Aus der Medizinischen Klinik und Poliklinik II
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Der Stellenwert echokardiographischer Begutachtung zur adäquaten periinterventionellen Entscheidungsfindung bei perkutaner Mitralklappenreparatur

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Die im Folgenden aufgelisteten fünf Originalarbeiten liegen dieser kumulativen Habilitationsschrift zu Grunde, in der aus echokardiographischer Sicht der herausfordernde periinterventionelle Entscheidungsprozess perkutaner Mitral-klappenreparatur bei inoperablen Patienten mit chronischer symptomatischer Mitral-klappeninsuffizienz untersucht und beleuchtet wird.

1. Schueler R*, **Öztürk C***, Sinning JM, Werner N, Welz A, Hammerstingl C, Nickenig G. Impact of baseline tricuspid regurgitation on long-term clinical outcomes and survival after interventional edge-to-edge repair for mitral regurgitation. Clin Res Cardiol. 2017 May; 106(5):350-358. doi: 10.1007/s00392-016-1062-1. **(IF: 4,73)**
2. **Öztürk C***, Becher MU*, Kalkan A, Kavsur R, Weber M, Nickenig G, Tiyerili V. The modified MIDA-Score predicts mid-term outcomes after interventional therapy of functional mitral regurgitation. PLoS One. 2020 Jul 22; 15(7): e0236265. doi: 10.1371/journal.pone.0236265. **(IF: 3,24)**
3. **Öztürk C**, Fasell T, Sinning JM, Werner N, Nickenig G, Hammerstingl C, Schueler R. Left atrial global function in chronic heart failure patients with functional mitral regurgitation after MitraClip. Catheter Cardiovasc Interv. 2020 Sep 1; 96(3):678-684. doi: 10.1002/ccd.28775. **(IF: 1,91)**
4. **Öztürk C**, Friederich M, Werner N, Nickenig G, Hammerstingl C, Schueler R. Single-center five-year outcomes after interventional edge-to-edge repair of the mitral valve. Cardiol J. 2021; 28(2):215-222. doi: 10.5603/CJ.a2019.0071. **(IF: 2,73)**
5. **Öztürk C**, Sprenger K, Tabata N, Sugiura A, Weber M, Nickenig G, Schueler R. The predictive value of intraprocedural mitral gradient for outcomes after MitraClip and its peri-interventional dynamics. Echocardiography. 2021 Jul; 38(7):1115-1124. doi: 10.1111/echo.15126. **(IF: 1,72)**

*Geteilte Erstautorenschaft

1 Inhaltsverzeichnis

Abkürzungsverzeichnis

6MWT	Sechs-Minuten-Gehtest
AUC	Fläche unter der Kurve
CT	Computertomographie
DMI	Degenerative Mitralklappeninsuffizienz
EuroSCORE	European System for Cardiac Operative Risk Evaluation
EROA	Effektive Regurgitationsöffnungsfläche
FMI	Funktionelle Mitralklappeninsuffizienz
LVEF	Linksventrikuläre Ejektionsfraktion
MI	Mitralklappeninsuffizienz
MIDA-Score	The Mitral Regurgitation International Database Score
MPG	Mittlerer Mitralklappengradient
MRT	Magnetresonanztomographie
NT-proBNP	N-terminal pro Brain natriuretic peptid
NYHA	New York Heart Association
PISA	Proximal Isovelocity surface area
RegVol	Regurgitationsvolumen
ROC	Receiver operating characteristics
RVSP	Rechtsventrikulärer systolischer Druck
sPAP	systolischer pulmonal-arterieller Druck
STS-Score	The Society of Thoracic Surgeons Score
TEE	Transösophageale Echokardiographie
TI	Trikuspidalklappeninsuffizienz
TTE	Transthorakale Echokardiographie
VC	Vena contracta

2 Einleitung

2.1 Epidemiologie, Ätiologie, Pathophysiologie sowie klinische Manifestation der Mitralklappeninsuffizienz

Die Mitralklappeninsuffizienz (MI) ist nach der Aortenklappenstenose das zweithäufigste Klappenvitium bei Erwachsenen in Europa mit einer Prävalenz bis zu 25 % in der Altersgruppe über 55 Jahren (Ruiz et al., 2018) und geht mit hoher Mortalität, häufigen stationären Aufnahmen, eingeschränkter Lebensqualität sowie körperlicher Belastbarkeit und weiteren Komorbiditäten einher (Prakash et al., 2014). Die Prävalenz der höhergradigen MI (≥ mittelgradig) steigt von 2 % auf 7,7 % korrespondierend mit zunehmendem Patientenalter von 65–74 Jahren auf ≥ 75 Jahren (Cahill et al, 2021). In Anbetracht der hohen Verbreitung mit assoziierter ungünstiger Prognose und gesundheitsökonomischen Auswirkungen ähnelt die MI einer Volkskrankheit. Durch die alternde Population und das globale Wirtschaftswachstum treten die nicht-rheumatischen Klappenvitien im klinischen Alltag häufiger auf, wohingegen die rheumatischen Ursachen seltener dokumentiert werden (Chen et al., 2020).

Bei Patienten mit höhergradiger MI unter konservativer Therapie beträgt die Ein-Jahres-Mortalitätsrate ca. 14 % und steigt nach fünf Jahren auf > 50 %, (Prakash et al., 2014; Messika-Zeitoun et al., 2022). Die Gesamtmortalität bei Patienten mit funktioneller MI (FMI) zeigte sich aufgrund der begleitenden linksventrikulären Dysfunktion tendenziell höher (> 35 %) (Cahill et al., 2021).

Anhand der zugrundeliegenden Pathophysiologie wird die MI in zwei ätiologische Gruppen aufgeteilt. Die erste und häufigere Gruppe ist die degenerative bzw. primäre MI (DMI). Die DMI entsteht hauptsächlich durch direkte Schädigungen der Klappenstrukturen (Klappensegel, Klappenapparat, Anulus, Sehnenfaden) (Vahanian et al., 2022). Die Mitralklappenendokarditis (ca. 1,6 % der DMI), das angeborene Mitralklappenvitium (ca. 1,5 % der DMI), Morbus Barlow (ca. 14 % der DMI) sowie die rheumatische Degeneration der Mitralklappe (ca. 10,1 % der DMI) stellen die weiteren Ursachen der DMI dar (Ruiz et al., 2018). Die Prävalenz der DMI in der Gesamtpopulation beträgt zwischen 55 % und 61 % (Ruiz et al., 2018; Cahill et al., 2021).

Die zweite ätiologische Gruppe der MI ist die funktionelle bzw. sekundäre MI (FMI). Der Pathomechanismus der FMI ist etwas komplexer als jener der DMI und besteht aus linksventrikulärer Dysfunktion mit konsekutiver Dilatation des linken Ventrikels und/oder Vorhofs (Vahanian et al., 2022) sowie hieraus resultierender Anulusdilatation ohne Vorhandensein organischer Pathologien des Klappenapparates. Patienten mit FMI zeigen überwiegend eine eingeschränkte Herzfunktion und häufigere schwerwiegende Komorbiditäten, weswegen sie eine chirurgische Hochrisiko-Konstellation darstellen.

Die andere charakteristische Entität ist die akute MI, die mit höherer Letalität sowie Morbidität verbunden ist (Nishino et al., 2016). Hier handelt es sich um einen klinischen Notfall. Patienten mit akuter MI stellen sich mit akuter kardialer Dekompensation aufgrund einer akuten gravierenden Volumen- bzw. Druckbelastung des vorher gesunden linken Ventrikels mit reduziertem Herzzeitvolumen durch den MI-bedingten erheblichen Rückfluss in den linken Vorhof. Das klinische Bild der akuten MI ist in der Regel kritischer als das der chronischen MI, da die Kompensationsmechanismen des linken Ventrikels aufgrund des Zeitmangels im akuten Prozess versagen. Endokarditis, Papillarmuskelabriss, ischämische Genese, iatrogene bzw. Device-assoziierte MI und Takotsubo-Kardiomyopathie sind als die häufigsten Ursachen der akuten MI zu erwähnen (Watanabe et al., 2019). Im Allgemeinen ist im Falle einer akuten MI eine chirurgische Versorgung mittels chirurgischem Klappenersatz indiziert (Vahanian et al., 2022).

Die chronische MI präsentiert sich klinisch durch die Symptome der Herzinsuffizienz (zunehmende Belastungsdyspnoe mit eingeschränkter Belastbarkeit, periphere prätibiale Ödeme, Pleuraergüsse, Zyanose, Husten, Müdigkeit, Nykturie), supra-ventrikulärer Rhythmusstörungen (Schwindel, Palpitationen, Synkope, zum Teil Angina pectoris) sowie der Rechtherzbelastung (Stauungsleber, Stauungsniere, Aszites, periphere Ödeme, Anasarka).

Neben der ausführlichen Patientenanamnese ist die strukturierte körperliche Untersuchung unverzichtbar. Ein Holosystolikum mit Fortleitung in die Axilla mit Punctum maximum im fünften Interkostalraum links medioklavikulär, das Vorhandensein des dritten Herztones als Zeichen für ventrikuläre Volumenbelastung, abgeschwächte Atemgeräusche bei relevanten Pleuraergüssen, Rasselgeräusche bei

Lungenödem, periphere Ödeme sowie Aszites sind die möglichen in der körperlichen Untersuchung feststellbaren Manifestationen einer klinisch relevanten MI.

Bei klinischem Verdacht ist die transthorakale Echokardiographie (TTE) die erste apparative Diagnostik im MI-Diagnosealgorithmus. Die TTE gibt neben der MI-Pathologie, der Klappenanatomie und dem Schweregrad der MI Auskunft über die globale Herzfunktion sowie koexistierende Klappenvitien, was für den adäquaten periinterventionellen Beurteilungs- bzw. Entscheidungsprozess essenziell ist. Die MI ist als hochgradig einzustufen, wenn die Vena contracta ≥ 7 mm, die effektive Regurgitationsöffnungsfläche (EROA) ≥ 0,4 cm^2, das Regurgitationsvolumen ≥ 60 ml sowie der endsystolische Diameter des linken Ventrikels ≥ 40 mm und/oder der Diameter des linken Vorhofes ≥ 55 mm (oder Volumen ≥ 60 ml/m^2) sind (Vahanian et al., 2022). Die echokardiographische Beurteilung der MI-Ätiologie ist für die Therapieentscheidung vonnöten, weil die Therapiegestaltung sich abhängig vom MI-Typ (funktionell versus degenerativ) unterscheidet.

Der andere wichtige, echokardiographische Parameter ist der Mitralklappengradient (MPG), wessen Erhebung für die suffiziente Patientenauswahl vor einer interventionellen Mitralklappenreparatur unerlässlich ist. Der systolische pulmonal-arterielle Druck (sPAP) zählt ebenfalls zu den unverzichtbaren Parametern im Rahmen der Beurteilung der Prognose sowie zur Entscheidung über die Notwendigkeit einer Mitralklappenreparatur. Ein sPAP > 50 mmHg ist mit einer schlechten Prognose verbunden (Vahanian et al., 2022).

Die transösophageale Echokardiographie (TEE) bietet eine optimale Darstellung der Klappenanatomie, der MI-Pathologie sowie eine adäquate Quantifizierung der MI – insbesondere bei Patienten mit eingeschränkter transthorakaler Schallbarkeit. Zudem sind Real-Time-3D-Darstellungen der MI mit Aufsicht (En-Face-View bzw. chirurgischer Sicht) der Mitralklappe mittels TEE realisierbar und im Entscheidungsprozess vor sowie während interventioneller Mitralklappenreparatur ausschlaggebend (Vahanian et al., 2022). Als weiterführende kardiale Bildgebung kommen die Computertomographie (CT) sowie die Magnetresonanztomographie (MRT) des Herzes zum Einsatz. Die kardiale CT zeigt einen hohen Stellenwert während der präinterventionellen Machbarkeitsanalyse vor perkutanen Klappenimplantationen. Hier werden die folgenden Kriterien evaluiert: die

Größenbestimmung der Prothese bzw. des Devices sowie des neuen links-ventrikulären Ausflusstraktes (Neo-LVOT), der Abstand zwischen dem Klappenanulus und dem Ramus circumflexus sowie die Evaluation der erforderlichen Zugangswege. Trotz des eher seltenen alltäglichen Einsatzes gibt die kardiale MRT wichtige Auskunft über die Ausdehnung der myokardialen Fibrose, die bei Patienten mit DMI als ein starker unabhängiger Prädiktor für die ungünstigen Ergebnisse im Sinne von häufigerem plötzlichem Herztod sowie ventrikulären Arrhythmien fungiert (Vahanian et al., 2022).

Die chirurgische Mitralklappenreparatur ist laut der aktuellen Leitlinien als kausale Therapie einer symptomatischen DMI weiterhin die Methode der ersten Wahl (Klasse IA-Empfehlung). Die medikamentöse Herzinsuffizienz-Therapie ist lediglich bei Patienten mit einer offensichtlichen Herzinsuffizienz zu erwägen. Auf der anderen Seite stellt aufgrund der zugrundeliegenden Pathomechanismen, eine optimale Herzinsuffizienz-Therapie bei Patienten mit FMI die Methode der ersten Wahl dar. Eine apparative Therapie der FMI kommt erst im Falle der therapierefraktären Symptome bei Patienten unter optimaler Herzinsuffizienz-Therapie inkl. Device-Therapie in Frage (Vahanian et al., 2022).

Gemäß den aktuellen Leitlinien kommen die perkutanen MI-Therapien, im Falle einer chirurgischen Hochrisiko-Konstellation und bestehenden echokardiographischen Eignung, als Klasse-IIb-Empfehlung für die DMI sowie Klasse-IIa-Empfehlung für die FMI zum Einsatz (Vahanian et al., 2022).

Die präinterventionelle Entscheidungsfindung aus adäquater Patienten- und Therapie-auswahl mit passendem Timing stellt einen umfassenden komplexen Prozess dar. Die in Frage kommenden Patienten werden in einem interdisziplinären Herzteam hinsichtlich des operativen Risikos, der geeigneten Therapieart (Chirurgie vs. Interventionell, Rekonstruktion vs. Ersatz oder konservativ) sowie Abschätzung des Therapieerfolgs ausgiebig diskutiert (Klasse-IC-Empfehlung). Das Herzteam besteht mindestens aus einem interventionellen Kardiologen, einem erfahrenen Herzchirurgen sowie einem Anästhesisten. Die wichtigen individuellen, prognostisch relevanten Faktoren sind das Alter, die Komorbiditäten, die Lebenserwartung (mindestens > 12 Monate) sowie die linksventrikuläre Pumpfunktion, die während der Abschätzung des chirurgischen Risikos neben den verfügbaren Risiko-Scores, z.B. EuroSCORE II

(European System for Cardiac Operative Risk Evaluation) oder STS-Score (The Society of Thoracic Surgeons Score), hilfreich sind (Nashef et al., 1999; O´Brien et al., 2009). Zur adäquaten Entscheidung der richtigen Therapieart sind die morphologischen (Klappenanatomie), pathophysiologischen (Ätiologie der MI) sowie MI-definierenden Parameter zu berücksichtigen. Weitere hilfreiche Faktoren zur Therapieentscheidung sowie Prognoseabschätzung sind die globale linksventrikuläre Funktion, die Geometrie des linken Ventrikels und Atriums, der pulmonal-arterielle Druck sowie das Vorhandensein von Vorhofflimmern (Baumgartner et al., 2017; Baldus et al., 2020).

2.2 Interventionelle Behandlungsoptionen der Mitralklappeninsuffizienz

Im klinischen Alltag hat die Inoperabilität eines großen Teils der Patienten mit chronischer und symptomatischer MI dazu geführt, dass minimal-invasiv anwendbare Medizinprodukte zur interventionellen MI-Therapie am schlagenden Herz ohne Notwendigkeit einer Herz-Lungen-Maschine in den letzten Jahren entwickelt und mittlerweile auch zahlreich erprobt worden sind.

Das interventionelle Verfahren zur Edge-to-Edge-Reparatur der MI wurde als Modifikation der chirurgischen Alfieri-Technik aufgrund seiner Unkompliziertheit sowie Vielseitigkeit entwickelt. Die chirurgische Alfieri-Technik wurde zum ersten Mal in den 1990er Jahren vom italienischen Herzchirurgen Ottavio Alfieri entworfen und angewendet (Maisano et al., 2011). Die schonende Edge-to-Edge-Rekonstruktion der Mitralklappe mit Hilfe des MitraClip™-Systems der Firma Abbot Vascular stellt die erste Generation dieser Art dar und steht seit 2008 in Deutschland zur Verfügung. Das zweite, seit 2019 CE-zertifizierte System zur interventionellen Edge-to-Edge-Therapie der MI ist das PASCAL™-System der Firma Edwards Lifesciences. Die beiden Firmen bieten verschiedene Größen der Medizinprodukte (MitraClip™: NT-Device, XT-Device sowie G4; PASCAL™: PASCAL Implantat und PASCAL Ace Implantat), die individuelle Therapieoptionen, beruhend auf den anatomischen sowie pathophysiologischen Gegebenheiten der Patienten, und hiermit assoziiertem vorteilhafterem Therapierfolg mit besseren Langzeitergebnissen ermöglichen.

Das katheterbasierte Verfahren zur Edge-to-Edge-Reparatur der MI wird am schlagenden Herz unter kontinuierlicher Bildgebung mittels TEE in Allgemein-

anästhesie durchgeführt. Das präinterventionell ausgewählte Clipping-Device (MitraClip™ oder PASCAL™) wird mit Hilfe einer steuerbaren Schleuse (24-French = 8,1 mm) über die rechte V. femoralis zuerst in den rechten Vorhof dann nach einer transseptalen Punktion in den linken Vorhof gebracht. Die Lokalisierung (superior und posterior) sowie die Höhe (> 3,5 cm) der transseptalen Punktion werden mit Hilfe von mittösophagealen Anlotungen der TEE (der bicavale Blick, der anteroposteriore Blick sowie der Vierkammerblick) bestimmt. Nach erfolgreicher transseptaler Punktion wird ein Pigtail-Draht bis in eine Lungenvene vorgeschoben. Währenddessen ist die kontinuierliche echokardiographische Beurteilung des linken Vorhofohres sowie des Drahtes ausschlaggebend. Nach transseptaler Vorführung des Clipping-Devices in das linke Atrium wird die Trajektorie des Katheters sowie die Ausrichtung des Clipping-Devices echokardiographisch beurteilt bzw. angepasst. Nach optimaler Positionierung wird das Device unter TEE-Kontrolle vorsichtig in den linken Ventrikel vorgeschoben. Die Klappensegel werden während des vorsichtigen sowie langsamen Rückzugs des Systems auf den Armen des Devices aufgeladen und anschließend im Device mit Hilfe von kleineren Greifern (MitraClip™: Gripper, PASCAL™: Clasp) fest gegriffen und durch die Arme des Devices fixiert. Abschließend ist zur Erfolgskontrolle im Sinne einer effektiven Reduktion der MI sowie einem adäquaten Greifen der Klappensegel eine ausführliche echokardiographische Beurteilung durchzuführen und eine relevante Mitralklappenstenose (mittlerer Mitralklappengradient > 5 mmHg) auszuschließen (Feldman et al., 2011; Barth et al., 2020) (siehe Abbildung 1).

Das interventionelle direkte Anuloplastie-Verfahren mittels Cardioband™-System der Firma Edwards Lifesciences bietet seit 2015 eine minimalinvasive Therapieoption zur interventionellen Raffung des Mitralklappenringes überwiegend für FMI-Patienten mit dilatiertem Mitralklappenanulus. Des Weiteren stellt die interventionelle indirekte Anuloplastie mit dem Carillon™-Koronarsinusimplantat der Firma Cardiac Dimensions eine CE-zertifizierte Alternative zu anderen interventionellen Behandlungsmodalitäten eher für Patienten in früheren Stadien der kongestiven Herzinsuffizienz dar (Baldus et al., 2020).

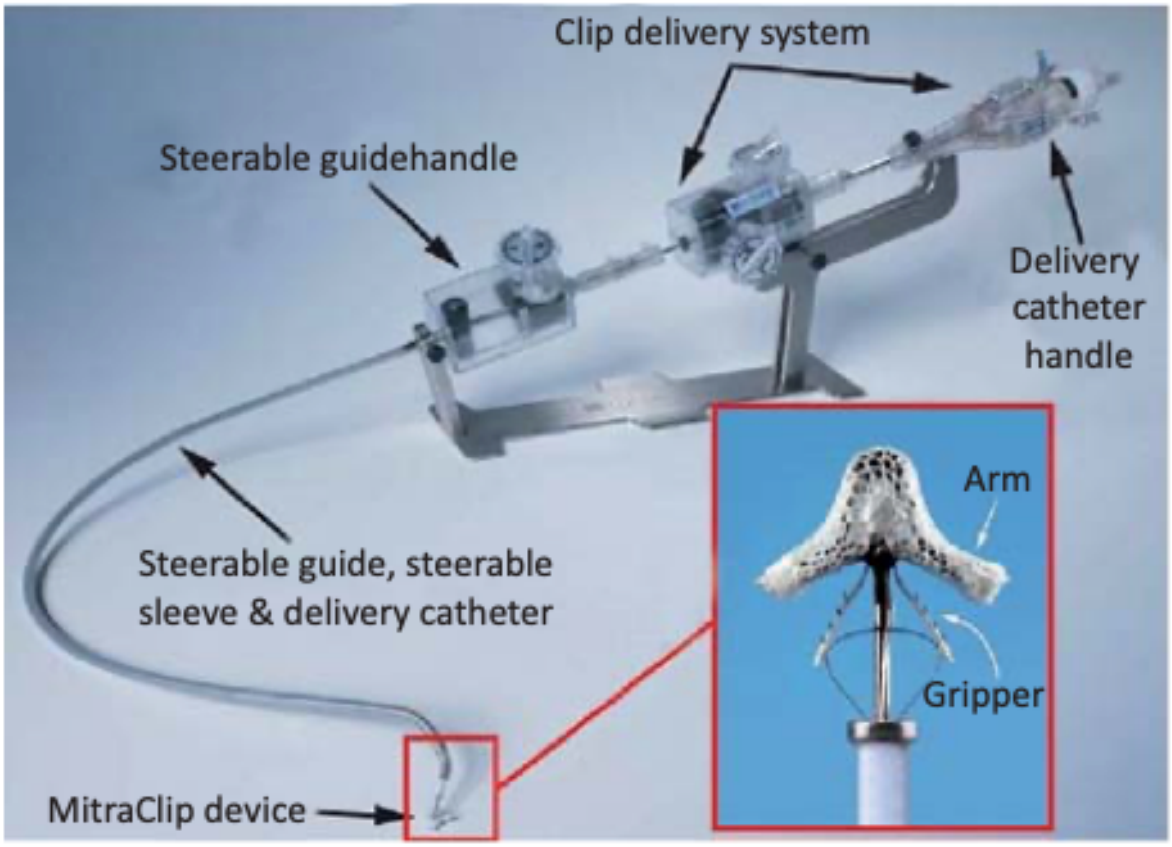

Abbildung 1: Bildliche Darstellung des MitraClip™-Systems (Ihlemann et al., 2011)

Das Cardioband™-Verfahren hat einen ähnlichen prozeduralen Ablauf wie die katheterbasierte Edge-to-Edge-Reparatur der Mitralklappe. Es unterscheidet sich jedoch im transvenösen Zugang (25-French) und in der Positionierung der Schrauben nach der transseptalen Punktion. Es wird je nach Anulusgröße ein Band mit 12–17 Schrauben über einen Teleskopkatheter in den linken Vorhof vorgeschoben und auf dem posterioren Mitralklappenanulus von anterolateral nach posteromedial unter TEE- und Fluoroskopie-Kontrolle implantiert. Hiernach wird der Anulus bis auf 40 % Reduktion des Ausgangsdiameters gerafft. Die abschließende echokardiographische Kontrolle (MI-Reduktion, Reduktion des Mitralklappenanulus, Ausschluss relevanter Mitralklappenstenose, Sitz des Bandes und der Schrauben) ist bei diesem Verfahren ebenfalls von großer Bedeutung (Nickenig et al., 2016).

Ein anderes erprobtes, interventionelles Verfahren ist die Implantation künstlicher Sehnenfäden. In diesem Bereich stehen in Deutschland zwei Medizinprodukte (NeoChord™-System der Firma NeoChord mit der CE-Zertifizierung seit 2012 sowie Harpoon™-System der Firma Edwards Lifesciences mit der CE-Zertifizierung seit

2019) zur Verfügung. Für dieses Verfahren kommen eher die Patienten mit elongierten oder rupturierten Sehnenfäden in Frage. Die Notwendigkeit eines transapikalen Zuganges beschreibt den größten Nachteil dieser Verfahren (Baldus et al., 2020).

Darüber hinaus sind perkutane Mitralklappenimplantationen bei Patienten mit besonderen anatomischen Herausforderungen in Erwägung zu ziehen. Die Tendyne™-Prothese der Firma Abbot Vascular stellt die einzige Option ihrer Art mit dem CE-Kennzeichen vom Jahr 2020 dar. Die restlichen Prothesen (beispielsweise EVOQUE™ der Firma Edwards Lifesciences, Cardiovalve™ der Firma Cardiovalve, Intrepid™ der Firma Medtronic) werden derzeit im Rahmen der Zulassungs- bzw. Machbarkeitsstudien implantiert (Baldus et al., 2020).

Die Sicherheit, die Machbarkeit und die Wirksamkeit der oben genannten Verfahren wurden durch diverse große multizentrische Studien belegt. Die im Jahr 2011 publizierte multizentrische, randomisierte EVEREST-II-Studie demonstrierte die perkutane Edge-to-Edge-Mitralklappenreparatur als eine sicherere Alternative zur chirurgischen Versorgung mit vergleichbaren klinischen Fünf-Jahres-Ergebnissen (Feldman et al., 2011). Da > 70 % der eingeschlossenen Patienten eine DMI hatten, ist die zusammenfassende Aussage dieser Studie als Grundlage für DMI anzunehmen. Die vor Kurzem veröffentlichten Daten aus dem multizentrischen prospektiven EXPAND-Register (NCT03502811) erbrachten die bemerkenswerte Machbarkeit sowie Wirksamkeit der dritten Generation der Clip-Systeme (NTR und XTR) der Firma Abbot Vascular sowohl bei DMI als auch bei FMI. Die CLASP-Studie erbrachte übereinstimmende Daten mit dem EXPAND-Register, wobei mittels PASCAL™-System behandelten Patienten mit Zwei-Jahres-Ergebnissen untersucht worden sind (Szerlip et al., 2021). Im Bereich der FMI ist die Studienlage uneindeutig. In der multizentrischen COAPT-Studie wurde der zusätzliche klinische Nutzen der interventionellen Mitralklappenreparatur bei Patienten mit FMI unter optimaler Herzinsuffizienz-Therapie (Stone et al., 2018) präsentiert. In Ergänzung dazu legen die Daten aus der MITRA-FR-Studie nahe, dass die adäquate Patientenauswahl eine Schlüsselrolle spielt, um bessere klinische Ein-Jahres-Ergebnisse nach interventioneller Edge-to-Edge-Therapie bei Patienten mit FMI erreichen zu können (Obadia et al., 2018).

Messika-Zeitroun et al. demonstrierten die angemessene Leistung und die Sicherheit des Cardioband™-Systems mit günstigen funktionellen Ein-Jahres-Ergebnissen bei Patienten mit symptomatischer FMI in einer multizentrischen Studie aus elf europäischen Zentren (Messika-Zeitroun et al., 2018). Die multizentrischen AMADEUS- sowie TITAN-Studien bewiesen die Sicherheit und Machbarkeit des Carillon™-Systems (Schofer at al., 2009; Lipiecki et al., 2016). Die Effektivität des Carillon™-Systems bei Patienten mit FMI wurde mit den Daten aus der randomisierten REDUCE-FMR-Studie belegt (Witte et al., 2019). Colli et al. (NeoChord™-System) sowie Gammie et al. (Harpoon™-System) präsentierten die Sicherheit, Machbarkeit sowie Effektivität der interventionellen Sehnenfadenimplantation bei Patienten mit DMI in den jeweiligen multizentrischen Studien (Colli et al., 2018; Gammie et al., 2018). In der multizentrischen Machbarkeitsstudie mit ersten 100 Patienten stellte sich die Tendyne™-Prothese bei Patienten mit DMI sowie FMI als sicher, machbar und effektiv heraus (Sorajja et al., 2019).

2.3 Fragestellung der vorliegenden Habilitationsschrift

In den letzten zehn Jahren wurden kontinuierliche beeindruckende Innovationen im Bereich der interventionellen Mitralklappentherapie entwickelt. Die bisherige Studienlage bewies die Sicherheit und die Machbarkeit der interventionellen Behandlungsoptionen der MI-Therapie bei Zielpatientengruppen mit erheblichem operativem Risiko. Darüber hinaus rufen diese Behandlungen wünschenswerte echokardiographische sowie klinische Outcomes hervor (Feldman et al., 2011; Stone et al., 2018; Messika-Zeitroun et al., 2018; Szerlip et al., 2021). Es wurde ebenfalls nachgewiesen, dass die adäquate Entscheidungsfindung mit der präzisen Patientenauswahl eine ausschlaggebende Rolle bei den postinterventionellen Ergebnissen spielt (Obadia et al., 2018; Stone et al., 2018). Die klinischen Prädiktoren für Outcomes sind bekannt, jedoch sind die prognostisch relevanten echokardiographischen Parameter nicht ausreichend erforscht. Diesbezüglich konzentriert sich die vorliegende Habilitationsschrift auf den echokardiographischen periinterventionellen Beurteilungsprozess mit der präzisen Entscheidungsfindung aus adäquater Patientenauswahl mit richtigem prozeduralem Timing und effektiver Prognoseabschätzung bei Patienten mit symptomatischer hochgradiger, chronischer MI, die mittels interventioneller Edge-to-Edge-Reparatur oder direkter Anuloplastie der

Mitralklappe versorgt wurden. Im Rahmen dieser kumulativen Habilitationsschrift werden die folgenden Fragestellungen evaluiert und beantwortet;

1) Wie ist der Effekt der begleitenden Trikuspidalklappeninsuffizienz (TI) – als ein echokardiographischer Parameter – auf das funktionelle Outcome und das Überleben bei Patienten, die mittels MitraClip™ behandelt wurden?
2) Welche klinischen bzw. echokardiographischen Parameter sind am relevantesten zur präzisen Entscheidungsfindung sowie zur adäquaten Prognoseabschätzung bei Patienten mit hochgradiger funktioneller, chronischer MI, die sich einer interventionellen MI-Therapie unterziehen? Wie ist die Reproduzierbarkeit bzw. die Diskriminierungskraft des modifizierten MIDA-Scores bei Patienten mit FMI?
3) Wie sehen die Langzeitergebnisse nach interventioneller Edge-to-Edge-Reparatur der MI aus? Welche Prädiktoren zeigen eine relevante Auswirkung auf das Fünf-Jahres-Outcome?
4) Welche Auswirkung hat das MitraClip™-Verfahren auf die linksatriale Funktion und die linksatrialen Volumina? Welchen Stellenwert zeigt das linke Atrium bezüglich des klinischen Outcomes sowie des Prozedurerfolges bei Patienten mit FMI, die mittels MitraClip™-Verfahren behandelt wurden?
5) Welchen Effekt hat der intraprozedural gemessene Mitralklappengradient auf die klinischen Ergebnisse? Wie ist die periinterventionelle Dynamik des Mitralklappengradienten? Welche Prädiktoren gibt es zur suffizienten Abschätzung des ungünstigen postinterventionellen Mitralklappengradienten?

3 Ergebnisse

3.1 Schueler R, Öztürk C, Sinning JM, Werner N, Welz A, Hammerstingl C, Nickenig G. Impact of baseline tricuspid regurgitation on long-term clinical outcomes and survival after interventional edge-to-edge repair for mitral regurgitation. Clin Res Cardiol. 2017 May; 106(5):350-358.

Zielsetzung der Arbeit: Die begleitende TI geht bei Patienten mit Mitralklappenvitium mit einem ungünstigen Outcome sowie einer höheren Mortalität einher. Im Hinblick auf die prognostischen echokardiographischen Prädiktoren war unsere Fragestellung, ob die begleitende TI einen Effekt auf die postprozeduralen Ergebnisse nach dem MitraClip™-Verfahren hat.

Methoden und Ergebnisse: Wir schlossen insgesamt 261 Patienten (80,5 ± 7,8 Jahre, 32,8 % weiblich) mit symptomatischer (93,5 % NYHA-Klasse > II) MI (75,2 % FMI) und chirurgischer Hochrisiko-Konstellation (mittlerer logistischer EuroSCORE 15,9%) ein, die zwischen Februar 2011 und Juni 2016 in unserem Herzzentrum mittels der MitraClip™-Prozedur behandelt wurden. Bei 96,2 % der durchgeführten Behandlungen zeigte sich eine MI-Reduktion um mindestens einen Grad ohne das Auftreten einer peri-prozeduralen Komplikation. Die Nachsorgeuntersuchungen (durchschnittlich zwei Jahre nach der Intervention) zeigten in der Gesamtkohorte eine signifikante Verbesserung der funktionellen Kapazität (35,7 % NYHA-Klasse > II, p = 0,001; Sechs-Minuten-Gehstrecke um 40 m, p = 0,05) und eine Reduktion des NT-proBNP-Wertes (um 5500 pg/ml, p =0,023) sowie des sPAP (um 6 mmHg, p = 0,01). Mit Hilfe einer univariaten Regressionsanalyse fanden wir den logistischen EuroSCORE (p = 0,03), die Sechs-Minuten-Gehstrecke beim Einschluss (p = 0.05), die NYHA-Klasse beim Einschluss (p = 0,012), den sPAP beim Einschluss (p = 0,018), die residuale MI (p = 0,04) sowie den Mitralklappengradienten beim Einschluss (p = 0,04) als signifikante Prädiktoren für das Zwei-Jahres-Überleben. Die multivariate Cox-Regressionsanalyse erbrachte, dass die begleitende TI > Grad II der stärkste unabhängige Prädiktor für die postinterventionelle Mortalität mit einer Hazard-Ratio (HR) von 2,04 (p = 0,007) ist (siehe Table 5, p. 355, Schueler et al. 2017). Zur weiteren Evaluation des prognostischen Effektes der begleitenden TI in Bezug auf den TI-Schweregrad auf das klinische sowie das echokardiographische Outcome nach dem MitraClip™-Verfahren unterteilten wir das Patientenkollektiv in zwei Gruppen (TI ≤ Grad II: 220 und TI > Grad II: 41). Die generierten Gruppen waren angesichts der klinischen sowie

echokardiographischen Kofaktoren vergleichbar und zeigten keine signifikanten Unterschiede hinsichtlich der links- und der rechtsventrikulären Funktion, der MI-Ätiologie, des prozeduralen Erfolges, der Anzahl der implantierten Clips, der residualen MI oder des postinterventionellen Mitralklappengradienten. Die Patienten mit begleitender TI > Grad II zeigten eine höhere NYHA-Klasse (p = 0,04), eine kürzere Sechs-Minuten-Gehstrecke (p = 0,04), eine häufigere Hospitalisierung (p = 0,05) und einen höheren NT-proBNP-Wert (p = 0,05). Der Log-Rank-Test ergab eine signifikant höhere Mortalität (p = 0,05) zwei Jahre nach dem MitraClip™-Verfahren bei Patienten mit vorliegender TI > Grad II (siehe Figure 1 und 2, p. 354, Figure 3, p. 355, Schueler et al., 2017).

Schlussfolgerungen**:** Die vorliegende relevante TI (> Grad II) ist als ein bedeutsamer echokardiographischer Indikator für ein schlechtes postinterventionelles klinisches Outcome mit hoher Mortalität zu betrachten. Daher sollte dieser Parameter während des periinterventionellen Entscheidungsprozesses berücksichtigt werden.

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ORIGINAL PAPER

Impact of baseline tricuspid regurgitation on long-term clinical outcomes and survival after interventional edge-to-edge repair for mitral regurgitation

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Abstract
Aims Tricuspid regurgitation (TR) in patients with mitral valve disease is associated with poor outcome and mortality. Only limited data on the impact of TR on functional outcome and survival in patients undergoing MitraClip procedures are available.
Methods and results 261 patients (mean age 76.6 ± 10, EuroScore 15.9 ± 15.1%) with symptomatic mitral regurgitation (MR) (75.2% functional MR) undergoing MitraClip procedure were included and followed for 721 ± 19.4 days. At baseline 54.7% presented with TR grade 0/I, 29.5% with grade II, 13.4% with grade III and 2.3% with grade IV. When dividing groups according to baseline TR grades, follow-up (FU)-NYHA class was significantly improved only in patients with TR ≤ II ($p = 0.05$). FU-6-min walking distance increased significantly in the overall cohort ($p = 0.05$), in patients with TR ≤ II ($p = 0.007$), but not in patients with TR > II ($p = 0.4$). Moreover, FU-NT-pro-BNP levels were higher in patients with TR > II ($p = 0.05$), compared to patients with TR ≤ II. There was a higher mortality according to baseline TR > II and multivariate Cox regression revealed TR > II as the strongest independent predictor for mortality (hazard ratio 2.04).
Conclusions Concomitant TR at baseline negatively influences functional outcome and mortality in patients undergoing MitraClip procedures. Our results underline the need for dedicated interventional strategies for the treatment of TR in patients with symptomatic MR.

Keywords Tricuspid regurgitation · Heart failure · Percutaneous repair · MitraClip

Abbreviations

EROA	Effective regurgitant orifice area
LV	Left ventricle/ventricular
LVEDV	Left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
MR	Mitral regurgitation
MV	Mitral valve
PISA	Proximal isovelocity surface area
RV	Right ventricle
TR	Tricuspid regurgitation

Introduction

Mitral regurgitation (MR) is the second most frequent valve disease in Europe and with the growing age of the population its prevalence increases continuously [1–3]. Different interventional devices (Cardioband, Mitralign, MitraClip, Carillon) for transcatheter mitral vale repair (TMVR) for the treatment of symptomatic MR in surgical high-risk patients have gained CE-mark in the last years [4]. The interventional edge-to-edge repair with the MitraClip procedure, with more than 30,000 patients

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treated worldwide, has been shown effective for the reduction of mitral regurgitation in up to 80% of cases with improvement of MR-related clinical symptoms [5, 6]. More than mild tricuspid regurgitation (TR) is a common finding in those patients who often suffer from chronic left heart disease and its prevalence rises up to 50% in patients with severe MR [7, 8]. Furthermore, TR in patients with mitral valve (MV) disease is associated with poor outcome and predicts poor survival, heart failure, and reduced functional capacity [9–12]. Because of the misconception that TR should resolve after treatment of the left-sided problem, tricuspid repair has been largely neglected. TR might appear years after primary surgery and might not resolve after correcting the MV lesion [9]. Therefore, TR is believed to be more than an innocent bystander and current research focuses on the development of dedicated interventional treatment options.

Although the negative influence of TR on outcomes in patients treated surgically for symptomatic MR is a known fact, the clinical relevance of TR in MitraClip patients and its impact on functional outcome and survival is not clear.

In this study, we aimed to determinate the impact of concomitant baseline TR on functional outcome and mortality in patients undergoing interventional edge-to-edge repair with the MitraClip procedure.

Patients and methods

Patients presenting at the Heart Centre of the University Hospital of Bonn with symptomatic MR were evaluated for TMVR versus surgery. TMVR was planned after heart team decision when a patient was deemed high-risk for open heart surgery or inoperable.

261 consecutive patients were subdivided according to baseline severity of TR. Follow-up (FU) visits were performed 2 years after TMVR with the MitraClip system and included echocardiographic evaluation of ventricular function and volumes, as well as assessment of clinical symptoms and functional capacity, which was estimated with the 6-min walking test (6MWT).

The study was approved by the Ethics Committee of the University of Bonn and in concordance with the Declaration of Helsinki and all patients had to provide written informed consent before study inclusion.

Interventional edge-to-edge repair

The MitraClip system has been described in detail previously [12].

The procedures were performed under general anesthesia with procedural guidance from 2- and 3-dimensional transesophageal echocardiography (2D, 3D TEE) and fluoroscopy in all cases. Unfractionated heparin was administered after sheath insertion aiming to reach an ACT of 250 s throughout the procedure.

Echocardiography

Echocardiographic assessment before, during and after TMVR was done following current recommendations and guidelines with echocardiographical determination of proximal isovelocity surface area (PISA), EROA, as well as vena contracta (VC) width and regurgitant volume (RegVol). RegVol and EROA were calculated using with the semi-quantitative PISA method [13]. MR was graded according to the recommendations of the European Society of Cardiology as “mild”, “moderate”, “moderate to severe” or “severe” [13]. 3D-TEE was performed with a commercially available echocardiographic system (iE 33, Philips Medical Systems, Andover, Massachusetts) and a TEE probe (X7-2t) allowing acquisition of 2D- and 3D-TEE data sets. All patients underwent transthoracic echocardiography (TTE) 1–2 days prior to clip implantation and at FU.

The severity of TR was graded in four stages as non/trivial, mild, moderate, and severe according to current guidelines using the determination of semiquantitative echocardiographic parameters (VC width, systolic hepatic flow reversal) as well as qualitative parameter (Color flow jet). In case of VC width >7 mm TR was scored as severe. Right ventricular anatomy and function were assessed as well and aided in the estimation of the severity of TR [13, 14]. There are, however, limited data regarding the normal dimensions of the RV and assessment of RV function is difficult due to the anatomic complexity of the RV. Volumetric quantification of RV function is challenging because of the many assumptions require and many physicians rely on visual estimation to assess RV size and function.

Statistics

Continuous variables are reported as mean values with standard deviations and categorical variables are reported as percentages, respectively. Statistical analysis was done with the paired Student’s t test for continuous variables. The Chi-square test was used for categorical variables. A two-tailed p value <0.05 was considered statistical significant. Comparisons between the groups were performed using χ^2 or Kruskal–Wallis test. Following univariate regression analysis, we conducted a multivariate analysis using Cox regression analysis with stepwise forward selection to assess predictors of clinical outcome and mortality including parameters, which were statistically significant in the univariate regression analysis. Survival was estimated plotting Kaplan–Meier graphs.

Statistics were performed using SPSS for Windows (PASW statistic, Version 23.0.0.0, SPSS Inc., Chicago, IL, USA) and MedCalc statistical software (MedCalc Software, Version 11.4.1.0, Mariakerke, Belgium).

Results

Patients and baseline characteristics

From February 2011 to June 2014 261 consecutive patients (age 80.5 ± 7.8, 32.8% female, EuroScore 15.9 ± 15.1%) deemed not to be appropriate candidates for open heart surgery by the heart team with symptomatic MR (75.2% functional MR) underwent TMVR with the MitraClip system. 92.1% of the patients presented with functional NYHA class III–IV.

Atrial fibrillation was present in 35.6% of the individuals. A relevant number of patients had a history of coronary artery disease (69.7%) (Table 1).

Mean FU time was 721 ± 19.4 days. During FU 50 (19.1%) patients were lost-to FU and 40 (15.3%) deceased.

Baseline echocardiography showed impaired left ventricular (LV) ejection fraction (EF) (43.3 ± 16.2%), sPAP was estimated as mildly elevated (42.9 ± 15.3 mmHg), and LV volumes presented moderately dilated (Left ventricle end diastolic volume [LVEDV]: 163.8 ± 69.9 ml; left ventricle end systolic volume [LVESV]: 98.7 ± 60.4 ml). Right ventricular (RV) measurements showed moderate RV dilatation (RVEDD: 33 ± 2 mm) with normal function [tricuspid annular plane systolic excursion (TAPSE): 1.8 ± 0.4, RV fractional area change: 49 ± 3] (Table 2).

Intraprocedural and in-hospital safety data

The procedure was successfully completed in 96.2% of patients with implantation of more than one clip in 46.7% of cases with a mean procedural time of 75.7 ± 43.9 min (14–275 min). No procedure-related adverse events occurred (Table 3). The mean duration of in-hospital stay was 12 ± 10.1 days.

Baseline criteria according to tricuspid regurgitation

Patients presented with non/trivial TR (TR grade 0–I, $n = 144$) in 54.8%, mild TR (TR grade II, $n = 77$) in 29.5%, moderate TR (TR grade III, $n = 35$) in 13.4% and severe TR (TR grade IV, $n = 6$) in 2.3%. For further analysis, we separated the patients with respect of baseline TR grades ≤II or >II. Regarding demographic baseline

Table 1 Functional and demographic baseline characteristics

	All patients ($n = 261$)	TR ≤ II ($n = 220$)	TR > II ($n = 41$)	p
Age	80.5 ± 7.8	80.5 ± 7.5	80.6 ± 8.3	0.9
BMI, kg/m^2	26 ± 4.3	26.3 ± 4.4	24.4 ± 3.1	0.1
Female, %	32.8	29.5	36.5	0.5
EuroSCORE	15.9 ± 15.1	15.7 ± 15.7	16.9 ± 11.3	0.7
NYHA, %				0.2
I	0	0	0	
II	6.5	6.8	4.8	
III	67.5	58.6	60.9	
IV	21.8	20	31.7	
6-MWT, m	231.39 ± 117.1	237.3 ± 123.2	208.4 ± 88.1	0.2
Atrial fibrillation, %	35.6	34.5	41.4	0.05
Hypertension, %	68.2	67.7	70.7	0.6
CAD, %	53.4	54.1	51.2	0.3
Diabetes mellitus, %	26.4	25.4	31.7	0.7
Dialyse, %	1.2	1.3	0	0.9
Dyslipidemia, %	43.3	44.5	36.5	0.2
ICD, %	18.7	16.8	29.2	0.1
Nicotine, %	24.5	25.4	19.5	0.5
PAD, %	16.1	14.1	26.8	0.1
Pacemaker, %	9.2	8.1	14.6	0.1
Stroke, %	6.9	6.3	9.7	0.1

TR tricuspid regurgitation, *BMI* body mass index, *ICD* implanted cardioverter defibrillator, *CAD* coronary arterial disease, *PAD* peripheral arterial disease

characteristics there was no significant difference between the groups (Table 1) with the exception of concomitant atrial fibrillation, which showed a higher prevalence in patients with TR > II ($p = 0.05$).

However, there was no difference in functional capacity as assessed by 6MWT ($p = 0.2$) (Table 1).

Regarding baseline echocardiographic parameters there were no differences for LV or RV function when subdividing the cohort (Table 2). Right ventricular enddiastolic diameter (RVEDD) and inferior vena cava diameter (IVC) were significantly larger in patients with higher grades of TR ($p = 0.02$, $p = 0.02$). Serum NT pro-BNP levels were not statistically different between the groups ($p = 0.5$) (Tables 1, 2).

Table 2 Echocardiographic baseline characteristics

	All patients ($n = 261$)	TR ≤ II ($n = 220$)	TR > II ($n = 41$)	p
MR, %				0.6
II	5.1	4.1	7.3	
III	72.1	71.3	78	
IV	10.3	10	12.2	
FMR, %	45	43.6	53.6	0.3
LVEF, %	43.3 ± 16.3	43.5 ± 16.4	42.6 ± 15.5	0.7
LVEDV, ml	163.8 ± 69.9	166.2 ± 68.2	153.3 ± 77.3	0.2
LVESV, ml	98.7 ± 60.3	99.5 ± 60.1	95.4 ± 62.4	0.6
LVEDD, cm	6.2 ± 1.2	6.2 ± 1.2	6 ± 1.1	0.3
LVESD, cm	4.6 ± 1.5	4.7 ± 1.5	4.2 ± 1.1	0.6
TAPSE, cm	1.8 ± 0.5	1.9 ± 0.4	1.8 ± 0.4	0.6
sPAP, mmHg	43.3 ± 14.3	43.3 ± 14.4	43.3 ± 14.5	0.9
RVEDD, mm	34 ± 6	38.2 ± 4	42.7 ± 5	0.02
IVC, mm	18.5 ± 2	17.3 ± 5	22 ± 1	0.02
FAC, %	46.9 ± 3	46.7 ± 4	47.1 ± 6	0.3

TR tricuspid regurgitation, *MR* mitral regurgitation, *FMR* functional mitral regurgitation, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular enddiastolic volume, *LVESV* left ventricular endsystolic volume, *LVEDD* left ventricular enddiastolic diameter, *LVESD* left ventricular endsystolic diameter, *TAPSE* tricuspid annular plane systolic excursion, *sPAP* systolic pulmonary arterial pressure, *RVEDD* right ventricular enddiastolic diameter, *IVC* inferior vena cava, *FAC* fractional area change

Clinical and echocardiographic outcomes at FU

FU 2 years after MitraClip procedure showed significant amelioration of functional NYHA class (baseline functional NYHA class >II: 92.1%, FU functional NYHA class >II: 35.7%, $p = 0.001$) and 6MWT (242.8 ± 121.9 m, 281.6 ± 110.9 m, $p = 0.05$), and decreased levels of NT pro-BNP (7125.1 ± 1502.7, 1561.5 ± 1931.4 pg/ml; $p = 0.023$). We furthermore found significant improvement of sPAP (43.3 ± 14.3, 37.1 ± 14.3 mmHg, $p = 0.01$) in all patients. LV volumes decreased, yet not significantly (LVEDV: 163.8 ± 69.9, 139.2 ± 54.6 ml, $p = 0.5$; LVESV: 86.4 ± 47.8, 82.3 ± 51.3 ml, $p = 0.5$) and LV function remained unchanged ($p = 0.9$). Measures for RV volumes and function were not statistically changed after FU (Supplemental Table 1).

TR-related clinical outcomes and mortality after TMVR

In comparison to patients with TR ≤ II at baseline, patients with baseline TR > II showed significantly less amelioration in functional capacity, presented with higher functional NYHA classes (NYHA class >II: TR > II: 42.37%, TR ≤ II: 28.3%, $p = 0.04$) and shorter 6-min walking distances (6MWT: TR > II: 269 ± 90.4 m, TR ≤ II: 273.6 ± 115.8 m, $p = 0.04$) (Figs. 1, 2). Patients with TR > II at baseline showed increased hospitalization rates ($p = 0.05$). Moreover, we found higher levels of NT pro-BNP at FU in patients with baseline TR > II (TR > II: 4525.1 ± 5918.4 pg/dl, TR ≤ II: 3116.5 ± 3918.7 pg/dl; $p = 0.05$) (Fig. 2; Table 4). Of note, residual MR was not different between the TR groups. RV function was not different between the patient groups and was not significantly changed from baseline measurements (Table 4). RVEDD ($p = 0.02$) and IVC diameter ($p = 0.03$) remained

Table 3 Procedural details and outcome

	All patients ($n = 261$)	TR ≤ II ($n = 220$)	TR > II ($n = 41$)	p
Post-clip MR, %				0.05
0–I	56.1	58.6	43.9	
II	41.2	39.1	53.6	
III	2.3	2.3	2.4	
IV	0	0	0	
Procedural success, %	96.2	97.3	92.6	0.2
Number of clips, *n*	1.5 ± 0.6	1.4 ± 0.6	1.6 ± 0.7	0.1
Procedure duration, min	75.6 ± 43.9	75.7 ± 44.8	75.3 ± 41	0.8
Fluoroscopy time, min	25.9 ± 19.4	25.8 ± 20.2	25.1 ± 16.3	0.9

TR tricuspid regurgitation, *MR* mitral regurgitation

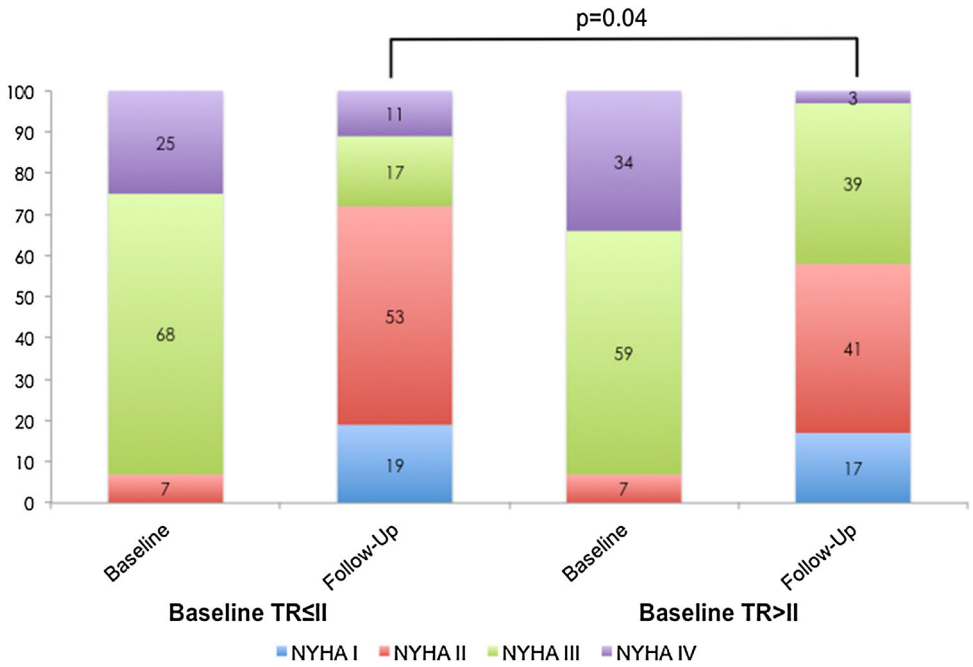

Fig. 1 Functional NYHA class at baseline and follow-up, separated following baseline TR > II and TR ≤ II

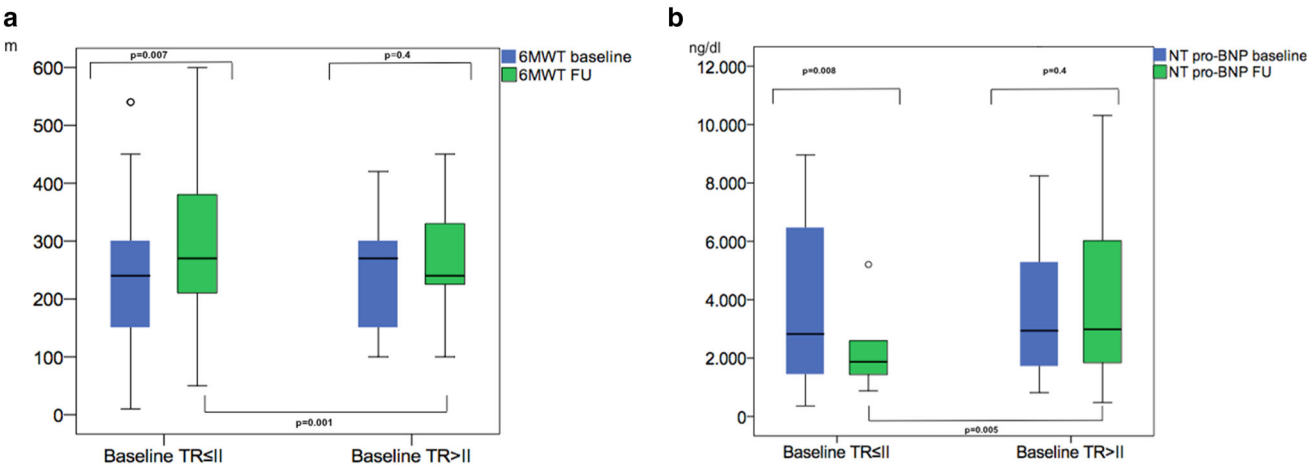

Fig. 2 *Boxplot* diagrams of changes in **a** 6-min walking distances and **b** NT pro-BNP levels in patients with TR > II and TR ≤ II

significantly larger in patients with TR grades >II but did not differ from baseline measurements. Of note, 30 days FU echocardiography revealed remaining TR > II in 35% of patients with baseline TR > II and after 2 years of FU the proportion of patients with TR > II in the baseline TR > II group was decreased to 31.7%.

Predictors of clinical outcomes and mortality

During FU 15.7% ($n = 41$) of patients deceased (82% due to cardiovascular causes, 18% due to other causes or unknown). The logistic EuroSCORE ($p = 0.03$), baseline 6MWT ($p = 0.05$), baseline functional NYHA class ($p = 0.012$), baseline sPAP ($p = 0.018$), residual MR after Clip implantation ($p = 0.04$), and baseline MVG ($p = 0.04$) were significant predictors of survival following univariate regression analysis.

Following multivariate analysis using Cox regression baseline only baseline TR > II (HR: 2.04) was an independent predictors of mortality after MitraClip procedure (Table 5). Kaplan–Meier analysis showed a higher mortality for patients with TR > II when compared to patients with TR ≤ II ($p = 0.05$) (Fig. 3).

Discussion

The main findings of our study are:

1. Concomitant TR is present in a relevant subset of patients undergoing MitraClip procedures (45%),

Table 4 Functional and echocardiographic outcomes, patients separated by baseline TR

	All patients	TR ≤ II	TR > II	*p*
NYHA, %				0.04
I	17.9	18.8	16.9	
II	46.4	52.8	40.6	
III	28.6	16.9	38.9	
IV	7.1	11.5	3.6	
6MWT, m	272.6 ± 112.1	286.4 ± 119.1	262.1 ± 106.1	0.04
NT pro-BNP, ng/dl	4055.6 ± 5314.2	3116.5 ± 3918.7	4525.1 ± 5918.4	0.05
MR, %				0.8
0/I	28.2	33.3	25	
II	69.2	60	75	
III	2.6	6.7	0	
IV	0	0	0	
TR, %				0.4
0/I	40.6	53.8	31.5	
II	37.5	38.5	36.8	
III	21.9	7.7	31.7	
IV	0	0	0	
Mean MVG, mmHg	3.5 ± 3	2.9 ± 1.3	3.8 ± 3.5	0.3
LVEF, %	43.9 ± 14.7	44.8 ± 15.2	43.1 ± 14.3	0.5
sPAP, mmHg	37.3 ± 14	36.2 ± 14.7	38.2 ± 13.4	0.4
TAPSE, cm	22 ± 6	21 ± 7	23 ± 4	0.6
RVEDD, mm	33 ± 2	36 ± 5	46 ± 7	0.02
FAC, %	49 ± 3	48 ± 5	46 ± 8	0.7
IVC, mm	18 ± 4	18 ± 6	24 ± 5	0.03

TR tricuspid regurgitation, *MR* mitral regurgitation, *FMR* functional mitral regurgitation, *LVEF* left ventricular ejection fraction, *TAPSE* tricuspid annular plane systolic excursion, *sPAP* systolic pulmonary arterial pressure, *RVEDD* right ventricular enddiastolic diameter, *IVC* inferior vena cava, *FAC* fractional area change, *MVG* mean mitral valve gradient, *6MWT* 6-min walking test, *NYHA* New York Heart Association, *NT pro-BNP* N terminal pro brain natriuretic peptide

Table 5 Multivariate Cox regression analysis of factors predicting mortality

	HR	95% CI	*p*
EuroScore	1.01	0.98–1.04	0.37
6MWT	0.99	0.99–1.91	0.06
NYHA class	1.08	0.43–2.71	0.86
sPAP	0.99	0.97–1.02	0.96
Residual MR	0.82	0.5–1.86	0.2
MVG	0.78	0.16–3.6	0.74
TR > II	2.04	1.2–3.5	0.007

HR hazard ratio, *CI* confidence interval, *6MWT* 6-min walking test, *NYHA* New York Heart Association, *sPAP* systolic pulmonary arterial pressure, *MR* mitral regurgitation, *MVG* mean mitral valve gradient, *TR* tricuspid regurgitation

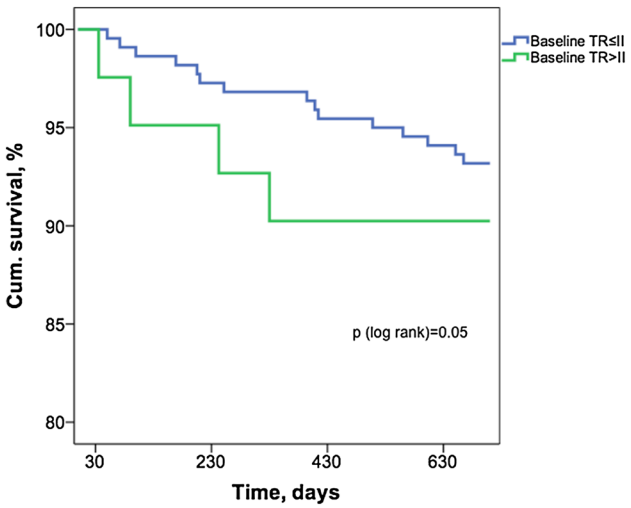

Fig. 3 Kaplan–Meier survival graph, stratified by baseline TR > II and TR ≤ II

thereof a relevant number of more than mild (>grade II) TR (15.7%).

2. TR grade >II at baseline is associated with adverse clinical and functional outcome, as assessed by 6MWT, NT pro-BNP levels and NYHA class.
3. TR grade >II at baseline is the strongest independent predictor for mortality in patients undergoing TMVR with the MitraClip system.

Incidence of concomitant TR in MR patients and impact on mortality

Concomitant TR is a common finding in patients with symptomatic MR [7, 15]. In our study we found a prevalence of TR of 45%, which is in line with other reports [7]. Of note, De Bonis and co-workers found a relatively high incidence of relevant TR (63%) in patients with dilative cardiomyopathy and functional MR and TR were found to be progressive if left untreated. The authors suggested a more aggressive surgical treatment approach for TR [9].

In patients with MV disease, concomitant TR has a detrimental effect on outcome and predicts poor survival [7].

Despite this fact, TR is currently under-treated maybe also due to the understanding that it resolves after treatment of left-sided pathologies. Furthermore, isolated surgical approaches for the treatment of TR are associated with an unreasonable high in-hospital mortality, which is reported as high as 30% [16].

TR is often due to pressure or volume overload of the RV, which results from left-sided heart pathologies such as myocardial infarction, aortic or mitral valve disease. However, TR is more than an innocent bystander: it is related to high morbidity rates and poor outcomes. TR may reflect a combination of more advanced mitral disease as well elevated pulmonary hypertension or RV dysfunction [17]. On the other hand, we found no statistic differences between comorbidities or echocardiographic parameters for RV or LV function.

Data from the national GRASP and TRAMI (unpublished data) registries suggests that patients undergoing a MitraClip procedure for symptomatic MR with concomitant TR at baseline might suffer a higher mortality and hospitalization for heart failure rates compared to patients without TR, as seen likewise in our study [17]. Of note, the GRASP registry demonstrated an association of TR > II with a combined endpoint of death and rehospitalization, in line with our findings [17].

Results from different researchers show, that mortality and functional outcome after MitraClip procedures depend on residual MR [18, 19].

However, Ohno et al. found no significant difference in residual MR after FU between the patients with or without TR, in line with our findings [17]. Thus, our results might suggest, that functional outcome and survival are limited in patients undergoing TMVR, who present with moderate-to-severe TR before MitraClip procedures, although the clip-procedure itself has been successful.

However, the FU was relevantly shorter in GRASP and patients were relevantly younger (73 versus 80 years) and presented with lesser comorbidities.

We found functional capacities to be limited in patients with TR > II as assessed by 6MWT and NT pro-BNP which is beyond the findings of the GRASP researchers, who did not present data on functional outcomes.

Clinical implications

Despite the considerable high incidence of significant TR in patients with MR planned for MitraClip procedures and the probable devastating consequences if left untreated, pharmacological and surgical treatment is limited and reserved for a fraction of patients.

According to the presented data, we speculate that treatment of TR could further improve clinical performance and, ultimately, outcome. As of now, surgical options apply only in patients scheduled for open heart surgery for other (left heart) reasons. In other patients, such as the herein analyzed MitraClip population, open heart surgery has been deferred for various reasons and therefore, TR would have also to be addressed by catheter-based strategies. Thus, there is an unmet need for interventional, low-risk alternatives for the treatment of concomitant TR in patients with (or without) symptomatic MR.

Some interventional approaches for the treatment of TR are in clinical testing, and only limited procedural and functional outcome data are available. The key pathology of functional TR is malcoaptation of the leaflets due to annular or RV dilatation.

Case reports from Schofer and our group indicated on the potential benefits of direct tricuspid valve annuloplasty by use of the Mitralign system (Mitralign Inc., Tewksbury, MA, USA) by placing pairs of pledgets at the septo-posterior and anterior annulus in order to possibly achieving bicuspidalization of the tricuspid valve mimicking the surgical Kay procedure [20, 21]. Furthermore, the interventional edge-to-edge repair with the MitraClip system has been successfully applied in isolated patients with TR [22].

The TriCinch (4Tech Inc., Galway, Ireland) device is currently under clinical investigation and preliminary data show that reduction of TR using this device seems to be feasible. The Forma repair system (Edwards Lifesciences, Irvine, California, USA) consists of a spacer that is placed between the tricuspid leaflets to enhance coaptation and reduce regurgitation. The cardioband device (Valtech Cardio, Or Yehuda, Israel) is implanted from the septo-posterior to the septo-anterior tricuspid commissure, cinching of the band may effectively reduce annular dimensions and regurgitation. However, all of those dedicated devices are in early stages of clinical development and investigation and have only been used in a very limited number of patients. Data on long-term mortality or functional outcomes are not existent, as pointed out before [23].

Herein we report on the impact of TR on long-term survival and functional outcomes in patients with symptomatic MR undergoing TMVR with the MitraClip system.

Study limitations

Our study is limited by its single center nature. Furthermore, our sample size is relatively small and FU could not be completed in all patients. Given the limited number of included patients, our findings might not hold true for a larger MitraClip-collective. Of note, we included mainly patients with FMR, and thus our results might not be fully reproducible in a cohort comprising predominantly DMR patients.

Assessment of TR grade included semi-quantitative echocardiographic parameters as well as qualitative parameter in our study. However, the tricuspid valve apparatus is, although comparable to the mitral valve, more variable and exact quantification of TR is more complex and interobserver variability is supposedly higher than in MR evaluation. Furthermore, standards for evaluation of TR severity are less robust than for MR and the algorithms for color-Doppler-derived parameters for the assessment of TR severity are less established. Our presented results should be reconfirmed with independent and larger patient cohorts. An independent echocardiographic core lab did not validate the echocardiographic studies.

Conclusion

TR > II at baseline negatively influences functional outcome and mortality in patients undergoing interventional edge-to-edge repair with the MitraClip system for symptomatic MR. Our results suggest the need for dedicated interventional strategies for the treatment of concomitant TR in patients with symptomatic MR. Larger, randomized studies are needed to validate our findings.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

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3.2 Öztürk C, Fasell T, Sinning JM, Werner N, Nickenig G, Hammerstingl C, Schueler R. Left atrial global function in chronic heart failure patients with functional mitral regurgitation after MitraClip. Catheter Cardiovasc Interv. 2020 Sep 1; 96(3):678-684.

Zielsetzung der Arbeit: Aufgrund der zunehmenden Volumenbelastung bei relevanter chronischer MI wird das LA kontinuierlich größer, gefolgt von einem korrespondierenden Remodeling und einer konsekutiven Reduktion der LA-Funktion. Ziel war es, die Auswirkung des MitraClip™-Verfahrens auf die linksatriale Geometrie und Funktion sowie den Stellenwert des LA während der Prognoseabschätzung und der Patientenauswahl mit prozeduralem Timing bei FMI-Patienten zu untersuchen.

Methoden und Ergebnisse: Wir schlossen von Februar 2014 bis zum November 2015 insgesamt 50 operative Hochrisiko-Patienten (77 ± 9 Jahre, 22 % weiblich, mittlerer logistischer EuroSCORE: 17,2%) mit chronischer Herzinsuffizienz und mittel- bis hochgradiger FMI ein. Alle Patienten wurden mittels MitraClip™-System versorgt. Beim Einschluss waren alle Patienten hoch symptomatisch (100 % NYHA-Klasse > II) mit eingeschränkter funktioneller Kapazität (Sechs-Minuten-Gehstrecke: 105,5 ± 15,2 m). Zur Vermeidung eines möglichen Bias wurden die Patienten mit vorliegendem Vorhofflimmern ausgeschlossen. Zur umfassenden linksatrialen Analyse verwendeten wir die 3D-Datensätze des apikalen Vierkammerblickes (Komplettvolumen). Die Bilder wurden mit Hilfe einer auf dem Markt verfügbaren, dedizierten Software (TomTec™ Image Arena) analysiert. Das linksatriale Endokard wurde manuell umfahren und halbautomatisch endsystolisch sowie enddiastolisch als Bereich des Interesses (Region of Interest – ROI) identifiziert. Anschließend wurde die Offline-Strain-Analyse durchgeführt und die Ergebnisse wurden angezeigt (siehe Figure 1, p. 680, Öztürk et al., 2019). Bei 27 Patienten (54 %) konnte eine Reduktion um zwei Grade und bei den restlichen 23 Patienten um einen Grad ohne periinterventionelle gravierende Komplikation erzielt werden. Die Nachbeobachtungsuntersuchungen zeigten eine anhaltende effektive MI-Reduktion (100 % MI ≤ Grad II) und verminderte Herzinsuffizienz-Symptome (95 % NYHA-Klasse ≤ II, p = 0,01) mit gesteigerter funktioneller Kapazität (Sechs-Minuten-Gehtest von 105,5 ± 15,2 m auf 210,3 ± 35,8 m, p = 0,01). Echokardiographisch sahen wir zwölf Monate nach dem erfolgreichen MitraClip™-Verfahren einen statistisch signifikanten Anstieg der E/E'-Ratio als Hinweis auf einen erhöhten linksventrikulären enddiastolischen Druck (15,6 ± 7,3 auf 24,1 ±

13,2 p = 0,05). Zudem wurde eine signifikante Zunahme der LA-Volumina (LA-EDV: 83,1 ± 39,5 ml auf 115,1 ± 55,1 ml, p = 0,013; LA-ESV: 58,4 ± 33,4 ml auf 80,1 ± 43,9 ml, p = 0,031) sowie der LA-Muskelmasse (105,1 ± 49,3 g auf 145,4 ± 70,6 g, p = 0,013) dokumentiert. Darüber hinaus stellte sich das LA-Schlagvolumen als signifikant verbessert dar (24,6 ± 12,5 ml auf 34,9 ± 19,1 ml, p = 0,016). Dennoch gab es keine relevanten Veränderungen der linksatrialen Ejektionsfraktion (LA-EF) sowie des linksatrialen globalen Strains (LA-Strain) bei den Nachbeobachtungsuntersuchungen. Zur weiteren Evaluation des linksatrialen Effektes auf die Gesamtsterblichkeit führten wir eine multivariate Cox-Regressionsanalyse durch. Es stellte sich heraus, dass die E/E'-Ratio beim Einschluss (Cut-off-Wert: 18,8), der LA- Strain (Cut-off-Wert: -8,7 %) und die LA-EF (Cut-off-Wert: 26,4 %) die unabhängigen Prädiktoren für die Ein-Jahres-Gesamtsterblichkeit sind. Figure 2 zeigt den Vergleich der ROC (Receiver operating charachteristics)-Kurven der genannten Parameter (p. 682, Öztürk et al., 2019).

Schlussfolgerungen**:** Das Schlagvolumen, die Volumina sowie die Muskelmasse des LA steigen nach dem MitraClip™-Verfahren. Trotz keiner relevanten Veränderungen während der Nachbeobachtungszeit fanden wir den LA-Strain als stärksten Indikator für die Ein-Jahres-Gesamtsterblichkeit sowie die residuale MI. Darüber hinaus ist die E/E'-Ratio ebenfalls als ein Prognose-relevanter echokardiographischer Parameter zu betrachten und während der präinterventionellen Entscheidungsfindung zu berücksichtigen, und zwar bei FMI-Patienten mit vorliegender eingeschränkter linksventrikulärer Dysfunktion.

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ORIGINAL STUDIES

EDITORIAL COMMENT: Expert Article Analysis for:
Left atrial function, the cherrie on top in understanding clinical outcomes in functional mitral regurgitation

Left atrial global function in chronic heart failure patients with functional mitral regurgitation after MitraClip

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Abstract

Background: Left atrial (LA) volumes and function are believed to improve following interventional reduction of mitral regurgitation (MR) with MitraClip. However, exact LA alterations after MitraClip in patients with functional MR and functional mitral regurgitation (FMR) are unknown.

Objectives: We aimed to evaluate the effect of MitraClip on LA volumes and global function in patients with FMR and its importance for patients' prognosis.

Methods: All patients underwent three-dimensionally transthoracic echocardiography with an offline evaluation of LA geometry and strain analysis at baseline and follow-up (FU). FU examinations were planned for 6 and 12 months after MitraClip.

Results: We prospectively included 50 consecutive surgical high-risk (logistic EuroSCORE: 17.2 ± 13.9%) patients (77 ± 9 years, 22% female) with symptomatic moderate-to-severe to severe functional MR without atrial fibrillation.

Echocardiographic evaluation showed that the E/E' ratio was significantly higher at FU (15.6 ± 7.3, 24.1 ± 13.2, p = .05) without relevant changes in systolic left ventricle (LV) function (p = .5). LA volumes (end-diastolic volume [LA-EDV] and end-systolic volume [LA-ESV]) (LA-EDV: 83.1 ± 39.5 ml, 115.1 ± 55.3 ml, p = .012; LA-ESV: 58.4 ± 33.4 ml, 80.1 ± 43.9 ml, p = .031), muscular mass (105.1 ± 49.3 g, 145.4 ± 70.6 g, p = .013), as well as LA stroke volume (24.6 ± 12.5 ml, 34.9 ± 19.1 ml, p = .016) significantly increased after the procedure. LA ejection fraction (LA-EF: 31.7 ± 12.8%, 31.1 ± 12.3%, p = .8) and atrial global strain (aGS: −10.8 ± 5.4%, −9.7 ± 4.45%, p = .4) showed no significant changes at FU.

Despite no relevant changes during FU, the baseline aGS was found to be the strongest predictor for mortality and adverse interventional outcome.

Abbreviations: aGS, atrial global strain; CHF, chronic heart failure; E/E' ratio, the ratio between early mitral inflow velocity and mitral annular early diastolic velocity. An indirect sign for left ventricular end-diastolic pressure; FMR, functional mitral regurgitation; FU, follow-up; LA-EF, left atrial ejection fraction; LV, left ventricle; LV-EF, left ventricular ejection fraction; MPG, mean mitral pressure gradient; MV, mitral valve; NYHA, New York Heart Association; TMVr, transcatheter mitral valve repair; TTE, transthoracic echocardiography.

Conclusion: MitraClip increases atrial stroke volume, atrial volumes, and muscular mass in patients with FMR. We found that the baseline aGS the strongest predictor for mortality, rehospitalization, and higher residual MR at FU.

KEYWORDS
chronic heart failure, functional mitral regurgitation, left atrium, MitraClip

1 | INTRODUCTION

Mitral regurgitation (MR) is a frequent valve disease in elderly (>75 years), chronic heart failure (CHF) patients. It is associated with reduced exercise capacity, recurrent hospitalizations, and impaired quality of life. MR, as reflux of a relevant volume during systole, causes chronic volume overload and consecutive enlargement of the left atrium (LA), followed by LA remodeling.[1,2]

Of note, chronically increased preload aggravates progressive heart failure and leads to recurrent hydropic decompensations. Chronic volume overload in LA increases the probability of developing supraventricular arrhythmias due to wall tension and remodeling of LA.[3,4]

Two dimensionally (2D) measured LA volumes are commonly used to assess LA function and geometry, which correlate with cardiac preload and LV diastolic dysfunction.[5] LA volumes are, furthermore, of use to grade MR severity and to evaluate for possible treatment options.[6] The assessment of LA function and geometry is established for patient selection and timing of mitral valve (MV) repair.[7–10] However, adequate assessment of LA function is challenging. 2D echocardiography obtains conventional static parameters of LA function. Besides, strain analysis of LA has been shown to be a feasible and practicable technique to sufficiently quantify virtual LA global function, not only contractile but also reservoir and conduit function.[11,12] Compared to the parameter from 2D transthoracic echocardiography (TTE), strain analysis of LA is angle-independent, not to be influenced by artifacts. It has been shown as a promising and effective parameter for evaluation of LA global function and remodeling in patients with chronic MR.[13]

Transcatheter mitral valve edge-to-edge repair (TMVr) with the MitraClip system (Abbot Vascular, Inc., Santa Clara, CA) is an established alternative to surgical MV therapy for symptomatic patients with MR at prohibitive surgical risk.[14–16]

Although more than 90,000 patients have undergone MitraClip procedures to date, the effects of MitraClip on LA volumes and function in patients with functional MR (FMR) and their prognostic value and importance for patient selection are not well understood. Except for a very limited number of studies comprising small patient numbers, most of the existing data on LA remodeling originate from patients with DMR or surgically treated patients.[17–19]

In this study, we aimed to analyze (a) LA global function using strain analysis, (b) the impact of TMVr with the MitraClip procedure on LA volumes and function in patients with FMR, and (c) its value in clinical routine concerning prognostic assessment, patient selection, and timing of therapy.

2 | METHODS

We prospectively included patients with impaired LV function and concomitant symptomatic FMR undergoing TMVr with the MitraClip procedure in our institution. Patients with atrial fibrillation at baseline were excluded to avoid discrepancies in LA analysis during the image acquisitions. All patients underwent three-dimensionally (3D) TTE prior to MitraClip and at Follow-up (FU). FU examinations were planned for 6 and 12 months ± 8 weeks after MitraClip.

2.1 | Patients

From February 2014 to November 2015, symptomatic (functional NYHA class >II), CHF patients with moderate-to-severe or severe FMR were evaluated for interventional versus surgical repair. All patients were on optimized heart failure therapy at baseline and underwent MitraClip according to heart team decision due to high surgical risk. At FU 3D-TTE, 6 min walking test (6-MWT) and clinical assessment were performed.

In line with the MV academic research consortium definitions, we defined the primary endpoint as all-cause mortality and secondary endpoints are the severity of MR at FU and rehospitalization during FU.

The study was authorized by the local ethics committee and in accordance with the Declaration of Helsinki. All patients signed written informed consent before study inclusion.

2.2 | Echocardiographic assessments

Echocardiographic assessment of patients was done following current recommendations and guidelines.[20,21] The echocardiographic studies were performed with a commercially available echocardiographic system (i.e., 33, Philips Medical Systems, Andover, MA) and echocardiography probes (X5-1), allowing acquisition of 2D and 3D data sets.

The echocardiographer who performed baseline and FU evaluation was blinded to the patients' characteristics and procedural outcomes. Study nurses carried out clinical FU evaluation, unattended by the interventionists or procedural echocardiographers.

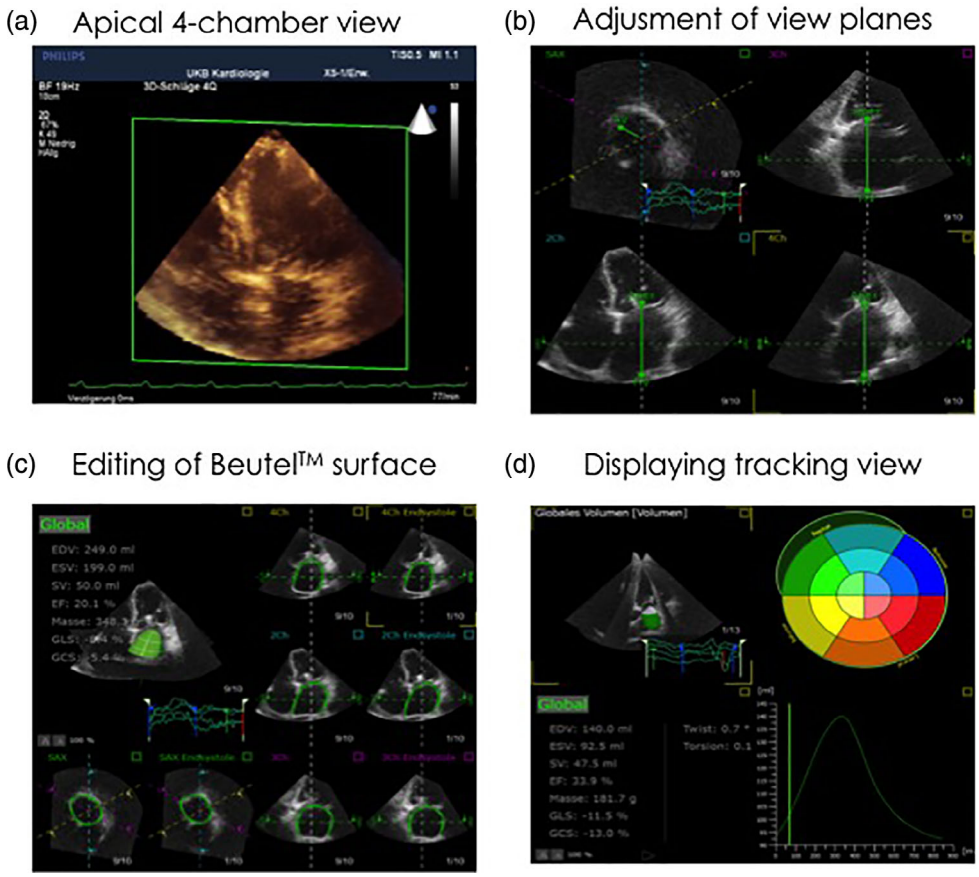

FIGURE 1 Left atrium (LA) analysis from three-dimensionally (3D) speckle tracking echocardiography. Complete volume data set from apical four-chamber view. Tracing myocardium (region of interest) during end-diastole (Beutel revision). Automated tracking revision during end-systole. Final results from 3D strain analysis of LA [Color figure can be viewed at wileyonlinelibrary.com]

2.3 | Evaluation of LA function and geometry, strain analysis of LA

The images were analyzed employing an offline workflow of dedicated software (TomTec Image Arena, four dimensional (4D) LV-Analysis, Munich, Germany) to assess LA function, geometry, and strain analysis. 3D complete volume datasets from apical four chamber views were used for the analyses. LA endocardium border was semi-automatically tracked (Beutel™) as a region of interest. In the case of suboptimal alignment, a manual adjustment was performed. Endocardium borders were automatically approved during end-diastole and end-systole. After that, the offline measurements from volumetric and strain analysis were automatically shown (Figure 1).

2.4 | Statistical analysis

The normal distribution of continuous variables was examined using the Kolmogorov–Smirnov test. Continuous data were expressed as mean values ± *SD*. Student's two-sample *t*-test or Man-Whitney *U*-test was performed to compare continuous variables. Categorical data were presented as frequencies and percentages. Fisher's exact test or chi-square test was used to compare categorical data. Two-tailed *p*-values were considered to be significant if ranging below .05. Cox proportional hazard regression analysis was performed to investigate LA-related predictors for all-cause mortality, rehospitalization, and echocardiographical outcome in patients with FMR after MitraClip. Statistics were performed using SPSS for Windows (PASW statistic, Version 20.0.0.0, SPSS Inc., Chicago, IL).

3 | RESULTS

We prospectively evaluated 70 CHF patients with symptomatic moderate-to-severe to severe FMR. Fifteen patients due to atrial fibrillation and five patients due to insufficient image quality were excluded. We included 50 patients (age: 77 ± 9 years, 22% female) with decreased functional capacity with high symptoms (100% functional NYHA class > II, walking distance: 105.5 ± 15.2 m). All patients underwent MitraClip procedures following heart team decisions due to high surgical risk (logistic EuroScore: 17.2 ± 13.9%).

Baseline echocardiography showed impaired left ventricular systolic function (LV ejection fraction [LVEF]: 32,6 ± 11.2%), moderate-to-severe to severe FMR (proximal isovelocity surface area: 0.8 ± 0.6 cm, effective regurgitant orifice area (EROA) 0.3 ± 0.6 cm^2, vena contracta width (VC) 0.8 ± 0.5 cm, regurgitant volume (RegVol) 51.4 ± 13.4 ml/beat, increased right ventricular systolic pressure (RVSP) (46.1 ± 10.5 mmHg) and increased E/E' ratio as a sign for elevated left ventricular end-diastolic pressure (LVEDP) (E/E' ratio: 15.6 ± 7.3). Further baseline characteristics are presented in Table 1.

TABLE 1 Demographical characteristics

	Value N = 50
Age, years	77.6 ± 9.1
BMI, kg/m^2	25.8 ± 3.7
Gender, female, % (*n*)	42 (21)
Logistic EuroScore, %	17.2 ± 13.9
STS score, %	5.8 ± 3.8
Race,	
Caucasian, % (*n*)	100 (50)
CAD, % (*n*)	62 (31)
PCI, % (*n*)	52 (26)
CABG, % (*n*)	30 (15)
Clinical frailty scale	6.1 ± 1.2
4, vulnerable, % (*n*)	16 (8)
5, mildly frail, % (*n*)	24 (12)
6, moderately frail, % (*n*)	40 (20)
7, severely frail, % (*n*)	20 (10)
Hypertension, % (*n*)	78 (39)
Hyperlipidemia, % (*n*)	64 (32)
Diabetes mellitus, % (*n*)	28 (14)
Nicotine consume, % (*n*)	40 (20)
Familial predisposition, % (*n*)	18 (9)
Stroke, % (*n*)	20 (10)
PAD, % (*n*)	32 (16)
COPD, % (*n*)	24 (12)
Creatinine, mg/dl	1.3 ± 0.9
Medical therapy, % (*n*)	
Beta-blocker, % (*n*)	80 (40)
ACE-blocker/ARB, % (*n*)	66 (33)
Diuretics, % (*n*)	78 (39)
Device therapy, % (*n*)	8 (4)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass surgery; CHD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STS-Score, Society of Thoracic Surgeons Score.

The MitraClip procedure was successfully performed in all patients with MR reduction to MR ≤ 2 or at least one grade reduction without any peri-interventional major complications. Twenty-seven (54%) patients had MR reduction of two grades, and 23 (46%) patients just one grade. Mean mitral pressure gradient (MPG) increased significantly without relevant mitral stenosis after the procedure (1.2 ± 0.2 mmHg, 3.3 ± 0.5 mmHg, p = .05).

There occurred no death in 30 days after the procedure. Seven patients (14%) died during the FU, and 42% due to cardiovascular causes. There were no significant changes in LV volumes (end-diastolic volume [LVEDV]: 161.3 ± 57.9 ml, 157.4 ± 55.5 ml, p = .6; end-systolic volume [LVESV]: 112.8 ± 53.1 ml, 113.1 ± 55.1 ml, p = .9) and LV systolic function (LVEF: 32.6 ± 11.2%, 30.1 ± 14%, p = .5) at FU. MR showed significant, sustained improvement (MR≤II) and heart failure symptoms decreased (functional NYHA class ≤II, 95%, p = .01) with increased functional capacity (walking distance: 105.5 ± 15.2 m vs. 210.3 ± 35.8 m, p = .01) in all surviving patients. Three patients with new onset of atrial fibrillation were documented during FU.

The E/E' ratio increased statistically significant at FU (15.6 ± 7.3, 24.1 ± 13.2, p = .05) as a surrogate parameter for an increased LVEDP. LA volumes increased significantly at FU (LA-EDV: 83.1 ± 39.5 ml, 115.1 ± 55.3 ml, p = .012; LA-ESV: 58.4 ± 33.4 ml, 80.1 ± 43.9 ml, p = .031) as well as LA-muscular mass (105.1 ± 49.3 g, 145.4 ± 70.6 g, p = .013). LA stroke volume was significantly improved after the procedure (24.6 ± 12.5 ml, 34.9 ± 19.1 ml, p = .016). Furthermore, LA-EF (31.7 ± 12.8%, 31.1 ± 12.3%, p = .8) and atrial global strain (aGS: −13.1 ± 4,4%, −11.6 ± 4.9%, p = .2) showed no changes at FU (Table 2).

For further evaluation of the effect of LA dynamics on mortality, we performed multivariate regression analysis. COX regression analysis showed baseline E/E' ratio (cutoff value: 18.8), aGS (cutoff value: −8.7%), and LA-EF (cutoff value: 26.4%) as independent predictors for all-cause mortality (Figure 2). Subsequently, in receiver operating characteristic (ROC) analysis, baseline aGS was found to be the strongest predictor for all-cause mortality (AUC: 0.796) (Figure 3). Moreover, we found baseline aGS (AUC: 0.740) as the strongest predictor for higher residual MR at FU (Figure 4).

4 | DISCUSSION

4.1 | Our major findings are as follows

First, atrial stroke volume, volumes, and muscular mass increase after TMVr with MitraClip in patients with FMR.

Second, E/E' ratio as a sign for LVEDP significantly increases after MitraClip, and baseline E/E' ratio > 18 indicates high all-cause mortality in patients with FMR postinterventionally.

Third, baseline aGS as a sufficient indicator for LA global function was found to be the strongest predictor for all-cause mortality, rehospitalization, and higher residual MR at FU without any significant alteration during FU.

Magnetic resonance imaging (MRI) is the gold standard for 3D assessing of LA function, geometry, and tissue patterns. However, it is not convenient for daily clinical routine due to high-cost and time-consuming acquisition. 3D-TTE was found to correlate well with MRI measurements, whereas 2D-TTE systematically underestimates LA volumes.[5,22,23] Of note, speckle tracking echocardiography (STE) was proven to be feasible to assess virtual LA global function and LA remodeling.[10,18,28]

Rammos et al. demonstrated improved LA function und reverse LA remodeling in 26 patients with functional MR after the MitraClip procedure. They performed STE in all patients at baseline and 3 months after the procedure. They found increased LV functions, LV-GLS, and improvement in LA global conduit and contractile function.[8] Compared with our study, we found no relevant changes in LV

TABLE 2 Echocardiographical characteristics: Comparison baseline and follow-up

	Baseline	Follow-up	*p*-value
LV-EF, %	32.6 ± 11.2	30.1 ± 14	.5
LV-EDV, ml	161.3 ± 57.9	157.4 ± 55.5	.6
LV-ESV, ml	112.8 ± 53.1	113.1 ± 55.1	.9
LV-muscular mass, g	237.3 ± 87.6	218.8 ± 86.3	.3
E/E´ ratio	15.6 ± 7.4	24.1 ± 13.2	.05
LV-GLS, %	−8.9 ± 4.7	−8.4 ± 5.2	.6
LA-EF, %	31.7 ± 12.8	31.1 ± 12.3	.8
LA-SV, ml	24.6 ± 12.5	34.9 ± 19.1	.016
LA-EDV, ml	83.1 ± 39.5	115 ± 55.3	.012
LA-ESV, ml	58.4 ± 33.4	80.1 ± 43.9	.031
LA-muscular mass, g	105.2 ± 49.3	145.5 ± 70.6	.013
aGS, %	−13.1 ± 4.4	−11.6 ± 4.9	.23
Mitral regurgitation, %	0	88	.00001
Grade I	0	10 (5)	
Grade II	0	78 (39)	
Grade III	86 (43)	12 (6)	
Grade IV	14 (7)	0	
PISA, cm	0.8 ± 0.6	0.2 ± 0.3	.0001
VC width, cm	0.8 ± 0.5	0.3 ± 0.1	.0001
EROA, cm^2	0.3 ± 0.6	0.1 ± 0.1	.0001
Regurgitation volume, ml	51.4 ± 13.4	15 ± 12.1	.0001
MPG, mmHg	1.2 ± 0.2	3.3 ± 0.5	.002
RVSP, mmHg	46.1 ± 10.5	32.1 ± 9.7	.005
TAPSE, cm	1.8 ± 0.3	1.9 ± 0.4	.09
Tricuspid regurgitation	2.1 ± 0.2	1.9 ± 0.4	.1

Abbreviations: EDV, end-diastolic volume; EF, ejection fraction; EROA, effective regurgitation orifice area; ESV, end-systolic volume; GLS, global longitudinal strain; LA, left atrium; LV, Left ventricle; MPG, mean mitral pressure gradient; PISA, proximal isovelocity surface area; RVSP, right ventricular systolic pressure; SV, stroke volume; VC, vena contracta.

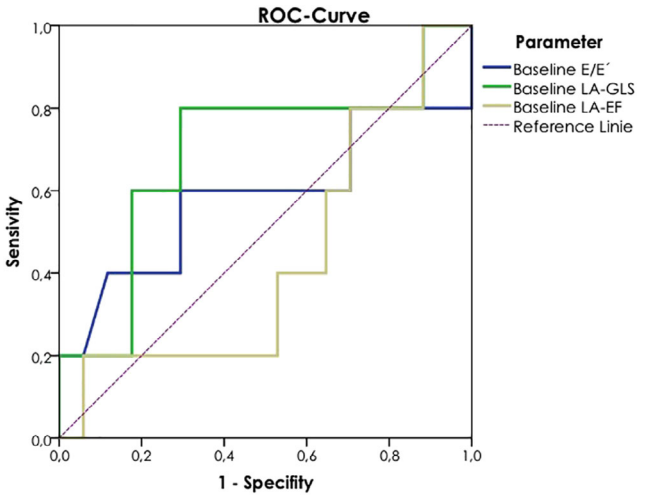

FIGURE 2 ROC curve analysis for showing the differential effect of predictors of mortality: Baseline left ventricle global longitudinal strain: (AUC: 0.694) > Baseline E/E' (AUC: 0.652) > Baseline left atrial ejection fraction: (AUC: 0.505) [Color figure can be viewed at wileyonlinelibrary.com]

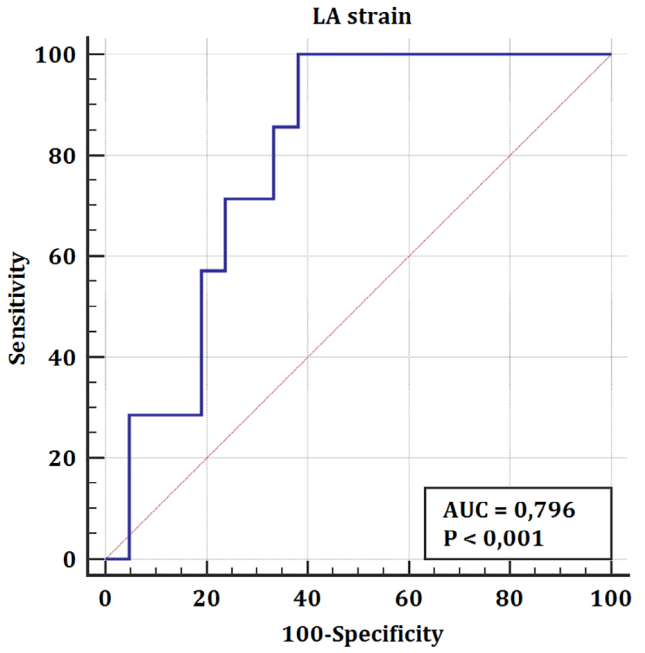

FIGURE 3 ROC curve analysis of the strongest predictor of mortality: atrial global strain [Color figure can be viewed at wileyonlinelibrary.com]

function and LA strain analysis. Furthermore, LA-EF was found to be unchanged in our patient cohort. Compared with the present study, they included patients with significantly better LV function (41% versus 32%) and followed up on the patients relevantly shorter (3 months vs. 12 months), which might account for the diverging findings between the studies.

Toprak et al. found improved LA strain rates and 3D LA volume index in 25 patients (92% FMR) 12 months after MitraClip as a possible explanation for reverse LA remodeling without changes in conventional LA indices. They showed LA reservoir strain and LA volume index as indicators for poor prognosis at 1-year-FU.[10] Conversely, we found increased LA volumes and unchanged aGS without relevant functional changes after the MitraClip procedure in our patient cohort. Despite the diverging findings in volumetrical and functional alterations after MitraClip, we found baseline aGS as the strongest predictor for survival in line with the study from Toprak and colleagues. Of note, they included mostly patients with DMR. On the other hand, our patient cohort presented with severely impaired baseline LV function, which might be a reason for a delayed or insufficient geometrical and functional adaptation of LA.

Although it is believed that LA volumes decrease due to lower LA volume overload through MR reduction, Radunksi et al. showed no decrease in LA volumes in 12 patients (58% with FMR) using cardiovascular magnetic resonance imaging (cMRI) 6 months after MitraClip.[21] These cMRI insights support our findings that LA volumes possibly tend to increase after the MitraClip procedure due to

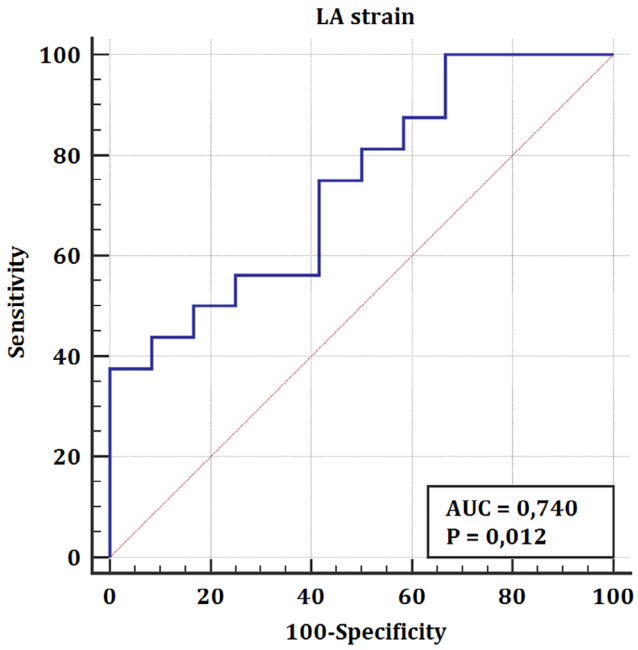

FIGURE 4 Predictor of interventional outcome: ROC curve analysis of baseline atrial global strain for interventional outcome [Color figure can be viewed at wileyonlinelibrary.com]

increased diastolic LV pressure through elevated MPG and lack of ability of the LV and LA to adapt to the changed pressure conditions. On the other hand, it might reflect preexisting irreversible LA remodeling in our patient cohort. Compared to our patient cohort, the patients in the study of Radunski and colleagues had normal LV systolic function (LV-EF: 53%) without LV dilatation (LVEDV: 98 ml, LVESV: 51 ml), thus "healthier" hearts at baseline.

Atrial reverse remodeling was shown by Avenatti et al. in 35 patients (21 DMR and 14 FMR). They found acutely decreased LA operating chamber stiffness correlated with improved functional capacity and systolic ventricular pressure, especially in patients with DMR 30 days after the MitraClip procedure.[24] In line with our cohort, they found no relevant alterations in LA strain, LA minimum volumes, and RVSP in patients with FMR. We additionally found elevated LA stroke volume 12 months after clipping. The diverging findings between patients with DMR and FMR might be explained by preexisting impaired LV and LA without sufficient capabilities to adapt and altered pulmonary circulation with high pulmonary pressures in patients with FMR compared with DMR. Decreased compensation capacity of LA for preload changes has been already shown in patients with rigid LA due to impaired LA reservoir function.[24,25] Due to lack of reverse remodeling and impaired function at baseline, LA could not compensate for the device-related increase in MPG (afterload) after MitraClip, which may cause further LA enlargement followed by recurrent MR or higher residual MR. This patient's cohort is probably delayed onset patients for transcatheter treatment. Therefore, no changes in LA function could be documented.

Ledwoch et al.[29] showed declined LA function (ejection fraction) in 32 patients with MR after MitraClip previously. In line with our data, they showed a significant linear correlation between impaired contractile LA function and all-cause mortality. Compared to our study, they used merely left atrial ejection fraction to assess LA function. Moreover, our patient cohort showed more impaired LV function with similar LA volumes and function.[24,29]

Different from DMR, diverging pathomechanisms are involved in patients with FMR: Firstly, impaired LV systolic and diastolic function. Secondly, severely enlarged LA with desolated function, and lastly, pathologic pulmonary circulation with elevated pulmonary pressure and right ventricular overload. Therefore, the treatment of CHF patients with FMR is more challenging concerning the optimization of medical therapy and the selection/timing of further (interventional) therapy. Furthermore, continued postinterventional treatment and FU are essential to get better outcomes.

Given the findings of MITRA-FR and COAPT, interventional treatment for FMR should be individually planned with interdisciplinary decision processes that have to take individual clinical and procedural aspects into account.[26,27]

The most of the cited previous studies have been performed mostly in patients with either only DMR or both (FMR and DMR). To the best of our knowledge, our study on the impact of MitraClip on LA function and geometry comprises the considerably largest patient cohort with CHF and concomitant only FMR, which were followed up and analyzed for LA volumes and function using 3D echocardiography.

4.2 | Limitations

This single-center study has several limitations. It was performed with a limited sample size and restricted duration of FU time. Echocardiographical analyses were not done by an independent blinded core-lab. We excluded the patients with atrial fibrillation at baseline. It might be a reason for bias. On the other hand, eliminating the patients with paroxysmal atrial fibrillation was not possible. The validity of mortality-predicting parameters should be proven either by subgroup analysis according to cutoff values or propensity matching. Furthermore, our study was not powered for the assessment of predictors of the secondary endpoint. Because of that, our preliminary results should be proven in multicentric, blinded, and randomized studies with independent, more extensive patient collective with longer FU.

5 | CONCLUSION

Following catheter-based edge-to-edge treatment of FMR with the MitraClip system atrial stroke volume, atrial volumes and muscular mass increased. It might partly be explained by increased LVEDP due to elevated MPG after the device implantation and a certain lack of compensation capacity of LA and LV with preexisting functional impairment. Despite no significant alteration, baseline aGS as a virtual parameter of LA global function was found to be the strongest predictor for clinical (mortality, rehospitalization) and echocardiographical (residual MR) outcomes. Besides, the baseline E/E' ratio (>18) significantly predicts postinterventional mortality as well. They may be

useful for challenging decision-making of therapy regimes and patient selection, especially in FMR patients with preexisting impaired LV function.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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3.3 Öztürk C, Sprenger K, Tabata N, Sugiura A, Weber M, Nickenig G, Schueler R. The predictive value of intraprocedural mitral gradient for outcomes after MitraClip and its peri-interventional dynamics. Echocardiography. 2021 Jul; 38(7):1115-1124.

Zielsetzung der Arbeit: Sowohl gemäß den Leitlinien als auch den großen multizentrischen Studien ist ein postinterventioneller mittlerer Mitralklappengradient (MPG) > 5 mmHg mit schlechteren klinischen Ergebnissen nach dem MitraClip™-Verfahren verbunden und daher zu vermeiden. Andererseits gibt es Studien, die keinen relevanten prädiktiven Wert des MPG hinsichtlich der postinterventionellen Outcomes nach dem MitraClip™-Verfahren insbesondere bei Patienten mit FMI zeigen. Bei einem anderen Aspekt wird die periinterventionelle Beurteilung des MPG anspruchsvoll und von diversen Faktoren (Herzfrequenz, Blutdruck, aktueller Rhythmus, Katecholamine, Echokardiographie-assoziierte Faktoren, Compliance des LA, linksventrikulärer enddiastolischer Druck sowie valvuläre Eigenschaften) beeinflusst. Diese Faktoren sind teilweise dynamische bzw. zeitvariante Parameter, die zu Fehlabschätzungen führen können. Die Ziele dieser Studie waren es, die dynamischen periinterventionellen Veränderungen des MPG zu evaluieren, die Auswirkung des intraprozedural erfassten MPG auf das klinische Outcome einzuschätzen und die Prädiktoren des erhöhten postinterventionellen MPG zu analysieren.

Methoden und Ergebnisse: Wir untersuchten 175 mittels MitraClip™-System behandelte Patienten (81,2 ± 8,2 Jahre, 61,2 % weiblich) sowohl mit DMI (40 %) oder FMI (42,8 %) als auch mit MI gemischter Ätiologie (17,2 %). In der initial durchgeführten multivariaten Regressionsanalyse mit anschließender ROC-Analyse fanden wir heraus, dass der intraprozedurale MPG ein signifikanter unabhängiger Prädiktor für die Ein-Jahres-Sterblichkeit mit einem Cut-off-Wert von 4,5 mmHg ist. Anhand dieses Cut-off-Wertes teilten wir unser Patientenkollektiv in zwei Gruppen auf (Gruppe 1: < 4,5 mmHg, Gruppe 2: ≥ 4,5 mmHg). Beim Einschluss zeigten alle Patienten eine symptomatische (100 % NYHA-Klasse > II) hochgradige MI (PISA: 0,8 ± 0,2 cm, VC: 0,8 ± 1,2 cm, EROA: 0,5 ± 0,3 cm^2, Regurgitationsvolumen: 51,1 ± 19,7 ml) mit einer eingeschränkten linksventrikulären systolischen Funktion (LV-EF: 44,7 ± 16,3 %) ohne relevante linksventrikuläre Dilatation (LVEDV: 96,9 ± 40,5 ml, LVESV: 56,6 ± 34,6 ml). Bezüglich der demographischen sowie klinischen Parameter waren

die beiden Gruppen beim Einschluss vergleichbar. Echokardiographisch zeigten die Patienten aus der Gruppe 2 einen höheren präinterventionellen MPG (2,6 ± 1,1 mmHg vs. 1,5 ± 1 mmHg, p = 0,001) ohne weitere signifikante Unterschiede zwischen den Gruppen. Es wurden bei 95 Patienten (54 %) ein Clip-Device erfolgreich verwendet, bei 75 Patienten (43 %) waren es zwei Clip-Devices und bei fünf Patienten (3 %) drei. In den postinterventionellen Echokardiographien stellten wir eine Reduktion des MPG auf < 4,5 mmHg bei elf Patienten der Gruppe 2 fest. Somit waren bei Entlassung nur noch zehn Patienten in der Gruppe 2. Während der sechsmonatigen Nachbeobachtungszeit wurde ein Anstieg des MPG auf ≥ 4,5 mmHg bei sieben Patienten dokumentiert. Die sechsmonatige Gesamtsterblichkeit betrug 8,5 % (n = 15) (siehe Figure 1, p. 1120, Öztürk et al., 2021). Obwohl in den beiden Gruppen die anhaltende MI-Reduktion vergleichbar war (MI ≥ Grad III 91 % auf 2 %, p < 0,01 vs. 94 % auf 6 %, p < 0,01), fanden wir die Verbesserung der NYHA-Klasse (NYHA-Klasse > II 100 % auf 26 %, p < 0,001) sowie der Gehstrecke (252,2 ± 127,8 m auf 348,3 ± 80,7 m, p = 0,05) nur in der Gruppe 1 signifikant verändert. Die Patienten der Gruppe 2 zeigten keine signifikanten Veränderungen der genannten Parameter (NYHA-Klasse > II 100 % auf 73 %, p = 0,5 sowie 210,8 ± 46,5 m auf 223,3 ± 25,8 m, p = 0,3). Dementsprechend stellte sich der NT-proBNP-Wert in der Gruppe 1 als rückläufig dar (2874 pg/ml auf 2436 pg/ml, p = 0,3), wohingegen er in der Gruppe 2 steigend war (2836 pg/ml auf 3462 pg/ml, p = 0,6). Im Log-Rang-Test fanden wir einen statistisch signifikanten Unterschied hinsichtlich der Ein-Jahres-Gesamtmortalität zwischen den Gruppen (20,7 % vs. 42,8 % p = 0,02). Die Überlebenszeitdaten sind anhand der Kaplan-Meier-Kurve in Figure 2 dargestellt (p. 1122, Öztürk et al., 2021). Der intraprozedurale MPG wurde als der stärkste unabhängige Prädiktor für die Ein-Jahres-Mortalität (OR: 1,70, 95 % CI: 0,95–3,05, p = 0,05) und für das ungünstige funktionelle Outcome (OR: 1,96, 95 % CI: 1,02–3,75, p = 0,04) ermittelt. Um den Effekt der Clip-Position auf den intraprozeduralen MPG zu evaluieren, führten wir den Kruskal-Wallis-Test bei Patienten mit Ein-Clip-Implantation durch. Er erbrachte einen signifikant höheren intraprozeduralen MPG bei der zentralen Clip-Implantation im Vergleich zur nichtzentralen Clip-Position (3,58 ± 1,7 mmHg vs. 2,83 ± 1,2 mmHg, p = 0,02). Unter diesem Gesichtspunkt fanden wir, dass die zentrale Clip-Orientierung den höchsten intraprozeduralen MPG (3,58 ± 1,7 mmHg) verursacht, gefolgt vom Cross-Clipping (3,2 ± 1,7 mmHg). Die nichtzentrale und nichtgekreuzte Clip-Implantation

führte zum niedrigsten intraprozeduralen MPG (2,66 ± 1,04 mmHg). Die Varianzanalyse bezugnehmend auf die Auswirkung der MI-Ätiologie auf den intraprozeduralen MPG ergab, dass die Patienten mit DMI (4,15 ± 1,6 mmHg) oder gemischter MI (4,19 ± 1,89 mmHg) einen statistisch signifikant höheren intraprozeduralen MPG als die Patienten mit FMI (3,58 ± 1,56 mmHg) hatten ($p = 0,001$). Zur weiteren Evaluation der Prädiktoren für einen ungünstigen intra-prozeduralen MPG wurde eine lineare Regressionsanalyse hinsichtlich der anatomischen Gegebenheiten der Mitralklappe durchgeführt (siehe Abbildung 9). Wir fanden eine signifikante negative lineare Korrelation zwischen dem intraprozeduralen MPG und dem anteroposterioren Diameter der Mitralklappe ($r = 3,75$, 95 % CI: 3,57–3,94, $p < 0,001$) mit einem Cut-off-Wert von 38 mm.

Schlussfolgerungen**:** Der intraprozedurale MPG ist ein starker Prädiktor – und zwar nicht nur für die Ein-Jahres-Mortalität (Cut-off-Wert: 4,5 mmHg), sondern auch für das ungünstige funktionelle Outcome (Cut-off-Wert: 3,9 mmHg). Zudem stellte sich der Leaflet-to-Annulus-Index (Cut-off-Wert: 1,11) als der stärkste Prädiktor für den höheren intraprozeduralen MPG heraus. Die anderen Indizes für den intraprozeduralen MPG sind der MPG bei Einschluss, die Anzahl der implantierten Clips und die Clip-Orientierung. Darüber hinaus sahen wir einen stärkeren Einfluss des intraprozeduralen MPG > 4,5 mmHg auf die Ein-Jahres-Mortalität sowie die klinischen Ergebnisse als die residuale MI > Grad II.

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ORIGINAL ARTICLE

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The predictive value of intraprocedural mitral gradient for outcomes after MitraClip and its peri-interventional dynamics

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Abstract

Background: The current data on the impact of the increased mitral gradient (MG) on outcomes are ambiguous, and intraprocedural assessment of MG can be challenging. Therefore, we aimed to evaluate (a) peri-interventional dynamics of MG, (b) the impact of intraprocedural MG on clinical outcomes, and (c) predictors for unfavorable MG values after MitraClip.

Methods: We prospectively included patients who underwent MitraClip. All patients underwent echocardiography at baseline, intraprocedurally, at discharge, and after 6 months. 12-month survival was documented.

Results: One hundred and seventy five patients (age 81.2 ± 8.2 years, 61.2% male) with severe mitral regurgitation (MR) were included. We divided our cohort into two groups according to intraprocedural MG with a threshold of 4.5 mm Hg, determined by a multivariate analysis of predictors for 12-month mortality (<4.5 mm Hg: Group 1, ≥4.5 mm Hg: Group 2).

Intraprocedural MG ≥4.5 mm Hg was found to be the strongest independent predictor for 12-month mortality (HR: 2.33, $P = .03$, OR: 1.70, $P = .05$), and >3.9 mm Hg was associated with adverse functional outcomes (OR: 1.96, $P = .04$).

The baseline leaflet-to-annulus index >1.1 was found to be the strongest independent predictor (OR: 9.74, $P = .001$) for unfavorable intraprocedural MG, followed by the number of implanted clips ($P = .01$), MG at baseline ($P = .02$), and central clip implantation ($P = .05$).

Conclusion: An intraprocedural MG <3.9 mm Hg appears to be the best strategy for 1-year survival and favorable functional outcomes after edge-to-edge MV repair with MitraClip independently from MR etiology. Peri-interventional echocardiographic and procedural parameters are useful for the adequate assessment of intraprocedural MG.

KEYWORDS

MitraClip, mitral gradient, mitral regurgitation, outcome

1 | INTRODUCTION

Transcatheter edge-to-edge mitral valve (MV) repair with the MitraClip system is increasingly regarded as a successful and effective therapeutic alternative to surgical therapy for relevant refractory mitral regurgitation (MR) in patients at high surgical risk.[1–3] The MitraClip procedure reduces the MV area and generates at least two new orifices, followed by an increase in the mean transmitral pressure gradient (MG). An MG over 5 mm Hg after clip attachment has been shown to be associated with adverse outcomes and should thus be avoided according to the current guidelines.[4,5] On the contrary, some recent studies found no predictive value of MG for clinical outcomes after interventional therapy for functional MR.[6,7]

Mean transmitral pressure gradient is assessed by transesophageal echocardiography using the MV peak-systolic velocity from intraprocedural continuous-wave Doppler measurements. Intraprocedural assessment of MG can be influenced by various factors: heart rate and rhythm, hemodynamics during general anesthesia and presence of inotropes, as well as measurement-related factors, such as angulation errors. Furthermore, there are additional heart-related factors: (a) left atrial compliance, (b) left ventricular end-diastolic pressure, and (c) valvular parameters.[8–10] Therefore, intraprocedural MG should be carefully and individually anticipated since the cofactors mentioned are dynamic and time-varying parameters and might lead to over-or underestimation of MG. Taken together, it is unknown how much the intraprocedurally measured MG values change following general anesthesia and restoration of "normal" hemodynamic conditions or following epithelialization of the clip devices.

We, therefore, aimed to (a) evaluate the dynamic changes of MG, both peri-interventionally and during the follow-up (FU), (b) assess the impact of peri-interventionally measured MG on clinical outcomes, and (c) analyze predictors for unfavorable MG after MitraClip.

2 | METHODS

2.1 | Patients, follow-up, and endpoints

We prospectively included consecutive patients with symptomatic moderate-to-severe or severe refractory MR undergoing the MitraClip™ procedure (NTR/XTR Clip Delivery System, Abbot Vascular, Inc) at the Heart Center of the University Hospital Bonn between February 2017 and January 2019.

All patients underwent standardized echocardiographic examinations for noninvasive MG assessments at baseline, intraprocedurally, at discharge, and 6 months after MitraClip. Clinical examinations comprised an evaluation of NYHA functional class, a 6-minute walk test (6MWT), and a comprehensive blood test, which included serum levels of NT pro-BNP. The 6-month FU was performed in our outpatient clinic and included transthoracic echocardiography, a routine physical examination, an electrocardiogram, and a blood test. Survival status was reassessed by either a FU visit in the outpatient clinic or a phone call 12 months after the procedure.

We defined all-cause mortality at 12-month FU as the primary endpoint in line with MVARC (Mitral Valve Academic Research Consortium) definitions.[11] Secondary endpoints were defined as follows: NYHA functional class at FU <III, amelioration in the walk distance of 25%, intraprocedural MG ≥4.5 mm Hg, residual MR>II at discharge, and MR at FU >II.

The study was authorized by the local ethics committee (Medical Faculty of University Bonn, Bonn, Germany) and in accordance with the Declaration of Helsinki. All patients signed their written informed consent before inclusion in the study. All patients' data were anonymized before use in the study. Echocardiographers and clinicians from the in- and outpatient clinics were blinded to the study parameters. Trained study nurses carried out clinical FU evaluation, unattended by the interventionalists or the procedural echocardiographer.

2.2 | Echocardiographic assessment

Echocardiographic assessments were performed in line with the current recommendations and guidelines of the European Association of Echocardiography, including comprehensive echocardiography.[12] All echocardiograms were performed after a relaxing time of 5 minutes to occasion a resting condition to avoid misinterpretations due to hemodynamic undulations. We presented LV volumes as indexed values – absolute value/body surface area. The severity of MR was assessed by the semiquantitative PISA method, using the radius of proximal isovelocity surface area (PISA radius), the effective regurgitant orifice area (EROA), as well as the vena contracta width (VC) and the regurgitant volume (RegVol).[13] Residual MR was assessed by a multiparametric approach consisting of a systemically visual estimation—eyeballing—by experts, determination of color Doppler jet (area, count, and localization), flow convergence, the peak velocity, and the density of the CW Doppler, as well as semiquantitative measurements based on residual PISAs—in case of single residual jet—and VCs intra- and postprocedurally.[14] MG was estimated from the peak-systolic velocity from continuous-wave Doppler imaging of the MV inflow profile. Multiple measurements were done to minimize angulation- and acquisition-related errors and exclude any relevant mitral valve stenosis (>5 mm Hg) during each examination or directly after clip deployment before clip release and at the end of the procedure after removing all catheters. We assessed intraprocedural MG only using transesophageal echocardiography. Right ventricular systolic pressure (RVSP) was estimated by the tricuspid systolic-peak velocity using the modified Bernoulli equation (instantaneous pressure gradient [ΔP] = 4 x velocity). The leaflet-to-annulus index (LAI) was calculated by a formula defined as the ratio between the summation of the lengths of the mitral valve leaflets (anterior mitral leaflet +posterior mitral leaflet) and the anteroposterior diameter (AP diameter), as published previously.[15] The leaflet lengths and AP diameter were measured at 120–150° (three-chamber view)

and SL diameter at 0–20° (four-chamber view) in transesophageal echocardiography. The echocardiographic studies were performed with currently available ultrasound machines (iE33, Philips Medical Systems; E9, GE Healthcare Vingmed Ultrasound).

2.3 | Statistical analysis

The normal distribution of continuous variables was examined using the Shapiro–Wilk test. Continuous data were expressed as mean values ±the standard deviation if normally distributed. Categorical data were presented as a percentage. The Student's two-sample *t* test or the Man–Whitney *U* test was performed to compare continuous variables. Fisher's exact test or the chi-square test was used to compare categorical data. To compare more than two variables, we used the one-way variance analysis or the Kruskal–Wallis test as an extension of the Student's *t* test. Univariate analysis was performed to assess the predictors of clinical outcomes. The predictors of 12-month mortality were estimated by multivariate regression analysis. Cumulative survival incidence was compared using the log-rank test between the groups and presented by the Kaplan–Meier curve. A ROC analysis was performed to determine independent predictors' sensitivity and specificity for unfavorable outcomes and mortality with defined cutoff values. Two-tailed p-values were considered to be significant if ranging below 0.05. Statistics were performed using SPSS (PASW statistic, Version 25.0.0.0, SPSS Inc) and MedCalc Statistical Software (Version 19.2, MedCalc Software Ltd).

3 | RESULTS

3.1 | Defining the groups

According to multivariate regression analysis and a receiver operating characteristic (ROC) analysis, we found intraprocedural MG—with a cutoff value of 4.5 mm Hg—was the only statically significant predictor for the primary endpoint. Consequently, we divided our patient cohort into two groups—patients with an intraprocedural MG <4.5 mm Hg were defined as *group 1* and ≥4.5 mm Hg as *group 2*.

3.2 | Baseline characteristics

One hundred and seventy five consecutive patients (61.2% male) with symptomatic (100% NYHA functional class >II), moderate-to-severe or severe MR (PISA: 0.8 ± 0.2 cm, VC: 0.8 ± 1.2 cm, EROA: 0.5 ± 0.3 cm^2, RegVol: 51.1 ± 19.7 mL) were included. 40% (n = 70) of the patients showed degenerative MR (DMR), 42.8% (n = 75) of patients had functional MR (FMR), and 17.2% (n = 30) of patients had a mixed etiology. At baseline, all patients were on guideline-directed medical heart failure therapy or device therapy, if needed. All patients were classified as inoperable or at a high surgical risk by the heart team owing to advanced comorbidities (Logistic EuroScore: 17.8 ± 5.2%), advanced age (mean age: 81.2 ± 8.2 years), and frailty assessed by clinicians' estimations.

Concerning the baseline demographical and clinical characteristics, there were no statistically significant differences between the groups. Of note, the serum level of NT pro-BNP was more elevated in group 2 than group 1, but without reaching the level of statistical significance (3382 pg/mL vs 3634 pg/mL, $P = .1$). The baseline demographical and clinical characteristics are presented in Table 1.

In the overall cohort, baseline echocardiography showed a relevant left ventricular (LV) dilation (end-diastolic volume [LV-EDV]: 96.9 ± 40.5 mL, end-systolic volume [LV-ESV]: 56.6 ± 34.6 mL) with a decreased LV ejection fraction (LV-EF: 44.7 ± 16.3%). There was no relevant mitral valve stenosis observed at baseline (1.5 ± 1.1 mm Hg). Furthermore, we found increased RVSP (45.4 ± 14.8 mm Hg) as a sign of pulmonary hypertension at baseline. The baseline echocardiographic parameters were comparable between the groups (Table 2).

3.3 | Interventional outcomes and technical success

All patients underwent a successful transcatheter edge-to-edge mitral valve repair using the MitraClip™ NTR/XTR Delivery System with a reduction in MR of at least one grade or to an MR grade <moderate-to-severe as previously described.[16–18] To maintain optimal procedural conditions and outcomes, all procedures were performed under general anesthesia with controlled hemodynamic conditions such as systolic blood pressure in the range of 110-130 mm Hg and the heart rate between 60 and 80 bpm.

54% (n = 95) of patients received one-clip device, and 43% (n = 75) of patients were treated using two clip devices. Three clip devices were implanted in 3% (n = 5) of patients, without a significant difference in the arithmetic mean of the number of clip devices used between the groups; however, the one-clip approach was performed significantly more often in group 1 (1.43 ± 0.58 vs 1.41 ± 0.7, $P = .9$). There was no significant difference in postprocedural residual MR between the groups (MR<III: Group 1:94.2% [n = 145] vs Group 2:86% [n = 18], $P = .3$). No major periprocedural complications, such as pericardial tamponade or vascular injury requiring additional surgical or interventional therapy, occurred. Furthermore, no relevant peri-interventional bleeding and related laboratory changes were documented.

3.4 | Follow-up in all patients

Regarding MG's peri-interventional dynamics, we found a decrease in MG to values below 4.5 mm Hg in 11 patients (52%) from group 2 at discharge. In total, 94% of patients (n = 165) presented with an MG <4.5 mm Hg and only 6% of patients (n = 10) had persistent increased MG ≥4.5 mm Hg at discharge.

TABLE 1 Baseline demographic and clinical characteristics

	All patients n = 175	Group 1 n = 154	Group 2 n = 21	*P*-value
Gender (female), n (%)	68 (38.8)	58 (37.6)	10 (47.6)	.4
Age, years mean ± SD	81.2 ± 8.2	81.2 ± 8	80.6 ± 0.6	.8
BMI, kg/m^2 mean ± SD	25.7 ± 4.3	25.7 ± 4.3	26.2 ± 4.1	.7
Logistic EuroSCORE, % mean ± SD	17.8 ± 5.2	18.8 ± 6.3	16.6 ± 7.8	.7
NYHA class ≥II, %	100	100	100	1
Class III, n (%)	119 (68)	102 (66.3)	17 (81)	.3
Class IV, n (%)	56 (32)	52 (33.7)	4 (19)	.06
CHF, n (%)	140 (80)	126 (81.8)	14 (66.6)	.1
CAD, n (%)	129 (73.7)	115 (74.6)	14 (66.6)	.3
Arterial hypertension, n (%)	118 (67.4)	104 (67.5)	14 (66.6)	.6
Atrial fibrillation or flutter, n (%)	101 (57.7)	90 (58.4)	11 (52.4)	.4
History of stroke, n (%)	4 (2.3)	3 (1.9)	1 (4.8)	.1
PAD, n (%)	21 (12)	18 (11.6)	3 (14.3)	.7
Diabetes mellitus, n (%)	68 (38.8)	62 (40.3)	6 (28.5)	.1
Hyperlipidemia, n (%)	69 (39.4)	62 (40.3)	7 (33.3)	.5
Smoking, n (%)	42 (24)	37 (24)	5 (23.8)	.5
CKD, n (%)	42 (24)	28 (18.8)	14 (66.6)	.09
NT pro-BNP, pg/mL *median (95% CI)*	3418 (2739.1–5070.2)	3382 (2739.8–5203.8)	3634 (1667.3–7725.3)	.1
Hemoglobin, gr/dL mean ± SD	12.04 ± 1.95	12.21 ± 1.96	11.59 ± 1.88	.7
Heart rate, bpm mean ± SD	74.5 ± 16.1	73.9 ± 15.7	75.3 ± 17.1	.6
Systolic blood pressure, mm Hg mean ± SD	122.1 ± 20	120.9 ± 19.2	125.8 ± 2.4	.1
Diastolic blood pressure, mm Hg mean ± SD	71.6 ± 11.4	71.7 ± 11.4	72.1 ± 1.4	.7
Medication				
Beta-blocker, n (%)	136 (77.7)	120 (77.9)	16 (76.1)	.3
ACEI/ARB, n (%)	113 (64.5)	95 (61.6)	18 (85.7)	.09
MRA, n (%)	87 (49.7)	76 (49.3)	11 (52.3)	.1
Diuretics, n (%)	160 (91)	142 (92.2)	18 (85.7)	.1

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-II receptor blocker; BMI = body mass index; CAD = coronary artery disease; CHF = chronic heart failure; CKD = chronic kidney disease; MRA = mineralocorticoid receptor antagonist; NT pro-BNP = N terminal pro-brain natriuretic peptide; NYHA = New York Heart Association classification; PAD = periphery artery disease.

Two patients (1.1%) were deceased during the 30-day FU due to cardiovascular causes. The 6-month all-cause mortality rate was 8.5% (n = 15), and the 12-month all-cause mortality rate was 23.4% (n = 41).

At 6-month FU, we found significantly improved NHYA functional class (NYHA>II: 100%–31.66%, P = .001) and increased 6-minute walk distance (247.23 ± 33.4 m–333.45 ± 60.5 m, P = .001) in the overall cohort.

Echocardiography at 6-month FU showed no significant changes in LV dimensions and function (LV-EDV: group 1, P = .6 vs group 2, P = .3; LV-ESV: group 1, P = .4 vs group 2, P = .5; LV-EF: group 1, P = .5 vs group 2, P = .9). We found a significant and sustained

TABLE 2 Baseline echocardiographic characteristics

	All patients n = 175	Group 1 n = 154	Group 2 n = 21	*P*-value
LV-EDV, mL/m^2 mean ± SD	96.9 ± 40.5	99.7 ± 34.7	88.3 ± 52.3	.4
LV-ESV, mL/m^2 mean ± SD	56.6 ± 34.6	58.6 ± 30.8	55.8 ± 42.9	.9
LV-EF, % mean ± SD	44.7 ± 16.3	44.9 ± 16.5	42.9 ± 15.5	.7
MV-MG, mm Hg mean ± SD	1.5 ± 1.1	1.5 ± 1	2.6 ± 1.1	**.001**
MV geometry, mm mean ± SD				
AP diameter	37.3 ± 0.5	37.3 ± 0.5	37.5 ± 0.5	.9
SL diameter	39.6 ± 6.9	39.9 ± 6.9	39.2 ± 5.9	.9
Mitral regurgitation	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	.8
Grade III, n (%)	136 (77.7)	121 (78.6)	15 (71.4)	.8
Grade IV, n (%)	39 (22.2)	33 (21.4)	6 (28.6)	.6
Etiology of MR				
Functional MR, n (%)	75 (42.8)	67 (43.5)	8 (38)	.2
Degenerative MR, n (%)	70 (40)	60 (39)	10 (47.7)	.1
Mixed MR, n (%)	30 (17.2)	27 (18)	3 (14.3)	.1
MR-PISA, cm mean ± SD	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	.2
MR-VC, cm mean ± SD	0.8 ± 1.2	0.8 ± 1.3	0.8 ± 0.2	.8
MR-EROA, cm^2 mean ± SD	0.5 ± 0.3	0.5 ± 0.3	0.5 ± 0.1	.6
MR-RegVol, mL mean ± SD	51.1 ± 19.7	50.3 ± 20	57.3 ± 17.2	.3
AP diameter, mm mean ± SD	37.4 ± 0.5	37.3 ± 0.5	37.5 ± 0.5	.9
SL diameter, mm mean ± SD	39.6 ± 7.1	39.9 ± 6.9	39.2 ± 5.9	.9
AML, mm mean ± SD	27.9 ± 0.5	28.1 ± 0.5	27.6 ± 0.5	.3
PML, mm mean ± SD	16.3 ± 0.4	16 ± 0.4	16.8 ± 0.4	.1
LAI mean ± SD	1.19 ± 0.1	1.18 ± 0.1	1.19 ± 0.1	.8
RVSP, mm Hg mean ± SD	45.4 ± 14.8	45.5 ± 14.6	44.6 ± 16.3	.8

Abbreviations: AML = anterior mitral leaflet; AP = anteroposterior; EROA = effective regurgitant orifice area; LAI = leaflet-to-annulus index; LV-EDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; LV-ESV = left ventricular end-systolic volume; MG = mitral gradient; MR = mitral regurgitation; MV = mitral valve; PISA = proximal isovelocity surface area, PML = posterior mitral leaflet; RegVol = regurgitation volume; RVSP = right-ventricular systolic pressure; SL = septolateral; VC = Vena contracta.

Bold values present parameters with statistical significance.

reduction in MR for the overall cohort 6 months after the procedure (MR >II; 91.36%–2.48%, P <.001). Moreover, RVSP significantly decreased within the 6-month FU period (45.4 ± 14.8 mm Hg, 34.7 ± 10.5 mm Hg, P = .01).

3.5 | Dynamic changes in MG

Mean transmitral pressure gradient significantly increased after the MitraClip procedure (1.5 ± 1.1 mm Hg–3.5 ± 1.7 mm Hg, P = .03)

in the overall cohort. Elevated MG values above 4.5 mm Hg were measured intraprocedurally in 21 patients (12%)—*group 2*.

At 6-month FU, the following MG values were documented: (a) increase to values above 4.5 mm Hg in nine patients (5.45%) from group 1 and (b) decrease to values below 4.5 mm Hg in two patients (20%) from group 2, in addition to 11 patients with a predischarge reduction in MG. Overall, we found 146 patients (91%) with MG <4.5 mm Hg and 14 patients (9%) with MG ≥4.5 mm Hg at 6-month FU. The dynamics of MG values over time are presented in Figure 1.

3.6 | Comparison of the groups

Concerning baseline echocardiography, we found higher MG in group 2 (1.5 ± 1 mm Hg vs 2.6 ± 1.1 mm Hg, $P = .001$), as expected. However, the MV geometry was comparable the groups—baseline AP diameter (37.3 ± 0.5 mm vs 37.5 ± 0.5 mm, $P = .9$) and baseline SL diameter (39.9 ± 6.9 mm vs 39.2 ± 5.9 mm, $P = .9$). The remaining baseline echocardiographic parameters were statistically comparable between the groups. Of note, there were no significant differences concerning MR etiology between the groups (Table 2).

At 6-month FU in survived patients (n = 160), the NYHA functional class was found to be significantly improved in group 1 (NYHA >II; 100%–26%, $P < .001$), but not in group 2 (NYHA >II; 100%–73%, $P = .5$). We, furthermore, found an increased walk distance (6MWT) in group 1 (252.2 ± 127.8 m–348.3 ± 80.7 m, $P = .05$), but this value was unchanged in group 2 (210.8 ± 46.5 m–223.3 ± 25.8 m, $P = .3$). Serum levels of NT pro-BNP tended to decrease in group 1 and increase in group 2 at 6-month FU (2874 pg/mL–2436 pg/mL, $P = .3$ vs 2836 pg/mL–3462 pg/mL, $P = .6$) (Table 3).

We found a significant and sustained reduction in MR severity in both groups 6 months after the procedure (MR ≥III; 91%–2%, $P < .001$, 94%–6%, $P < .001$). RVSP significantly decreased only in group 1 (44.6 ± 11.3 mm Hg–33.3 ± 4.2 mm Hg, $P = .016$). Patients with an intraprocedural MG ≥4.5 mm Hg showed no significant RVSP changes (49.4 ± 18.3 mm Hg–45.6 ± 18.7 mm Hg, $P = .5$) at FU (Table 3).

3.7 | Predictors for clinical outcomes

There was a statistically significant difference in 12-month mortality between the groups (20.7% [n = 32] vs 42.8% [n = 9], $P = .02$). Survival status within the 12-month FU period is graphically depicted by the Kaplan–Meier curve (Figure 2). A Cox-regression analysis showed significantly higher 12-month mortality in group 2 compared to group 1 (HR: 2.33, 95% CI: 1.11–4.88, $P = .03$), and a multivariate analysis relieved that intraprocedural MG is the strongest predictor (OR: 1.70, 95% CI: 0.95–3.05, $P = .05$) for 12-month mortality compared to MGs at another time points, residual MR>II at discharge and residual MR>II at FU (Table 4).

According to multivariate regression analysis, including ROC curve analysis of MGs at three different time points (intraprocedurally, at discharge, and 6-month FU) concerning the prediction of adverse functional outcomes (NYHA at FU >II, improvement in walk distance <25%), we found intraprocedural MG to be the strongest predictor for unfavorable clinical outcomes (OR: 1.96, 95% CI: 1.02–3.75, $P = .04$) with a cutoff value of 3.9 mm Hg (specificity of 80% and sensitivity of 63.9%) followed by MG at FU (OR: 1.56, 95% CI: 0.85–2.86, $P = .14$) with a cutoff value of 2.6 mm Hg; however, this finding was without statistical significance (Table S1).

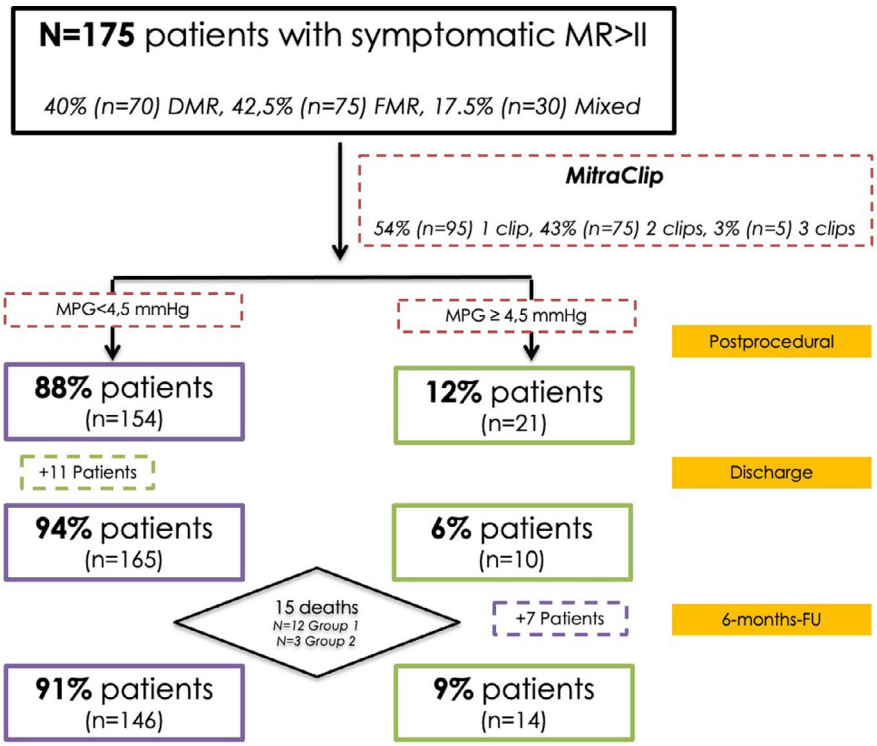

FIGURE 1 Flow chart for dynamic changes of MG: peri-interventionally and during FU

TABLE 3 Clinical and echocardiographic outcomes at 6-mo FU (the parameter referred to the survived patients at 6-mo FU, therefore Tables 2 and 3 show different values for baseline parameters)

	Baseline	Follow-up	*P*-value
NYHA class mean ± SD			
Group 1 (n = 142):	3.2 ± 0.4	1.6 ± 1.1	.041
Group 2 (n = 18):	3.5 ± 0.7	2.5 ± 0.7	.1
6-MWT, m mean ± SD			
Group 1 (n = 142):	252.2 ± 127.8	348.3 ± 80.7	.05
Group 2 (n = 18):	210.8 ± 46.5	223.3 ± 25.8	.3
NT pro-BNP, pg/mL *median (95 CI)*			
Group 1 (n = 142):	2874 (2093.1–4337.6)	2436 (1596.3–2782)	.3
Group 2 (n = 18):	2826 (1348.8–8237.9)	3462 (1096.4–5980.1)	.6
LV-EDV, mL/m^2 mean ± SD			
Group 1 (n = 142):	97.1 ± 31.5	90.5 ± 28.5	.6
Group 2 (n = 18):	106.6 ± 24.5	92.3 ± 33.5	.3
LV-ESV, mL/m^2 mean ± SD			
Group 1 (n = 142):	54.9 ± 27.1	43.8 ± 21.5	.4
Group 2 (n = 18):	55.3 ± 32.4	48.1 ± 18.7	.5
LV-EF, % mean ± SD			
Group 1 (n = 142):	47.3 ± 14.7	50.7 ± 16.2	.5
Group 2 (n = 18):	48.1 ± 12.2	48.4 ± 9.7	.9
Residual MR<III, %			
Group 1 (n = 142):	0	98	<.001
Group 2 (n = 18):	0	94	<.001
MV-MG, mm Hg mean ± SD			
Group 1 (n = 142):	2 ± 1.5	3.6 ± 2.7	.18
Group 2 (n = 18):	1.5 ± 0.9	4.8 ± 4.5	.02
RVSP, mm Hg mean ± SD			
Group 1 (n = 142):	44.6 ± 11.3	33.3 ± 4.2	.016
Group 2 (n = 18):	49.4 ± 18.3	45.6 ± 18.7	.5

Abbreviations: 6-MWT = 6-min walking test; LV-EDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; LV-ESV = left ventricular end-systolic volume; MG = mitral gradient; MR = mitral regurgitation; NT pro-BNP = N terminal pro-brain natriuretic peptide; RVSP = right-ventricular systolic pressure.

According to the one-way variance analysis of group 1, group 2 without predischarge MG reduction, and group 2 with predischarge MG reduction concerning adverse functional outcome—higher NYHA functional class (>II) and lower walk distance (improvement <25%)—we found a significant difference between the groups (24% vs 75% vs 55%, $P < .001$). Group 2—with/without predischarge MG reduction—showed a somewhat higher 12-month mortality rate than group 1 but without statistical significance (40% vs 33%, vs 29%, $P = .4$). Remarkably, the worst outcomes—functional and mortality—occurred in group 2 without predischarge MG reduction.

3.8 | Predictors for unfavorable intraprocedural MG

We evaluated the impact of clip localization on intraprocedural MG in patients with one-clip implantation (n = 95) using the Kruskal–Wallis test. Central clip implantation (segment A2-P2) was found to induce higher intraprocedural MG (3.58 ± 1.7 mm Hg), followed by the technique with cross-clipping (ie, segment A2-P3, A2-P1; 3.2 ± 1.7 mm Hg). Noncentral noncross clip implantation (segment A3-P3; 2.98 ± 1.3 mm Hg or A1-P1; 2.66 ± *1.04 mm Hg*) led to a lower MG after clipping in our cohort. Of note, there was a significant

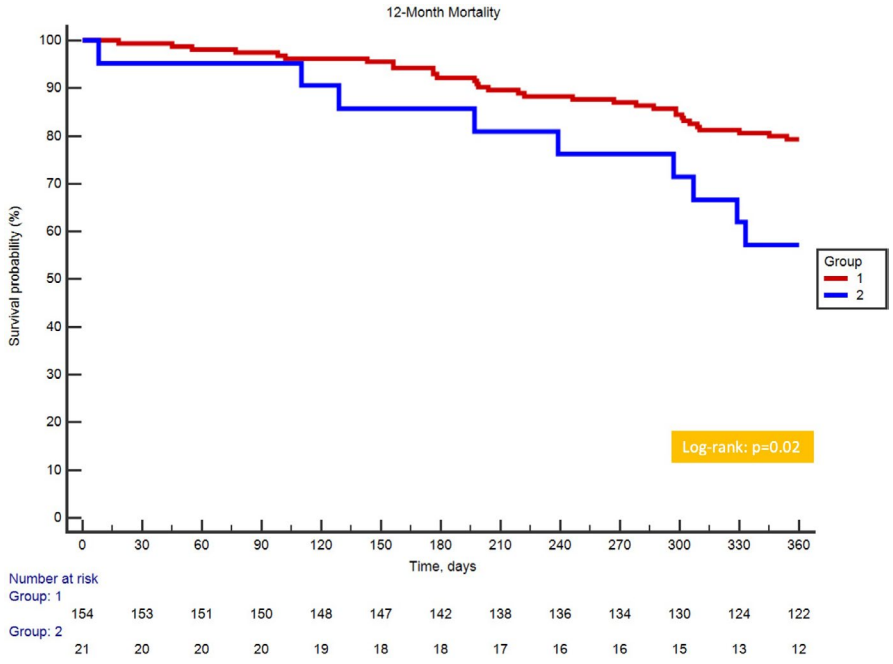

FIGURE 2 Kaplan–Meier curve for 12-mo mortality in MG groups

TABLE 4 Multivariate analysis of predictors of 12-mo mortality

Parameters	OR	95% CI	*P*-value
Intraprocedural MG	1.70	0.95–3.05	.05
MG at discharge	0.81	0.51–1.27	.36
MG at FU	1.43	0.82–2.50	.120
Residual MR>II at discharge	6.46	0.43–95.23	.17
Residual MR>II at FU	0.34	0.02–5.36	.44

difference of intraprocedural MG between central and noncentral clip localization (3.58 ± 1.7 mm Hg vs 2.83 ± 1.2 mm Hg, $P = .02$).

Furthermore, we performed an additional analysis of variance (ANOVA) test to assess the impact of MR etiology on intraprocedural MG in patients with the one-clip approach. It showed that patients with DMR or mixed MR had higher intraprocedural MG than FMR (DMR: 4.15 ± 1.6 mm Hg vs FMR: 3.58 ± 1.56 mm Hg vs mixed: 4.19 ± 1.89 mm Hg, $P = .001$).

To further evaluate our data for predictors of unfavorable intraprocedural MG, we analyzed MV's anatomical features. According to linear regression analysis, the AP diameter had a significant negative correlation with intraprocedural MG in patients who underwent one-clip implantation ($r = 3.75$, 95% CI: 3.57–3.94, $P < .001$). Thus, patients with smaller annular dimensions (cutoff value: 38 mm) had higher intraprocedural MG values. In addition, the leaflet-to-annulus index (LAI) (<1.11) was found to be a strong predictor (AUC: 0.595, 95% CI: 0.542–0.647, $P = .0031$) for unfavorable intraprocedural MG (≥4.5 mm Hg) and showed a significant negative correlation with intraprocedural MG values in the regression analysis (OR: 18.43 95% CI: 8.86–125.49, $P = .0029$). According to the multivariate regression analysis, we found LAI (OR: 9.74, 95% CI: 0.43–217.17, $P = .001$) to be the strongest, independent predictor for unfavorable intraprocedural MG (≥4.5 mm Hg) followed by the count of implanted clips >2 (OR: 7.54, 95% CI: 1.24–87.67, $P = .01$), MG at baseline (OR: 2.06, 95% CI: 1.58–2.68, $P = .02$), and central clip implantation (OR: 1.87, 95% CI: 0.67–3.45, $P = .05$).

4 | DISCUSSION

The major findings of the present study are as follows:

1. Intraprocedural MG was found to be a strong predictor for 12-month mortality (cutoff value: 4.5 mm Hg) and adverse functional outcomes (cutoff value: 3.9 mm Hg) independently from MR etiology.
2. Leaflet-to-annulus index (<1.11) was found to be the strongest predictor for unfavorable intraprocedural MG followed by baseline MG, the number of implanted clips, and central clip localization.
3. Concerning 12-month mortality and functional outcomes, intraprocedural MG≥4.5 mm Hg was more influential than residual MR>II.

It is recommended that an intraprocedural MG above 5 mm Hg should be avoided due to associated adverse outcomes.[11,20–22] On the other hand, some contradicting studies currently show no relevant association between MG and outcomes after the MitraClip procedure, particularly in patients with functional MR.[6,7] Therefore, the effect of MG on outcomes after MitraClip is ambiguous.

Intraprocedural echocardiographic assessment of mitral inflow patterns and hemodynamics might be challenging and inadequate owing to altered mitral geometry, such as multi-orifice MVs after transcatheter MV repair. Despite difficulties in MG assessment

using continuous-wave Doppler in the setting of catheter-based MV repair, it was proven to be superior over planimetric evaluation of MVA for intraprocedural stenosis assessment due to unacceptably time-consuming assessment and misestimations, in a study with 38 patients by Biaggi and coworkers.[19] Accordingly, we used the Doppler-based assessment of MG in the present study.

In a monocentric study including 51 elderly patients (mean age: 75 years), Boerlage-van Dijk et al demonstrated that intraprocedural assessment of MG systematically underestimates the value compared to real life. Of note, the authors found no correlation between higher intraprocedural MG and increased heart failure symptoms at FU.[9] In contrast, we found worse clinical outcomes—lower functional capacity and higher 1-year mortality—in patients with intraprocedural MG ≥4.5 mm Hg, which might be due to the fact that the majority of patients included in the cited study suffered from chronic heart failure with concomitant FMR (74%). This might hamper discerning persistent advanced heart failure symptoms and symptoms due to elevated MG at FU—high competing risk. Our cohort comprised a balanced number of MR etiologies (DMR: 40%, FMR: 42.8%, mixed: 17.2%), which might be a reason for the divergent finding.

An intraprocedural MG >4.4 mm Hg was shown by Patzelt et al to be predictive for a combined endpoint consisting of all-cause mortality, redo procedure, and LVAD implantation after MitraClip only in patients with DMR, but not with FMR. The authors found the patient's age to be the strongest independent predictor for the combined endpoint, followed by residual MR >II and intraprocedural MG.[7] Differently, we found intraprocedural MG more influential than residual MR concerning clinical outcomes in our patients' cohort in more advanced stages of heart failure with more FMR (42.5%). Additionally, we found a negative influence of elevated intraprocedural MG on clinical outcomes regardless of MR etiology.

Itabashi et al[23] showed that increased LV and MV dimensions might be accountable for a somewhat lower intraprocedural MG in a comparable cohort after one-clip implantation. Contrary to our findings, patients with FMR showed a tendency for developing higher intraprocedural MG in this study, which might be due to smaller annular dimensions in their study cohort (AP diameter: 32 vs 38 mm).

We found LAI as a surrogate parameter of MV geometry to be the strongest predictor for unfavorable MG after clip deployment. This new parameter, which reflects on the length of the leaflets in relation to annular dimensions and offers an adequate geometrical assessment of the MV, was not assessed in all of the studies cited but seemed to be associated with residual MR, MG, and outcomes after the MitraClip procedure.[15]

Apart from residual MR as a well-known prognostic parameter, postinterventional MG appears to be an independent predictor for clinical outcomes. It shows a dynamic postinterventional process and is influenced by various hemodynamic parameters such as blood pressure, heart frequency, volume condition of the patient, sedation or anesthesia, hemoglobin, and inotropes. Therefore, its sporadic assessment may lead to misestimations intrainterventionally. Understanding of MG dynamics, its predictors, and its effect of outcomes is desirable to get more favorable outcomes after MitraClip compared to just residual MR based decision-making. In the present study, intraprocedural MG appears to be more influential on all-cause mortality and clinical outcomes compared to residual MR>II. The definite pathomechanism of this clinical entity stays still unexplained as an encouraging reason for further prospective multicentric studies. Considering that higher postprocedural MG is associated with worse clinical outcome and increased mortality, forthcoming procedural and device/system-related improvements are desirable.

4.1 | Limitations

This single-center study has several limitations. It was performed with a limited sample size and short FU duration. Echocardiographic analyses were not performed or validated by an independent core laboratory. Neither an invasive assessment of the left atrial pressure and intraprocedural MG nor exercise echocardiography was done in every patient. There was no assessment of postinterventional interatrial shunt. Further evaluation of the MG's impact on outcomes based on the MR etiology (FMR vs DMR) was not possible owing to the too low number of patients with elevated MG. To validate the predictive value of parameters for adverse outcomes and unfavorable MG appropriately powered multicentric studies with a larger patient cohort, a longer FU and subgroup and multivariate analysis according to cutoff values and/or propensity matching are required.

5 | CONCLUSION

Intraprocedural MG was found to be a strong predictor for 12-month mortality (cutoff value: 4.5 mm Hg) and adverse functional outcomes (cutoff value: 3.9 mm Hg), irrespective of the etiology of MR. Moreover, intraprocedural MG≥4.5 mm Hg appears more influential than residual MR>II regarding clinical outcomes. To aim for an MG of <3.9 mm Hg would be the safest strategy for not negatively influencing survival and functional outcomes after edge-to-edge repair of the MV with the MitraClip system. Additionally, LAI (>1.11) as a surrogate parameter of MV geometry was the strongest predictor for unfavorable intraprocedural MG, followed by MG at baseline, the number of implanted clips, and central implantation. These parameters might help for appropriate patient selection, sufficient intraprocedural decision-making, and more favorable clinical outcomes.

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CONFLICT OF INTEREST

Öztürk C, Sprenger Kim, Sugiura A, Weber M, Tabata N, and Schueler R have no conflict of interest. Nickenig G has received speaker honoraria and research grants from Medtronic, Boston Scientific, Edwards Lifesciences, and Abbott.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table S1. Predictors for adverse functional outcome. A, Predictive values of MGs assessed by the ROC analysis. B, Comparison of outcome-predicting parameters by the multivariate regression analysis concerning functional outcomes

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3.4 Öztürk C, Becher MU, Kalkan A, Kavsur R, Weber M, Nickenig G, Tiyerili V. The modified MIDA-Score predicts mid-term outcomes after interventional therapy of functional mitral regurgitation. PLoS One. 2020 Jul 22; 15(7): e0236265.

Zielsetzung der Arbeit: Im Vergleich zur DMI sind das Management und die Planung der FMI-Therapie aufgrund des fortgeschritteneren Patientenalters, der vorliegenden linksventrikulären Dysfunktion mit erhöhtem pulmonalem sowie linksventrikulärem enddiastolischem Druck und häufigerer Komorbiditäten kompliziert und anspruchsvoll. Diesbezüglich ist eine präzise Entscheidungsfindung von zentraler Bedeutung. In diesem Sinne erfordert die angemessene Prognoseabschätzung eine multifaktorielle und umfassende Evaluation der Gesamtkonstellation mit klinischen Untersuchungen sowie bildgebenden Verfahren. Die bestehenden konventionellen Scores (STS-Score, EuroSCORE) beruhen lediglich auf der perioperativen Risikoabschätzung inklusive operationsbezogener Komorbiditäten anstelle der Abschätzung der Langzeitprognose. Aufgrund dessen veröffentlichten Grigionie et al. den neuen MIDA-Score (The Mitral Regurgitation International Database) für die suffiziente Abschätzung der Kurzzeit- sowie der Langzeitprognose bei Patienten mit DMI. In dieser Hinsicht beabsichtigten wir, in dieser Studie einen leicht handhabbaren Score für die adäquate Prognose-abschätzung bei FMI zu entwickeln.

Methoden und Ergebnisse: Wir selektierten insgesamt 105 Patienten (76,7 ± 8,8 Jahre, 50,6 % weiblich), die zwischen Januar 2014 und August 2016 aufgrund symptomatischer, therapierefraktärer, höhergradiger MI (PISA: 0,7 ± 0,4 cm, VC: 0,8 ± 0,3 cm, EROA: 0,22 ± 0,1 cm^2, RegVol: 38,1 ± 19,2 ml) eine perkutane Mitralklappen-reparatur (82,8 % MitraClip™, 17,2 % Cardioband™) in unserem Herzzentrum erhielten. In der präinterventionellen Echokardiographie sahen wir eine relevante LV-Dilatation (LVEDD: linksventrikulärer enddiastolischer Diameter, 6,2 ± 0,3 cm) mit mittelgradig reduzierter LV-Funktion (LVEF: 40,1 ± 15,2 %). Zudem stellten sich der linke Vorhof dilatiert (LAV: linksatriales Volumen, 91,7 ± 39,5 ml) und der rechtsventrikuläre systolische Druck (RVSP: 43,4 ± 13 mmHg) erhöht dar. Als auffallend dokumentierten wir eine normale rechtsventrikuläre Funktion (TAPSE: tricuspid annular plane systolic excursion, 21 ± 3 mm). Achtzehn Monate nach erfolgreicher Intervention (92% aller Interventionen) waren 7 % der Patienten verstorben; 30 Patienten (30,7 %) wurden aufgrund kardialer Dekompensation

während der Nachbeobachtungszeit wieder stationär aufgenommen. Im Rahmen der Modifikation bestimmten wir die Cut-off-Werte der Score-relevanten Faktoren mit Hilfe der ROC-Analyse neu (Alter von 65 auf 75, LVEF von 60 % auf 45 % und RVSP von 50 auf 45 mmHg). Im nächsten Schritt ordneten wir die Punkteverteilung im Hinblick auf die Gewichtungsergebnisse der Cox-Regressionsanalyse mit Bezug auf den primären Endpunkt. Die vergleichende tabellarische Darstellung der Parameter des originalen und des modifizierten MIDA-Scores ist in Table 3 ersichtlich (p. 6, Öztürk et al., 2020). Daraufhin definierten wir die drei Grade des modifizierten MIDA-Scores anhand der Ergebnisse der Regressionsanalyse (siehe Table 7, p. 10, Öztürk et al., 2020). In verschiedenen Vorhersageanalysen stellte sich der modifizierte MIDA-Score > 9 Punkte als der stärkste unabhängige Prädiktor für den kombinierten Endpunkt mit hoher Sensitivität und Spezifizität > 80 % heraus (siehe Figure 3, p. 9 und Figure 5, p. 11, Öztürk et al., 2020). In der ROC-Analyse zeigte sich eine deutliche Überlegenheit des modifizierten MIDA-Scores bezüglich der Prädiktion des kombinierten Endpunktes im Vergleich zu den konventionellen Scores (siehe Figure 6, p. 12, Öztürk 2020).

Schlussfolgerungen**:** Der modifizierte MIDA-Score ist ein aussichtreiches neuartiges Werkzeug zur adäquaten Abschätzung der individuellen Prognose bei Patienten mit FMI nach interventioneller Mitralklappenreparatur und ermöglicht infolgedessen eine suffiziente Entscheidungsfindung mit angemessenem Therapiemanagement der FMI.

PLOS ONE

RESEARCH ARTICLE

The modified MIDA-Score predicts mid-term outcomes after interventional therapy of functional mitral regurgitation

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Abstract

Aims

The preprocedural assessment of outcomes and patients' prognosis after interventional therapy of functional MR (FMR) is uncertain. Therefore, we aim to develop an easy-to-handle scoring system for adequate prediction of individual outcomes in patients with FMR after the interventional treatment.

Materials and methods

We retrospectively used medical data of patients with symptomatic FMR, who underwent transcatheter mitral valve repair (TMVR) from January 2014 to August 2016 in our heart center. All patients had the mean follow-up of 18 months. All clinical and echocardiographic data originate from the "*Bonner Mitral Valve Register Database*".

Results

We included 105 patients (76,7±8,8 years, 50,6% female) with symptomatic (NYHA functional class>II) moderate-to-severe or severe FMR at surgical high-risk. We modified the MIDA-Score for degenerative MR (DMR) according to the varying underlying pathomechanisms of FMR, called as "The modified MIDA Score". We found all-cause mortality of 7% within 18 months after the procedure. 34,1% of our cohort was rehospitalized; 90% of those were due to cardiovascular causes. The modified MIDA score was found to be a strong predictor for mortality and rehospitalization in patients with FMR (AUC: 0,89) and superior to the other conventional scoring systems in prediction of mortality (The modified MIDA-Score: AUC: 0,8, EuroSCORE II: AUC: 0,57, STS-Score: AUC: 0,51). The logistic regression analysis showed the modified MIDA score > 9 points to be the strongest predictor for mortality and rehospitalization after TMVR (OR: 3,35, p = 0,011).

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Conclusion

The modified MIDA score was found to be a promising, easy-to-handle, elementary scoring system for adequate prediction of individual postinterventional prognosis in patients with FMR undergoing TMVR. Further evaluation and validation of this novel scoring system in prospective multicentric studies with a large number of patients is warranted.

Introduction

Mitral regurgitation (MR) is common valvular heart disease and associated with high mortality and reduced quality of life. According to the underlying pathomechanism, there are mainly two etiological types of MR. First, degenerative MR (DMR) is caused by the organic pathology of the mitral valve or the mitral valve apparatus. Second, functional MR (FMR) is a disease of the left ventricle, which is accompanied by ventricular dilation, displacement of papillary muscle, and annular dilation followed by tethering of the leaflets and coaptation deficiency without any organic pathology of the mitral valve. FMR is an often finding in patients with chronic heart failure (CHF) and correlates with adverse prognosis, reduced quality of life, and high mortality [1].

Compared to DMR, the management of FMR is more complex and challenging concerning advanced age, pronounced left ventricular (LV) dysfunction with high LV enddiastolic pressure, elevated systolic pulmonary artery pressure, and more often comorbidities. The standard treatment of FMR consists of guidelines-directed optimal medical heart failure therapy, cardiac resynchronization therapy (if appropriate), and valve repair or replacement (surgical or interventional) [2]. Transcatheter mitral valve repair (TMVR) has been established in clinical practice and is increasingly and successfully performed in patients at surgical high-risk [3], [4], [5].

The precise decision-making for MR therapy in CHF patients is essential and challenging, particularly in patients with FMR is even more complicated due to more prevalent comorbidities. The proper assessment of patients' prognosis and patient management require a multifactorial, comprehensive evaluation with clinical examinations and imaging issues. There are two established conventional scoring systems (EuroSCORE and STS-Score) for the surgical risk assessment in patients with structural heart diseases [6], [7]. These traditional scoring systems focus on the evaluation of the surgical risk concerning surgery-related mortality and morbidity instead of the prediction of postprocedural long-term patients' prognosis or outcomes. Grigioni et al. have recently published the Mitral Regurgitation International Database (MIDA) Score as a novel scoring system, which sufficiently predicts short- and long-term outcomes in patients with DMR [8].

In clinical practice, a prognostic scoring system for FMR patients is essential to overcome the challenging management of FMR treatment followed by favorable outcomes. This scoring system should be easy-to-handle and should not require further unnecessarily complex examinations, i.e., cardiac computed tomography. A novel FMR-focused scoring system may lead to the sufficient pre- and postprocedural management of FMR in CHF patients, which may additionally enable the adequate patient selection following with smoother decision-making and superior postinterventional outcomes.

In this present study, we aimed to develop a novel easy-to-handle scoring system for the proper management of patients with FMR that enables the adequate assessment of postprocedural outcomes and patient's prognosis.

Materials and methods

Patients and endpoints

We retrospectively selected patients with symptomatic, moderate-to-severe or severe FMR, who underwent transcatheter mitral valve repair (TMVR) from January 2014 to August 2016 in Heart Center of University Hospital Bonn. All patients were discussed in the heart team and classified as surgical high-risk due to comorbidities and advanced age. All included patients had the mean follow-up (FU) of 18 months. The present study is a retrospective subgroup of patients, who were registered in the Bonner Mitral Valve Register previously. Therefore, all clinical and echocardiographic data originate from the "*Bonner Mitral Valve Register Database*".

In line with MVARC (Mitral valve academic research consortium) definitions, the primary endpoint was defined as a combined endpoint consisting of cardiovascular mortality and rehospitalization due to cardiac decompensation. Secondary endpoints were all-cause mortality and rehospitalization.

The Bonner Mitral Valve Register is following the Declaration of Helsinki and was authorized by the local ethics committee "Ethics Committee of the Faculty of Medicine at the University of Bonn, Germany". All patients signed written informed consent for using their medical records for research issues before the registration in Bonner Mitral Valve Register Database. All patient-related data were fully anonymized before data entry in the Database and analyzed for the study.

Clinical assessment and imaging

All patients underwent a comprehensive echocardiographic examination before and after TMVR according to current recommendations and guidelines, including additional 3D echocardiography [4], [9].

According to the Simpson's method, the left ventricular ejection fraction (LV-EF) was determined by volumetric analysis of the LV in the apical four-chamber view. The pulsed-wave Doppler of the inflow profile of the mitral valve (MV) and the tissue Doppler on the medial MV annulus were used to assess the LV's diastolic dysfunction. The dimensional assessment of the LV and the left atrium were done by volumetric measurement using point-and-click tracing method from the apical four-chamber view. The grading of MR severity was performed using the radius of proximal isovelocity surface area (PISA), effective regurgitant orifice area (EROA), as well as vena contracta width (VC) and regurgitant volume (RegVol) according to current guidelines [10]. EROA and RegVol were calculated by the semi-quantitative PISA-method. According to the modified Bernoulli equation, the right ventricle systolic pressure (RVSP) was estimated from the peak systolic velocity of tricuspid regurgitation in the continuous-wave Doppler equation.

Delta-pressure = 4 x velocity

Transesophageal echocardiography (TEE) was performed for the accurate assessment of MR pathology and MV geometry. The images from TEE were conducive to evaluate the feasibility of TMVR. The echocardiographic studies were performed with commercially available echocardiographic systems (iE 33, Philips Medical Systems, Andover, Massachusetts; Vivid 7, General Electric Medical Health, Waukesha, Wisconsin, USA) and echocardiography probes (X5-1, X7-2t; M4S, 6VT) allowing acquisition both 2D and 3D data sets.

Transcatheter mitral valve repair

Procedural details of TMVR with the MitraClip® or Cardioband® system have been previously described [4], [5], [11]. The number of clips and cinching size required for procedural

success were left to the discretion of the treating physician. The size of Cardioband prosthesis was decided by geometrical measurements from cardiac computed tomography preinterventionally.

Acute changes in MR severity were assessed by intraprocedural real-time TEE. Acute procedural success was defined as a reduction of MR to Grade < II or at least one grade reduction after the clip deployment or completed cinching. Relevant MV stenosis (mean valve pressure gradient (MVG)>5mmHg) was excluded before clip release or after completed cinching of the Cardioband system.

Statistical analysis

The Shapiro Wilk test was used to analyze the normal distribution. Continuous data were expressed as mean values ± standard deviation if normally distributed. Categorical data were presented as percentage values. The Student's two-sample t-test was performed to compare mean values of continuous variables. The Fisher's exact test and the Chi-square test were used to compare categorical data. Two-tailed p-values were considered to be significant if ranging below 0.05.

The Cox proportional hazard analysis was performed to assess predictive values of parameters from the modified MIDA-Score (age, presence of atrial fibrillation, symptoms, left atrial diameter, RVSP, left ventricular enddiastolic diameter, LVEF) for the combined primary endpoint. The multivariate analysis with adjustment on age and atrial fibrillation was performed to evaluate the influence of echocardiographic parameters on the clinical outcome. The ROC analysis was used to assess the predictive power and cut-off values of the score-related parameter in FMR patients. The area under the curve (AUC) shows the positive predictability of the parameters. AUC above 0,5 indicates a good measure of separability. The univariate analysis was performed to assess the impact of factors on clinical outcomes. According to grades of the modified MIDA score, risk categories were evaluated using the weight-distribution determined by hazard ratio (HR) and p-value from the cox proportional-hazard regression analysis. The points (0–4) with HR < 1,2 and p>0.5 were assumed to be low risk (Grade 1); 5–9 points with 5>HR>1.2 and 0.5>p>0.01 were moderate risk (Grade 2); 10–12 points with HR>5 and p>0.01 high risk (Grade 3). The predictors of survival were depicted with the Kaplan-Meier curve. Survival in groups was compared by the Logrank test. Statistics were performed using SPSS for Windows (PASW statistic, Version 25.0.0.0, SPSS Inc., Chicago, Illinois, USA) and MedCalc statistical software (MedCalc Software, Version 11.4.1.0, Mariakerke, Belgium).

Results

Patients, intervention, and FU

We retrospectively included 105 patients (76,7±8,8 years, 50,6% female) with symptomatic (100% NYHA functional class>II) moderate-to-severe or severe FMR (PISA: 0,7±0,4 cm, VC width: 0,8±0,3 cm, EROA: 0,22±0,1 cm^2, RegVol: 38,1±19,2 ml) at surgical high-risk (EuroSCORE II: 5,4±3,8%, STS-Score: 4,7±2,8%) from the "*Bonner Mitral Valve Register Database*". All patients were on guidelines-directed optimal medical heart failure therapy at baseline and FU. The majority of patients (87,5%) had at least triple anti-congestive therapy at baseline.

The mean LVEF was 40,1±15,2% with dilated LV (left ventricular end-diastolic dimension; 6.2±0.3 cm). We found dilated left atrium (the mean left atrial volume: 91,7±39,5 ml) and increased right ventricular systolic pressure (the mean RVSP: 43,4±13 mmHg) with normal right ventricular function (the mean tricuspid annular pre-systolic excursions (TAPSE): 2,1 ±0,3 cm) at baseline.

Eighty-seven patients (82,8%) were treated by interventional edge-to-edge repair (MitraClip system®) and the remaining 18 patients (17,2%) by interventional annuloplasty (Cardioband system®). 92% of procedures were successfully performed without periprocedural mortality. Eight procedures (7,6%) were terminated due to irreducible MR and anatomical challenges. Devices and delivery systems were retracted without complication in those patients. Four patients (3,8%) showed pericardial effusion; two (1,9%) of them presented with hemodynamical relevance, who were successfully treated with prompt pericardiocentesis. Those patients were discharged without any remained complications.

The mean FU duration was 18,2±6,4 months. All-cause mortality was 7% at FU within 18 months after the procedure. 34,1% (n = 33) of successfully treated patients were rehospitalized during FU; 90% (n = 30) of them were due to cardiac decompensation. Demographical and echocardiographical characteristics are presented in Tables 1 and 2.

A novel scoring system for FMR; the modified MIDA-Score

In contrast to DMR patients, patients with FMR are older and show predominantly deteriorated LV function with dilated LV and normal mitral valve anatomy without organic pathology. In addition, elevated LV enddiastolic filling pressure with elevated right ventricular systolic pressure is an often finding in patients with FMR. The broad impact scale of outcome-related parameters based on different underlying pathomechanisms in both types of MR has been previously shown in four meta-analyses with large number of patients (8864) [12, 13, 14, 15]. They are entirely two different patients' cohort–FMR and DMR patients; therefore, they should be separately evaluated.

Owing to varying underlying pathomechanisms, we performed the following modification of the original MIDA-Score. First, we re-determined cut-off values of score-related

Table 1. Demographical characteristics (N = 105).

	Values
Age, years	76,7±8,8
Female, n (%)	53 (50,3)
NYHA Functional Class > II, n (%)	105 (100)
Arterial hypertension, n (%)	83 (79)
Diabetes mellitus, n (%)	19 (18,1)
History of stroke, n (%)	16 (15,2)
Atrial fibrillation or flutter, n (%)	83 (79)
Coronary artery disease, n (%)	69 (65,7)
Previous cardiac surgery, n (%)	13 (12,3)
Chronic renal failure, n (%)	30 (28,5)
Medication	
Beta-Blocker, n (%)	89 (84,7)
ACE-Inhibitor/ AT- Blocker, n (%)	67 (63,8)
Calcium Channel Blocker, n (%)	28 (26,6)
Potassium-sparing diuretics, n (%)	30 (28,5)
Other diuretics, n (%)	83 (79)
Device therapy, n (%)	13 (12,3)
EuroScore II, %	5,4±3,8
STS-Score, %	4,7±2,8

NYHA: New York Heart Association, ACE: Angiotensin-converting enzyme, AT: Angiotension II receptor, CRT: Cardiac resynchronization therapy, STS-Score: Society for Thoracic Surgeons Score.

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Table 2. Echocardiographic characteristics (N = 105).

Parameters	Mean±SD
LV-EF, %	40,1±15,2
LV-EDV, ml	156,6±73,2
LV-ESV, ml	97,7±60,6
LV-EDD, cm	6,2±0.3
LV-ESD, cm	3,7±0.4
LAV, ml	91,7±39,5
LAD, cm	4,9±0.6
MR-PISA, cm	0,7±0,4
MR-VC, cm	0,8±0,3
MR-EROA, cm^2	0,22±0,1
MR-RegVol, ml	38,1±19,2
RVSP, mmHg	43,4±13
TAPSE, cm	2,1±0,3

LV: Left ventricle, EF: Ejection fraction, EDV: enddiastolic volume, ESV: end-systolic volume, EDD: enddiastolic diameter, ESD: end-systolic diameter, LAV: left atrial volume, LAD: left atrial diameter, MR: Mitral regurgitation, PISA: proximal isovelocity surface area, VC: Vena contracta, EROA: Ejection regurgitant orifice area, RegVol: Regurgitation volume, RVSP: Right ventricle systolic pressure, TAPSE: Tricuspid annular systolic excursion.

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parameters–Adaption of cut-off values- based on the previous metanalysis with large number of patients and, additionally, using the summarized ROC analysis of our patient cohort:

Age: Cut-off: 76 years Modification: >65 to >75;

LV-EF: Cut-off: 47% Modification: ≤60 to ≤45;

RVSP: Cut-off: 46 mmHg Modification: ≥50 to ≥45

The comparison between the original and modified MIDA score is presented in Table 3.

Second, we performed the Cox proportional hazard analysis and the adjusted multivariate analysis to evaluate the power of effect (statistically weighting) of each parameter from the modified MIDA score (Tables 4 and 5). We consequently re-arranged the weighting distribution of the score-related factors by the Cox regression analysis regarding the combined

Table 3. Detailed presentation of the difference between the original and modified MIDA score.

	The original MIDA Score		The modified MIDA Score	
	Cut-off	**Points**	**Cut-off**	**Points**
Age, years	≥65	3	≥75	2
Symptoms	y/n	3	y/n	1
AF	y/n	1	y/n	2
LAD, mm	≥55	1	≥55	1
RVSP, mmHg	>50	2	>45	2
LVEDD, mm	≥40	1	≥40	2
LVEF, %	≤60	1	≤45	2
Total		12		12

AF: Atrial fibrillation, LV: Left ventricle, EF: Ejection fraction, EDD: enddiastolic diameter, LAD: left atrial diameter, RVSP: Right ventricle systolic pressure.

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Table 4. Statistical re-weighting of parameters for the modified MIDA Score and re-arrangement of the point distribution using the Cox proportional hazard analysis.

Parameter	HR	95% CI	p-Value	Points
Age≥75 years	2,95	1,07 to 8,1	0,03	2
Symptoms, NYHA>II	1,03	0,49 to 2,43	0,75	1
Presence of atrial fibrillation	1,2	0,41 to 3,4	0,25	2
LAD≥55 mm	1,04	0,5 to 2,19	0,8	1
LVEDD≥40 mm	1,68	0,7 to 4,01	0,24	2
LVEF≤45%	1,4	0,68 to 2,87	0,35	2
RVSP≥45 mmHg	1,59	0,75 to 3,39	0,2	2

NYHA: New York Heart Association, LAD: Left atrial diameter, LVEDD: Left ventricle enddiastolic diameter, LVEF: Left ventricle ejection fraction, RVSP: Right ventricle systolic pressure.

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primary endpoint. The re-arrangement of the point-distribution was as follows: Age: 2 points, Symptoms: 1 point, atrial fibrillation (AF): 2 points, left atrial diameter (LAD): 1 point, right ventricle systolic pressure (RVSP): 2 points, left ventricle end-systolic diameter (LVEDD): 2 points, left ventricle ejection fraction (LVEF): 2 points. The predictive value of each parameter was analyzed by the ROC analysis, as shown in Fig 1. The modified MIDA score showed a positive homogeneous correlation with the original MIDA score (Fig 2).

Predictive value of the modified MIDA Score

The Cox proportional hazard analysis showed age (HR: 2,95, p = 0,03) as the most reliable parameter for the prediction of the combined outcome (Table 3). The adjusted multivariate analysis (on age>75) showed baseline LVEF as the strongest predictor for the combined endpoint (OR: 3,8, 95% CI: 1,04 to 13,83, p = 0,04). On the other hand, we found baseline LVEF and baseline RVSP strong predictors for the combined endpoint in adjusted multivariate analysis for age > 75 and presence of atrial fibrillation (LVEF: OR: 2,8, 95%CI: 0,97 to 8,1, p = 0,05; RVSP: OR: 2,7, 95%CI: 0,93 to 7,13, p = 0,05) (Table 5).

According to the Longrank test, the MIDA Score for DMR showed no statistically significant predictability for mortality and rehospitalization in patients with FMR at follow-up

Table 5. The adjusted multivariate regression analysis: Only age>75 and age>75 & presence of atrial fibrillation.

Parameter	OR (95%CI)	p-Value
Adjusted on age>75		
LVEF	3,8 (1,04 to 13,84)	0,04
LAD	2,09 (0,42 to 10,24)	0,36
LVESD	0,98 (0,22 to 4,29)	0,98
AF	6,65 (0,73 to 60,48	0,09
RVSP	2,84 (0,76 to 10,55)	0,11
Adjusted on Age>75 & AF		
LVEF	2,8 (0,97 to 8,1)	0,05
LAD	1,9 (0,88 to 6,1)	0,1
LVESD	0,65(0,22 to 1,94)	0,45
RVSP	2,9 (0,93 to 7,2)	0,05

AF: Atrial fibrillation, LV: Left ventricle, EF: Ejection fraction, ESD: endsystolic diameter, LAD: left atrial diameter, RVSP: Right ventricle systolic pressure.

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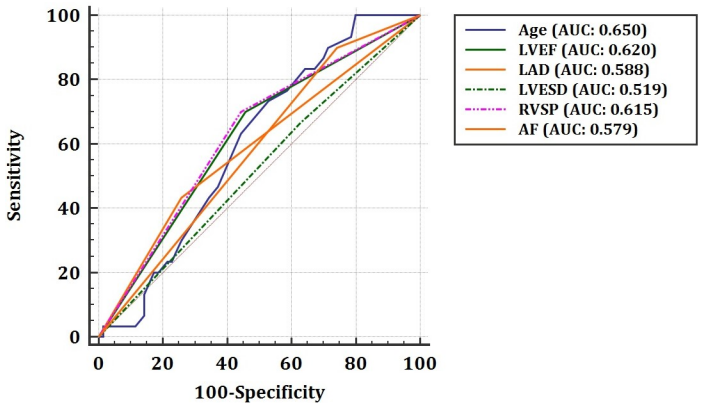

Fig 1. Predictive values of each parameter according to the ROC analysis. (*AF*: *Atrial fibrillation*, *LAD*: *Left atrial diameter*, *LVEF*: *Left ventricular ejection fraction*, *LVESD*: *Left ventricular end-systolic diameter*, *RVSP*: *Right ventricular systolic pressure*).

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(p = 0,5). Although, the modified MIDA score > 9 (Grade III) was found to be a strong predictor for the combined endpoint with statistical significance and high sensitivity > 80% (AUC: 0,89, p = 0,03) (Fig 3). The Cox proportional hazard regression analysis revealed that the modified MIDA score above 9 (Grade III) points as a strong predictor for mortality and rehospitalization as well (p>0,001) (Table 6). According to the Longrank test, we found the highest mortality in patients with the modified MIDA score above 9 (Grade III) followed by patients with Grade II (4<Points<10) (Fig 4).

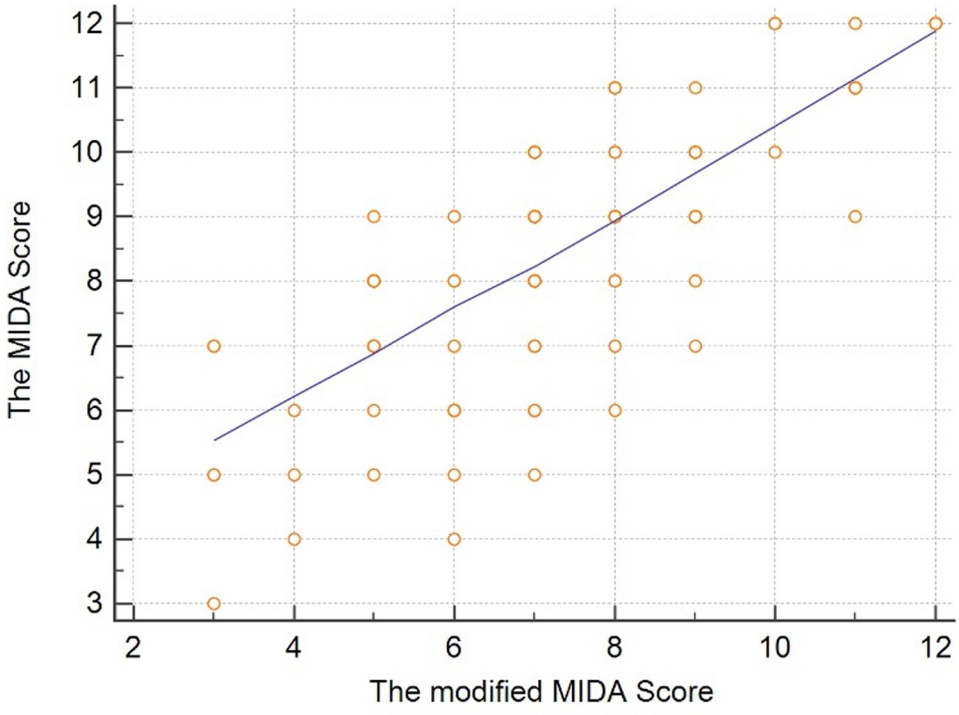

Fig 2. Scatter diagram showing the linear relationship between the original and modified MIDA score.

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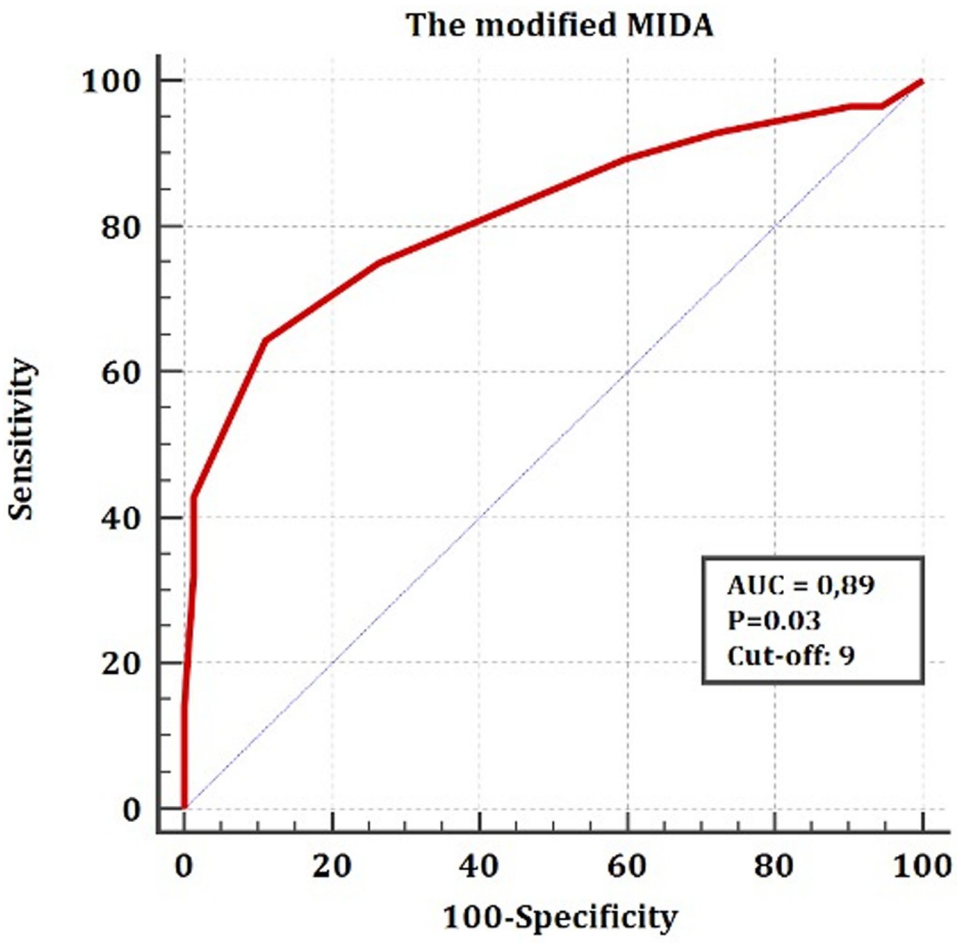

Fig 3. Prediction capability of the modified MIDA Score concerning the combined endpoint: The ROC analysis.

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Related to the grading of the modified MIDA Score, 12,5% of patients with grade I, 27% of patients with grade II, 57% of patients with grade III attained the primary combined endpoint at FU. According to the logistic regression analysis, grade III was significantly associated with the combined endpoint (p = 0,038) (Table 7 and Fig 5).

Table 6. Risk stratification of the modified MIDA Score concerning the combined endpoint: A detailed list with point distribution using the cox proportional hazards regression analysis.

The modified MIDA Score	HR	95% CI	p Value
3 Points	1,15	0,1 to 12,6	0,9
5 Points	1,84	0,4 to 8,32	0,4
6 Points	2,06	0,62 to 8,07	0,1
8 Points	1,25	0,25 to 6,22	0,7
9 Points	3,24	1,17 to 8,9	0,02
10 Points	10,2	2,8 to 37,1	>0,001
11 Points	6,9	2,3 to 20,1	>0,001
12 Points	7,0	2,2 to 22,4	>0,001

CI: Confidence interval, HR: Hazard ratio.

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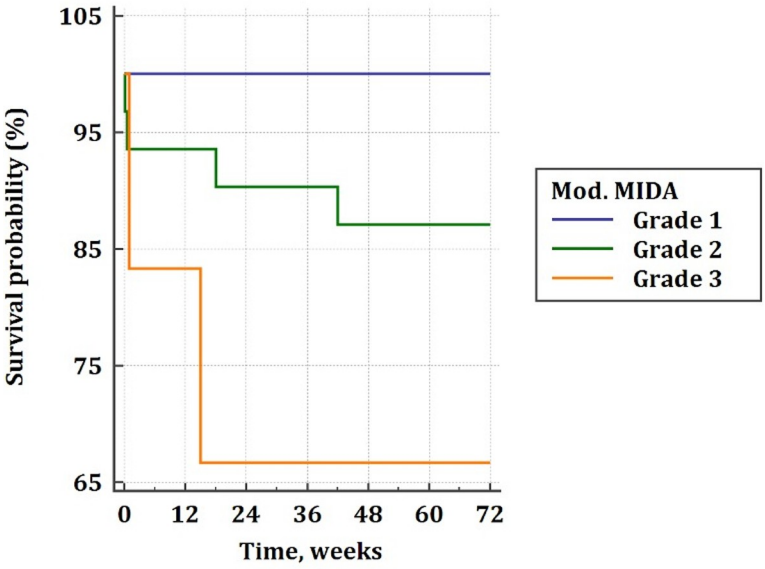

Fig 4. Presentation of survival according to grades of the modified MIDA Score: The Kaplan-Meier curve.

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The modified MIDA score was found to be superior regarding prediction of the combined endpoint in FMR patients with high sensitivity (>80%) and specificity (> 80%) compared to the other conventional surgical score systems according to the comparison of ROC curves (The modified MIDA-Score AUC: 0,8, EuroSCORE II; AUC: 0,57, STS-Score; AUC: 0,51) (Fig 6).

Discussion

MR is common valvular heart disease and presents a public health problem associated with impaired quality of life and high mortality. Concomitant MR is a known predictor for unfavorable outcomes in patients with chronic heart failure [3]. MR treatment is complex and influenced by many clinical and echocardiographic parameters. Hence, it is a teamwork from an interdisciplinary team, and every patient should be decided and evaluated individually. The decision-making regarding the type and timing of MR therapy is challenging due to preexisting impaired LV function and advance comorbidities. The guideline-directed optimal heart failure medical therapy (GDOMT) and surgical treatment are standard of care and essential in such patients [2]. On the other hand, interventional treatment of MR should also be taken into account in patients at surgical high-risk, which is not an exotic and rare phenomenon. Therefore, the preprocedural assessment of patients' prognosis and potential procedural outcomes plays a pivotal role in the management of MR.

Recent studies showed conflicting results concerning outcomes after interventional MR therapy. Interventional treatment of DMR is superior to alone GDOMT in almost all

Table 7. Predictive values of grades of the modified MIDA Score: The Logistic regression analysis.

The modified MIDA score	%	Combined endpoint (%)	OR (95%CI)	p- Value
Grade 1 (0–4 points)	8	12,5	0,38 (0,04 to 3,34)	0,011
Grade 2 (5–9 points)	78	26,92	1,4 (0,4 to 4,3)	0,09
Grade 3 (10–12 points)	14	57,14	3,35 (1,3 to 8,58)	0,038

OR: Odds ratio.

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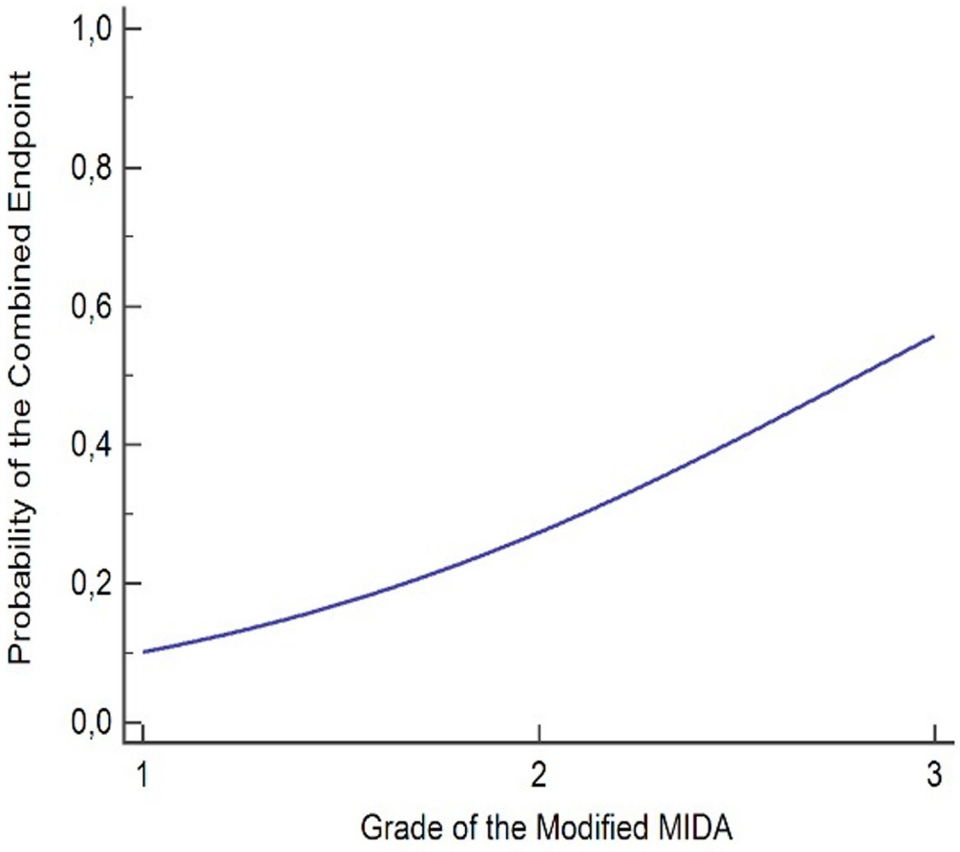

Fig 5. Probability of the combined endpoint in grades of the modified MIDA score: The Logistic regression analysis.

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published studies. However, outcomes after the interventional FMR treatment are inconsistent. Although several studies presented superior outcomes of interventional FMR therapy, there are also some studies showing no beneficial impact of the interventional FMR treatment compared to GDOMT alone [3, 12, 13, 16, 17]. Thus, management, especially preprocedural, of the interventional MR treatment should be appropriately performed. Adequate management of FMR patients requires, first and most important, sufficient assessment of patients' prognosis and outcomes of the potential procedure. Second, decision-making based on selection of type and timing of therapy should be interdisciplinary and carefully done. Third, postprocedural management of patients is essential and should be planned according to preprocedurally assessed potential outcomes of the intended procedure. Therefore, a novel scoring system predicting patients' prognosis and long-term outcomes for patients with FMR is urgently needed for challenging management of complex MR treatment.

There are already two derived and validated scoring systems (EuroScore II and STS-Score) with excellent predictive values (AUC>0,8) to assess the surgical risk in patients with structural heart disease [6, 7]. However, they were developed only for assessment of the surgical risk and focus solely on surgery-related short-term outcomes. Compared to conventional risk scoring systems, the modified MIDA score is generated from seven important parameters consisting of three clinical and four echocardiographic prognosis-relevant parameters. On the other hand, the modified MIDA score is explicitly adapted to FMR patients based on the underlying

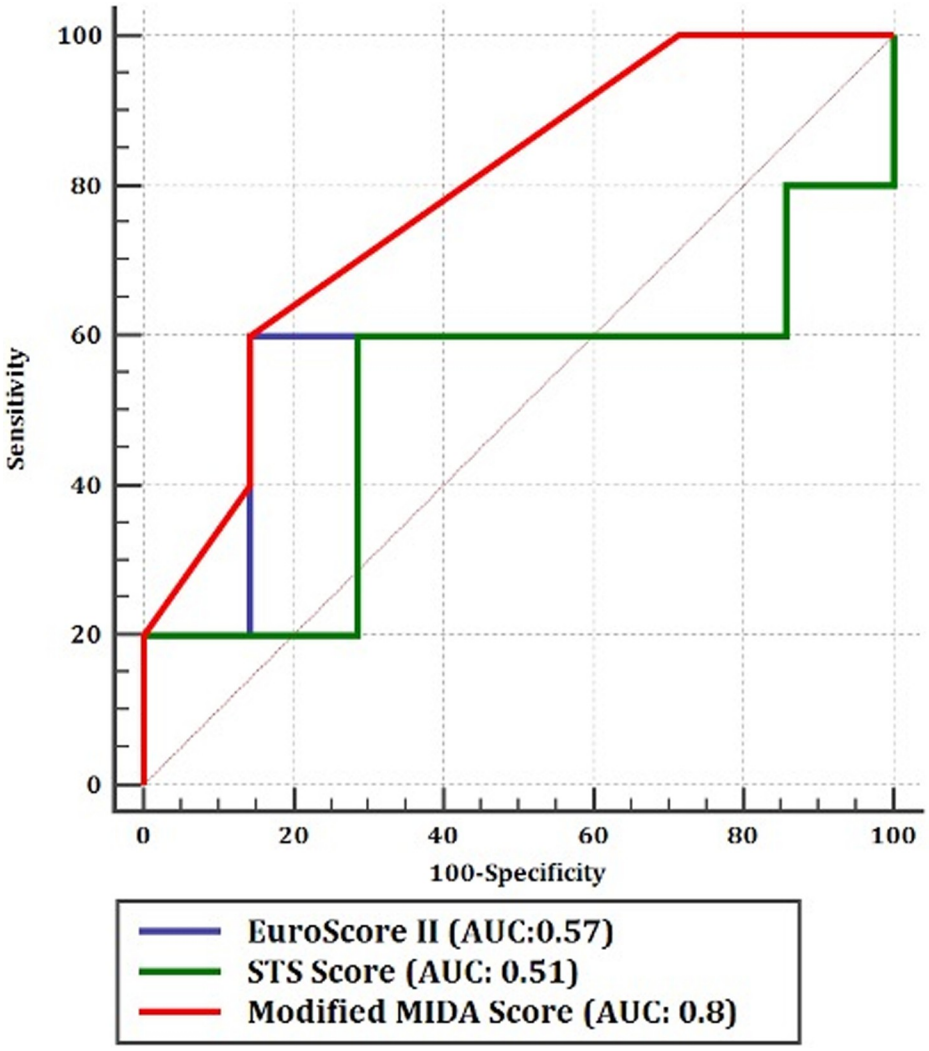

Fig 6. Comparison of score systems in FMR patients: Comparison of ROC curves. (AUC: Area under the curve, STS: The Society of Thoracic Surgeons, MIDA: The Mitral Regurgitation International Database).

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pathomechanism of FMR according to the meta-analysis with large number of patients and monocentric analysis of our patients' cohort. It might lead to a proper, etiology-adapted, and individual assessment of patients' prognosis and procedural outcomes in patients with FMR undergoing interventional therapy. In addition, it might achieve the selection of eligible patients with potentially favorable outcomes for interventional treatment of FMR.

Grigioni et al. have presented the MIDA mortality risk score as a novel risk scoring system that enables appropriate outcome assessment in patients with DMR under medical or surgical therapy [8]. This risk score is based on patients with DMR and focuses on the risk of mortality. However, rehospitalization is another crucial prognostic parameter, which leads to impaired quality of life, increased mortality, and high health care costs. Therefore, it should be a pivotal and inevitable part of prognostic assessment. Of note, compared to patients with DMR, recurrent rehospitalization is more often in FMR, and it is considered to be one of main problems in patients with FMR, who frequently decompensate due to impaired LV function with concomitantly persisting MR despite GDOMT [18].

The modified MIDA score lead to adequate prediction of the combined endpoint consisting of cardiovascular mortality and rehospitalization, which may enable sufficient prognostic assessment in patients with FMR postprocedurally. We found statistically significant adverse outcomes (high mortality and often rehospitalization) in patients with the modified MIDA Score >9 (Grade III) within 18 months after the procedure. It might be explained by preexisting worse cardiac conditions (impaired LV function, high RVSP) and/or the late-onset treatment–preexisting irreversible remodeling, myocardial fibrosis, and already adapted pulmonary circulation. Interventional treatment of FMR should be more critically discussed in such patients due to unfavorable outcomes.

In line with the MITRA-FR and COAPT studies, adequate assessment of patient's prognosis and outcomes of the intended procedure with proper decision-making (type and timing of therapy) plays a pivotal role in getting favorable outcomes in patients with FMR undergoing TMVR [16, 17]. Traditional surgical risk scores is lacking for sufficient assessment of individual long-term outcomes of the interventional FMR treatment. The modified MIDA score might facilitate sufficient assessment of postprocedural outcomes and patients' prognosis in FMR patients undergoing TMVR, which might lead to more favorable outcomes owing to proper management of patients with FMR.

Limitations

This single-center retrospective study has several limitations. We retrospectively selected the small number of patients (n = 105) with completed data from the *Bonner Mitral Valve Register Database*, which reflects just a tiny part of FMR patients in the real world. The retrospective nature of this study and the targeted patient selection from the Database might be reasons for bias. Furthermore, our echocardiographic data weren´t adjudged by an independent core-lab.

Moreover, FU was just for 18 months. Our small size cohort included only the patients who underwent interventional treatment of FMR. The surgically and conservatively treated patients were not included in the present study, which should be considered as bias. Hence, the modified MIDA score should be proven in multicentric statistical validation studies with a large number of patients inclusively surgical and conservative treatment.

Conclusion

The modified MIDA Score was found to be a promising, elementary, easy-to-handle tool, which might lead to adequate prediction of individual postprocedural outcomes in patients with FMR undergoing TMVR. It might enable proper management of the FMR treatment. Our preliminary data should be validated by a multicentric study with the large number of patients.

Supporting information

S1 Fig. Histogram of the point distribution of the modified MIDA Score.
(TIF)

S2 Fig. Predictive value of the modified MIDA Score > 9 points: The ROC curve.
(TIF)

S3 Fig. Probability of the combined endpoint in grades of the modified MIDA Score: The Cox regression analysis.
(TIF)

S4 Fig. The Kaplan-Meier curve for grades of the modified MIDA Score regarding the combined endpoint.
(TIF)

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Methodology: Can Öztürk, Marc Ulrich Becher, Alev Kalkan, Vedat Tiyerili.

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Supervision: Marc Ulrich Becher, Marcel Weber, Georg Nickenig, Vedat Tiyerili.

Validation: Can Öztürk, Georg Nickenig.

Visualization: Refik Kavsur.

Writing – original draft: Can Öztürk.

Writing – review & editing: Can Öztürk, Marc Ulrich Becher, Georg Nickenig, Vedat Tiyerili.

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Zielsetzung der Arbeit: Im klinischen Alltag bietet die interventionelle Edge-to-Edge-Mitralklappenreparatur mittels der MitraClip™-Prozedur seit ihrer CE-Kennzeichnung im Jahr 2008 eine sichere therapeutische Option bei älteren inoperablen Patienten mit verschiedenen Komorbiditäten. Mit weltweit zunehmenden Erfahrungen stellten sich die Prädiktoren für die schlechten postinterventionellen Kurzzeitergebnisse heraus – zum Beispiel erhöhter rechtsventrikulärer systolischer Druck, hoher Mitralklappen-gradient, chronische Niereninsuffizienz, chronische Anämie, periphere arterielle Verschlusskrankheit oder konkomitante TI. Dennoch sind die Daten über die Langzeitergebnisse mit Durabilität der MI-Reduktion und die Prädiktoren für die Outcomes begrenzt. Ziel dieser Arbeit war es, die Fünf-Jahres-Ergebnisse nach dem MitraClip™-Verfahren zu evaluieren.

Methoden und Ergebnisse: Wir untersuchten zwischen Februar 2011 und Februar 2014 in unserem Herzzentrum die mittels MitraClip™-System behandelten 265 Patienten (81,4 ± 8,1 Jahre, 46,7 % weiblich) mit symptomatischer (100 % NYHA-Klasse ≥ II, Sechs-Minuten-Gehstrecke: 243,8 ± 121,3 m) hochgradiger (PISA: 0,9 ± 0,2 cm, VC: 1,4 ± 0,4 cm, EROA: 0,6 ± 0,3 cm^2, Regurgitationsvolumen: 54,4 ± 16 ml) MI (60,4 % FMI und 39,6 % DMI). Die Patienten mit DMI zeigten eine höhere interventionelle Misserfolgsrate im Vergleich zu Patienten mit FMI (DMI 8,6 % vs. FMI 3,1 %, p = 0,04). Fünf Jahre nach dem erfolgreichen MitraClip™-Verfahren dokumentierten wir in der Gesamtkohorte eine 74%ige anhaltende MI-Reduktion (MI ≤ Grad II) mit hieraus resultierender Verbesserung der funktionellen Kapazität (Delta der NYHA-Klasse: 1,2, Delta der Sechs-Minuten-Gehstrecke: 55 m). Echokardiographisch sahen wir eine signifikante Zunahme der rechtsventrikulären Funktion (TAPSE: 1,8 ± 0,3 cm auf 1,9 ± 0,4 cm, p = 0,008) mit relevanter Abnahme des rechtsventrikulären systolischen Drucks (RVSP: 49,7 ± 17,3 mmHg auf 40,7 ± 17,5 mmHg, p = 0,02) ohne relevante Veränderungen der linksventrikulären Parameter. Der Serumspiegel des NT-proBNP zeigte ebenfalls eine tendenzielle Senkung nach fünfjähriger Nachbeobachtungszeit, jedoch ohne statistische Signifikanz (5987,3 ± 9989,3 pg/ml auf 4614,7 ± 5596,6 pg/ml, p = 0,5). Im weiteren Verlauf teilten wir die

Gesamtkohorte nach zugrundeliegender MI-Ätiologie in zwei Gruppen auf (DMI und FMI). Bezüglich der demographischen sowie der klinischen Charakteristika der Patienten ergab sich kein statistisch signifikanter Unterschied zwischen den Gruppen. Allerdings zeigte die FMI-Gruppe eine prädominante Einschränkung in der funktionellen Kapazität (Sechs-Minuten-Gehstrecke: 253,3 ± 107,7 m vs. 267,1 ± 160,2 m, p = 0,2) mit prävalenten Herzinsuffizienz-Symptomen (NYHA-Klasse > III 44,2 % vs. 13,8 %, p = 0,06) ohne statistische Signifikanz. Klinisch wiesen die beiden Gruppen eine signifikante Verbesserung der funktionellen Kapazität und der Herzinsuffizienz-Symptome fünf Jahre nach erfolgreicher MI-Reduktion mittels MitraClip™-System auf, die in der FMI-Gruppe deutlich hervorstachen (siehe Figure 1, p. 218, Figure 2, p. 220, Öztürk et al., 2021). Fünf Jahre nach dem erfolgreichen MitraClip™-Verfahren stellten wir eine statistisch signifikante Verbesserung des rechtsventrikulären systolischen Druckes (RVSP: 50 ± 17,4 mmHg auf 39,3 ± 17,3 mmHg, p = 0,05) und der rechtsventrikulären Funktion (TAPSE: 1,7 ± 0,4 cm auf 1,9 ± 0,4, p = 0,03) lediglich bei Patienten mit FMI fest, aber nicht in der DMI-Gruppe (RVSP: 49,4 ± 18,3 mmHg auf 41,6 ± 18,7 mmHg, p = 0,3; TAPSE: 2 ± 0,2 cm auf 2,1 ± 0,4 cm, p = 0,5). Außerdem ermittelten wir eine höhere Fünf-Jahres-Gesamtsterblichkeit bei Patienten mit FMI mit statistischer Signifikanz (FMI 19 % vs. DMI 10 %, p = 0,05). Des Weiteren zeigten die ROC-Analyse und die Cox-Regressionsanalyse, dass ein vorliegender RVSP > 45 mmHg, ein vorliegender MPG > 1,5 mmHg sowie ein vorliegendes Kreatinin > 2 mg/dl die unabhängigen Prädiktoren für die Fünf-Jahres-Sterblichkeit und die funktionellen Langezeitergebnisse sind.

Schlussfolgerungen**:** Das MitraClip™-Verfahren bietet bei chirurgischen Hochrisiko-Patienten unabhängig von der MI-Ätiologie eine sichere und anhaltende MI-Reduktion mit einem vorteilhaften klinischen Outcome. Das akute Verfahrensversagen war signifikant höher bei Patienten mit DMI. Die Patienten mit FMI wiesen eine signifikant höhere Fünf-Jahres-Gesamtsterblichkeit auf. Ein vorliegender RVSP > 45 mmHg, vorliegendes Kreatinin > 2 mg/dl und ein vorliegender MPG > 1,5 mmHg erwiesen sich als unabhängige Prädiktoren für die Fünf-Jahres-Gesamtsterblichkeit und für ungünstige funktionelle Langzeitergebnisse.

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Single-center five-year outcomes after interventional edge-to-edge repair of the mitral valve

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Abstract

Background: *The MitraClip procedure was established as a therapeutic alternative to mitral valve surgery for symptomatic patients with severe mitral regurgitation (MR) at prohibitive surgical risk. In this study, the aim was to evaluate 5-year outcomes after MitraClip.*

Methods: *Consecutive patients undergoing the MitraClip system were prospectively included. All patients underwent clinical follow-up and transthoracic echocardiography.*

Results: *Two hundred sixty-five patients (age: 81.4 ± 8.1 years, 46.7% female, logistic EuroSCORE: 19.7 ± 16.7%) with symptomatic MR (60.5% secondary MR [sMR]). Although high procedural success of 91.3% was found, patients with primary MR (pMR) had a higher rate of procedural failure (sMR: 3.1%, pMR: 8.6%; p = 0.04). Five years after the MitraClip procedure, the majority of patients presented with reduced symptoms and improved functional capacity (functional NYHA class: p = 0.0001; 6 minutes walking test: p = 0.04). Sustained MR reduction (≤ grade 2) was found in 74% of patients, and right ventricular (RV) function was significantly increased (p = 0.03). Systolic pulmonary artery pressure (sPAP) was significantly reduced during follow-up only in sMR patients (p = 0.05, p = 0.3). Despite a pronounced clinical and echocardiographical amelioration and low interventional failure, 5-year mortality was significantly higher in patients with sMR (p = 0.05). The baseline level of creatinine (HR: 0.695), sPAP (HR: 0.96) and mean mitral valve gradient (MVG) (HR: 0.82) were found to be independent predictors for poor functional outcome and mortality.*

Conclusions: *Transcatheter mitral valve repair with the MitraClip system showed low complication rates and sustained MR reduction with improved RV function and sPAP 5 years after the procedure was found in all patients, predominantly in patients with sMR. Despite pronounced functional amelioration with low procedure failure, sMR patients had higher 5-year mortality and worse outcomes. Baseline creatinine, MVG, and sPAP were found to be independent predictors of poor functional outcomes and 5-year mortality.* (Cardiol J 2021; 28, 2: 215–222)

Key words: MitraClip, transcatheter mitral valve repair, long-term outcomes, mitral regurgitation

Introduction

Mitral regurgitation (MR) is the second most frequent valve disease, with an increasing prevalence in elderly (> 75 years) patients, and is related to reduced functional capacity and impaired quality of life. Transcatheter mitral valve repair (TMVR) with the MitraClip system (Abbot Vascular, Inc.,

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Santa Clara, California) is a therapeutic alternative to mitral valve (MV) surgery in symptomatic patients with moderate to severe MR at prohibitive surgical risk [1–3]. TMVR with the MitraClip procedure can be successfully performed in patients with secondary MR (sMR) and primary MR (pMR) if mitral valve (MV) anatomy is suitable [4]. Its clinical efficacy and safety have been proven in a large number of patients [4–6].

Acute procedural success rates are reported to be up to 99% and are followed by symptomatic improvement in about 80% of cases [7].

A high baseline systolic pulmonary artery pressure (sPAP), an elevated baseline mitral valve mean gradient (MVG), concomitant chronic kidney disease, anemia, peripheral artery disease, and tricuspid regurgitation have been previously reported as independent predictors of poor short-term outcomes after MitraClip procedures [8, 9, 10].

Although more than 70,000 patients have undergone MitraClip procedures to date, data on long-term outcome and durability of MR reduction are limited, and parameters predicting adverse long-term outcomes are not well defined.

The objectives of the present study were to evaluate functional and echocardiographic long-term outcomes 5 years subsequent to transcatheter edge-to-edge mitral valve repair with the MitraClip procedure in a single high-volume center and assess predictors of poor outcomes.

Methods

Patients and endpoints

In this single-center study, consecutive patients undergoing TMVR with the MitraClip system were prospectively included. From February 2011 to February 2014 symptomatic (New York Heart Association [NYHA] functional class > II), and surgical high-risk patients with moderate-to-severe MR were evaluated for TMVR. All patients underwent TMVR following heart team judgement according to surgical high-risk (logistic EuroSCORE II > 10%).

All patients underwent clinical and echocardiographic examinations before and 5 years after the MitraClip procedure.

According to Mitral Valve Academic Research Consortium (MVARC) definitions, the primary endpoint was defined as all-cause mortality [11]. The secondary endpoint was an improvement in functional capacity: NYHA functional class at follow-up was < II; 25% amelioration in exercise capacity (six minute walk test [6MWT]).

The study was authorized by the local ethics committee and in accordance with the Declaration of Helsinki. All patients signed written, informed consent before study inclusion.

Echocardiography and follow-up assessment

Echocardiographic assessment before and after TMVR was done following current recommendations and guidelines which included a comprehensive echocardiography [4, 12]. The severity of MR was graded using the radius of proximal isovelocity surface area (PISA radius), effective regurgitant orifice area (EROA), as well as vena contracta (VC) width and regurgitant volume. EROA and regurgitation volume were calculated using the semi-quantitative PISA-method [13]. The echocardiographic studies were performed with a commercially available echocardiographic system (iE 33, Philips Medical Systems, Andover, Massachusetts) and echocardiography probes (X5-1, X7-2t) allowing acquisition of two- (2D) and three-dimensional (3D) data sets. sPAP was estimated from Doppler-based tricuspid regurgitation systolic peak velocity according to use of the modified Bernoulli equation (Delta-pressure: 4 × velocity) to approximate differences of pressure between the right ventricle and the right atrium.

The echocardiographer who performed follow-up evaluation was blinded to procedural outcomes and patient characteristics. Trained personnel carried out clinical follow-up evaluation, unattended by the interventionalists or procedural echocardiographer.

Interventional edge-to-edge repair of MR

Procedural details of TMVR with the MitraClip system have been described previously [14, 15]. During the MitraClip procedure, acute changes of MR severity were assessed by intraprocedural transesophageal echocardiography as supposed by Armstrong and Foster [16], and Wunderlich and Siegel [17]. Acute procedural success was defined as a reduction of MR by at least one grade having a residual MR < 2+. The number of clips required for procedural success was left to the discretion of the treating physician. Before the clip release, echocardiography was performed to exclude clinically relevant MV stenosis (mean MVG > 5 mmHg).

Statistical analysis

Normal distribution of continuous variables was examined using the Kolmogorov–Smirnov test. Continuous data were expressed as mean values ±

Table 1. Baseline demographical characteristics.

	All patients (n = 265)	sMR (n = 160)	pMR (n = 105)	P
Gender (female)	46.7%	40.9%	56.7%	0.1
Age [years]	81.4 ± 8.1	79.1 ± 8.7	84.6 ± 5.7	0.1
BMI [kg/m^2]	25.4 ± 4.2	26 ± 4.6	24.5 ± 3.4	0.1
Logistic EuroSCORE [%]	19.7 ± 16.7	21.4 ± 17.5	16.9 ± 15.2	0.3
NYHA ≥ II	100%	100%	100%	1
NYHA III	68.1%	55.8%	86.2%	
NYHA IV	31.9%	44.2%	13.8%	0.06
Chronic heart failure	70.7%	81.4%	66.7%	0.1
Coronary heart diesease	71.4%	75.9%	65%	0.3
Arterial hypertension	66.7%	70.5%	61.3%	0.3
History of stroke	4%	2.3%	6.5%	0.4
Peripheral artery diesease	10.7%	11.4%	9.7%	0.6
Diabetes mellitus	34.7%	45.5%	29.4%	0.09
Hyperlipidemia	36%	45.5%	31.6%	0.1
Nicotine	24%	25%	22.6%	0.5
Creatinine [mg/dL]	1.5 ± 0.8	1.6 ± 0.9	1.4 ± 0.7	0.2

sMR — secondary mitral regurgitation; pMR — primary mitral regurgitation; BMI — body mass index; NYHA — New York Heart Association functional classification

standard deviation. The Student two-sample t-test or the Mann-Whitney-U test was performed to compare continuous variables. The Fisher exact test or χ^2 test was used to compare categorical data. Two-tailed p-values were considered to be significant if ranging below 0.05. Univariate analysis was performed to assess the impact of etiology of MR on clinical outcomes. The predictors of 5-year mortality were estimated employing the Cox proportional regression analysis. Survival and cumulative incidence of re-do in groups were compared using the Log-rank test and were estimated with the Kaplan-Meier curve. The regression and receiver operating characteristic (ROC) analysis were performed to determine independent predictors with cut-off values of functional outcomes and mortality.

Statistics were performed using SPSS for Windows (PASW statistic, Version 20.0.0.0, SPSS Inc., Chicago, Illinois, USA).

Results

Baseline data and procedural outcomes

Two hundred sixty-five consecutive, surgical high-risk patients (81.4 ± 8.1 years, 46.7% female, Logistic EuroSCORE: 19.7 ± 6.7%, 60.5% sMR) underwent TMVR with the MitraClip system, and the majority of patients (88%, n = 233) completed a 5-year follow-up including physical, laboratory and echocardiographical examinations. Patients lost to follow-up (n = 32) were contacted concerning quality of life, complaints and hospitalization via telephone.

The baseline characteristics are presented in Table 1. There were no differences between groups in demographic baseline characteristics. However, at baseline, patients with sMR presented worse functional capacity (6MWT: 253.3 ± 107.7 m vs. 267.1 ± 160.2 m; p = 0.2; NYHA > III: 44.2% vs. 13.8%; p = 0.06) compared to patients with pMR.

The procedure was successfully performed in 242 (91.3%) patients with implantation of more than one clip in 32% of cases. Six MitraClip procedures were aborted due to relevant MV stenosis (MVG > 5 mmHg) after the clip closure. Four of those patients were treated for pMR. 13 procedures were aborted due to irreducible MR.

Of note, there was no procedural-related mortality, 10 (23.8%) patients had minor bleeding, and one patient had pericardial tamponade, which could be effectively treated with pericardiocentesis. All acute complications could be successfully managed before discharge. Overall, interventional failure rates were low, however, patients with pMR showed statistically significant higher interventional failure rates (pMR: 8.6%, sMR: 3.1%; p = 0.04).

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Table 2. Baseline echocardiographical characteristics.

	All patients (n=265)	sMR (n = 160)	pMR (n = 105)	P
LVEDV [mL]	154.4 ± 59	165.3 ± 62.6	135.8 ± 49.2	0.03
LVESV [mL]	87.3 ± 52.4	106.4 ± 53.3	59.3 ± 36.6	0.0001
LVEF [%]	46.3 ± 17.4	38.3 ± 14.1	58.1 ± 15	0.0001
sPAP [mmHg]	47.5 ± 15	46.2 ± 15.7	50 ± 14	0.4
MV gradient [mmHg]	1.6 ± 0.9	1.4 ± 0.8	1.8 ± 1	0.03
Severity of MR	3.2 ± 0.4	3.1 ± 0.3	3.4 ± 0.5	0.1
MR grade III	79.7%	90.9%	63.3%	0.02
MR grade IV	18.9%	6.8%	36.7%	0.03
E/A ratio	2.4 ± 1	2.6 ± 1.2	2.2 ± 0.8	0.2
PISA radius [cm]	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.3	0.2
VC width [cm]	1.4 ± 4.4	1.5 ± 5.3	1.2 ± 2.3	0.7
EROA [cm^2]	0.6 ± 0.3	0.5 ± 0.1	0.6 ± 0.4	0.3
Regurgitation volume [mL]	54.4 ± 16	53.2 ± 16	56.3 ± 16.2	0.4
Tricuspid regurgitation	2.1 ± 0.8	2.1 ± 0.8	2 ± 0.8	0.6
TAPSE [cm]	1.8 ± 0.4	1.7 ± 0.4	2 ± 0.2	0.09

sMR — secondary mitral regurgitation; pMR — primary mitral regurgitation; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; LVEF — left ventricular ejection fraction; sPAP — systolic pulmonary artery pressure; MV — mitral valve: MR — mitral regurgitation; PISA — proximal isovelocity surface area; VC — vena contracta; EROA — effective regurgitant orifice area; TAPSE — tricuspid annular systolic excursion

During 5-year follow-up three patients underwent surgery for recurrent MR (pMR: 1.9%, sMR: 0.6%; p = 0.3), 16 patients required a second clipping (sMR: 6.8%, pMR: 4.7%, p = 0.5) and four patients were treated with additional catheter-based approaches (Carillon®, Cardiac Dimension, Kirkland, The USA; Cardioband®, Edwards Lifesciences, United Kingdom) due to recurrent severe MR and decompensated heart failure (sMR: 1.8%, pMR: 0.9%, p = 0.6) (**Suppl. Fig. 4**).

Echocardiographic measures at baseline and five-year follow-up

Concerning baseline echocardiographic characteristics, there were no significant differences in MR defining parameters and sPAP between sMR and pMR. Patients with sMR had larger baseline left ventricle (LV) volumes (LVEDV: 165.3 ± 62.6 mL, 135.8 ± 49.2 mL; p = 0.03; LVESV: 106.4 ± ± 53.3 mL, 59.3 ± 36.6 mL; p = 0.001) and significantly impaired baseline LV systolic function (38.3 ± ± 14.1%, 58.1 ± 15%; p = 0.0001). Patients with sMR showed impaired right ventricle (RV) function at baseline as well (TAPSE: 1.7 ± 0.4 cm, 2 ± 0.2 cm; p = 0.09) (Table 2).

At 5-year follow-up a sustained reduction of MR (MR ≤ 2) was found in 74% of patients (sMR: 77%, pMR: 71.5%; p = 0.9) (Fig. 1). There were no significant changes in LV volumes ($LVEDV_{sMR}$: 162.4 ± ± 56.7 mL, 154.5 ± 66.9 mL; p = 0.5; $LVEDV_{pMR}$: 127.8 ± 47.3 mL, 116.6 ± 26.4 mL; p = 0.3; $LVESV_{sMR}$: 105.2 ± 45.5 mL, 99.6 ± 57.8 mL; p = 0.6; $LVESV_{pMR}$: 56.2 ± 34.5 mL, 51.6 ± 20.2 mL; p = 0.5). Left ventricular ejection fraction (LVEF) was not significantly changed 5 years after the MitraClip procedure (EF_{sMR} 36.9 ± 12.6%, 38.7 ± ± 13.6%, p = 0.5; EF_{pMR} 58.1 ± 12.2%, 58.4 ± 9.7%, p = 0.9). In sMR patients, sPAP was significantly reduced at follow-up (50 ± 17.4 mmHg, 39.3 ±

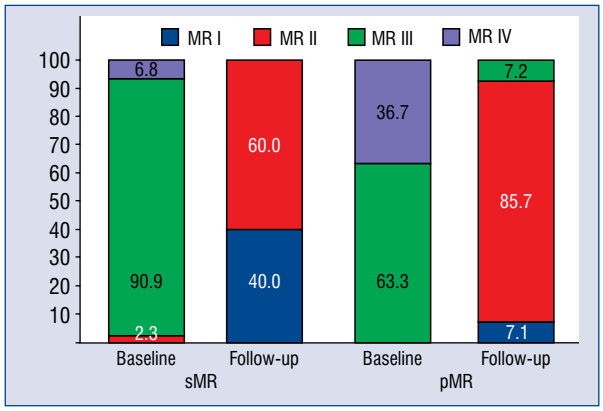

Figure 1. Reduction of mitral regurgitation (MR) at 5-year follow-up; pMR — primary mitral regurgitation; sMR — secondary mitral regurgitation.

Table 3. Echocardiographical and clinical outcomes at follow-up.

	Baseline	Follow-up	P
LVEDV [mL]	150 ± 55.5	140.9 ± 58.4	0.3
sMR	162.4 ± 56.7	154.5 ± 66.9	0.5
pMR	127.8 ± 47.3	116.5 ± 26.4	0.3
LVESV [mL]	87.6 ± 47.7	82.4 ± 52.8	0.4
sMR	105.2 ± 45.5	99.6 ± 57.8	0.6
pMR	56.2 ± 34.5	51.6 ± 20.2	0.5
LVEF [%]	44.5 ± 16.1	45.8 ± 15.5	0.5
sMR	36.9 ± 12.6	38.7 ± 13.6	0.5
pMR	58.1 ± 12.2	58.4 ± 9.7	0.9
IVSDD [cm]	1.2 ± 0.3	1 ± 0.2	0.04
sMR	1.2 ± 0.3	1 ± 0.2	0.04
pMR	1.3 ± 0.3	1.2 ± 0.3	0.3
MR	3.1 ± 0.4	1.7 ± 0.5	0.0001
sMR	3 ± 0.3	1.6 ± 0.5	0.0001
pMR	3.4 ± 0.5	2 ± 0.4	0.0001
MR ≤ II [%]	0	97.4	0.0001
sMR	0	100	0.0001
pMR	0	92.9	0.0001
MR > II [%]	100	2.6	0.0001
sMR	100	0	0.0001
pMR	100	7.1	0.0001
Mitral gradient [mmHg]	1.4 ± 0.8	3.5 ± 2.9	0.0001
sMR	1.4 ± 0.8	2.8 ± 1.3	0.0001
pMR	1.5 ± 0.9	4.8 ± 4.5	0.02
TAPSE [cm]	1.8 ± 0.3	1.9 ± 0.4	0.008
sMR	1.7 ± 0.4	1.9 ± 0.4	0.03
pMR	2 ± 0.2	2.1 ± 0.4	0.5
sPAP [mmHg]	49.7 ± 17.3	40.7 ± 17.5	0.02
sMR	50 ± 17.4	39.3 ± 17.3	0.05
pMR	49.4 ± 18.3	41.6 ± 18.7	0.3
NYHA functional class	3.4 ± 0.5	2.2 ± 0.9	0.0001
sMR	3.5 ± 0.5	2.1 ± 0.9	0.0001
pMR	3.2 ± 0.4	2.2 ± 1	0.004
6MWT [m]	243.8 ± 121.3	298.1 ± 118.6	0.04
sMR	235.3 ± 107.7	305.3 ± 123.1	0.03
pMR	267.1 ± 160.2	278.6 ± 111.9	0.8
NT-proBNP [pg/mL]	5987.3 ± 9989.3	4614.7 ± 5596.6	0.5
sMR	3844.7 ± 3099.4	4581.1 ± 4356.1	0.2
pMR	10510.6 ± 16770.4	4685.8 ± 7939.8	0.4

sMR — secondary mitral regurgitation; pMR — primary mitral regurgitation; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; LVEF — left ventricular ejection fraction; IVSDD — diastolic interventricular septum diameter; MR — mitral regurgitation; TAPSE — tricuspid annular systolic excursion; sPAP — systolic pulmonary artery pressure; NYHA — New York Heart Association; 6MWT — six minutes walking test; NTpro-BNP — N-terminal pro-B-type natriuretic peptide

± 17.3 mmHg, p = 0.05), however, not significantly in pMR patients (49.4 ± 18.3 mmHg; 41.6 ± 18.7 mmHg, p = 0.3) (Table 3). RV function increased significantly just in patients with sMR (1.7 ± 0.4 cm, 1.9 ± 0.4 cm, p = 0.03; 2 ± 0.2 cm, 2.1 ± 0.4 cm, p = 0.5). MVG significantly increased after

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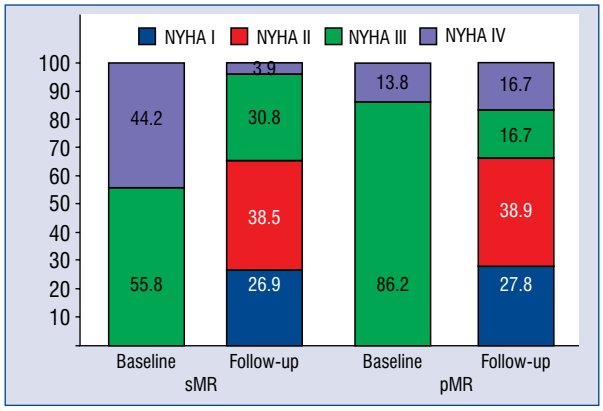

Figure 2. Changes in functional New York Heart Association (NYHA) class; pMR — primary mitral regurgitation; sMR — secondary mitral regurgitation.

MitraClip procedures (1.4 ± 0.8 mmHg, 3.5 ± 2.9 mmHg; p = 0.001) without incidence of clinically relevant MV stenosis.

Clinical outcomes and predictors of outcome

At 5-year follow-up the majority of patients (65.4%) presented with improved heart failure related symptoms (functional NYHA class ≤ II) and improved exercise tolerance (6MWT: 243.8 ± 121.3 m, 298.1 ± 118.6 m; p = 0.04). The functional capacity at follow-up did not differ between the groups (NYHA > II: sMR 34.6%, pMR 33.3%; p = 0.6). However, functional amelioration was more pronounced in sMR patients as assessed by functional NYHA class (sMR: 3.5 ± 0.5, 2.1 ± 0.9, p = 0.0001; pMR: 3.2 ± 0.4, 2.2 ± 1; p = 0.04) (Fig. 2) and 6MWT (sMR: 235.3 ± 107.7 m, 305.3 ± ±123.1 m; p = 0.03; pMR: 267.1 ± 160.2 m, 278.6 ± ± 111.9 m; p = 0.8). Decreased levels of N-terminal pro-B-type natriuretic peptide were documented in both groups (sMR: 7635.3 ± 13639.8 pg/mL, 3943.4 ± ± 4190.5 pg/mL; p = 0.01; pMR: 7157.2 ± 10920 pg/mL, 4313.7 ± 7574.8 pg/mL; p = 0.02) (Table 3).

All-cause mortality was 16% at 5-year follow-up and was significantly higher in patients with sMR (sMR: 19%, pMR: 10%; p = 0.05) (**Suppl. Table 1, Suppl. Fig. 3**).

According to the ROC analysis baseline sPAP > 45 mmHg, baseline MVG > 1.5 mmHg and baseline level of creatinine > 2 mg/dL were found to be independent predictors for all-cause mortality at 5-year follow-up. Furthermore, baseline level of creatinine (cut-off value: 1.33 mg/dL; HR: 0.695), baseline sPAP (cut-off value: 50 mmHg; HR: 0.96) and baseline MVG (cut-off value: 1.4 mmHg; HR: 0.82) were used as independent predictors for poor functional outcomes at 5-year follow-up (**Suppl. Figs. 1, 2**).

Discussion

The main findings of the present study are as follows: (1) Acute procedural failure was higher in pMR patients. (2) A majority of patients (74%) showed sustained MR reduction, increased RV function and reduced sPAP at 5-year follow-up. (3) Despite pronounced clinical and echocardiographic amelioration at follow-up and lower interventional failure rates, all-cause 5-year mortality was significantly higher in sMR patients. Baseline levels of creatinine > 2 mg/dL, MVG > 1.5 mmHg and sPAP > 50 mmHg were independent predictors of the 5-year mortality and poor functional outcomes.

Survival and re-intervention rates

Mortality after TMVR with the MitraClip device has been evaluated previously in different studies. Toggweiler et al. [18] found in 75 patients, a patient mortality of 4% at 30 days, 9% at 1 year and 25% (sMR 28%, pMR 18%) at 2 years after the MitraClip procedure. Comparable data were presented in 304 patients by Capodanno et al. [19] (4% at 30 days, 11% at 1-year, and 19% at 2-years). The EVEREST II study found a 20% 5-year mortality without statistical difference between MR etiologies [20].

In line with those studies, sustained MR reduction was found with improved functional capacity and quality of life 5 years after the MitraClip procedure. Although patients in the present study were considerably older (mean age: 81 years), they had more often sMR and in higher baseline NYHA functional classes, long-term mortality rates (16%) were comparable to the cited studies. In contrast to EVEREST II, higher mortality in patients with sMR was found despite noticeable improvement of functional capacity at follow-up. Of note, in the early EVEREST studies, echocardiographic feasibility criterias were far more restrictive, and the majority of patients were treated for pMR, which might account for different acute and long-term procedural success rates.

Higher all-cause mortality at follow-up in sMR patients was found, and might be explained by the advanced age of sMR patients, a more impaired baseline LV and RV function compared to pMR patients. Similar findings were presented in the

COAPT (Cardiovascular Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial. In this trial, Stone et al. [21] found 29.1% 2-year mortality in 302 patients with sMR despite being younger patients, was relevantly higher than the present collective. This might be explained through the present findings "predictors of mortality" such as impaired baseline renal function (creatinine clearance < 51 mL/min), advanced systolic heart failure (LVEF 31%), and elevated RV systolic pressure (> 44 mmHg).

Buzzatti et al. [22] showed higher 5-year mortality (about 50%) with good mid-term results including reduction of MR and improved symptoms in 339 patients with relevant MR. In line with current results, they found pronouncedly worse outcomes and higher mortality in patients with secondary MR associated with worse LV remodelling and function.

Predictors of adverse outcome

Azzalini et al. [23] showed that an impaired LV function was associated with increased mortality in 77 patients with sMR 1 year after the MitraClip procedure. This finding is in line with the present data. A higher 5-year mortality in sMR patients with reduced baseline LV function was found (EF < 40%) compared to pMR patients with a baseline LVEF > 55%.

Another independent marker for secondary endpoint was the baseline level of creatinine (> 2 mg/dL) in the current study. This finding is supported by a study from Ohno et al. [24]. They found a significant adverse effect of concomitant chronic kidney disease on MR reduction, functional capacity (NYHA functional class), survival and frequency of re-repair in 214 patients with severe MR one year after the MitraClip procedure.

Toggweiler et al. [18] (baseline MVG > 3 mmHg) and Neuss et al. [9] (post-procedural MVG > 5 mmHg) showed a devastating impact of higher MVG on clinical outcomes and procedural success. In concordance with those results, baseline MVG (> 1.5 mmHg) as an independent predictor for both primary and secondary endpoints at 5-year follow-up was found in the present study.

Moreover, Matsumoto et al. [10] found that pre-existing pulmonary hypertension was a strong predictor of higher all-cause mortality 12 months after the MitraClip procedure. The association between worse outcomes and advanced heart disease and symptoms have been presented by Buzzatti et al. [22] in more than 300 patients with relevant MR at 5-year follow-up. The cited study validates present findings; elevated baseline sPAP values are an independent predictor of (> 45 mmHg) adverse outcomes and (> 50 mmHg) all-cause mortality at 5-year follow-up.

Limitations of the study

This single-center retrospective study has several limitations. Data was reported from a single-center experience, and all echocardiographic analyses were not verified by an independent core lab. Furthermore, the 5-year follow-up was sufficiently completed in 233 (88%) patients. Because of this, the present results should be proven in multi-center studies with a larger patient collective.

Conclusions

Transcatheter mitral valve repair with the MitraClip procedure was found to be safe, lead to sustained MR reduction, and increase RV function during 5 years subsequent to the procedure. Despite pronounced functional and echocardiographical amelioration and lower procedural failure, sMR patients showed a higher all-cause mortality at 5-year follow-up compared to patients with pMR. Elevated baseline creatinine, baseline levels of MVG and baseline sPAP were associated with poor functional outcome and high all-cause mortality 5-year after MitraClip.

Conflict of interest: None declared

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4 Diskussion

Die dieser Habilitationsschrift zugrundeliegenden Originalarbeiten lieferten die folgenden Ergebnisse:

- Die perkutane Mitralklappenreparatur mittels dem MitraClip™-Verfahren ist bei Patienten mit einem fortgeschrittenen Alter und einem erheblichen operativen Risiko sicher und führt zu einer anhaltenden effektiven MI-Reduktion mit konsequenter Verbesserung der körperlichen Belastbarkeit sowie zum Anstieg der rechtsventrikulären Funktion. Patienten mit FMI zeigen eine höhere Fünf-Jahres-Gesamtsterblichkeit im Vergleich zu Patienten mit DMI, obwohl diese im Hinblick auf die funktionelle Kapazität sowie die echokardiographische Verbesserung tendenziell mehr von der MitraClip™-Prozedur profitierten und seltener Verfahrensfehler aufzeigten. Das Vorliegen eines erhöhten Kreatinins, eines elevierten MPG und eines erhöhten RVSP sind mit einem schlechteren klinischen Outcome und einer höheren Sterblichkeit verbunden.
- Die begleitende höhergradige TI> Grad II wies einen negativen Einfluss auf die klinischen Ergebnisse nach der erfolgreichen MitraClip™-Prozedur auf.
- Nach einer perkutanen Therapie der FMI mittels MitraClip™-Verfahren stiegen das atriale Schlagvolumen, die atrialen Volumina sowie die Muskelmasse des linken Vorhofes an, was am ehesten auf den postinterventionell erhöhten MPG zurückzuführen ist. Die postinterventionelle Erhöhung des MPG ist mit der durch das Clipping reduzierten Klappenöffnungsfläche sowie dem eingeschränkten globalen Kompensationsmechanismus des Herzes bei vorliegender Herz-insuffizienz zu erklären.
- Trotz der fehlenden postinterventionellen Änderungen fungierte der LA-Strain als unabhängiger Prädiktor für die klinischen (Mortalität und Hospitalisierung) sowie die echokardiographischen (residuale MI) Ergebnisse. Zudem wies die E/E'-Ratio (> 18) ebenfalls einen prädikativen Stellenwert zur Abschätzung der post-interventionellen Mortalität auf.
- Bezugnehmend auf den intraprozeduralen MPG fanden wir heraus, dass dieser einen hohen prädiktiven Wert für die Ein-Jahres-Mortalität (Cut-off-Wert: 4,5 mmHg) und die unerwünschten funktionellen Outcomes (Cut-off-Wert: 3,9 mmHg) hat. Darüber hinaus zeigten unsere Analysen, dass ein intraprozeduraler MPG ≥ 4,5 mmHg prognostisch relevanter als eine residuale MI > Grad II ist. Zusätzlich

konnten wir beweisen, dass der Leaflet-to-Annulus-Index der Mitralklappe (> 1,11) eine signifikante Korrelation mit einem ungünstigen intraprozeduralen MPG aufweist. Die restlichen Prädiktoren für den intraprozeduralen MPG sind der MPG beim Einschluss, die Anzahl der implantierten Clips und die zentrale Clip-Implantation.

- Der modifizierte MIDA-Score bietet ein aussichtvolles bedienerfreundliches und einfaches Werkzeug zur adäquaten und individuellen Prognoseabschätzung bei Patienten mit FMI, die mittels MitraClip™-Verfahren behandelt wurden.

Seit seiner Markteinführung im Jahr 2008 bietet das MitraClip™-System der Firma Abbott vascular eine minimalinvasive Therapie der – hauptsächlich chronischen – MI für Patienten mit einem erheblichen operativen Risiko bzw. bedeutsamer Gebrechlichkeit. Mit dieser Methode können Patienten mit DMI und FMI erfolgreich behandelt werden (Vahanian et al., 2022).

Die Hauptziele dieser Therapie bestehen darin, die Symptome der Patienten zu reduzieren, die körperliche Belastbarkeit zu verbessern und die Herzinsuffizienz-bedingte Hospitalisierung bzw. die kardiovaskuläre Mortalität zu verringern. Um eine zielgerechte und effektive MI-Therapie mittels MitraClip™-Verfahren zu ermöglichen, ist eine effektive Entscheidungsfindung mit einem passenden Timing und einer adäquaten Prognoseabschätzung unverzichtbar. Die postinterventionellen Langzeit-ergebnisse und ihre Prädiktoren stellten den Hauptfokus der bisher publizierten multizentrischen Studien dar. In einer randomisierten Post-Marketing-Studie (Endovascular Valve Edge-to-Edge Repair Study II) zeigten Feldmann et al. eine vergleichbare MI-Reduktion mit vergleichbaren klinischen Ergebnissen und einer vergleichbaren Mortalität (Fünf-Jahres-Mortalität lag bei 20 %) nach der MitraClip™-Prozedur im Vergleich zu den chirurgischen Mitralklappen-Therapien (Feldmann et al., 2011). Hier ist zu erwähnen, dass die in diese Studie eingeschlossenen Patienten vornehmlich (73%) eine DMI hatten. In diesem Kontext fokussierten sich Stone et al. auf die FMI-Patienten und berichteten einen additiven signifikanten Effekt des MitraClip™-Systems auf die funktionelle Kapazität, die Hospitalisierung sowie die Mortalität zusätzlich zur konservativen Therapie mit leitliniengerechter optimaler Herzinsuffizienz-Therapie bei 614 Patienten mit symptomatischer hochgradiger FMI in einer multizentrischen randomisierten Studie (Stone et al., 2018). Im Gegensatz dazu

fanden Obadia et al. keinen signifikanten Unterschied bezüglich wiederkehrender Hospitalisierungen und postinterventioneller Mortalität zwischen Patienten mit medikamentöser Therapie (n = 152) und Patienten mit medikamentöser Therapie samt MitraClip-Prozedur (n = 152) (Obadia et al., 2018). Obwohl die interventionelle MI-Reduktion in allen genannten Studien erfolgreich und effektiv war, sind die publizierten postinterventionellen Ergebnisse in hohem Maße unterschiedlich. Der mögliche Hauptgrund dafür ist, dass unterschiedliche Patientengruppen eingeschlossen worden sind. Aus diesem Blinkwinkel ist die Entscheidungsfindung mit richtiger Patientenauswahl und passendem Timing von großer Bedeutung, um ein besseres Outcome erzielen zu können.

Während der präinterventionellen Entscheidungsfindung kommen diverse Faktoren zum Einsatz. Die Nierenfunktion beim Einschluss nimmt bei der Entscheidungsfindung und der Prognoseabschätzung eine bedeutende Rolle ein. Ohno et al. konnten bei 214 mittels MitraClip™-System versorgten Patienten mit hochgradiger symptomatischer MI zeigen, dass das Vorliegen einer chronischen Niereninsuffizienz mit einer glomerulären Filtrationsrate < 60 ml/min mit einer höheren Ein-Jahres-Mortalität, einer häufigeren Hospitalisierung und einer frequenten residualen MI ≥ Grad III assoziiert ist (Ohno et al., 2016). Darüber hinaus stellten Toggweiler et al. eine positive Korrelation zwischen einer vorliegenden guten Nierenfunktion und den zufriedenstellenden postinterventionellen Ergebnissen nach der MitraClip™-Prozedur bei 74 Patienten mit mittel- bis hochgradiger symptomatischer MI fest (Toggweiler et al., 2014).

Im Einklang mit diesen wissenschaftlichen Feststellungen ermittelten wir in unserem Kollektiv aus 265 Patienten mit hochgradiger chronischer MI, dass das Ausgangs-Kreatinin als ein unabhängiger Prädiktor für eine höhere Fünf-Jahres-Gesamtsterblichkeit (Cut-off-Wert: 2 mg/dL) wie auch für ein ungünstiges funktionelles Outcome (Cut-off-Wert: 1,3 mg/dL) fungiert (Öztürk et al., 2021). Zudem stellt die Nierenfunktion einen essenziellen Parameter für die im klinischen Alltag verwendeten Scores – beispielweise EuroSCORE oder STS-Score – dar (Andreson et al., 1994; Roques et al., 2003; Grigoni et al., 2018).

Aus echokardiographischer Sicht präsentierten Azzalini et al., dass die Einschränkung der linksventrikulären Funktion mit einer hohen Ein-Jahres-Mortalität nach dem MitraClip™-Verfahren einhergeht (Azzalini et al., 2016). Übereinstimmend fanden wir

eine höhere Fünf-Jahres-Gesamtsterblichkeit bei FMI-Patienten mit einer Ausgangs-LVEF < 40 % im Vergleich zu DMI-Patienten mit einer besseren Ausgangs-LVEF > 55 % (Öztürk et al., 2021). Die linksventrikuläre Funktion macht einen wichtigen Bestandteil der üblichen Score-Systeme (EuroSCORE II, STS-Score, MIDA-Score) aus (Andreson et al., 1994; Roques et al., 2003; Grigoni et al., 2018). In unseren Analysen zur Entwicklung des modifizierten MIDA-Scores stellte sich die linksventrikuläre Funktion ebenfalls als ein statistisch signifikanter Prädiktor für ein schlechtes Outcome mit einer Odds-Ratio von 3,8 heraus. Anhand dessen reduzierten wir den Cut-off-Wert von 60 % auf 45 % sowie erhöhten wir die Gewichtung von einem Punkt auf zwei Punkte, um eine adäquatere Prognoseabschätzung mittels des modifizierten MIDA-Scores bei FMI-Patienten zu ermöglichen (Öztürk et al., 2020).

Es wurde mehrfach bewiesen, dass eine vorliegende pulmonale Hypertonie mit einem erhöhten rechtsventrikulären systolischen Druck (RVSP oder sPAP) eine hohe Mortalität mit ungünstigen Ergebnissen nach der MitraClip™-Prozedur vorhersagt (Matsumoto et al., 2014; Buzatti et al., 2018). Auf der anderen Seite findet der RVSP in allen üblichen Score-Systemen Anwendung. In gleicher Weise fanden wir bei unseren 265 Patienten heraus, dass ein RVSP > 45 mmHg mit einer höheren Mortalität und ein RVSP > 50 mmHg mit unerwünschten klinischen Ergebnissen zusammenhängt (Öztürk et al., 2021).

Ein weiterer echokardiographischer Prognose-relevanter Parameter ist der MPG. Leitliniengemäß ist ein relevanter MPG > 5 mmHg intraprozedural zu vermeiden (Vahanian et al., 2022). In diesem Kontext zeigten Toggweiler et al., dass ein präinterventioneller MPG < 3 mmHg mit den vorteilhaften Zwei-Jahres-Ergebnissen nach dem MitraClip™-Verfahren einherging (Toggweiler et al., 2014). Überdies präsentierten Neuss et al. einen nachteiligen Zusammenhang zwischen einem hohen postinterventionellen MPG (invasiv gemessen > 5 mmHg, echokardiographisch gemessen > 4,4 mmHg) und den ungünstigen postinterventionellen Zwei-Jahres-Outcomes (Neus et al., 2017). Wir fanden in unserer Studie an 265 mittels MitraClip™-System behandelten Patienten, dass der präinterventionelle MPG schon ab einem Wert von 1,5 mmHg mit den ungünstigen klinischen Outcomes sowie einer hohen Fünf-Jahres-Mortalität verbunden ist (Öztürk et al., 2021).

Auf der anderen Seite gibt es Studien mit widersprüchlichen Daten, in denen der Effekt des MPG auf die postinterventionellen Ergebnisse nach dem MitraClip™-Verfahren – insbesondere bei Patienten mit FMI – kontrovers diskutiert wird. Beispielweise stellten Halaby und Patzelt et al. keinen Zusammenhang zwischen dem MPG und den klinischen Ergebnissen nach erfolgreicher Behandlung der FMI mittels MitraClip™-Prozedur (Halaby et al., 2021 und Patzelt et al., 2019) fest.

Angesichts der uneindeutigen Studienergebnisse bezüglich des MPG-Effektes auf die postinterventionellen Outcomes führten wir eine Studie mit einer gemischten Kohorte bestehend aus 42,8 % DMI, 40 % FMI und 17,2 % gemischter Ätiologie durch, um den prädiktiven Wert des intraprozeduralen MPG für die Outcomes nach dem MitraClip™-Verfahren und seine periinterventionelle Dynamik zu evaluieren.

In unserer umfassenden Analyse des periinterventionellen MPG und seiner Dynamik konnten wir dokumentieren, dass der intraprozedurale MPG ab einem Wert von 4,5 mmHg mit einer höheren Ein-Jahres-Gesamtmortalität sowie bereits ab einem Wert von 3,9 mmHg mit ungünstigen klinischen Ergebnissen einhergeht. Zusätzlich konnten wir feststellen, dass ein intraprozeduraler MPG > 4,5 mmHg Prognose-relevanter als eine residuale MI > Grad II ist. Interessanterweise waren diese Feststellungen unabhängig von der MI-Ätiologie (Öztürk et al., 2021).

Zudem konnten wir zeigen, dass der Leaflet-to-Annulus Index (der stärkste Prädiktor), der präinterventionelle MPG, die Anzahl der implantierten Clips sowie die zentrale Clip-Implantation als unabhängige Prädiktoren für einen ungünstigen intraprozeduralen MPG anzunehmen sind (Öztürk et al., 2021).

Abseits der residualen MI scheint der periinterventionelle MPG ein unabhängiger und wichtiger Prädiktor für die klinischen Ergebnisse nach der MitraClip™-Prozedur zu sein und zeigt eine wechselhafte periinterventionelle Dynamik. Zudem wird er von verschiedenen Faktoren beeinflusst – zum Beispiel Blutdruck, Herzfrequenz, Volumenzustand des Patienten, Sedativum oder Anästhesie, Hämoglobinwert und Katecholamine. Deshalb können die sporadischen Erfassungen des MPG irrtümlicherweise zu Fehlschätzungen führen. Um das zu vermeiden und positive Outcomes zu ermöglichen, sind die adäquaten Erkenntnisse über MPG, seine periinterventionelle Dynamik, seinen prädiktiven Stellenwert und die Prädiktoren für einen ungünstigen MPG ausschlaggebend. Demgemäß sind während der

präinterventionellen Entscheidungsfindung und der Prognoseabschätzung sowohl die residuale MI als auch der MPG zu berücksichtigen.

Die begleitende TI ist einer der häufigsten echokardiographischen Nebenbefunde bei Patienten mit chronischer Herzinsuffizienz sowie hochgradiger MI und geht bekanntermaßen mit einer ungünstigen Prognose einher. In unserer Studie mit 261 mittels MitraClip™-Verfahren behandelten Patienten betrug die Prävalenz der begleitenden TI 45 %, was den früheren Studien entspricht (Shiran et al., 2009; De Bonis et al., 2008). Im Einklang mit den vorangegangenen nationalen Register-Daten (GRASP und TRAMI) (Ohne et al., 2016; Kalbacher et al., 2017) erbrachten unsere Analysen, dass die begleitende TI > Grad II (die Prävalenz betrug 15,7 %) mit den unvorteilhaften klinischen sowie funktionellen Ergebnissen verbunden ist und einen starken unabhängigen Prädiktor für die Gesamtmortalität nach perkutaner Mitralklappenreparatur mittels MitraClip™-System darstellt (Schueler und Öztürk et al., 2016). In Anbetracht dessen ist die begleitende höhergradige TI ebenfalls als therapiebedürftig anzunehmen und im Intervall zu behandeln.

Die andere echokardiographisch messbare anatomische Struktur ist das linke Atrium (LA). Der linke Vorhof (LA) erweitert sich im Falle einer hochgradigen chronischen MI aufgrund einer erhöhten Volumen- bzw. Druckbelastung durch den stetigen Rückfluss. Anschließend kommt es zur progredienten Spannung des linksatrialen Myokards mit einem konsekutiven Umbauprozess des LA, was zu supraventrikulären Tachykardien führt. Zudem sind die eingeschränkte LA-Funktion sowie die Dilatation des LA mit hoher Mortalität und Morbidität verbunden – insbesondere bei Patienten mit chronischer Herzinsuffizienz (Nagueh et al., 2016). Die linksatriale Funktion und Geometrie sind gemäß den aktuellen Leitlinien im Rahmen der Patientenauswahl und Entscheidungsfindung vor der Mitralklappenreparatur ebenfalls zu beachten (Vahanian et al., 2022). Die linksatrialen Dimensionen sind nicht nur zur Festlegung des MI-Schweregrades und zur Abschätzung der Vorlast mit diastolischer Dysfunktion (Hagendorff et al., 2020), sondern auch zur Entscheidung des Timings und der Art der MI-Therapie zu berücksichtigen (Vahanian et al., 2022). Die Beurteilung der LA-Funktion und der LA-Geometrie ist anspruchsvoll und kann mit Hilfe von einer konventionellen zwei-dimensionalen Echokardiographie und/oder einer Speckle-Tracking-Echokardiographie durchgeführt werden. Das LA-Assessment durch die Strain-Analyse ist winkelunabhängig und wird von den Artefakten nicht beeinflusst,

weswegen die Strain-Analyse ein adäquates und reproduzierbares Tool zur LA-Beurteilung darstellt. Vorherige Studien zu diesem Thema fokussierten sich überwiegend auf Patienten mit DMI. Die Daten über die linksatrialen Veränderungen nach dem erfolgreichen MitraClip™-Verfahren bei Patienten mit FMI sind dementsprechend lückenhaft. Deshalb führten wir eine prospektive Beobachtungsstudie mit 50 FMI-Patienten und zwölfmonatiger Nachbeobachtungszeit durch. Bei allen eingeschlossenen Patienten wurde eine zusätzliche dreidimensionale Aufnahme (Komplett-volumen) vom apikalen Vierkammerblick zur Nachverarbeitung (Strain-Analyse) angefertigt. Im Gegensatz zu den früheren Studien fanden wir die Zunahme der LA-Volumina und der LA-Muskelmasse ohne signifikante Veränderungen des LA-Strains oder der LA-Ejektionsfraktion. Die E/E'-Ratio stellte sich signifikant eleviert dar. Darüber hinaus wurde festgestellt, dass die E/E'-Ratio und der LA-Strain als unabhängige Prädiktoren für die Gesamtsterblichkeit, die residuale MI und die Hospitalisierung fungieren. Rammos et al. präsentierten die Verbesserungen der LA-Funktion drei Monate nach der MitraClip™-Prozedur als Hinweis auf das Reverse Remodeling mit Hilfe der Speckle-Tracking-Echokardiographie bei 26 Patienten mit FMI (Rammos et al., 2016). Gleichermaßen fanden Toprak et al. die gebesserten Strain-Daten des LA zwölf Monate nach dem MitraClip™-Verfahren bei 25 Patienten vorwiegend mit FMI (92%). Zudem wurde festgestellt, dass der LA Reservoir-Strain und der LA Volumen-index Indikatoren für die Ein-Jahres-Ergebnisse sind. Dahingegen fanden wir heraus, dass der globale LA-Strain trotz fehlender signifikanter Veränderungen während der zwölfmonatigen Nachbeobachtungszeit der stärkste Prädiktor für das Überleben bei mittels MitraClip™-Verfahren behandelten Patienten mit FMI ist (Öztürk et al., 2020).

Korrespondierend zu unseren Daten zeigten Radunksi et al. mit Hilfe von kardialer Magnetresonanztomographie keine Reduktion der LA-Volumina mit dem fehlenden Reverse Remodeling des LA sechs Monate nach dem MitraClip™-Verfahren bei zwölf Patienten mit hochgradiger MI (58 % FMI) in einer multizentrischen Studie (Radunski et al., 2014). Diese fehlende Verbesserung der LA-Volumina nach effektiver MI-Reduktion ist in erster Linie auf den postinterventionell erhöhten linksventrikulären enddiastolischen Druck zurückzuführen. Dieser Erhöhung des linksventrikulären enddiastolischen Drucks liegen möglicherweise die postinterventionelle Erhöhung des MPG sowie die fehlende Anpassungsfähigkeit des globalen Herzes bei Patienten mit

vorliegender fortgeschrittener Herzinsuffizienz zugrunde. Unsere Ergebnisse legen nahe, dass das richtige prozedurale Timing hinsichtlich der postinterventionellen Ergebnisse ebenfalls eine entscheidende Rolle spielt.

Nach den bisher diskutierten Studien, die vor allem einzelne Prädiktoren für die postinterventionellen Ergebnisse nach dem MitraClip™-Verfahren behandelten, wurde in der letzten Studie ein klinischer Ansatz verfolgt. Im klinischen Alltag verwenden wir zwei bereits validierte Score-Systeme (EuroSCORE II und STS-Score) mit einer ausgezeichneten Vorhersagekraft (AUC > 0,8), um das perioperative Risiko bei Patienten mit struktureller Herzerkrankung abzuschätzen (Roques et al., 2003; Shahian et al., 2009). Jedoch sind diese Score-Systeme ausschließlich zur Begutachtung des operativen Risikos entwickelt worden und fokussieren sich lediglich auf die Chirurgie-assoziierten Kurzzeitergebnisse. Im Vergleich zu den konventionellen Score-Systemen bietet der von Grigioni et al. konzipierte MIDA-Score ein innovatives Werkzeug zur adäquaten und individuellen Beurteilung bzw. Abschätzung der Kurz- und der Langzeitergebnisse unter medikamentöser oder apparativer Behandlung der Patienten mit DMI. Der MIDA-Score besteht aus drei klinischen (Patientenalter, Herzinsuffizienz-Symptomen, Vorhofflimmern) und vier echokardio-graphischen Parametern (Diameter des linken Vorhofes ≥ 55 mm, rechtsventrikulärer systolischer Druck > 50 mmHg, systolischer Diameter des linken Ventrikels ≥ 40 mm, linksventrikuläre Ejektionsfraktion ≤ 60 %), die mehrfach als ein unabhängiger Prädiktor für ein schlechtes postinterventionelles Outcome bewiesen worden sind (Grigioni et al., 2017).

Im Gegensatz zur degenerativen MI ist das Management der FMI unter Berücksichtigung des fortgeschrittenen Patientenalters, der deutlich hervortretenden linksventrikulären Dysfunktion mit erhöhtem linksventrikulärem enddiastolischem Druck, des vorliegenden erhöhten rechtsventrikulären systolischen Drucks und häufigerer Komorbiditäten komplexer und aufwändiger. Daher ist eine präzise Entscheidungsfindung bei Patienten mit chronischer Herzinsuffizienz und FMI essenziell und anspruchsvoll.

Zur adäquaten Ätiologie-spezifischen Prognoseabschätzung entwickelten wir ein neues Score-System, den modifizierten MIDA-Score, für Patienten mit FMI. Der modifizierte MIDA-Score führt zur suffizienten Vorhersage des kombinierten

Endpunktes, bestehend aus kardiovaskulärer Mortalität und Hospitalisierung, und ermöglicht dadurch eine präzise Prognoseabschätzung bei mittels MitraClip™-Verfahren behandelten Patienten mit FMI. Wir fanden eine statistisch signifikant häufigere Hospitalisierung und eine höhere Gesamtsterblichkeit 18 Monate nach interventioneller Therapie der FMI mit dem MitraClip™-Verfahren bei Patienten mit einem modifizierten MIDA-Score > 9 Punkte, was in erster Linie durch eine vorliegende linksventrikuläre Dysfunktion, eine bereits existierte pulmonale Hypertonie und ein bereits eingesetztes unwiderrufliches Remodeling mit fortgeschrittener myokardialer Fibrose mit bereits angepasstem Lungenkreislauf aufgrund verspäteter Behandlung zu erklären ist (Öztürk et al., 2020).

Schließlich bietet der modifizierte MIDA-Score ein erfolgversprechendes, grundlegendes und einfach handhabbares Tool zur adäquaten und individuellen Prognoseabschätzung bei Patienten mit FMI, was eine angemessene präinterventionelle Entscheidungsfindung vor der MitraClip™-Prozedur ermöglicht.

Unsere einleitenden aussichtsreichen Daten sollen mithilfe von multizentrischen randomisierten Studien mit einer größeren Probandenzahl und einer längeren Nachbeobachtungszeit validiert werden.

5 Zusammenfassung

Die relevante chronische MI führt zu hoher Symptomlast, zunehmender Einschränkung der Lebensqualität, häufigerer Hospitalisierung und hoher Mortalität bei älteren, gebrechlichen Patienten mit chronischer Herzinsuffizienz und den verschiedenen Begleiterkrankungen. Neben der leitliniengerechten optimierten medikamentösen antikongestiven Erstlinientherapie, inklusive kardialer Resynchronisationstherapie, spielen die interventionellen Therapiemodalitäten im Falle therapierefraktärer Beschwerden eine entscheidende Rolle.

In Anbetracht der aktuellen wissenschaftlichen Evidenzlage bietet die perkutane Edge-to-Edge-Mitralklappenreparatur mittels MitraClip™-Verfahren eine sichere, plausible und effektive Belhandlungsoption bei inoperablen Patienten mit einer hochgradigen symptomatischen MI unabhängig von der pathologischen Genese. Diese führt nicht nur zu einer Verbesserung der Symptome und einer Verringerung der Mortalität, sondern ist auch gesundheitsökonomisch bedeutend, um die wiederkehrenden Hospitalisierungen in diesem gebrechlichen Patientenkollektiv zu reduzieren.

Um eine präzise Entscheidungsfindung mit korrespondierenden besseren Ergebnissen gewährleisten zu können, sind eine adäquate und möglichst individualisierte Prognoseabschätzung, eine ausführliche echokardiographische Beurteilung der unterliegenden MI-Pathologie und der Machbarkeit diverser interventionellen Therapiemodalitäten sowie eine richtige Patientenauswahl mit einem passenden prozeduralen Timing von großer Bedeutung. In allen Phasen der Entscheidungsfindung ist neben der klinischen Evaluation der Patienten die kompetente und umfassende echokardiographische Begutachtung der Gesamtkonstellation – bestehend aus globaler Herzfunktion mit vorbestehendem myokardialem Remodeling, begleitenden Klappenvitien, den Druckverhältnissen im rechten und linken Ventrikel, den MI-assoziierten Parametern und der Machbarkeit der in Frage kommenden Interventionen mit der Beurteilung der visuellen Sichtbarkeit – unerlässlich.

Der Stellenwert der Echokardiographie im Bereich der interventionellen Bildgebung ist weitestgehend bekannt, jedoch ist der Nutzen periinterventioneller Echokardiographie hinsichtlich der präzisen Entscheidungsfindung unzureichend. In diesem Sinne behandelten wir in dieser Habilitationsschrift Studien den ausschlaggebenden Nutzen

und den klinischen Stellenwert der Echokardiographie für die periinterventionelle Entscheidungsfindung bei inoperablen Patienten mit symptomatischer chronischer MI, die mittels der MitraClip™-Prozedur behandelt wurden.

Unterstützend zur aktuellen Studienlage deuten unsere Fünf-Jahres-Langzeitergebnisse darauf hin, dass die MitraClip™-Prozedur zu einer sicheren und anhaltenden MI-Reduktion mit konsequenter Verbesserung des rechten Ventrikels führt. Zudem fanden wir, den vorherigen multizentrischen Studien entsprechend, eine höhere Fünf-Jahres-Gesamtsterblichkeit bei Patienten mit FMI, obwohl die Patienten mit DMI häufiger frustrane Therapieversuche und geringere klinische sowie echokardiographische Verbesserungen zeigten.

Wir konnten an 261 mittels MitraClip™-Verfahren behandelten Patienten mit verschiedener MI-Ätiologie (75,2 % FMI) zeigen, dass das Vorliegen einer begleitenden TI > Grad II mit schlechteren funktionellen Outcomes und einer höheren Zwei-Jahres-Mortalität verbunden ist. Unsere Daten deuten darauf hin, dass die TI zum einen im Rahmen der präinterventionellen echokardiographischen Beurteilung unbedingt zu betrachten und zum anderen je nach echokardiographischer bzw. klinischer Relevanz ebenfalls bezüglich der apparativen Therapie zu evaluieren ist.

Im Gegensatz zu den vorangegangenen Studien fanden wir in unserer echokardiographischen Studie mit Hauptfokus auf der Strain-Analyse des linken Vorhofes bei 50 mittels MitraClip™-Verfahren behandelten Patienten mit chronischer FMI keine statistisch signifikanten Veränderungen des LA-Strains. Trotzdem fungierte er als der stärkste Prädiktor für die klinischen (Mortalität und Hospitalisierung) wie auch für die echokardiographischen (residuale MI) Outcomes. Bemerkenswert ließen sich die LA-Volumina und die LA-Muskelmasse statistisch signifikant steigend darstellen, was am ehesten auf den postinterventionell erhöhten LVEDP aufgrund des nach Clip-Implantation elevierten MPG und des eingeschränkten globalen Kompensationsmechanismus bei vorliegender fortgeschrittener Herzinsuffizienz zurückzuführen ist. Darüber hinaus scheint die E/E'-Ratio > 18 ein signifikanter Parameter zur Abschätzung postinterventioneller Gesamtmortalität zu sein.

In der anderen oben vorgestellten Studie bei 175 Patienten mit chronischer relevanter MI kam zum Vorschein, dass der intraprozedurale MPG ein starker Prädiktor für die Ein-Jahres-Mortalität mit einem Cut-off-Wert von 4,5 mmHg und die ungünstigen

funktionellen Outcomes mit einem Cut-off-Wert von 3,9 mmHg ohne eine feststellbare Abhängigkeit von der MI-Ätiologie ist. Zudem scheint ein intraprozeduraler MPG ≥ 4,5 mmHg mehr Einfluss als eine residuale MI > Grad II auf die klinischen Ergebnisse zu haben. Darüber hinaus fanden wir, dass der Leaflet-to-Annulus-Index den intraprozeduralen MPG statistisch signifikant vorhersagt. Zudem sind der präprozedurale MPG, die Anzahl der implantierten Clips und die zentrale Clip-Implantation als Gradient-relevante Parameter zu betrachten.

Abschließend konnten wir bei 105 mittels der perkutanen Edge-to-Edge-Mitralklappenreparatur versorgten Patienten mit FMI nachweisen, dass der hauptsächlich aus den echokardiographischen Faktoren bestehende modifizierte MIDA-Score eine adäquate und individuale Prognoseabschätzung bietet.

Zusammenfassend ist hervorzuheben, dass zusätzlich zu den MI-definierenden Parametern und klinischen Charakteristika der Patienten die weiteren echokardiographischen Parameter für den linken (LVEF, LVEDP, LVESD) und den rechten Ventrikel (RVSP, TAPSE, TI) sowie für den linken Vorhof (LAD, LA-Strain) im Rahmen der präzisen präinterventionellen Entscheidungsfindung zu berücksichtigen sind.

Auf diesem sich rasant entwickelnden Gebiet der interventionellen Kardiologie ist eine enge und komplementäre Zusammenarbeit mit der kardiovaskulären Bildgebung unabdingbar, um zielorientierte und vorteilhafte Ergebnisse generieren zu können.

6 Überlappung durch geteilte Autorenschaften

Dieser kumulativen Habilitationsschrift liegen fünf veröffentlichte Originalarbeiten zugrunde. In drei Publikationen fungiere ich als Erstautor (Öztürk et al., 2020, 2021, 2021). Eine Arbeit publizierten wir zusammen mit Herrn PD Dr. med. Robert Schueler in geteilter Erstautorenschaft (Schueler und Öztürk et al., 2016). Sie wurde in der Habilitationsschrift von Herrn PD Dr. med. Robert Schueler aus dem Jahr 2017 mit aufgeführt. Obwohl die vom Dekanat vorausgesetzte Mindestanzahl von vier Originalarbeiten ohne diese Publikation erfüllt wird, schloss ich sie dennoch aufgrund des additiven Wertes bezüglich der Gesamtkonstellation dieser Habilitationsschrift ein. Meine Leistungen in dieser Originalarbeit waren Mitarbeit an Konzeption und Planung der Arbeit, wissenschaftliche Beiträge hinsichtlich Beschaffung, Analyse und Interpretation der Daten sowie Mitarbeit an Formulierung und endgültiger Zusammenstellung des Manuskripts. In einer weiteren Arbeit wurde Herr PD Dr. med. Ulrich March Becher aufgrund seiner wissenschaftlichen Unterstützung – während der komplexen statistischen Analysen, der Datenerhebung und der Bestimmung der Ein- und Ausschlußkriterien – und aufgrund seines außerordentlichen Beitrags zur Verfassung und Fertigstellung des Manuskripts als zweiter geteilter Erstautor festgelegt (Öztürk und Becher et al., 2020). Diese Arbeit wurde in keiner anderen Habilitationsschrift eingereicht. Eine wesentliche inhaltliche Überlappung mit anderen Habilitationsschriften ist auszuschließen.

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Wissenschaftliche Veröffentlichungen als Erstautorenschaft

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*geteilte Erstautorenschaft.

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