rates following isolated TV surgery and poor long-term outcomes, that have remained relatively stable during the last decade. Previous studies have indeed reported an in-hospital mortality ranging from 8.8 to 37%, associated to a 30 day all-cause death rate ranging from 3.2 to 16% and a 5-year mortality rate of 55% (18, 20–22). Furthermore, these studies reported a trend toward increasing patient complexity over time, and a significant impact on outcomes of factors associated with disease duration and late clinical presentation (17, 19). Recent data has underlined how early referral for surgical correction results in excellent both short and long-term outcomes (23–27). These findings support the message that the cardiac surgery community has recently tried to deliver regarding "early referral and treatment" in TR. The surgical act of TV repair or replacement is not technically demanding in itself and the outcome is therefore almost exclusively dependent on the baseline patient's profile, and in particular, on right ventricular (RV) function (28) and the overall right heart physiological status. While American guidelines (6) tend to be more conservative, and suggest waiting for the development of signs or symptoms of right heart failure (RHF) before recommending TV repair or replacement (Class IIa), European guidelines (7) have recognized that surgery might be considered in patients prior to development of RV dysfunction and end-organ damage, even in asymptomatic patients, whenever there is evidence of ongoing right heart remodeling.

However, to date, the questions of when to perform isolated TV surgery for severe TR, when is referral considered "early" and when is late referral considered "too late" are of crucial importance.

Quite a few authors have tried to identify predictors of a favorable outcome in order to better aid in the stratification of surgical risk (Table 1).

Dreyfus et al. (28) analyzed patients treated with TV surgery in 12 French tertiary centers. Only a minority (8%, 466) underwent isolated TV surgery, and were mainly older (mean age 60 years), 24% had had previous left-sided valve surgery, ∼50% presented with New York Heart Association (NYHA) class III and IV heart failure symptoms and 35% experienced heart failure within the year prior to surgery. Moreover, >50% presented with RHF, 8% with ascites and chronic kidney and liver disease were present in 33% and 12% of patients, respectively. Regarding echocardiographic data, ∼20% of patients had moderate and severe RV dysfunction and a systolic pulmonary artery pressure (sPAP) $\geq$ 50 mmHg. More than half of patients received TV replacement. In terms of outcomes, in-hospital mortality was 10%, and at 1- and 5-years follow-up the rates of all-cause death and cardiovascular readmissions were 25 and 38%, respectively. Independent predictors associated to in-hospital mortality and mid-term follow-up were NYHA III/IV heart failure symptoms, low prothrombin time and moderate and severe RV dysfunction. These data underline the importance of timely referral. In fact, chronic severe TR leads to RV dilation and dysfunction, and when patients present with symptoms despite medical therapy it is often too late for intervention (29).

These results were further confirmed by a single-center retrospective study published by our group (26, 27). The 172 patients analyzed were divided according to a new classification based not only on TR grade, but also symptoms, RV remodeling and function, RHF episodes and medical therapy (30), ranging from Stage 1 (less than moderate TR, no symptoms) to Stage 5 (severe TR, RHF episodes despite maximal medical therapy, organ damage, severe RV dysfunction). In our experience, patients operated upon in early stages of the disease (Stage 2 and 3), without prominent symptomatology, RV dilation or dysfunction, and without organ involvement, most frequently received TV repair with no in-hospital mortality, fewer postoperative complications and shorter postoperative length-of-stay. Moreover, patients at early stages of the disease, following TR treatment, experienced 100% survival at 5 years and no further hospitalizations for RHF. On the contrary, patients in more advanced stages (Stage 4 and 5) experienced higher in-hospital mortality (15.3%), postoperative complications (such as acute kidney injury and low cardiac output syndrome), and longer both intensive care

TABLE 1 Characteristics of the surgical studies in the literature.

Study	No. of patients	Age (years)	Procedure TVR	NYHA III/IV	REDO	RHF episodes	RHF signs	End-organ involvement	LVEF (%)	≥Moderate RV dysfunction	sPAP (mmHg)	Outcomes
Dreyfus (28)	466	60 ± 16	57%	47%	24%	35%	57%	33% CKD, 12% liver disease	58 ± 9%	17%	40 ± 11	10% in-hospital mortality 38% 5–years all-cause death
Sala (26, 27)	172	66 [55–74]	75%	62.2%	57.6%	34.3%	21.5%	22.7% CKD	60% [55–60]	13.6%	40 [35–48]	5.8% in-hospital mortality 15% 5-years all-cause death
Weiss (31)	43	65.2 ± 13.8	41.9%	72.1%	27.9%	–	34.9%	14% CKD	60% [IQR 2.5]	7%	–	0% in-hospital mortality 9.3% 1-year all-cause death
Kawsara (24)	1,513	55.7 ± 16.6	36.5%	–	–	85.9%	41%	36.2% CKD 36% liver disease	–	–	–	8.7% in-hospital mortality 26.8% cardiogenic shock

CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RHF, right heart failure; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TVR, tricuspid valve replacement.

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unit and hospital lengths-of-stay. In these stages, survival at 5 years was 60.5% and 20% of patients experienced at least one hospitalization for RHF following surgery.

Similar results were also reported by Weiss et al. (31) in their single-center study assessing clinical outcome and functional capacity following isolated TV surgery. Within the study, patients with severe right or left heart failure, severe pulmonary hypertension, end-stage renal disease and liver disease were excluded. No in-hospital mortality was reported and at 1-year follow-up 9% mortality was documented together with a significant improvement in functional capacity, reduction in clinically apparent peripheral edema and daily oral furosemide therapy. The population treated by Weiss et al. was highly selected and not advanced in disease progression resulting in good short-term outcomes and improved functional capacity.

On the same line are results reported by Kawsara et al. (24) that studied 1,513 patients from the Nationwide Readmissions Database, that underwent isolated TV surgery. Surrogates of late referral in the patient population were frequent, such as admission with decompensated heart failure (41%), non-elective surgery (44%), and advanced liver disease (17%). These factors were the strongest predictors of in-hospital mortality, further supporting the idea that the poor outcomes of isolated TV surgery are related to the late referral for intervention.

Even though all the recent data in the literature regarding surgical treatment of isolated TV disease stress the importance of early referral and treatment, no specific parameter and cut-off value had been identified in order to guide the decision-making process of optimal patient management. In this regard, a novel dedicated risk score has been recently made available that aims at predicting the outcome of patients following isolated TV surgery (32). The TRI-SCORE managed to identify eight parameters not only related to right and left ventricular function, but also end-organ involvement (both liver and kidney), medical therapy and clinical status. More specifically, age, NYHA functional class, RHF signs, daily dose of furosemide, renal insufficiency determined by glomerular filtration rate, elevated total bilirubin, left ventricular ejection fraction and moderate/severe RV dysfunction, were all found to be independent predictors of in-hospital mortality. Even though this scoring system still requires external validation, the TRI-SCORE, based on eight easy to ascertain parameters, is the first example of an attempt to predict favorable vs. non favorable responders to isolated TV surgery.

Transcatheter treatment

Transcatheter treatment of severe isolated TR is becoming an accepted option for the management of patients considered high-risk or surgically ineligible. Available transcatheter treatment options mimic surgical techniques and include leaflet approximation, incomplete ring annuloplasty, heterotopic valve implantation (caval valve devices) and percutaneous tricuspid valve replacement. At present, the most widely applied technique is edge-to-edge repair of the tricuspid valve (33). Retrospective analyses have reported a reduction in TR grade, symptomatic improvement (reduced RHF hospitalizations) and lower mortality at 1 year with various devices compared to medical therapy alone (34–36). In fact, results from the TRILUMINATE trial have shown that, despite residual TR being associated with worse outcomes, reduction of at least one degree of TR is associated with improved symptoms at follow-up. Furthermore, reverse remodeling of the right ventricle, improved cardiac output and reduction of liver enzymes were also reported following TV treatment using the TriClip device (Abbott Vascular, Chicago, USA) (37–39). Results are further improving with the advent of new platforms. Despite these promising and encouraging results, it has recently emerged that, just as for surgical correction, indication and timing of any transcatheter tricuspid valve intervention (TTVI) are of paramount importance and should take into consideration multiple aspects, such as patients' clinical characteristics, disease stage, end-organ function and anatomical factors (Table 2).

According to current guidelines, in patients undergoing evaluation for TR treatment, a comprehensive RV assessment should be performed, including measures of RV size and morphology, RV function and tissue remodeling (7). Non-invasive assessment of the RV is a complex task, requiring the integrated evaluation of multiple parameters, and taking advantage of emerging imaging modalities, such as speckle-tracking and 3D echocardiography or cardiac computed tomography and magnetic resonance (CMR). Nevertheless, RV dilatation and systolic function are key determinants in the evaluation and management of patients with significant TR owing to their prognostic relevance. Patients presenting with RV systolic dysfunction irrespective of RV size experience 5-years survival rates (29). Similarly, the presence of RV dysfunction has been shown to be a risk factor associated with adverse outcome in patients with TR and in tricuspid valve surgery, as underlined previously (29, 40). Schlotter et al. (41) decided to analyze the clinical impact of RV dysfunction in patients undergoing TTVI from the TriValve registry, in order to try and shed some light on favorable responders and patient selection. Patients from the TTVI cohort were compared to patients treated conservatively, and the whole population was further stratified in three subgroups according to longitudinal RV function expressed by the tricuspid annular plane systolic excursion (TAPSE): preserved (TAPSE >17 mm), mid-range (TAPSE 13–17 mm) and reduced RV function (TAPSE <13 mm). Not surprisingly, TTVI was associated with reduced mortality in patients with severe TR as compared to conservative treatment (13% vs. 25.4%, respectively). However, this survival benefit was not seen in cases of procedural failure. Even more importantly, TTVI was associated with a survival benefit solely in patients with mid-range RV function, improving their outcome to the level of patients with preserved RV function. No improvement

TABLE 2 Characteristics of the transcatheter studies in the literature.

Study	No. of patients	Age (years)	Procedure	NYHA III/IV	RHF episodes	End-organ involvement	LVEF (%)	≥Moderate RV dysfunction	sPAP (mmHg)	Outcomes
Schlotter (41)	TTVI: 288 Control: 562	78 [74–82] 76 [69–82]	MitraClip, PASCAL, Trialign, Cardioband etc. None	261 (90.6%) 520 (92.5%)	–	eGFR 42 (30–58) eGFR 52 (37–71)	55 (43–61) 50 (35–60)	54% 49%	43 (34–53) 48 (37–60)	13.1% 1-year mortality 25.4% 1-year mortality
Orban (43)	75	77 [74–82]	67 MitraClip 8 PASCAL	100%	–	–	55 [49.9–62.4]	3D-RVEF 41 ± 7.8%	–	33% 1-year mortality
Brener (44)	444	76.7 ± 9.1	MitraClip, PASCAL, Trialign, Cardioband, FORMA, Tricinch, Navigate	91.4%	72.3%	eGFR 46.1±20.1	50.6±13.3	TAPSE 16.4 ± 4.6 mm	40.8 ± 15.3	2.3% in-hospital mortality 14.2% 1-year mortality
Lurz (49)	243	77 ± 9	MitraClip	92%	76%	eGFR 48±22	51±14	TAPSE 17 ± 5 mm	49±15	19% 1-year morality
Stocker (50)	236	78 [74–82]	MitraClip, PASCAL	89%	–	eGFR 46 (33–59)	55 (50–60)	TAPSE 17 (13–20mm)	41 (32–49)	8% 1-year mortality with no PH; 22% 1-year mortality with post-capillary PH; 62% 1-year mortality with pre-capillary PH
Muntané-Carol (51)	300	77 ± 9	MitraClip, PASCAL, Trialign, Cardioband, FORMA, Tricinch, Navigate	93%	68.7%	eGFR 44.7±20.3	49±13	TAPSE 15 ± 4 mm	44 ± 17	3% in-hospital mortality 18% 6-months mortality

eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PH, pulmonary hypertension; RHF, right heart failure; RV, right ventricle; RVEF, right ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TTVI, transcatheter tricuspid valve interventions.

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was instead reported for patients with preserved or reduced RV function, and the latter was associated with impaired outcome in both patients treated conservatively and with TTVI. These findings may seem in contrast with those reported by Miura et al. (42), who identified RV dysfunction as an independent predictor of all-cause mortality and RHF hospitalizations in patients treated with TTVI. However, these results underline the importance of adequate timing and patient selection also in patients undergoing percutaneous procedures: patients treated in late stages of the disease, with pronounced RV dysfunction, may not benefit from the reduction in venous congestion and reverse remodeling, ultimately impacting on clinical events.

Orban et al. (43) investigated the prognostic impact of global RV function assessed using 3-dimensional (3D) echocardiography in 75 patients undergoing transcatheter tricuspid edge-to-edge repair, stratified according to preprocedural 3D RV ejection fraction (3d-RVEF). Patients in the highest tertile (3D-RVEF 44.6–61.8%) had a better survival than those in the intermediate or lower tertiles. Furthermore, at follow-up, patients in the highest RVEF tertile were more likely to be in NYHA class $\leq$ II and experienced greatest improvement in 6-min walking distance. Both pre-procedural RVEF and NYHA functional class IV were independent predictors of all-cause mortality. Interestingly, RV function identified by TAPSE was not predictive of outcome in these patients.

These discordant findings emphasize the complexity of non-invasive assessment of RV function by the adoption of single parameters and the need for a comprehensive evaluation. Indeed, both TAPSE and 3D-RVEF might fail to capture the actual relationship between RV contractility and afterload, leading to overestimation of RV systolic function in patients with severe TR. RV-pulmonary artery (PA) coupling helps to determine whether RV function is adequately compensated for specific loading conditions. In compensated states, RV contractile function increases together with the increase in afterload to maintain a steady RV-PA ratio. On the other hand, in decompensated states, RV contractile function does not rise together with the afterload, resulting in lower RV-PA coupling ratios. Brener et al. (44) evaluated the prognostic value of non-invasively derived RV-PA coupling in patients from the TriValve registry undergoing TTVI for severe TR. A high baseline TAPSE/systolic pulmonary artery pressure (sPAP) ratio was found to be independently associated to lower all-cause mortality with respect to lower baseline TAPSE/sPAP ratios. Furthermore, patients with higher baseline TAPSE/sPAP ratios experienced fewer hospitalizations for RHF within 12 months from TTVI treatment. Interestingly enough, the benefits associated to a high RV-PA coupling ratio were irrespective of baseline TAPSE and sPAP values, implying that this coupling measurement takes into account a contractile reserve that the single parameters are not capable of assessing.

The RV contractile reserve in response to pharmacological or physical stress has shown prognostic relevance in patients with pulmonary hypertension and severe baseline RV dysfunction, however, further studies are warranted to explore the role of stress imaging in severe TR (45).

Finally, detection of myocardial fibrosis by CMR or by speckle-tracking echocardiography has recently demonstrated prognostic importance in RV failure and might represent a promising tool to define the optimal timing of intervention in severe TR (46).

Right ventricular function and pulmonary hypertension are not the only factors responsible for an unfavorable outcome in patients undergoing TTVI. Indeed, pulmonary circulation status plays a relevant role in determining the prognosis of patients with severe TR and the outcome of TTVI. Right heart catheterization is the gold standard for the invasive assessment of the right heart, providing information regarding the severity and mechanism of pulmonary hypertension (PH), pulmonary vascular resistance, preload conditions, RV function and RV-PA coupling.

Pulmonary hypertension frequently coexists with severe TR, being a marker of poor prognosis and high operative risk (47). Furthermore, it has been shown to be responsible for adverse outcomes in patients with heart failure and patients undergoing TV surgery (48). To date, PH is often solely assessed by echocardiography. However, recent data have shown that the diagnostic sensitivity of echocardiography in accurately detecting PH is only 55%, since the determination of sPAP might be limited in severe TR (49). Lurz et al. (49) analyzed the impact of PH on clinical outcomes of 243 patients with severe TR undergoing transcatheter tricuspid edge-to-edge repair. Invasive PH (iPH) and echocardiographic PH (ePH) were defined as sPAP $\geq$50 mmHg. The presence of iPH resulted associated with the primary composite endpoint of death, heart failure hospitalization and re-intervention at 1 year. The echocardiographic diagnostic accuracy to detect iPH was low (55%). A discordance between non-invasive and invasive RHC assessments (iPH+/ePH-) and an impaired invasive RV-PA coupling resulted as independent predictors of the primary composite endpoint at 1 year.

The invasive cardiopulmonary hemodynamic profile predicts survival in patients undergoing TTVI, allowing risk stratification and identification of those patients that could benefit the most from intervention. Stocker et al. (50) decided to analyze RHC data of 238 patients with severe TR undergoing transcatheter tricuspid valve repair. Authors identified mean PAP, diastolic PAP, transpulmonary gradient (TPG), pulmonary vascular resistance (PVR) and right ventricular stroke work as significant hemodynamic predictors of 1-year mortality. On the other hand, pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), cardiac output (CO), and pulmonary artery pulsatility index were not associated with 1 year mortality following TTVI. The following cutoff values were identified: mPAP >30 mmHg, sPAP >50 mmHg, dPAP >20 mmG, TPG >17 mmHg and PVR >5 WU. Moreover, stratification of

patients according to mPAP and TPG resulted associated with 1 year mortality following TTVI: patients with pre-capillary dominant PH (high mPAP >30 mmHg and high TPG>17 mmHg) had an unfavorable prognosis (38% 1-year survival), while patients without or with post-capillary PH (mPAP>30 mmHg and TPG <17 mmHg) had a favorable outcome (92% and 78% survival at 1-year, respectively). These data suggest that echocardiography alone might not be sufficient in accurately detecting PH and, even more importantly, they highlight the need for a comprehensive, multimodality assessment of PH and RV function in patients undergoing TTVI. Therefore, RHC should be performed systematically as a pre-procedural assessment tool in order to better characterize TR and PH and consequently stratify patients and define their prognosis.

Recently, Muntané-Carol et al. (51) reported the outcome of a cohort of 300 patients undergoing TTVI with RV dysfunction (TAPSE <17 mm) or pulmonary hypertension (sPAP ≥50 mmHg) from the TriValve registry. Reported procedural success was 80% with 3% in-hospital mortality following TTVI. At 6 months follow-up, there was an improvement in NYHA functional class, with more than two thirds of patients in NYHA class I-II. However, at follow-up ∼20% of patients died. Factors identified as independent predictors of outcome were hepatic congestion, renal dysfunction and lack of procedural success. Furthermore, the estimated 1-year mortality in patients with more advanced heart failure, with both renal dysfunction and significant hepatic congestion at baseline, was close to 50%. Therefore, transcatheter procedures may result futile in candidates with end-stage heart failure, untreated pulmonary hypertension and end-organ damage.

The gray zones and the future

Long forgotten, the tricuspid valve has now gained great momentum. Isolated tricuspid valve treatment, both surgical and transcatheter, is matter of great debate. Even though surgery is the only definitive treatment for isolated TR, it is rarely performed in response to the historically reported high in-hospital morbidity and mortality and poor long-term outcomes (18, 52). These results have led to lengthy medical management and late referral for surgery. However, severe TR can precede right heart failure by many years until late in the natural history of the disease. This is responsible for a vicious circle that further delays or even rejects the referral for surgery. Transcatheter tricuspid treatments have therefore emerged as treatment options for severe symptomatic TR in patients considered ineligible for cardiac surgery (53). Despite numerous devices and increasing awareness of early intervention, when and in whom to perform surgical or transcatheter procedures remains a clinical conundrum. In fact, regardless the type of intervention, the ultimate focus has been on patient selection, surgical or transcatheter indication, timing of intervention and identification of predictors of outcome following treatment in order to identify favorable and non-favorable responders to treatment. The less invasive nature of transcatheter procedures, however, allow to investigate more appropriately the influence of baseline predicting factors by eliminating the influence of the surgical insult, as well as by including more patients. Transcatheter interventions will therefore help a better understanding of right heart physiology and support decision making in the future. In the future, earlier referral will also increase the rate of surgical procedures on isolated TR patients (a trend already happening in high volume centers offering transcatheter procedures).

In both treatment options, specific parameters capable of predicting outcome have been of difficult identification.

The cardiac surgery community has stressed the idea of early referral following recent data published in the literature. Early referral and early treatment, before the development of overt symptomatology, right heart dysfunction and failure and end-organ damage, are associated to excellent in-hospital outcomes, with a higher rate of TV repair vs. replacement, and good long-term outcomes, with low-to-none mortality at 5 years and significant improvement in symptomatology (24, 26, 27). To better define early referral and therefore aid in the stratification of surgical risk, the TRI-SCORE was recently developed (32). The most relevant predictors of outcome, and as a consequence of favorable and unfavorable responders, are symptomatology (NYHA class and medical therapy), end-organ involvement (hepatic congestion and renal dysfunction) and RV function [TAPSE and tissue doppler imaging (TDI)]. Interestingly enough, what has emerged in the literature, is that patient selection and optimal timing are crucial also in percutaneous tricuspid procedures. The same above-mentioned parameters were also identified as independent predictors of outcome of patients undergoing TTVI. In particular, the greatest attention in recent years was entirely directed toward the identification of the most appropriate parameter capable of defining RV function (54). Adequate assessment of RV function is extremely complex and many parameters, such as TAPSE, have given contradictory results. RV-PA coupling appears to be a powerful predictor of outcome, by assessing whether RV function is correctly compensated for specific loading conditions. Preoperative echocardiographic data concerning both right ventricular size and function are of paramount importance in order to guide when to intervene and how to treat patients with severe TR. Relevant parameters have been identified: surgery should be considered in patients with mild RV dysfunction, while transcatheter procedures result beneficial in patients with moderate RV dysfunction. However, more thorough assessment of RV function is still required, especially with the new approaches in transcatheter tricuspid valve replacement (55). In this setting, misdiagnosis of RV dysfunction may result in acute right heart failure

due to sudden increase in afterload and development of afterload mismatch.

In this moment of great enthusiasm for the treatment of TR, a comprehensive evaluation by the Heart Team is mandatory, in order to thoroughly assess clinical characteristics, define the surgical and percutaneous risks and identify the most appropriate treatment strategy for each patient. However, in order to define whether either intervention is truly beneficial and in which populations, randomized controlled trials analyzing optimal medical therapy vs. surgical treatment vs. transcatheter interventions are necessary.

Author contributions

AS made substantial contributions in the design and drafting of the work. AB made substantial contributions in revision. FM made substantial contributions by critically revising the manuscript adding important intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Right ventricular function in transcatheter mitral and tricuspid valve edge-to-edge repair

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Since transcatheter edge-to-edge repair (TEER) has become a valuable therapy in the treatment of both, mitral (MR) and tricuspid regurgitation (TR), the question of optimized patient selection has gained growing importance. After years of attributing rather little attention to the right ventricle (RV) and its function in the setting of valvular heart failure, this neglect has recently changed. The present review sought to summarize anatomy and function of the RV in a clinical context and aimed at presenting the current knowledge on how the RV influences outcomes after TEER for atrioventricular regurgitation. The anatomy of the RV is determined by its unique shape, which necessitates to use three-dimensional imaging methods for detailed and comprehensive characterization. Complex parameters such as RV to pulmonary artery coupling (RVPAc) have been developed to combine information of RV function and afterload which is primary determined by the pulmonary vasculature and LV filling pressure. Beyond that, TR, which is closely related to RV function also plays an important role in the setting of TEER. While mitral valve transcatheter edge-to-edge repair (M-TEER) leads to reduction of concomitant TR in some patients, the prognostic value of TR in the setting of M-TEER remains unclear. Overall, this review summarizes the current state of knowledge of the outstanding role of RV function and associated TR in the setting of TEER and outlines the unsolved questions associated with right-sided heart failure.

KEYWORDS

mitral regurgitation, tricuspid regurgitation, edge-to-edge repair, right ventricular function, MitraClip, PASCAL

Introduction

The clinical importance of transcatheter mitral and tricuspid valve repair has steadily increased within the past two decades. Despite a growing number of transcatheter techniques, edge-to-edge valve repair (TEER) remains the most commonly used clinical procedure until today and has been proven to improve prognosis in case of mitral regurgitation (MR) (1, 2). The health and socio-economic importance of these procedures is immense, since both tricuspid (TR) and MR have an increasing prevalence, especially in elderly patients, and are associated with high rates of heart failure hospitalizations (HHF), morbidity, and mortality (3–5).

While the beneficial effect of mitral valve transcatheter edge-to-edge repair (M-TEER) has been proven in randomized controlled trials (1, 6), studies comparing tricuspid TEER (T-TEER) to diuretic treatment alone are still ongoing. So far, observational studies reported high rates of procedural TR reduction and suggest low mortality rates in propensity-matched analysis, especially compared to conventional surgical treatment (7–9).

Historically, both the right ventricle (RV) and the tricuspid valve, often referred to as the "forgotten valve" have received less scientific attention than the left ventricle (LV). This could be partly explained by high procedural/perioperative and short-term mortality rates for right heart surgical procedures in this high-risk population. Another reason was the lack of comprehensive three-dimensional imaging models that could reflect the complex and irregular anatomy of the RV (10). As this has changed in parallel with the advance of transcatheter repair techniques, the geometry and function of the right ventricle (RV) have increasingly become the focus of research in the field of TEER. The right ventricle plays an important role in the complex interplay between the left ventricle (LV), pulmonary and systemic circulation. Understanding function and geometry of the RV with echocardiographic methods remains challenging and is subject to constant technical and methodological progress.

The aim of this review was to provide a comprehensive overview about (1) RV anatomy, (2) RV function, and (3) the role of RV geometry and function in the context of mitral and tricuspid TEER.

Anatomy of the right ventricle and tricuspid valve

The RV is the most anteriorly located chamber of the human heart (11). Its shape is difficult to approach geometrically but is commonly referred to as being crescent shaped in an axial and triangular in a lateral view (**Figure 1**) (11, 12). Usually, the right-convex interventricular septum is assigned to the left ventricle. While being 10% larger than the LV on average in volume, the RV muscular mass is significantly lower due to low pressure conditions and a relatively thin free wall (12–14). Anatomically it can be divided into three distinguishable regions, the inlet, apex, and outlet. The RV inlet includes the tricuspid valve (TV), the chordae tendineae and extends to a more variable number of papillary muscles compared to the LV (11, 12). The apex consists of much more trabecularized myocardium compared to the LV. The outlet (also described as infundibulum or conus) forms the complete muscularly shaped outflow tract of the RV (RVOT) (11, 12). Three prominent muscle bands can be delineated within the RV. Together, the parietal band and the infundibular septum are described as the crista supraventricularis and separate RVOT and TV (11–13, 15). The septomarginal band is described as Y-shaped which is connected to the medial papillary muscle with one arm and to the subpulmonary infundibulum with the other arm (15). The trunk of the Y continues into the moderator band which contains a prominent fascicle of the right bundle of the conduction system (12, 15).

The TV separates the right atrium (RA) from the RV and consists of leaflets (endocardial duplications), the annulus, papillary muscles, and chordae tendineae (16, 17). Contrary to what the name suggests, the TV does not always consist of three leaflets but can be subject to considerable anatomical variation (18). The TV is located further apically than the MV and does not have any fibrous connection to the pulmonary valve (PV) (19). The septal leaflet is characteristically connected to the interventricular septum by several direct small chordae tendineae (15). The septal and anterior leaflets are usually supported by a small medial (septal) papillary muscle. The anterior and posterior leaflets additionally are attached to a comparably large anterior papillary muscle originating from the moderator band (15). The posterior leaflet receives support from a variety of papillary muscles arising from the diaphragmatic RV wall which are sometimes summarized as the posterior papillary muscle (15, 16).

Function and dynamics of the right ventricle

To describe RV function and its contraction patterns, it is crucial to understand the RVs myoarchitecture. The muscular wall of the RV is arranged in two layers. The outer (superficial) layer of cardiomyocytes is arranged circumferentially to the TV annulus. Toward the RV apex, the fibers turn slightly oblique and continue into the superficial layer of the LV myocardium (11). The deep layer of myocytes is longitudinally aligned (12). Contraction of the RV usually begins at the inlet and apex, followed by the outlet approximately 25–50 ms later (11, 12). Some authors even describe the RV's contraction pattern as "peristalsis-like" (20). Compared to the

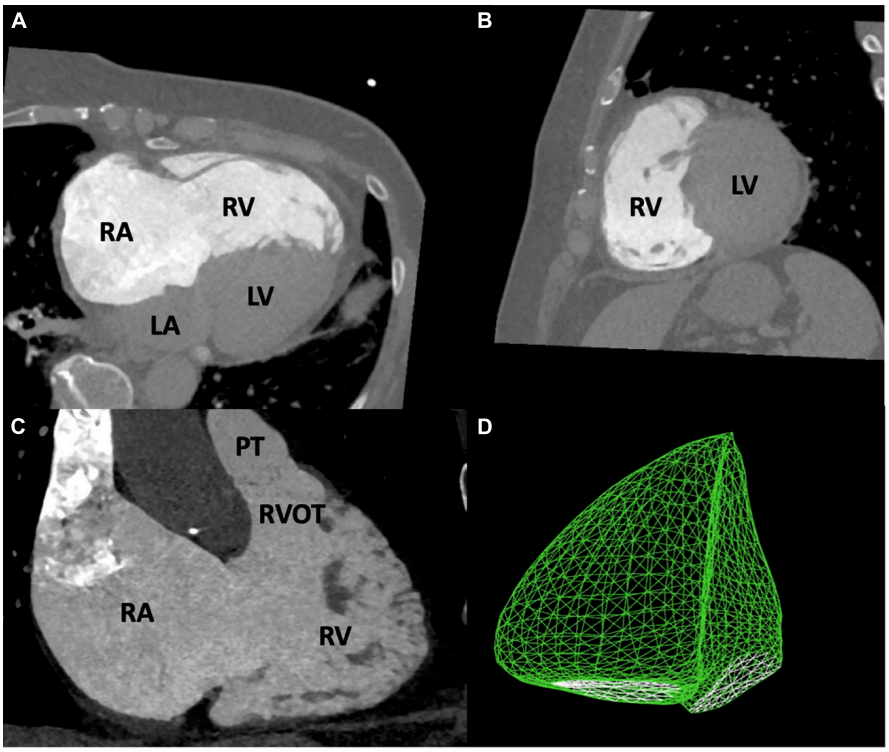

FIGURE 1
Anatomy of the right ventricle. This figure shows images of the right heart derived from multidetector computed tomography **(A–C)** and three-dimensional echocardiography **(D)**. The RV is crescent shaped in an axial **(A,C)** and triangular in a lateral view **(B)**. LA, left atrium; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract.

LV, the RV has significantly fewer oblique fibers, allowing longitudinal contraction to account for a large proportion of ventricular function (12). While circular fibers lead to an inward movement of the RV, the connection of RV and LV myofibers and the common interventricular septum lead to a significant proportion of RV function being attributable to LV contraction (12). Blood flow through the RV is believed to be relatively well streamlined within the inflow and curved apex until it becomes helical when entering the pulmonary circulation through the outflow and PV (12, 21, 22).

The overall systolic function of the RV is a complex interplay of preload (systemic venous return), contractility, and afterload (pulmonary pressure). Due to the large surface compared to the RV volume and a relatively thin wall, according to Laplace's law, the RV can adopt to a broad spectrum of preload alterations but struggles with rapid changes in afterload (23). Rapid changes in pre- or afterload lead to dilation of the RV which normalizes once contractility has adequately been increased (12, 23).

The TV annulus shows a unique saddle-shaped anatomic configuration with the most atrial located point in the antero-posterior direction and the most ventricular located point in the medio-lateral direction (24). It is a highly dynamic structure within the cardiac cycle and depending on loading conditions (19). Of note, the tricuspid annulus is apically displaced compared to the MV annulus. In patients with functional TR, the TV annulus dilates in an lateral and posterior direction toward the RV free wall which leads to flattening and rounding of the annular geometry (24).

Right ventricular/tricuspid valve geometry and function in the context of transcatheter edge-to-edge repair

Routine echocardiographic parameters of right ventricular function

Since echocardiographic assessment of right ventricular function is challenging, routine RV function parameters [tricuspid annular plane systolic excursion (TASPE), RV fractional area change (RVFAC)] are subject to a variety of limitations. TAPSE is usually measured using the M-mode in an apical four chamber view and represents the longitudinal shortening of the tricuspid annulus and hence RV in one plane. Even though longitudinal contraction significantly contributes to the overall RV function, it does not consider shortening

in the other two dimensions (25). Further, measurement of TAPSE is dependent of proper M-mode alignment which can be challenging in case of small echo windows (26). In contrast, RVFAC also respects the above-mentioned radial contraction component of the RV as it is derived from RV end-systolic and end-diastolic areas. Measuring RVFAC highly depends on the image plane acquired and shows comparably low interobserver agreement (26). In order to overcome the above-mentioned limitations, novel parameters and three-dimensional echocardiography were introduced.

Right ventricular to pulmonary artery coupling

Recently, a parameter called RV to pulmonary artery coupling (RVPAc) was introduced to quantify the close interdependency of the RV and its afterload (27, 28). Under physiological conditions, RVPAc is intact, and the function of the RV can adapt to the changes in pulmonary pressure conditions. In addition to the Frank Starling mechanism, neurovegetative and humoral mechanisms also contribute to this (29). In the case of RVPA uncoupling the afterload exceeds a certain threshold, and the RV cannot adequately increase its contractility (30). As a result, pathological dilatation of the RV occurs, often accompanied by the development of TR, as well as reduced RV function resulting in systemic congestion and secondary organ dysfunction (31, 32) (**Figure 2**).

Echocardiographically, RVPAc can be quantified as a ratio of, in principle, any RV functional parameter (e.g., TASPE, RV fractional area change RVFAC, RV longitudinal strain RVLS) and pulmonary artery pressure (PAP). In 2021, a large European multicentric registry of patients who underwent M-TEER for severe SMR found RVPA uncoupling as defined by a TAPSE/sPAP ratio <0.274 mm/mmHg to be associated with significantly impaired 2-year survival rates (33). A subanalysis of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) study defined RVPA uncoupling as RVLS of the free RV wall/sPAP ratio. A RVPA value of <0.5%/mmHg was associated with significantly higher rates of mortality or heart failure hospitalizations in both the treatment (M-TEER + GDMT) and control (GDMT only) group (30). Of note, M-TEER improved outcome of SMR patients independent of RVPA uncoupling (30). In the meantime, the prognostic value of RVPAc has also been shown in patients with primary mitral regurgitation (PMR) (34).

In patients with severe MR, RVPA uncoupling, and thus biventricular failure is most likely the consequence of long standing regurgitant blood flow across the MV in systole and development of secondary pulmonary hypertension. In patients undergoing T-TEER for severe TR, RVPA uncoupling may occur if the etiology of TR is secondary to any kind of left sided disease.

Recently, a large observational study identified RVPA uncoupling defined as TAPSE/sPAP ratio <0.406 mm/mmHg as independent predictor for 1-year all-cause mortality after T-TEER for severe TR (35). sPAP is usually approximated by using transtricuspid pressure gradients and width of the inferior vena cava. Even though the calculated cut-off in the studied T-TEER population had predictive value, the absolute

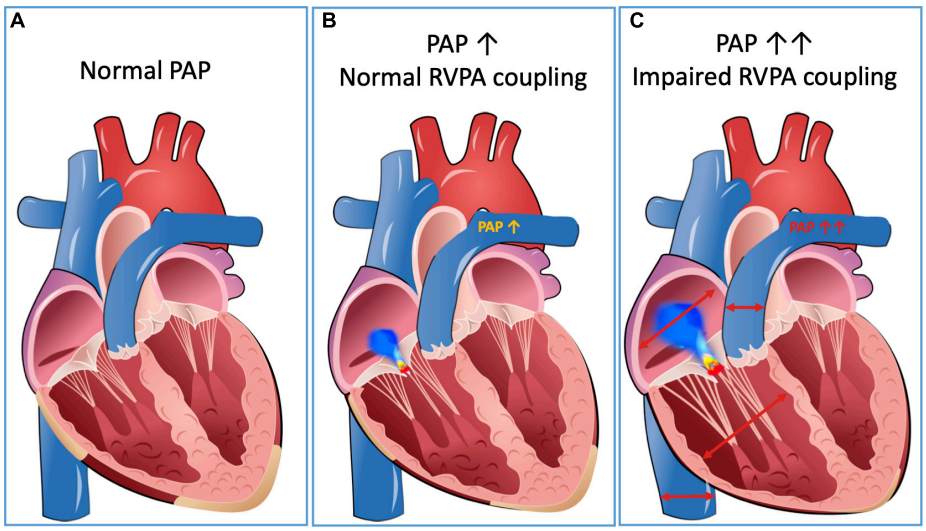

FIGURE 2
RV-PA interdependency. Panel **(A)** represents a compensated situation with normal PAP and RV function. In panel **(B)**, RVPAc is intact, and the RV can compensate increasing afterload by mild dilation. In panel **(C)**, RVPA uncoupling occurs, which is accompanied by significant TR and dilation of the IVC. IVC, inferior vena cava; PAP, pulmonary artery pressure; RV, right ventricle; RVPA, right ventricular to pulmonary artery; TR, tricuspid regurgitation.

values should be interpreted with caution. Especially in severe, massive or torrential TR with large coaptation gaps and high EROA, rapid systolic pressure equalization between RA and RV occurs leading to false low transtricuspid pressure gradients and underestimation of sPAP (36). Future studies are needed to evaluate whether calculating RVPA coupling should rather be performed using invasive PAP values in the setting of TR and T-TEER.

Right ventricular contraction patterns

Right ventricular contraction is a complex process in both spatial and temporal dimensions. Using up-to-date imaging protocols in echocardiography and cardiac magnetic resonance (CMR) have resolved the technical challenges in visualizing and adequately measuring RV function. These methods have provided important insights into the role of the RV for atrioventricular regurgitation.

A recent study focused on the prognostic impact of RV contraction patterns in the setting of T-TEER for severe TR using CMR imaging (37). The authors distinguished three different contraction patterns. Pattern I: Preserved longitudinal (TAPSE $\geq$ 17 mm) and preserved global RV function (RVEF $>$ 45%). Pattern II: Impaired longitudinal (TAPSE $<$ 17 mm) and preserved global RV function (RVEV $>$ 45%). Pattern III. Impaired longitudinal (TAPSE $<$ 17 mm) and global RV function (RVEF $\leq$ 45%). Patients who underwent T-TEER and presented with RV contraction pattern III had a significantly higher risk of death or HHF. The authors conclude that TAPSE alone is not sufficient to characterize RV function in T-TEER patients, because especially in the presence of pressure overload circumferential RV function increases by hypertrophy of the outer myocardial layer to compensate the functional decline in a longitudinal direction (37). Especially in combination with additional volume overload, the RV dilates and finally loses its ability to compensate RV function which may lead to right heart decompensation and impaired survival (37). Of note, RVEF $<$ 45% itself was a strong and independent predictor for the combined endpoint.

The value of three-dimensional echocardiography in transcatheter edge-to-edge repair

Within the past few years, three-dimensional echocardiography (3DE) has emerged as state-of-the-art imaging technique, as it is better suited to the geometric and functional complexity of the RV than biplane methods (**Figure 1D**) (38). A recent study evaluated the prognostic value of 3DE-derived RV function in patients undergoing T-TEER (39). In agreement with the cut-off established in CMR studies on RV function (RVEF $<$ 45%) (37), the authors were able to identify an RVEF value $<$44.6% as a negative prognostic predictor for postinterventional survival in T-TEER patients (39). Additionally, comparative studies have confirmed this agreement of RVEF derived from CMR and 3DE measurements (40, 41).

As recent data show, T-TEER treatment not only leads to a significant reduction in TR, but was also associated with RV reverse remodeling (RVRR) (42). RV dimensions as well as tricuspid annular diameter (TAD) significantly decreased within the first 6 month after treatment. Of note, TAPSE remained unchanged while RVEF declined significantly. The authors interpreted this phenomenon as "ejection fraction normalization" due to the reduction of the regurgitant blood flow across the tricuspid valve and subsequent increase in effective forward RV stroke volume (42). Beyond that, RVPAc improved significantly after T-TEER (42). RVRR was even associated with better prognosis after T-TEER. Now that M-TEER treatment is also known to reduce concomitant TR, further studies are needed to investigate a possible RVRR in this patient population.

Anatomic variability of the tricuspid valve in the context of transcatheter edge-to-edge repair

A crucial point in treatment planning and device selection in high-grade TR is the anatomy of the TV, which is often challenging due to the high variability. In 2021 Hahn et al. presented a systematic classification of different TV morphologies (18). In this context, they proposed to distinguish between six different anatomical configurations (Type I, II, IIIA-C, IV) (**Figure 3**) (18). While Type I showed a "normal" leaflet configuration with one anterior, one septal and one posterior leaflet, in Type II fusion of the anterior and posterior leaflet led to a "two-leaflet configuration" of the TV. In Type III, one leaflet was subdivided and leads to a "four-leaflet-configuration" (IIIA: Anterior leaflet divided; IIIB: Posterior leaflet divided; IIIC: Septal leaflet divided). Finally Type IV TV was defined as having five leaflets (18). In descending order, the different anatomic subtypes were observed with varying frequency (Type I: 54%, Type IIIB: 32%, Type II: 5%, Type IIIC: 4%, Type IIIA: 3%, Type IV: 2%) (18).

In an additional study, the authors investigated the influence of this classification on outcome after T-TEER (43). They observed no significant outcome differences regarding the number of implanted TEER devices, TR reduction, NYHA functional class, HHF and 1-year all-cause mortality (43). In contrast, Sugiura et al. investigated the impact of a three vs. four leaflet anatomy of the TV on residual TR

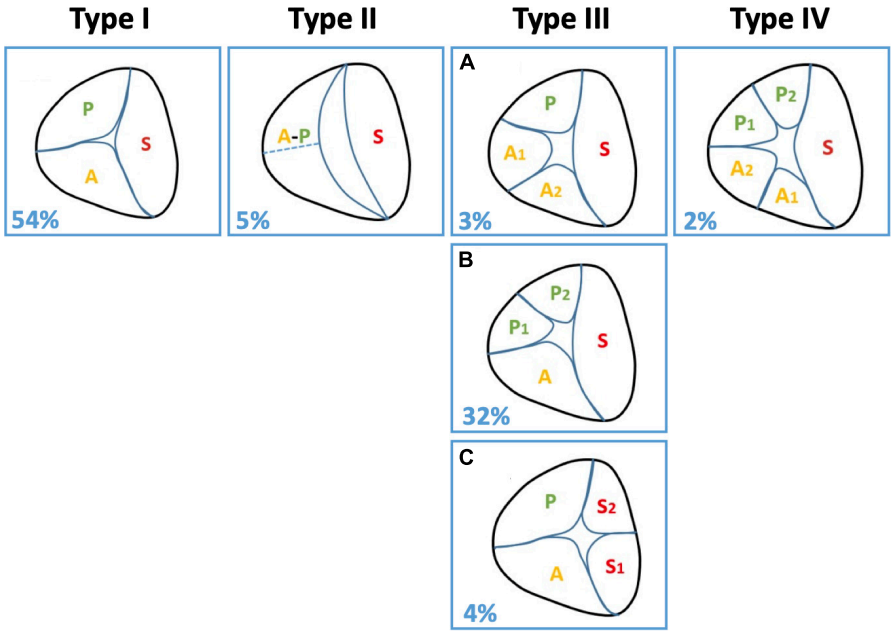

FIGURE 3
TV anatomic patterns. This figure illustrates the different types of TV anatomy. A, anterior; P, posterior; S, septal; TV, tricuspid valve.

after T-TEER (44). The latter was observed in about 30% of patients and showed association with increased rates of postprocedural residual TR ≥ 3+ (44). Recently, a retrospective study outlined the prognostic importance of the "leaflet-to-annulus-index" (LAI) on procedural TR reduction after T-TEER (45). The LAI is calculated as anterior leaflet length plus septal leaflet length divided by the septolateral tricuspid annulus diameter and was a significant and independent predictor as postprocedural TR ≥ 3+ (45). Even though the overall rates of TR reduction after T-TEER are excellent, TV anatomy might impact procedural outcomes.

The role of tricuspid regurgitation in mitral valve transcatheter edge-to-edge repair

Development of pulmonary hypertension and right ventricular dysfunction (RVD) in patients undergoing M-TEER might be associated with concomitant TR. Recent studies focused on the change in TR severity after M-TEER by hemodynamic pulmonary circulatory relief after MR reduction. Successful M-TEER was associated with modest reduction in TR severity as early as 1 month after procedure (46, 47). Nevertheless, in a significant proportion of patients, TR remains stable or even worsens. Several retrospective observational studies sought to identify predictors for worsening TR after M-TEER. Identified predictors were atrial fibrillation, the degree of residual postprocedural MR, TAD and less procedural sPAP reduction (47, 48). Consequently, effective reduction of MR, as well as preserved RV dimensions seem to be important prerequisites for reduction of concomitant TR. Although studies have shown promising success rates of simultaneous mitral and tricuspid transcatheter repair (M/T-TEER) (9), the question of optimal patient selection for M/T-TEER and its added benefit remains open.

Furthermore, it is controversial whether moderate or advanced TR has independent prognostic importance in patients undergoing M-TEER for severe MR. A subanalysis of the COAPT trial sought to assess on outcomes in patients with HF and severe secondary MR in both the treatment and control-group. Of note per protocol, patients with TR requiring surgery or transcatheter treatment were excluded. Overall, 15.4% presented with moderate and, 0.8% with moderate-to-severe and 0.2% with severe TR. Interestingly, TR ≥ 2+ was a significant independent predictor for the combined endpoint (HHF/2-year mortality) in the GDMT, but not in the M-TEER group (49). Of note, due to the fact that patients with more severe concomitant TR presented with smaller LV dimensions while having comparable LV function and RV dimensions, the authors hypothesize that these individuals represent a certain MR phenotype with combined pre- and postcapillary pulmonary hypertension (49). In contrast to the controlled conditions of the COAPT study, under "real-world" conditions also patients with severe TR are treated. To what extent the results are applicable to such a patient population is unclear at the

moment. Real-world observational studies are inconclusive about the prognostic impact of high-grade TR after M-TEER (50–52).

Summary, gap of evidence and conclusion

The "renaissance" of the RV and TV in cardiovascular medicine and research has clearly a significant impact on the dynamic field of transcatheter edge-to-edge repair. For both mitral and tricuspid valve repair, the RV is gaining importance in clinical decision making due to its eminent pathophysiologic and therefore prognostic role.

The interplay of RV, MV, and TV and their respective extravalvular structures needs a detailed preprocedural multimodal imaging evaluation for treatment planning. This is of utmost importance for the TV, as anatomic and functional variability is high (18). Valve imaging is still a relatively novel field with recent advances in 3D assessment. These have improved our understanding of their valve anatomy and have contributed to the ongoing success of TEER. While CMR is currently the "state-of-the-art" imaging modality for MR and RV assessment, its wide-spread availability is limited. For TR, the best imaging modality has yet to be defined. Therefore, 3D echocardiography of the RV is rapidly evolving and getting closer to the gold standard in terms of prognostic information and reliability, as it is the primary imaging modality in most transcatheter-treated patients.

Optimizing patient selection for T-TEER or combined M/T-TEER is an important question to be resolved in the future. Although some observational studies have addressed this issue, randomized data are urgently needed. In fact, randomized trials of T-TEER are underway, and will confirm or refuse the prognostic impact of e.g., proposed cut-off values of RV dysfunction (37, 39). But even in the case of valid prognostic value, the decision to refuse a T-TEER treatment in case of severe RV dysfunction is not based on one parameter but on the combined knowledge expressed by the heart team.

For combined M/T-TEER, it is currently unknown whether an approach similar to surgery has added benefit over isolated TEER or a staged procedure. In the surgical field, current guidelines recommend concomitant tricuspid surgery for severe TR when primary left-sided valve surgery is indicated. In case of mild or moderate TR, certain anatomic parameters have to be taken into account for this concomitant surgical approach. For the transcatheter approach, there is no such recommendation, as concise data is missing. Potentially, RV and LV function could give us the answer which patients needs concomitant, staged, or isolated treatment with a meaningful clinical benefit in each of the latter cases.

Even though numerous retrospective studies were performed to shed light into the world of T-TEER, until today, there have been no randomized-controlled studies which have shown the benefit of T-TEER and optimal medical therapy (OMT) vs. OMT alone. Currently, four large, randomized trials are ongoing in order to close this gap in evidence (TRILUMINATE, CLASP II TR; TRI-FR; TRIC-I-HF). Beyond that, it remains unclear which patients with concomitant mitral and tricuspid regurgitation need to be treated simultaneously and in which patients' treatment of MR alone might be sufficient.

In conclusion, we believe that RV function is of key prognostic importance in patients undergoing TEER and its evaluation needs to be performed using state of the art 3DE technologies in order to comprehend the RVs anatomical and functional complexity. We believe that the journey toward a comprehensive understanding of RV function and hemodynamics has only begun but can further improve the quality of TEER treatment through optimized patient selection.

Author contributions

LS and MatO wrote the preliminary version after conceptual development. CH, DB, JH, LW, MarO, MN, MW, PD, SM, and TS edited the text and figures according to their expertise. All authors contributed to the article and approved the submitted version.

Conflict of interest

Author MatO has received speaker fees from Tomtec Imaging System. Authors DB and MN were received speaker honoraria from Abbott Vascular. Author MarO has received speaker honoraria from Abbott Medical, AstraZeneca, Abiomed, Bayer vital, BIOTRONIK, Bristol Myers Squibb, CytoSorbents, Daiichi Sankyo Deutschland, Edwards Lifesciences Services, and Sedana Medical. Author JH has received speaker honoraria from and serves as consultant for Edwards Lifesciences.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Hemodynamics of transcatheter tricuspid valve replacement with Lux-Valve

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Objective: Transcatheter tricuspid valve intervention (TTVI) has emerged as an alternative treatment option for high-risk and inoperable patients with symptomatic tricuspid regurgitation (TR). However, scarce data in hemodynamic profiles were available on TTVI. In this paper, we attempt to report the hemodynamic profiles of LuX-Valve.

Methods: 30 patients from July 2020 to July 2021 were enrolled in this study. The patient was diagnosed with severe symptomatic TR. The clinical, invasive hemodynamic, and echocardiographic data were collected.

Results: The surgical success rate was 100%. The cardiac index and stroke volume increased sharply from 2.42(2.27, 2.85) and 47.8(43.6, 62.0) to 3.04 ± 0.63 and 57.2 ± 14.7, respectively. With the elimination of TR and the increase of forward blood flow of the tricuspid valve, the extravascular lung water [798.0 (673.0, 1147.0) vs. 850.3 ± 376.1, $P < 0.01$] increased subsequently. The peak right atrium pressure decreased after Lux-Valve implantation (21.0 ± 6.4 vs. 19.4 ± 6.5, $P < 0.05$). On the contrary, the nadir right atrium pressure increased [10.0(8.0, 15.0) vs. 12.0(10.0, 17.0), $P < 0.01$]. Notably, the right atrium pressure difference dropped sharply from 9.0(5.0, 13.0) to 5.0(4.0, 8.0) after Lux-Valve implantation. There was no significant change in the pulmonary artery pressure. The right atrium volume decreased from 128(83, 188) to 91(67, 167) mL at 1 month and 107(66,157) mL at 6 months. With the remolding of the right heart chamber, the tricuspid annulus diameter shrank significantly from 42.5 ± 5.6 to 36.6 ± 6.3 mm at 1 month and 36.0 (33.0, 38.0) at 6 months.

Conclusion: Invasive right atrium pressure may act as a potential candidate for TR evaluation and procedural guidance. Elimination of TR by LuX-Valve implantation improves the cardiac output and right atrium pressure and has no significant effect on the pulmonary artery pressure even with the increment of forward blood flow, suggesting the hemodynamic superiority of transcatheter tricuspid valve replacement but needs further study.

KEYWORDS

hemodynamics, tricuspid regurgitation, transcatheter tricuspid valve intervention (TTVI), LuX-Valve, transcatheter tricuspid valve replacement

What is known?

Compared with conservative medical treatment alone, transcatheter tricuspid valve intervention can significantly reduce the risk of rehospitalization and mortality due to heart failure.

The cardiac function and exercise tolerance were significantly improved during follow-up in severe TR patients after LuX-Valve implantation procedure, suggesting that LuX-Valve system was safe and effective in symptomatic severe TR patients.

What the study adds?

Elimination of TR by LuX-Valve implantation improves the cardiac output and has no significant effect on the pulmonary artery pressure even with the increment of forward blood flow.

The decreased tricuspid annulus diameter and right atrium volume suggest the remolding of right heart after TR elimination.

Invasive right atrium pressure is an important parameter in hemodynamics.

Introduction

Tricuspid regurgitation (TR) is the most common and neglected valvular heart disease of the right heart system. Secondary TR with the characteristics of right heart enlargement and tricuspid annulus (TA) dilation, which arises as a consequence of pulmonary hypertension induced by left-heart valve surgery and atrial fibrillation, takes the predominant position (1). The majority of TR patients are with the manifestation of chronic hepatic and renal insufficiency, coagulation dysfunction, and poor nutritional status on account of long-term right ventricular dysfunction (2). Hence, the mortality and complication risks of redo tricuspid valve surgery are high (3, 4). It is worth mentioning that most patients received diuretic therapy, but the symptoms of cardiac failure were not well controlled. Compared with conservative medical treatment alone, transcatheter tricuspid valve intervention (TTVI) can significantly reduce the risk of rehospitalization and mortality due to heart failure, suggesting the importance of TTVI (5). Based on the aforementioned characteristics, the 2021 European Society of Cardiology guidelines for valvular heart disease for the first time recommends TTVI as a treatment option for severe symptomatic TR patients at IIb level C (6).

Abbreviations: RA, right atrium; RV, right ventricle; TTVI, transcatheter tricuspid valve intervention; TTVR, transcatheter tricuspid valve replacement; TR, tricuspid regurgitation; TA, tricuspid annulus; PICCO, pulse indicator continuous cardiac output.

TTVI is in its infancy but with a booming tendency, and gradually becomes an alternative option to minimally invasive surgery (7–9). Nowadays, TTVI includes leaflet repair, valvuloplasty, heterotopic valve replacement, and orthotropic valve replacement. The approaches include transjugular, transfemoral, and right atrium. However, the concerns for TTVI complications, including low implantation success rate, damage to the surrounding structures of the tricuspid valve (right coronary artery and conduction bundle), and device migration, have been reported in previous studies cohort. Transcatheter tricuspid valve replacement (TTVR) has captured our attention for its merit of eliminating TR instead of degradation of TR. Nevertheless, TTVR is challenging from a technical perspective. At first, the TA is a 3D shape with little calcification, which is insufficient to provide a reliable anchoring zone (10). Secondly, the diameter of the TA changes dynamically with the cardiac cycle, leading to an incomplete fit of the bioprosthesis and the native TA, which may lead to paravalvular leakage. At last, most of the currently reported orthotopic TTVR devices are based on the principle of radial force-dependent, the size of bioprosthesis is unavailable once TA is excessively dilated.

Notably, invasive hemodynamic monitoring has been the cornerstone of surgical management of valvular heart disease. With the popularity of echocardiography, the application of invasive hemodynamic monitors was once limited. However, invasive hemodynamics have been revived with the rise of TTVI recently (11). Exploring hemodynamic changes could not only guide TTVI patient selection and predict patient prognosis, but also deepen the understanding of the pathophysiology of valvular heart disease (12). Previous studies have confirmed that TR elimination after Lux-valve implantation could improve the clinical symptoms, cardiac function, and exercise tolerance of patients (13). However, scarce data in hemodynamic profiles were available on TTVI. In this paper, we attempt to report the hemodynamic changes of LuX-Valve.

Methods

Design and patient enrollment

A total of consecutive 30 patients (11 males) between July 2020 and July 2021 with severe TR were enrolled in this prospective study. All patients who underwent TTVR were with informed consent. The patients were comprehensively evaluated by a multidisciplinary team before surgery and deemed unsuitable for open-heart surgery. The exclusion criteria were listed below: Patients with severe pulmonary hypertension ($\geq$55 mmHg), low left ventricular function (left ventricular ejection fraction $<$50%), low right ventricular function (tricuspid annular plane systolic excursion (TAPSE) $<$ 10 mm or right ventricle fractional area change (FAC) $<$

20%), untreated severe coronary heart disease, coagulation dysfunction, and life expectancy < 12 months.

The design of LuX-Valve has been described accurately previously, including a tri-leaflet bioprosthesis, ventricular septal anchor "tongue," two leaflet-grasping clips, and an atrial disc (13–15). Preoperative evaluation of the degree of TR, hemodynamics, and right heart anatomy were achieved by echocardiography, right heart catheterization, and gated cardiac contrast-enhanced CT. Because of the complexity of the anatomical structure of the tricuspid valve complex, preoperative imaging analysis is a key factor for successful implantation. The optimal projection angle and bioprosthesis size were determined by analyzing CT before surgery. The invasive pressure of pulmonary artery, right atrium, and right ventricular were recorded before and after Lux-Valve implantation. The echocardiography data at baseline, 1 month after discharge, and 6 months after discharge were required to collect for all enrolled patients.

Operative procedure

TTVR was performed under general anesthesia in the digital subtraction angiography operating room, and transesophageal echocardiography (TEE) was prepared in advance. The pulse indicator continuous cardiac output (PICCO, PULSION, Germany) was monitored by catheterization of the internal jugular vein and femoral artery. The cardiac output was calculated by thermodilution. The right atrial incision was adopted for the surgical approach. Double-layer 4–0 Prolene purse string suture was used for assisting the implantation of the delivery sheath. TEE was used to guide the implantation of the delivery sheath and LuX-Valve positioning during the operation.

Given the unique anchoring method of LuX-Valve and the periodic changes of the TA with the cardiac cycle, there was no requirement for strict alignment between TA and bioprosthesis plane from our experience. The delivery sheath was adjusted under the guidance of fluoroscopy and TEE to ensure its parallel direction to the interventricular septum for facilitating the fixation of the interventricular septum anchoring component. The bioprosthesis was slowly released with the retrieval of the delivery sheath. The periodical shake of grasping clips could be observed under fluoroscopy once the tricuspid anterior leaflet was hooked. And then, the atrial disc was gradually rebounded. Finally, the ventricular septal anchor "tongue" was secured to the anchoring zone. The time interval from the entry of the delivery sheath into the right atrium and the withdrawal of the sheath out of the right atrium was defined as the device time. As for the TR patients with prior permanent pacemaker implantation, the pacing lead was placed between the bioprosthesis and the native TA after Lux-Valve reimplantation. The hemodynamics was measured immediately before and after Lux-Valve implantation by PICCO.

The study design for hemodynamics management of Lux-Valve was shown in Figure 1. Dopamine was used when necessary for inotropic support after surgery. Anticoagulation of warfarin was resumed once pleural fluid drainage was reduced after surgery, and low-molecular-weight heparin bridging anticoagulation was not used in this study. The average time of initiation of warfarin anticoagulation was 2.0 days post-operation. Of note, optimization of intravascular volume was performed during the perioperative period and follow-up.

Statistical analysis

Statistical analysis was performed using SPSS V21.0 (Chicago, Illinois, USA). Normally distributed continuous variables were expressed as mean ± standard deviation, and non-normally distributed continuous variables were expressed as median (interquartile range). Categorical variables are expressed as frequencies (proportions). The comparison of normally distributed continuous variables was tested with a paired-sample *t*-test or two-way ANOVA properly. The comparison of non-normally distributed continuous variables was tested with Wilcoxon or Friedman test properly. $P < 0.05$ was considered statistically significant.

Results

Baseline

Table 1 presented the baseline data of the TR patients with a mean age of 65.2 years. The Society of Thoracic Surgeons (STS) and CRS scores were 8.966 ± 4.968 and 8.0 (8.0, 8.2). Kansas City Cardiomyopathy Questionnaire (KCCQ) and 6-min walk distance (6MWD) were 49.0 ± 13.0 and 259.3 ± 70.3 m, respectively. 20 patients were classified as NYHA class III. The main complaint of the patients was chest distress in 28 cases, peripheral edema in 23 cases, and abdominal distension with anorexia in 18 cases. Twenty seven patients received regular oral diuretics before surgery, 24 patients had previous left heart valve replacement surgery, including 13 cases of mitral valve replacement, 11 cases of double valve replacement. Five patients received previous permanent pacemaker implantation. The results of preoperative outcomes were shown in Table 2. The average brain natriuretic peptide was 164.9 pg/mL. The electrocardiogram result indicated that 25 patients were with atrial fibrillation. Ascites was identified by abdominal ultrasound in 3 cases. Echocardiography showed all patients were with severe TR with an instantaneous regurgitation volume of 51.7 ± 27.4 mL. The tricuspid annular plane systolic excursion (TAPSE) and fractional area change (FAC) were 15.0(13.0, 18.0) mm and 46.5 ± 6.8%, respectively. The diameter of the TA was 42.5 ± 5.6 mm (Range: 31–55 mm). Right heart catheterization

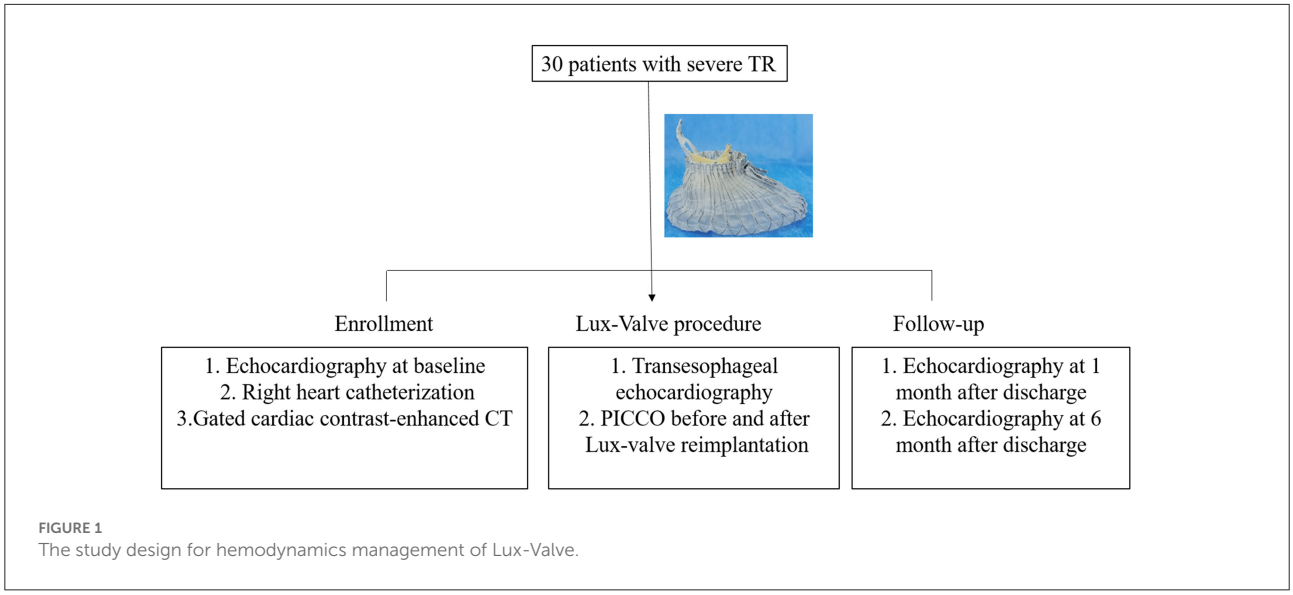

FIGURE 1
The study design for hemodynamics management of Lux-Valve.

result indicated that the pulmonary systolic and diastolic blood pressures were 40.2 ± 7.6 and 18.7 ± 5.1 mmHg, respectively.

Perioperative outcome

The perioperative outcome was shown in Table 3. Surgical success was achieved in all patients. The average operation time and device time were 180.0 (140.0, 180.0) and 11.5 ± 4.4 min, respectively. The main valve size used in this study was 28–50 mm. Two cases underwent secondary thoracotomy for hemostasis due to excessive pleural fluid drainage. Additionally, 1 patient underwent redo surgery 10 days after LuX-Valve implantation on account of valve migration and died perioperatively. One patient had moderate paravalvular leakage after valve implantation. There was no occurrence of hemodialysis, new-onset of permanent pacemaker implantation, and prolonged ventilation. The ICU time and in-hospital time were 2.0 (2.0, 2.0) and 24.5 ± 7.8 days, respectively.

Hemodynamic study

Of note, we monitored the hemodynamics during operation by PICCO, and the results were shown in Table 4. The cardiac index and stroke volume increased sharply from 2.42(2.27, 2.85) and 47.8(43.6, 62.0) to 3.04 ± 0.63 and 57.2 ± 14.7, respectively. The stroke index and global ejection fraction after LuX-Valve implantation were significantly higher than before operation. With the elimination of TR and the increase of forward blood flow of the tricuspid valve, the extravascular lung water increased subsequently. The extravascular lung water index and pulmonary vascular permeability index decreased significantly from 16.3 ± 6.7 and 2.7 (1.7, 3.5) to 13.0 (9.0, 20.5) and 2.0 (1.3, 3.4), respectively. In contrast, there was no significant change in the pressure of systemic circulation and pulmonary circulation.

In addition, the invasive pressure of right atrium and right ventricle were recorded during operation (Table 5). The peak right atrium pressure decreased after Lux-Valve implantation (21.0 ± 6.4 vs. 19.4 ± 6.5, $P<0.05$). On the contrary, the nadir right atrium pressure increased [10.0(8.0, 15.0) vs. 12.0(10.0, 17.0), $P<0.01$]. Notably, the RA pressure difference dropped sharply from 9.0(5.0, 13.0) to 5.0(4.0, 8.0) after Lux-Valve implantation. The volume of right atrium decreased from 128(83,188) mL to 91(67,167) mL at 1 month and 107(66,157) mL at 6 months after elimination of TR and the remodeling of the right heart during follow-up (Table 6). The volume of left ventricle increased significantly with the increment of forward blood flow. The TAPSE decreased significantly from 15.0(13.0, 18.5) to 10.5 ± 3.2 mm after 1 month and 11.0 ± 3.3 mm after 6 months. The FAC and LVEF decreased slightly but without significance. With the remolding of the right heart, the TA diameter shrank significantly from 42.5 ± 5.6 to 36.6 ± 6.3mm at 1 month and 36.0 (33.0, 38.0) at 6 months.

Discussion

In this paper, we reported the hemodynamic profiles of LuX-Valve implantation. Elimination of TR by LuX-Valve implantation improves the cardiac output and has no significant effect on the pulmonary artery pressure even with the increment of forwarding blood flow. Our previous studies have demonstrated that TTVR using LuX-Valve system was safe and effective in symptomatic severe TR patients. The cardiac function and exercise tolerance were significantly improved

TABLE 1 Patients' profile.

	Patient ($N = 30$)
Male	11(36.7%)
Age /years	65.2 ± 7.9
Height/cm	161.6 ± 6.7
Weight/kg	57.9 ± 8.9
Body surface area	1.62 ± 0.13
STS score	8.966 ± 4.968
CRS score	8.0(8.0, 8.2)
KCCQ score	49.0 ± 13.0
NYHA class	
III	20(66.7%)
IV	10(33.3%)
6MWD/m	259.3 ± 70.3
Symptoms	
Chest distress	28(93.3%)
Peripheral edema	23(76.7%)
Abdominal distention	18(60.0%)
Comorbidities	
Hypertension	6(20.0%)
Diabetes mellitus	3(10.0%)
Coronary artery disease	4(13.3%)
Permanent pacemaker implantation	5(16.7%)
Cerebrovascular accident	3(10.0%)
Prior surgery	
MVR	13(43.3%)
DVR	11(36.7%)
PCI	1(3.3%)
CABG	1(3.3%)
Medication	
ACEI/ARB	3(10.0%)
Beta blocker	4(13.3%)
Calcium channel blocker	2(6.7%)
Diuretic	27(90.0%)

6MWD, 6 Min Walk Distance; MVR, Mitral valve replacement; DVR, Double valve replacement; PCI, Percutaneous Coronary Intervention; CABG, Coronary Artery Bypass Grafting; ACEI, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker.

TABLE 2 Preoperative outcomes.

	Patient ($N = 30$)
Laboratory test	
Leukocyte	4.75(3.57,5.99)
Hemoglobin (g/L)	122.0(106.0,133.0)
Platelet	144.3 ± 40.8
Creatinine (μmol/L)	77.0 ± 25.1
Total bilirubin(μmol/L)	20.0 ± 9.1
Direct bilirubin(μmol/L)	6.8(4.9, 10.1)
Albumin(g/L)	41.3 ± 3.6
Brain natriuretic peptide(pg/mL)	164.9(103.2, 307.5)
Electrocardiography	
Atrial fibrillation	25(83.3%)
Pacing rhythm	5(16.7%)
Ascites	3(10.0%)
Pleural effusion	0(0%)
Echocardiography	
Left ventricular ejection fraction (%)	62.9 ± 8.8
Transient Tricuspid regurgitation Volume (mL)	51.7 ± 27.4
TAPSE (mm)	15.0(13.0,18.0)
FAC (%)	46.5 ± 6.8
Tricuspid annulus (mm)	42.5 ± 5.6
Flow reversal in the inferior vena cava	30(100%)
Right heart catheterization	
Pulmonary artery systolic pressure/mmHg	40.2 ± 7.6
Pulmonary artery diastolic pressure/mmHg	18.7 ± 5.1

TAPSE, Tricuspid Annular Plane Systolic Excursion; FAC, Fractional Area Change.

during follow-up (13). Moreover, we, for the first time, proved the feasibility of elimination of TR by Lux-Valve instead of degradation of TR from the hemodynamic aspect.

Prolonged TR leads to hemodynamic abnormalities were verified to be associated with congestive hepatopathy and kidney dysfunction, which was associated with decreased forward cardiac output and circulation perfusion, as well as increased right-sided filling pressure and venous congestion. TR reduction by TTVR device was demonstrated to improve liver function (16). Once TR is eliminated, right atrial pressure should theoretically drop significantly. Instantaneous right atrial pressure changes combined with a marked increase in cardiac output were observed in our study, which may contribute to improved organ function and increased exercise tolerance. Further, intraprocedural invasive right atrial pressures were demonstrated to be associated with TR severity and patient outcomes after transcatheter tricuspid edge-to-edge repair. A lower RA pressure difference was proved with improved outcomes (17). Dannenberg V and colleagues assumed hemodynamic assessment before TTVR was a significant factor for patient prognosis, the logistic regression analysis verified a significant relationship between mean RA pressure and ≥1 grade TR reduction (18). Collectively, a more comprehensive investigation of invasive right atrial pressures may be needed in larger tricuspid TTVI cohorts.

It is also worth noting that in another study of transcatheter tricuspid valve-in-valve therapy for bioprosthetic valve failure, pulmonary artery pressure was increased after valve replacement. In this study, however, pulmonary artery pressure was not significantly changed. This finding led us to focus on hemodynamic studies of Lux-valve. Our results suggest that Lux-valve implantation directly eliminates TR and the

TABLE 3 Perioperative outcome.

	Patient ($N = 30$)
Operation time/min	180.0(140.0,180.0)
Device time/min	11.5 ± 4.4
Lux–valve size	
28–40	4(13.3%)
28–50	10(33.3%)
28–55	4(13.3%)
30–40	2(6.7%)
30–50	5(16.7%)
30–55	5(16.7%)
Postoperative 24h chest drainage volume (mL)	95.0(40.0,210.0)
Complications	
Hemodialysis	0(0%)
IABP	0(0%)
Permanent pacemaker implantation	0(0%)
Prolonged Tracheal Intubation (>72h)	0(0%)
Reoperation for bleeding	2(6.7%)
Reoperation for valve migration	1(3.3%)
Paravalvular leakage	1(3.3%)
ICU time/day	2.0(2.0,2.0)
In–hospital time/day	24.5 ± 7.8
Death	1(3.3%)

IABP, Intra Aortic Balloon Pump; ICU, Intensive Care Unit.

TABLE 4 PICCO results.

	Before TTVR	After TTVR
Central venous pressure	14.9 ± 4.5	14.8 ± 4.7
Heart rate	82.1 ± 11.8	87.7 ± 11.5*
Systolic blood pressure	116.3 ± 13.9	126.5 ± 22.4*
Diastolic blood pressure	63.5 ± 12.1	66.6 ± 13.2
Cardiac index	2.42(2.27,2.85)	3.04 ± 0.63***
Stroke Volume	47.8(43.6,62.0)	57.2 ± 14.7**
SVR	1297.0(1025.5,1670.5)	1245.0 ± 376.6
SI	29.4(26.7,35.5)	33.5(30.6,38.4) ***
GEF	14.4 ± 4.0	15.0 ± 3.9*
SVV	23.0 (19.5,25.8)	17.7 ± 8.9
EVLW	798.0 (673.0,1147.0)	850.3 ± 376.1 **
GEDI	906.0 (759.0, 1030.0)	928.0 (866.5, 1016.0) *
EVLWI	16.3 ± 6.7	13.0 (9.0,20.5) **
PVPI	2.7 (1.7, 3.5)	2.0 (1.3, 3.4) **
PAPS	41.1 ± 7.5	42.6 ± 8.4
PAPD	20.0 ± 4.7	20.8 ± 4.3

PICCO, pulse indicator continuous cardiac output;TTVR, transcather tricuspid valve replacement; SVR, systemic vascular resistance; GEF, global ejection fraction; SVV, Stroke Volumee Variation; SI, stroke index; EVLW, extravascular lung water; EVLWI, extravascular lung water index; GEDI, global enddiastolic index; PVPI, Pulmonary Vascular Permeability Index.
PAPS, systolic pulmonary artery pressure; PAPD, Diastolic pulmonary artery pressure. *P < 0.05; **P < 0.01; ***P < 0.001.

TABLE 5 Catheterization results.

	Before implantation	After implantation
Peak RV pressure	41.5 ± 7.7	44.0 ± 9.2
Nadir RV pressure	9.4 ± 7.1	7.0 ± 5.1*
Mean RV pressure	21.9 ± 5.4	22.1 ± 5.0
Peak RA pressure	21.0 ± 6.4	19.4 ± 6.5*
Nadir RA pressure	10.0(8.0,15.0)	12.0(10.0,17.0)**
Mean RA pressure	15.0 ± 4.9	15.4 ± 5.4
RA pressure difference	9.0(5.0,13.0)	5.0(4.0,8.0)**
Systolic PAP	41.4 ± 7.2	42.7 ± 8.4
Diastolic PAP	19.8 ± 5.0	20.3 ± 5.2
Mean PAP	28.0(24.0,32.0)	28.8 ± 6.0

RA, right atrium; RV, right ventricle pressure; PAP, pulmonary artery pressure. *P < 0.05; **P < 0.01.

increased forward flow does not result in a significant elevation of the pulmonary artery. However, with the increase of forward blood flow, it will inevitably lead to an increase in pulmonary perfusion and left ventricular preload. Therefore, the left ventricular function of TR patients must be in a normal range. For patients with abnormal left ventricular function, the choice of TTVR should be prudent. Additionally, a strengthened diuretic therapy for optimization of intravascular volume was necessary after TTVR since extravascular lung water was elevated as evidenced by PICCO.

As for the significant increase in cardiac stroke volume, it could be explained from the Frank-Starling relationship. Right ventricular stroke volume rise on account of the increase of right ventricular preload. However, a sudden increase in right ventricular filling pressure can lead to decreased compliance of the right ventricular with chronic low right ventricular preload. This may explain the reason why the right ventricular systolic function (TAPSE and FAC) decreased after surgery. Long-term chronic right and left ventricular adaptations after surgery may lead to improved postoperative exercise capacity of TR patients (19). Previous studies have also confirmed that different TTVI devices could significantly improve the clinical symptoms of TR patients, which was demonstrated by the NYHA class, 6MWD, and KCCQ score (20). Additionally, right ventricular remodeling during follow-up, including the decreased TA and the increased TAPSE and FAC level, was verified by echocardiography in previous study (21). However, a decline in TAPSE level was observed in the majority of patients during follow-up in our study. Previous studies have shown that TAPSE has no significant effect on the prognosis of TTVI patients (22). On the contrary, the patient's exercise tolerance and NYHA class during follow-up were significantly improved compared with before operation, which further suggested that TAPSE may not be suitable for assessing right ventricular

TABLE 6 Echocardiography results.

	Before operation	1 month after TTVR	6 months after TTVR
RA volume/mL	128(83,188)	91(67,167)*	107(66,157)*
RV volume/mL	66(45,94)	58.6 ± 21.0	52(41,64)
LA volume/mL	133(106,213)	147(104,203)	151(107,218)
LV volume/mL	90.9 ± 23.8	104.8 ± 32.0**	103.3 ± 32.0*
Tricuspid annulus /mm	42.5 ± 5.6	36.6 ± 6.3 ***	36.0(33.0,38.0) ***
TAPSE/mm	15.0(13.0,18.0)	10.5 ± 3.2***	11.0 ± 3.3***
FAC/%	46.5 ± 6.8	45.1(40.8,48.1)	43.2 ± 11.8
LVEF/%	62.9 ± 8.8	57.0(53.5,66.0)	57.6 ± 10.3

RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. TAPSE, Tricuspid Annular Plane Systolic Excursion; FAC, Fractional Area Change; LVEF, Left ventricular ejection fraction. *P < 0.05 compared to before operation; **P < 0.01 compared to before operation; ***P < 0.001 compared to before operation.

function. A novel parameter may be needed for right ventricular function assessment in the future.

The application of TTVR devices was in a backward position when compared to other transcatheter repair devices. TTVR may be applicable to a broader indication because of incomplete degrees of TR reduction and functional improvement of the repair devices. In 2017, the GATE bioprosthesis (NaviGate, California, USA) was first reported for clinical application, which was implanted through the transatrial access with 100% technical success, 20% reoperation, and 20% mortality (23, 24). In addition, the EVOQUE system was also used in a compassionate cohort including 25 patients with a technical success rate of 92%. There was no occurrence of intraprocedural mortality, coronary injury, and valve migration, combined with a 100% TR level decrease (25).

TR induced by pacemaker lead could not be neglected in TTVI study, in addition, the TR patients with prior permanent pacemaker implantation were not uncommon. In this study, 5 (16.7%) of 30 cases were with prior permanent pacemaker implantation. The pacing lead was placed between the bioprosthesis and the native TA after Lux-Valve reimplantation. The risk of paravalvular leakage was low on account of the design of atrial disc. Anderson JH et al. identified that the TTVR in the setting of trans-tricuspid valve pacemaker leads without lead extraction or re-replacement can be performed safely with a low risk for complications after analyzing the data from the Valve-in-Valve International Database including 329 cases (26). Similarly, Taramasso M and colleagues verified that TTVI is feasible in selected patients with cardiac implantable electronic device and acute procedural success and short-term clinical outcomes are comparable to those observed in patients without a trans-tricuspid valve lead by analyzing the data from the TriValve registry (27).

In our previous work, we have reported the results of a compassionate multicenter study of Lux-Valve that enrolled 46 TR cases. The surgical success rate was 97.8% with 13.0% in-hospital mortality and 15.2% residual TR (13). 6 cases of 12-month follow-up data after LuX-Valve implantation have also been reported by Sun Z and colleagues (15). Of note, the incidence of paravalvular leakage in this study was 3.3%, which was lower than our previous study, further suggesting the importance of the learning curve in TTVR and emphasizing the importance of a more comprehensive understanding of tricuspid valve anatomy, hemodynamics, and surgical imaging guidance. At last, there are several limitation for our study. At first, the cardiac output was calculated by the thermodilution method in this study, which may lead to underestimation in the presence of significant TR. Secondly, this study was limited by its small cases.

Conclusions

In summary, this study demonstrates that elimination of TR by LuX-Valve implantation improves the cardiac output and right atrium pressure instantaneously and has no significant effect on the pulmonary artery pressure even with the increment of forward blood flow. Additionally, the decreased tricuspid annulus diameter and right atrium volume further verifies the long-term remodeling of right heart after TR elimination. A more comprehensive investigation of invasive right atrial pressures may be needed in larger TTVI cohorts.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Shanghai Changhai Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Experiment design: QF and LF. Data collection, analysis, and paper draft: LN, WW, and NX. Experiment: XZ, LB, CC, YF, BY, HL, QF, LF, and ZG. Paper revision: LF, QF, and HL. Funding: LF and LN. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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MitraClip for the treatment of heart failure with mitral regurgitation: A cost-effectiveness analysis in a Chinese setting

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Background: Heart failure (HF) with mitral regurgitation is associated with decreased survival. Guideline-directed medical therapy and transcatheter edge-to-edge repair (TEER) are the main options for HF patients with severe mitral regurgitation who are considered high-risk or prohibitive. To date, there have been no studies investigating the cost-effectiveness of MitraClip vs. optimal medical therapy (OMT) in a Chinese setting.

Methods: A combined decision tree and Markov model were developed to compare the cost-effectiveness MitraClip vs. OMT with a lifetime simulation. The primary outcome was the incremental cost-effectiveness ratio (ICER), which represented incremental costs per quality-adjusted life-year (QALY). The willingness-to-pay (WTP) threshold was set three times of per capita gross domestic product (GDP) in China in 2021, which was 242,928 CNY. MitraClip would be considered cost-effective if the ICER obtained was lower than the WTP threshold. Otherwise, it would be not considered cost-effective. One-way sensitivity and probabilistic sensitivity analyses were performed to validate the robustness of the results.

Results: After a simulation of the lifetime, the overall cost for a patient in the MitraClip cohort was 423,817 CNY, and the lifetime cost in the OMT was 28,369 CNY. The corresponding effectiveness in both cohorts was 2.32 QALY and 1.80 QALY per person, respectively. The incremental cost and increment effectiveness were 395,448 CNY and 0.52 QALY, respectively, and the ICER was 754,410 CNY/QALY. The ICER obtained was higher than the WTP threshold. Sensitivity analysis validated our finding.

Conclusion: MitraClip provided effectiveness but with more costs compared with OMT, and the incremental cost-effectiveness ratio obtained was higher than the WTP threshold. MitraClip was considered not cost-effective in Chinese HF patients with secondary mitral regurgitation.

KEYWORDS

MitraClip, heart failure, mitral regurgitation, transcatheter mitral valve repair, cost-effectiveness analysis

Introduction

Heart failure (HF), a clinical consequence arising from various causes, accounts for at least 20% of hospital admissions among patients older than 65 years (1). Uncorrected valvular diseases, such as mitral regurgitation (MR), often cause diastolic HF. The remodeling of the left ventricle (LV) caused by ischemic or dilated cardiomyopathy leads to displacements of papillary muscles and tethering of leaflets, contributing to secondary MR (2).

Studies have suggested that there is an association between MR and decreased survival in HF patients (3). MR could deteriorate LV function, resulting in adverse clinical outcomes due to a progression of LV remodeling (2). The coexistence of MR and HF significantly worsens the prognosis, and MR is an important therapeutic target for those patients (4). However, surgery is not recommended in patients with severe MR who are considered at high risk or prohibitive. For those patients, guideline-directed medical therapy (MT) and transcatheter edge-to-edge repair (TEER) are the main options (5). MitraClip, the most commonly used device of TEER, is significantly safer than surgery and improves the New York Heart Association functional class and overall survival rates (6, 7).

Since the global problem of HF is growing, the economic burden needs to be addressed. China has recently experienced an increase in HF prevalence of about 2% in recent years, with an estimated 8–10 million patients (8). In 2012, the medical security system of China faced a cost of approximately $5.4 billion related to HF (9). Although TEER is more effective than MT, the relatively high cost has hampered its widespread clinical use in China. Even in developed countries, MitraClip is highly expensive among cardiac therapies. Therefore, evaluating the cost-effectiveness of MitraClip is important for the healthcare system in China.

Materials and methods

Aims and population

This study aimed to compare the cost-effectiveness of MitraClip plus optimal medical therapy (OMT) with OMT alone in Chinese HF patients with secondary MR from the perspective of a healthcare payer. The study was based on a Chinese setting, but the population was a hypothetical cohort with similar baseline characteristics to the patients in the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) (7). In the cohort, the mean age was 72 years, 0.2% of patients had an NYHA classification of NYHA I, 39.0% of patients had an NYHA classification of NYHA II, 52.5% of patients had an NYHA classification of NYHA III, and 8.3% of patients had an NYHA classification of NYHA IV. The patients had a moderate-to-severe or severe secondary MR before enrollment and were randomized to receive MitraClip plus OMT or OMT alone. The inclusion and exclusion criteria of the study were similar to those in the COAPT trial and shown in the Supplementary material.

Model overview

The basic structure of the model consisted of two parts: one was a 30-day decision tree model, and another was a lifetime Markov model. In the 30-day decision tree model, Chinese HF patients with secondary MR were randomly allocated to receive the MitraClip procedure or OMT and would enter different NYHA classifications at the end of this stage. After this stage, the patients included would enter the Markov model with a cycle length of 1 month and a time horizon of a lifetime. In this model, patients would transition among four transition states, including NYHA I, NYHA II, NYHA III, and NYHA IV. If patients died during the cycle, they would enter the absorbed state of "dead," meaning their cycle was finished. During the cycle, all the patients received OMT, and they also might have experienced HF hospitalization or no event. As the mean age in the study was 72 years and the time horizon was a lifetime, there would be 336 cycles, equal to 28 years, until the life of 100 years, which was far higher than the life expectancy in China. A half-cycle correction was employed in the Markov model to prevent the overestimation of effectiveness and cost. The details of the model are illustrated in Figure 1, which has been validated by another study (10).

Input parameters

Transition probability

The transition probability in our model was mainly derived from the COAPT trial (7, 11). The 30-day outcome was directly extracted from the COAPT trial, and the transition probability in the Markov model was transformed from the COAPT trial to better represent the real efficacy of MitraClip *vs.* OMT. The transition probability in the COAPT trial was not reported in the published paper, but it was calculated by Estler et al. (10). The transition probability between NYHA classifications is presented in Table 1.

Costs

The cost of the MitraClip device and other MitraClip-related costs were accessed from a Chinese hospital (12), as there was no study on the cost of MitraClip in China. The cost of the MitraClip device was 322,000 Chinese Yuan (CNY) (equal to 49,922 USD, according to the average ratio of 6.45

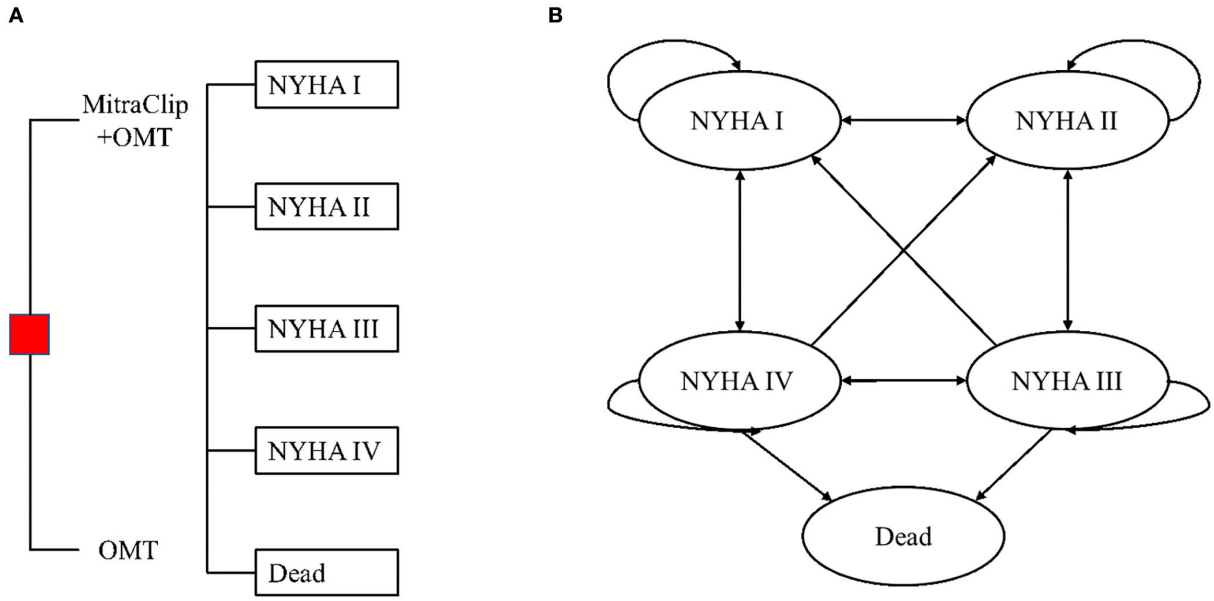

FIGURE 1
(A) Decision tree and **(B)** state transition diagram of the Markov model. OMT, optimal medical therapy. HF patients with moderate-to-severe or severe secondary MR were randomly allocated to receive MitraClip plus OMT or OMT alone. One month after the MitraClip procedure/OMT, patients would enter the Markov model and transition among these four NYHA classifications until they entered the terminal node of the dead.

TABLE 1 Transition between NYHA classifications in MitraClip and OMT cohort.

From / To	NYHA I	NYHA II	NYHA III	NYHA IV	HF death	References
MitraClip/OMT						
NYHA I	0.960/0.950	0.040/0.050	0/0	0/0	0/0	(7, 10)
NYHA II	0.005/0.010	0.945/0.940	0.050/0.040	0/0.010	0/0	(7, 10)
NYHA III	0/0	0.025/0.020	0.895/0.920	0.070/0.050	0.010/0.010	(7, 10)
NYHA IV	0/0	0/0	0/0	0.800/0.750	0.200/0.250	(7, 10)

NYHA, New York Heart Association; OMT, optimal medical therapy; HF, heart failure.

in 2021), accounting for over 80% of the overall cost. Other MitraClip-related costs included procedure costs, nursing costs, ward costs, diagnosis costs, medicine costs, complication costs, etc. The cost of the MitraClip device and other MitraClip-related costs were only calculated in the MitraClip cohort, but the cost of OMT and HF hospitalization was calculated in both cohorts. The cost of OMT was derived from a study investigating the burden of HF in China, and the annual cost of OMT and cost of HF hospitalization were 5,138 CNY and 10,926 CNY, respectively (13). Regarding the cost of the MitraClip device and other MitraClip-related and HF hospitalization costs, a one-time cost was employed. However, for the cost of OMT, the annual cost was converted into the monthly cost and input into the model. All the costs were converted to the corresponding costs in China in 2021 using the Consumer Price Index (CPI) in China in the past few years (Table 2). The healthcare CPI in China from 2015 to 2021 were 1.027, 1.038, 1.06, 1.043, 1.024, 1.018, and 1.004, separately (23).

Utility

The utility of MitraClip-related cost was derived from a study of cost-effectiveness analysis, which reported that the one-month disutility for the MitraClip procedure was −0.043 (10, 19). The utility of different NYHA classifications was obtained from a study of the Chinese population (17). The utilities of NYHA I, II, III, and IV were 0.78, 0.78, 0.715, and 0.66, respectively. Regarding the utility of HF hospitalization, the common disutility of −0.1 was employed in the model (20, 21). Similar to the input of costs, the input of NYHA utilities was also converted to monthly utility, but other one-time utilities were not converted (Table 2).

TABLE 2 Input parameters of decision tree and Markov model.

Parameters	Base	Range	Distribution	References
Cost of MitraClip related (CNY)				
Device	322,000	161,000–386,400	γ	(12)
Procedure	12,172	6,086–24,343	γ	(12)
Diagnosis	16,249	8,125–32,499	γ	(12)
Medicine	5,018	2,509–10,037	γ	(12)
Complications	15,070	7,535–30,140	γ	(12)
Ward	683	341–1,365	γ	(12)
Nursing	659	330–1,319	γ	(12)
Others	23,808	11,904–47,616	γ	(12)
Monthly cost of OMT (CNY)[a]	428	214–856	γ	(13)
Cost of HF hospitalization (CNY)[b]	10,926	5,463–21,852	γ	(13)
Cost in scenario analysis				
German MitraClip device cost	247,478	/	/	(10)
US MitraClip device cost	197,597	/	/	(14)
Japanese MitraClip device cost	179,504	/	/	(15)
UK MitraClip device cost	143,951	/	/	(16)
Utility (Monthly)				
NYHA I[c]	0.065	0.062–0.068	β	(17)
NYHA II	0.065	0.062–0.068	β	(17)
NYHA III	0.060	0.057–0.063	β	(17)
NYHA IV	0.055	0.052–0.058	β	(17)
Average disutility of complications	0.005	0.003–0.007	β	(10, 18)
Disutility of MitraClip procedure	0.043	0.034–0.051	β	(10, 19)
Disutility of HF hospitalization	0.10	0.08–0.13	β	(20, 21)
Discount rate	0.05	0–0.08	/	(22)

[a]Monthly cost of OMT is 428 = (679*29/2 + 711.1*19.2)/(29/2 + 19.2)*6.75*1.043 *1.024*1.018* 1.004/12.
[b]Cost of HF hospitalization is 10926 = (1218.4*36.7/2 + 1646.8*29.6) /(29.6 + 36.7/2)*6.75*1.043 *1.024 *1.018*1.004.
[c]Monthly utility of NYHA I is 0.065 = 0.780/12.

Analysis

The primary outcome of the study was the incremental cost-effectiveness ratio (ICER), which represented incremental costs per quality-adjusted life-year (QALY). The willingness-to-pay (WTP) threshold was set three times of per capita gross domestic product (GDP) in China in 2021, according to the China Guidelines for Pharmacoeconomic Evaluations (22), which was $242,928\ CNY = 80,976\ CNY\ x\ 3$. MitraClip would be considered cost-effective if the ICER obtained was lower than the WTP threshold. Otherwise, it would be considered not cost-effective. Moreover, if MitraClip was not cost-effective, the cost-effective cost would be calculated, mainly including the overall cost and the cost of the MitraClip device. Scenario analysis based on the cost of the MitraClip device in other regions was also performed.

Sensitivity analysis included one-way sensitivity analysis and probabilistic sensitivity analysis (PSA). In the one-way sensitivity analysis, input parameters varied between their 95% confidence interval (CI), and the results of one-way sensitivity were shown with a Tornado Diagram. In the PSA, 10,000 times of Monte Carlo simulation based on probabilistic sensitivity sampling was employed. Costs were assumed to follow the gamma distribution. Transition probability and utility were assumed to follow the beta distribution in the PSA. The results of PSA were illustrated using a scatter plot and cost-effectiveness acceptability curve.

Results

Table 3 shows model input values for baseline patient characteristics of the COAPT population.

Base case analysis

In the base case analysis, the lifetime cost for a patient in the MitraClip cohort was 423,817 CNY, and the lifetime cost in the OMT cohort was 28,369 CNY. The corresponding effectiveness

TABLE 3 Model input values for baseline patient characteristics of the COAPT population.

Parameters	COAPT population
Age, years (mean)	72.3
Male (%)	64.1
Diabetes (%)	37.3
Hypertension (%)	80.5
Previous myocardial infarction (%)	51.5
Chronic obstructive pulmonary disease (%)	23.3
History of atrial fibrillation or flutter (%)	55.3
Body-mass index (kg/m^2)	27.1
Anemia (%)	61.3
STS risk score	8.2
Mean (%)	
≥8% (%)	42.7
Cause of cardiomyopathy (%)	
Ischemic	60.8
Nonischemic	39.2
NYHA class (%)	0.2
I	
II	39.0
III	52.5
IV	8.3
Hospitalization for heart failure within previous 1 year (%)	57.2
Previous cardiac resynchronization therapy (%)	36.5
Previous implantation of defibrillator (%)	31.3
B-type natriuretic peptide level (pg/ml)	1016.0
N-terminal pro–B-type natriuretic peptide level (pg/ml)	5559.1
Severity of mitral regurgitation (%)	52.2
Moderate-to-severe, grade 3+	
Severe, grade 4+	47.9
Effective regurgitant orifice area (cm^2)	0.41
Left ventricular end-systolic dimension (cm)	5.3
Left ventricular end-diastolic dimension (cm)	6.2
Left ventricular end-systolic volume (ml)	134.9
Left ventricular end-diastolic volume (ml)	192.7
Left ventricular ejection fraction	
Mean (%)	31.3
≤40% (%)	82.1
Right ventricular systolic pressure (mm Hg)	44.3

in both cohorts was 2.32 QALY and 1.80 QALY, respectively. The incremental cost and increment effectiveness were 395,448 CNY and 0.52 QALY, respectively; thus, an ICER of 754,410 CNY/QALY was obtained. The ICER was higher than the WTP threshold of 242,928 CNY/QALY (Table 4).

In the lifetime simulation, an HF patient with secondary MR who received MitraClip would suffer approximately 1.16 HF hospitalizations, and it was 1.51 if OMT alone was given. Additionally, an HF patient who received MitraClip had a life expectancy of 3.72 life years, and it was 2.90 life years for those who received OMT alone.

Scenario analysis

As shown in Table 4, the cost of the MitraClip device ranged from 143,951 CNY to 247,478 CNY in different regions, and the ICER based on these costs and the Chinese setting was always higher than the WTP threshold. When the MitraClip device cost was lower than 54,319 CNY (about 16.9% of the current price), or the overall cost of MitraClip was lower than 127,978 CNY (about 32.3% of the current cost), the ICER would be lower than the WTP threshold.

Sensitivity analysis

One-way sensitivity analysis showed that the cost of the MitraClip device impacted most ICER fluctuations, and the discount rate impacted the ICER secondly. Whatever the cost of the MitraClip device or the discount rate ranged, the ICER was always higher than the WTP threshold (Figure 2).

A scatter plot based on PSA showed that under the WTP threshold of 242,928 CNY/QALY, there was a <1% probability that MitraClip was of cost-utility (Figure 3). Cost-utility acceptability curve showed that when the WTP threshold was about 750,000 CNY/QALY, MitraClip shared similar acceptability with OMT in Chinese patients (Figure 4).

Discussion

The present study was the first one to investigate the cost-effectiveness of MitraClip in Chinese HF patients with secondary MR. In our analysis, we found that a patient treated with MitraClip could gain an additional 0.52 QALY than those treated with OMT, but the incremental cost was 395,448 CNY, causing an ICER of 754,410 CNY/QALY (equal to 116,963 USD/QALY), which is higher than the WTP threshold in China in 2021. MitraClip was considered not cost-effective in the current Chinese setting.

Three previous studies have tested the cost-effectiveness of MitraClip against OMT in the UK. One of the studies used data from the EVERSET II trial that included patients with primary and secondary MR and found that the ICER was £52,947 /QALY (equal to 469,956 CNY/QALY or 72,844 USD/QALY) (24). The second study based on the COAPT trial has reported an ICER of £30 057/QALY (equal to 266,785 CNY/QALY or 41,352 USD/QALY) (25). Another study also based on the COAPT trial has shown that the ICER of MitraClip was £23,270/QALY [equal

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TABLE 4 Base case analysis and scenario analysis.

	Arm	Cost of MitraClip device (CNY)	Cost of overall MitraClip (CNY)	Lifetime cost (CNY)	Lifetime eff (QALY)	Incre cost (CNY)	Incre eff (QALY)	ICER (CNY/QALY)	ICER/WTP
Base case	OMT	/	/	28,369	1.80	/	/	/	
	MitraClip	322,000	395,659	423,817	2.32	395,448	0.52	754,410	3.1
Scenario 1: German MitraClip device cost	MitraClip	247,478	321,137	349,295	2.32	320,926	0.52	612,241	2.5
Scenario 2: US MitraClip device cost	MitraClip	197,597	271,256	299,414	2.32	271,045	0.52	517,082	2.1
Scenario 3: Japanese MitraClip device cost	MitraClip	179,504	253,163	281,321	2.32	252,952	0.52	482,566	2.0
Scenario 4: UK MitraClip device cost	MitraClip	143,951	217,610	245,768	2.32	217,399	0.52	414,740	1.7
Scenario 5: Cost-effective cost 1	MitraClip	54,319	/	155,707	2.32	127,339	0.52	242,928	1
Scenario 6: Cost-effective cost 2	MitraClip	/	127,978	155,707	2.32	127,339	0.52	242,928	1

OMT, optimal medical therapy; CNY, Chinese Yuan; QALY, quality-adjusted life-year; Incre, incremental; Eff, effectiveness; ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay. Cost of overall MitraClip included the cost of the MitraClip device, procedure cost, nursing cost, ward cost, diagnosis cost, medicine cost, complication cost, and others.

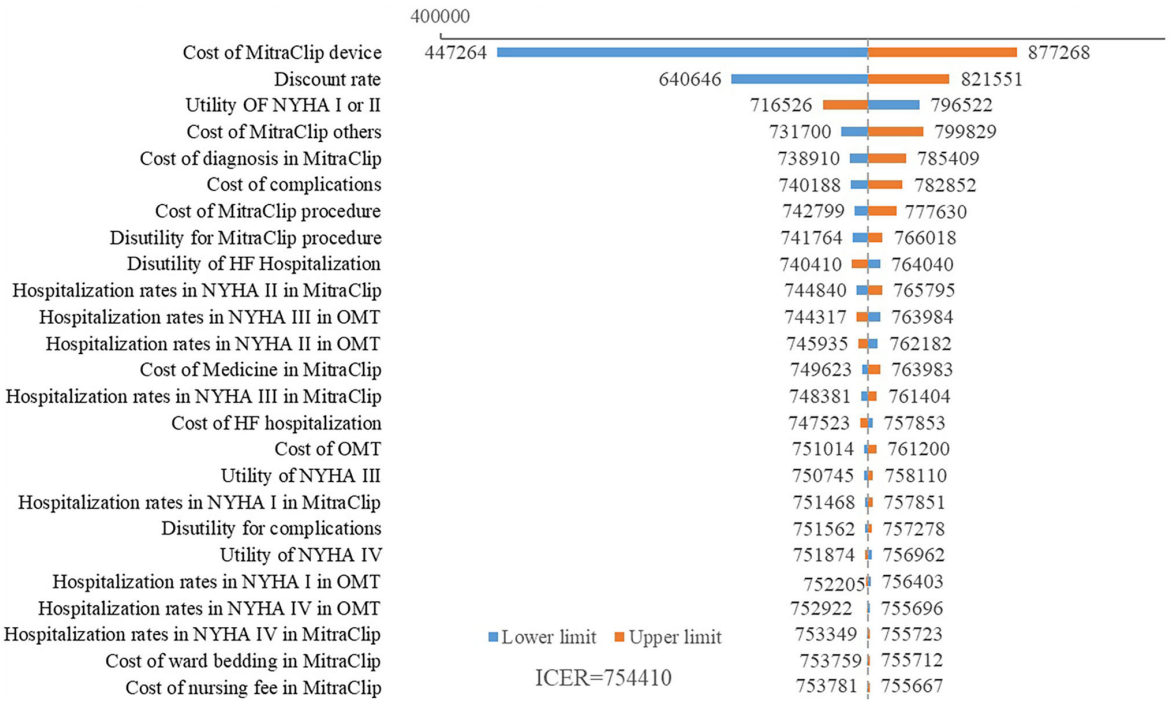

FIGURE 2
Tornado diagram of ICER based on different input parameters. The cost of the MitraClip device had the largest impact on the ICER fluctuation. The discount rate also impacted the ICER. Other parameters had little impact on the ICER.

to 206,544 CNY/QALY or 32,015 USD/QALY] (16). One study from Germany has shown that the MitraClip was cost-effective, with an ICER standing at €59,728 (equal to 455,736 CNY/QALY or 70,640 USD/QALY) (26). Additionally, MitraClip has been considered a cost-effective procedure in Italy (27). Almost all published papers have concluded that the obtained ICER ranged from 9,353 to 72,844 USD/QALY (24, 27). However, the ICER in our study was much higher than that in other studies. It might be attributed to the following aspects. First, the cost of overall MitraClip in China is higher than in other regions. According to our search of published articles, the cost of a MitraClip device ranged from 143,951 to 247,478 CNY in different countries (10, 16), but the price in China is 322,000 CNY, which is about twice the price abroad. Moreover, there is not so much difference in other MitraClip-related costs in China and other countries. Second, the cost of OMT in China is much lower than that in other regions (13), partly due to the collective purchasing policy launched by the Chinese government to provide better healthcare services. Third, the effectiveness of our study was lower than in other studies. The incremental effectiveness in Sakamaki's study was 1.44 QALY, but it was 0.52 QALY in our study mainly because their study was based on an observational study while our study was based on an RCT study (15). The incremental effectiveness in our study was almost consistent with Estler's one as we adopted the same model but was not completely consistent as the discount rate in China was higher than that in Germany (10).

As the largest developing country, China has 1.4 billion people, with 3.41% having MR (28), but the current cost of MitraClip is above the WTP threshold, which might partly account for the low proportion of Chinese HF patients with MR. Moreover, collective purchasing has decreased the cost of OMT in China, and novel agents, such as sodium-glucose cotransporter inhibitors and angiotensin receptor neprilysin inhibitors, have been widely used in Chinese HF patients and improved clinical outcomes (29). The ICER of MitraClip vs. OMT is 754,410 CNY/QALY, which is far higher than the WTP threshold of 242,928 CNY/QALY in China. Although the WTP threshold in some regions in China may be higher than that value due to the uneven economic development, the obtained ICER is still higher than the WTP threshold of the most developed regions in China. Additionally, we adopted the lowest cost abroad in our scenario analysis, and the ICER was still higher than the WTP threshold, suggesting the WTP threshold was lower in China than in other countries (10, 30). The deterministic analysis and uncertain analysis confirmed our findings. In our Tornado diagram, we found that the cost of MitraClip had the largest impact on the ICER fluctuation. However, although the 50% discount on the current price was adopted, the ICER was still higher than the WTP threshold.

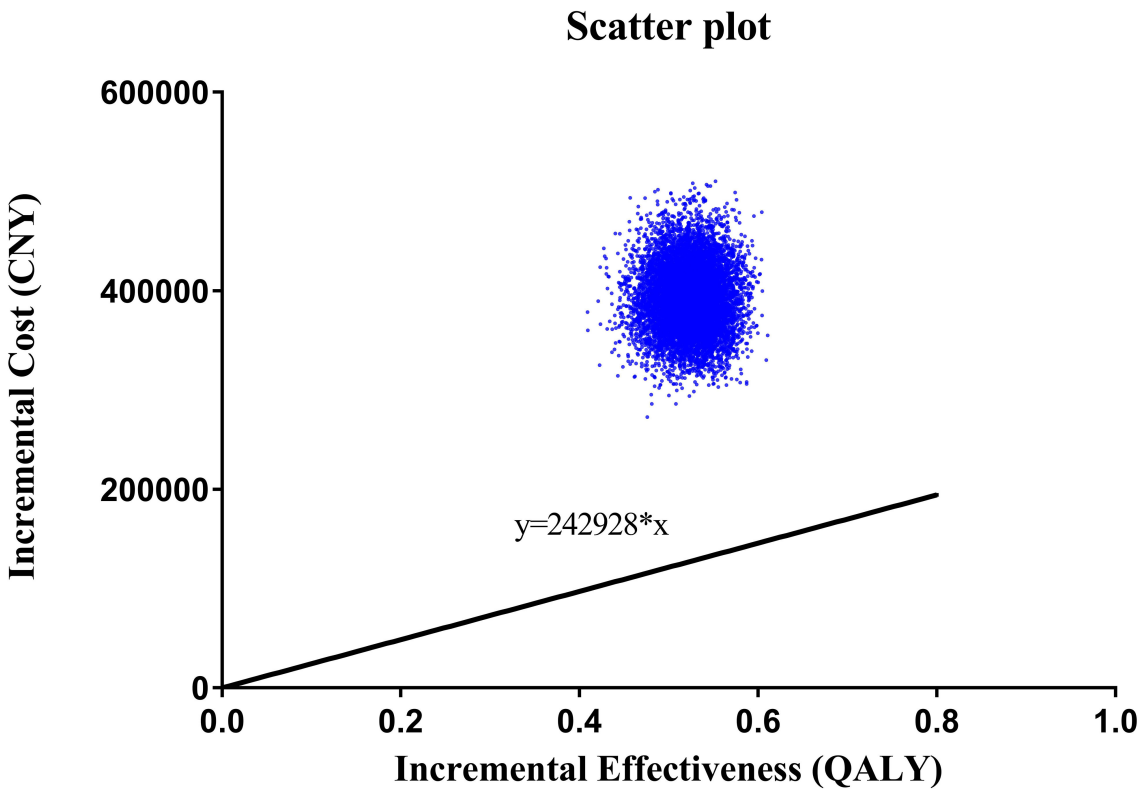

FIGURE 3
Scatter plot based on 10,000 times Monte Carlo simulation. The straight line indicated the WTP threshold. The dots were almost all above the line.

The cost-effectiveness acceptability curve indicated that the acceptability of MitraClip was <1% under the current context.

Although MitraClip could benefit HF patients with MR, it is still not cost-effective in the current Chinese setting. One reason is that the MitraClip device was introduced to China in 2020, and the first MitraClip procedure was performed in 2021. Furthermore, the number of MitraClip procedures in China is not currently high. The Chinese government launched a collective purchasing policy in 2017 to lower the price of drugs, and medical services, drugs, or medical devices only with cost-effectiveness could be included in the purchasing lists and be purchased by Chinese public hospitals, which provided over 80% healthcare in China. MitraClip could be cost-effective only with a discount of 83% on the MitraClip device or a 68% discount on the overall cost.

Notably, our study was based on the COAPT study, demonstrating that MitraClip resulted in a lower HF hospitalization rate and lower all-cause mortality compared with OMT alone. However, the MITRA-FR proved that MitraClip did not improve the clinical outcomes compared with OMT (31). The main difference between the two studies lies in the population selection. In the COAPT study, enrolled patients had more severe MR, smaller LV end-diastolic volume, better guideline-directed medical therapy, and more experienced surgeons. Moreover, observational studies have also demonstrated that MitraClip entailed better survival outcomes compared with OMT (32, 33). These results suggested that the selection of proper patients is critical to clinical outcomes.

There were several limitations in our study. First, our study was performed based on validated mathematical models, and a real-world study might provide more powerful evidence, although one-way sensitivity analysis and PSA demonstrated the robustness of our results. Second, the cost of MitraClip was derived from an institution, which might not completely represent the real cost in China, and we resolved it by one-way sensitivity analysis using a 50% discount on the current price. Third, the transition probabilities were accessed from a published study and validated by authors but not from the raw data, which might have caused bias. Last, the study was performed from the perspective of a healthcare payer, and perhaps a perspective from society could offer more comprehensive information, but it was too difficult for us to finish it as we could not access the non-direct cost of MitraClip.

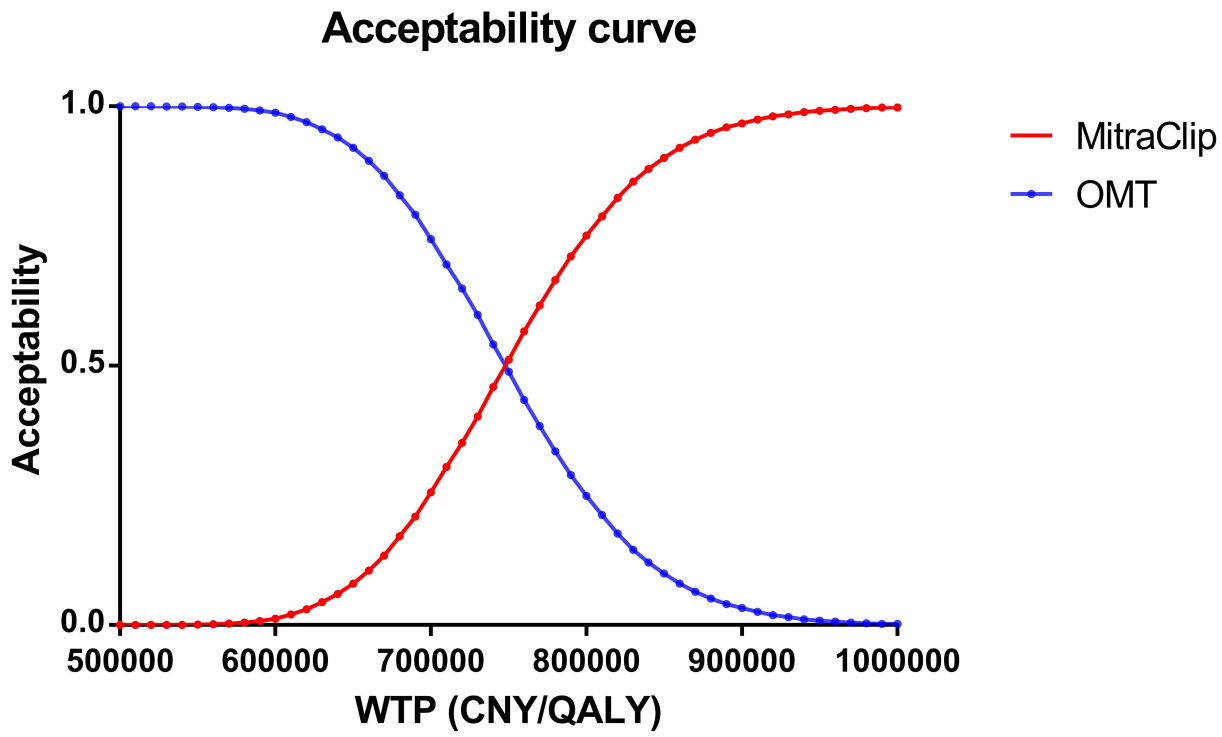

FIGURE 4
Cost-effectiveness acceptability curve based on probabilistic sensitivity analysis. The acceptability of MitraClip grew higher as the WTP threshold increased. When the WTP threshold was about 750,000 CNY/QALY, MitraClip shared similar acceptability with OMT.

Conclusion

In a lifetime simulation of MitraClip for HF treatment with secondary MR, MitraClip resulted in an additional 0.52 QALY in effectiveness and 395,448 CNY in cost compared with OMT. The ICER in the simulation was 754,410 CNY/QALY, which was higher than the WTP threshold in the current Chinese context. Thus, MitraClip was considered not cost-effective in Chinese HF patients with secondary MR.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

WX and KH collected data and drafted the manuscript, and YL came up with the idea and developed the model. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.970118/full#supplementary-material

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Mitral annular calcification in patients with significant mitral valve disease: An old problem with new solutions

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Mitral annular calcification (MAC) is a chronic process involving mitral valve annulus, linked with an increased cardiovascular mortality and morbidity. Since its first autoptic description, a progressive evolution in diagnostic tools brought cardiac computed tomography (CT) scan to become the gold standard in MAC detection and classification. The treatment of significant mitral valve disease in patients with annular calcifications has always represented an issue for cardiac surgeons, being it linked with an increased risk of atrioventricular groove rupture, circumflex artery injury, or embolism. As a consequence, different surgical techniques have been developed over time in order to reduce the incidence of these fearsome complications. Recently, transcatheter mitral valve replacement (TMVR) has emerged as a valid alternative to surgery in high-risk patients. Both hybrid transatrial, transfemoral, or transapical approaches have been described to deliver balloon-expandable or self-expanding aortic transcatheter valves into the calcified annulus, with conflicting early and long-term results. Tendyne (Abbott Structural Heart, Santa Clara, CA, USA) is a promising transapical-delivered option. Early results have shown effectiveness and safety of this device in patients with MAC and severe mitral valve disease, with the lowest rate of embolization, mortality, and left ventricular outflow tract obstruction (LVOTO) reported so far.

KEYWORDS

mitral valve regurgitation, mitral annular calcification (MAC), Tendyne, TMVR in MAC, MAC quantification

Introduction

Mitral annular calcification (MAC) is a chronic process characterized by a progressive calcium deposition at the level of mitral annulus. Its prevalence is estimated between 8 and 15% (1), but it significantly increases with age and has been especially associated with altered calcium metabolism, for example in patients with chronic kidney disease.

The presence of MAC itself has been linked with an increased cardiovascular mortality and morbidity (2). Moreover, the coexistence of MAC and significant mitral regurgitation or stenosis has historically represented a challenge for cardiac surgeons, being mitral valve interventions in this context associated with an increased risk of cardiac rupture at the atrioventricular junction, perivalvular leaks, circumflex artery injury, and embolism (1). For these reasons, patients with severe annular calcifications are often deemed too high risk to undergo surgery. On the other hand, according to a recent report (3), subjects with MAC and significant mitral disease, if left untreated, show poor outcomes. These may be improved with either surgical or transcatheter interventions.

Aim of this paper is therefore to describe MAC and its classification and review all the available approaches to treat coexistent significant mitral disease: surgical treatment, transatrial hybrid procedures, and percutaneous treatment.

Mitral annular calcification and its diagnosis

Mitral annulus is a complex saddle-shaped structure separating left atrium and left ventricle. Anteriorly, it is in close continuity with aortic root and aorto-mitral curtain. Posteriorly, the fibrous layer is discontinuous and periodically interrupted by fat tissue (1).

Calcifications involving mitral annulus have been already described in the early nineties in autoptic studies (4), but the first comprehensive evaluations came later in the context of surgical series.

Carpentier et al. (5), specifically, analyzed 68 patients with MAC referred in a 10-years span (1986–1995) to surgery for concomitant mitral regurgitation. As a result of a broad assessment, based on both pre-operative and intra-operative findings, calcifications were described as involving at least one third of the posterior annulus in 88% of the cases, the whole posterior annulus in 10% and also the attachment of the anterior leaflet in 1.5% of the cases. Furthermore, the degenerative process was limited to the annulus itself in most of the patients, while extra-annular structures were interested by calcifications in 25% of the subjects (12% ventricular wall, 6% posterior leaflet, and 4.5% papillary muscles). Interestingly, MAC was found to be usually coated by a fibrous sheath, so that calcifications are basically separated from the surrounding structures. This distinction is not well demarcated where the degenerative process infiltrates left ventricular myocardium.

Both chest X-ray and coronary angiography may reveal annular calcifications as a C or O-shaped ring lying at left atrioventricular junction, but they cannot help in defining the extension of the degenerative process (1).

Ecocardiography had been considered for a long time the best tool to detect MAC (**Figure 1**). Annular calcifications are visible, using M-mode, as a dense echo band lying below the posterior mitral leaflet, with a motion pattern paralleling that of free ventricular wall (6). Two-dimensional echo, on the other hand, is useful to define MAC morphology. With this ultrasound modality, calcifications appear as highly reflective irregular structures at the junction between atrioventricular groove and posterior mitral leaflet, with associated acoustic shadowing (1). Different echocardiographic methods to define MAC severity have been described. Barash et al. (7) proposed a qualitative classification, based on parasternal long axis view projections. MAC was defined as "mild" in presence of only focal calcifications, confined to mitral annulus, "moderate" when more than 1/3 but less than 1/2 of mitral annulus is involved and "severe" when more than half of ring circumference is affected, with calcifications intrusion into left ventricular wall. A subsequent quantitative classification (8), based on MAC maximal thickness when measured at its greatest width, defined MAC as severe when a value > 4 mm is recorded.

With the diffusion of cardiac computed tomography (CT), ECG-gated methods rapidly took over echocardiography as gold standard in MAC diagnosis and quantification (**Figure 1**). Cardiac CT scan shows a higher spatial resolution in distinguishing heart structures, allowing a better identification of calcifications exact location (1). As a consequence, it has been used to develop MAC quantification scores.

Guerrero et al. (9), through a retrospective analysis of 87 baseline cardiac CT scan of Valve-in-MAC candidates, proposed a scoring system of MAC severity.

Four characteristics are taken into account: calcium thickness, calcium distribution in the annulus circumference, calcification of one or both fibrous trigones, and leaflet involvement. The sum of points acquired in each of these categories makes the final score, with a score of 3 or less representing mild MAC, 4 to 6 moderate MAC and 7 or more severe MAC (**Figure 2**).

The authors used this score to predict the risk of valve embolization/migration after transcatheter mitral valve replacement (TMVR) using aortic transcatheter heart valves. Embolization/migration rates were lower in higher scores, with a score of 6 or less identified as an independent predictor of valve embolization/migration.

Treatment options

Patients with MAC and significant mitral valve disease represent a high-risk surgical population. In fact, mitral surgery in this context is linked to an increased threat of atrioventricular junction rupture, circumflex artery injury, and embolism (1). As a consequence, alternative treatments have been developed over time. At first, transcatheter aortic valve prosthesis delivery inside the calcified annulus has been proposed as an option, with

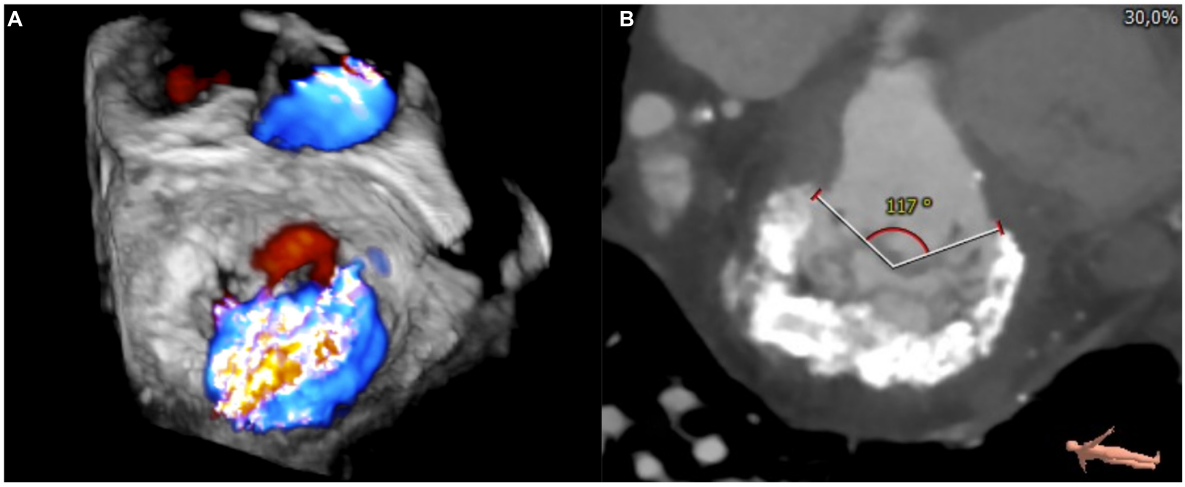

FIGURE 1
3D transesophageal echocardiography **(A)** and cardiac computed tomography (CT)-scan **(B)** showing severe mitral annular calcification (MAC) and coexisting severe mitral regurgitation.

CT-Based MAC score

- 0-3 points: mild
- 4-6 points: moderate
- 7-10 points: severe

1) Calcium thickness	2) Calcium distribution	3) Trigone Involvement	4) Leaflet Involvement
< 5 mm = 1	< 180° = 1	None = 0	None = 0
5 – 9.99 mm = 2	180 – 270° = 2	One = 1	One leaflet = 1
≥ 10 mm = 3	≥ 270° = 3	Both = 2	Both leaflets = 2

FIGURE 2
Computed tomography (CT)-based mitral annular calcification (MAC) score according to Guerrero et al. (9).

both open access to left atrium, a transfemoral, or a transapical approach.

New devices, specifically designed to fit the complex shape of mitral annulus, have been lately developed in order to treat mitral valve disease in patients deemed too high risk to undergo conventional surgery. Among them, Tendyne system showed very interesting results in MAC population.

Surgical treatment

Surgical mitral valve repair or replacement remain the gold standard to treat patients with mitral valve pathology, even in presence of severe MAC (**Figure 3**).

Historically, two possible approaches have been depicted: either extensive annular decalcification and reconstruction ("resect" strategy) or a more conservative approach, that minimizes the risks linked with calcium removal (10).

Several "resect" strategies have been described.

Carpentier et al. (5) pioneered the en-bloc removal of posterior annular calcifications, from one trigone to the other, by sharp dissection. After atrial endocardium incision and posterior leaflet detachment to expose both atrial and ventricular side of MAC, the calcium bar is removed with its fibrous sheath. Annular reconstruction is then performed either by interrupted sutures between atrial and ventricular annular edges or, if decalcification reaches the ventricular myocardium, with the so called "sliding atrium technique." It consists of atrial annular edge dissection to create an atrial flap, which is then mobilized and used to cover the decalcified area. Following annular reconstruction, mitral valve repair or replacement is then performed.

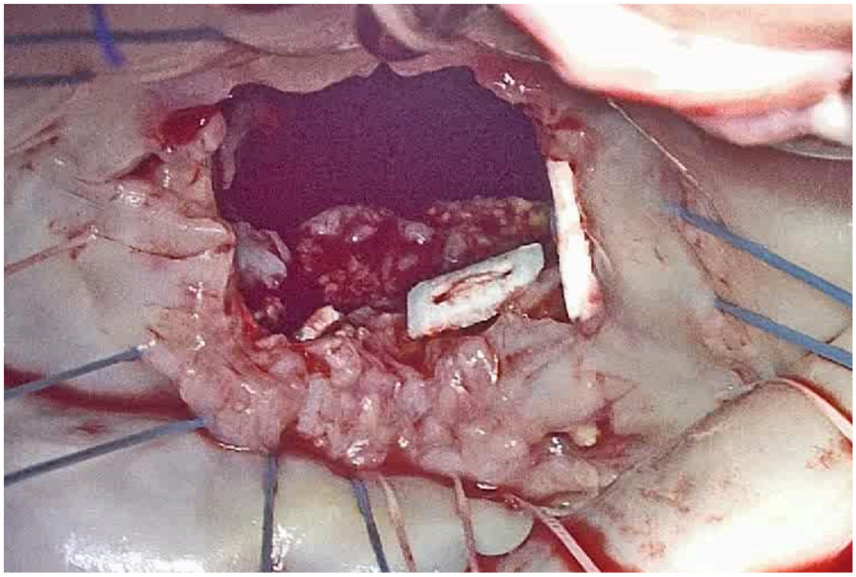

FIGURE 3
Intra-operative appearance of mitral annular calcification (MAC) during surgical inspection, after anterior mitral leaflet removal.

Results of this aggressive approach in 67 patients (5) showed an in-hospital mortality rate of 3.3%, a 7-years survival of 93.1%, a freedom from reoperation for mitral regurgitation at 9 years of 87.1% and significant valvular leaks at follow-up in about 10% of the patients.

David et al. (11) described a similar extensive decalcification approach, but annular reconstruction was achieved using autologous pericardium. However, the long-term results of this aggressive strategy were significantly worse in their series, with a survival rate of 49% at 8 years.

More conservative approaches include partial decalcification or MAC avoidance instead of removal, with suture placement around the calcium bar, both behind it or on mitral leaflets (10).

More recent results about mitral valve surgery in patients with MAC showed an operative mortality between 1 and 5.8% and a survival rate at 5 years between 38.8 and 78.8% (10).

Transatrial hybrid procedure

Looking for alternatives to conventional mitral valve surgery, one of the first options to be explored was the direct delivery of a balloon expandable transcatheter valve inside the calcified annulus, using a hybrid strategy that involves cardiopulmonary bypass, cardioplegic arrest and surgical left atriotomy. The first successful implantation was achieved in 2012 (12).

Different types of transcatheter aortic valves were used, even if most of the patients received SapienXT prosthesis or Sapien3 (Edwards Lifesciences, Irvine, CA, USA) (13). Before valve delivery, anterior mitral leaflet is usually resected and thus transatrial access offers a very low risk of left ventricular outflow tract obstruction (LVOTO). Moreover, a felt strip is typically sutured around the inflow of the valve and, through pledgeted stiches, directly onto valve leaflets remnants. These steps help to reduce the risk of valve embolization and perivalvular leaks (14).

The biggest experience reported so far, on a sample of 26 patients with severe MAC (14), revealed a procedural success in 100% of patients. However, both in-hospital and 30-days mortality were high (20 and 27%, respectively).

This unsatisfactory survival results were confirmed also by a prospective trial (MITRAL), that showed an in-hospital, 30-days, and 1-year mortality of 9.5, 20.0, and 40%, respectively (13).

Percutaneous treatment (transfemoral, transapical)

Since the beginning of TMVR experience, other delivery strategies were explored, alternatively to direct implantation through left atriotomy. These approaches, differently from the hybrid procedure, are performed on a beating heart, without cardiopulmonary bypass assistance.

Both transfemoral and transapical TMVR have been described.

In the first case, the delivery system is advanced through the femoral vein until the right atrium, where a transeptal puncture allows access to the left atrium. The transapical approach, on the other hand, requires a left anterior thoracotomy, and mitral valve is then reached from its ventricular side.

Most of the available reports about these approaches are retrospective and include a small cohort of patients. The most used valves were SapienXT prosthesis or Sapien3 (Edwards Lifesciences, Irvine, CA, USA) (13).

Data collected so far showed a variable technical success (between 62 and 92%), with an embolization rate ranging from 0 to 16.7%. LVOTO occurred in 10 up to 39.7% of the cases. The reported 30-days mortality ranged from 11.1 to 34.5% (13).

The only available prospective study (MITRAL) (13), who enrolled 100 patients, substantially confirmed what previously stated, with a technical success in 68.8% of the cases, LVOTO in 13.4% of the cases and a 30-days mortality of 13.4%.

A recent systematic review (13) calculated a median incidence of at least moderate post-procedural mitral regurgitation of 4.1%. Overall, the median in-hospital, 30-days, and 1-year mortality rates for non-transatrial TMVR in MAC were 16.7, 22.7, and 43%, respectively.

Tendyne

Tendyne (Abbott Structural Heart, Santa Clara, CA, USA) is a self-expanding, repositionable nitinol prothesis that is delivered *via* a transapical sheath and anchored at cardiac apex with a tether connected to an epicardial hemostatic pad (15). It has been specifically designed to fit the complex 3-dimensional shape of mitral annulus [lower occurrence of paravalvular leaks (PVL)], and, thanks to its anchoring pad, to reduce the risk of embolization.

The Global Feasibility Study (30 subjects enrolled) showed safety and efficacy of this device in treating patients with significant mitral regurgitation, deemed too high-risk to undergo conventional surgery (15).

Gössl et al. (16) recently published early outcomes of TMVR with Tendyne in patients with severe MAC (**Figure 4**). Among 20 enrolled patients (9 compassionate use, 11 taken from the Feasibility Study of Tendyne in MAC), both acute and midterm outcomes were encouraging. In fact, 30-days all-cause mortality and 1-year cardiac mortality were 5 and 20%, respectively, with no recurrence of mitral regurgitation and clinical improvement in 92% of patients who were alive at 1-year follow-up.

The SUMMIT trial (NCT03433274), still ongoing, is the pivotal clinical trial testing feasibility and safety of the Tendyne device in the United States. The primary endpoint is survival free of heart failure hospitalization at 12 months (15). Among the 3 available cohorts, one is dedicated to evaluate results in the subgroup of patients with severe MAC. With more than one hundred enrolled subjects in this cohort so far, this prospective study will help to understand what's the role Tendyne valve may have in treating patients with significant mitral regurgitation and severe annular calcifications.

Discussion

The presence of MAC in patients with significant mitral valve disease represents a challenging anatomical scenario, both from a surgical and a transcatheter point of view.

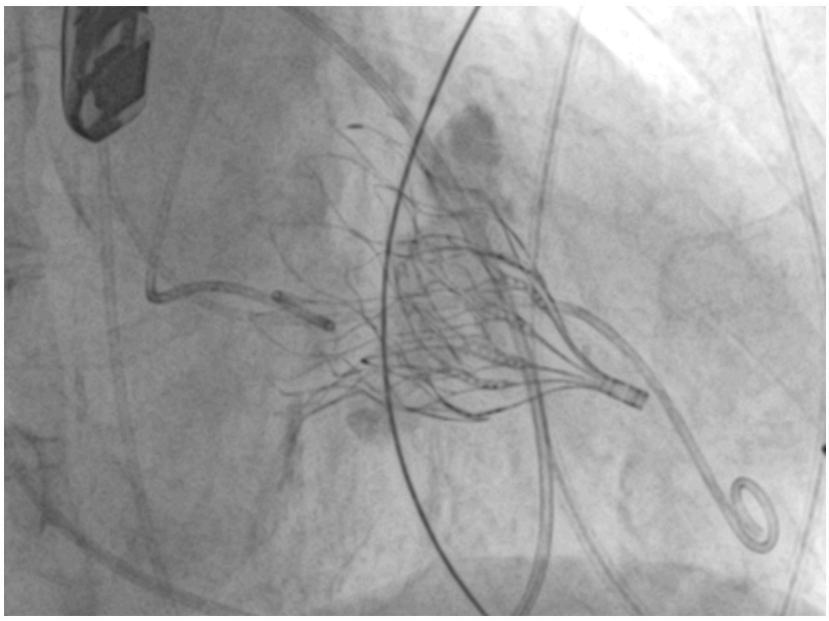

FIGURE 4
Fluoroscopy image showing a successful Tendyne implantation in severe mitral annular calcification (MAC).

This complexity has fostered the introduction of different treatment options.

Conventional surgery still remains the preferred intervention in patients with acceptable surgical risk. However, both extensive annular decalcification or conservative, calcium-respectful, approaches are linked with an increased risk of atrioventricular groove rupture, and circumflex artery injury. As a consequence, even if the results of mitral valve repair in terms of recurrence of significant MR are positive (freedom from reoperation 87% at 9 years) (5), reported mortality rates are still high (operative mortality between 1 and 5.8% and a survival rate at 5 years between 38.8 and 78.8%) (10).

It must be considered, however, that most of the available surgical series are old and small in size. A recent report (17), retrospectively analyzing 9,551 patients with MAC undergoing mitral valve surgery, has on the other hand the big limitation of not assessing long term outcomes.

The introduction of TMVR options has widened the armamentarium available to treat this complex population. Differently from surgical mitral valve repair/replacement, transcatheter delivery is linked with different intra-procedural threats, namely PVL, valve migration, and LVOTO.

Even if the first two complications were more frequent at the beginning of TMVR experience, better patients' and device selection significantly reduced their incidence. In fact, both PVL and embolization usually resulted from device undersizing, or insufficient MAC to ensure adequate valve anchoring (13).

Unlike in surgical mitral valve replacement, anterior mitral leaflet cannot be removed during TMVR, thus increasing the risk of LVOTO.

In a recent systematic review (13), the median incidence of LVOTO in transatrial, transfemoral, and transapical TMVR (not including Tendyne) was 13.4%. Different strategies have been developed to prevent obstruction, including alcohol septal ablation (both precautionary or as a bailout), intraoperative resection of the anterior mitral leaflet and septal myectomy during transatrial implantation and the LAMPOON (Laceration of the Anterior Mitral Leaflet to Prevent LVOTO) approach (18).

The latter, albeit technically complex, showed a procedural success of 100% and was able to reduce LVOT gradient to less than 30 mmHg in 97% of patients in a retrospective study on TMVR in MAC (19).

As a matter of fact, even if linked with a low rate of LVOTO (less than 10% in the prospective trial MITRAL) (13), transatrial hybrid TMVR remains a surgical operation, with a non-negligible mortality (20% at 30 days, 40% at 1 year) and an in-hospital major bleeding rate ranging from 6.7 to 25% (13).

Tranfemoral and transapical approaches, on the other hand, showed comparable survival rates (median 30-days mortality 22.7%, median 1-year mortality 43%), with a risk up to 16.7% of valve embolization (20), and an LVOTO rate ranging from 7.4 to 39.4% (13).

In this scenario, Tendyne represents a promising alternative.

In fact, the early available results (16) show a 95% technical success, with a 30-days mortality rate of 5% and a 1-year cardiac mortality of 20%. Only one patient of the cohort developed LVOTO, successfully treated by septal ablation.

However, these encouraging outcomes are, to some extent, the result of a very selective patients' recruitment process, with a screen failure rate due to unfavorable anatomy of at least 40% (13).

Larger perspective studies are needed to confirm the available results.

Conclusion

In the complex anatomical and clinical context of patients with MACs and significant mitral valve disease, conventional surgery still represents in eligible subjects the gold standard of treatment, capable of ensuring durable results. TMVR has emerged as an interesting alternative in high-risk patients, and the progressive technological and procedural evolution is gradually reducing the incidence of PVL, embolization, and LVOTO.

With its promising early results, Tendyne valve may set a new benchmark in transcatheter treatment of mitral valve disease in patients with annular calcifications.

Further steps include optimization of patient selection and pre-procedural planning, in order to create a standardized treatment algorithm that could offer the best solution for each patient.

Author contributions

GA: conceptualization, data curation, investigation, visualization, and writing – original draft. PD: validation, supervision, and writing – review and editing. Both authors contributed to the article and approved the submitted version.

Conflict of interest

PD received speaker honoraria from Abbott and Edwards Lifesciences and was a consultant for InnovHeart.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Safety, efficacy, and clinical outcomes of transcatheter tricuspid valve replacement: One-year follow-up

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Objective: The aim was to evaluate the safety and efficacy of TTVR in patients with severe TR at the 1-year follow-up.

Materials and methods: This project was a single-center, observational study. From September 2020 to May 2021, 15 patients with severe or extremely severe TR at high risk of traditional surgery were enrolled. All patients had preoperative imaging assessments to evaluate the tricuspid valve and the anatomy of the right heart. All patients were planned to treated with the LuX-Valve (Ningbo Jenscare Biotechnology, Ningbo, China). The LuX-Valve was implanted under the intraoperative guidance of TEE and X-ray fluoroscopy. Data were collected at baseline, before discharge, and at 30 days, 6 months, and 1 year postoperatively.

Results: The LuX-Valves were successfully implanted in all 15 patients. TR was significantly reduced to $\leq$ 2 +. One patient died on postoperative day 12 of a pulmonary infection that was considered unrelated to the procedures or the devices. The remaining 14 patients (100.0%) reached the primary end point. One patient (7.1%) was rehospitalized during 1-year follow-up because of device thrombosis. The number of patients who survived at 1 year with New York Heart Association (NYHA) functional class II was higher than that before TTVR (11/14 vs. 0/15, $P = 9.11 \times 10^{-4}$). Patients with peripheral edema and ascites decreased from 100.0 to 46.7% at baseline to 28.6% and 14.3% at 1 year ($P = 1.57 \times 10^{-3}$ and 2.53×10^{-2}).

Conclusion: TTVR is associated with RV remodeling, increased cardiac output, and improvement in NYHA functional class. Using the LuX-Valve for TTVR to treat patients with severe TR is a feasible and relatively safe method with reliable clinical results. Further studies are needed to determine long-term outcomes.

KEYWORDS

tricuspid regurgitation, transcatheter tricuspid valve replacement, LuX-Valve, follow-up, tricuspid valve

Introduction

Tricuspid regurgitation (TR) is a common heart valve disease that is associated with increased mortality (1, 2). The prognosis of patients with severe TR is short of expectations, and the 5-year survival rate is less than 50% (2–5). TR is mainly secondary to dilation of the right ventricle (RV) and the tricuspid ring, which are closely associated with atrial fibrillation (AF) and pulmonary hypertension (6). The etiology of primary TR includes congenital tricuspid valve (TV) malformation, endocarditis, and a pacemaker implant. The traditional surgical treatment of TR involves TV repair and replacement assisted by a cardiopulmonary bypass device. Most patients with severe TR are treated with medication because interventions are associated with a high mortality rate, especially in the elderly (7–9). These results indicate that, for patients, annular repair may not be sufficient (10). Furthermore, the number of patients with TR is seriously underestimated, and less than 5% of patients receive surgical treatment (11).

In recent decades, transcatheter tricuspid valve replacement (TTVR) has become one of the research hotspots in cardiovascular medicine. Several interventional devices for different anatomical structures of the TV have been used clinically. Early reports from studies with these devices showed varying degrees of reduction of TR (12–20). The LuX-valve (Ningbo Jenscare Biotechnology, Ningbo, China) is one TTVR device unrelated to radial force that has been successfully implanted in patients with severe TR (21, 22). Our goal was to report the results of the 1-year follow-up in 15 patients with severe TR who received LuX-Valve implants.

Materials and methods

Study population

The study was a single-center, observational investigation. From September 2020 to May 2021, a total of 15 patients with severe TR [9 women; 62.0 (56.0, 78.0) years] were enrolled in this study. The severity of TR is classified as mild, moderate, severe, very severe, and extremely severe (23). All patients were carefully evaluated by the multidisciplinary cardiac team and considered to be either contraindicated or at high risk for surgery. According to European Society of Cardiology (ESC) and European Association of Cardiothoracic Surgery (EACTS) guidelines for the management of valvular heart disease, TR severity was graded as mild, moderate and severe in the present study evaluating by TR area (24). Meanwhile, TV is not a simple flat structure, but similar to the saddle oval. Therefore, in addition to assessing TR severity, the team also assessed the extent of TV annulus dilatation and cusp convolution (25). Inclusion criteria included age > 50 years old; TR severity ≥ severe; New York Heart Association (NYHA) class ≥ III; Patients at high risk for surgical tricuspid valve replacement as assessed by the multidisciplinary cardiac team [Society of Thoracic Surgeons (STS) score > 8.0%]. Exclusion criteria included left ventricular ejection fraction < 50%; systolic pulmonary arterial pressure > 55 mm Hg (1 mm Hg = 0.133 kPa); bioprosthetic valve replacement within 6 months; Ebstein's malformation or structural dysplasia of the right ventricle; active infective endocarditis; cardiogenic shock; severe chronic renal insufficiency [glomerular filtration rate (GFR)< 30 mL/min]; combined with other heart disease requiring surgery. The clinical trial was registered in the ClinicalTrials.gov protocol registration system (NCT02917980). All procedures were in accordance with the ethical guidelines set out in the Declaration of Helsinki, and all patients signed the informed consent forms.

Preoperative imaging

Coronary angiography was used to exclude severe coronary artery diseases; invasive RV catheterization was used to evaluate the hemodynamics of the right heart, and gated cardiac computed tomography and 3-dimensional reconstruction were used to evaluate anatomical structures. Functional TR is considered to be a disease that depends not only on the size and shape of the TV but also on the function of the RV, ventricular septal displacement, and pulmonary artery pressure (26). Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were both performed in all patients preoperatively to assess RV and TV functions (**Figure 1**).

Device description

The LuX-Valve (Ningbo Jenscare Biotechnology, Ningbo, China) has a unique design concept of radial force independence, which consists of a biological valve stent, 3 valve lobules, and a steerable delivery system (**Figure 2**). It is funnel-shaped and consists of four parts: (a) A three-lobe artificial semilunar valve made of bovine pericardium treated with the GeniGal anticalcification process; (b) a self-expanding nitinol valve stent covered with polytetrafluoroethylene cloth, consisting of an atrial disc and soft adaptive annular sealing edges designed to prevent it from entering into the RV and to reduce paravalvular leakages; (c) the 20-mm "tongue" of the interventricular anchor (IVA), using a three-pronged nitinol anchor to grasp the valve stent to the diaphragm; (d) two 8-mm extended grips designed to capture the anterior TV ring. The delivery system consists of a 32 Fr sheath and a steerable tube. Four knobs, a plug, and a button on the handle control the bending of the sheath and the release of the valve.

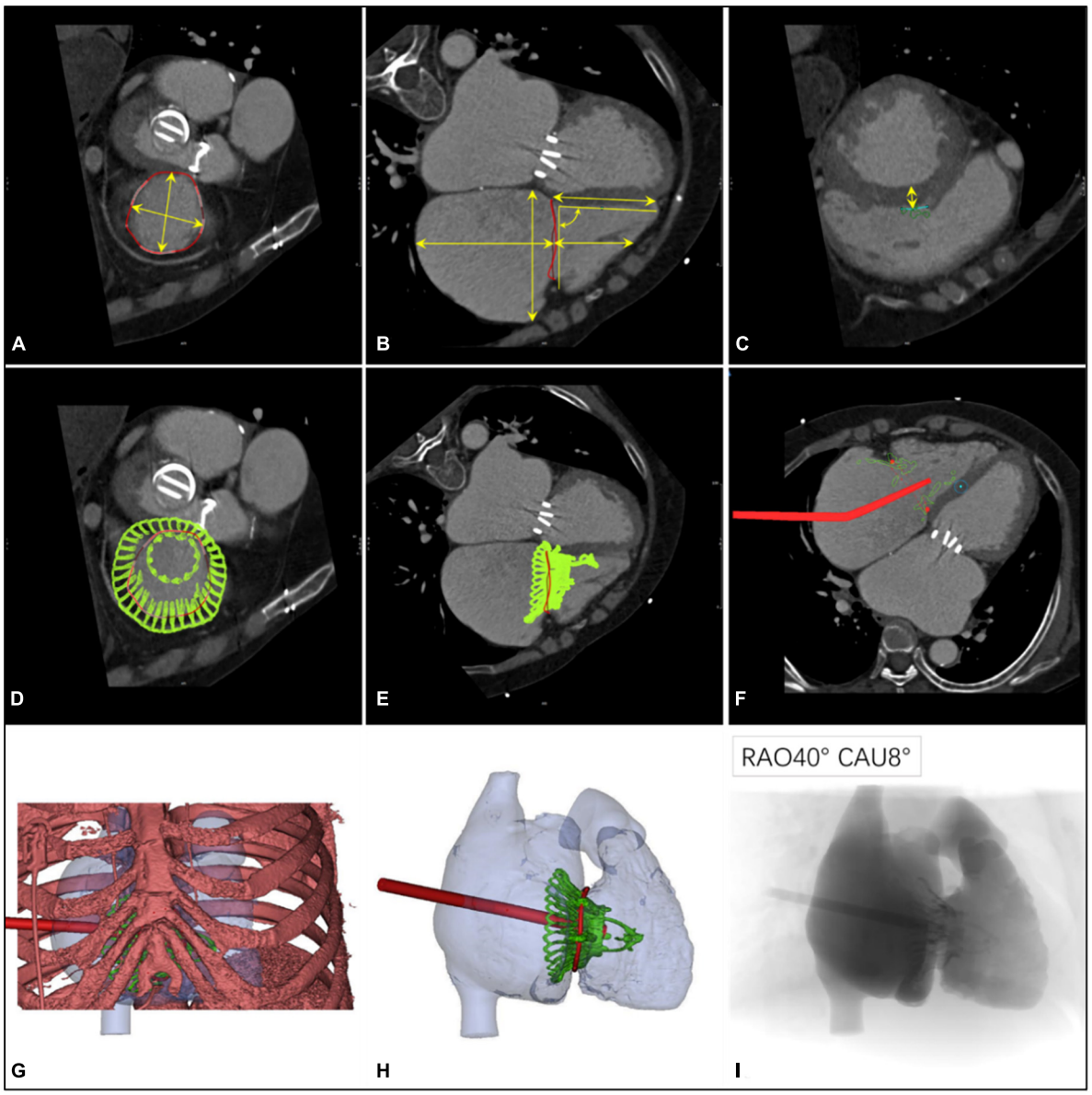

FIGURE 1
Preprocedural computerized tomography angiography assessment of transcatheter tri-cuspid valve replacement. **(A)** The diameter and perimeter of the tricuspid annulus (TA) were determined. **(B)** Measurements of the distance from the septal valve to the apex of the right ventricle, the height of the right atrium, and its relationship with the TA; the angle between the TA and the ventricular septum was 90° ± 10°. **(C–E)** Computer simulation of the LuX-Valve implant to observe the location of the anchor points and to measure the thickness of the ventricular septum in this position (30 mm below the TA). **(F)** Materialize Mimics 21.0 software (Materialize, Leuven, Belgium) was used to analyze the position and the angle of the delivery system on a 2-dimensional image. **(G)** The position of the right intercostal incision was determined with a digital 3-dimensional image. **(H)** The shape and the release position of the LuX-Valve were observed using 3-dimensional virtual models. **(I)** Simulation using fluoroscopic images provided an ideal projection angle for the transcatheter tricuspid valve replacement.

Procedural steps

The procedure was performed in the intubation laboratory. After the patient was given general anesthesia, the TV was entered with a right minimally invasive thoracotomy through the path of the right atrium (RA) (**Figures 3A,B**). TEE and X-ray fluoroscopy were used for guidance. TEE was mainly used to guide catheter delivery, valve release, and adjustment of the intraoperative valve position. A coronary artery guide wire was placed in the right coronary artery to help determine the annulus plane of the TV. Systemic heparinization was administered to achieve an activated coagulation time of > 200 s; then 4-0 Prolene sutures with felt sheets were used with a double purse-string suture in the RA. The delivery catheter was placed into

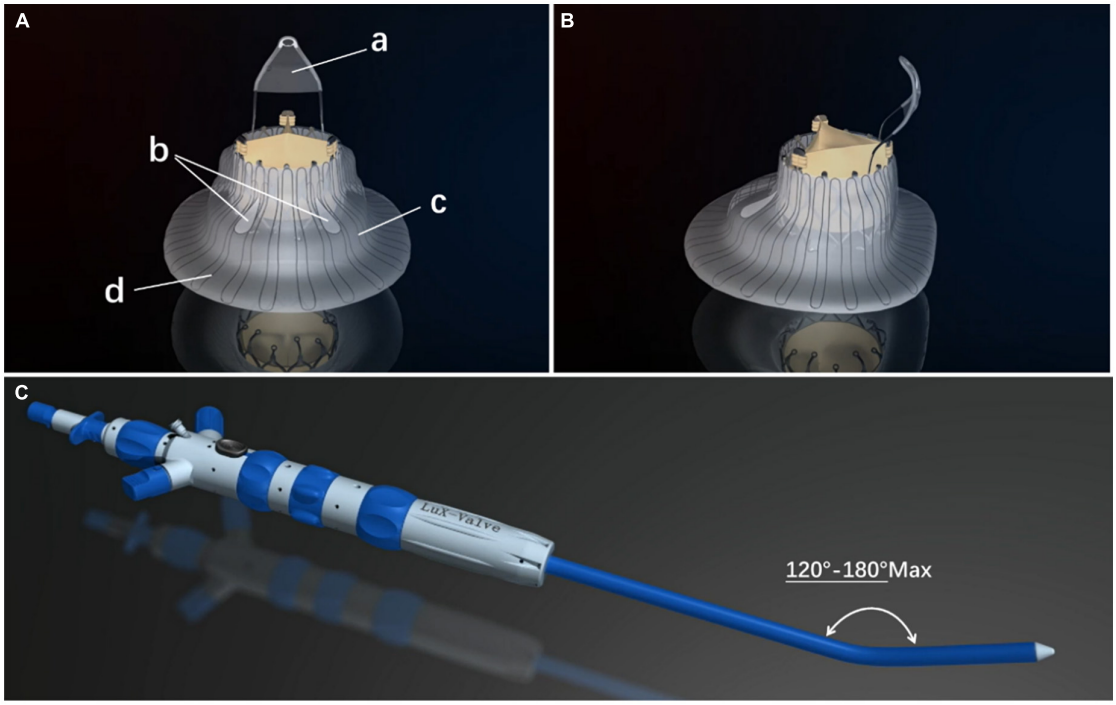

FIGURE 2
The LuX-Valve (Ningbo Jenscare Biotechnology, Ningbo, China) is self-expandable. The stent is made of a nickel–titanium alloy and the biological leaflet is bovine pericardium. The bio-prosthesis is implanted *via* the right atrial approach and fixed in the tricuspid annulus with its own unique anchoring device, independent of the radial support force. The part of the prosthesis located in the right atrium also prevents paravalvular leakage. **(A)** Right atrial view of the LuX-Valve. The four parts of the LuX-Valve stent include (a) the interventricular anchor, (b) two graspers, (c) the annulus skirt, and (d) the right atrial disc. **(B)** Lateral view of the LuX-Valve. **(C)** The delivery system of the LuX-Valve.

the RV under the guidance of TEE and X-ray fluoroscopy. The angle of the catheter was adjusted to ensure that the catheter was coaxial and centered with the ring. When the catheter was positioned under the loop, which was approximately 5 cm, the IVA and two clamping keys of the anterior lobes were released in turn by adjusting the knob system on the catheter (**Figure 3C**). Then, the clamping keys were positioned properly under the anterior lobe, and the entire delivery system was gently retracted so that the clamping keys hooked the anterior lobe. The atrial plate was released, the IVA was deployed, and the anchor pin was inserted into the septum for fixation (**Figure 3D**). Finally, the catheter was withdrawn and removed; then, the heparin was neutralized and the atrial incision was closed (**Figures 3E,F**).

Data collection

Baseline data were collected from the electronic medical record system. The operative time, the device time, and the X-ray fluoroscopy time were recorded. The device time was defined as the time from catheter entry into the RA to withdrawal from the RA. In addition, data were collected during hospitalization (including the time in the intensive care unit and in the hospital and the postoperative TTE data).

Follow-up

Follow-up data were collected from enrolled patients at baseline, before discharge, and at 30 days, 6 months, and 1 year postoperatively. Primary end points included a successful operation and a successfully implanted device. Successful surgery was defined as the successful implantation of the valve and removal of the delivery system; the correct and stable placement of the prosthesis; and no serious or life-threatening adverse events during the operation. The function of the TV was recovered satisfactorily [TR severity is reduced by $\geq$ 2, TV pressure gradient (PG) $\leq$ 6 mmHg], and there were no cardiovascular-related deaths, implant displacements, valve failures, or other major adverse events related to the device (including myocardial infarction, embolism, conduction disturbances, and a new transventricular septal shunt).

Statistical analyses

Continuous variables were reported as the median (25th and 75th percentile), whereas classified variables were expressed by frequency and percentage. The paired *t*-test was used to compare continuous variables for each patient before and after

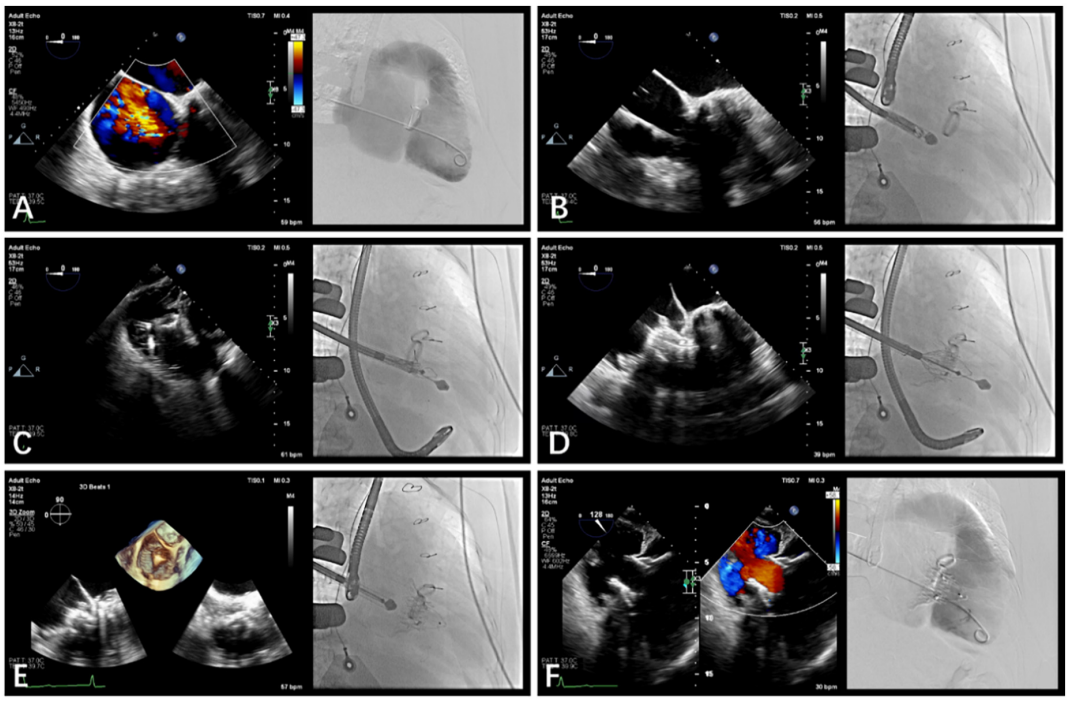

FIGURE 3
Guidance using transesophageal echocardiography (TEE) and fluoroscopic imaging in transcatheter tricuspid valve replacement. **(A)** TEE and fluoroscopy showed severe tricuspid re-gurgitation. **(B)** LuX-Valve guided by TEE was used to deliver the bioprosthesis to TA *via* the right intercostal approach. **(C)** The delivery system released the interventricular anchor and 2 graspers, and the graspers were guided by TEE to clamp the anterior leaflet. **(D)** The annulus skirt and the atrium disc were released in turn, and the position of the implant was adjusted by TEE to ensure that there was no obvious paravalvular leakage. **(E)** The bioprosthesis was completely re-leased after fixation with the interventricular anchor. **(F)** Postoperative computerized tomography angiography and TEE showed that tricuspid regurgitation disappeared immediately.

the procedures, and other continuous variables were determined with the Student *t*-test. We compared the classification variables using the Wilcoxon signed rank test. A two-tailed *P*-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) version 25.0.

Results

Baseline data

The baseline clinical features of the 15 patients are listed in Table 1. Despite receiving aggressive diuretic therapies, all patients had typical symptoms of severe right heart failure with ascites (46.7%) or peripheral edema (100.0%). In these 11 patients who had left-sided valvular surgery, 9 patients (81.8%) had been treated with surgical mitral valve replacement, and other 2 patients (18.2%) had been accepted with surgical mitral valve replacement and transcatheter aortic valve replacement. The causes of TR were left heart surgery (73.3%), permanent pacemaker or cardioverter defibrillator implants (40.0%), and AF (86.7%). Baseline echocardiographic and computed tomography (CT) parameters are listed in Table 2. All 15 patients had severe TR at baseline. Preoperative right heart catheterization showed that the systolic pulmonary arterial pressure of the included patients was 41.0 (32.0, 48.0) mm Hg, and 8 patients had pulmonary hypertension preoperatively. In addition, all patients were New York Heart Association (NYHA) functional class III/IV; the median European system for cardiac operative risk evaluation II was 9.5 (7.4, 11.6)% and the Society of Thoracic Surgeons score was 10.3 (7.8, 12.4)%, which indicated a high risk of cardiopulmonary bypass.

Intraoperative and hospitalization data

The intraoperative and hospitalization details are shown in Table 3. All patients were treated 3 to 5 days preoperatively and were given intravenous diuretics to reduce their weight and improve their peripheral edema. Surgical success was achieved in all patients (100%), with the individual valves in place in all cases. The operating time was 140.0 (110.0, 180.0) min, and the device time was 10.0 (7.0, 12.0) min, with no persistent ventricular arrhythmias, atrioventricular block, or cardiac rupture. In 6 patients who had previously

been implanted with a permanent pacemaker or implantable cardioverter defibrillator, the lead remained attached to the RV with no change in threshold after the valve was implanted. After the procedures, TEE detected mild paravalvular leakage in 1 patient (6.6%), and moderate paravalvular leakage occurred in 1 patient (6.6%), possibly due to leaflet damage during the crimping of the valve. Postprocedural CT showed the precise location of the IVA and the two graspers (Figure 4). The remaining 13 patients (86.7%) had no/trace regurgitation. The mean postoperative times in the intensive care unit were 2.0 (1.0, 12.0) days, and the postoperative hospitalization times were 13.0 (7.0, 19.0) days. In patients with no preexisting renal impairment, RV angiography was performed to confirm the position and function of the implanted valve. Before discharge, CT was used to confirm the position and fixation details of the prosthesis. One patient died on postoperative day 12 of pulmonary infection, which was considered unrelated to the procedures or the devices. In addition, there were no pulmonary

TABLE 1 Baseline patient characteristics (N = 15).

Characteristics	
Age (years)	62.0 (56.0, 78.0)
Female	9 (60.0)
Body mass index (kg/m^2)	21.6 (19.1, 25.7)
NYHA class III or IV	15 (100.0)
STS score (%)	10.3 (8.2, 12.4)
EuroSCORE II (%)	9.5 (7.4, 11.6)
6MWT (m)	210.0 (155.0, 270.0)
KCCQ	32.0 (26.0, 39.0)
Clinical symptoms	
Peripheral edema	15 (100)
Ascites	7 (46.7)
Blood sampling	
Hemoglobin (g/L)	101.8 (91.4, 118.6)
Albumin (g/dL)	3.6 (3.2, 4.2)
Bilirubin (mg/dL)	1.2 (0.8, 1.5)
Creatinine (mg/dL)	1.0 (0.7, 1.3)
eGFR (mL/min)	56.7 (43.2, 69.8)
Troponin I (ng/mL)	3.9 (0.7, 11.7)
BNP (pg/mL)	202.1 (96.4, 353.9)
NT-proBNP (pg/mL)	775.0 (537.2, 1258.8)
Alanine transaminase (U/L)	16.3 (10.8, 25.6)
Aspartate transaminase (U/L)	28.0 (17.7, 41.0)
INR	1.5 (0.9, 2.1)
Right heart catheterization	
sPAP (mm Hg)	41.0 (32.0, 48.0)
mPAP (mm Hg)	24.0 (16.0, 32.0)
Pulmonary hypertension*	8 (53.3)
Comorbidities	
Diabetes	5 (33.3)
Atrial fibrillation	13 (86.7)
RBBB	3 (20.0)
LBBB	2 (13.3)
Coronary artery disease	2 (13.3)
Anemia	10 (66.7)
Dyslipidemia or hyperlipidemia	9 (60.0)
Chronic obstructive pulmonary disease	6 (40.0)
Chronic kidney disease†	7 (46.6)
Severe liver disease‡	5 (33.3)
Prior gastrointestinal hemorrhage	4 (26.6)
Prior stroke/TIA	1 (6.7)
Previous cardiac intervention	
Coronary artery bypass grafting	2 (13.3)
Left-sided valvular surgery	11 (73.3)
PPM/ICD	6 (40.0)

Values are presented as n (%) or median (25th, 75th percentile).
*mPAP ≥ 25 mm Hg.
†Defined as eGFR < 60 mL/min.
‡Defined as MELD-albumin score > 12. BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; EuroSCORE, European system for cardiac operative risk evaluation; ICD, implantable cardioverter defibrillator; INR, international normalized ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; LBBB, left bundle branch block; MELD, Model for End-Stage Liver Disease; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PPM, permanent pacemaker; RBBB, right bundle branch block; 6MWT, 6-min walk test; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack.

TABLE 2 Baseline echocardiographic and computed tomography parameters (N = 15).

Echocardiographic parameters	
RV basal diameter (mm)	55.3 (43.5, 68.3)
RV mid diameter (mm)	42.0 (35.3, 50.5)
Fractional area change (%)	38.0 (32.7, 43.2)
TAPSE (mm)	13.0 (11.5, 16.0)
RV systolic TDI (cm/s)	10.0 (7.0, 14.0)
RA volume index (mL/m^2)	88.0 (77.1, 121.2)
EROA PISA (mm^2)	71.1 (62.0, 77.2)
LVIDD (mm)	40.0 (34.0, 55.0)
LVIDS (mm)	27.0 (21.0, 48.0)
LVEF (%)	54.0 (51.0, 65.0)
Transient regurgitation volume (mL)	72.6 (56.2, 110.3)
TR velocity (m/s)	2.86 (1.80, 3.67)
TA maximum diameters (mm)	48.4 (43.0, 52.1)
TA minimum diameters (mm)	40.5 (32.4, 47.0)
Computed tomography parameters	
TA maximum diameters (mm)	50.3 (44.8, 55.7)
TA minimum diameters (mm)	41.1 (36.1, 45.6)

EROA, effective regurgitation orifice area; LVEF, left ventricular ejection fraction; LVIDD, left ventricular internal dimension in diastole; LVIDS, left ventricular internal dimension in systole; PISA, proximal isovelocity surface area; RA, right atrium; RV, right ventricular; TA, tricuspid annular; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; TR, tricuspid regurgitation.

TABLE 3 Intraoperative and in-hospital outcomes (N = 15).

Intraoperative outcomes	
Procedural success	15 (100.0)
Procedural time (min)*	140.0 (110.0, 180.0)
Device time (min)†	18.0 (8.0,xf 26.0)
Fluoroscopy time (min)	23.0 (16.0, 31.0)
Bleeding volume (mL)	60.0 (30.0, 160.0)
Intraoperative, postdevice TEE	
Peak trans tricuspid gradient (mm Hg)	17.0 (8.0, 27.0)
Mean trans tricuspid gradient (mm Hg)	3.6 (1.8, 5.5)
Tricuspid valve area (cm^2)	3.2 (2.1, 3.8)
Complications	
Conversion to median sternotomy	0 (0.0)
Right coronary injury	0 (0.0)
Perforation of right ventricle wall	0 (0.0)
New-onset conduction block	0 (0.0)
Atrioventricular block	0 (0.0)
Left bundle branch block	0 (0.0)
Right bundle branch block	0 (0.0)
In-hospital outcomes	
ICU length (days)	2.0 (1.0, 12.0)
Postoperative hospitalization length (days)	13.0 (7.0, 19.0)
Residual TR ≥ moderate‡	1 (6.6)
Postoperative 24-h chest drainage (mL)	170.0 (120.0, 875.0)
Myocardial infarction	0 (0.0)
Renal failure requiring dialysis	0 (0.0)
Gastrointestinal hemorrhage	0 (0.0)
Device migration	0 (0.0)
Device thrombosis	0 (0.0)
Pulmonary embolism	0 (0.0)
Pulmonary infection	1 (6.6)
Stroke/TIA	0 (0.0)
In-hospital deaths§	1 (6.6)
Troponin I (ng/mL)	0.16 (0.02, 0.30)
NT-proBNP (pg/mL)	689.3 (368.7, 1029.4)

Values are presented as n (%) or median (25th, 75th percentile).
*Defined as the duration from initial skin incision to final wound closure.
†Defined as the duration from guiding sheath insertion into the RA to retrieval of the delivery system.
‡One had central regurgitation and the others had perivalvular leakage. §One died during hospitalization of a lung infection. ICU, intensive care unit; TIA, transient ischemic attack; TR, tricuspid regurgitation.

embolisms, cerebrovascular events, or new conduction blocks during hospitalization. All discharged patients were treated with anticoagulants. All patients had a ≥ 2 grade reduction in severity of TR from preoperative levels.

One-year follow-up data

Major follow-up outcomes at 1 year are shown in Table 4. Baseline to 1-year echocardiographic measurements are listed in Table 5. For 14 patients, TR severity measured by TTE decreased from 100.0% severe to 85.7% no/trace ($P = 5.32 \times 10^{-4}$). Of the remaining patients, 1 patient had mild paravalvular leakage, and another patient had moderate paravalvular leakage. TA diameter and RV diameter were both decreased compared with preoperative measurements, indicating RV remodeling. All patients exhibited significant improvement in symptoms at 6 months. For the 6-month follow-up data, the TR decreased to no/trace in 13 patients (92.9%, $P = 3.11 \times 10^{-4}$). One patient had mild paravalvular leakage. At the 1-year follow-up, TR decreased to no/trace in 12 patients (85.7%, $P = 5.32 \times 10^{-4}$). Two patients had mild paravalvular leakage. In addition, the reduction of the TV ring diameter and the increased deviation of the TV annular plane in systole indicated improvement in RV structure and function. Meanwhile, the TAPSE measurement improved significantly [16.3 (14.4, 18.8) vs. 13.0 (11.5, 16.0), $P = 3.63 \times 10^{-5}$], and the RV volume showed remarkable improvement [59.3 (47.5, 68.5) vs. 80.5 (66.0, 96.5), $P = 1.06 \times 10^{-11}$]. Furthermore, peripheral edema and ascites decreased to 28.6 and 14.3%, respectively ($P = 1.57 \times 10^{-3}$ and 2.53×10^{-2}). The proportion of patients in NYHA functional class II was higher than that before the operation (11/14 vs. 0/15, $P = 9.11 \times 10^{-4}$). The 6-min walking test results showed significant improvement in motion performance [355.0 (310.0, 390.0) m vs. 210.0 (155.0, 270.0) m, $P = 9.56 \times 10^{-14}$). Kansas City cardiomyopathy questionnaire scores also improved significantly at the 1-year follow-up [62.0 (60.0, 66.0) vs. 32.0 (26.0, 39.0), $P = 9.29 \times 10^{-15}$]. Thirteen patients (92.9%) met the primary end points. One patient (7.1%) was re-hospitalized because of device thrombosis (Figure 5). Due to the LuX-Valve has a larger atrial plate compared to other devices, the bioprosthetic valve effectively prevents paravalvular leakage but is apt to thrombose. Furthermore, the lower pressure of the RV results in slower blood flow in comparison to blood flow through the left ventricle, and the dosage of anticoagulation has not been determined in the current studies.

Discussion

In this single-center, observational study, the LuX-Valve was successfully implanted in all 15 patients, and good clinical results were achieved without the complex TV anatomical structures and different etiologies. The unique anatomical structures and pathophysiological characteristics of the TV make the TTVR device difficult to design. From a physiological point of view of, the TV has a 3-dimensional structure similar to that of a saddle that exhibits dynamic changes during the cardiac cycle to ensure that the valve closes completely. Primary TR is caused by congenital or acquired abnormalities of the TV itself. However, secondary (or functional) TR, which is far more common than primary TR, is secondary to excess RV pressure and/or volume load. When TR occurs, the TV loses its normal shape and dilates under the strain of the dilated RA and RV. Recent studies suggest

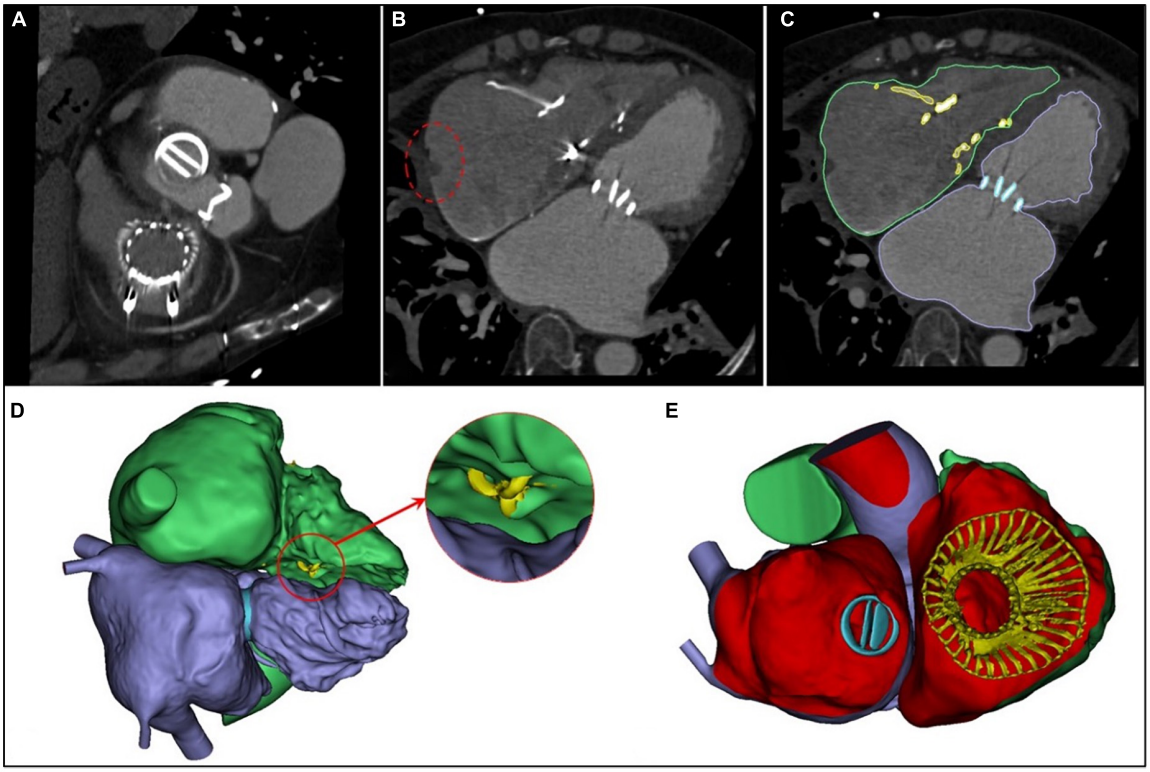

FIGURE 4
Postprocedural evaluation of the interventricular anchor. **(A)** A multislice computed tomography scan showed the precise positions of the two graspers. **(B)** The incision of the right atrium (the red circle) corresponds with **Figure 1F**. **(C)** The right heart is outlined in green; the left heart, in purple; the mechanical valve, in blue, and the LuX-Valve is yellow. **(D)** The yellow area in the red circle is the interventricular anchor. **(E)** The 3-dimensional reconstructed image from the right atrial plane demonstrates that the LuX-Valve is located in the normal position.

TABLE 4 Follow-up outcomes at 1 year after discharge (*N* = 14).

1-year deaths	0 (0.0)
Myocardial infarction	0 (0.0)
Rehospitalization*	1 (7.1)
Renal complications requiring dialysis	0 (0.0)
Need for renal replacement therapy	0 (0.0)
Non-elective tricuspid valve reintervention	0 (0.0)
Device migration	0 (0.0)
Device thrombosis	1 (7.1)
Severe bleeding	0 (0.0)
Major cardiac structural complications	0 (0.0)
Pulmonary embolism	0 (0.0)
Gastrointestinal hemorrhage	0 (0.0)
Stroke/TIA	0 (0.0)
New-onset third-degree atrioventricular block	0 (0.0)

Values are presented as n (%).
*One patient was rehospitalized due to device thrombosis.
TIA, transient ischemic attack.

that the overloading of the RV caused by long-term TR may lead to irreversible myocardial injury of the RV (27). As a result, as the focus on TR has increased, the number of operations on the TV has increased (27). Most studies have reported incomplete reduction of TR (14, 28, 29). A recent large registry of patients who had transcatheter aortic valve replacement showed that the severity of preoperative TR was independently associated with 1-year postoperative mortality and rehospitalization for heart failure (30). In general, the TV may not provide stable support for traditional radial TTVR devices. The LuX-Valve is an *in situ* TTVR device with a non-radial support force that has unique advantages compared with those of the traditional radial support force devices. The selection of the valve size is based on the effective orifice area rather than on the expanded TV, which renders the selection of diameter sizes smaller. This design also ensures that the diameter of the annulus decreases as the RV remodeling reverses. In addition, the smaller valve has no radial support on the TV, so it is almost impossible to induce right ventricular outflow tract (RVOT) obstruction, right coronary artery injury, or conduction block (13). The LuX-Valve has a larger atrial plate compared to other devices, which effectively prevents paravalvular leakage after the valve is implanted. These advantages suggest that the LuX-Valve is suitable for the treatment of TR caused by a variety of etiologies, including functional TR, TR caused by the pacemaker lead, and

TABLE 5 Baseline to 1-year echocardiographic measurements.

Echocardiographic parameters	Baseline (N = 15)	30 days (N = 14)		6 months (N = 14)		1 year (N = 14)	
		Results	*P* value	Results	*P* value	Results	*P* value
TR severity							
None/trace	0 (0.0)	12 (85.7)	5.32×10^{-4}	13 (92.9)	3.11×10^{-4}	12 (85.7)	5.32×10^{-4}
Mild	0 (0.0)	1 (7.1)	0.32	1 (7.1)	0.32	2 (14.3)	0.16
Moderate	0 (0.0)	1 (7.1)	0.32	0 (0.0)	—	0 (0.0)	—
Severe	15 (100.0)	0 (0.0)	1.08×10^{-4}	0 (0.0)	1.08×10^{-4}	0 (0.0)	1.08×10^{-4}
TAPSE (mm)	13.0 (11.5, 16.0)	13.9 (12.4, 16.5)	6.31×10^{-4}	15.7 (13.6, 18.0)	6.48×10^{-5}	16.3 (14.4, 18.8)	3.63×10^{-5}
Fractional area change (%)	38.0 (32.7, 43.2)	39.6 (34.3, 46.4)	2.87×10^{-8}	40.8 (35.2, 47.5)	3.10×10^{-9}	41.3 (35.7, 47.8)	3.75×10^{-11}
EROA PISA (mm^2)	71.1 (62.0, 77.2)	—	—	—	—	—	—
Peak transtricuspid gradient (mm Hg)	18.5 (8.0, 32.0)	6.5 (4.0, 11.0)	5.73×10^{-15}	5.0 (3.0, 8.0)	3.82×10^{-15}	5.5 (3.0, 13.0)	4.33×10^{-15}
Mean transtricuspid gradient (mm Hg)	2.0 (1.3, 3.3)	3.5 (2.4, 4.5)	5.92×10^{-14}	2.6 (1.8, 3.6)	7.91×10^{-10}	2.3 (1.4, 3.0)	4.04×10^{-3}
RV basal diameter (mm)	55.3 (43.5, 68.3)	52.5 (41.7, 62.3)	9.62×10^{-4}	49.8 (41.4, 58.5)	6.96×10^{-4}	48.9 (40.5, 56.6)	6.80×10^{-5}
RV mid diameter (mm)	42.0 (35.3, 50.5)	37.7 (32.1 46.4)	4.52×10^{-12}	36.0 (31.6, 44.0)	5.58×10^{-13}	35.2 (30.8, 43.3)	2.48×10^{-13}
RV volume (mL)	80.5 (66.0, 96.5)	68.3 (54.8, 77.0)	1.59×10^{-11}	63.0 (50.5, 73.8)	1.37×10^{-11}	59.3 (47.5, 68.5)	1.06×10^{-11}
RA volume (mL)	188.0 (134.5, 253.0)	159.8 (120.3, 220.0)	5.69×10^{-8}	142.0 (112.8, 206.3)	2.55×10^{-9}	131.5 (104.5, 201.0)	7.33×10^{-10}

Values are presented as N (%) or median (25th, 75th percentile).

EROA, effective regurgitation orifice area; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; PISA, proximal isovelocity surface area; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

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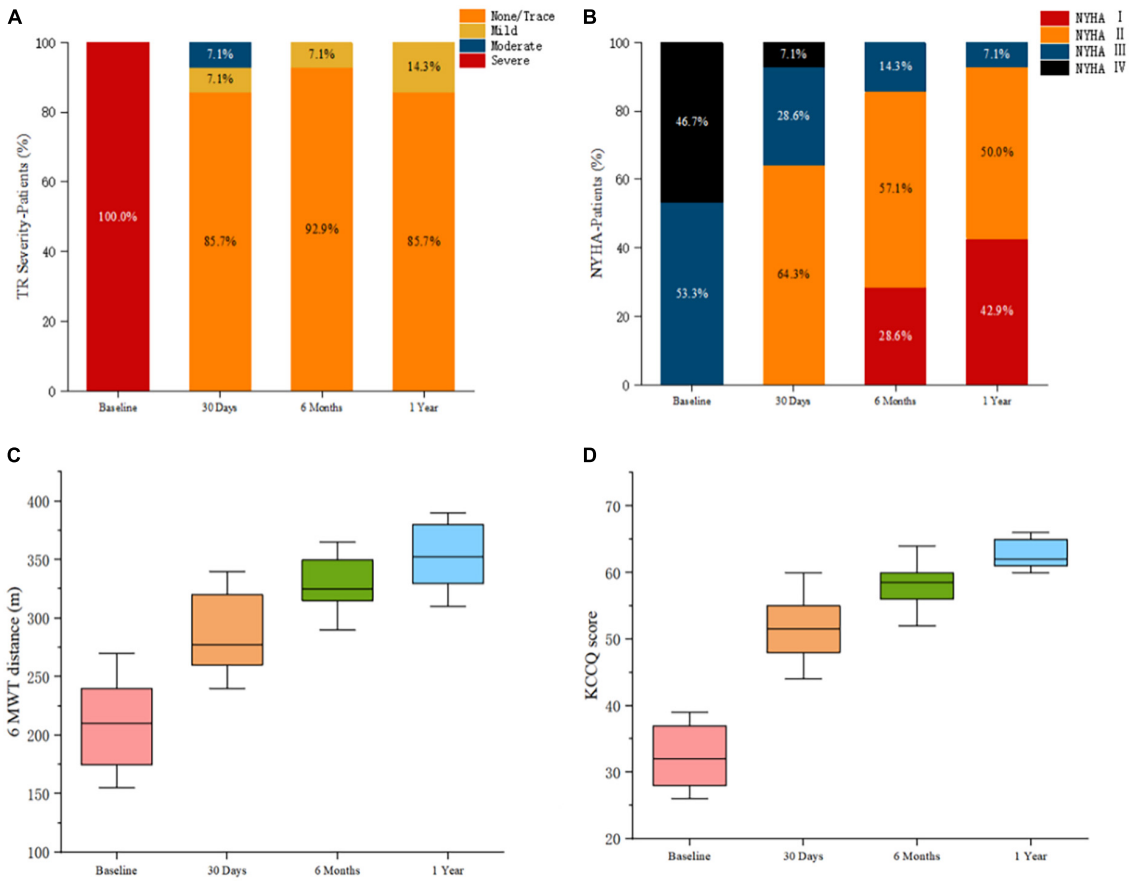

FIGURE 5
Postprocedural evaluation showed reduced severity of triscuspid regurgitation and improved clinical, functional, and quality-of-life outcomes. **(A)** Assessment of severity of tricuspid regurgitation. *P*-value calculated from the Wilcoxon signed rank test. **(B)** Comparison of New York Heart Association functional class pre-and post-procedures. *P*-value calculated from the Wilcoxon signed rank test. **(C)** Assessment of the 6-min walk test distances. *P*-value deter-mined from the paired Student *t*-test. **(D)** Assessment using the Kansas City Cardiomyopathy Questionnaire. *P*-value determined from the paired Student *t*-test.

chronic AF. Hahn reported that NaviGate system (NaviGate Cardiac Structures, Lake Forest, CA, USA), which was a radial force-dependent TTVR device. However, the patients who received NaviGate implantation had a high prevalence of bioprosthesis failure, atrioventricular block and paravalvular leakage (31). During the 1-year follow-up of this small series of patients with severe, symptomatic TR treated with TTVR, there were a number of important observations. First, TTVR virtually eliminates TR or underlying disease. Despite multiple comorbidities, those who survived to 1 year had RV remodeling and increased cardiac output. Previous studies have shown that changes of RV dimensions and function would predict TR after TTVR. RV systolic function is mainly determined by afterload, preload, and intrinsic myocardial contractility (32). With the significant decrease in TR after procedures, an increase in afterload may affect RV function or even induce irreversible changes. However, the further studies are needed to proceed. Second, successful procedures depend on the guidance of TEE and CTA. Preimplantation sizing may be adjusted in a number of different ways. In fact, even advanced 3-dimensional reconstruction tools are used. Third, due to the lack of obvious anatomical markers of TV under the guidance of digital subtraction angiography, accurate positioning is required when the LuX-Valve is implanted. Fourth, the increased incidence of pulmonary complications caused by bleeding in the chest should be prevented during the procedures. Fifth, the lower pressure of the RV results in slower blood flow in comparison to blood flow through the left ventricle, so anticoagulation is needed to prevent valve thrombosis. However, further research is needed to determine whether vitamin K antagonists, direct oral anticoagulants, or dual antiplatelet agents should be used.

At present, the morbidity of patients with severe TR is high, but the treatment effect is not satisfied, so the market prospect of interventions for TR in the future is broad. However, not all patients with TR meet the indications for interventions. In addition, many patients present with right heart failure

and other manifestations at the time, so the perioperative management of patients with TR is more challenging. When selecting patients in the future, it is necessary to strengthen the evaluation of anatomical characteristics and comorbidities of the specific patient at the same time, and continuously improve the quality of surgical and perioperative management.

Limitations

This study has some limitations. First, this study lacks a control group undergoing traditional surgery (Such as a propensity score matched control group of patients with surgical tricuspid valve replacement *via* right thoracotomy), which requires a larger sample size and a well-designed clinical trial to confirm its long-term safety and effectiveness. Second, the use of the LuX-Valve is limited because the surgical approach is still through a thoracic incision, and its delivery system needs to be further improved to be implanted through the peripheral vein path. Third, whereas an average of multiple cardiac cycles is used to measure most RV parameters, strain imaging uses a single cycle and may not represent the entire RV function for patients with AF. Finally, the follow-up time was limited.

Conclusion

The patients with severe functional TR were treated by TTVR, which is a feasible, relatively safe and low-complication approach that improves RV remodeling and relieves symptoms of right heart failure with reliable clinical outcomes.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Xijing Hospital Ethics Committee, ClinicalTrials.gov protocol registration system (NCT02917980). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YuM, LL, and YL were responsible for wrote the manuscript. MZ and YaM were responsible for the figures. CX and PJ were responsible for the data collecting. JY was responsible for the manuscript reviewing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Outcomes of transcatheter edge-to-edge mitral valve repair with percutaneous coronary intervention vs. surgical mitral valve repair with coronary artery bypass grafting

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Aims: Patients with severe ischemic mitral regurgitation (IMR) may receive concurrent coronary artery bypass graft (CABG) with surgical mitral valve repair (SMVr) or percutaneous coronary stent implantation (PCI) with transcatheter edge-to-edge mitral valve repair (TMVr). However, there is no consensus on the management of severe IMR in this setting. We aimed to compare the outcomes of combined SMVr with CABG to concurrent TMVr with PCI among patients with IMR in the National Inpatient Sample (NIS) database.

Methods and results: The National Inpatient Sample was queried for all patients diagnosed with IMR who underwent SMVr with CABG or TMVr with PCI during the years 2016–2018. Study outcomes included all-cause in-hospital mortality, periprocedural complications, and resources used. A total of 1,360 potentially eligible patients were included in the study. After 1:5 propensity score matching, 133 patients were classified in the SMVr + CABG group and 29 patients in the TMVr + PCI group. Adjusted mortality was higher in the TMVr + PCI group compared with the SMVr + CABG group (13.8% vs. 4.5%, $P = 0.034$). Perioperative complications were higher among patients who underwent SMVr + CABG including blood transfusions (29.3% vs. 6.9%, $P = 0.01$) and post-procedural cardiogenic shock (11.3% vs. 0%, $P = 0.044$). The cost of care was higher (USD$783548.80 vs. USD$331846.523, $P = 0.001$) and the length of stay was longer (17.9 vs. 15.44 days, $P < 0.001$) in the TMVr + PCI group. On multivariable analysis, age (OR, 1.039 [95% CI, 1.006–1.072]; $P = 0.032$), renal failure (OR, 3.465 [95% CI, 1.867–6.433]; $P < 0.001$), and liver disease (OR, 5.012 [95% CI, 2.578–9.686]; $P < 0.001$) were associated with in-hospital mortality.

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Conclusion: TMVr + PCI was associated with higher resource use and in-hospital mortality but with improved perioperative complications compared with SMVr + CABG.

KEYWORDS

transcatheter mitral valve repair, surgical mitral valve repair, functional mitral regurgitation, ischemic mitral regurgitation, National Inpatient Sample

Introduction

The prevalence of ischemic etiology was reported to be 50% in patients with functional mitral regurgitation (FMR) (1). Previous studies had demonstrated that there were still plenty of patients with severe mitral regurgitation despite guideline-guided medical treatment (GDMT), cardiac resynchronization therapy, or coronary artery revascularization which were the first-line therapies for heart failure (HF) with ischemic mitral regurgitation (IMR) and used to improve the underlying left ventricular (LV) dysfunction (2). Surgical mitral valve repair (SMVr) for severe IMR in patients with LV systolic dysfunction has been demonstrated to improve symptoms and quality of life (3). However, a large number of patients are not referred for open-heart surgery (SMVr) because of their prohibitive surgical risk (4).

The COAPT randomized controlled trial (RCT) has shown that the use of transcatheter edge-to-edge mitral valve repair (TMVr) therapy is beneficial for the IMR (5), and TMVr is the only procedure that has gained widespread use in clinical practice. Although less effective than surgery in reducing MR, TMVr showed fewer perioperative adverse events and achieved a similar durable improvement in function (6, 7).

In the current clinical practice, patients with severe IMR and LV systolic dysfunction with suitable coronary targets affected by high-grade proximal stenosis may receive concurrent coronary artery bypass graft (CABG) with SMVr (8), and some patients may receive the concurrent TMVr and percutaneous coronary stent implantation (PCI). However, there is no consensus on the management of severe IMR in this setting. Given the limited literature on this topic, we aimed to investigate the in-hospital clinical outcomes of combined SMVr + CABG vs. concurrent TMVr + PCI in patients with IMR using a National Inpatient Sample (NIS) database.

Materials and methods

Study data

In this study, we used the NIS data from January 2016 to December 2018, which was developed by the Agency of Healthcare Research and Quality of the United States through a federal–state–industry partnership. The NIS database has more than 8 million inpatients and represents 20% of all hospital admissions in the United States. It is updated annually, thus we can use these data to analyze the disease trend over time (9). Because the NIS database is publicly available, we do not need to get the approval of the institutional review board or informed consent in our clinical study.

Study design and data selection

The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes, and ICD-10-Procedure Coding System (PCS) codes were used to analyze these data. The NIS data from 2016 to 2018 were used in the present study (**Supplementary Table 1**). Consecutive patients with severe IMR, scheduled for concurrent CABG with TMVR or PCI with TMVr, were retrospectively analyzed in the NIS database. TMVR and CABG were performed as a single procedure, TMVr and PCI were performed as a staged procedure, and TMVr was performed after the PCI procedure. IMR with mitral valve insufficiency and without any other valvular disease was selected using the ICD-10-CM code. Patients who underwent TMVr or SMVr were selected by ICD-10-PCS codes, respectively. PCI or CABG were selected by ICD-10-PCS codes, and the periprocedural complications post the procedure were identified by the ICD-10-CM codes; the detailed ICD-10-CM codes and ICD-10-PCS codes are shown in **Supplementary Table 1**. Patients who were younger than 50 years old with mitral stenosis, mitral stenosis with insufficiency, aortic valve disease, tricuspid valve disease, pulmonary valve disease, mitral valve surgery, tricuspid valve surgery, pulmonary artery surgery, mitral prolapse, rupture of papillary muscle, rupture of chordae tendinae, and atrial functional mitral regurgitation (atrial flutter and atrial fibrillation) were excluded from our study. Propensity score matching was performed to adjust for confounding factors, resulting in 133 patients being assigned to SMVr + CABG and 29 patients assigned to TMVr + PCI groups, respectively. A flowchart of our patient selection criterion is shown in **Figure 1**.

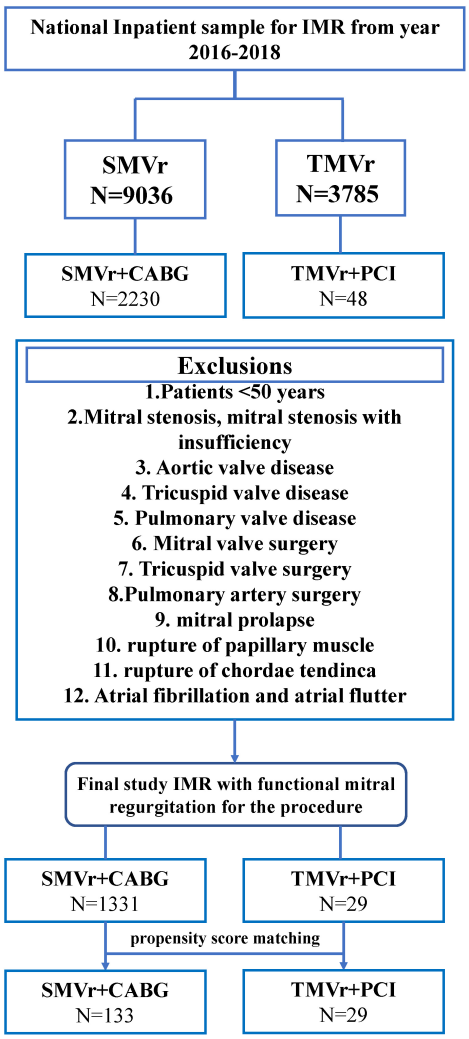

FIGURE 1
Flowchart of the study cohort. ICD-10-PCS indicates International Classification of Diseases, Tenth Revision, Procedure Coding System.

Study outcomes

The primary endpoints of our study were in-hospital mortality and periprocedural complications between the SMVR + CABG and TMVr + PCI groups. The secondary outcomes of interest were resources used and operative procedure-related trends over time, such as the length of hospital stay, total charges, and the age of patients who underwent SMVR + CABG and TMVr + PCI.

Statistical analysis

Propensity score matching (PSM), a method to balance covariates in two groups by reducing the selection bias, was conducted to match patients who underwent SMVr + CABG to those who underwent TMVr + PCI. In our study, we included variables that may be associated with the outcome of patients with IMR of the NIS database in the propensity score model. Matching factors for 1:5 PSM include age, sex, hypertension, diabetes, heart failure, renal failure, and ICD implantation.

Pearson χ^2 exact test was used for categorical variables, and the independent *t*-test was used for the continuous variables. The categorical variables and continuous variables were presented as frequency and median of standard deviations, respectively. Univariate and multivariate logistic regression analyses were performed to find the predictors of in-patient mortality, blood transfusion, and acute kidney injury. Model 1 indicates the univariate regression analysis; model 2 adjusted for SMVr + CABG, TMVr + PCI, age, female, race; model 3 adjusted for SMVr + CABG, TMVr + PCI, age, female, race, deficiency anemia, heart failure, renal failure, liver disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, atrial fibrillation, peripheral vascular disease, cerebral infarction, coagulopathy, obesity, smoking, alcohol use, and hyperlipidemia. After SMVr + CABG and TMVr + PCI operations using relevant demographic and clinical variables were shown in Table 1. For all analyses, a two-sided *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25 (IBM, Armonk, NY, USA) and R version 3.5 (version 3.6.3, R Core Team).

Results

Characteristics of study participants selected from the NIS database

Between January 2016 and December 2018, a total of 9,036 patients who underwent SMVr and 3,785 patients who underwent TMVr were identified. After elimination, we finally selected 1,331 patients who underwent SMVr + CABG procedures and 29 patients who underwent TMVr + PCI procedures (Figure 1 and Table 1). Patients who underwent TMVr + PCI procedures were older compared to those who underwent SMVr + CABG procedures (72.38 years vs. 68.25 years, $P = 0.078$) (Table 1). Both cohorts included predominantly White patients (77.9% SMVr + CABG vs. 86.2% TMVr + PCI) (Table 1). The use of SMVr + CABG and TMVr + PCI was similar among Hispanic patients (7.8% vs. 6.9%) (Table 1). Compared to patients who received SMVr + CABG, those who received TMVr + PCI had higher proportions of female participants (51.7% vs. 20.9%, $P = 0.017$) and had a higher prevalence of heart failure (96.6% vs. 62.8%, $P < 0.001$), chronic renal failure (72.4% vs. 43.1%, $P = 0.001$), and ICD implantation (10.3% vs. 1.9%, $P = 0.001$), but SMVr + CABG had a higher prevalence rate of hypertension (35.3% vs. 10.3%, $P = 0.05$) (Table 1).

TABLE 1 Basic characteristics of the patients who underwent SMVr + CABG and TMVr + PCI (2016–2018).

	Unmatched groups			Propensity-matched groups		
Characteristic	SMVr + CABG (*n* = 1,331)	TMVr + PCI (*n* = 29)	*P*-value	SMVr + CABG (*n* = 133)	TMVr + PCI (*n* = 29)	*P*-value
Age, years (mean ± SD)	68.25 ± 8.46	72.38 ± 10.93	0.078	71.93 ± 8.22	72.07 ± 10.44	0.199
Female sex, *n* (%)	411 (30.9)	15 (51.7)	0.017	68 (51.1)	15 (51.7)	0.911
Race			0.851			0.593
White	1003 (77.9)	25 (86.2)		104 (78.8)	26 (89.7)	
African American	98 (7.6)	1 (3.4)		15 (11.4)	1 (3.4)	
Hispanic	101 (7.8)	2 (6.9)		4 (3)	2 (6.9)	
Asian/Pacific Islander	39 (3.0)	1 (3.4)		6 (3.7)	1 (3.4)	
Native American	7 (0.5)	0 (0)		3 (2.3)	1 (3.4)	
Other races	39 (3.0)	0 (0)		1 (0.75)	0 (0)	
Comorbidities and medical history						
Coronary heart disease	1331 (100)	29 (100)				
Hypertension, *n* (%)	473 (35.3)	3 (10.3)	0.05	14 (10.5)	3 (10.3)	0.932
Type 2 Diabetes mellitus, *n* (%)	512 (38.5)	8 (27.6)	0.233	62 (46.6)	13 (44.8)	0.146
Myocardial infarction, *n* (%)	1094 (82.2)	24 (82.8)	0.210	85 (73.9)	20 (69)	0.527
Heart failure, *n* (%)	836 (62.8)	28 (96.6)	<0.01	128 (96.2)	28 (96.6)	0.911
Cerebral infarction, *n* (%)	43 (3.2)	2 (6.9)	0.275	5 (3.8)	2 (6.9)	0.478
Liver disease, *n* (%)	65 (4.9)	2 (6.9)	0.620	15 (11.3)	3 (10.3)	0.840
Renal failure, *n* (%)	574 (43.1)	21 (72.4)	0.002	95 (71.4)	22 (75.9)	0.834
Peripheral vascular disease, *n* (%)	56 (4.2)	0 (0)	0.259	10 (7.5)	1 (3.4)	0.121
Chronic obstructive pulmonary disease, *n* (%)	314 (23.6)	7 (24.1)	0.945	41 (30.8)	7 (24.1)	0.416
Deficiency anemia, *n* (%)	56 (4.2)	0 (0)	0.259	7 (5.3)	1 (3.4)	0.199
Coagulopathy, *n* (%)	101 (7.6)	0 (0)	0.123	17 (12.8)	1 (3.4)	0.096
Obesity, *n* (%)	250 (18.8)	6 (20.7)	0.795	29 (21.8)	6 (20.7)	0.828
Alcohol use, %	43 (3.2)	0 (0)	0.325	3 (2.3)	1 (3.4)	0.406
Tobacco abuse, *n* (%)	433 (32.5)	7 (24.1)	0.339	30 (22.6)	7 (24.1)	0.927
Permanent pacemaker implantation	52 (3.9)	1 (3.4)	0.900	5 (3.8)	1 (3.4)	0.911
ICD implantation	25 (1.9)	3 (10.3)	0.001	4 (3.0)	3 (10.3)	0.088
Primary payer, *n* (%)			0.400			0.298
Medicare	829 (62.3)	23 (79.3)		104 (78.2)	20 (69)	
Medicaid	94 (7.1)	0 (0)		9 (6.8)	1 (3.4)	
Private insurance	343 (25.8)	5 (17.2)		34 (25.6)	6 (20.7)	
Other	64 (4.8)	1 (3.4)		9 (6.8)	2 (6.8)	

TMVr indicates transcatheter mitral valve repair; SMVR indicates surgical mitral valve repair; CABG indicates coronary artery bypass grafting; PCI indicates percutaneous coronary stent implantation.

Clinical outcomes in study cohort

To determine whether SMVr + CABG in patients with IMR leads to a higher risk of in-hospital mortality, periprocedural complications, and resource use, PSM was applied to reduce the bias due to confounding variables (Tables 1, 2). The results demonstrated that the in-hospital mortality was higher in the TMVr + PCI group compared with the SMVr + CABG group (11.8% vs.4.5%; $P = 0.034$, Table 2). The cost of care ($783548.80 ± 1743146.11 vs. $331846.523 ± 235718.27, $P < 0.001$) and the length of stay (17.9 ± 19.02 days vs. 15.44 ± 8.26 days, $P < 0.001$) were considerably higher for

TABLE 2 Clinical outcomes in patients who underwent SMVr + CABG and TMVr + PCI (2016–2018).

	Unmatched groups			Propensity-matched groups		
Variable	SMVr + CABG (*n* = 1,329)	TMVr + PCI (*n* = 29)	*P*-value	SMVr + CABG (*n* = 133)	TMVr + PCI (*n* = 29)	*P*-value
In-hospital mortality, *n* (%)	66 (5.0)	4 (13.8)	0.042	6 (4.5)	4 (13.8)	0.034
Length of hospital stay, days	12.23 ± 8.397	17.28 ± 19.309	<0.001	15.44 ± 8.26	17.9 ± 19.02	<0.001
Total charges, US$	294891.003 ± 232632.009	796410.72 ± 1772279.528	<0.001	331846.523 ± 235718.27	783548.80 ± 1743146.11	0.001
Cardiac complications						
Post-procedural cardiac tamponade, *n* (%)	11 (0.8)	0 (0)	0.623	3 (2.3)	0 (0)	0.406
Post-procedural cardiogenic shock, *n* (%)	61 (4.6)	0 (0)	0.238	15 (11.3)	0 (0)	0.044
Post-procedural cardiac arrest, *n* (%)	49 (3.7)	1 (3.4)	0.947	7 (5.3)	2 (6.7)	0.761
IABP, *n* (%)	182 (13.7)	7 (24.1)	0.107	27 (20.3)	8 (2.8)	0.443
ECMO, *n* (%)	14 (1.1)	0 (0)	0.579	1 (0.8)	0 (0)	0.634
Post-procedural pericardial complications, *n* (%)	52 (3.9)	0 (0)	0.278	8 (6.0)	1 (3.4)	0.561
Respiratory complications						
Post-procedural respiratory failure, *n* (%)	98 (7.4)	3 (10.3)	0.545	16 (12.0)	4 (13.3)	0.844
Post-procedural respiratory complications, *n* (%)	117 (8.8)	3 (10.3)	0.770	17 (12.8)	4 (13.3)	0.935
Post-procedural mechanical ventilation use, *n* (%)	203 (15.3)	6 (20.7)	0.422	35 (26.3)	7 (23.3)	0.736
Other perioperative complications						
Bleeding/hematoma post-procedure, *n* (%)	39 (2.9)	1 (3.4)	0.870	9 (6.8)	1 (3.4)	0.479
Post-procedural thrombosis due to cardiac prosthetic devices, *n* (%)	8 (0.6)	0 (0)	0.675	1 (0.8)	0 (0)	0.634
Post-procedural acute embolism and thrombosis, *n* (%)	22 (1.7)	2 (6.9)	0.034	2 (1.5)	2 (6.9)	0.099
Post-procedural blood transfusion, *n* (%)	304 (22.8)	2 (6.9)	0.042	39 (29.3)	2 (6.9)	0.01
Post-procedural acute kidney injury, *n* (%)	445 (33.4)	15 (51.7)	0.078	47 (35.3)	15 (51.7)	0.082
Fluid and electrolyte disorders, *n* (%)	578 (43.4)	10 (34.5)	0.336	72 (54.1)	11 (37.9)	0.084
Post-procedural cerebrovascular infarction or TIA, *n* (%)	19 (1.4)	0 (0)	0.517	2 (1.5)	0 (0)	0.499

TMVr indicates transcatheter mitral valve repair; SMVR indicates surgical mitral valve repair; CABG indicates coronary artery bypass grafting; PCI indicates percutaneous coronary stent implantation.

the TMVr + PCI group (Table 2). Patients who underwent SMVr + CABG were more likely to suffer from more blood transfusion (29.3% vs. 6.9%, $P = 0.01$; Table 2) post-procedural cardiogenic shock (11.3% vs. 0%, $P = 0.044$; Table 2).

Temporal trends

Over the study period, patients in the SMVr + CABG group had the tendency of younger than those in the TMVr + PCI group, and the SMVr + CABG group had tendency of a lower total charge and a shorter length of stay when compared with the TMVr + PCI group (Figures 2A–C).

Predictors of clinical outcomes

Logistic regression showed that age (OR, 1.039 [95% CI, 1.006–1.072]; $P = 0.032$), renal failure (OR, 3.465 [95% CI, 1.867–6.433]; $P < 0.001$), and liver disease (OR, 5.012 [95% CI,

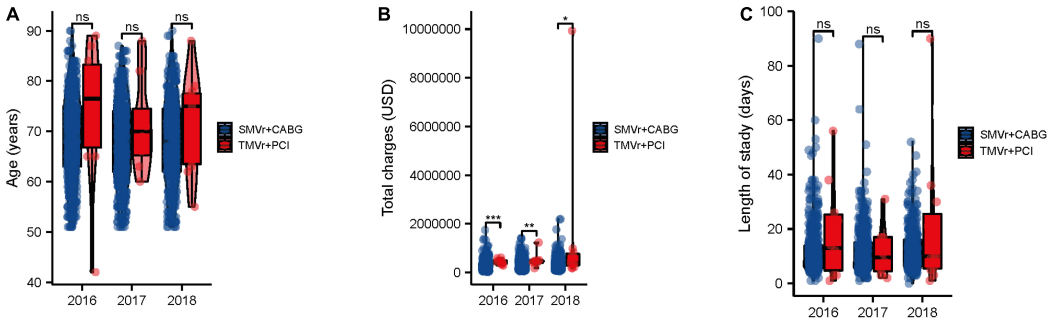

FIGURE 2
Trends in SMVr + CABG and TMVr + PCI from 2016 to 2018. Trends in age **(A)**, cost of stay **(B)**, and length of stay **(C)** of patients undergoing SMVr + CABG and TMVr + PCI from 2016 to 2018 in the National Inpatient Sample (NIS) database. TMVr indicates transcatheter mitral valve repair; SMVR indicates surgical mitral valve repair; CABG indicates coronary artery bypass grafting; PCI indicates percutaneous coronary stent implantation. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Characteristics	OR (95% CI)	*P* value
Model 1		
SMVr+CABG	Reference	
TMVr+PCI	2.979(1.108–8.796)	0.032
Model 2		
SMVr+CABG	Reference	
TMVr+PCI	2.176 (0.728–6.579)	0.176
Age	1.032 (1.022–1.065)	0.017
Female	1.578 (0.969–2.567)	0.056
Race	*N.S*	*N.S*
Model 3		
SMVr+CABG	Reference	
TMVr+PCI	1.276 (0.396–4.213)	0.678
Age	1.039 (1.006–1.072)	0.032
Female	1.535 (0.879–2.596)	0.138
Race	*N.S*	*N.S*
Deficiency anemia	0.856 (0.283–2.619)	0.768
Heart failure	1.493 (0.786–2.767)	0.232
Renal failure	3.465 (1.867–6.433)	<0.001
Liver disease	5.012 (2.578–9.686)	<0.001
Chronic obstructive pulmonary disease	1.642 (0.934–2.897)	0.093
Diabetes mellitus	0.676 (0.383–1.156)	0.149
Hypertension	0.976 (0.493–1.932)	0.905
Atrial fibrillation	1.054 (0.617–1.779)	0.864
Peripheral vascular disease	1.743 (0.663–4.587)	0.371
Cerebral infarction	3.867 (0.679–5.786)	0.214
Coagulopathy	1.854 (0.889–3.843)	0.093
Obesity	1.254 (0.646–2.376)	0.486
Smoking	0.978 (0.569–1.744)	0.968
Alcohol use,	0.534 (0.068–4.173)	0.554
Hyperlipidemia	0.765 (0.463–1.323)	0.346

FIGURE 3
Predictors of mortality in mitral valve insufficiency patients undergoing SMVr + CABG or TMVr + PCI. TMVr indicates transcatheter mitral valve repair; SMVR indicates surgical mitral valve repair; CABG indicates coronary artery bypass grafting; PCI indicates percutaneous coronary stent implantation; model 1 indicates the univariate regression analysis; model 2 adjusted for SMVr + CABG, TMVr + PCI, age, female, race; model 3 adjusted for SMVr + CABG, TMVr + PCI, age, female, race, deficiency anemia, heart failure, renal failure, liver disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, atrial fibrillation, peripheral vascular disease, cerebral infarction, coagulopathy, obesity, smoking, alcohol use, and hyperlipidemia.

2.578–9.686]; $P < 0.01$) (Figure 3) were associated with higher mortality.

Our results also suggested that SMVr + CABG was significantly related to blood transfusion (OR, 0.194 [95% CI, 0.046–0.828]; $P = 0.029$) (Figure 4). Factors associated with a higher rate of blood transfusion post-procedure included female sex (OR, 1.489 [95% CI, 1.139–1.963]; $P = 0.006$), renal failure (OR, 1.456 [95% CI, 1.086–1.951]; $P = 0.012$), and coagulopathy (OR, 1.883 [95% CI, 1.251–2.891]; $P = 0.004$) (Figure 4).

Factors associated with a higher rate of post-procedural acute kidney injury included age (OR, 1.031 [95% CI, 1.017–1.043]; $P < 0.01$), deficiency anemia (OR, 2.441

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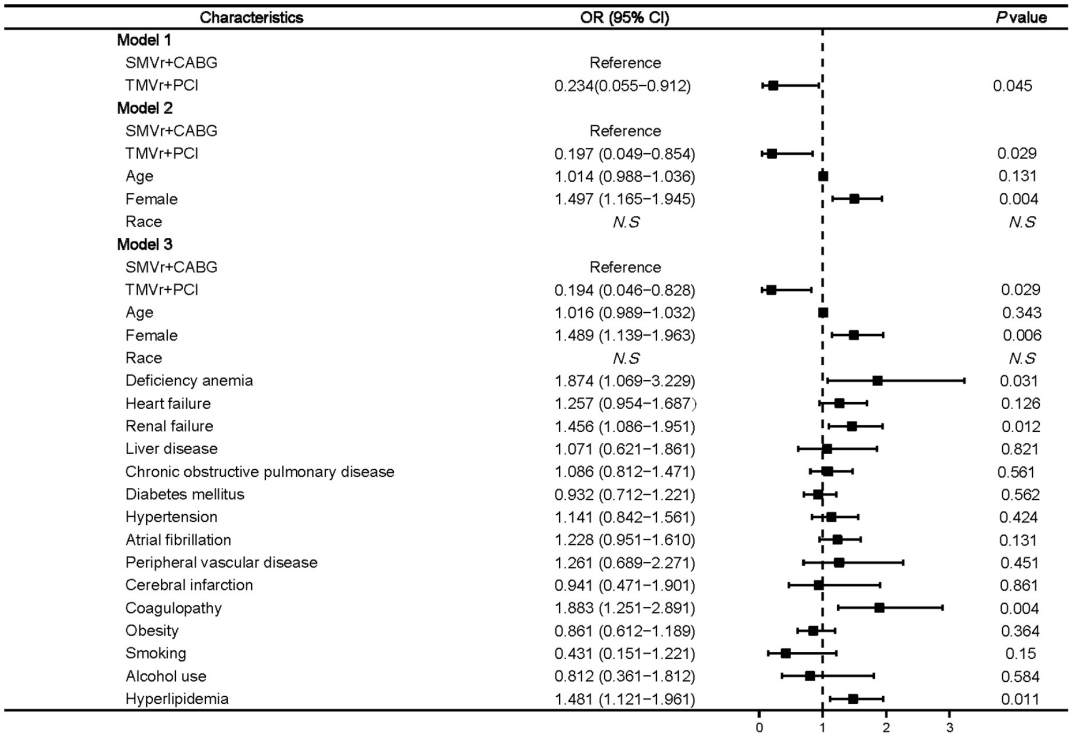

FIGURE 4
Predictors of post-procedural blood transfusion in mitral valve insufficiency patients undergoing SMVr + CABG or TMVr + PCI. TMVr indicates transcatheter mitral valve repair; SMVR indicates surgical mitral valve repair; CABG indicates coronary artery bypass grafting; PCI indicates percutaneous coronary stent implantation; model 1 indicates the univariate regression analysis; model 2 adjusted for SMVr + CABG, TMVr + PCI, age, female, race; model 3 adjusted for SMVr + CABG, TMVr + PCI, age, female, race, deficiency anemia, heart failure, renal failure, liver disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, atrial fibrillation, peripheral vascular disease, cerebral infarction, coagulopathy, obesity, smoking, alcohol use, and hyperlipidemia.

[95% CI, 1.411–4.213]; $P = 0.004$), heart failure (OR, 1.651 [95% CI, 1.251–2.171]; $P = 0.002$), liver disease (OR, 3.541 [95% CI, 2.096–5.976]; $P < 0.01$), diabetes mellitus (OR, 1.556 [95% CI, 1.221–2.011]; $P < 0.01$), and hypertension (OR, 1.343 [95% CI, 1.239–1.451]; $P < 0.01$) (**Figure 5**).

Discussion

The following main findings were reported in our contemporary real-world study of outcomes for SMVr + CABG vs. concurrent TMVr + PCI: (1) The length of stay in the hospital, medical cost, and in-hospital mortality were significantly higher for TMVr + PCI compared to SMVr + CABG; (2) TMVr + PCI was associated with improved perioperative complications compared with SMVr + CABG.

To date, there are very limited studies that have evaluated the efficacy and safety of SMVr for the treatment of patients with HF and FMR, and only several small observational studies have shown that SMVr improves LV functional status (10–12). SMVr and TMVr have been compared in several small observational studies, as well as in a subgroup of the EVEREST randomized trial for the treatment of patients with HF and FMR. Kortlandt and colleagues compared 365 FMR patients treated with TMVr to 95 patients treated with TMVR and showed that there was no significant difference in survival between the two groups at 3 years of follow-up (13). In the EVEREST trial subgroup of the 56 patients with FMR, the study compared the TMVr and SMVR for the 5 years of follow-up, and the results showed that there were no significant differences between TMVr and SMVr regarding the mortality, mitral valve surgery or reoperation, and 3+ or 4+ mitral regurgitation. Two other studies specifically compared SMVr using ring annuloplasty with TMVr in patients with unmatched FMR (14, 15). There was a single-center retrospective study including 76 patients treated with SMVr and 95 patients treated with TMVr; results showed that SMVr significantly reduced mitral regurgitation and mortality after 6 months of follow-up. Likewise, in another retrospective cohort study of 65 patients treated with SMVr and other 55 patients treated with TMVr, SMVr was founded to reduce mitral regurgitation more consistently and with more comparable mortality at a median 4 years of follow-up.

Most patients with moderate to severe IMR are primarily treated with GDMT, cardiac resynchronization therapy,

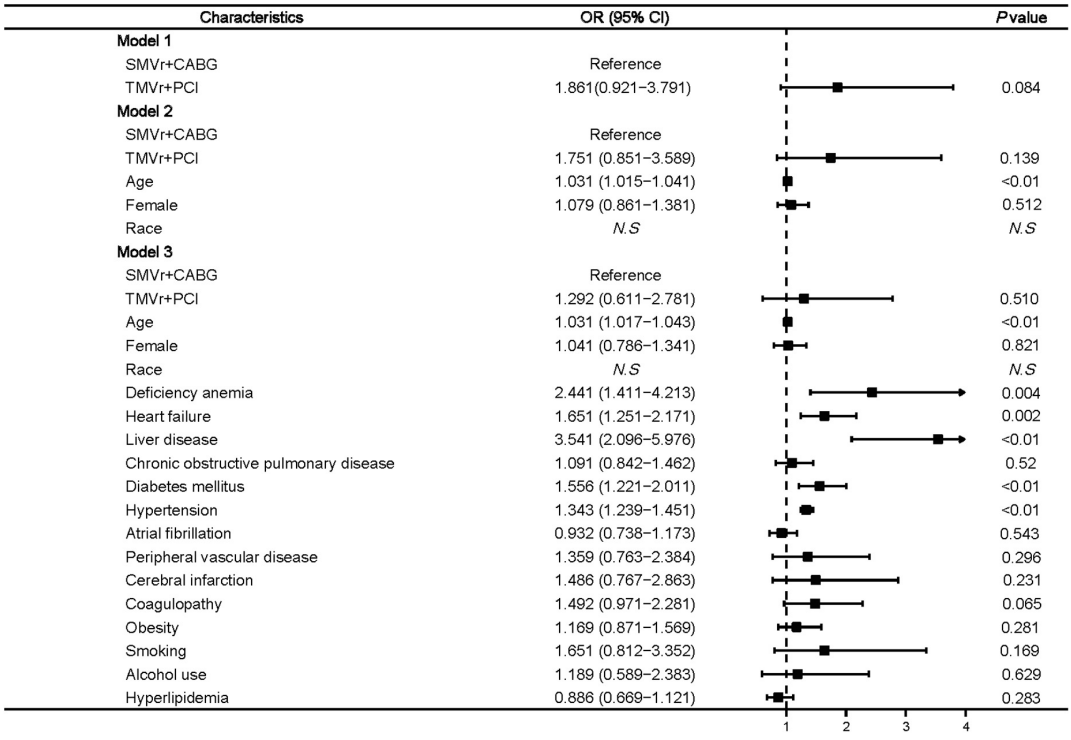

FIGURE 5
Predictors of post-procedural acute kidney injury in mitral valve insufficiency patients undergoing SMVr + CABG or TMVr + PCI. TMVr indicates transcatheter mitral valve repair; SMVR indicates surgical mitral valve repair; CABG indicates coronary artery bypass grafting; PCI indicates percutaneous coronary stent implantation; model 1 indicates the univariate regression analysis; model 2 adjusted for SMVr + CABG, TMVr + PCI, age, female, race; model 3 adjusted for SMVr + CABG, TMVr + PCI, age, female, race, deficiency anemia, heart failure, liver disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, atrial fibrillation, peripheral vascular disease, cerebral infarction, coagulopathy, obesity, smoking, alcohol use, and hyperlipidemia.

and coronary artery revascularization for their underlying cardiomyopathy (8). The role of SMVr as the primary approach to ameliorating clinical outcomes of patients with FMR needs to be further determined (16). And according to a recent RCT study, using SMVr in combination with CABG for IMR treatment remains debatable for patients with moderate IMR (17). Although the benefits regarding the outcomes of perioperative complications are uncertain, the benefits seen in patients with remodeled ventricles and scar favor combined SMVr and CABG (18). Here, in our study, we demonstrated that TMVr + PCI was associated with higher resource use and in-hospital mortality, but associated with improved perioperative complications when compared with SMVr + CABG.

Recently, the effectiveness of TMVr in addition to GDMT compared with GDMT alone was investigated in the two RCT studies of MITRA-FR and COAPT (5, 19). Although the MITRA-FR results demonstrated neutral results without any benefit of TMVr (MitraClip) for the composite outcomes events of mortality and HF rehospitalization at 1 and 2 years of follow-up, the COAPT study displayed that TMVr (MitraClip) was favorable regarding cumulative HF rehospitalizations, as well as mortality at 2 and 3 years of follow-up (20). In addition, some of the studies have evaluated the efficacy and clinical outcomes of transcatheter TMVr (MitraClip) and SMVr among patients with secondary mitral regurgitation (21–23). However, there are very limited studies to compare the efficacy and clinical outcomes of TMVr + PCI and SMVr + CABG among patients with FMR.

In this study, our data suggested that the patients who underwent TMVr + PCI were accompanied by higher in-hospital mortality, post-procedural acute kidney injury, and more resources used, and multivariable analysis showed that TMVr + PCI is not associated with improved outcomes compared with SMVr + CABG. The reason for the more mortality in the TMVr + PCI group may be because there were more high risks patients in this group.

There are some limitations to this study because of the inherent weakness of the NIS database. First, NIS is a database based on administrative claims that use ICD codes for diagnosis, and that may lead to error or result in inaccuracy when we use the NIS samples to estimate the burden of comorbidities and complications. Second, NIS collects data on in-patient discharges, and each admission was registered as an

independent event. Third, the long-term endpoints could not be evaluated in the NIS samples because the NIS database was not designed to follow-up the patients longitudinally, and for the patients in the TMVr + PCI group, the TMVr intervention for IMR may be too early, because there may have a reverse remodeling after PCI.

In conclusion, TMVr + PCI was associated with higher resource use and in-hospital mortality but with improved perioperative complications compared with SMVr + CABG. More clinical studies and RCTs are needed to compare TMVr + PCI vs. SMVr + CABG in patients with IMR.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not provided for this study on human participants because the NIS database is publicly available, we do not need to get the approval of the institutional review board or the informed consent in our clinical study. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XW conceived the study and wrote the manuscript. XF provided the data and revised the manuscript. YM analysis the data and revised the manuscript. JL, TW, LZ, CL, and QC revised the manuscript and reviewed the results. GG and JW revised the manuscript and provided comments of this research. SP, ZL, and YZ revised the manuscript and provided guidance for this study.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.953875/full#supplementary-material

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Transcatheter mitral valve replacement versus redo surgery for mitral prosthesis failure: A systematic review and meta-analysis

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Background: Transcatheter mitral valve replacement (TMVR) has emerged as an alternative to redo surgery. TMVR compared with redo surgical mitral valve replacement (SMVR) in patients with mitral prosthesis failure remains limited. In this study, we performed a meta-analysis to assess the outcomes of TMVR (including valve-in-valve and valve-in-ring) versus redo surgery for mitral prosthesis failure.

Methods: We comprehensively searched the PubMed, Embase, and Cochrane library databases according to predetermined inclusion and exclusion criteria, and then we extracted data. We compared the outcomes of TMVR and redo SMVR for mitral prosthesis failure in terms of the in-hospital mortality, stroke, renal dysfunction, vascular complication, pacemaker implantation, exploration for bleeding, paravalvular leak, mean mitral valve gradient, 30-day mortality, and 1-year mortality.

Results: Nine retrospective cohort studies and a total of 3,038 patients were included in this analysis. Compared with redo SMVR for mitral prosthesis failure, TMVR was associated with lower in-hospital mortality [odds ratios (OR): 0.44; 95% confidence interval (CI): 0.30–0.64; $P < 0.001$], stroke (OR: 0.44; 95% CI: 0.29–0.67; $P = 0.0001$), renal dysfunction (OR: 0.52; 95% CI: 0.37–0.75; $P = 0.0003$), vascular complication (OR: 0.58; 95% CI: 0.43–0.78; $P = 0.004$), pacemaker implantation (OR: 0.23; 95% CI: 0.15–0.36; $P < 0.00001$), and exploration for bleeding (OR: 0.24; 95% CI: 0.06–0.96; $P = 0.04$). Conversely, redo SMVR had lower paravalvular leak (OR: 22.12; 95% CI: 2.81–174.16; $P = 0.003$). There was no difference in mean mitral valve gradient (MD: 0.04; 95% CI: −0.47 to 0.55; $P = 0.87$), 30-day mortality (OR: 0.65; 95% CI: 0.36–1.17; $P = 0.15$), and 1-year mortality (OR: 0.96; 95% CI: 0.63–1.45; $P = 0.84$).

Conclusion: In patients with mitral prosthesis failure, TMVR is associated with lower in-hospital mortality and lower occurrence of postoperative complications, except for paravalvular leak. TMVR offers a viable alternative to the conventional redo surgery in selected patients.

KEYWORDS

redo, surgical mitral valve replacement, mitral prosthesis failure, transcatheter mitral valve replacement (TMVR), meta-analysis

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1. Introduction

Mitral bioprostheses replacement or implantations of valve reconstructive rings provide benefit to patients due to better hemodynamics and shorter anticoagulation time. However, mitral bioprostheses and reconstructive rings might fail within a few years since surgery (1, 2). Up to 35% of patients who have had mitral valve surgery may need to undergo redo surgery (3). Redo surgical mitral valve replacement (SMVR) is associated with a greater operative risk and high mortality (4–6). Recently, transcatheter mitral valve-in-valve or valve-in-ring replacement has emerged as a minimally invasive option (7–9). Data comparing the outcomes of this approach with those of open redo surgery are limited (10). Herein, we performed a systematic review and meta-analysis to provide a more comprehensive review of the clinical and echocardiographic outcomes of transcatheter mitral valve replacement (TMVR) (including valve-in-valve and valve-in-ring) compared with redo SMVR for the treatment of degenerated mitral prosthesis. The aim of the present study was therefore to evaluate the safety and efficacy of TMVR compared with redo SMVR for mitral prosthesis failure.

2. Methods

2.1. Literature search

The systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Systematic search using PubMed, Embase, and Cochrane Library databases was independently carried out by two authors to identify potentially relevant studies, with keywords including "transcatheter mitral valve implantation," "transcatheter mitral valve replacement," "TMVI," "TMVR," "valve in valve," "VIV," "redo," "mitral valve replacement," and "SMVR," until 15 September 2022.

2.2. Study selection and data extraction

The inclusion criteria were as follows: (I) failure of mitral valve bioprosthesis or mitral valvuloplasty ring; (II) available comparative information between TMVR (including valve-in-valve and valve-in-ring) and redo SMVR; (III) studies that reported the outcomes of the TMVR and redo SMVR groups. The exclusion criteria were as follows: (I) case reports, reviews, meta-analyses, animal studies; (II) duplicated publications; (III) conference abstracts without sufficient data.

Data were extracted by two investigators independently for the following variables: year of publication, study design, number of patients, patients' sex, patients' age, country, study period, in-hospital mortality, stroke, renal dysfunction, vascular complication, pacemaker implantation, exploration for bleeding, paravalvular leak, mean mitral valve gradient, 30-day mortality, and 1-year mortality. All discrepancies were resolved by seeking the opinion of a third reviewer or by consensus.

TABLE 1 Characteristics of the studies included in the meta-analysis.

References	Country	Patients (*n*)		Female (*n*)		Age (years)		Study period	Quality score	Design
		TMVR	Redo SMVR	TMVR	Redo SMVR	TMVR	Redo SMVR			
Zahid et al. (11)	USA	791	841	438	455	75 (M)	73 (M)	2015–2019	8	Retrospective cohort
Szlapka et al. (12)	Germany	79	79	47	46	74.7	72.2	2014–2019	8	Retrospective cohort
Simard et al. (26)	USA	86	129	54	81	74.9	64.5	2014–2020	7	Retrospective cohort
Gill et al. (13)	USA	310	310	160	190	73.0	72.0	2016–2018	8	Retrospective cohort
Liu et al. (27)	China	25	54	11	42	75 (M)	67.5 (M)	2013–2021	7	Retrospective cohort
Zubarevich et al. (28)	Germany	41	33	19	22	73.6	63.7	2012–2020	7	Retrospective cohort
Simonetto et al. (29)	Italy	49	29	30	13	77.6	67.7	2012–2019	7	Retrospective cohort
Kamioka et al. (30)	USA	62	59	38	36	74.9	63.7	2007–2017	7	Retrospective cohort
Murzi et al. (7)	Italy	21	40	13	23	77.0	67.0	2005–2015	7	Retrospective cohort

TMVR, transcatheter mitral valve replacement; Redo SMVR, redo surgical mitral valve replacement; M, median.

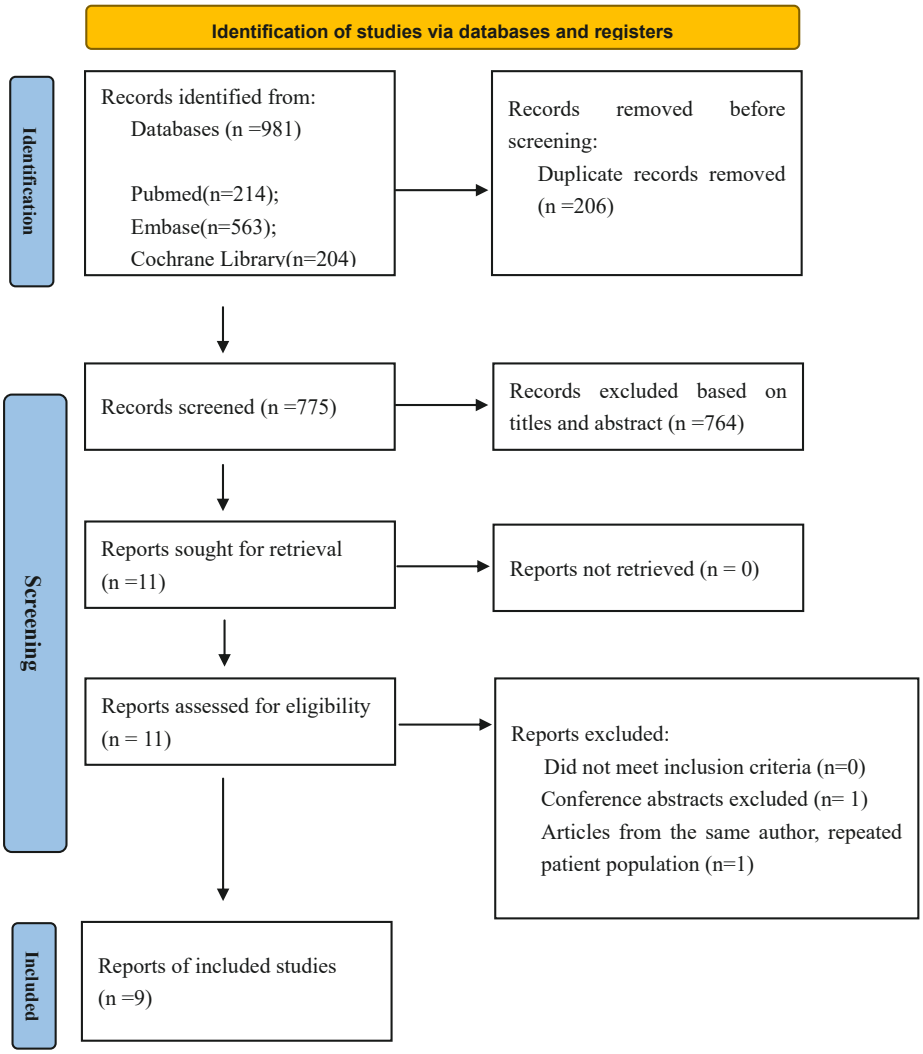

FIGURE 1
PRISMA flowchart showing the selection of studies for analysis.

2.3. Risk-of-bias assessment

The Newcastle–Ottawa scale (NOS) was used to assess the risk of bias by two investigators independently. NOS was used to assess retrospective cohort studies. All disagreements between the two investigators were resolved by negotiated settlement. The results are shown in Table 1.

2.4. Statistical analysis

RevMan 5.4 (Cochrane; Oxford, UK) was used for statistical analysis. We used I^2 to assess the heterogeneity of the included studies as follows: 25–49%, low heterogeneity; 50–74%, moderate heterogeneity; $\geq$ 75%, high heterogeneity. Random-effects models were used to assess summary estimates and 95% confidence intervals (CIs) for each outcome event. The odds ratios (OR) of all outcome events were meta-analyzed. If significant heterogeneity was found, sensitivity analyses were conducted, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 981 potentially relevant publications were identified in the initial search. After removing the duplicates, 775 citations remained, and then, 764 publications were removed after screening the titles and abstracts. Next, 11 full-text articles were obtained and assessed in accordance with the predetermined inclusion and exclusion criteria. Ultimately, nine published articles were included in our meta-analysis. Figure 1 shows the flowchart of the study selection. The characteristics of the selected studies are listed in Table 1. The period of study was 2005–2021. All of the studies were retrospective cohort studies. Three studies used the propensity score matching method to reduce differences in baseline data (11–13). Patient characteristics are shown in Table 2. A total of 3,038 patients with mitral prosthesis failure undergoing mitral valve replacement were analyzed, including 1,464 patients with TMVR and 1,574 patients with redo SMVR.

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TABLE 2 Patients characteristics.

References	NYHA III–IV, *n* (%)			STS score, %			TR ≥ moderate, *n* (%)			BMI (kg/m^2)		
	TMVR	Redo SMVR	*P*	TMVR	Redo SMVR	*P*	TMVR	Redo SMVR	*P*	TMVR	Redo SMVR	*P*
Zahid et al. (11)	–	–		–	–	–	–	–		–	–	
Szlapka et al. (12)	3 (3.80)	4 (5.33)	–	15.7 (EuroSCORE II)	15.0 (EuroSCORE II)	0.533	32 (40.5)	29 (36.7)	0.174	–	–	
Simard et al. (26)	85 (98.8)	89 (69.0)	**0.0003**	–	–	–	41 (47.7)	78 (60.4)	0.07	27.1 ± 5.6	27.6 ± 6.5	0.56
Gill et al. (13)	–	–		–	–		–	–		–	–	
Liu et al. (27)	25 (100.0)	54 (100.0)	0.06	10.82 (7.72, 12)	3.36 (1.43, 5.23)	< **0.01**	24 (96.0)	54 (10.0)	0.11	20.81 ± 2.39	22.95 ± 3.97	< **0.05**
Zubarevich et al. (28)	41 (100.0)	24 (72.7)	–	11.9 ± 10.8	10.2 ± 14.3	**0.003**	25 (61.0)	16 (48.5)	0.35	26.4 ± 4.8	26.3 ± 4.3	0.59
Simonetto et al. (29)	42 (85.7)	16 (57.2)	–	8.7	3.6	–	15 (30.6)	4 (14.3)	–	24.4	24.2	–
Kamioka et al. (30)	–	–	–	12.7 ± 8.0	8.7 ± 10.1	< **0.001**	39 (62.9)	32 (54.2)	0.33	–	–	
Murzi et al. (7)	18 (85.7)	29 (70.7)	0.25	39 ± 19 (EuroSCORE II)	23 ± 10 (EuroSCORE II)	**0.005**	2 (9.5)	4 (9.8)	0.653	–	–	

NYHA, New York Heart Association; STS, the Society of Thoracic Surgeons; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; TR, tricuspid regurgitation; BMI, body mass index. Bold values mean $P < 0.05$.

3.2. In-hospital mortality

Seven of the nine included studies reported in-hospital mortality. In total, 41 of 1,299 patients (3.2%) in the TMVR group died in hospital compared with 93 of 1,366 patients (6.8%) in the redo SMVR group. The OR for the comparison was 0.44 (95% CI: 0.30–0.64, $P < 0.001$; $I^2 = 0\%$, $P = 0.88$; **Figure 2A**), indicating that there was a statistically significant difference in in-hospital mortality between the two groups. Redo SMVR had higher in-hospital mortality than TMVR. I^2 was 0%, which indicated low heterogeneity.

3.3. Stroke

Postoperative stroke was reported by eight of the nine articles. The merged outcome suggested that TMVR was associated with a lower stroke rate compared with redo SMVR (OR: 0.44; 95% CI: 0.29–0.67, $P = 0.0001$; $I^2 = 0\%$, $P = 0.73$; **Figure 2B**).

3.4. Renal dysfunction

Five studies reported the rate of renal dysfunction after the operation. When the random-effects model was used for the meta-analysis, we found that redo SMVR had a higher rate of renal dysfunction compared with TMVR. Moreover, there was a statistically significant difference (OR: 0.52; 95% CI: 0.37–0.75, $P = 0.0003$; $I^2 = 0\%$, $P = 0.73$; **Figure 2C**).

3.5. Vascular complication

Data on vascular complications were available from three studies. After meta-analysis, TMVR was associated with a lower vascular complication rate than redo SMVR (OR: 0.58; 95% CI: 0.43–0.78, $P = 0.004$; $I^2 = 0\%$, $P = 0.94$; **Figure 3A**).

3.6. Pacemaker implantation

Pacemaker implantation rates were reported in three studies. Pooled analysis of outcome suggested that TMVR was associated with lower pacemaker implantation rates (OR: 0.23; 95% CI: 0.15–0.36, $P < 0.00001$; $I^2 = 0\%$, $P = 0.84$; **Figure 3B**).

3.7. Exploration for bleeding

In total, two out of 87 patients (2.3%) had an exploration for bleeding in the TMVR group compared with 13 of 127 patients (10.2%) in the redo SMVR group. TMVR was associated with a significant decrease in the risk of exploration for bleeding (OR: 0.24; 95% CI: 0.06–0.96, $P = 0.04$; $I^2 = 0\%$, $P = 0.95$; **Figure 3C**).

3.8. Paravalvular leak

Postoperative paravalvular leak was reported in three studies. The rate of paravalvular leak was significantly greater in the TMVR group

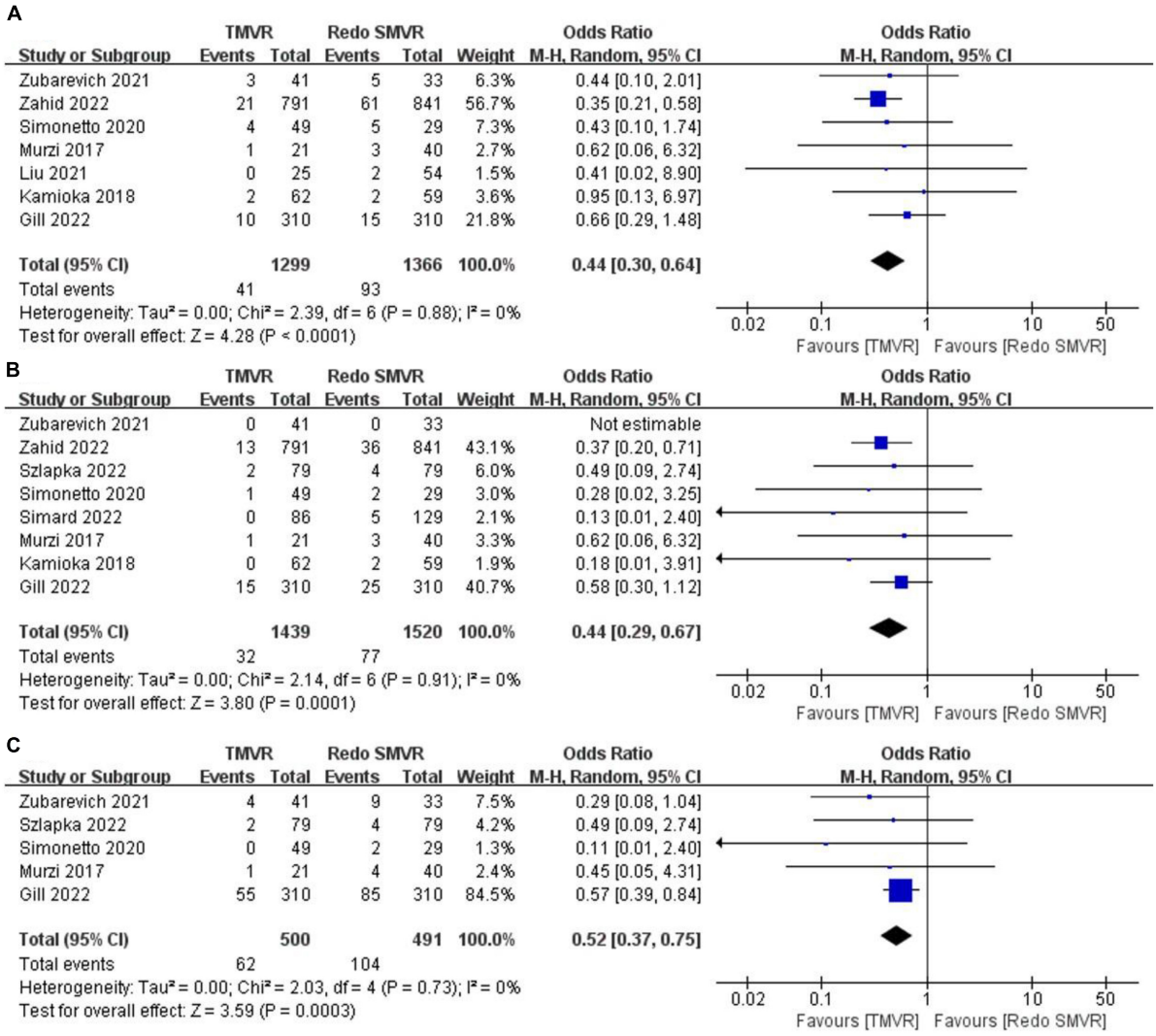

FIGURE 2
Forest plot comparing TMVR with redo SMVR for **(A)** in-hospital mortality, **(B)** stroke, and **(C)** renal dysfunction. CI, confidence interval; df, degrees of freedom; MH, Mantel–Haenszel.

than in the redo SMVR group (OR: 22.12; 95% CI: 2.81–174.16, $P = 0.003$; $I^2 = 0\%$, $P = 0.55$; **Figure 4A**).

3.9. Mean mitral valve gradient

Three studies reported the postoperative mean mitral valve gradient. The pooled outcome suggested that there was no significant difference in the mitral valve gradient between the TMVR group and the redo SMVR group (MD: 0.04; 95% CI: −0.47 to 0.55, $P = 0.87$; $I^2 = 0\%$, $P = 0.30$; **Figure 4B**).

3.10. 30-Day mortality

Data on 30-day mortality were available from five studies. There was no significant difference between TMVR and redo SMVR in 30-day mortality (OR: 0.65; 95% CI: 0.36–1.17, $P = 0.15$; $I^2 = 0\%$, $P = 0.41$; **Figure 5A**).

3.11. 1-Year mortality

Data on 1-year mortality were available from six studies. There was no significant difference between TMVR and redo SMVR in 1-year mortality (OR: 0.96; 95% CI: 0.63–1.45, $P = 0.84$; $I^2 = 0\%$, $P = 0.96$; **Figure 5B**).

4. Discussion

Mitral prosthesis failure represents a challenging therapeutic dilemma. The traditional and standard treatment is redo SMVR (14). However, redo SMVR is associated with an increased operative risk due to a number of factors, such as comorbidities and broad adhesions (14). For patients at a high surgical risk, TMVR is another viable treatment option (15). Following the development of transcatheter technologies in aortic valve replacement, transcatheter mitral valve-in-valve or valve-in-ring implantation has recently also been rapidly developing as an alternative to conventional surgical mitral valve redo procedures (16, 17). To date, the outcomes of both

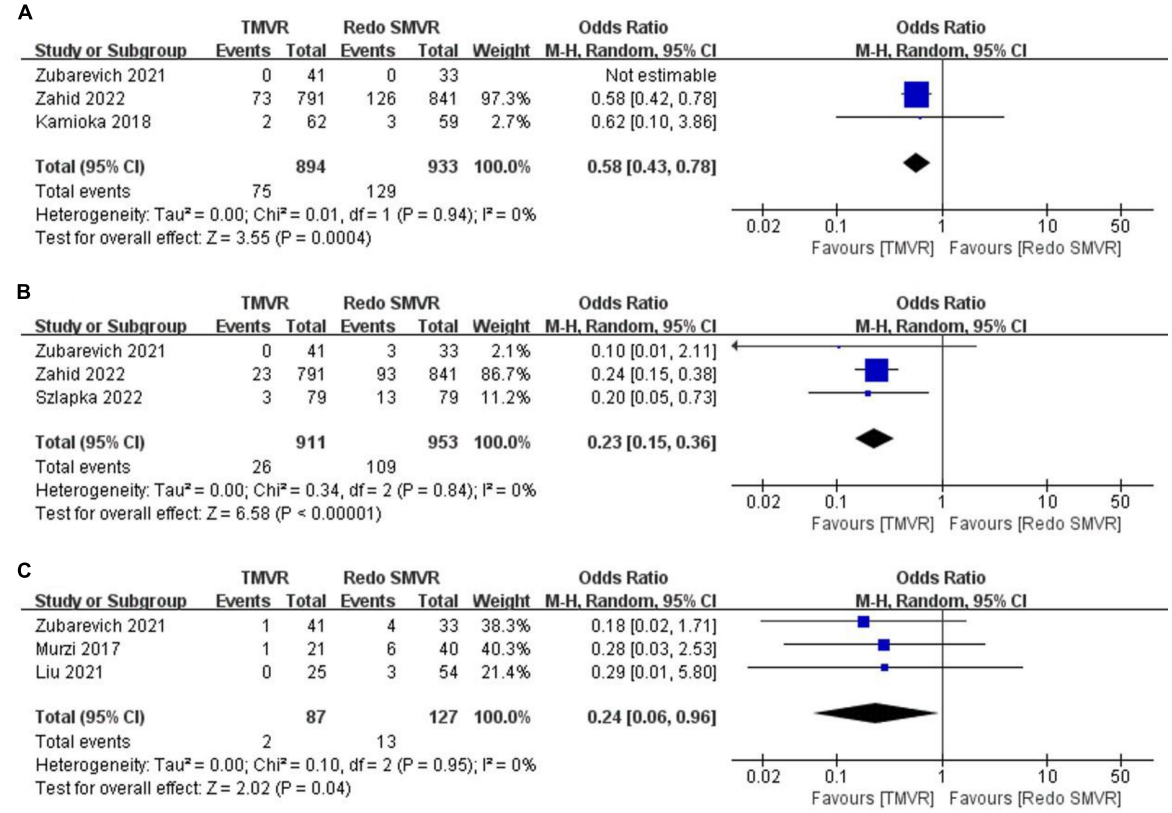

FIGURE 3
Forest plot comparing TMVR with redo SMVR for **(A)** vascular complication, **(B)** pacemaker implantation, and **(C)** exploration for bleeding. CI, confidence interval; df, degrees of freedom; MH, Mantel–Haenszel.

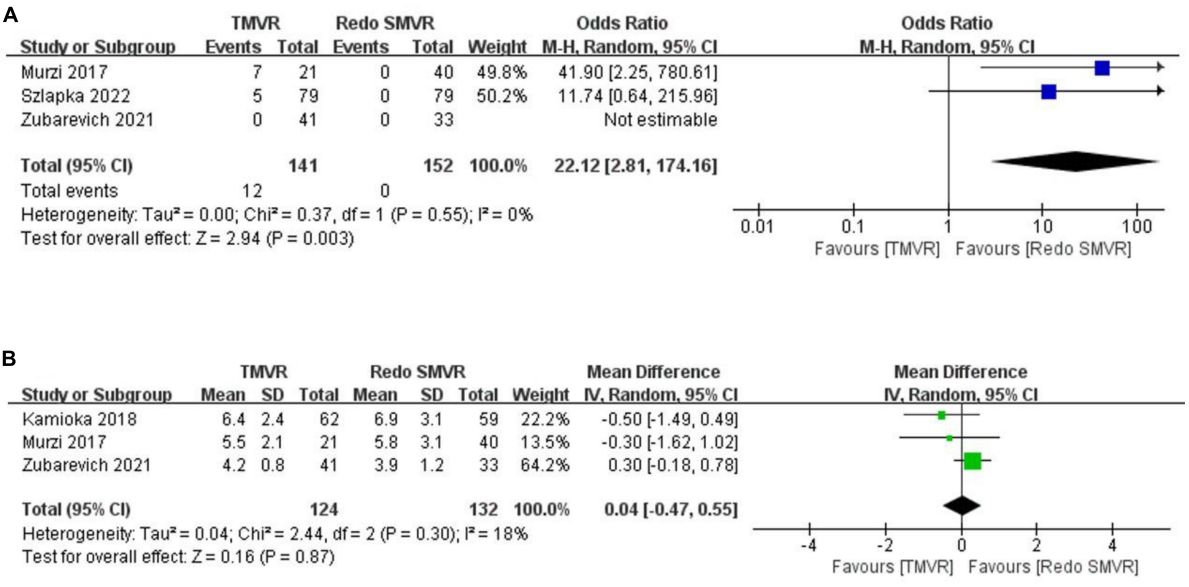

FIGURE 4
Forest plot comparing TMVR with redo SMVR for **(A)** paravalvular leak and **(B)** mean mitral valve gradient. CI, confidence interval; df, degrees of freedom; MH, Mantel–Haenszel; IV, inverse variance.

redo SMVR and TMVR therapy have been reported (5, 18). However, comparisons between redo SMVR and TMVR are limited. Therefore, we performed a meta-analysis to assess the outcomes of redo SMVR and TMVR for patients with mitral prosthesis failure.

In this meta-analysis of nine studies (3,038 patients), we found TMVR to be associated with lower rates of in-hospital mortality, stroke, renal dysfunction, vascular complication, pacemaker implantation, and exploration for bleeding, compared with redo

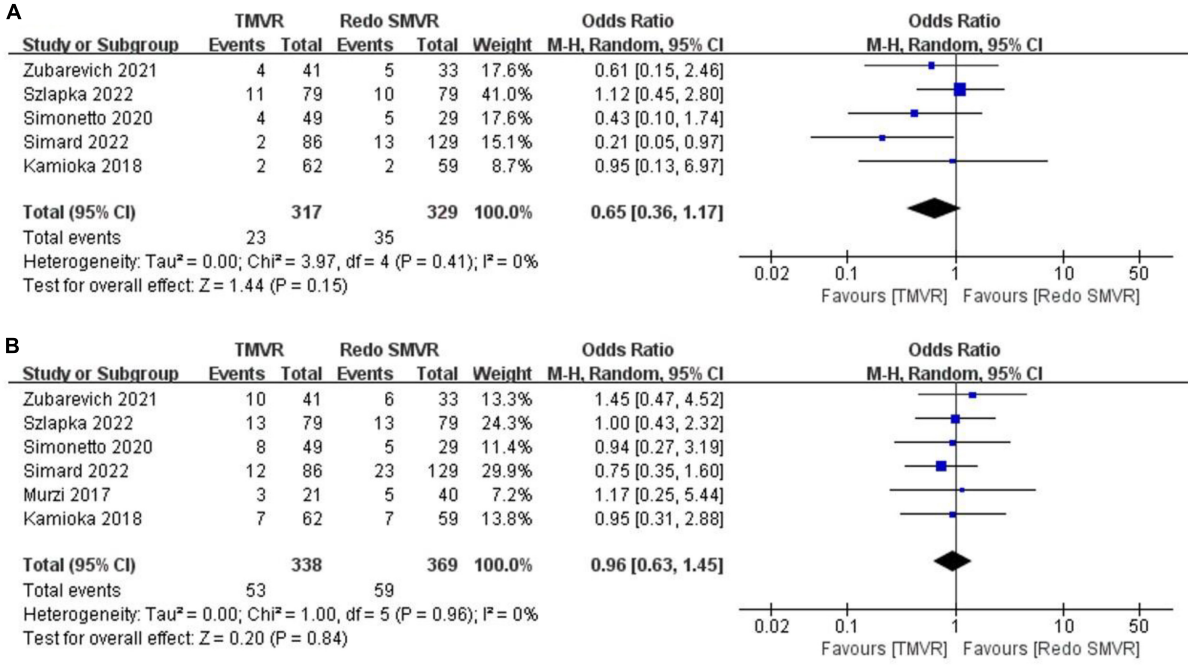

FIGURE 5
Forest plot comparing TMVR with redo SMVR for **(A)** 30-day mortality and **(B)** 1-year mortality. CI, confidence interval; df, degrees of freedom; MH, Mantel–Haenszel.

SMVR. However, TMVR was associated with higher rates of paravalvular leak. There was no significant difference in postoperative mean mitral valve gradient, 30-day mortality, and 1-year mortality between the two groups.

In our study, in-hospital mortality was significantly higher in redo SMVR. Heterogeneity between studies was low (0%). All seven studies included in our pooled analysis showed a significantly increased in-hospital mortality rate in redo SMVR compared with TMVR. However, a previous meta-analysis that included only three articles (260 patients) showed no difference in in-hospital mortality between TMVR and redo SMVR (19). The reason for the discrepancy between the results of the two meta-analyses may be the small number of patients included in the previous meta-analysis and the lack of higher-quality studies. Although TMVR patients are older and have higher risk scores, in-hospital mortality is lower. This indicates that TMVR is safe and feasible to a certain extent. Gill et al. (13) reported that the only factor associated with higher mortality with TMVR was advanced kidney disease; in contrast, predictors of mortality unique to SMVR were age > 75 years, cirrhosis, sleep apnea, low body mass index, and obesity. Therefore, TMVR may also be a more suitable treatment for these patients.

Transcatheter mitral valve replacement was associated with a decreased incidence of vascular complications, despite having more vascular procedures. The physicians' skillful puncture technique and the use of a vessel-closure device may be the reasons. In addition, TMVR was associated with lower rates of pacemaker implantation compared with redo-SMVR. The redo SMVR requires extensive debridement of the bioprostheses or reconstructive rings, whereas during TMVR, the failed bioprosthesis or ring may protect the conduction system from injury.

Our analysis suggested that patients with redo SMVR had a higher risk of stroke. Surgery performed under hypothermic ventricular fibrillation and retrograde perfusion through the femoral artery might be the factors associated with stroke after redo SMVR (7). Patients with redo SMVR had a higher risk of renal dysfunction. Patients with poor preoperative basic status combined with the influence of cardiopulmonary bypass are prone to renal dysfunction, and some patients need dialysis treatment. Of note, acute kidney injury is also considered a risk factor for death after surgery (20). In our report, SMVR was associated with a high risk of exploration for bleeding, which can be due to re-thoracotomy, large wound, long operation time, and difficulty in hemostasis. TMVR includes transapical and percutaneous approaches, both of which are less invasive than thoracotomy.

The incidence of perivalvular leakage was higher in patients with TMVR, which is consistent with findings reported in previous studies (12). Murzi et al. (7) reported the results of transapical TMVR versus redo SMVR; they showed that 28% of patients in the TMVR group had less than mild perivalvular leakage, compared with none of the patients in the SMVR group. These findings further suggest that for patients at an elevated risk of poor postoperative hemodynamics due to improper mitral valve position anatomy, redo SMVR may be the preferred intervention. Nevertheless, mild perivalvular leakage does not seem to have much of an adverse effect on the patients.

Redo surgery allows for the implantation of a bigger bioprosthetic valve. An elevated postoperative mean gradient can still be a limitation after a transcatheter valve-in-valve procedure, but transcatheter bioprosthetic valve fracture during TMVR offers a solution for patients with a small mitral bioprosthetic valve (21, 22). Interestingly, in our study, no significant differences were found in the mean mitral valve gradient between TMVR and redo SMVR. Hence, both procedures provide excellent and comparable hemodynamic results with low mitral valve gradients at follow-up. This indicates that TMVR does not affect the mitral valve gradient

and does not cause hemodynamic abnormalities in patients. In this way, the long-term prognosis of patients can be guaranteed. Among the nine included studies, the implanted transcatheter valve included Sapien series and J-valve (Jiecheng Medical Technology, Suzhou, China), with predominance of Sapien. However, since the size of the largest prostheses on the market is only 29 mm, TMVR is not suitable for patients previously implanted with larger prostheses.

In our analysis, 30-day mortality and 1-year mortality were comparable between the two cohorts. Patients treated with TMVR can achieve comparable short-term outcomes to SMVR while reducing surgical trauma and the invasiveness of the procedure, especially in transseptal TMVR. Long-term follow-up results are needed to further confirm the effect of TMVR.

The current guidelines recommend concomitant tricuspid valve repair (TVR) in patients presenting with more than moderate tricuspid valve regurgitation (23). However, due to the lack of commercial transcatheter tricuspid products, concomitant TVR was performed only in the SMVR group. Although current guidelines recommend concomitant TVR, long-term outcomes of concomitant TVR in redo patients remain controversial (24, 25). A higher number of patients and longer-term follow-up are necessary to answer this question.

5. Study limitations

As the major limitation of this systematic review, all of the included studies were retrospective cohorts, which may reduce the value of this meta-analysis. In addition, this was a study-level meta-analysis; therefore, one relevant limitation is the lack of patient-level data. Furthermore, procedure bias or detection bias may have also influenced the outcomes of this meta-analysis. Thus, further studies, preferably in the form of randomized, large-scale, and strictly conducted trials, are needed to accurately evaluate TMVR in patients with mitral prosthesis failure.

6. Conclusion

Our results suggest that TMVR is effective at decreasing in-hospital mortality compared with redo SMVR in patients with mitral prosthesis failure. TMVR is also associated with lower rates of stroke, renal dysfunction, vascular complication, pacemaker implantation, and exploration for bleeding. Conversely, redo SMVR is associated with decreased paravalvular leak. There are no significant intergroup differences in postoperative mean mitral valve gradient, 30-day mortality, and 1-year mortality.

Transcatheter mitral valve replacement is a safe, feasible alternative to conventional redo surgery and may offer an effective and less invasive treatment for patients. Large randomized trials are necessary to elucidate the efficacy of TMVR as an alternative to redo SMVR for treating mitral prosthesis failure.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JZ and YL conceived and designed the study. JZ and ZC collected and analyzed the data and wrote the manuscript. YL and HZ reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Transcatheter mitral and tricuspid interventions—the bigger picture: valvular disease as part of heart failure

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The prevalence of mitral (MR) and tricuspid regurgitation (TR), especially in heart failure (HF) populations, is high. However, the distinct role of atrioventricular valve diseases in HF, whether they are merely indicators of disease status or rather independent contributors in a vicious disease cycle, is still not fully understood. For decades, tricuspid regurgitation (TR) was considered an innocent bystander subsequent to other heart or lung pathologies, thus, not needing dedicated treatment. Recent increasing awareness towards the role of atrioventricular valve diseases has revealed that MR and TR are, in fact, independent predictors of outcome in HF, thus, warranting attention in the HF treatment algorithm. This awareness arose, especially, with the development of minimally invasive transcatheter solutions providing new treatment options, which can also be used for patients considered as having increased surgical risk. However, outcomes of such transcatheter treatments have, in part, been sub-optimal and likely influenced by the status of the concomitant HF disease. Thus, this review aims to summarize data on the current understanding regarding the role of MR and TR in HF, how HF impacts outcomes of transcatheter MR and TR interventions, and how the understanding of this relationship might help to identify patients that benefit most from these therapies, which have proven to be lifesaving in properly selected candidates.

KEYWORDS

transcatheter treatment, mitral regurgitation, tricuspid regurgitation, heart failure, valvular disease of the heart

Introduction

Severe symptomatic mitral (MR) and tricuspid regurgitation (TR) have been identified as independent predictors of mortality (1, 2). Furthermore, patients with significant forms of MR or TR show a significantly increased risk of heart failure (HF) hospitalizations, prolonged hospitalizations, and repetitive re-hospitalizations (3–7). When followed up for at least two years, untreated MR results in HF hospitalization in over 50% of patients, and in patients with untreated TR, over 35% are hospitalized by that time and these HF hospitalizations are independently associated with increased mortality (3, 6). In recent years, this sparked the evolution of novel, less invasive transcatheter treatment approaches, especially as the population of MR and TR patients is often elderly, multi-morbid, and at high risk for surgery (8, 9). A broad range of devices underwent pre-clinical and clinical testing, and several techniques have been established in actual practice (10, 11). Besides other approaches like annuloplasty or valvular replacement, the most

prominent and most frequently used treatment modality to date is transcatheter edge-to-edge (TEER) repair of either the mitral (MV) or the tricuspid valve (TV) (12, 13).

A lot of attention has been paid to outcomes after interventional treatment in patients with secondary forms of MR (SMR) or TR (STR) most often presenting in the setting of chronic HF. For mitral TEER (M-TEER) in patients with HF and reduced ejection fraction (HFrEF), two large randomized trials, namely the COAPT trial and the Mitra-FR trial, have resulted in diverging outcomes. In the COAPT trial, a significant benefit of M-TEER, when added to optimal guideline-directed medical therapy (GDMT), was evident, while in the Mitra-FR trial, the additive effect of interventional treatment was neutral (14, 15). These results initiated ongoing discussions regarding potential explanations for such a divergence. The first agreement has been reached that an assessment of potential M-TEER candidates must not only look at the valvular lesion itself but also has to incorporate a distinct assessment of ventricular function and dimensions, and concomitant HF has to be addressed as a holistic disease entity, in general (**Figure 1**) (16–18).

Interventional treatment of severe TR, on the other hand, has caught up at a rapid pace in the last years, first using established M-TEER devices in the tricuspid position (T-TEER) but now also utilizing dedicated devices, including several replacement solutions (19–22). The identification of TR as an independent predictor of mortality as well as bad outcomes of isolated TV surgery with high in-hospital mortalities of up to 10% in these patients meant an unmet clinical need that these new devices are now trying to address (1, 23, 24). However, following the historic belief that TR is only secondary to left-sided heart disease and would diminish with treatment, the awareness towards TR still is too little (25). Thus, patients are referred late in their disease course, often presenting multi-morbid and complex chronic HF status (9). In such patients, even though a propensity-matched analysis of the TriValve registry demonstrated a benefit with transcatheter TR treatment compared to GDMT alone, even when treated, rates of 1-year mortality and HF rehospitalization are high (26). Thus, in such cohorts, the delineation between patients benefiting from intervention and those in whom a transcatheter treatment may be futile represents a challenge for heart teams when evaluating patients suffering from persistent HF symptoms and valvular heart disease.

Given this interplay of chronic HF with SMR and STR, this review aims to define the role of these valvular lesions in the HF disease complex and summarize the reported response to transcatheter treatment according to different HF characteristics, and based on this, tries to understand which parameters might be of use to identify those patients most likely to benefit from interventional MR and/or TR treatment.

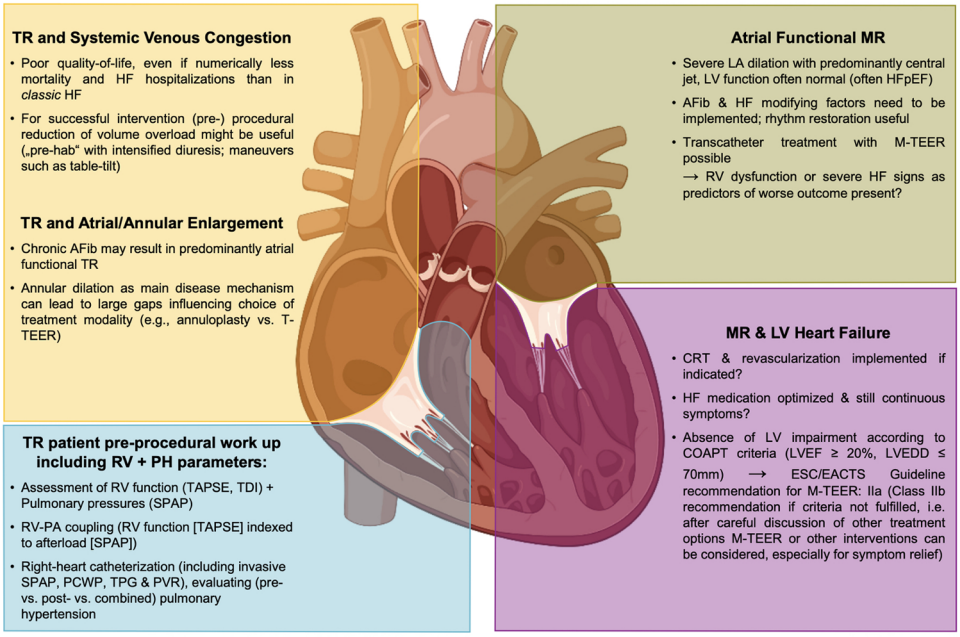

FIGURE 1
MR and TR in the HF disease conundrum and as part of a systemic disease—implications for interventional therapies. AFib, atrial fibrillation; CRT, cardiac resynchronization therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; M-TEER, mitral transcatheter edge-to-edge repair; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RV, right ventricle; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion, TDI, tissue Doppler imaging; TPG, trans pulmonary gradient; T-TEER, tricuspid transcatheter edge-to-edge repair, TR, tricuspid regurgitation.

Mitral regurgitation

MR in the context of heart failure

In the European population, MR represents the most common heart valve disease and is the second most common reason for heart valve surgery after aortic stenosis: MR is present in 2% of the overall population, being ≥ moderate in 2.3% of people ≥65 years, and in 9.3% of people ≥75 years (27, 28). Rossi et al. found that in patients with chronic HF due to non-ischemic or ischemic dilated cardiomyopathy [mean left ventricular (LV)EF: 32% ± 8%], 49% had mild to moderate and 24% had severe SMR (29). Trichon et al. reported that in patients with left ventricular systolic dysfunction (LVEF <40%), any MR was present in 56%, and of these, 30% had severe MR (30). Goliasch et al. identified ≥ moderate MR in 53% of patients in a large HFrEF cohort [median LVEF: 27 (20–35) %] (31). In all these HFrEF cohort studies, MR was independently associated with increased mortality and HF rehospitalization rates. Interestingly, Goliasch et al. found that SMR, especially, is associated with worse outcomes in an intermediate type of HFrEF patients (NYHA class II/III, moderately reduced LVEF of 30%–40%, and NT-proBNP in the second quartile of 871–2,360 pg/ml) (31).

In addition to established SMR definitions, atrial functional MR has been recently discussed as a distinct form of SMR (32–35). Typically, these patients present with long-standing atrial fibrillation or HF with preserved LVEF, leading to atrial enlargement and annular dilation, while ventricular dimensions are without any impairment. Identifying such specific anatomical factors may impact the therapeutic management like patients' rhythm management, or an intervention focusing on aspects of annular dilation may be the preferred treatment.

For any form of SMR, it is important to highlight that its severity may dynamically vary depending on loading conditions (36). Thus, during the work-up of patients who suffer from HF symptoms and show some form of SMR, the additional performance of exercise echocardiography can unmask significant changes in SMR severity, which has been identified as an important prognostic marker of poor outcomes (37, 38). It might be that patients with such dynamic and exercise-induced severe SMR derive particular benefits from a timely intervention; however, it is important to highlight that there is currently no sufficient data regarding transcatheter treatment in this specific subset of patients.

Outcomes of transcatheter treatment in HF patients

Over half of the patients with severe SMR and HF will not undergo surgery because their disease state has a direct impact on outcomes. This scenario represents an unmet clinical need, potentially addressable with M-TEER and other transcatheter solutions (39).

Two large randomized controlled trials evaluated the role of M-TEER in addition to GDMT in the HFrEF population. In the COAPT trial, patients treated with MitraClip (Abbott Laboratories, Chicago, Illinois, USA) when compared to patients with GDMT alone (device group [$n = 302$] baseline characteristics: LVEF: 31.3 ± 9.1%, left ventricular end-diastolic dimension: 6.2 ± 0.7 cm, left ventricular end-diastolic volume [LVEDV]: 101 ± 34 ml/m^2, NT-proBNP: 5,174.3 ± 6,566.6 pg/ml; see **Table 1**) experienced significantly fewer annualized HF hospitalizations within 24 months [35.5% vs. 67.9% in GDMT only; HR = 0.53 (95% CI: 0.4–0.7), $p < 0.001$], and had a significantly lower rate of mortality within 24 months [29.1% vs. 46.1% in GDMT only; HR = 0.62 (95% CI: 0.46–0.82), $p < 0.001$]. This corresponds to the number needed to treat 5.9 patients (95% CI: 3.9–11.7) to prevent one death (14). Conversely, in the randomized controlled Mitra-FR trial, there were no significant differences in the rate of HF hospitalizations at 12 months [48.7% vs. 47.4% in GDMT only; HR = 1.13 (95% CI: 0.81–1.56)] and the rate of death from any cause (24.3% vs. 22.4% in GDMT only; HR = 1.11 [95% CI: 0.69–1.77] between patients treated with MitraClip (device group [$n = 152$] baseline characteristics: LVEF: 33.3 ± 6.5%, LVEDV: 136.2 ± 37.4 ml/m^2, NT-proBNP: 3,407 (1,948–6,790); see **Table 1**) and patients receiving GDMT only (15).

The EuroSMR registry for over 1,000 patients with SMR and HFrEF (baseline LVEF: 35.1 ± 12.8%; other baseline HF characteristics see **Table 1**) reported 1-year and 2-year mortality rates after M-TEER of 20% and 32%, respectively (43). In the

TABLE 1 Baseline heart failure characteristics in main transcatheter mitral intervention studies.

	COAPT ($n = 302$) (14)	Mitra-FR ($n = 152$) (15)	EuroSMR ($n = 1,016$) (40)	Cardioband 1 year ($n = 60$) (41)	CHOICE-MI (42)
Treatment	M-TEER (MitraClip)	M-TEER (MitraClip)	M-TEER (MitraClip)	Annuloplasty (Cardioband)	Replacement (10 different devices)
Longest follow-up	3 years	2 years	2 years	1 year	1 year
Mortality last follow-up	42.8%	63.80%	32%%	13%%	28%
Baseline HF characteristics					
NYHA class III/IV	57%	63%	89%	87%	87%
LVEF (%)	31.3 ± 9.1	33.3 ± 6.5	35.1 ± 12.8	33 ± 11	40 (35–54)
LVEDV (ml)	194.4 ± 69.2	136.2 ± 37.4	182.3 ± 82.6	N/A	153.4 (116.5–198.0)
NT-proBNP (pg/ml)	5,174.3 ± 6,566.6	3,407 (1,948–6,790)	N/A	N/A	N/A

MitraClip device by Abbott Laboratories; Cardioband by Edwards Lifesciences, Irvine, California, USA.
HF, heart failure; LVEDD, left ventricular end diastolic diameter, LVEF, left ventricular ejection fraction, M-TEER, mitral transcatheter edge-to-edge repair.

registry by the Italian Society of Interventional Cardiology (GISE) on the transcatheter treatment of mitral valve regurgitation (GIOTTO registry) for the cohort with SMR [$n = 986$, baseline LVEF: 32 (27–40)] following M-TEER, all-cause mortality at 1 year and 2 years was 19.0% and 30.8%, while HF hospitalization rates were 15.7% and 25.9%, respectively (44).

For MV repair using annuloplasty with the Cardioband system (Edwards Lifesciences, Irvine, California, USA) in an SMR and HFrEF population (baseline LVEF: 33 ± 11%; other baseline HF characteristics see **Table 1**), 1-year survival rates of 87% and 1-year survival rates free from HF readmission of 66% have been reported (41). The experience with replacement technologies to treat MR is still limited and mainly based on collective registries merging several different investigational devices. Interestingly, in the CHOICE-MI registry involving patients with midrange or preserved LVEF [baseline LVEF: 50.0 (38.1–60.0) %], the 1-year composite of all-cause mortality or HF hospitalization after transcatheter MV replacement was 39.2% (42). Similarly, the TENDER registry that collected data on patients who underwent trans-apical MV replacement using the Tendyne prosthesis (Abbott Laboratories, Chicago, Illinois, USA) reported 30-day all-cause mortality of 12%, with mean LVEF of 48 ± 12% (45).

MR interventions in the HF disease conundrum

Following the remarkable divergence of the COAPT and the Mitra-FR trial, it is only consequential that the search for predictors of favorable outcomes after M-TEER is based on the quest for any potential explanatory discrepancy between these two trials. The concept of proportionate and disproportionate MR, namely a large coaptation defect (effective regurgitant orifice area >0.3 cm^2) sitting over a still not too much dilated left ventricle (LVEDV index <96 ml/m^2) as a predictor of ideal treatment response, seemed intriguing (16). However, following the positive reception of this framework, it failed to prove external validity in other M-TEER cohorts beyond the two trials it was derived from (43, 46). Based on the multi-center EuroSMR registry, Koell et al. stratified M-TEER patients per COAPT trial inclusion criteria and found that the COAPT-eligible sub-group, indeed, showed significantly lower mortality (40). Interestingly, via this stratification, they identified a sub-group of patients with preserved RV function, less TR, lower systolic pulmonary artery pressures (SPAP), and lower NT-proBNP, suggesting an earlier stage in the HF disease course. However, COAPT-ineligible patients experienced a symptomatic benefit following the M-TEER procedure. Also, a stratification of EuroSMR patients per EROA < vs. ≥0.3 cm^2 could not add any predictive value (47). Thus, the recommendation given by the 2021 ESC/EACTS guidelines on the management of valvular heart disease seems very reasonable. In patients who meet the criteria, suggesting an increased chance of response to M-TEER, (as per **Supplementary Table S7** of the guidelines these criteria are following the COAPT criteria: LVEF 20%–50%, LVESD ≤70 mm, SPAP ≤70 mmHg, absence of hemodynamic instability, and moderate or severe RV dysfunction), IIaB recommendation for M-TEER is given. However, in patients not meeting these criteria at a level, IIbC recommendation M-TEER can be performed for symptom improvement after a careful evaluation of other alternatives such as left ventricular assist device implantation or heart transplant (48). As in the COAPT trial, the exact definition of right ventricular failure is not stated and the guidelines do not give an exact cut-off; however, the value of <15 mm for tricuspid annular systolic excursion (TAPSE), based on previous literature, seems very reasonable (40).

Apart from these cardiac parameters, it is likely important to also take a more holistic perspective on the systemic status of HF patients who at the end stages of the disease may suffer from multi-organic failure (49). In line with the findings by Goliasch et al. that MR, especially, in mid-range HF has an independent negative predictive impact, it might very well be that HF patients with mid-range LVEF derive most benefits from valvular interventions. Conversely, in end-stage severe chronic HF, where the multi-organic systemic disease is the main and predominant driver of mortality, valvular intervention might be futile (31).

Additionally, not only left-sided but also right-sided HF may impact outcomes after M-TEER. In SMR patients undergoing M-TEER, Karam et al. identified right ventricular dysfunction (defined as impaired right-ventricular-to-pulmonary artery coupling, i.e., a TAPSE/sPAP ratio ≤0.274 mm/mmHg) as a significant predictor of increased 2-year mortality (50). Thus, while only left-sided interventions are being planned. Therefore, it is important to note that an additional assessment of right ventricular parameters seems to be crucial.

Another important aspect when placing M-TEER intervention in the context of HF is GDMT and its optimization. As the pre-procedural optimization of GDMT has been a crucial part of the trial, when aiming to achieve COAPT-like results, it is a prerequisite to ensure optimized GDMT before discussing M-TEER or other transcatheter treatments. On the other hand, it is important to highlight that M-TEER in the COAPT trial showed a number needed to treat (NNT) that is lower than those of almost any HF medication or intervention (**Figure 2**) (51). Based on published data from respective landmark trials (SOLVD, Group M-HS, EMPHASIS-HF, SCD-HeFT, RAFT, CHARM, and PARADIGM-HF), with the assumption that all-cause mortality rates and treatment effects were constant after trial conclusion, Srivastava et al. estimated NNTs to prevent one patient from dying from several HF medications, and for all of them, they found numbers higher than the NNT of M-TEER based on COAPT data (52). Unfortunately, while in interventional trials, HF medication is assessed very rigorously in landmark HF trials; the incidence and the course of MR—and TR—are often underreported (53, 54). Thus, it is challenging to estimate each and any exact interconnection; however, it is likely key to identify the ideal interplay be it timing, dosing, or a combination of both between medical and interventional MR treatment.

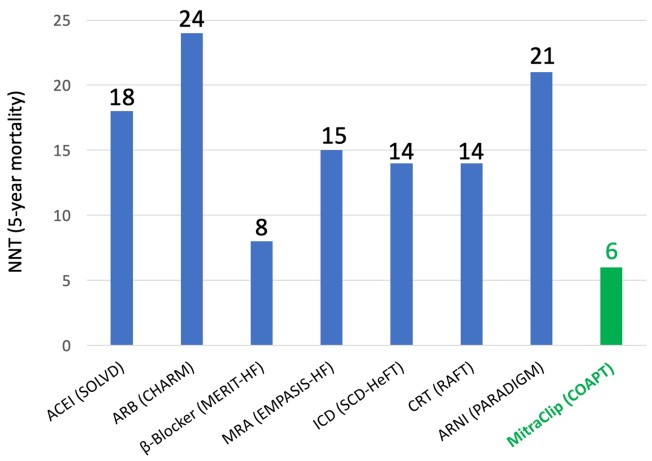

FIGURE 2
The number needed to treat (NNT) to prevent one mortality for established heart failure medications in comparison to MitraClip based on data from respective landmark trials of heart failure medications and data from the COAPT trial. Adapted from Pfister et al. (51).

Indeed, a recent study by Higuchi et al. based on the EuroSMR registry of SMR patients who underwent M-TEER was able to highlight the beneficial effects of maximized GDMT at the baseline of M-TEER and during subsequent follow-up (55). In patients who received triple GDMT (including beta-blockers, renin-angiotensin system inhibitors, and mineralocorticoid receptor antagonists), 2-year survival was higher than in those who did receive less than three GDMT drugs. The beneficial effect was confirmed, especially, in patients with kidney disease and right heart failure, and also in patients who did not have an optimal technical result after M-TEER (i.e., residual MR $\geq$ 2+). This, again, highlights the complementary role of M-TEER and GDMT in the complex clinical setting of HF.

Tricuspid regurgitation

TR in the context of heart failure

Tricuspid regurgitation has historically been considered a subsequent consequence of left-sided heart disease, and following this conception, no dedicated treatment was recommended, believing that TR would vanish after successful treatment of the left-heart disease (25). However, recently emerging evidence has proved that moderate or severe TR represents a significant predictor of mortality, independent of SPAP or LVEF (1, 56, 57). This is of high relevance as, according to the Framingham Heart Study, the incidence of TR increases with age, and severe TR is present in over 5% of women and up to 2% of men aged $\geq$70 years (58). A recent analysis evaluating almost 1 Million echocardiography reports from 35 community and academic cardiology centers in the US even found TR to be the most common valvular heart disease present in 7% of the overall population (median age 68 years) and up to 14% of patients $\geq$75 years (59). Only 8 to 10% of patients suffer from primary TR, while the vast majority of patients present with STR (60). STR may be associated with the left-sided disease even after surgical correction thereof driven by further aging, being a woman, and the presence of atrial fibrillation (61). Apart from that, STR can arise from chronic pulmonary hypertension (SPAP $\geq$50 mmHg) characterized by less annular dilation but severe tenting driven by long right ventricles (RVs) with elliptical/spherical deformation (62).

Koelling et al. in an HFrEF cohort (LVEF $\leq$ 35%) identified $\geq$ moderate TR in 34.5% of patients, with severe TR being a significant predictor of mortality in a multivariable analysis (63). Similar to the findings for MR by Goliasch et al., Neuhold et al. in an analysis of almost 600 patients with chronic HF identified severe TR as a significant predictor in patients with mildly or moderately impaired LVEF or with NT-proBNP levels below the median ($\leq$280 fmol/ml) but not in those with severely impaired LVEF or with NT-proBNP levels above the median (31, 64).

Outcomes of transcatheter treatment of TR in HF patients

The limited outcomes of TV surgery paired with the high prevalence of relevant symptomatic disease historically led to large undertreatment of TR; for example, in the US, out of the 1.6 million patients with $\geq$ moderate TR, less than 8,000 per year undergo surgery, resulting in a large unmet clinical need (24, 65). In-hospital mortality of isolated tricuspid valve surgery with rates of approximately 10% remains high, which is why the dedicated TRI-SCORE was developed to further stratify these high-risk patients and to allow for more suitable individualized patient management pathways (66). The large number of patients in need of treatment and the limited surgical outcomes led to the rapid development and early adoption of less invasive transcatheter treatment solutions.

Evaluating the role of transcatheter TR treatment as the first prospective single-arm trial of T-TEER using TriClip (Abbott

Laboratories, Chicago, Illinois, USA), the TRILUMINATE trial presented 1-year outcomes in 85 patients (TAPSE [cm]: 1.44 ± 0.31, SPAP [mmHg]: 38.9 ± 16.0, LVEF [%]: 59.4 ± 8.1; other baseline HF characteristics see **Table 2**) (68). At the baseline, only 8% of patients had ≤ moderate TR, which improved to 71% at 1 year. Additionally, the functional status (NYHA class, 6MWT, KCCQ score) significantly improved and 1-year mortality was 7.1%. In the real world post-market bRIGHT study with the TriClip device at 30 days in 200 patients (TAPSE [cm]: 1.8 ± 0.9, SPAP [mmHg]: 38.8 ± 11.8, LVEF [%]: 55.6 ± 11.0; other baseline HF characteristics see **Table 2**), mortality was extremely low at 0.5% and TR was reduced by ≥1 grade in 81% of patients, leaving 70% of them with ≤ moderate TR (71). The prospective single-arm CLASP TR study tested the Pascal T-TEER device (Edwards Lifesciences, Irvine, California, USA) in a similar cohort ($n = 65$, $n = 46$ at 1-year follow-up; TAPSE [cm]: 1.53 ± 0.47, SPAP [mmHg]: 68% at ≥30, LVEF [%]: 57.4 ± 7.0; other baseline HF characteristics see **Table 2**) and at 1 year found 86% of patients at TR ≤ 2 (100% of patients with at least one grade TR reduction and 75% with at least two grades), with a significantly improved quality of life and 10.8% mortality (69, 70). In the TRI-REPAIR study, the Cardioband annuloplasty system was tested in the tricuspid position in 30 patients (TAPSE [cm]: 1.4 ± 0.3, SPAP [mmHg]: 35.9 ± 10.5, LVEF [%]: 57.5 ± 10.8; other baseline HF characteristics see **Table 2**), leading to 72% of patients with ≤ moderate TR and significant improvements in their quality of life at 2 years, while mortality was 26.7% at that point in time (72). With fewer hurdles (e.g., no risk of right ventricular outflow obstruction) compared to the mitral side, TV replacement is moving forward at a much higher pace. For the EVOQUE valve (Edwards Lifesciences, Irvine, California, USA), up to 6 months follow-up for 43 patients (for baseline characteristics see **Table 2**) was available, with 100% of patients being at none/trace or mild TR, 89% of them being in NYHA class I/II associated with a survival rate of 96% and a rate of patients free from HF hospitalization at 94% (73, 74).

Recently, the first randomized trial in the field of transcatheter treatment of TR has been published. The TRILUMINATE Pivotal trial randomized 350 patients to receive either T-TEER or optimized medical treatment only, with the combined primary endpoint being in favor of T-TEER treatment (67). This result mainly was driven by a marked improvement in quality of life according to the change in KCCQ score, while the other primary endpoint components mortality or TV surgery and heart failure hospitalization after a 1-year follow-up did not differ between groups. The extent of quality of life improvement was directly linked to the extent of achieved TR reduction, likely reflecting the effectiveness of the treatment. T-TEER proved to be exceptionally safe with a 30-day cardiovascular mortality of only 0.6%. While the patients according to their baseline KCCQ scores had a notably bad quality of life, the event rates for mortality and heart failure hospitalization in both groups were markedly lower than what has been observed in studies on HF patients receiving left-sided interventions, suggesting that the impact of the valvular disease on such endpoints does differ between MR and TR patients. Furthermore, the enrolled patients seem to represent a particular subset of TR patients, who mainly suffered from isolated TR, LVEF, pulmonary pressures, and pulmonary vascular resistance and were largely free from left-sided disease or pulmonary hypertension. Longer follow-up of the trial and additional studies on different patient populations will further inform the longer-term impact of T-TEER on hard endpoints and will help to identify ideal candidates for therapy.

Additional dedicated trials have started enrollment and are already close to their primary completion date (see **Table 3**).

TABLE 2 Baseline heart failure characteristics in main transcatheter tricuspid intervention studies.

	TRILUMINATE Pivotal RCT ($n = 350$) (67)	TRILUMINATE ($n = 85$) (68)	CLASP TR ($n = 65$, 46 at 1 year) (69, 70)	bRIGHT ($n = 200$) (71)	TRI-REPAIR ($n = 30$) (72)	TRISCEND ($n = 132$, 56 at 6 m) (73, 74)
Treatment	T-TEER (TriClip)	T-TEER (TriClip)	T-TEER (Pascal)	T-TEER (TriClip)	Annuloplasty (Cardioband)	Replacement (EVOQUE)
Implant success	98.8%	100%	91%	98%	100%	96.20%
Longest follow-up	1 year	1 year	1 year	30 days	2 years	6 months
Mortality last follow-up	9.4%	7.1%	10.8%	0.5%	26.7%	4%
Baseline HF characteristics						
NYHA class III/IV	59.4%	75%	79%	79%	83%	88%
LVEF (%)	59.3 ± 9.3	59.4 ± 8.1	57.4 ± 7.0	55.6 ± 11.0	57.5 ± 10.8	N/A
TAPSE (cm)	in 48% ≥ 1.7 cm	1.44 ± 0.31	1.53 ± 0.47	1.8 ± 0.9	1.4 ± 0.3	N/A
SPAP (mmHg)	39.7 ± 9.2	38.9 ± 16.0	in 68% ≥ 30	38.8 ± 11.8	35.9 ± 10.5	39.6 ± 10.8
RVEDD (cm)	5.0 ± 0.8	5.27 ± 0.67	3.99 ± 0.89	4.7 ± 0.9	3.8 ± 6.5	N/A
NT-proBNP (pg/ml)	382.0 ± 347.5 (BNP)	1,559.5 [1,002.5–2,278.0]	N/A	3,610 ± 5,662	2,925 ± 3,030	N/A

TriClip device by Abbott Laboratories; Pascal device by Edwards Lifesciences, Irvine, California, USA; Cardioband by Edwards Lifesciences, Irvine, California, USA; EVOQUE device by Edwards Lifesciences, Irvine, California, USA.
HF, heart failure; LVEF, left ventricular ejection fraction; RVEDD, right ventricular end diastolic diameter; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; T-TEER, tricuspid transcatheter edge-to-edge repair.

TABLE 3 Ongoing randomized controlled trials evaluating transcatheter treatment of tricuspid regurgitation.

	TRILUMINATE Pivotal (NCT03904147)	TRI-FR (NCT04646811)	CLASP II TR Pivotal (NCT04097145)	TRICI-HF (NCT04634266)
Device	TriClip (T-TEER)	TriClip (T-TEER)	Pascal (T-TEER)	TriClip, Pascal (each T-TEER)
Design	RCT; vs. GDMT	RCT; vs. GDMT	RCT; vs. GDMT	RCT; vs. GDMT
Estimated enrollment (*n*)	700	300	825	360
Primary completion date	August 2022 [first results published (67)]	August 2025	December 2024	December 2025
Primary endpoint	Hierarchical composite all-cause mortality, TV surgery, HF hospitalizations, QoL with KCCQ	Milton Packer clinical composite score	Composite of all-cause mortality, RVAD implantation or heart transplant, TV intervention, HF hospitalizations, QoL by KCCQ	All-cause mortality or HF hospitalization
HF inclusion/ exclusion criteria	Exclusion criteria: SPAP >70 mmHg or fixed pre-capillary PHT by RHC; LVEF ≤ 20%	Exclusion criteria: Uncontrolled pre-capillary PHT (RHC required), SPAP >60 mmHg; LVEF ≤ 35%	Exclusion criteria: Refractory HF requiring advanced intervention (i.e. has or will need LVAD or transplantation), ACC/AHA Stage D HF	Exclusion criteria: RHC with SPAP >70 mmHg or substantial pre-capillary PHT (mean PAP >30 mmHg plus transpulmonary gradient >17 mmHg or pulmonary vascular resistance >5 wood units)

TriClip device by Abbott Laboratories; Pascal device by Edwards Lifesciences, Irvine, California, USA.
GDMT, guideline directe medical therapy; HF, heart failure; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; PHT, pulmonary hypertension; QoL, quality of life; RCT, randomized controlled trial; RHC, right heart catheterization; RVAD, right ventricular assist device; SPAP, systolic pulmonary artery pressure; T-TEER, tricuspid transcatheter edge-to-edge repair; TV, tricuspid valve.

TR interventions in the setting of (right-sided) HF

Patients currently undergoing treatment are referred at the late stages of their disease as, previously, there were no treatment options available to address their persistent symptoms (75). Even though propensity-matching analyses transcatheter TR treatment could reduce mortality and HF hospitalizations in comparison to GDMT alone, the benefit seen in the randomized TRILUMINATE trial and other currently performed single-arm studies is mostly related to the quality of life measures (26, 76). Given these soft endpoints, as well as often small treatment effects, it is challenging to identify precise predictors of treatment response for the broader population based on such very selected cohorts (26, 76).

However, some first parameters potentially predicting treatment response could be identified. In general, while SMR populations present with HFrEF, in STR, LVEF is often preserved or only mildly reduced. Explanatory concepts evaluated that MR on the left side, such as a disproportionate degree of regurgitation, cannot simply be translated to the right side. For a response to interventional correction of TR, the interaction of the ventricle and the pulmonary vasculature seems to be of high relevance. Patients undergoing T-TEER showed significantly higher survival when mean (m) PAP was ≤30 mmHg and when the trans-pulmonary gradient (TPG) was ≤17 mmHg (77). If mPAP was >30 mmHg but TPG still was ≤17 mmHg (post-capillary pulmonary hypertension), treatment response was still good, but when mPAP was >30 mmHg and TPG >17 mmHg (pre-capillary hypertension), mortality after the intervention was significantly increased. This highlights the mandatory role of right heart catheterization in the work-up and evaluation of patients with STR screened for transcatheter treatment.

Not only the pulmonary vasculature itself is of predictive importance as the coupling between the right ventricle (RV) and the pulmonary arterial (PA) system can also bear prognostic implications. RV-PA coupling can be assessed as the ratio of TAPSE and SPAP, representing the contractile response of the RV to increased afterload, with lower ratios implying insufficient RV response. In the TriValve registry, when divided per TAPSE/SPAP ratio >0.406 vs. ≤0.406, patients with a lower rate of RV-PA coupling had a significantly higher risk of post-procedural mortality (78).

Of note, when assessing SPAP via echocardiography, the estimated values might differ from what would be measured invasively. Lurz et al. demonstrated that patients who echocardiographically present without pulmonary hypertension but then discordantly show pulmonary hypertension when measured invasively (pulmonary hypertension defined as SPAP ≥50 mmHg; discordant diagnosis considered when estimated SPAP differed >10 mmHg from invasive measurement) have a significantly worse prognosis (death, HF rehospitalization, and reintervention) after T-TEER (79).

In all of this, it is important to consider that most of these evaluations have been based on patient collectives that predominantly underwent T-TEER. Especially in the case of TV replacement, the role of the RV after intervention might substantially differ; as with abolished TR, the ventricle faces a substantial after-load increase that might lead to failure of the RV even though it may be only temporary.

TR patients often present even later in their disease course than those suffering from MR; thus, apart from cardiac parameters, it is important to holistically assess the status of the patient. A chronic TR state might lead to complex hypercirculatory HF impacting hepatic, renal, and intestinal function. Even though a prognostic benefit of treatment might be possible, it may be smaller among

patients with chronic right HF, who show advanced congestive hepatopathy, decreased peripheral vascular tone, and potentially lack the ability to respond with venous pressures to TR reduction (80).

Multi-valvular disease

One specific additional aspect to consider in the treatment planning of MR and/or TR might arise in the case of multi-valvular disease. The EURObservational Research Programme Valvular Heart Disease II Survey found that among over 5,000 patients with valvular heart disease, over 20% suffered from more than one valvular lesion (81). For surgical intervention, Gammie et al. recently evaluated the prognostic value of tricuspid annuloplasty performed during MV surgery whenever ≤ moderate TR was present (82). While the endpoint of less TR progression was met, this came at the cost of an increased rate of pacemaker implantations necessary in those who received TV annuloplasty, and, thus, at 2 years, no clinical benefit of such a combined approach could be demonstrated. Less invasive transcatheter treatment options, however, bring the intriguing opportunity to intervene at one valve, then wait and reevaluate other valvular lesions after a certain follow-up, and then decide whether an additional procedure is really needed (83).

Future perspectives

It is obvious that transcatheter MR and TR interventions are addressing a complex disease conundrum often characterized by chronic HF; thus, a simple, standardized, and straightforward treatment algorithm, for example in aortic stenosis, does not likely exist.

To allow transcatheter MR and TR interventions to fully exploit the potential they bear for HF patients, a paradigm shift regarding the intended role of these procedures might be needed. Only when such interventions are considered synergistic with HF medications and, thus, are included in the discussion of treatment options along the whole course of progressing HF, they can then be applied at that exact point of the disease course when they will be most beneficial. However, if these transcatheter interventions continue to be only considered bailouts when GDMT has been fully optimized and failed to optimally control HF symptoms, they will often be likely applied after the occurrence of irreversible changes to cardiac structures and other organs that otherwise could have been prevented. An open and cooperative heart team, including sub-specialties such as HF experts, clinical cardiologists, and geriatricians, is the ideal platform for such discussion and at the same time represents the key prerequisite to establishing a future-oriented HF treatment armamentarium, including transcatheter MR and TR interventions.

It has become evident that HF cannot be sufficiently characterized by only one cut-off value, namely LVEF, which itself is an often dynamic parameter and at times imprecise. A more distinct characterization of HF must include several different cardiac parameters as well as a holistic appreciation of the organic status in elderly patients. Assessing cardiac structures must incorporate a broad appreciation of the ventricular-annular unit, including assessment of LV dimensions, pressure and contractility, annular dimensions and contractility, as well as synchrony and synergy of the whole atrio-annular-ventricular valve apparatus with its impact on coaptation and tethering (84). Here, utilizing new technologies such as machine learning approaches, scanning already existing multi-parametric data, new phenotypes of HF, and structural heart alterations that might remain hidden with conventional methods, could be identified (85). When assessing HF from a more holistic perspective, that also appreciates other organs apart from the heart itself, a realistic and self-critical appraisal is warranted, considering what, given such a multi-morbid complex late-stage disease setting, might be the remaining potential of an intervention addressing only the cardiac structure.

Conclusions

As patients with severe symptomatic SMR and STR are often suffering from chronic HF, evaluating such patients for treatment and finally performing transcatheter interventions in such a condition poses a challenge for inter-disciplinary heart teams. Following the growing experience, especially with TEER, the first markers of likely treatment response could be identified. In SMR, patients should match the COAPT trial criteria, as then an actual prognostic benefit from intervention can be drawn. However, also in COAPT-ineligible patients, intervention should be discussed as a substantial alleviation of symptoms is still achievable for them. In STR patients, an RHC should be performed when evaluating potential treatment candidates, and pre-capillary pulmonary hypertension should be excluded before interventional treatment of TR.

Finally, in the future, the heart team should discuss transcatheter interventions for SMR and STR ideally as one part of a synergistic framework alongside established HF medications. In chronic HF, only a multifaceted holistic treatment approach can likely bring the potential lifesaving therapeutic effects of current medical and interventional innovations to these patients in need.

Data availability statement

The original data presented in the manuscript are derived from previously published studies that are reported in the references.

Author contributions

All the authors have written and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1091309/full#supplementary-material.

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Innovative use of a self-expanding valve for valve-in-valve transcatheter mitral valve replacement: experience from a four-year single-center study

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Background: Valve-in-valve transcatheter mitral valve replacement (ViV-TMVR) is a minimally invasive option for patients with bioprosthetic mitral valve failure. Since January 2019, our center has been using a new innovative option, J-Valve, to treat patients with bioprosthetic mitral valve failure who were at high risk for open heart surgery. The aim of this study is to explore the effectiveness and safety of J-Valve and report the results from the four-year follow-up period of the innovative application of the transcatheter valve.

Methods: Patients who underwent the ViV-TMVR procedure between January 2019 and September 2022 in our center were included in the study. J-Valve™ system (JC Medical Inc., Suzhou, China) with three U-shape grippers was used for ViV-TMVR via transapical approach. Data on survival, complications, transthoracic echocardiographic results, New York Heart Association functional class in heart failure, and patient-reported health-related quality of life according to the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) were collected during the four-year follow up.

Results: Thirty-three patients (mean age 70.1 ± 1.1 years, 13 men) were included and received ViV-TMVR. The surgery success rate was 97%: only one patient was converted to open-heart surgery due to intraoperative valve embolization to the left ventricle. During the first 30 days all-cause mortality was 0%, risk of stroke 2.5% and risk of mild paravalvular leak 15.2%; mitral valve hemodynamics improved (179.7 ± 8.9 at 30 days vs. 269 ± 49 cm/s at baseline, $p < 0.0001$). Median time from operation to discharge was six days, and there were no readmissions within 30 days from operation. The median and maximum follow-up durations were 28 and 47 months, respectively; during the entire follow-up, all-cause mortality was 6.1%, and the risk of cerebral infarction 6.1%. Cox regression analysis did not identify any variables significantly associated with survival. The New York Heart Association functional class and the KCCQ-12 score improved significantly compared with their preoperative values.

Conclusion: The use of J-Valve for ViV-TMVR is safe and effective with a high success rate, low mortality and very few associated complications, representing an alternative surgical strategy for the elderly, high-risk patients with bioprosthetic mitral valve failure.

KEYWORDS

valve-in-valve transcatheter mitral valve replacement, failed mitral bioprosthetic valves, transapical approach, health-related quality of life outcomes, Kansas city cardiomyopathy questionnaire-12

Introduction

The use of mechanical prostheses requires long-term anticoagulation, leading to an increased risk of bleeding in patients (1). In contrast, bioprosthetic valves are associated with a low rate of thrombosis and do not require lifetime anticoagulation. As a result, the preference for bioprosthetic valves has increased among patients with mitral valve disease over the past two decades (1). Guidelines for the treatment of valvular heart disease (2, 3) recommend patient preference as the primary criterion in selecting the type of prosthetic valve, further contributing towards the use of bioprosthetic valves. However, because of the limited durability, bioprosthetic valves need to be replaced over time. One study has shown that up to one-third of patients need to receive redo surgical treatment for mitral valve replacement (4). Since redo open-heart valve replacement surgery poses a risk of perioperative death (5), transcatheter valve-in-valve implantation technologies with less invasive alternatives for the treatment of bioprosthetic heart valve failure, which have been proven to be associated with lower risk of death, lower periprocedural morbidity, lower risk of complications, and lower need of resources, have gradually emerged since 2007 (4, 6).

However, valve-in-valve transcatheter mitral valve replacement (ViV-TMVR) still faces several challenges. Sapien 3 (Edwards Lifesciences Inc., Irvine, CA, USA) is the only transcatheter heart valve (THV) currently approved by the US Food and Drug Administration for ViV-TMVR and was also approved for the market by the Chinese National Medical Products Administration in 2020. Studies have also reported some disastrous complications associated with ViV-TMVR, such as valve migration or embolization and left ventricular outflow tract (LVOT) obstruction (7–11).

To avoid the above-mentioned complications, and also due to the fact that Sapien 3 was not available in China until 2019, we attempted to perform ViV-TMVR without changing the valve and transmitter structure using reverse-loaded J-Valve (JC Medical Inc., Suzhou, China), and concluded a standardized valve release process. J-Valve is a self-expanding transcatheter valve consisting of three U-shaped grippers, a crowned nitinol stent, porcine aortic valve leaflets, and an inner liner skirt. It was approved by China's Food and Drug Administration in 2017 with a dual indication for aortic stenosis and aortic regurgitation. Unlike cylindrical balloon-expanded valves, the anchoring of the J-Valve does not rely solely on radial forces. The three U-shaped grippers limit the movement of the valve towards the left atrium under left ventricular pressure, reducing the risk of valve migration or embolization. In addition, the three U-shaped grippers facilitate accurate commissural alignment, and the combined crowned stent and inner liner skirt both reduce the risk of left ventricular outflow tract obstruction and prevent the occurrence of paravalvular leaks.

In this study, we present the outcomes among elderly, high-risk patients with bioprosthetic mitral valve failure who were managed successfully by ViV-TMVR using J-Valve via transapical approach.

Methods

Patients

We included patients with failed surgical bioprosthetic valves who underwent ViV-TMVR in Beijing Anzhen Hospital (Capital Medical University, Beijing, China) between January 2019 and September 2022.

Preoperative electrocardiographic gated multislice computed tomographies (CT) were performed for all patients. Each patient was independently evaluated by at least two cardiac surgeons before the operation. We included patients aged ≥60 years for whom conventional redo valve surgery was associated with high risks (Society of Thoracic Surgery (STS) Risk Score or European System for Cardiac Operative Risk Evaluation (EuroSCORE) II of ≥8). Patients with the following conditions were excluded: (1) Combined moderate to severe mitral valve perivalvular leak (PVL); (2) History of stroke over the past three months; (3) Presence of left atrial or appendage thrombus; (4) Failed bioprosthetic valve type of ≤23 mm; (5) Presence of infective endocarditis; (6) Presence of LVOT obstruction; or (7) Combined multiple organ system failure or other diseases associated with a life expectancy of less than one year.

Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki (2013 revision). The study design was approved by the Ethics Review Committee of Beijing Anzhen Hospital (No. 2022083X).

Procedure details

The procedure was performed in a hybrid operating room. Transesophageal echocardiography (TEE) was performed under general anesthesia to determine the presence of left atrial appendage thrombus and mitral valve PVL. All patients were treated with a transapical approach using the J-Valve™ System (**Figure 1**). The J-Valve was reverse loaded and sized according to the measured internal diameter of the failed bioprosthetic valve. The THVs' oversize ratio ranged from 5%–10%.

The step-by-step procedure is shown in **Figure 2** and **Supplementary Video S1**. After apical puncture, the failing bioprosthetic mitral valve can usually be crossed easily using J-tip guidewires. A transesophageal echocardiography was used to further confirm the guide wire into the left atrium. The wire was subsequently exchanged for an extra-stiff guide wire with curved tip. Conveyor curvature could be adjusted as needed to provide optimal coaxiality. After entering the left ventricle along the extra-stiff guidewire (**Figure 2A**), the conveyor first released three U-shaped grippers and subsequently staggered them between three struts of the bioprosthetic valve (**Figure 2B**). To improve the success and accuracy of this step, a preoperative computed tomography assessment was performed to calculate the C-arm angle at which the tips of the three struts are located at the same level. This is particularly important for the epic valve (St Jude

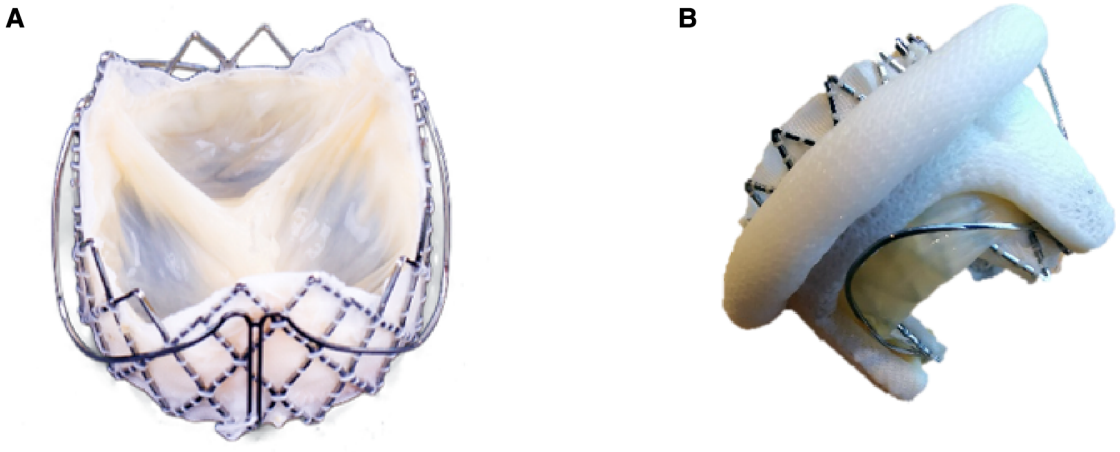

FIGURE 1
Features of J-Valve. The J-Valve is a self-expanding transcatheter valve with three U-shaped grippers and notches (A). The grippers help achieve commissure alignment (B) and further reduce the risk of left ventricular outflow tract obstruction.

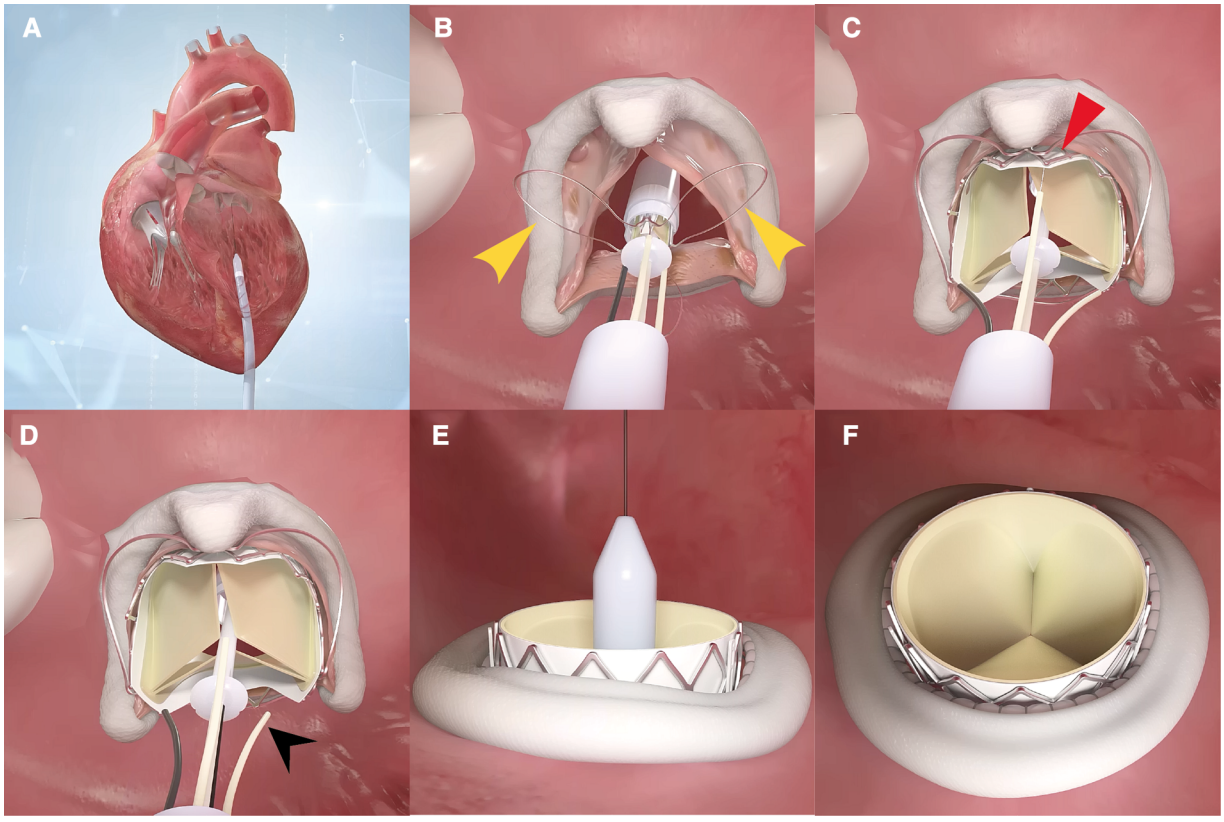

FIGURE 2
A step-by-step demonstration of the procedure of how J-valve functions. The conveyor enters the left ventricle along the extra-stiff guidewire (A), then the three U-shaped grippers are first released and subsequently staggered them between three struts of the bioprosthetic valve (B). The valve is then slowly released under rapid ventricular pacing (C). Subsequently, the conveyor anchor device is controlled to de-load the valve (D). The conveyer is withdrawn, and the guidewire retained (E). If balloon valvuloplasty is not required, the guidewire is withdrawn. The ideal implantation depth is 80% of the transcatheter heart valve stent frame in the left ventricle and 20% in the left atrium (F).

Medical, Inc, St Paul, MN, USA) because its struts are radiolucent (**Figure 3A**). The valve was slowly released under rapid ventricular pacing (**Figure 2C**). Subsequently, the conveyor anchor device was controlled to de-load the valve (**Figure 2D**), the conveyer was withdrawn, and the guidewire retained (**Figure 2E**). Mitral flow velocity and paravalvular leak were explored using transesophageal echocardiography. Detection of mitral flow velocity and paravalvular leak using transesophageal echocardiography were utilized to determine whether to perform balloon valvuloplasty. The ideal implantation depth was considered to be 80% of the THV stent frame in the left ventricle and 20% in the left atrium (**Figure 2F**). Coincident native aortic valve disease or prosthetic bioprosthetic valve failure can also be managed concurrently (**Figure 3B**).

The strategy for postoperative anticoagulation is based on the current guidelines (2, 3) for the management of valvular heart disease and atrial fibrillation (12). Warfarin was administered on the first postoperative day and was continued for 3–6 months. The International Normalized Ratio value was maintained at 2.5. Anticoagulation or antiplatelet therapy was selected depending on the presence or absence of atrial fibrillation and the history of percutaneous coronary intervention with stent implantation or coronary artery bypass surgery.

Follow-up

All patients were followed up by four researchers (YL, JZ, KW and JS), including telephone interviews and in person visits. Follow-up data included complications reported according to the Valve Academic Research Consortium-2 definition (13), results of transthoracic echocardiography, NYHA functional class for heart failure, and patient-reported health-related quality of life outcome measured by the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) score. The KCCQ-12 score quantitatively assesses the frequency of incident symptoms, physical limitations, social limitations, and quality of life in four areas through 12 questions. The scores can take values between 0 and 100, with higher scores meaning better health status (14).

Statistical analysis

Continuous variables were expressed as means ± standard deviations (SD) or medians with interquartile ranges, depending on whether they conformed to a normal distribution. Two-sample t-test or Wilcoxon rank sum test was used for comparisons between groups. Categorical variables were expressed as frequencies and percentages. Adverse event rates were based on Kaplan-Meier estimates, and all comparisons were made using the log-rank test. The data were analyzed using SPSS version 26.0 software (SPSS, Chicago, IL, USA). The Kaplan-Meier survival curve and bar chart with error bars were plotted using https://www.bioinformatics.com.cn (last accessed on 31 Oct. 31, 2022), an online platform for data analysis and visualization.

Results

Baseline characteristics

Baseline characteristics of the participants are shown in **Table 1**. Thirty-three consecutive patients underwent a ViV-TMVR procedure in the study cite, with a mean age of 70.1 ± 1.1 years. Thirteen (39.3%) patients were male. The mean time between surgical mitral valve replacement and ViV-TMVR was 10.7 ± 0.6 years. The New York Heart Association functional

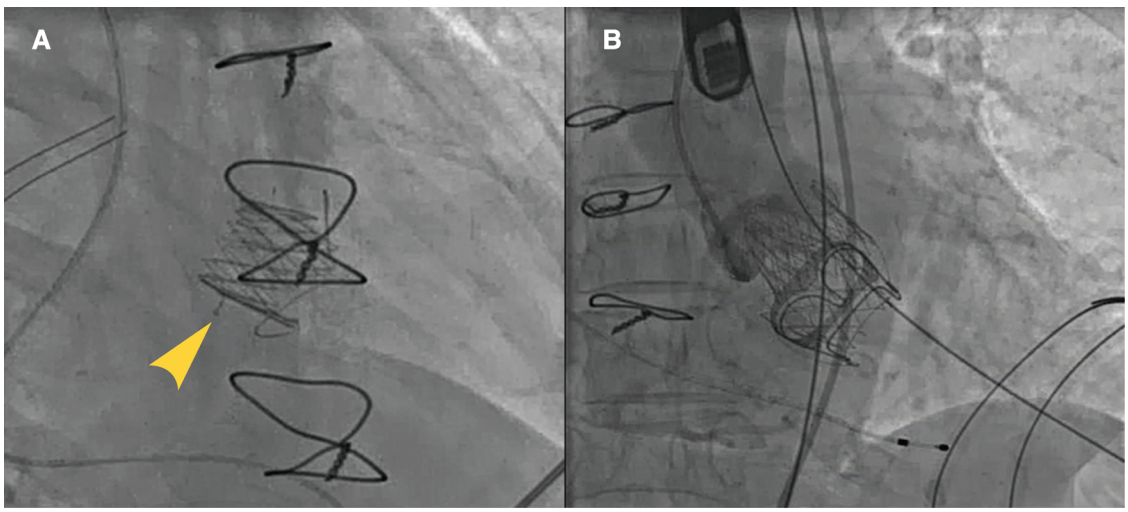

FIGURE 3
Typical cases of utilization of J-Valve. J-Valve applied to a strut-radiolucent epic valve (St Jude Medical) for ViVTMVR (**A**). Combined aortic valve disease with concomitant TAVR and ViV-TMVR procedures (**B**).

TABLE 1 Baseline characteristics ($n = 33$).

Characteristic	Value
Male (%)	13 (39.3%)
Age (years)	70.1 ± 1.1
BMI (kg/m^2)	22.3 ± 0.6
Time to ViV-TMVR from surgical MVR (years)	10.7 ± 0.6
NYHA functional classification III/IV (%)	28 (84.9%)
Chronic obstructive pulmonary disease (%)	4 (12.1%)
Coronary artery disease (%)	9 (27.2%)
Previous coronary artery bypass (CAB) (%)	4 (12.1%)
Prior CVA/TIA (%)	3 (9.0%)
Peripheral vascular disease (%)	5 (15.1%)
Currently receiving dialysis (%)	1 (3.0%)
Diabetes mellitus (%)	6 (18.1%)
Hypertension (%)	14 (42.4%)
Atrial fibrillation (%)	23 (69.6%)
Previous permanent pacemaker (%)	5 (15.1%)
EuroSCORE II	27.4 ± 2.3
STS score	11.8 (7.6, 17.1)

Values are presented as mean ± SD, *n* (%), or median (interquartile range).
ViV TMVR, valve-in-valve transcatheter mitral valve replacement; BMI, body mass index; NYHA, New York Heart Association; CVA/TIA, Cerebrovascular Accident/ Transient Ischemic Attack; STS, Society of Thoracic Surgeons.

TABLE 2 Preoperative echocardiographic assessment ($n = 33$).

Variable	Value
Mitral valve pathology	
Stenosis (%)	7 (21%)
Regurgitation (%)	12 (36%)
Combined (%)	14 (43%)
LVEF (%)	63 (59, 68)
LVEDd (mm)	45 (43, 50)
LVESd (mm)	30 (28, 32)
LAd (mm)	50 (44, 56)
Peak transvalvular jet velocity (Vmax)(cm/s)	269 ± 49
Tricuspid insufficiency (moderate to severe) (%)	28 (85%)
Combined aortic valve disease	
Aortic insufficiency (moderate to severe) (%)	7 (21%)
Aortic stenosis (moderate to severe) (%)	0 (%)
Combined aortic stenosis with regurgitation (%)	1 (3%)
Combined pulmonary hypertension (moderate to severe) (%)	8 (24%)

Values are presented as mean ± SD, *n* (%), or median (interquartile range).
LVEF, Left Ventricular Ejection Fraction; LVEDd, Left Ventricular End-Diastole diameter; LVESd, Left Ventricular End-Systole diameter; LAd, Left atrial diameter; MVR, Mitral Valve Replacement.

class was III/IV in 28 patients (84.9%). Surgical bioprosthetic valves included Carpentier-Edwards porcine and pericardial (Edwards Lifesciences, Inc., Irvine, CA, USA), Hancock II and Mosaic (Medtronic, Minneapolis, MN, USA), Epic heart valve (St Jude Medical, Inc, St Paul, MN, USA), and BalMedic bovine pericardial (Balance Medical, Beijing, China). In some patients we were unable to verify the valve type. All patients were subjected to surgical risk assessment, with a mean STS score of 11.8% and a mean (±SD) EuroSCORE II score of 27.4% ± 2.3%. All patients were considered as having high risks associated with conventional surgery.

Echocardiographic characteristics

Echocardiographic characteristics are presented in Table 2. Preoperative echocardiographic evaluation results showed that seven patients (21%) had stenosis but no regurgitation, 12 patients (36%) had regurgitation but no stenosis, and 14 patients (43%) had both stenosis and regurgitation. The left ventricular ejection fraction and left ventricular size were in the normal range in 28 patients (85%). Mostly combined with moderate to severe tricuspid valve insufficiency. A total of eight patients (24%) had coexisting moderate to severe aortic valve disease. Eight patients (24%) had moderate to severe pulmonary hypertension.

Intraoperative outcomes

The surgery success rate was 97% according to the definition of the Mitral Valve Academic Research Consortium. One patient's procedure was converted to open-heart surgery due to intraoperative valve embolization to the left ventricle. Transapical access was used for all procedures with the J-Valve^{TM} system. THV sizes ranged from 23 mm ($n = 11$, 33.3%) to 27 mm ($n = 6$, 18.2%), with 25 mm being the most utilized size in a total of 16 patients (48.5%). Pre-dilatation was performed in eight patients (24.2%) and post-dilatation in 10 patients (30.3%) due to a postoperative perivalvular leak. Perivalvular leak or concern about long-term migration due to suboptimal THV release position in two patients (5.1%) were resolved by implanting a second valve. Seven patients (21.2%) were concurrently treated for aortic valvular lesions. The valve in valve transcatheter aortic valve replacement (ViV-TAVR) was concurrently performed in four patients (12.1%) and transcatheter aortic valve replacement (TAVR) in three patients (9.1%).

Early outcomes

The early clinical outcomes (within 30 days from operation) are shown in Table 3. The median postoperative time to discharge was six days, with no hospital readmissions within 30 days from operation. There were no deaths or other serious complications, except for one patient (2.5%) who experienced stroke. Mild perivalvular leaks occurred in five patients (15.2%). Mitral valve hemodynamics improved postoperatively as demonstrated by the lower transvalvular flow velocity compared to the respective preoperative value (180 ± 9 vs. 269 ± 49 cm/s, $p < 0.0001$).

Follow-up outcomes

The median and maximum follow-up times were 28 and 45 months, respectively. Follow-up outcomes are shown in

TABLE 3 Clinical outcomes ($n = 33$).

Outcome	Value
Early outcomes (30 days from the operation)	
All-cause mortality (%)	0 (0.0%)
Cardiovascular death (%)	0 (0.0%)
Duration of hospital stay (days)	6 (5,10)
Readmission within 30 days (%)	0 (0.0%)
Permanent peacemaker required (%)	0 (0.0%)
Complications	
Acute kidney injury (%)	0 (0.0%)
Stroke (%)	1 (2.5%)
Respiratory failure (%)	0 (0.0%)
Left ventricular output tract obstruction (%)	0 (0.0%)
Myocardial infarction (%)	0 (0.0%)
Paravalvular leak	
None (%)	28 (84.8%)
Mild (%)	5 (15.2%)
Moderate to severe (%)	0 (0.0%)
Mitral valve forward flow (cm/s)	179.7 ± 8.9
Peak pressure gradient (mmHg)	11 (8, 15)
Mean pressure gradient (mmHg)	5 (4, 6)
Follow up outcomes (median follow-up was 28 months)	
All-cause mortality (%)	2 (6.1%)
Cardiovascular death (%)	0 (0.0%)
Stroke (%)	2 (6.1%)
Mitral valve reintervention (%)	0 (0.0%)
Myocardial infarction (%)	0 (0.0%)
New dialysis requirement (%)	0 (0.0%)
New pacemaker (%)	0 (0.0%)
NYHA functional classification	
I (%)	29 (87.9%)
II (%)	2 (6.1%)
III/IV (%)	0 (0.0%)

Values are presented as mean ± SD, *n* (%), or median (interquartile range).
NYHA, New York Heart Association.

Table 3. The all-cause mortality was 6.1% (**Figure 4**): one patient died from pulmonary infection, and another experienced a sudden death for unknown reasons while sleeping at night. No cardiac deaths were recorded. Cerebral infarction occurred in two patients (6.1%): in one patient 10 months after surgery followed by left atrial appendage occlusion performed 7 months later; the other patient failed the ViV-TMVR due to a large left atrium and was converted to direct cardiac surgery with a mechanical prosthetic valve. There were no significant sequelae after thrombolytic therapy. Univariable Cox regression showed that only chronic obstructive pulmonary disease had a significant effect on survival. However, a multivariate Cox regression analysis did not identify any variables that significantly affected survival outcomes. The NYHA classification (**Figure 5**) and the KCCQ-12 score (**Figure 6**) were significantly improved when compared to their preoperative values. The mean changes in KCCQ-12 score from baseline three months and one year after the operation were 48.0 (95% confidence interval 46.0, 50.0) and 48.8 (95% confidence interval 47.1, 50.5), respectively ($p < 0.001$).

Discussion

The standard treatment for bioprosthetic valve failure is redo valve replacement (15, 16). However, studies (4, 6) have shown that ViV-TMVR is associated with lower in-hospital mortality, lower risk of complications, and lower need of resources. Previous studies have reported 30-day mortality rates between 3.2% and 7.5% and one-year mortality rates between 11.3% and 16.9% after ViV-TMVR (17–21). Outcomes from long-term follow-up are less commonly reported (22), with one study reporting a four-year mortality rate of 37.5%, a stroke incidence of less than 3%, and an LVOT obstruction incidence of 0% to 5% (18).

Our study demonstrated good mid-term clinical outcomes and health-related quality of life in patients who received ViV-TMVR, which is clearly better than reported by previous studies. In our study, no patients died immediately after the operation and the all-cause mortality during the follow-up with a median of 28 months was also low (6.1%). No LVOT obstructions were observed either. Mitral valve hemodynamics, NYHA classification and health-related quality of life were also significantly improved in patients after ViV-TMVR. This study used the KCCQ-12 score to reflect patients' health-related quality of life, which is a patient-reported outcome and more accurate than the NYHA classification for detecting changes in health status in patients with heart failure (23).

The advantages of J-Valve for ViV-TMVR

The J-Valve system consists of a self-expanding transcatheter valve and a transapical interventional device. Several studies (24–27) have confirmed its short- or medium-term safety and efficacy in the treatment of aortic valve disease.

Our center was the first to successfully complete ViV-TMVR using a reverse-loaded J-Valve in January 2019. ViV-TMVR was accomplished in an innovative way by changing the loading direction and release sequence without changing the structure of the J-Valve and conveyors. J-Valve has several advantages when applied to ViV-TMVR. First, its three grippers make leaflet-to-leaflet and commissure-to-commissure positioning simple, without the need to consider commissural misalignment (**Figure 1B**). The problem of misalignment due to ViV-TMVR has until now been largely ignored in clinical research. Correct orientation is mandatory for surgical bioprosthetic valve replacement (28), which means that commissural posts should not face the LVOT. The risk of LVOT obstruction may be increased if the THV commissure posts point toward the LVOT. There is however no way of preventing misalignment for balloon-expandable THV. Second, J-Valve also has U-shaped notches (**Figure 1B**) instead of a complete cylindrical metal stent, which minimizes the risk of LVOT obstruction and has particular advantages in patients with small left ventricular volumes (29), meaning that an evaluation of the neo-LVOT is not required (30). Third, because of the fixation of the grippers,

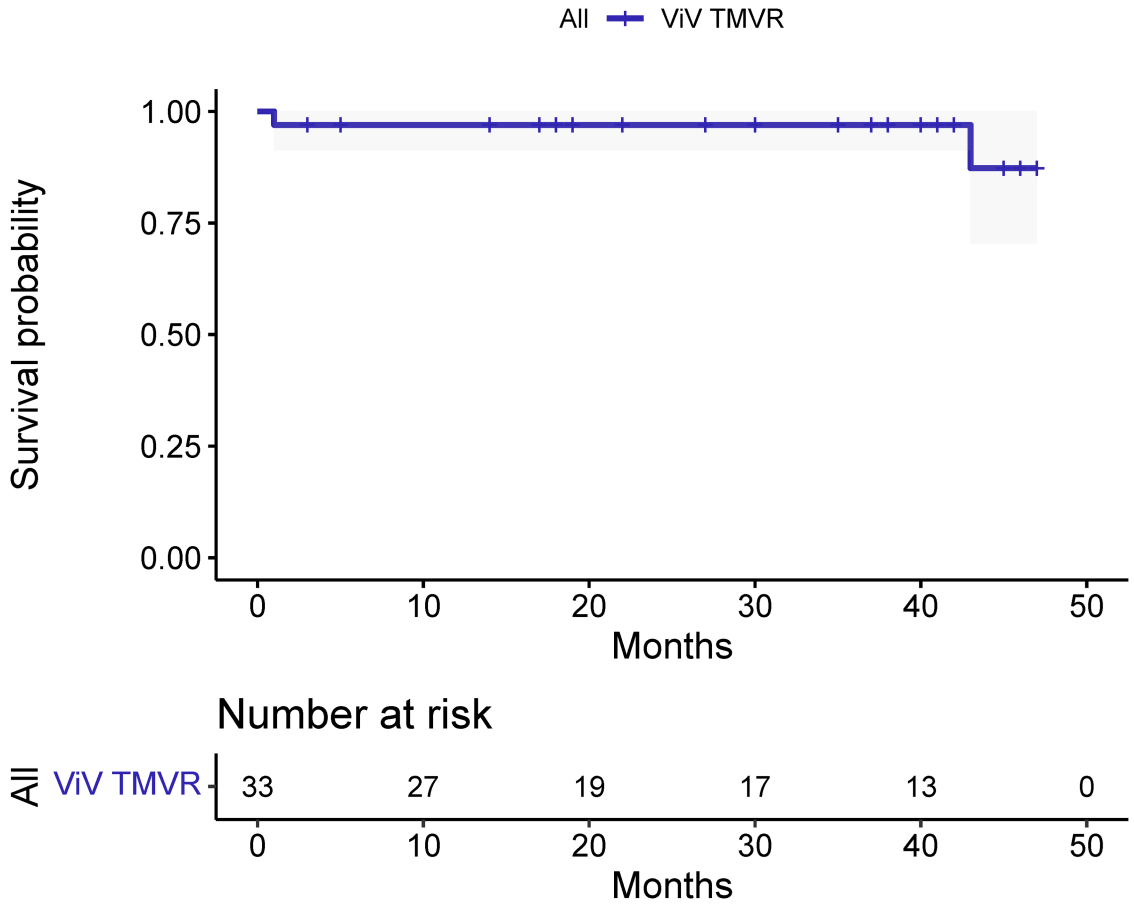

FIGURE 4
Results of the survival analysis (Kaplan-Meier curve).

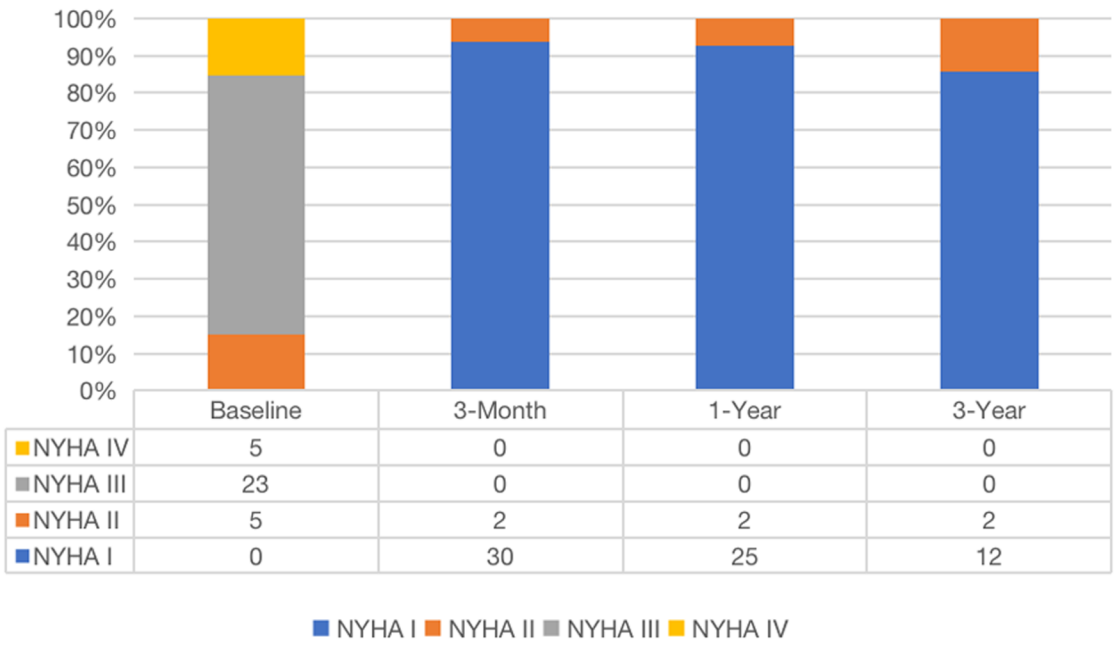

FIGURE 5
Changes in NYHA classification after surgery.

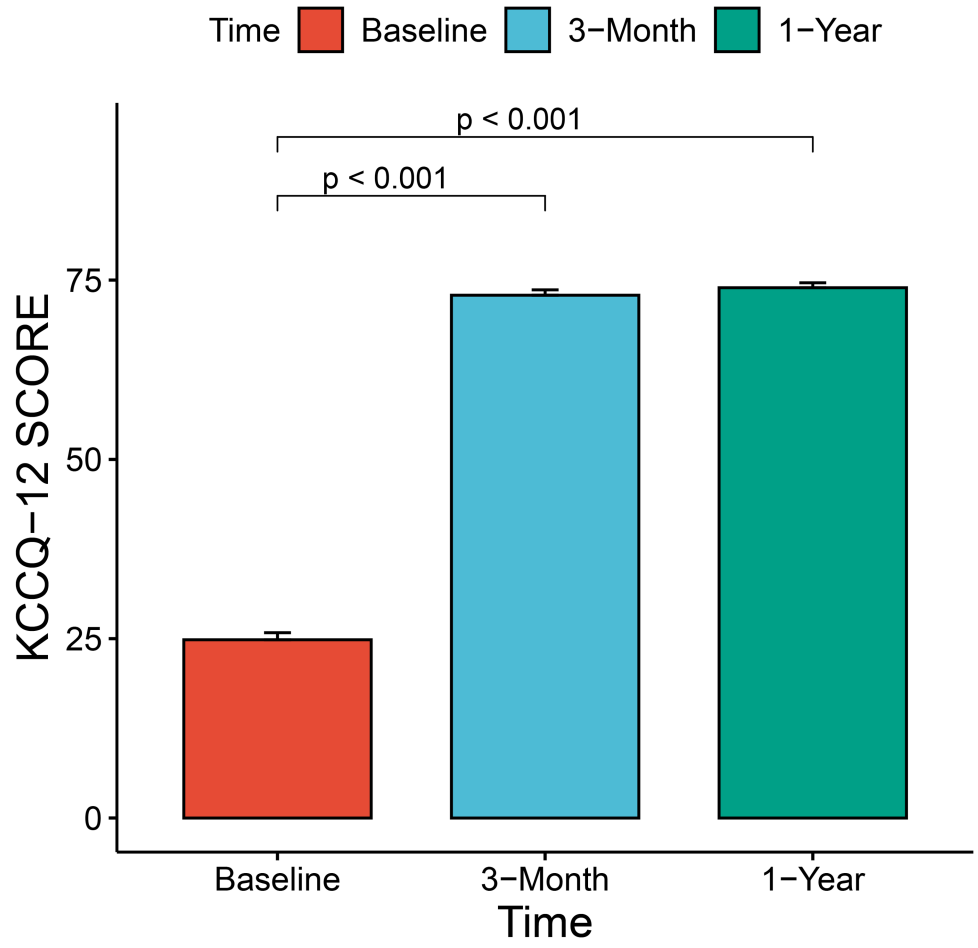

FIGURE 6
Change in patient health-related quality of life using the Kansas city cardiomyopathy questionnaire-12 score.

the risk of the potentially fatal distant THV migration to the left atrial side (7–10) was reduced. Fourth, J-Valve can be used for both ViV-TAVR and ViV-TMVR, and even for tricuspid bioprosthetic valve failure, which allows valve-in-valve transcatheter tricuspid replacement (ViV-TTVR) using a right atrial approach. Fifth, the self-expanding THV can continuously apply a radial support force on the failed bioprosthetic valve's stents, so that the failed leaflets remain strongly anchored at the frame.

A CT imaging analysis should be considered during preoperative evaluation and planning, especially for evaluating the risk of LVOT obstruction. The two main risk factors for LVOT obstruction are the aortomitral angle and neo-LVOT area (31). The optimal size for the neo-LVOT is unknown, but a minimum of 200–250 mm^2 has been suggested (32). In our study, LVOT obstruction has to our knowledge been never detected with postoperative TEE. Therefore, preoperative assessment of the risk of LVOT obstruction appeared to be unnecessary for J-Valve when ViV-TMVR was performed. The possibility to avoid CT imaging simplifies the pre-operative assessment procedure, demonstrating a further advantage of the J-Valve structure.

In addition, in our study, contrast agent were not needed to be used during the whole operation. This benefits patients with allergic asthma, abnormal thyroid function, and chronic renal insufficiency, and can reduce the risk of perioperative complications for such patients.

Surgical approach

The approach to ViV-TMVR can be divided into surgical access and complete percutaneous access. The corresponding approaches are transapical and transseptal, respectively. Currently, transapical approach is by far the most common way for transcatheter valve implantation in the mitral position. Updated data from the Valve-in-Valve-International-Data (VIVID) registry shows that the transapical approach is utilized in 81% of valve in valve cases and 68% in valve in ring cases (33). The proximity of the apex to the mitral valve allows for better control of the position of the delivery device with better coaxiality, does not require many guidewires and sheaths, and is suitable for surgeons with limited experience in performing this intervention. Attention should be drawn to the fact that

transcatheter apical-related complications include not only the impairment of left ventricular apical function (34, 35), but also pleural effusion, bleeding, atrial fibrillation, and prolonged intubation time (36–39). Transseptal mitral valve implantations are becoming more common worldwide, and have the main advantage of being less invasive and not requiring open surgery or left ventricular trauma; unfortunately, the device has poor coaxiality with the mitral orifice plane. In addition, transseptal access requires puncture of the atrial septum and balloon atrial septostomy, which remains technically challenging and may present complications such as iatrogenic atrial septal defect (iASD), cardiac perforation and tamponade (40). Consequently, the transseptal approach is mainly suitable for surgeons with rich intervention experience.

In our study, only the transapical approach was used. The J-Valve system provides the most direct, shortest, and most coaxial access to the mitral valve. The transapical approach also enables treatment of aortic valve diseases or mitral perivalvular leak occlusion while performing ViV-TMVR. Seven patients in our study were treated for aortic valvular lesions and one patient for mitral perivalvular leak occlusion simultaneously while performing ViV-TMVR. From our experience, the transapical approach for simultaneous ViV-TMVR and ViV-TAVR appears to be operationally more convenient, allowing sequential release of both THVs from the same puncture site. In addition, none of the patients in this study experienced postoperative apical bleeding or complications such as guidewire-related cardiac injury, demonstrating the good safety of the transapical approach.

Limitations and future directions

The present investigation was a real-world, retrospective clinical study, which consequently comes with the limitations of an observational study. First, the study was conducted in a single center, so the selection of the patients may have been biased and the results are not necessarily generalizable for broader populations; however, the study population was enrolled consecutively to minimize selection bias. Second, considering that there are no long-term results of J-Valve for ViV-TMVR, we only performed this surgery on patients who are elderly, high-risk or surgically contraindicated, which resulted in a small sample size. Longer-term follow-up data are therefore needed. Third, in the absence of an echocardiographic core laboratory, echocardiographers were able to only determine the presence or absence of left ventricular outflow tract obstruction without recording the outflow tract flow velocities, making it impossible to track the values of the related variables or to compare differences in preoperative and postoperative outflow tract flow velocities. Fourth, some outcome measures were patient-reported, which may also cause bias.

Future multicenter clinical trials are needed to validate the safety and efficacy of the surgical approach addressed in our study. Studies that have sufficiently large sample sizes and long follow-up duration, and that include a control group, are needed also to identify the factors independently associated with survival.

Conclusion

This study demonstrates that J-Valve system is a safe and effective option for ViV-TMVR: it has a high success rate and low mortality, and resulted in very few complications. Mitral valve hemodynamics, NYHA classification and health-related quality of life also significantly improved in patients after ViV-TMVR with J-Valve. The innovative use of the J-Valve for ViV-TMVR is a promising alternative surgical option for the elderly, high-risk patients with bioprosthetic mitral valve failure. Future multicenter clinical trials with long-term follow-up are however needed to strengthen the evidence on the safety and efficacy of this surgical approach.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Beijing Anzhen Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YL conducted the literature search and data acquisition, statistical analysis, manuscript preparation and revision; RL revised the paper, JZ, KW and JS helped with data collection and patient follow-up, ZZ edited the paper, JW revised the paper and provided administrative support, and HZ performed the surgery as the primary operator, drafted and revised the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1137663/full#supplementary-material

SUPPLEMENTARY VIDEO S1
Animated demonstration of applying J-Valve to ViV-TMVR surgical procedure.

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Transcatheter edge-to-edge-repair of functional mitral regurgitation induces significant remodeling of mitral annular geometry

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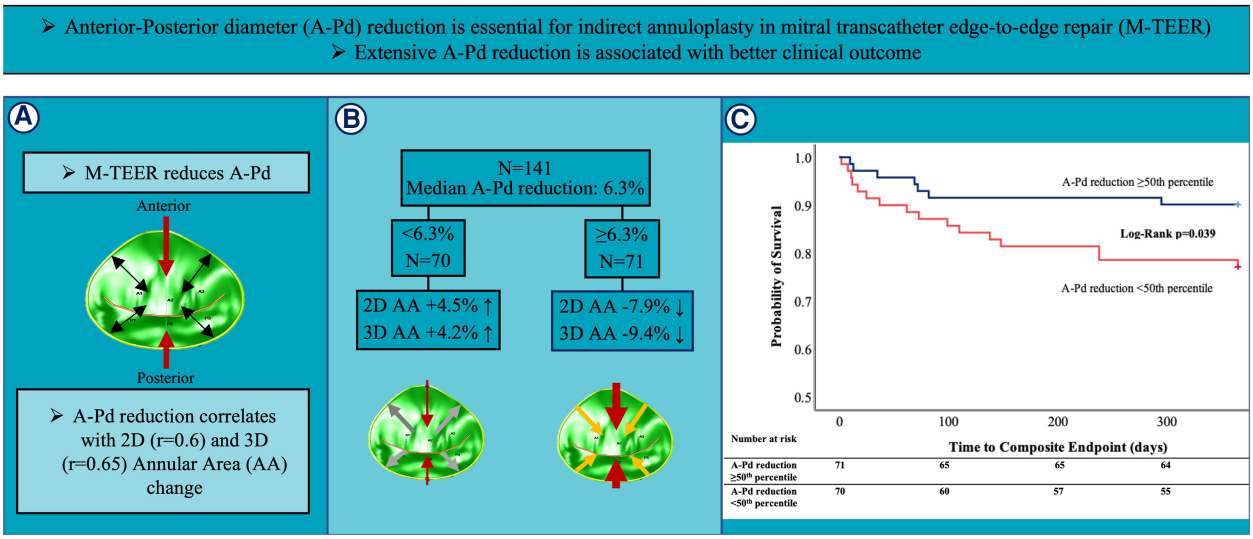
Background: Mitral annular alterations in the context of heart failure often lead to severe functional mitral regurgitation (FMR), which should be treated with transcatheter edge-to-edge repair (M-TEER) according to current guidelines. M-TEER's effects on mitral valve (MV) annular remodeling have not been well elucidated.
Methods: 141 consecutive patients undergoing M-TEER for treatment of FMR were included in this investigation. Comprehensive intraprocedural transesophageal echocardiography was used to assess the acute effects of M-TEER on annular geometry.
Results: Average patient age was 76.2 ± 9.6 years and 46.1% were female patients. LV ejection fraction was reduced (37.0% ± 13.7%) and all patients had mitral regurgitation (MR) grade ≥III. M-TEER achieved optimal MR reduction (MR ≤ I) in 78.6% of patients. Mitral annular anterior-posterior diameters (A-Pd) were reduced by −6.2% ± 9.5% on average, whereas anterolateral-posteromedial diameters increased (3.7% ± 8.9%). Overall, a reduction in MV annular areas was observed (2D: −1.8% ± 13.1%; 3D: −2.7% ± 13.7%), which strongly correlated with A-Pd reduction (2D: $r = 0.6$, $p < 0.01$; 3D: $r = 0.65$, $p < 0.01$). Patients that achieved A-Pd reduction above the median (≥6.3%) showed significantly lower rates of the composite endpoint rehospitalization for heart failure or all-cause mortality than those with less A-Pd reduction (9.9% vs. 28.6%, $p = 0.037$, log-rank $p = 0.039$). Furthermore, patients reaching the composite endpoint had an increase in annular area (2D: 3.0% ± 15.4%; 3D: 1.9% ± 15.3%), whereas those not reaching the endpoint showed a decrease (2D: −2.7% ± 12.4%; 3D: −3.6% ± 13.3%), although residual MR after M-TEER was similar between these groups ($p = 0.57$). In multivariate Cox regression adjusted for baseline MR, A-Pd reduction ≥6.3% remained a significant predictor of the combined endpoint (OR: 0.35, 95% CI: 0.14–0.85, $p = 0.02$).
Conclusion: Our findings indicate that effects of M-TEER in FMR are not limited to MR reduction, but also have significant impact on annular geometry. Moreover, A-Pd reduction, which mediates annular remodeling, has a significant impact on clinical outcome independent of residual MR.

KEYWORDS

functional mitral regurgitation (FMR), anterior-posterior mitral annulus diameter, transcatheter edge-to-edge repair, transesophageal echocardiography, annuloplasty

Abbreviations
AA, annular area; AL-PMd, anterolateral-posteromedial diameter; A-Pd, anterior-posterior diameter; FMR, functional mitral regurgitation; LV, left ventricular; M-TEER, mitral transcatheter edge-to-edge repair.



GRAPHICAL ABSTRACT
Summary of study design and key results of this comprehensive 3D TEE analysis investigating alterations in MV annular geometry during M-TEER and its impact on outcome in 141 FMR patients. (A) M-TEER reduces A-Pd (red arrows) and induces changes in annular geometry (black arrows). (B) 3D TEE assessment showed a median A-Pd reduction of 6.3%. In patients with less extensive A-Pd reduction (<6.3%) 2D and 3D AA increased (white arrows), whereas patients with extensive A-Pd reduction (≥6.3%) showed 2D and 3D AA decrease (orange arrows). (C) Kaplan-Meier analysis for the composite endpoint of rehospitalization for heart failure and all-cause mortality showed significantly better outcomes in patients with extensive A-Pd reduction.

Introduction

Mitral transcatheter edge-to-edge repair (M-TEER) is both an established and foremost minimally invasive treatment for symptomatic degenerative (DMR) and functional (FMR) mitral regurgitation. In particular, FMR has become the dominating etiology in patients treated with M-TEER (1–3) due to a lack of other treatment options and its acceptable interventional risk (4, 5). A randomized-controlled trial was able to prove lower rates of rehospitalization for heart failure as well as lower all-cause mortality after M-TEER compared to optimal medical therapy in selected patients with FMR (4). Accordingly, this is reflected in a higher level of recommendation for FMR compared to DMR in current guidelines (6, 7). Using a single or multiple devices, M-TEER alters mitral annular geometry (8–11) and reduces annular anterior-posterior diameters (A-Pd) (8–10, 12, 13). Based on few available studies, these changes are more pronounced in FMR compared to DMR (14) or lack entirely in DMR (8). Furthermore, A-Pd reduction has been suggested to correlate with improved symptomatic patient outcome (8, 12, 14, 15) especially in FMR patients (8). Unlike DMR, FMR is not a pure valvular disease, but rather the consequence of atrial or ventricular impairment affecting the mitral valve (MV) apparatus.

We hypothesized that A-Pd reduction might be an important underlying mechanism in countering the cause of disease in FMR patients and could also correspond to favorable outcomes. In order to investigate the impact and effects of A-Pd reduction, we analyzed FMR patients undergoing M-TEER according to the extent of AP-d reduction.

Methods

Study population

This is a retrospective, single-center study that included 141 consecutive FMR patients undergoing M-TEER between October 2019 and September 2021 at the University Hospital Ulm. 149 (64.5%) out of 231 patients treated with M-TEER during the enrollment period suffered from FMR. 2 FMR patients undergoing reintervention were excluded and 6 FMR patients were found to have insufficient image quality for proper 3D analysis. Eventually, subgroups of classical ventricular and atrial FMR were differentiated. Patients with preserved LV ejection fraction and left atrial dilation as the main mechanism of MR were classified as having isolated atrial FMR, whereas patients showing impaired LV function and significant leaflet tethering were classified as having ventricular FMR.

We investigated the acute changes in MV annular geometry during M-TEER procedures performed with the two commercially available M-TEER systems (MitraClip™ Abbott Vascular, Santa Clara, CA, USA and PASCAL™, Edwards Lifesciences, Irvine, CA, USA). All included patients had symptomatic moderate-to-severe (III) or severe (IV) FMR, which remained symptomatic despite guideline-directed medical therapy. All patients were evaluated by the local heart team and referred to M-TEER.

Written informed consent was obtained from all patients prior to data collection. This study was approved by the local ethics board and complies with the Declaration of Helsinki. The authors declare that all supporting data are available within the article and its Online Supplementary Files.

M-TEER procedure and echocardiography

All procedures were performed by our local team of interventional cardiologists specialized in M-TEER. A treatment strategy was set out by the interventionalists in concurrence with the interventional imagers for each individual patient. Transesophageal echocardiography (TEE) and fluoroscopy were used for procedural guidance. Details of M-TEER have been described elsewhere (16). M-TEER was performed under general anesthesia using either the MitraClip™ third and fourth generation (NTR, XTR, NT, NTW, XT, XTW) or the PASCAL™ first and second generation (P10, Ace) repair systems. Choice of type and number of devices to be implanted were based on a combination of factors including MR jet width and location, MV leaflet length and MV orifice area. In patients with A-Pd ≥36 mm and leaflet lengths ≥9 mm rather large devices, whereas in pathologies showing broad MR jets wider devices were implanted.

2D and 3D MV imaging were employed for device positioning and leaflet grasping. MV gradients and orifice areas were measured before device positioning as well as before and after device deployment. MR was assessed based on an integrative approach with qualitative and quantitative parameters according to current guidelines (17, 18).

In preprocedural transthoracic echocardiography, standard views (apical 4/3/2-chamber, parasternal long-axis and short-axis, subcostal views) were obtained for evaluation of heart chambers and function (see **Table 1**). Left ventricular (LV) ejection fraction and volumes were calculated using the Simpson's biplane method. Philips EPIQ™ ultrasound system and the X8-2t probe were used for TEE and the X5-1 probe for transthoracic echocardiographic examinations.

Imaging and quantification of the MV apparatus

2D and 3D TEE images obtained during M-TEER procedure were processed offline using a commercially available semi-automatic assessment tool (TOMTEC-ARENA, TOMTEC Imaging Systems, Munich). This tool allows 4D MV modeling and produces measurements of the MV apparatus such as A-Pd, anterolateral-posteromedial diameter (AL-PMd), annular circumference (AC) as well as 2D and 3D annular areas (AA). Application of this tool requires a 3D image of the MV and landmarks to be set within the MV apparatus in two-chamber and three-chamber views using multiple plane reconstruction (MPR). The reference plane was positioned in line with the MV annulus. This enabled placing the landmarks of leaflet insertion at the MV annulus, orientation of the aortic annulus, and coaptation point. Thus, both static and dynamic 4D models of the MV apparatus were generated and all parameters and their numerical values were measured by the software. These models were optimized manually by adjusting annulus and leaflet contours as well as commissural positions in order to provide better accuracy of the 3D model. Adjusting was performed in different MV planes in order to calculate A-Pd and AL-PMd. For measurements after device deployment, the coaptation point (three-chamber view) was set at the intersection of leaflets and device. In case of two devices the MV coaptation point was set within the device closest to the intersection of the A-Pd and AL-PMd. All parameters were measured in the end-systolic phase of the cardiac cycle. To determine changes in mitral annular geometry, measurements were performed before and after device implantation using images from intraprocedural TEE exclusively. Changes in MV annular diameters were measured in 2D using 3D MPR.

Follow-up

Follow-up data were collected during clinical visits or telephone interviews performed by trained study nurses. All patients had scheduled appointments at our hospital every 3 months and if they would not show up for any reason, they were called and data was collected remotely. Follow-up was available for at least 12 months.

Statistical methods

Analysis included evaluation of the whole cohort of patients, as well as a comparison between groups with different levels of relative A-Pd reduction. The median of relative A-Pd reduction was used as cut-off. The validity of this cut-off value (sensitivity and specificity) with regard to the composite endpoint was tested in receiver operating characteristic (ROC) curve. The cut-off value with optimal sensitivity and specificity was calculated using Youden's index. Continuous variables were expressed using mean and standard deviation or median and interquartile range. For paired variables mean change and mean relative change were calculated. Distribution of variables was analyzed graphically using histograms and Q–Q plots. Continuous variables were compared using *t*-test if they showed normal distribution or Wilcoxon test where appropriate. In case of paired variables, the paired Student *t*-test or the Wilcoxon test were utilized. Categorical variables are shown as frequencies and percentages and were compared using Chi-square test or Fisher exact test, where appropriate. Univariate and multivariate binary logistic regression were used to analyze parameters related with A-Pd reduction. Correlation analysis was performed using Pearson and Spearman's correlation coefficients where appropriate. Kaplan–Meier analysis and the log-rank test were used for time-to-event comparison of the composite endpoint of all-cause death or rehospitalization. For outcome analysis and as a primary endpoint the composite endpoint of death and/or rehospitalization for heart failure was used.

For variables significantly differing between patient groups ($p < 0.05$) or possibly impacting the combined endpoint ($p < 0.2$) univariate Cox regression was performed. Multivariate

TABLE 1 Baseline patient characteristics and echocardiography.

	Total ($N = 141$)	A-Pd reduction ≥6.3% ($N = 71$)	A-Pd reduction <6.3% ($N = 70$)	*p*-Value
Age (years)	76.2 ± 9.6	75.5 ± 9.7	77.0 ± 9.6	0.34
BMI (kg/m^2)	26.0 ± 5.3	25.7 ± 5.7	26.2 ± 4.9	0.57
Female, *N* (%)	65 (46.1)	36 (50.7)	29 (41.4)	0.31
Arterial hypertension, *N* (%)	109 (77.3)	57 (80.3)	52 (74.3)	0.43
CAD, *N* (%)	90 (63.8)	43 (60.6)	47 (67.1)	0.48
Prior MI	43 (30.5)	22 (31.0)	21 (30.0)	1.0
Hyperlipidemia, *N* (%)	88 (56.3)	40 (56.3)	48 (68.6)	0.17
Pulmonary hypertension, *N* (%)	52 (36.9)	24 (33.8)	28 (40.0)	0.49
COPD, *N* (%)	14 (9.9)	10 (14.1)	4 (5.7)	0.16
Family disposition, *N* (%)	19 (13.6)	8 (11.4)	11 (15.7)	0.62
AFib, *N* (%)	98 (69.5)	46 (64.8)	52 (74.3)	0.27
CRT-D/P, *N* (%)	15 (10.6)	7 (9.9)	8 (11.4)	0.79
DCM, *N* (%)	37 (26.2)	17 (23.9)	20 (28.6)	0.57
NYHA II, *N* (%)	15 (10.6)	9 (12.7)	6 (8.6)	0.67
NYHA III, *N* (%)	100 (70.9)	50 (70.4)	50 (71.4)	
NYHA IV, *N* (%)	26 (18.4)	12 (16.9)	14 (20.0)	
Euro SCORE II	6.3 ± 6.1	5.2 ± 7.2	6.5 ± 4.8	0.34
STS score	4.9 ± 5.0	4.4 ± 5.3	5.5 ± 4.6	0.2
Troponin T pre (µg/L)	30.0 (18.0–45.0)	29.5 (21.0–45.0)	31.0 (17.0–47.0)	0.94
NT-proBNP pre (pg/ml)	2,953 (1,323–5,969)	3,109 (1,396.5–6,750.5)	2,546 (1,189.0–5,307.0)	0.23
eGFR (ml/min)	46.6 ± 19.1	46.2 ± 19.3	47.03 ± 19.1	0.8
CKD III/IV	107 (76.4)	55 (77.5)	52 (75.4)	0.84
BB, *N* (%)	119 (84.4)	62 (87.3)	57 (81.4)	0.36
ACEI, *N* (%)	34 (24.1)	15 (21.1)	19 (27.1)	0.44
ARB, *N* (%)	43 (30.5)	21 (29.6)	22 (31.4)	0.86
ARNI, *N* (%)	41 (29.1)	19 (26.8)	22 (31.4)	0.58
MRA, *N* (%)	86 (61.0)	40 (45.3)	46 (65.7)	0.3
SGLT-2 inhibitors, *N* (%)	19 (13.5)	5 (7.0)	14 (20.0)	0.03
Loop diuretics, *N* (%)	118 (83.7)	58 (81.7)	60 (85.7)	0.65
Statins, *N* (%)	97 (68.8)	49 (69.0)	48 (68.6)	1.0
ASS, *N* (%)	37 (26.2)	22 (31.0)	15 (21.4)	0.25
NOAC, *N* (%)	87 (61.7)	39 (54.9)	48 (68.6)	0.12
P2Y12 inhibitor, *N* (%)	42 (29.8)	24 (33.8)	18 (25.7)	0.36
LVEF (%)	37.0 ± 13.7	38.0 ± 13.8	36.0 ± 13.7	0.43
LVEDd (mm)	61.0 ± 13.2	60.5 ± 12.6	61.5 ± 14.0	0.69
LVEDV (mm)	174.1 ± 83.5	176.2 ± 91.7	171.9 ± 74.4	0.78
LVESd (mm)	48.0 ± 14.7	47.4 ± 13.3	48.6 ± 16.4	0.69
LVESV (ml)	109.2 ± 73.4	110.7 ± 80.4	107.6 ± 66.5	0.82
LA Diameter (mm)	55.3 ± 10.8	55.2 ± 12.6	55.3 ± 8.6	0.98
TAPSE (mm)	17.9 ± 4.6	17.9 ± 4.5	17.9 ± 4.8	0.97
sPAP (mmHg)	51.1 ± 16.4	51.3 ± 16.0	50.8 ± 16.9	0.88
Average grade of TR	1.9 ± 0.9	1.8 ± 1.0	2.0 ± 0.9	0.32
Severe TR, *N* (%)	41 (29.1)	19 (26.8)	22 (31.4)	0.54
Average Grade of MR pre	3.6 ± 0.5	3.7 ± 0.5	3.5 ± 0.5	**0.02**
MR grade III, *N* (%)	57 (40.4)	22 (31.0)	35 (50.0)	**0.02**
MR grade IV, *N* (%)	84 (59.6)	49 (69.0)	35 (50.0)	
Mean PG (mmHg) pre	2.3 ± 1.5	2.0 ± 1.0	2.7 ± 1.7	**<0.01**
ERO A (cm^2)	0.3 ± 0.1	0.3 ± 0.2	0.3 ± 0.1	0.97
Vena contracta (mm)	8.8 ± 3.0	8.9 ± 3.3	8.6 ± 2.6	0.49
PISA (cm)	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.59
MR RV (ml)	39.2 ± 19.6	39.4 ± 20.8	39.0 ± 18.6	0.92
MV orifice area pre (cm^2)	4.1 ± 1.5	4.1 ± 1.5	4.0 ± 1.6	0.89

Values are shown as frequencies (N) and percentages (%), mean ± standard deviation (SD).
BMI, body mass index (kg/m^2); CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; LBBB, left bundle branch block; CRT, cardiac resynchronization therapy; DCM, dilatative cardiomyopathy; NYHA, New York heart association; STS, society of thoracic surgeons; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; eGFR, estimated glomerular filtration rate; BP, blood pressure; BB, beta blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, AT receptor blocker; ARNI, angiotensin-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT-2, sodium-glucose cotransporter-2; ASS, acetylic salicylic acid; NOAC, novel oral anticoagulant; P2Y12 inhibitor, adenosine diphosphate receptor antagonists; LVEF, left-ventricular ejection fraction; LVEDd, left-ventricular end-diastolic diameter; LVEDV, left-ventricular end-diastolic volume; LVESd, left-ventricular end-systolic diameter; LVESV, left-ventricular end-systolic volume; LA, left atrium; IVSd, septum diameter; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; MR, mitral regurgitation; ERO A, effective regurgitant orifice area; PISA, proximal isovelocity surface area; RV, regurgitant volume.
Bold values indicate significant *p*-values.

TABLE 2 Procedural outcomes.

	Total ($N = 141$)	A-Pd reduction ≥6.3% ($N = 71$)	A-Pd reduction <6.3% ($N = 70$)	p-Value
Average grade of MR post	1.1 ± 0.6	1.1 ± 0.5	1.1 ± 0.6	0.73
MR grade ≤I, N (%)	111 (78.7)	58 (81.7)	53 (75.7)	0.36
MR grade II, N (%)	30 (21.3)	13 (18.3)	17 (24.3)	
Mean PG (mmHg) post	3.1 ± 1.2	3.0 ± 1.2	3.1 ± 1.2	0.77
MV orifice area post (cm^2)	2.7 ± 1.5	2.7 ± 1.3	2.8 ± 1.7	0.78
Number of implanted devices	1.4 ± 0.5	1.4 ± 0.5	1.3 ± 0.5	0.33
Device type				
NTR/NT/NTW, N (%)	43 (30.5)	24 (33.8)	19 (27.1)	0.17
XTR/XT/XTW, N (%)	25 (17.7)	16 (22.5)	9 (12.9)	
PASCAL P10, N (%)	33 (23.4)	16 (22.5)	17 (24.3)	
PASCAL Ace, N (%)	40 (28.4)	15 (21.1)	25 (35.7)	

Values are shown as frequencies (N) and percentages (%) or mean ± standard deviation (SD).
MR, mitral regurgitation; MV, mitral valve, PG, pressure gradient.

Cox regression included all variables that showed potential influence in the univariate regression analysis ($p < 0.2$). To ensure model stability, collinearity was tested using Spearman's and Pearson's correlation coefficients. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS, IBM Statistics, Versions 28 and 29 software packages.

Results

Patient characteristics and annular change in the overall cohort

In the overall cohort, average patient age was 76.2 ± 9.6 years (see Table 1). The majority (59.6%) of patients suffered from severe (IV) FMR (see Table 1). Optimal MR reduction (MR ≤ I) was achieved in 78.7% of patients (see Table 2). Risk of procedural mortality as defined by the Society of Thoracic Surgeons and EUROScoreII was 4.9% ± 5.0% and 6.3% ± 6.1%, respectively. Technical success was achieved in all patients. An average LV ejection fraction of 37.0% ± 13.7% was observed (see Table 1). Regarding the overall cohort, M-TEER reduced A-Pd (−6.2% ± 9.5%, $p < 0.01$) as well as 2D (−1.8% ± 13.1%, $p < 0.01$) and 3D (−2.7% ± 13.7%, $p = 0.26$) MV AA (see Table 3). AL-PMd increased by 3.7% ± 8.9% ($p < 0.01$).

For outcome analysis of MV annular change, patients were grouped according to the composite endpoint rehospitalization for heart failure or all-cause mortality one year after M-TEER (see Supplementary Table S1). Follow-up data were available for all included patients. There was no difference in preprocedural A-Pd (4.0 cm ± 0.5 cm vs. 4.1 cm ± 0.6 cm, $p = 0.22$) nor in relative (%) A-Pd change (−6.3 ± 10.1 vs. −5.3% ± 6.5%, $p = 0.64$) between these groups and preprocedural (3.6 ± 0.5 vs. 3.7 ± 0.5, $p = 0.13$) as well as postprocedural (1.1 ± 0.5 vs. 1.2 ± 0.7, $p = 0.57$) MR severity was similar. However, annular size reduction measured as reduction of AA was only observed in patients who did not reach the composite endpoint (2D AA: −2.7% ± 12.4% vs. 3.1% ± 15.4%, $p = 0.05$; 3D AA: −3.6% ± 13.3% vs. 1.9% ± 15.3%, $p = 0.08$). Similarly, paired testing showed that significant annular change occurred only in patients not reaching the composite endpoint [p(pre-post) 2D AA: < 0.01 vs. 0.47; 3D: < 0.01 vs. 0.84]. Moreover, further analysis revealed a strong correlation between %A-Pd reduction with %2D and %3D AA reduction ($r = 0.6$, $p < 0.01$; $r = 0.65$, $p < 0.01$; see Table 4). To corroborate these interesting findings, we divided the overall cohort by the median of %A-Pd reduction into one group with extensive and another group showing less extensive A-Pd reduction.

Annular change in patients with extensive A-Pd reduction

Median A-Pd reduction was found to be −6.3% in the overall cohort (interquartile range −1.5% to −12.0%). Accordingly, 71 patients with A-Pd reduction ≥6.3% (extensive) were compared to 70 patients showing <6.3% (less extensive) A-Pd reduction. There were no significant differences regarding baseline characteristics such as age ($p = 0.34$), female gender ($p = 0.31$) or comorbidities like atrial fibrillation ($p = 0.27$) and chronic kidney disease stage III/IV ($p = 0.84$) between both groups (see Table 1). Society of Thoracic Surgeons score (4.4 ± 5.3 vs. 5.5 ± 4.6, $p = 0.2$) and EUROScoreII (5.2 ± 7.2 vs. 6.5 ± 4.8, $p = 0.34$) as well as NYHA class (NYHA III: 70.4% vs. 71.4%, $p = 0.67$) as a surrogate for symptom burden and NT-proBNP ($p = 0.23$) as a biomarker for heart failure were also found to be similar. Except for more frequent use of SGLT2 inhibitors in patients with less extensive A-Pd reduction (7% vs. 20%, $p = 0.03$), there were no significant differences regarding heart failure medication (see Table 1). Preprocedural MR was found to be more severe in patients with extensive A-Pd reduction (MR grade IV: 69.0% vs. 50.0%, $p = 0.02$), while preprocedural mean MV pressure gradients were significantly lower (2.0 ± 1.0 vs. 2.7 ± 1.7 mmHg, $p < 0.01$) in this group (see Table 1). However, no differences were observed regarding postprocedural MR severity (1.1 ± 0.5 vs. 1.1 ± 0.6, $p =$ 0.73), optimal MR reduction (residual MR ≤ I: 81.7% vs. 75.4%, $p = 0.36$) and postprocedural mean MV gradients (3.0 ± 1.2 vs. 3.1 ± 1.2 mmHg, $p = 0.77$). Baseline LV end-diastolic volume

TABLE 3 4D MV analysis according to the median relative change in A-Pd reduction.

	Total ($N = 141$)	A-Pd reduction ≥6.3% ($N = 71$)	A-Pd reduction <6.3% ($N = 70$)	p-Value
A-Pd pre (cm)	4.0 ± 0.5	4.0 ± 0.5	4.0 ± 0.5	0.84
A-Pd post (cm)	3.8 ± 0.6	3.5 ± 0.5	4.00 ± 0.5	**<0.01**
mean relative change (%)	−6.2 ± 9.5	−13.0 ± 6.1	0.8 ± 7.1	**<0.01**
***p* (pre-post)**	**<0.01**	**<0.01**	**<0.01**	
AL-PMd pre (cm)	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	0.56
AL-PMd post (cm)	4.3 ± 0.5	4.2 ± 0.5	4.3 ± 0.5	0.18
mean relative change (%)	3.7 ± 8.9	2.6 ± 7.3	4.9 ± 10.2	0.13
***p* (pre-post)**	**<0.01**	**<0.01**	**<0.01**	
Nonplanar angle pre (°)	152.0 ± 11.6	152.7 ± 11.2	151.3 ± 12.1	0.47
Nonplanar angle post (°)	149.7 ± 13.6	150.7 ± 14.8	150.7 ± 12.4	0.4
mean relative change (%)	−1.2 ± 9.5	−1.2 ± 9.5	−1.3 ± 8.8	0.84
***p* (pre-post)**	0.055	0.26	**<0.01**	
AC pre (cm)	13.5 ± 1.4	13.4 ± 1.4	13.5 ± 1.4	0.53
AC post (cm)	13.3 ± 1.5	12.9 ± 1.5	13.8 ± 1.5	**<0.01**
mean relative change (%)	−0.9 ± 6.4	−3.8 ± 4.9	2.0 ± 6.4	**<0.01**
***p* (pre-post)**	0.061	**<0.01**	**<0.01**	
2D AA pre (cm^2)	13.0 ± 2.7	12.8 ± 2.7	13.1 ± 2.8	0.56
2D AA post (cm^2)	12.7 ± 3.0	11.8 ± 2.7	13.6 ± 3.0	**<0.01**
mean relative change (%)	−1.8 ± 13.1	−7.9 ± 8.9	4.5 ± 13.7	**<0.01**
***p* (pre-post)**	**0.049**	**<0.01**	**<0.01**	
3D AA pre (cm^2)	13.6 ± 3.1	13.6 ± 3.3	13.6 ± 2.8	0.92
3D AA post (cm^2)	13.1 ± 3.1	12.2 ± 2.8	14.1 ± 3.0	**<0.01**
mean relative change (%)	−2.7 ± 13.7	−9.4 ± 10.3	4.2 ± 13.4	**<0.01**
***p* (pre-post)**	0.26	**<0.01**	**<0.01**	
Tenting volume pre (cm^3)	4.8 ± 2.6	4.5 ± 2.5	5.2 ± 2.7	0.15
Tenting volume post (cm^3)	4.7 ± 2.6	4.0 ± 2.2	5.3 ± 2.6	**<0.01**
mean relative change (%)	2.1 ± 37.2	−8.1 ± 36.9	12.1 ± 34.9	**<0.01**
***p* (pre-post)**	0.27	**0.01**	**<0.01**	
Tenting area pre (cm^2)	2.7 ± 1.2	2.6 ± 1.2	2.8 ± 1.3	0.3
Tenting area post (cm^2)	2.4 ± 1.1	2.1 ± 0.9	2.7 ± 1.1	**<0.01**
mean relative change (%)	−1.0 ± 58.8	−8.0 ± 71.4	6.0 ± 41.9	0.16
***p* (pre-post)**	**<0.01**	**<0.01**	0.44	
Annular height pre (cm)	1.0 ± 1.3	1.1 ± 1.8	1.0 ± 0.3	0.47
Annular height post (cm)	0.9 ± 0.3	0.8 ± 0.3	0.9 ± 0.3	**<0.01**
mean relative change (%)	−4.1 ± 29.3	−9.5 ± 31.6	1.3 ± 25.9	**0.03**
***p* (pre-post)**	0.11	0.14	0.16	

AA, Annular area; AC, Annular circumference; AL-PMd, anterolateral-posteromedial diameter; A-Pd, Anterior-posterior diameter; MV, mitral valve.
Values are shown as mean ± standard deviation (SD); p(pre-post) refers to testing for paired variables.
Bold numbers indicate significant p-values.

TABLE 4 Correlation analysis for mitral valve annular dimensions.

	Mean % change APd	Mean % change AL-PMd	Mean % change AA 2D	Mean % change AA 3D	Mean % change AC
% Change A-Pd		0.053 (0.54)	0.6 (**<0.01**)	0.65 (**<0.01**)	0.6 (**<0.01**)
% Change AL-PMd			0.74 (**<0.01**)	0.67 (**<0.01**)	0.56 (**<0.01**)
% Change AA 2D				0.97 (**<0.01**)	0.88 (**<0.01**)
% Change AA 3D					0.94 (**<0.01**)
% Change Ac					

Bold numbers indicate significant p-values.

(176.1 ± 91.7 vs. 171.9 ± 74.4 ml, $p = 0.78$), left atrial diameter (55.2 ± 12.6 vs. 55.3 ± 8.6 mm, $p = 0.98$) and LV ejection fraction were comparable (38.0 ± 13.8 vs. 36.0% ± 13.7%, $p = 0.43$). Single and multiple device implantations were equally prevalent in both groups (single device: 57.7% vs. 65.7%, $p = 0.39$).

Pre- and postprocedural measurements of the MV annulus and corresponding relative changes according to the extent of A-Pd reduction are depicted in Table 3. A histogram of A-Pd change is shown in Supplementary Figure S1. Average relative A-Pd reduction was −13.0% ± 6.1% in patients with extensive compared to 0.8% ± 7.1% in patients with less extensive A-Pd reduction, respectively ($p < 0.01$). At baseline, both groups showed similar A-Pd (4.0 cm ± 0.5 cm vs. 4.0 cm ± 0.5 cm, $p = 0.84$), AL-PMd (4.1 cm ± 0.5 cm vs. 4.1 cm ± 0.5 cm, $p = 0.56$), AC (13.4 cm ±

1.4 cm vs. 13.5 cm ± 1.4 cm, $p = 0.53$) as well as 2D AA (12.8 ± 2.7 vs. 13.1 ± 2.8 cm^2, $p = 0.56$) and 3D AA (13.6 ± 3.3 vs. 13.6 ± 2.8 cm^2, $p = 0.92$). After M-TEER, these parameters significantly changed in both groups (see Table 3), however, inverse alterations in annular geometry were observed according to the extent of A-Pd reduction.

Patients with extensive A-Pd reduction showed a decrease in relative change of AC, 2D and 3D AA, whereas these parameters increased in patients with less extensive A-Pd reduction (AC: −3.8% ± 4.9% vs. 2.0% ± 6.4%, $p < 0.01$; 2D AA: −7.9% ± 8.9% vs. 4.5% ± 13.7%, $p < 0.01$; 3D AA: −9.4% ± 10.3% vs. 4.2% ± 13.4%, $p < 0.01$; see also Table 3). Consequently, the decrease in annular sphericity index (ratio of A-Pd/AL-PMd) was more pronounced in patients with extensive A-Pd reduction (−13.8 ± 8.8 vs. −2.4 ± 13.4, $p < 0.01$) and postprocedural comparison of annular dimensions confirms significantly smaller AC (12.9 cm ± 1.5 cm vs. 13.8 cm ± 1.5 cm, $p < 0.01$), 2D AA (11.8 ± 2.7 vs. 13.6 ± 3.0 cm^2, $p < 0.01$) and 3D AA (12.2 ± 2.8 vs. 14.1 ± 3.0 cm^2, $p < 0.01$) in this group of patients. AL-PMd increased in both patient groups with a tendency toward greater increase in patients with extensive A-Pd reduction (4.9% ± 10.2% vs. 2.6% ± 7.3%, $p = 0.13$) and the postprocedural annular sphericity index was significantly smaller in these patients (0.94 ± 0.1 vs. 0.83 ± 0.1, $p < 0.01$).

A strong and significant correlation between mean %A-Pd reduction and reduction of mean %AC ($r = 0.6$, $p < 0.01$), %2D AA ($r = 0.6$, $p < 0.01$) and %3D AA ($r = 0.65$, $p < 0.01$) was also found in the study population (see also Table 4). Preprocedural tenting volumes (4.5 ± 2.5 vs. 5.2 ± 2.7 cm^3, $p = 0.15$) and areas (2.6 ± 1.2 vs. 2.8 ± 1.3 cm^2, $p = 0.3$) tended to be smaller in patients with extensive A-Pd reduction. This corresponds well with a significantly smaller postprocedural tenting area (2.1 ± 0.9 vs. 2.7 ± 1.1 cm^2, $p < 0.01$) and volume (4.0 ± 2.2 vs. 5.3 ± 2.6 cm^3, $p < 0.01$) in these patients. Thus, a significant correlation was also found between %A-Pd reduction and postprocedural tenting area ($r = 0.4$, $p < 0.01$) and volume ($r = 0.32$, $p < 0.01$). Based on the notion that greater preprocedural tenting might explain A-Pd reduction these factors were further tested in logistic regression (see Table 5 and Suplemmental Table 2). Yet neither preprocedural tenting area (OR: 0.86, 95% CI: 0.65–1.14, $p = 0.3$) nor volume (OR: 0.91, 95% CI: 0.8–1.04, $p = 0.15$) were found to be predictors of extensive A-Pd reduction. However, in univariate analysis preprocedural MR severity increased (OR: 2.3, 95% CI: 1.12–4.3, $p = 0.02$), while mean MV pressure gradient decreased the likelihood for extensive A-Pd reduction (OR: 0.64, 95% CI: 0.45–0.91, $p = 0.01$). In multivariate logistic regression, mean MV pressure gradient remained the only significant predictor of extensive A-Pd reduction (OR: 0.65, 95% CI: 0.45–0.93, $p = 0.02$), whereas preprocedural MR severity showed a non-significant tendency (OR: 2.02, 95% CI: 0.94–4.33, $p = 0.07$).

Outcomes in patients with extensive A-Pd reduction

Outcomes were analyzed using a composite endpoint of rehospitalization and all-cause mortality within the first year after M-TEER. Mean time to follow-up/combined endpoint was 320.8 days (95% CI: 302.6–339.0 days) (Median: 365.0 days, IQR: 365.0–365.0 days). Kaplan–Meier analysis revealed significantly better outcome in patients with greater A-Pd reduction ($p = 0.039$, see Grahical Abstract, Figure 3). The composite endpoint

TABLE 5 Cox regression for possible predictors of the combined endpoint of death or rehospitalization (further see Supplemental Table S2).

	Univariate			Multivariate		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
NYHA class	2.56	1.19–5.54	**0.02**	1.32	0.51	**0.57**
NT-proBNP	1.07	1.02–1.13	**0.01**	1.08	1.02–1.14	**0.01**
A-Pd reduction ≥6.3%	0.41	0.17–0.98	**0.046**	0.31	0.11–0.89	**0.03**
Mean % change A-Pd	1.01	0.97–1.05	0.63			
A-Pd post	1.6	0.82–3.16	0.17			
Mean % change AC	1.04	0.98–1.11	0.2			
AC post	1.17	0.89–1.52	0.26			
Mean % change AA 2D	1.03	1.002–1.06	**0.04**			
AA 2D post	1.12	0.98–1.28	0.1			
Mean % change AA 3D	1.03	0.99–1.06	0.06			
AA 3D post	1.11	0.97–1.26	0.13			
Annular height post	0.4	0.07–2.27	0.3			
Tenting area post	1.18	0.8–1.75	0.41			
Tenting volume post	1.08	0.93–1.27	0.32			
Grade of MR pre	2.05	0.81–5.19	0.13			
mPG pre	1.03	0.76–1.4	0.86			
SGLT-2i	0.57	0.14–2.45	0.45			
A-Pd reduction ≥6.3% (adjusted for grade of preprocedural MR)				0.35	0.14–0.85	**0.02**
A-Pd reduction >6.3% (adjusted for grade of preprocedural MR, NT-proBNP and NYHA class)				0.29	0.10–0.83	**0.02**

NYHA class, New York Heart association class; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; AA, Annular area; AC, Annular circumference; AL-PMd, anterolateral-posteromedial diameter; A-Pd, anterior-posterior diameter; MR, mitral regurgitation; mPG, mean pressure gradient; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.
Each variable is shown with its odds ratio (OR), respective 95% confidence interval (CI) as well as *p*-value.
Bold numbers indicate significant *p*-values.

occurred significantly more often in the group with less extensive A-Pd reduction (22.9% vs. 9.9%, $p = 0.037$). Univariate Cox regression analysis (see **Table 5** and **Supplementary Table S2**) demonstrated that preprocedural MR severity (HR: 2.05, 95% CI: 0.81–5.19, $p = 0.13$), mean MV pressure gradient (HR: 1.03, 95% CI: 0.76–1.4, $p = 0.86$) and SGLT-2 inhibitors (HR: 0.57, 95% CI: 0.14–2.45, $p = 0.45$) did not predict the composite endpoint. After adjustment for preprocedural MR severity in multivariate Cox regression, the effect of A-Pd reduction on the composite endpoint remained (HR: 0.35, 95% CI: 0.14–0.85, $p = 0.02$). When testing A-Pd reduction ≥6.3% in multivariate Cox regression together with NT-proBNP and NYHA class, extensive A-Pd reduction also remained a significant predictor of the composite endpoint (HR: 0.31; 95% CI: 0.11–0.89; $p = 0.03$).

To perform a sensitivity analysis regarding the cut-off for relevant A-Pd reduction the coordinates of a receiver operating characteristic (ROC) curve and its respective Youden's index were used. Based upon these calculations, the optimal cut-off value for A-Pd change as a predictor of the composite 1-year endpoint was −6.3% (sensitivity: 0.70, specificity: 0.55).

Annular change in relevant subgroups

In the overall study cohort, 24 patients were classified as having isolated atrial FMR. The remaining 117 patients showed typical signs of ventricular FMR (see **Supplementary Table S3**). Both atrial as well as ventricular FMR patients had similar preprocedural AP-d (4.0 cm ± 0.5 cm vs. 4.0 cm ± 0.5 cm, $p = 0.83$) and relative annular change did neither differ regarding A-Pd ($p = 0.25$) nor AL-PM-d ($p = 0.67$), AC ($p = 0.94$) and 2D AA ($p = 0.75$) as well as 3D AA ($p = 0.68$).

In **Supplementary Table S4**, a comparison of annular geometry and M-TEER induced changes in patients with optimal (MR ≤ I, $N = 111$) and non-optimal (MR ≥ II, $N = 30$) MR results is shown. Patients with optimal MR results showed a non-significant tendency toward greater %AP-d reduction ($p = 0.2$), borderline significance in 2D AA change ($p = 0.07$) and a significant reduction of 3D AA ($p = 0.02$).

Device comparison regarding A-Pd reduction was performed for MitraClip™ vs. PASCAL™ as well as third vs. fourth generation MitraClip™. Significantly greater A-Pd reduction was achieved using the MitraClip™ compared to PASCAL™ (−8.6% ± 9.8% vs. −3.9% ± 8.8%, $p < 0.01$). A comparison of third and fourth generation MitraClip™ did not reveal any relevant differences between devices with or without the option of independent leaflet capture (−8.2% ± 10.1% vs. −8.8% ± 9.8%, $p = 0.83$).

To elucidate the possible influence of a larger spacer as it is a special feature of the original PASCAL™ platform, we also compared A-Pd reduction between the PASCAL™ P10 and other devices (single device procedures). However, no significant differences regarding A-Pd reduction were observed at least in this relatively small group of patients (−5.0% ± 9.0% vs. −6.5% ± 10.5%, $p = 0.54$).

Finally, 18.1% (25/141) of patients in the overall cohort experienced an increase in A-Pd (see also **Supplementary Figure S1 and Table S5**). These patients also showed a tendency toward greater increase in AL-PMd (3.3% vs. 5.7%, $p = 0.23$) and a significant increase in 2D and 3D AA (2D: 10.0% ± 16.9%, $p < 0.01$; 3D: 10.2% ± 16.8%, $p < 0.01$). Preprocedural annular size and A-Pd did not differ compared to patients with decreasing A-Pd after M-TEER. Notably, mean mitral gradient was significantly greater before ($p < 0.01$) and after device implantation ($p = 0.02$). Additional analysis of anatomical and procedural details in this group of patients revealed frequent commissural device positioning, pronounced and atypical device clocking, incongruity between leaflet and device length as well as a more frequent utilization of shorter MitraClip™ devices (NTR/NT/NTW) and the PASCAL™ Ace.

Discussion

Our study investigated changes of MV annular geometry during M-TEER and its relationship with 1-year outcomes in FMR patients. It confirmed results of previous studies regarding A-Pd reduction and showed some novel and important findings regarding the acute annular remodeling after M-TEER as well as its impact on outcome of patients with significant FMR. To the best of our knowledge, this is the largest study investigating the impact of A-Pd reduction in FMR patients using comprehensive 3D TEE analysis so far. The main findings of our study can be summarized as follows:

- Extensive A-Pd reduction is associated with significant reductions in AA (2D and 3D), while these parameters increased in patients with less extensive A-Pd reduction.
- Changes in MV geometry, and particularly A-Pd reduction were related with indirect MV annuloplasty.
- M-TEER induced indirect annuloplasty is associated with better clinical outcome represented by a composite endpoint of death or rehospitalization for heart failure.
- Therefore, our study suggests that M-TEER induces changes well beyond leaflet approximation and MR reduction and emphasizes the positive impact of A-Pd reduction on outcome in FMR patients.

The focus of previous studies investigating the effects of M-TEER on MV annular geometry has been directed toward differences in patients with optimal (residual MR ≤ I) and suboptimal/non-optimal (residual MR ≥ II) results (9, 14, 19). Moreover, suboptimal MR reduction was found to be an independent predictor of adverse outcome (14, 19). Obtaining optimal MR reduction is reasonable, however, understanding M-TEER induced changes in annular geometry and their importance for successful treatment go beyond residual MR severity. As shown in our study cohort, extensive A-Pd reduction is associated with favorable outcome independent of residual MR severity. Moreover, comparison of M-TEER induced annular remodeling in patients with optimal and non-optimal MR results emphasizes the importance of indirect annuloplasty in addition to MR reduction.

During M-TEER, one or more devices are usually positioned within the central MV segment between the anterior and

posterior leaflet and consequently exert tensile forces on the MV annulus predominantly in anterior-posterior direction. Several studies also using 3D TEE echocardiography were able to show A-Pd reduction during M-TEER (8–12, 14, 15, 20). However, some of these studies did not distinguish between FMR and DMR patients, but provided cumulative results for both entities (9, 13). Other authors selectively included FMR patients (20) or observed A-Pd reduction only among FMR patients in their analyses (8, 11, 12). Few studies reported significant A-Pd reduction in both etiologies (10) with more pronounced A-Pd reduction among FMR patients (15). In terms of additional annular parameters, many investigators similarly reported a decrease in AA (2D or 3D) aside from A-Pd reduction (8, 9, 11, 13, 20), while others did not detect a reduction in AC or AA (14, 20). Based on the number of studies, stronger evidence is found for reduction of AA and AC in FMR (8, 11, 15) compared to DMR (15). Our investigation confirmed M-TEER to reduce A-Pd and extensive A-Pd reduction to be associated with decreased AC and AA. Moreover, we were able to show contrary effects associated with less extensive A-Pd reduction. To our knowledge, no other study investigating M-TEER-induced changes in annular geometry has yet made a similar observation.

The concept of indirect annuloplasty through edge-to-edge repair has already been demonstrated in the earlier days of M-TEER (11). To a certain extent, M-TEER may thus mimic surgical MV repair, where direct annuloplasty through ring implantation is a standard procedure and, interestingly, edge-to-edge repair using the Alfieri stitch was reported to show better outcome when combined with annuloplasty (21, 22). Our study demonstrated M-TEER to be able to induce indirect annuloplasty through A-Pd reduction. However, our findings also suggest that reshaping of the MV annulus requires A-Pd reduction beyond a certain threshold.

Nevertheless, when summarizing the observed changes in our study, no restoration of the saddle-shaped form of the MV annulus occurred. A significant, yet not differing increase in AL-PMd was observed between FMR patients with extensive and less extensive A-Pd reduction. Annular sphericity index significantly decreased when extensive A-Pd reduction occurred. Non-planarity decreased non-significantly in the overall cohort ($-1.2\% \pm 9.5\%$, p\{pre-post\} =0.055), however, neither preprocedural ($p = 0.47$)/postprocedural ($p = 0.4$) absolute values nor change in non-planarity ($p = 0.84$) differed between patient groups. On the other hand, annular height was reduced significantly greater in patients with extensive A-Pd reduction. Our cohort exclusively consists of FMR patients who typically show some degree of tenting, which is normally reduced after M-TEER (9, 11, 21). In this investigation, tenting was reduced significantly greater in patients with extensive A-Pd reduction (relative tenting volume change: $-8.1\% \pm 36.9\%$ vs. $12.12\% \pm 34.9\%$, $p < 0.01$). This seems to come at the expense of saddle-shape restoration as the annulus flattens while being reduced in its overall size (AC, 2D and 3D AA). Given that patients with extensive A-Pd reduction showed greater preprocedural MR severity, yet had similar residual MR after M-TEER compared to those with less A-Pd reduction, it seems as if interventionalists automatically aim at greater A-Pd reduction in the presence of more severe MR. However, this is difficult to prove retrospectively and in multivariate logistic regression for predictors of A-Pd reduction preprocedural MR severity narrowly failed to be a significant predictor (OR: 2.02, 95% CI: 0.94–4.33, $p = 0.07$). MV pressure gradient on the other hand, decreased the likelihood of extensive A-Pd reduction suggesting a possible risk of M-TEER induced MV stenosis (OR: 0.65, 95% CI: 0.45–0.93, $p = 0.02$).

Subgroup analysis of patients with atrial and ventricular FMR showed similar annular size reduction. Tenting was far more pronounced in ventricular FMR, which is inherent to its pathophysiological mechanism. Parameters of annular size and change showed little difference between these etiologies probably due to secondary annular enlargement in ventricular FMR. However, as the number of patients with atrial FMR in our study cohort was small further investigation of differences in atrial and ventricular FMR are warranted.

When investigating device specific differences, the MitraClip™ facilitated significantly greater A-Pd reduction ($p < 0.01$), which could be explained by its stronger mechanical force opposed to the softer and spring-based design of the PASCAL™ platform. Results from a randomized head-to-head comparison between the two M-TEER systems in FMR patients provided by the CLASP IIF trial will further elucidate such differences. No relevant differences were observed between third and fourth generation MitraClip™ ($p = 0.83$) implying that independent leaflet capture is of minor importance particularly in FMR.

The paradoxical increase in A-Pd after M-TEER observed in 25 patients was associated with several anatomical as well as procedural characteristics and their combination. Commissural device positions as well as pronounced and atypical device clocking might induce converse alterations in annular geometry. The use of shorter devices in relation to the respective leaflet length can correct MR. However, it is likely that this mismatch impedes indirect annuloplasty or even causes increase in A-Pd by stretching the MV annulus when LV volume and pressure raises. Finally, utilization of the elastic PASCAL™ design presumably aggravates these conditions.

Implications of A-Pd reduction for clinical outcome

Few studies have investigated A-Pd reduction in association with patient outcome so far. In a cohort of mixed etiologies, Patzelt et al. observed significantly smaller A-Pd in patients with less residual MR at follow-up and an inverse correlation between these parameters (15). Schueler et al. investigated 111 consecutive patients (71 with FMR) and found acute A-Pd reduction ≥6.4% to significantly predict clinical response (8). In a second cohort, their working group was later able to confirm the finding of favorable clinical outcome in relation to sustained A-Pd reduction ≥6.4% (12). Our study is in concordance with these results. Relative A-Pd reduction above the median of 6.3% was found to significantly predict outcomes after adjusting for preprocedural MR severity in multivariate Cox regression (HR: 0.35, 95% CI: 0.14–0.85, $p = 0.02$) as well as after adjusting in multivariate regression for other outcome related factors such as NT-proBNP, NYHA class and MR

severity (HR: 0.31; 95% CI: 0.11–0.89; $p = 0.03$). A-Pd reduction correlated with annular size reduction (AC, 2D and 3D AA) in our study, which implicates that indirect annuloplasty might be responsible for the observed differences in outcome. Eventually, Kreidel et al. demonstrated persistent annular dilation after device implantation in patients with suboptimal results (residual MR ≥ II), which correlated with higher 1-year mortality (19). In summary, there is growing evidence for the importance of indirect annuloplasty with M-TEER especially in FMR, which is reassured by our group's findings.

Strengths and limitations

This investigation is a single-center observational study with a medium-size cohort. Only patients with FMR were included and therefore, results cannot be applied to all patients with MR, particularly not to those with DMR. At the same time, this represents an important strength of our study as we investigated only one entity and avoided possible confounding factors related to DMR. The cut-off value for A-Pd reduction that we used in our analysis was calculated based on our patient cohort and may vary in different populations. However, the number of included subjects is large enough to allow statistical evaluation. Moreover, the median of A-Pd reduction in our patient cohort is similar to previous investigations (8, 12). Finally, we did not perform follow-up TEE reevaluating the MV annulus for durability of the observed acute changes which limits long-term interpretation. Especially, volume status may influence annular geometry over time and was not investigated in this study.

In our study A-Pd change ≥6.3% (binary variable) was a significant predictor of the composite endpoint, while % A-Pd change as a continuous variable did not remain a significant predictor. Hence, the use of a binary variable might possibly overestimate the impact of AP diameter change.

Prospective and multicenter studies at best need to further evaluate the role of A-Pd reduction and indirect annuloplasty in M-TEER.

Conclusion

Our findings indicate that effects of M-TEER in FMR are not limited to the reduction of MR severity, but further entail an impact on annular geometry. Moreover, A-Pd reduction, which mediates indirect annuloplasty, significantly impacts mid-term clinical outcome independent of residual MR. Extensive A-Pd reduction is the prerequisite for annular remodeling in patients with FMR treated with M-TEER. Therefore, periprocedural imaging and assessment should also include annular dimensions and remodeling besides standard evaluation of residual MR. Future longitudinal multicenter studies with larger number of participants and longer follow-up will determine the importance of comprehensive 3D periprocedural assessment of MV annular geometry and its alterations on outcome in patients with different types of MR (FMR vs. DMR).

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission der Universität Ulm. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design: MP, SM, LS, WR. Manuscript drafting: MP, LS, MT. Critical manuscript revision: all authors. Acquisition of data: MP, MJ, MT, MG. Analysis and interpretation of data: MP, LS, WR, DF, SM. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1143702/full#supplementary-material.

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Case report: Transcatheter tricuspid valve intervention using K-Clip™ system after prior Kay's annuloplasty

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The K-Clip™ system is emerging as an alternative to correct tricuspid regurgitation (TR) for patients with high surgical risk. However, patients with recurrent severe tricuspid regurgitation after prior Kay's annuloplasty are not generally deemed to be candidates for K-Clip™ implantation. Herein, we report a case of a 63-year-old woman with recurrent symptomatic torrential tricuspid regurgitation 5 years after double valve replacement with Kay's annuloplasty of the tricuspid valve. The K-Clip™ was successfully implanted, and the severity of tricuspid regurgitation and dimensions of tricuspid annulus achieved significant reduction. In conclusion, K-Clip™ can still be feasible and effective for patients with prior Kay's annuloplasty. However, indications become more rigorous, and evaluation should be more comprehensive.

KEYWORDS

tricuspid regurgitation, K-Clip™, annuloplasty, transcatheter, tricuspid valve

Introduction

Tricuspid regurgitation (TR) is divided into two stages, primary TR and functional TR, the latter accounting for more than 90%. Most commonly, functional TR results from tricuspid annulus (TA) dilation due to left-sided heart disease and pulmonary vascular disease (1). A current guideline states that surgery is recommended in symptomatic patients with severe functional TR in the absence of severe ventricular dysfunction and pulmonary hypertension (2). However, isolated tricuspid valve surgery has been seldom performed due to its reported high mortality rates (3). In recent years, various transcatheter tricuspid valve intervention (TTVI) devices are emerging as an alternative for patients with prohibitive surgical risk (4), among which the K-Clip™ system (**Figure 1**) is designed to mimic the Kay's annuloplasty and achieve posterior annular reduction and bicuspidization of the tricuspid valve (5).

Generally, patients with recurrent severe functional TR after prior Kay's annuloplasty are not deemed to be candidates for K-Clip™ implantation. Nevertheless, based on the experience of more than 40 cases of K-Clip™ implantation in our institution, we believe that it can also achieve acceptable outcomes in this specific population. Herein, we introduced a typical case and the process of diagnosis and treatment.

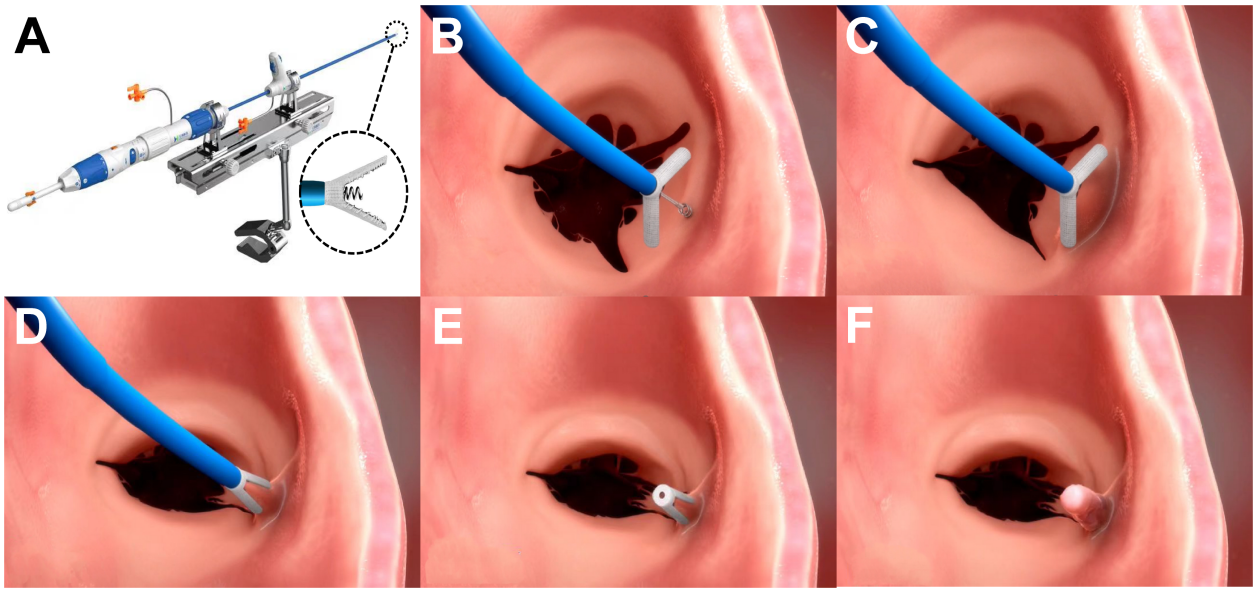

FIGURE 1
The K-Clip^{TM} system and the main steps of implantation. (**A**) Showing the delivery system of K-Clip^{TM}, and the clip consists of clamp arms and the tapping screw-shaped anchor. (**B**) Open the clamp arms and insert the tapping screw-shaped anchor to the middle of posterior tricuspid annulus. (**C**) Pull back the annular tissue into the clip. (**D**) Clamp the clip. (**E**) Release the clip and withdraw the guidewire. (**F**) Showing endothelialization of the implanted clip. Images provided by Huihe Medical Technology with permission.

Case presentation

The patient was a 63-year-old woman with a history of rheumatic heart disease, involving moderate mitral stenosis with regurgitation, moderate aortic stenosis with regurgitation, and mild TR. Five years ago, she had undergone double valve replacement combined with Kay's annuloplasty of the tricuspid valve.

The patient complained of worsening chest tightness and peripheral edema in recent half a year. Upon admission, the physical examination revealed significant edema of both lower extremities, arrhythmia, and moderate murmur in the auscultation area of the tricuspid valve. The electrocardiogram showed atrial fibrillation. The transthoracic echocardiography suggested a normal function of double mechanical prostheses and torrential functional TR. Anticoagulation was achieved by an appropriate dose of warfarin, and the international normalized ratio was 2.32. The patient was evaluated as being at high risk for redo surgical tricuspid annuloplasty and was considered for TTVI using the K-Clip^{TM} system (Huihe Medical Technology, Shanghai, China).

The patient was horizontally positioned and under general anesthesia. A 16-mm-clip arm would be preprocudurally applied according to the comprehensive evaluation of the patient's TA. The K-Clip^{TM} procedure was performed with the real-time monitor of fluoroscopy and transesophageal echocardiography (TEE). The TEE confirmed the torrential TR (vena contracta width of 0.71 cm), as well as that the distance between the target sites for clip implantation and the knot of the prior Kay's procedure (**Figure 2A**) was approximately 18–20 mm, which was enough space for a 16 mm clip to clamp the posterior annular tissue. The K-Clip^{TM} system was percutaneously inserted via the right jugular vein and steered toward the posterior TA. Then, the tapping screw-shaped anchor was inserted through the target location, and the clip was tangentially opened and oriented to the annulus, slowly pulled back with the surrounding TA tissue, and then clamped the clip, achieving tissue plication and re-bicuspidization (**Figure 2B**). A significant reduction in the TR grade (torrential to mild, vena contracta width of 0.25 cm) and TA dimensions was immediately observed (**Figure 2C**). Throughout the whole procedure, it was carefully confirmed that the original knot was not loose and meanwhile the right coronary artery flow was not interfered by the manipulation. Subsequently, the patient had an uneventful recovery and was discharged 2 days after the procedure. After 3 months of follow-up, repeated transthoracic echocardiography demonstrated mild TR (**Figure 3A**) and the secure position of the device (**Figure 3B**). Additionally, the patient reported that the previous symptoms were eliminated.

Discussion

Isolated tricuspid valve surgery should be considered in symptomatic patients with severe functional TR (with or without prior left-sided valve surgery) who have right ventricular dilation and preserved ventricular function (2). Nowadays, surgical tricuspid valve repair using an annuloplasty ring to reduce the TA dimension under cardiopulmonary bypass remains the mainstream, but it carries high risks for elderly patients and those who require reoperation or have ventricular dysfunction.

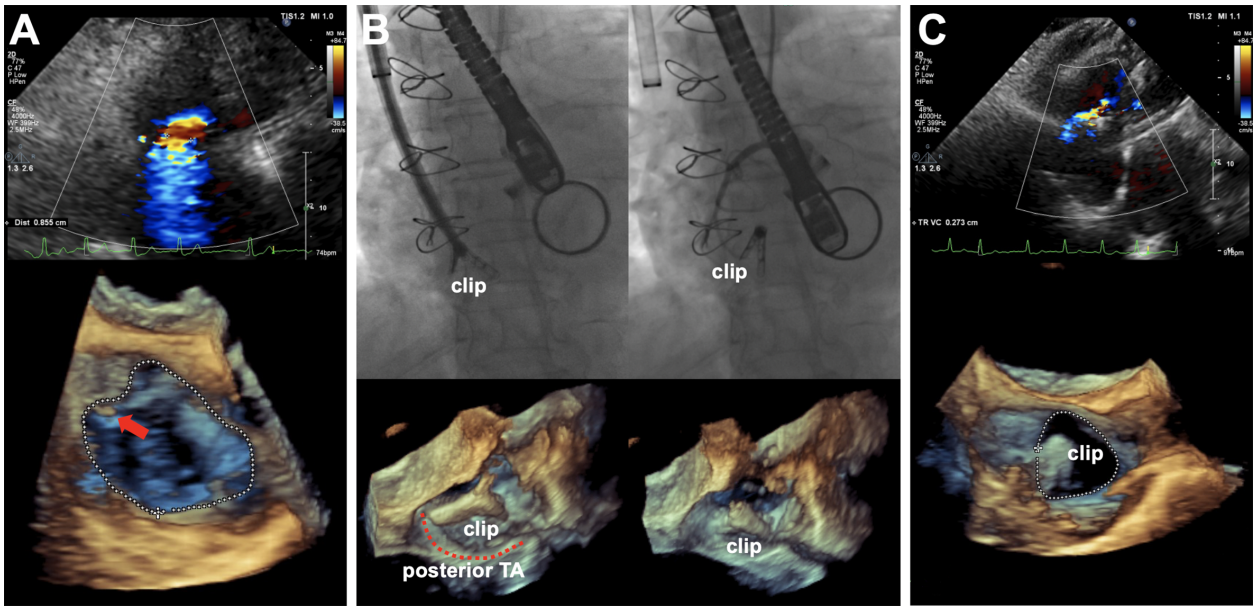

FIGURE 2
(A) Intraprocedural TEE showing torrential TR with EROA of 0.74 cm^2, regurgitation volume of 51 ml, and vena contracta width of 0.71 cm (upper panel) and 3D work plane revealing the original knot of the Kay's procedure (red arrow) and TA morphology before K-Clip™ implantation (lower panel). (B) Real-time fluoroscopy (upper panel) and 3D work plane of TEE (lower panel) showing the opening clamp and the clip on the target location after release. (C) Postprocedural TEE showing an immediate reduction of TR grade with an EROA of 0.16 cm^2, regurgitation volume of 12 ml, and vena contracta width of 0.27 cm (upper panel) and 3D work plane (lower panel) showing the TA morphology after K-Clip™ implantation (red arrow). TEE, transesophageal echocardiogram; TR, tricuspid regurgitation; EROA, effective regurgitant orifice area; TA, tricuspid annulus.

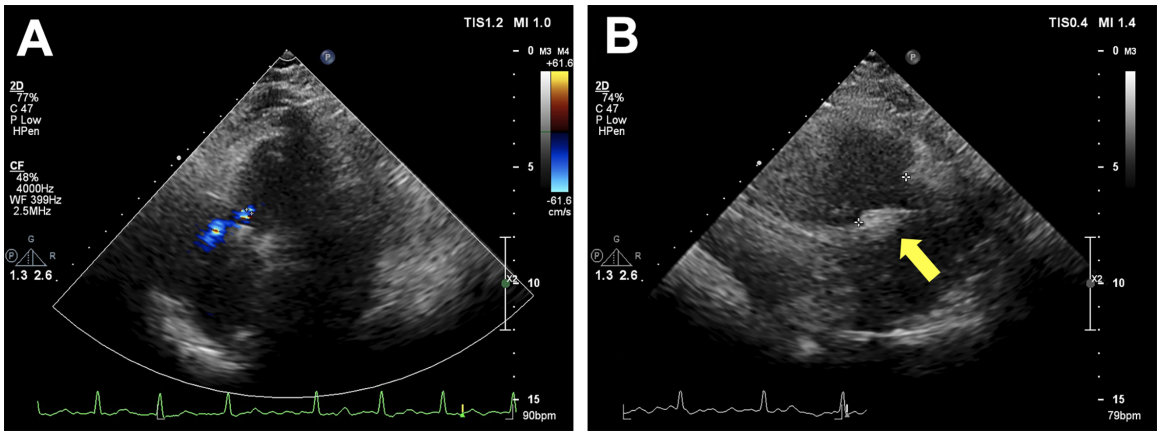

FIGURE 3
Transthoracic echocardiography after 3 months of follow-up. (A) Showing mild residual tricuspid regurgitation. (B) Showing the secure position of the device (yellow arrow).

As for these patients, TTVI is a feasible option for treating functional TR with acceptable safety and simplicity (4).

Indirect annuloplasty devices of TTVI, such as TriClip and PASCAL system, aimed to restore leaflet coaptation by edge-to-edge tricuspid valve repair through a transcatheter approach, have been reported effective and safe to address functional TR (6, 7). As for direct annuloplasty of TTVI devices, Cardioband has been the only system to be approved of clinical use yet. The Cardioband system is delivered through a transfemoral approach, and the Dacron band is fixed on the TA using a series of anchors deployed from the anteroseptal to posteroseptal commissure, which was contracted afterward by a size-adjustment tool to achieve annular dimension reduction (8). Two-year outcomes of TRI-REPAIR study (NCT02981953) about Cardioband showed its favorable results in patients with symptomatic, moderate functional TR (9). Similarly, the K-Clip™ system is a transcatheter-direct annuloplasty device mimicking the Kay's annuloplasty, which plicates the posterior annular tissue via a clip to achieve TA reduction and bicuspidization of the tricuspid valve. The first-in-human study of K-Clip™ has demonstrated acceptable procedural

safety and efficacy (5, 10). Of note, it is critical to utilize the TEE and fluoroscopy to verify the target site and angle for the clip implantation. If the tapping screw-shaped anchor is inserted too close to the atrial side, the anchor might cause atrial wall perforation and further lead to less or no reduction in annular size, and it might cause leaflet tear when pulled back if the anchor is inserted too close to the leaflet. What's more, the right coronary artery flow might be interfered by the clamping clip, so a coronary angiogram should be immediately performed after the implantation.

It is generally recognized that K-Clip^{TM} may not be suitable for patients with recurrent TR after prior Kay's annuloplasty, the reasons are as follows: (1) doubtful space for K-Clip^{TM} implantation due to posterior annular plication and bicuspidization of the tricuspid valve by previous Kay's procedure and (2) the scars caused by prior Kay's procedure potentially interfering K-Clip^{TM} implantation. Nonetheless, in our clinical practice, we have observed that in this population the prior Kay's procedure often appears abnormal, presenting annular re-dilation or failure of the tricuspid valve bicuspidization due to a loose knot. In some patients, although the bicuspidization of the tricuspid valve remained intact, massive TR can be observed between the anteroposterior commissure due to significant dilation in local annular area. For this kind of patients, using the K-Clip^{TM}, TTVI may still be an effective treatment option.

The feasibility of K-Clip^{TM} implantation for this population can be determined by evaluating whether there is an overlap with the original knot of the prior Kay's procedure when the clip clamps. Combined with the TEE and fluoroscopy, the K-Clip^{TM} system can simulate the clamping process and analyze where to implant the clip to achieve an effective reduction in both vena contracta width and TA size, as well as provide a guide for choosing the appropriate size of one or more clips. In this case, the preprocedural evaluation showed that the distance between the target site and the original knot was approximately 18–20 mm, which was enough for a 16-mm-size clip implantation to avoid overlapping with the original knot. After the clip was clamped, the TR grade was immediately reduced from "torrential" to "mild." Luckily, we encountered the optimal circumstances that one clip perfectly achieved annular and TR reduction with no overlap with the original knot. Moreover, if a smaller-sized clip can avoid overlapping with the original knot but expected effect cannot be achieved, the second or more clips to be implanted in the dilated annulus should be considered to achieve optimum results. However, the K-Clip^{TM} would be prohibited if all sizes of the clip overlapped with the original knot. In addition, a posterior TA length that exceeds 36 mm may not achieve meaningful TR reduction (more than one grade) because the longest clip arm available of the K-Clip^{TM} is 18 mm, and, correspondingly, the maximal annular reduction length of K-Clip^{TM} is only 36 mm. Moreover, the K-Clip^{TM} may not be a valid choice for TR that involves the septal annulus, which is away from the free wall of the right ventricle, and thus clamping of this site may damage the adjacent tissue (5).

As an emerging TTVI device to correct TR, the preprocedural evaluation parameters, indications, and manipulation process of the K-Clip^{TM} system still need to promote perfection. In addition, the long-term clinical outcome's durability compared with surgical annuloplasty needs high-quality randomized controlled trials as proof. At present, the K-Clip^{TM} is mainly applicable to elderly and high-risk patients with severe secondary TR. Regarding the implantation of K-Clip^{TM} in patients with recurrent TR who have undergone prior Kay's annuloplasty, comprehensive and careful evaluation is needed both preprocedurally and intraprocedurally.

Conclusion

TTVI via the K-Clip^{TM} system is a novel alternative for patients with high surgical risk to correct severe secondary TR. As for symptomatic patients with recurrent TR who have undergone prior Kay's annuloplasty, the indications for the K-Clip^{TM} procedure are more rigorous, and the evaluation should be more comprehensive and careful.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

SW, XD and LL wrote the original manuscript. SW, SY, PT, and YN treated the patient involved in this case report. YN revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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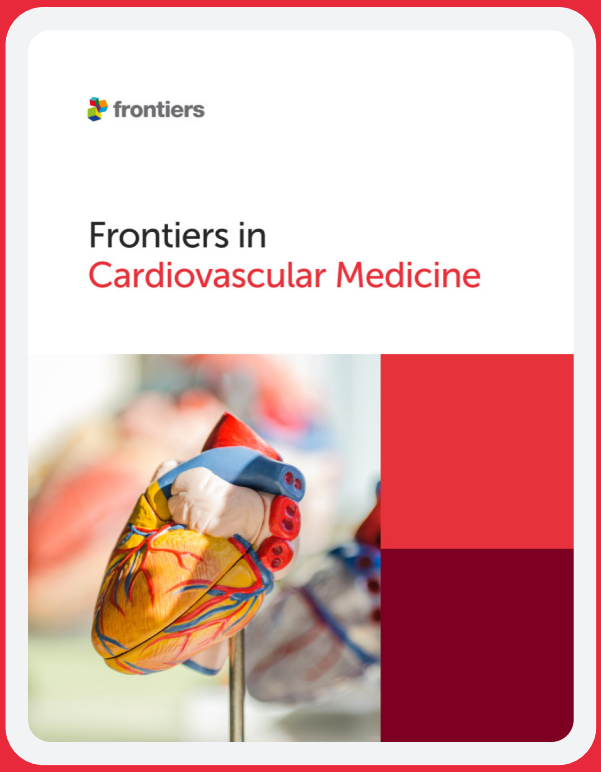

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