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Predicting Outcome In Patients Undergoing Mitral Valve Transcatheter Edge-to-Edge Repair For Secondary Mitral Regurgitation

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List of abbreviations

ALA	=	anterior mitral valve leaflet angle
EF	=	ejection fraction
EROA	=	effective regurgitant orifice area
GDMT	=	guideline directed medical therapy
HHF	=	hospitalization for heart failure
LA-V	=	left atrial volume
LV	=	left ventricle
LV-EDD	=	left ventricular end-diastolic diameter
LV-ESD	=	left ventricular end-systolic diameter
MR	=	mitral regurgitation
M-TEER	=	mitral valve transcatheter edge-to-edge repair
MV	=	mitral valve
NYHA	=	New York Heart Association
PA	=	pulmonary artery
PISA	=	proximal isovelocity surface area
PLA	=	posterior mitral valve leaflet angle
PMR	=	primary mitral regurgitation
RA-A	=	right atrial area
RV	=	right ventricle
RV-FAC	=	right ventricular fractional area change
RV-EDA	=	right ventricular end-diastolic area
RV-ESA	=	right ventricular end-systolic area
RVD	=	right ventricular dysfunction
SMR	=	secondary mitral regurgitation
sPAP	=	systolic pulmonary artery pressure
TEE	=	transesophageal echocardiogram
TR	=	tricuspid regurgitation
TTE	=	transthoracic echocardiogram

List of publications

1. **Impact of Asymmetric Tethering on Outcomes after Edge-to-Edge Mitral Valve Repair for Secondary Mitral Regurgitation**
   Lukas Stolz, Mathias Orban*, Daniel Braun, Philipp Doldi, Martin Orban, Konstantin Stark, Michael Mehr, Julius Steffen, Kornelia Löw, Christian Hagl, Steffen Massberg, Michael Näbauer, Jörg Hausleiter, *equal contribution*
   Clinical Research in Cardiology: 2022, doi: 10.1007/s00392-021-01961-5

2. **Impact of Right Ventricular Dysfunction on Outcomes after Transcatheter Edge-to Edge Repair for Secondary Mitral Regurgitation**
   Nicole Karam Lukas Stolz*, Mathias Orban, Simon Deseive, Fabien Praz, Daniel Kalbacher, Dirk Westermann, Daniel Braun, Michael Näbauer, Michael Neuss, Christian Butter, Mohammad Kassar, Aniela Petrescu, Roman Pfister, Christos Iliadis, Matthias Unterhuber, Sang-Don Park, Holger Thiele, Stephan Baldus, Ralph Stephan von Bardeleben, Stefan Blankenberg, Steffen Massberg, Stephan Windecker, Philipp Lurz, Jörg Hausleiter, *equal contribution*
   Journal of the American College of Cardiology (JACC): Cardiovascular Imaging, 2021, doi: 10.1016/j.jcmg.2020.12.015

1. Contribution to each publication

1.1 Contribution to both publications

The data basis of both *de novo* research papers was the analysis of more than 300 patients who underwent mitral valve transcatheter edge-to-edge repair (M-TEER) for moderate-to-severe or severe secondary mitral regurgitation (SMR) at the *Klinikum der Universität München* of the *Ludwig-Maximilians-Universität München (LMU)* between 2009 and 2019. The author retrospectively evaluated transthoracic and transesophageal echocardiograms (TTE/TEE) of the corresponding patients recorded within routine clinical practice. The evaluation included a wide range of standard as well as specific anatomic parameters and was based on the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (1,2).

Echocardiographic evaluation included left ventricular (LV) ejection fraction (LV-EF), LV end-diastolic and end-systolic volume (LV-EDV, LV-ESV), LV end-diastolic and end-systolic diameter (LV-EDD, LV-ESD), left atrial volume (LA-V), LV length (LV-L), LV width (LV-W), LV sphericity index (LV-I), effective regurgitant orifice area (EROA), regurgitant volume (RegVol), vena contracta of the mitral regurgitant jet (MR-VC), mean mitral valve (MV) inflow gradient (MVmeanPg), as well as mitral and tricuspid regurgitation (MR and TR) severity grades.

The author further collected clinical baseline characteristics for each patient using electronic patient files. Baseline characterization included demographic data, medication at admission, comorbidities, prior cardiac surgical or interventional treatments, laboratory parameters of kidney function and calculation of surgical risk scores (EuroSCORE II, Society of Thoracic Surgeons [STS] Score) (3).

Finally, the author completed follow-up data on phone calls with the patients themselves, their local practitioners or the next of kin and by requesting information from the national death registry. Follow-up data included survival information, latest available New York Heart Association (NYHA) functional class and MR severity.

1.2 Contribution to "Impact of Asymmetric Tethering on Outcomes after Edge-to-Edge Mitral Valve Repair for Secondary Mitral Regurgitation"

Together with Prof. Dr. Jörg Hausleiter and Priv.-Doz. Dr. Mathias Orban, the author created the textual and methodological frame for this publication.

Investigating the impact of MV tethering patterns on outcomes after M-TEER required detailed anatomic echocardiographic characterization of the study cohort. The author performed detailed measurements of the MV in each valvular segment (medial, lateral and central) which comprised anterior and posterior MV leaflet angles (ALA, PLA), anterior MV leaflet (AML) and posterior MV leaflet (PML) length, tenting height and area, anteroposterior and septolateral MV annular diameter and papillary muscle distance.

The author performed all statistical analyses and created images and tables used in this publication. Analyses were conducted using SPSS (version 25, IBM, USA) and R (version 4.0.4, R Foundation, Vienna) and included Cox-proportional hazard models, spline curves, Kaplan-Meier charts and receiver operating characteristics (ROC) statistics.

In cooperation with Priv.-Doz. Dr. Mathias Orban, the author wrote the first draft of the manuscript, which was then revised by Prof. Dr. Jörg Hausleiter and the co-authors.

1.3 Contribution to "Impact of Right Ventricular Dysfunction on Outcomes after Transcatheter Edge-to-Edge Repair for Secondary Mitral Regurgitation"

The publication was based on data of the *European Registry on Outcomes in Secondary Mitral Regurgitation* (EuroSMR registry). This registry included patients who underwent M-TEER for relevant SMR between November 2008 and January 2019 at eight European cardiac valve centers (München, Hamburg, Berlin-Bernau, Bern, Mainz, Köln, Herzzentrum Leipzig, and Paris-Pompidou).

Dr. Nicole Karam, Prof. Dr. Jörg Hausleiter, Priv.-Doz. Dr. Mathias Orban and the author together prepared a draft of the projects thematic and methodological framework.

The author completed echocardiographic evaluation of right ventricular (RV) function in patients who underwent M-TEER at the *Klinikum der Universität München (LMU).* These measurements included RV fractional area change (RV-FAC), RV end-diastolic and end-systolic areas (RV-EDA, RV-ESA), right atrial area (RA-A), tricuspid valve (TV) annulus diameter, tricuspid annular plane systolic excursion (TAPSE), estimated systolic pulmonary artery pressure (sPAP) and TR vena contracta (TR-VC).

The author merged each centers data, performed the statistical analyses and created all figures. The statistical analyses included Cox-proportional hazard models, Kaplan-Meier statistics and ROC analyses, which were all performed by the author. Sensitivity analyses were supported by Priv.-Doz. Dr. Simon Deseive.

Dr. Nicole Karam and the author created the first draft of the manuscript based on the authors statistical results and gathered data. Prof. Dr. Jörg Hausleiter, Priv.-Doz. Dr. Mathias Orban, the author and all further co-authors then revised the manuscript.

2. Introduction

2.1 Epidemiology and etiology of mitral regurgitation

Besides aortic stenosis, MR is the most common valvular heart disease in the western world (4). MR is a comprehensive term, resulting from a broad variety of pathologic findings of the MV. The common mechanism is an inadequate MV leaflet closure during systole. MR can occur either in an acute or chronic setting. From a pathophysiologic viewpoint, MR can be subdivided into primary MR (PMR) and SMR (5). PMR is a consequence of pathologic processes within the valvular apparatus itself, and predominantly affects the MV leaflets. The most common causes of PMR are MV prolapse due to fibroelastic myxomatous degeneration (e.g., Morbus Barlow) or other tissue abnormalities, leading to abnormal leaflet motion, configuration, and/or chordal rupture (5).

SMR is usually encountered in patients suffering from heart failure with reduced ejection fraction (HFrEF), which is a major economic and health burden with more than 26 million people being affected worldwide (6). HFrEF and SMR mutually aggravate each other and hence are accompanied by reduced quality of life, frequent hospitalizations for heart failure as well as substantial morbidity and mortality (7). Deterioration of LV function can either be a consequence of ischemic or non-ischemic cardiomyopathies. In both cases, the left ventricle becomes hypertrophic and dilates to maintain a sufficient forward stroke volume. Long standing MR may eventually lead to dilation of the left atrium due to volume overload caused by the regurgitant blood flow. Without appropriate treatment, MR might cause secondary pulmonary hypertension and right ventricular dysfunction (8). Subsequently, systemic organs as the kidney or liver can suffer significant damage (9,10). In clinical practice, a smaller subgroup of patients with SMR presents with preserved ejection fraction (HFpEF) and relatively normal LV geometry and dimensions. In these patients, SMR is a consequence of pathological atrioventricular interaction and hence referred to as atrial SMR (ASMR) (11-13). This etiologic subgroup has been underreported within the last decades and now is an important field of research with a growing number of studies focusing on this entity (11,12).

2.2 Treatment options for severe secondary mitral regurgitation

The prevalence of SMR substantially increases with progressing age (4). Accordingly, SMR patients often present with a considerably large number of comorbidities, which complicate therapeutic considerations. In current versions of the European and American guidelines for the management of patients with valvular heart disease, the role of M-TEER has been strengthened (5,14-16). Whereas in American guidelines M-TEER is the treatment of choice for SMR, the European guidelines demand evaluation of surgical options before decision for M-TEER. Both guidelines stress the importance of meticulous preprocedural evaluation of SMR etiology and severity by both TTE and TEE (5,14-16). Accordingly, each patient needs to be discussed in an interdisciplinary heart team consisting of cardiologists, heart failure specialists and cardiac surgeons. Patients with ischemic HFrEF-SMR and indication for myocardial revascularization by coronary artery bypass graft (CABG) should primarily be treated by MV surgery. If no revascularization is needed, application of optimal guideline recommended medical treatment (GDMT) and - if indicated - cardiac resynchronization therapy (CRT), are the basis of SMR treatment. If heart failure symptoms persist despite the application of maximum tolerable conservative treatment in HFrEF patients, M-TEER is the therapy of choice in case of suitable MV anatomy and technical feasibility (5,14-16).

2.3 Mitral valve transcatheter edge-to-edge repair

M-TEER has been introduced into clinical practice in the first decade of the 21^{st} century. Briefly summarized, this transcatheter MV repair technique reduces MR by approximating both MV leaflets and hence minimizing the regurgitant systolic blood flow across the MV. The procedure mimics a surgical reconstruction technique, the so-called “Alfieri stich”, which approximates both mitral valve leaflets through a central suture (17-19).

The first M-TEER system was approved in Europe in 2008 (20). Within the past ten years, further device generations with additional features were introduced and enabled the treatment of an even broader variety of anatomic MV configurations (21,22).

The M-TEER procedure is performed under general anesthesia by fluoroscopic, as well as two-and three-dimensional echocardiographic guidance (23,24). After access through the femoral vein, the device is advanced into the right atrium. The interatrial septum is then punctured at the location of the fossa ovalis. After entering the left atrium, the device is aligned perpendicular to the mitral annular plane at the position of the MR jet origin (25). The two device arms are then opened, and the device is advanced into the LV. After gentle retraction of the device to mount the leaflets onto the arms, both MV leaflets can be grasped by closing the device arms. Reopening of the device arms is possible and enables the interventionalist to reposition the device to optimize MR reduction (23,25). Before releasing the device from the catheter, the echocardiographer quantifies the degree of MR and measures the transmitral pressure gradient to avoid generation of significant mitral valve stenosis. The catheter and device are then disconnected, and the device stays in place within the valve. The guiding catheter is retracted, and the venous puncture site compressed (23).

Initially, the EVEREST (Endovascular valve edge-to-edge repair study) I and II trials investigated the safety and efficacy of M-TEER in reducing both PMR and SMR severity and heart failure symptoms, with additional comparison to surgical MR treatment in the EVEREST I trial (25-27). In 2012 and 2013, two large randomized-controlled trials started enrolling patients for the comparison of SMR treatment by GDMT plus M-TEER versus GDMT only in predominantly HFrEF patients (COAPT: "*Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation"*(28) and MITRA-FR: *"Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation"*(29)). In 2018, both trails published diverging results regarding their primary endpoint. While the COAPT trial observed significantly lower rates of HHF or death within two years after M-TEER plus GDMT versus GDMT alone, the MITRA-FR trial failed to show superiority of M-TEER on top of GDMT. Since then, many studies and registries tried to explain these outcome differences, but until today no sufficient explanation could be identified (30,31). It is now believed that the key to optimized M-TEER results is the best possible selection of patients. A recent analysis of the EuroSMR registry showed that real-world M-TEER patients who would have fulfilled the inclusion criteria of the COAPT study had a significantly better survival prognosis compared to those who would have been excluded from the study (32). Nevertheless, conclusive data is still lacking and the research on this topic remains ongoing worldwide.

2.4 Predictors for survival outcome after transcatheter mitral valve edge-to-edge repair

In the light of the ongoing MITRA-FR versus COAPT controversy, there is an international consensus, that meticulous preprocedural patient characterization is the key for optimized M-TEER results. Therefore, various studies identified predictors for survival and symptomatic benefit after percutaneous SMR treatment (33). Those comprise left- and right heart function, as well as cardiac and non-cardiac comorbidities.

LV function is one of the main factors predicting survival after M-TEER (34-36) as the degree of LV dysfunction correlates with progression of the underlying cardiomyopathy. Accordingly, also dilated LV dimensions are associated with worse outcome (36,37). Furthermore, several studies reported about the negative impact of atrial fibrillation or flutter on survival after M-TEER (36,38).

Reduced RV function as represented by impaired TAPSE and elevated sPAP or maximum systolic TV pressure gradient (TrMaxPg), have also been associated with impaired survival after M-TEER treatment in various studies (37,39-42). Biventricular heart failure is believed to be an indicator for progressive heart failure and worst clinical outcome (8).

The degree of concomitant pre- and postprocedural TR as a sign of RV dilation and/or volume overload has been identified to negatively impact prognosis after M-TEER (34,43).

Furthermore, residual MR after M-TEER is an important predictor for postinterventional mortality, as it reflects the degree of MR reduction and hence procedural success (37,44,45). As this is a parameter that can be modified by the interventionalist, it is probably the aim to reduce MR as much as possible in the majority of cases.

In addition to the abovementioned factors, several comorbidities have been singled-out to negatively affect survival rates after M-TEER. Among those are impaired renal function (34,46-48), peripheral artery disease (43), age (49) and cardiac risk-scores integrating each patients overall health status (EuroSCORE II, STS Score) (41,50).

Several research groups recently published their approaches to classify SMR patients into disease-specific subgroups according to the natural disease course of SMR based on simple echocardiographic parameters (8,51). Combining these different parameters into a unified classification and prognostic system remains a major task for future research in the field of M-TEER.

2.5 Two open questions in the treatment of secondary mitral regurgitation: Mitral valve anatomy and right ventricular dysfunction

2.5.1 Asymmetric mitral valve tethering patterns

So far, detailed data regarding the impact of mitral valve anatomy on outcomes after M-TEER are lacking. Merely one study reported about the negative impact of excessively restricted systolic PML motion on MR reduction after interventional MR treatment (52). Restricted systolic PML motion is referred to as Carpentier Type IIIb MR and is caused by pronounced tethering of the PML. Tethering of the mitral valve can be asymmetric in two directions. First, the systolic movement of the PML can be disproportionately restricted compared to the AML and leads to postero-anterior tethering asymmetry (53). The development of this anatomical configuration may be the consequence of pathologic atrioventricular remodeling reflecting the underlying cardiomyopathic etiology, especially in ischemic SMR.

Second, tethering can be asymmetric in the medio-lateral direction. The MV is subdivided into three segments (lateral, central and medial). Myocardial infarction especially of the inferoposterior myocardium leads to apical displacement of the medial papillary muscle (54), which causes more pronounced tenting of the medial compared to the lateral MV segment. This condition is referred to as asymmetric medio-lateral tethering (54).

Both patterns have been reported to be associated with inferior prognosis after surgical MV repair (55,56). As the impact of the abovementioned conditions on outcomes after M-TEER treatment remained unclear, these open questions were evaluated in the first publication (Publication 1, "*Impact of asymmetric tethering on outcomes after edge-to-edge mitral valve repair for secondary mitral regurgitation*").

2.5.2 Right ventricular dysfunction

So far, only the COAPT trial, but not the MITRA-FR trial published data on right ventricular function within their study cohort (57). Accordingly, asking the "right" question might help to explain outcome differences of both randomized-controlled trials.

Recently, right ventricular to pulmonary artery (RVPA) uncoupling as a measure of RV dysfunction, was found to have particular prognostic importance in patients with severe aortic stenosis (58), pulmonary hypertension (59) and HFpEF (60). In the presence of compensated RVPA coupling, the RV is capable of increasing contractility proportionate to increased afterload in the pulmonary vasculature. Patients with uncoupling of the RVPA interdependency are unable to maintain sufficient blood flow through the pulmonary circulation (61). This uncoupling of RVPA leads to right heart decompensation and worsens symptomatic status and prognosis in a broad variety of cardiac pathologies as mentioned above.

The second publication was the first to apply the concept of RVPA coupling to real-world patients undergoing M-TEER for relevant SMR (Publication 2 "*Impact of Right Ventricular Dysfunction on Outcomes After Transcatheter Edge-to-Edge Repair for Secondary Mitral Regurgitation*").

3. Abstract (German)

HINTERGRUND: Das perkutane „edge-to-edge" Reparaturverfahren der Mitralklappe (M-TEER) ist die am häufigsten angewandte, nicht chirurgische Behandlungsoption jenseits einer medikamentösen und Resynchronisationstherapie bei Patienten mit relevanter sekundärer Mitralklappeninsuffizienz und eingeschränkter linksventrikulärer Pumpfunktion. Eine große Anzahl an Studien und klinischen Registern hat in der Vergangenheit Faktoren identifiziert, die das Überleben nach perkutaner Mitralklappenreparatur abschätzen können. Die Ergebnisse verdeutlichen, dass eine sorgfältige präprozedurale Patientenselektion von zentraler Bedeutung für den Therapieerfolg und die langfristige Prognose dieser Patienten ist. Zwei möglicherweise relevante Faktoren wurden bisher im Kontext der M-TEER Behandlung nicht untersucht. Dabei könnte vor allem das sogenannte *„Tethering"* der Mitralklappensegel eine Rolle spielen. Bei diesem pathologischen Vorgang kommt es zu einer Segelverlagerung in Richtung des Ventrikels aufgrund einer fortschreitenden Herzinsuffizienz, sodass der systolische Klappenschluss zunehmend kompromittiert wird. Zudem könnten anatomische und funktionelle Varianten der Mitralklappenanatomie von Bedeutung für das Behandlungsergebnis sein. Darüber hinaus ist der Einfluss einer gleichzeitig vorliegenden rechtsventrikulären Dysfunktion (RVD) auf die Prognose nach einer M-TEER Behandlung noch unklar.

ZIELE: Das Ziel dieser Arbeit war es, den Einfluss asymmetrischer *„Tethering"*-Muster und der rechtsventrikulären Dysfunktion auf die Ergebnisse nach einer M-TEER Behandlung zu evaluieren. Die untersuchten Endpunkte umfassten dabei neben der Mortalität im Beobachtungszeitraum von zwei Jahren auch die anhand der *New York Heart Association (NYHA)* Klasse gemessene symptomatische Verbesserung der Patienten.

METHODEN: Das Verhältnis der endsystolischen Winkel von hinterem und vorderem Mitralklappensegel im zentralen Klappensegment wurde als Maß der postero-anterioren „*Tethering*“-Symmetrie definiert. Medio-laterales „*Tethering*“ definierte sich durch das Verhältnis der sogenannten „*Tenting*“-Flächen von medialem und lateralem Mitralklappensegment. „*Tenting*“ beschreibt dabei eine ventrikelwärts verlagerte Koaptation der Klappensegel. Patienten, die zwischen 2013 und 2019 am *Klinikum der Universität München* der *Ludwig-Maximilians-Universität München (LMU)* eine M-TEER Prozedur und gleichzeitig eine ausführliche echokardiographische Bildgebung erhielten, wurden in die Analyse eingeschlossen. Die RVD wurde mithilfe des sogenannten *right ventricular to pulmonary artery (RVPA) coupling* quantifiziert. Das Maß des *RVPA Coupling* berechnet sich als Verhältnis von rechtsventrikulärer Funktion (ein Maß hierfür ist die *tricuspid annular plane systolic excursion*: TAPSE) und systolischem Pulmonalarteriendruck (sPAP). Die RVD Analyse schloss alle Patienten des *European Registry on Outcomes in Secondary Mitral Regurgitation* (EuroSMR) mit verfügbaren TAPSE und sPAP Werten ein. Unter Zuhilfenahme einer Sensitivitätsanalyse wurde für beide Maße der „*Tethering*“-Symmetrie sowie des *RVPA Coupling* Quotienten der optimale Grenzwert bezüglich der Vorhersagekraft für die Mortalität nach M-TEER Behandlung identifiziert. Die Patienten wurden dann gemäß dem ermittelten Grenzwert in zwei Gruppen eingeteilt. Der Einfluss der dichotomisierten Parameter auf die Mortalität nach interventioneller Mitralklappenbehandlung wurde schließlich in einem Cox-Regressionsmodell geprüft. Die symptomatische Entwicklung nach M-TEER wurde unter Zuhilfenahme der NYHA Klasse evaluiert.

ERGEBNISSE: Von insgesamt 175 eingeschlossenen Patienten, wiesen 37.6% ein asymmetrisches postero-anteriores „*Tethering*“ auf. Die Prävalenz des asymmetrischen medio-lateralen „*Tetherings*“ war mit 27.5% geringer. Asymmetrisches postero-anteriores „*Tethering*“ war mit einer signifikant schlechteren prozeduralen Reduktion des

Schweregrades der Mitralklappeninsuffizienz assoziiert. Ein multivariates Cox-Regressionsmodell bestätigte sowohl postero-anteriores (*hazard ratio [HR])* =2.77, Konfidenzintervall *[KI]* =1.43-5.38, p<0.01) als auch medio-laterales (HR=2.90, KI=1.54-5.45, p<0.01) „*Tethering“* als unabhängige Prognosefaktoren der Mortalität im Zweijahreszeitraum. RVD wurde als TAPSE/sPAP Verhältnis <0.274 mm/mmHg definiert und wies unter den insgesamt 817 untersuchten Patienten des EuroSMR Registers eine Prävalenz von 25.8% auf. Nach multivariater Adjustierung bestätigte sich das Vorliegen einer RVD als starker und unabhängiger Mortalitätsprädiktor (HR = 1.62, KI = 1.14-2.31, p<0.01) innerhalb des Studienkollektivs.

Weder asymmetrische „*Tethering"*-Muster noch RVD beeinflussten negativ die Verbesserung des symptomatischen Status der behandelten Patienten.

SCHLUSSFOLGERUNG: Die Überlebensprognose von M-TEER-Patienten mit relevanter Mitralklappeninsuffizienz wird durch eine Vielzahl kardialer und nicht kardialer Begleiterkrankungen beeinflusst. Asymmetrische „*Tethering“*-Muster und das Vorliegen einer RVD zeigten eine Prävalenz von mindestens 25% und hatten einen signifikanten Einfluss auf den Erfolg der M-TEER Behandlung und damit auch auf die Prognose nach der Therapie. Diese Ergebnisse verdeutlichen den großen Stellenwert einer sorgfältigen und interdisziplinären Patientenauswahl unter Berücksichtigung klinischer und echokardiographischer Einflussfaktoren.

4. Abstract (English)

BACKGROUND: Transcatheter edge-to-edge repair (M-TEER) is the most commonly used non-surgical treatment technique for patients with relevant secondary mitral regurgitation (SMR) and heart failure with reduced ejection fraction (HFrEF). A broad variety of studies and registries have identified different survival predictors after M-TEER and hence outlined the importance of meticulous preprocedural patient selection. So far, two major possible outcome predictors have not been evaluated in the setting of M-TEER treated SMR. First, anatomic and functional variabilities of the mitral valve leaflets and second the presence of right ventricular dysfunction (RVD) as represented by impairment of right ventricular to pulmonary artery (RVPA) coupling.

OBJECTIVES: The aim of this work was to evaluate the impact of asymmetric mitral valve tethering patterns and RVD on outcome after M-TEER in patients with SMR. Endpoints were defined as two-year all-cause mortality after M-TEER, and symptomatic outcome as represented by New York Heart Association (NYHA) functional class.

METHODS: Postero-anterior MV tethering symmetry was defined as the ratio of the posterior to the anterior mitral valve leaflet angle (PLA/ALA) in the central mitral valve (MV) segment. The ratio of the tenting area in the medial and lateral MV leaflet segment was referred to as medio-lateral tethering. Tethering analyses were performed in all patients with retrospectively assessable tethering symmetry who underwent M-TEER for SMR at the *Klinikum der Universität München* from 2013 until 2019. Right ventricular dysfunction was expressed by RVPA coupling, which was calculated as the ratio of tricuspid annular plane systolic excursion (TAPSE) and the estimated systolic pulmonary artery pressure (sPAP). RVD was evaluated using patients from the *European Registry on Outcomes in Secondary Mitral Regurgitation* (EuroSMR) registry with available TAPSE and sPAP data. Receiver operating characteristics and Youden's J were used to identify the optimal cut-off for RVPA coupling, as well as postero-anterior and medio-lateral tethering asymmetry in terms of two-year all-cause mortality. The impact of each dichotomized parameter was adjusted for potential confounders using Cox regression models. The influence of RVPA coupling and asymmetric tethering patterns on symptomatic outcome was evaluated by observing the development in NYHA functional class from baseline to follow-up.

RESULTS: Among a total of 175 eligible patients for the tethering analysis, asymmetric postero-anterior tethering as defined by a PLA/ALA ratio >1.57 was prevalent in 37.6% of patients. Medio-lateral tethering asymmetry (tenting area ratio >1.49) was less frequent (27.5%). Asymmetric postero-anterior tethering was associated with less procedural MR reduction. In a multivariate cox regression model, both, asymmetric postero-anterior (HR=2.77, CI=1.43-5.38, p<0.01) and medio-lateral (HR=2.90, CI=1.54-5.45, p<0.01) tethering were confirmed as independent predictors for two-year all-cause mortality. RVD was defined as a TAPSE/sPAP ratio <0.274 mm/mmHg. Among a total of 817 eligible patients from the EuroSMR registry, 25.8% presented with RVD. After adjustment for potential clinical and echocardiographic confounders, RVD remained a strong and independent mortality predictor after M-TEER for SMR (HR=1.62, CI= 1.14-2.31, p<0.01). The improvement in NYHA functional class was neither influenced by asymmetric tethering patterns, nor by RVD.

CONCLUSIONS: Survival outcome after M-TEER for SMR is influenced by a broad variety of cardiac- and non-cardiac conditions. Asymmetric tethering patterns as well as RVD were prevalent in up to 25% of patients undergoing M-TEER but their impact on outcome has been underestimated so far. Patient selection for M-TEER is complicated and needs to be performed in an interdisciplinary setting in order to account for all important clinical and echocardiographic parameters.

5. Publication I

Title: Impact of Asymmetric Tethering on Outcomes after Edge-to-edge Mitral Valve Repair for Secondary Mitral Regurgitation

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6. Publication II

Title: Impact of Right Ventricular Dysfunction on Outcomes after Transcatheter Edge-to Edge Repair for Secondary Mitral Regurgitation

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