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Kiefer, Franziska Leandra

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**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

Franziska Leandra Kiefer

**IMPACT OF INTERVENTIONAL CARDIOLOGY UNDER THE INFLUENCE OF
COVID-19**

Diploma Thesis

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Prof. Johannes Brachmann, MD, PhD**

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List of abbreviations

ACEI - Angiotensin converting enzyme inhibitors

AF - atrial fibrillation

AIDS - Acquired Immunodeficiency Syndrome

AP - Angina pectoris

ARB - Angiotensin receptor blockers

ASA - Acetylsalicylic acid

AV - Atrioventricular

BMI - Body mass index

CABG - Coronary artery bypass grafting

CAD - Coronary artery disease

CHF - congestive heart failure

CKD - Chronic kidney disease

COPD - Chronic obstructive pulmonary disease

COSMO - COVID-19 Snapshot Monitoring

COVID-19 - coronavirus disease 2019

CPB - Cardiopulmonary bypass

Cr - Creatinine

CRT - Cardiac resynchronization therapy

DAPT - Dual antiplatelet therapy

DGK - German Cardiac Society

DM - Diabetes mellitus

DOAC - Direct oral anticoagulants

EF - Ejection fraction

eGFR - Estimated glomerular filtration

FDA - Food and Drug Administration

HCM - hypertrophic cardiomyopathy

HIV - Human immunodeficiency virus

IMR - Ischemic mitral regurgitation

IRB - Institutional review board

LA - Left atrium/left atrial
LV - Left ventricle/left ventricular
LVEF - Left ventricular ejection fraction
LVESD - Left ventricular end-systolic diameter
MI - Myocardial infarction
MR - Mitral valve regurgitation
MV - Mitral valve
MVP - Mitral valve prolapse
MVr - Mitral valve repair
NSTEMI - Non-ST elevation myocardial infarction
NT-pro BNP - N-terminal pro-brain natriuretic peptide
NYHA - New York Heart Association
OAC - Oral anticoagulation
PMR - Primary mitral regurgitation
PMVR – Percutaneous mitral valve repair
RHD - Rheumatic heart disease
SAM - Systolic anterior motion
SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2
SD - Standard deviation
SMR - Secondary mitral regurgitation
SPAP - Systolic pulmonary arterial pressure
STEMI - ST elevation myocardial infarction
TAVI - Transcatheter aortic valve implantation
TEE - Transesophageal echocardiography
TEER - Transcatheter edge-to-edge repair
TMVR - Transcatheter mitral valve repair
Trop T - Troponin T
VHD - Valvular heart disease
VKA - Vitamin-K-antagonists

1. INTRODUCTION

1.1. Introductory words

Among the valvular heart diseases, mitral valve regurgitation (MR) is the second-most common valvular heart disease (VHD) in Europe, affecting more than 2% of the world population (1, 2). The risk of disease increases with age (3). One differentiates between the primary and the secondary form which also determines the therapeutic approach (4). Primary MR is classified as a disease of the mitral valve itself, whereas the secondary form has its origin in the left ventricle. Primary MR is also known under the terms degenerative or organic MR. In this category falls any MR that is caused by structurally changed or damaged valvar leaflets, chordae, or papillary muscles which in turn leads to inadequate leaflet closure during systole. This commonly happens due to papillary muscle rupture, mitral valve prolapse or a perforation of a leaflet. Secondary mitral regurgitation (SMR) is also termed functional or ischemic MR and is characterized by left ventricular wall motion abnormalities, found in for instance ischemic cardiomyopathy, but also by left ventricular remodeling which can be seen in dilated cardiomyopathy. Note, that in this category there are no structural changes in the mitral valve itself. This scenario leads to dilation of the mitral annulus or papillary muscle displacement, resulting in retrograde blood flow due to the inadequately closed mitral valvar leaflets (3).

Even though this condition is widely prevalent within society, the diagnosis and the management of MR are frequently difficult and necessitate an organized strategy that incorporates findings from history, physical examination, and modern imaging techniques. Treatment decisions are based on understanding of the etiology, natural history, and outcome of therapies for these mitral valve disease patients (5). Modern techniques, such as 3D echocardiography and cardiac magnetic resonance are used by clinicians. Echocardiography is in fact the first choice to grade primary mitral regurgitation (PMR) (6). An integrative approach that includes qualitative, semi-quantitative, and quantitative mitral regurgitation parameters, in addition to quantification of left ventricular (LV) and left atrial (LA) dimensions, is suggested to decide on the correct interventional timing, with the goal to identify the exact etiology of disease, the degree of regurgitation, and the effect of volume overload on the left ventricle (5,6). In addition, there are two techniques for repair surgery: surgical and catheter-based therapy. Because of advancements in both approaches, it is now possible to treat even elderly patients who are suffering from various stages of MR (5).

But how did the Covid-19 pandemic affect patients with MR? Did a potential fear of infection influence their timing of catheter-based therapy? Since the first cases of SARS-CoV-2 were reported in China at the end of 2019 the novel corona virus, which can cause COVID-19 disease with potentially fatal outcomes has been spreading globally (7, 8). The first laboratory-confirmed COVID-19 case was reported in Germany in the last week of January 2020. Because of the high infection dynamics, every federal German state reported COVID-19 cases during the second week of March 2020 (9, 10). Comprehensive non-pharmaceutical efforts to contain the SARS-CoV-2 outbreak were thus implemented at the federal and state levels in March 2020. These included both population-based measures like broad contact restrictions (for example, by prohibiting events, closing educational facilities, and permitting sick leave via phone) and individual infection hygiene measures, such as keeping a minimum distance and wearing a medical mask (9, 10). Furthermore, intensive care and ventilation capacities were expanded for Covid-19 patients. To allow that, sometimes planned medical interventions needed to be postponed (11).

The extent of these measures was always dependent on the respective phase of the pandemic. These measures were gradually reduced beginning in late April 2020 and reinforced again in November 2020 (10). Initial assessments of the consequences of the COVID-19 pandemic and the containment measures implemented on the population's health care condition in 2020 have been reported (12). Statistics published by the Associations of Statutory Health Insurance Physicians indicate that the number of medical and psychotherapeutic outpatient services in 2020 fell significantly from March onwards compared to the same period in 2019, with the decrease only normalizing in May and declining further in the third and fourth quarters (13). From a year-on-year comparison of inpatient services based on AOK billing for the year 2020, a German health insurance, one can tell that there was a decrease, which was more pronounced in terms of numbers in the period from March to May than in the period from October to December. This decrease was mainly, but not exclusively, related to postponable treatment needs (14, 15). Based on a multi-center data collection in emergency rooms, a drop in the frequency of emergency room visits was also noted with the initiation of containment efforts in 2020 (16). The explanations for reduced treatment cases are not only attributable to shifts or modifications in the range of care as a result of COVID-19 cases being treated with priority, but also, at least in part, to worries regarding a possible SARS-CoV-2 infection (12). The analyses from the perspective of the service providers allow only limited conclusions regarding the population's requirements.

The results of the Robert Koch Institute's (RKI) nationwide population-based survey study “Gesundheit in Deutschland aktuell (GEDA)” also show a decrease in general and specialist outpatient services during the first phase of the containment measures in self-reported use compared to the previous year (17). However, results of the online survey study COVID-19 Snapshot Monitoring (COSMO) indicate that even though a significant proportion of the participants postponed check-up appointments that could potentially be rescheduled due to the COVID-19 pandemic, most respondents perceived an adequate medical and pharmaceutical care as guaranteed throughout the phases of containment measures in 2020 (18, 19, 20).

How did the Covid-19 pandemic affect catheter-based therapy of MR? Was there a statistically relevant difference in severity of disease and outcome of patients undergoing MitraClip procedure in at the Regiomed clinic in Coburg? A German study shows that 11.8% of involved patients have cancelled specialist appointments after the implementation of containment measures in March 2020 and 5.8% have cancelled family doctor appointments. In general, 35.5% of study participants skipped at least one medical care service. 9.7% of participants have not visited a physician despite having medical complaints (21).

To see how especially cardiologic patient behavior has changed during the pandemic and if that affects their health outcome, we decided to conduct a study at the department of cardiology of our clinic (Regiomed Klinikum Coburg). In this thesis, two patient groups are compared. The first group of pre-pandemic patients is compared with the second group of pandemic patients. Each group consists of all patients who underwent MitraClip procedure within two timespans of one year each.

1.2 Anatomy of the mitral valvular apparatus

In the following, the mitral valve in general, its anatomy and the pathophysiology behind mitral regurgitation will be explained. Further the function of mitral valve for the heart itself will be explained and how its functionality, but also diseased state affects the human body as a whole. The term “mitral”, according to Walmsley, comes from Andreas Vesalius who compared the appearance of the mitral valve with the plan view of a bishop’s mitre (22). Representing the entrance to the left ventricle, the mitral valve’s main function is to prevent backflow to the left atrium at the time of ventricular systole.

When opened, the valvar leaflets resemble a funnel, reaching from the atrioventricular junction to the free margins. The two groups of papillary muscles and the leaflets are interconnected by tendinous cords, where the interchordal spaces serve as a crucial passage for blood flow (23). Perloff *et al.* emphasize the importance of functionality of the whole valvular apparatus, including the adjacent atrial and ventricular musculature, for the mitral valve to work properly (24). In Figure 1A one can see that the mitral valve is in fact located right next to the aortic valve. Figure 1B shows that the mitral valve is directly adjacent to the aortic valve, without a separating muscle as it is the case for the tricuspid valve (23).

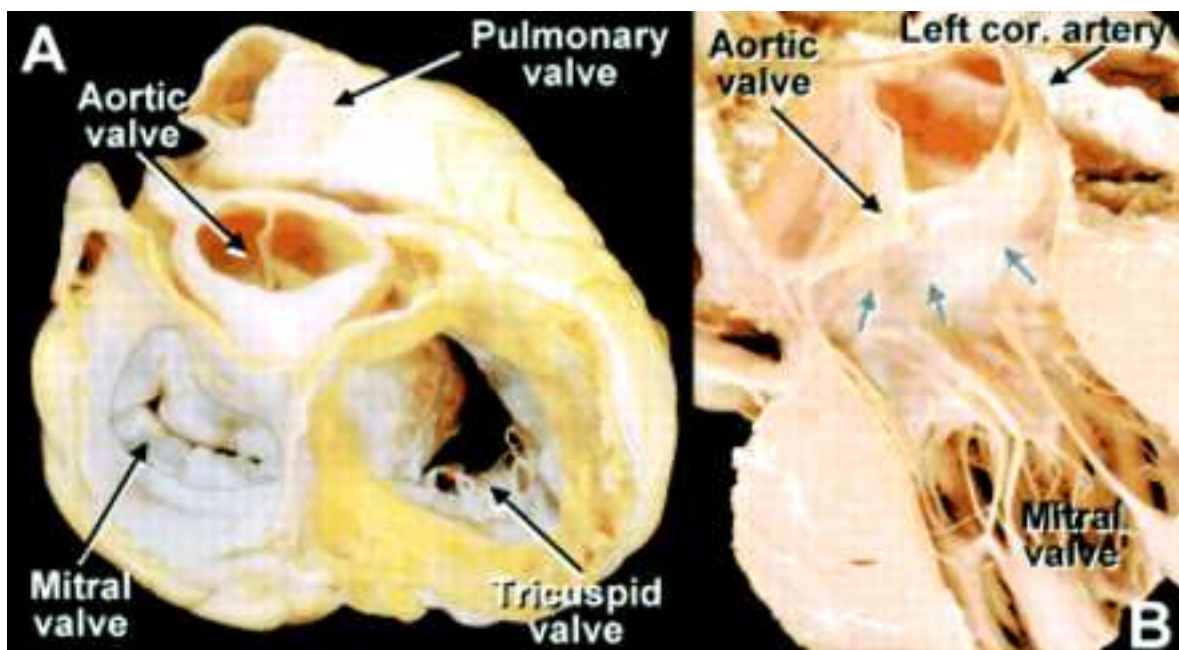


Figure 1. (A) An anatomical view of the heart's base reveals the spatial relationships of all four cardiac valves. The left heart valves are located closely together, contrary to the right heart valves being separated by myocardium. The dotted line denotes the border of the atrial myocardium around the mitral orifice. (B) An anterior view of a heart dissection reveals the proximity between the aortic and mitral valves in situ. The fibrous continuity in between the valves (indicated by blue arrows) is associated with the aortic non- and left coronary sinuses.

Source: Ho SY. Anatomy of the mitral valve. *Heart*. 2002 Nov 1;88(suppl 4):iv5-10. Available from: https://heart.bmj.com/content/heartjnl/88/suppl_4/iv5.full.pdf (last accessed 28.11.2023).

For the mitral valve to close adequately, the two leaflets need to align on the same level as they coapt along their solitary apposition zone. To accomplish this, several factors are required, including an optimal size of the valvular annulus, a correct orientation of the papillary muscles in a geometrical sense, which give rise to the tendinous cords, and lastly an appropriate muscular contraction to produce the necessary closing forces. Also, one must consider the functionality of the surrounding structures, like the aortic valve, the coronary sinus, the circumflex coronary artery, but also the atrioventricular conduction axis (25).

1.2.1 The left atrioventricular junction

Essentially, the valvular leaflets are supported by the left atrioventricular junction, which is a D-shaped orifice that is found at the confluence in between the left atrial walls and the adherent left ventricular structures (23, 24, 26, 27). Apart from myocardial matter, an extensive area of fibrous continuity is found on the ventricular aspect which is also known as the aortic-mitral curtain. This structure is located between the anterior leaflet of the mitral valve and the aortic valve in the left ventricular roof (25). Looking at the heart in 3D, the atrioventricular junction is nonplanar, as its septal and lateral elements at the end of its solitary zone of apposition are elevated. With its leaflets and corresponding depressed medial segments along the zone of apposition's central component, the characteristic saddle-shape is created (28). One of the leaflets is connected to the noncoronary and left coronary leaflets of the aortic valve along the depressed anterior section of the junction. This wide area is often referred to as the aortic-mitral curtain.

The central part of the fibrous curtain, which serves as the base or annulus for the anterior or aortic leaflet of the valve, is connected to the ventricular myocardium on both ends through fibrous extensions called the left and right fibrous trigones (25). The right trigone is connected to the membranous septum, the two together forming the central fibrous body, and the penetrating section of the atrioventricular conduction axis going through the membranous septum's atrioventricular component (27). From the fibrous trigones, fibroelastic cords of varying quality and structure run through the mural section of the left atrioventricular junction. It is uncommon for the cords to create a complete ring to support the valve's mural, or posterior, valvar leaflet. The annulus is significantly more resistant to pathological enlargement along the aortic leaflet compared to the mural leaflet. Particularly in its posterior aspects, various deficiencies of the annular structure are filled with adipose tissue.

The lack of a properly formed fibrous cord in this specific position, opposite the aortic-mitral curtain, explains why it is more prone to enlargement and calcification of the annulus. This leads to an uneven increase in the aortic-to-mural or septal-to-lateral diameter of the valve opening, potentially impairing proper leaflet coaptation (25).

1.2.2 The valvular leaflets

The mitral valve is characterized by bifoliate leaflets. The anterior leaflet is in fibrous continuity with two of the leaflets of the aortic valve, leading to its alternative name "aortic leaflet" (25). The posterior leaflet, situated opposite, is also correctly referred to as the mural leaflet (23, 27). The aortic leaflet comprises one-third of the left atrioventricular junction and has a larger surface with a shorter base. It is responsible for separating the LV input and outflow tracts. The opposing mural leaflet is shallower but larger, encircling the junctional circumference by two-thirds. The combined surface area of both leaflets is 2.5 times that of the valvular orifice. During systole, the leaflets coapt over an average of 8 mm in height, resulting in an "overlapping" or "coaptation reserve" in the event of annular dilatation. The apposition zone in between the leaflets is positioned obliquely relative to the orthogonal planes of the body, but it can be seen as "mitral smile" using short-axis echocardiography (26). Its two ends are inferoseptally and superolaterally positioned, even though these orientations are now mistakenly defined as posteromedial and anterolateral (29). Openings in the mural leaflet form three scallops, and more leaflet tissue can be discovered at the edges of the solitary zone of apposition, which represents the actual valvular commissure. The mural leaflet's numerous components generate a more flexible structure than the more rigid aortic leaflet. When combined with the dynamic movements of the junction, they form what is known as the sphincter mechanism (25).

1.2.3 Tendinous cords and papillary muscles

The mitral valve leaflets are linked to the LV free wall in a manner similar to how the shrouds of a parachute are connected, through the tendinous cords and papillary muscles (23, 24, 27). The chordae tendineae, or fibrocollagenous tendinous cords, arising from the papillary muscles, bifurcate numerous times, and attach to the free margins and ventricular aspects of the two leaflets. Chordal rupture tends to occur at the point of insertion, where the cords are the most fragile.

Commonly, the cords attach consistently along the leaflet edges, limiting marginal prolapse and ensuring adequate alignment of the zone of coaptation. The so-called strut cords are attached to the ventricular side of the aortic mitral leaflet, preventing bulging, and distributing stress evenly.

The basal cords originate from the ventricular wall and exclusively attach to the ventricular surface of the mural leaflet, helping to maintain the ventricular shape and strengthen the atrioventricular junction from the ventricular perspective.

The cords are formed by paired papillary muscles that emerge from the apical to middle thirds of the LV free wall, with each muscle having a different number of heads. According to the accepted view, the superolateral muscle is supplied by one or more circumflex artery branches or diagonal branches. The inferoseptal papillary muscle is on the other hand supplied by either a single circumflex or right coronary artery branch. Especially the inferoseptal muscle is prone to myocardial ischemia due to its single vascular supply (25). Organic illness frequently includes these mitral valvular complex components (30). Myxomatous degeneration can cause the cords to become overly long and may impair their distinctive elastic qualities, resulting in prolapse. Fibroelastic insufficiency will have the exact opposite effect. Tissue retraction may occur which can result in rupture, leading to either a partial or complete flail leaflet (25).

1.2.4 Integration of the LA and LV

The myocardium throughout the left atrium and ventricle has an inextricable connection supporting the mural leaflet of the mitral valve (MV) (25). Hence the valvular tissue is maintained by the heart directly, without the support of anatomical cordlike structures, it is termed a “disjunction” (31). In contrast to the LV myocardium, which has no link with the MV's aortic leaflet, the LA myocardium aligns with the shape of the junction (25). Certainly, the LV outflow tract is situated between the aortic leaflet of the MV and the ventricular septum (23).

On the other hand, the posterior-inferior wall of the left ventricle directly provides support to the mural leaflet via the basal cords (25). Changes regarding the ventricular geometry can have substantial effects on mitral valvular dynamics, as the ventricular free wall highly interdepends with the distinctive arrangements (32). LV mural dyskinesia may exert tractive power on the mural leaflet by changing the orientation of the basal cords.

A greater overall LV enlargement can cause papillary muscle displacement towards the apex, a more global dilation of the LV can cause papillary muscle displacement in an apical direction, potentially causing the leaflets to tent and preventing proper coaptation, which can ultimately lead to regurgitation (25).

1.2.5 Coronary venous and arterial anatomy

Regarding its anatomy, the venous system in general shows a high range of variability. In this system, the great cardiac vein and the coronary sinus seem to be consistent components (33, 34). The great cardiac vein, also called anterior interventricular vein, commonly arises from the lower or middle portion of the anterior interventricular groove (35). It adheres to the groove directed to the cardiac base before turning inferiorly at the atrioventricular junction and merging with the LA oblique vein, a relic of the embryonic left superior caval vein, to form the coronary sinus. The inferior interventricular groove paves the way for the middle cardiac vein, which finally empties into the coronary sinus near its opening in the right atrium. The semicircular Thebesian valve lines the opening of the coronary sinus (25). Known for its significant morphological variability, it can even become a significant impediment to sinus cannulation (34). As it passes through the left atrioventricular (AV) junction, the position of the coronary sinus changes (25). The body of the sinus is close to the inferior LA wall in 90% of cases, considerably above and cranial to the deeper AV junction (33, 36, 37). The sinus body is closest to the atrioventricular junction's lateral segment at the center of the mural leaflet and farthest distant at the outer edges of the solitary zone of apposition (25).

In the case of substantial regurgitation, especially in patients with ischemic cardiomyopathy, the sinus is raised away from the posterior segment and advances further towards the endpoints of the solitary zone of apposition within the leaflets (33, 38). Apart from that, one can observe a flattening of the saddle-shaped "annulus" combined with an increased septal-to-lateral annular diameter (39). The diameter of the sinus increases, as it reaches its right atrial termination and acquires multiple tributaries. As a rule, the sinus is located close to the circumflex artery, which in up to 80% of patients crosses the venous structure. Contrary, the crossing point, the length of the overlapping segment, as well as the length of the parallel course, but also the crossing point and the distance between the crossing point and the atrioventricular junction are all extremely individual (25). In one-sixth of population, the great cardiac vein traverses diagonal or intermediate arterial branches (40).

1.3 Mitral regurgitation

1.3.1 Epidemiology

Mitral regurgitation is a widespread valve condition that affects around 10% of the population (41). The most prevalent cause of primary MR is mitral valve prolapse (MVP) caused by myxomatous degeneration of the mitral valve (42). It is the most frequent cardiac mitral valvular pathology in the world, accounting for 2% to 3% of the entire population (43). Rheumatic heart disease (RHD) is still frequent in developing countries and is the leading cause of mitral valvular disease resulting in hospitalizations (44, 45).

1.3.2 Etiology and classification

As already mentioned, MR can be classified as primary or secondary. Talking about primary MR first, the most prevalent pathophysiologic cause of degenerative mitral regurgitation is myxomatous degeneration of the MV, which results in mitral valve prolapse (MVP). This prolapse can either be a primary and non-syndromic process or alternatively a secondary and syndromic process. The main driver of disease progression in primary MVP is an increasing age (42). Secondary MVP can be provoked by connective tissue disorders such as Marfan syndrome, Ehlers-Danlos syndrome, the MASS phenotype, systemic lupus erythematosus, osteogenesis imperfecta, and pseudoxanthoma elasticum (46). The MASS phenotype is described as an incomplete variant of Marfan syndrome. This term is an acronym, and the condition consists of MVP, a nonprogressive aortic root dilatation, musculoskeletal findings and skin striae (47).

Among the causes for primary causes are also congenital conditions, such as an isolated cleft of the mitral valve, a double orifice mitral valve and the so-called parachute mitral valve (PMV) (48). In the latter, the chordae tendineae are attached to only one papillary muscle (49). Despite their rarity, in the literature they are a well-defined cause of primary MR (42). Together with degenerative and congenital reasons for MR, there is a third category: RHD is highly prevalent in developing countries because of a lack of health care and vaccinations, with an estimated 15 million cases globally (50).

Chronic RHD is linked with pancarditis and mitral valve involvement, resulting in regurgitation in nearly all instances due to scarring of the valve and the valvular apparatus (51, 52).

As previously stated, the mitral valve itself is not changed pathologically in secondary MR. Instead, secondary MR occurs when left ventricular dilatation caused by either ischemic or nonischemic cardiomyopathy inhibits leaflet coaptation in a structurally normal MV (42). Dysfunction and remodeling can result in an apical and lateral displacement of the papillary muscle, which in turn results in leaflet tethering, enlargement, and flattening of the mitral annulus, as well as in reduced valve closing forces (53). Decreased closing forces encompass a decline in LV contractility, modified systolic annular contraction, diminished coordination between the two papillary muscles, and overall LV desynchrony, particularly in the basal segments. Among the reasons for SMR are the rupture of papillary muscles, ischemic mitral regurgitation (IMR), those associated with congestive heart failure (CHF), those linked with atrial fibrillation (AF) and hypertrophic cardiomyopathy (HCM). Papillary muscle rupture is an extremely rare condition that occurs in 1% to 2% of individuals, following a myocardial infarction (MI) or infective endocarditis (42). It causes severe mitral regurgitation due to papillary muscle failure (54, 55). Prior MI combined with normal MV leaflets and chordae leads to ischemic mitral regurgitation (IMR). Ischemia of the segments beneath the papillary muscles induces remodeling (42). This condition contributes to papillary muscle displacement, resulting in a more apical leaflet position described as a "seagull sign" (56). According to Carpentier's classification, the most prevalent form of IMR is type IIIb, which is caused by limited movements of the leaflet(s) during systole.

Exercise-induced changes in MR are related to changes in LV remodeling and valve deformation, as well as to changes in LV and papillary muscle synchrony (42). In a study including 558 patients diagnosed with severe congestive heart failure ($EF \leq 35\%$), MR was classified as severe in 4.3% of patients, moderate to severe in 12.5% of patients, moderate in 21.9% of patients, mild to moderate in 11.8% of patients, mild in 39.1% of patients, and absent or present in 10.4% of study participants (57). The link between severe CHF and MR was discovered in this study. Furthermore, a retrospective cohort study discovered that atrial fibrillation (AF) increases atrial and valvar annular size, leading to functional MR (42). Controlling AF and reestablishing sinus rhythm resulted in a greater reduction in functional MR in the patients tested (57).

A randomized trial further revealed a relationship between AF and deteriorating valvular disease (58). MR can happen as well due to hypertrophic cardiomyopathy (HCM). HCM is characterized by significant left ventricular hypertrophy, that results in an increased papillary muscle mass, causing them to move closer together (42). This process causes the mitral valve leaflets to grow extended and floppy, drawing them closer to the left ventricular outflow tract and resulting in a regurgitant retrograde flow (59, 60).

Mitral regurgitation is defined as a retrograde flow from the left ventricle back into the left atrium. Mitral regurgitation results in LV volume overload as a consequence of an increased stroke volume, which in turn is caused by an increase in blood volume in the left atrium. This ultimately leads to an increased preload. In patients with chronic progressive MR, ventricular remodeling will occur, allowing cardiac output to be maintained, and an initial rise in ejection fraction (EF) is common. The effective EF, however, can be significantly smaller dependent on the regurgitant fraction. Volume overload from MR promotes ventricular dilatation, expansion of the mitral annulus, and decreased coaptation of leaflets over time, leading to further deterioration of MR (42).

1.3.4 Symptoms

Clinical symptoms connected with MR can be classified into two categories: those that are associated with the MR directly and those attributed to the underlying etiology. It is critical to keep a broad differential diagnosis, but overall, with an early-on focused anamnesis and a thorough physical examination, one can identify if the MR has an acute or chronic cause, narrowing the probable etiologies dramatically. Talking about acute mitral regurgitation, the clinical examination will typically reveal symptoms linked with a rapid decrease in cardiac output and potentially even a cardiogenic shock. The patient will typically complain of severe dyspnea at rest, which worsens being in a supine position, along with a cough with clear or even pink, frothy sputum. They may also show symptoms of myocardial ischemia, which could include chest discomfort radiating to the head and neck region and the shoulders. Nausea and diaphoresis may also occur. During physical examination, one might notice an altered mental status and even tachycardia or bradycardia, if the conduction system happens to be ischemic. Other symptoms can be hypotension, tachypnea, hypoxemia, as well as cyanosis.

Looking at the patient's neck, one can occasionally notice jugular venous distension, diffuse crackles on the lung during auscultation, and a holosystolic murmur radiating to the axilla when listening at the apex of the heart. Acute MR typically results from either rupture of a papillary muscle which in turn happens due to acute coronary syndrome. Another typical reason would be an intense destruction of the valvular apparatus arising from an acute bacterial endocarditis. As a result, additional clinical evaluation should concentrate on identifying these potentially fatal diseases. Symptoms of sepsis, including fever and chills, are expected in the case of acute bacterial endocarditis. Patients dealing with intravenous drug abuse are at greater risk to have other medical conditions that lead to immunocompromise, which include diabetes mellitus, HIV/AIDS, or alcoholic abuse. With the embolization of vegetative material, additional clinical findings may occur determined by the final destiny of the emboli - that would for instance mean focal neurologic deficits if the brain is involved, hematuria or oligoanuria if the kidneys are involved, and Janeway lesions or petechiae if the skin is involved. Acute infections, in contrast to subacute bacterial endocarditis, often occur in individuals with structurally normal heart valves; thus, rheumatic heart disease as well as prosthetic valves are not as prevalent in this population. Furthermore, because the path of bacterial supply to the mitral valve travels through the right heart, simultaneous involvement of the tricuspid and pulmonic valves is prevalent, and these are generally detectable on physical examination (61,62).

Symptoms of patients with chronic mitral regurgitation differ from those of acute mitral regurgitation in that they tend to be asymptomatic until later in the course of the disease. Possible signs and symptoms can be fatigue, dyspnea that is seen on exertion, orthopnea, and paroxysmal nocturnal dyspnea, but also a distention of the jugular veins, a displaced apical impulse, a holosystolic murmur at the apex, dependent edema, widening of pulse pressure and weight gain. As the regurgitation becomes more severe, additional symptoms may manifest, including syncope, cyanosis, digit clubbing, hepatomegaly, anasarca, ascites, shifting dullness, and even pleural or pericardial effusions. The last findings represent the onset of pulmonary hypertension and the subsequent right ventricular systolic dysfunction caused by chronic pressure overload. The range of differential diagnoses is much wider though and clinical signs vary depending on the etiology (61).

1.4 Therapy

1.4.1 Pharmacotherapy

As already mentioned, the etiology of MR defines the therapeutic approach. Starting with PMR, nitrates and diuretics are used to decrease filling pressures in acute mitral regurgitation. Afterload and regurgitant fraction are reduced by sodium nitroprusside. Hypotension and hemodynamic instability can be treated with inotropic medicines and an intra-aortic balloon pump (6). There is no evidence that favors the use of vasodilators as a preventive measure in chronic PMR with maintained left ventricular ejection fraction (LVEF). Medical treatment for patients suffering from overt heart failure follows current heart failure guidelines (63).

For individuals with SMR, ideal medical therapy in accordance with heart failure management recommendations should be the first and most important step in the care of all SMR patients, and it should include the substitution of ACEI or ARB with sacubitril/valsartan, sodium-glucose co-transporter 2 inhibitors, and/or ivabradine as needed (63, 64). Also, the criteria for cardiac resynchronization therapy (CRT) shall be evaluated based on relevant guidelines, as can be seen in Figure 2 (63). If symptoms continue after classic heart failure medication has been optimized, it is crucial to promptly assess the possibility of mitral valve intervention to prevent a further decline of LV systolic function or the occurrence of cardiac remodeling (6).

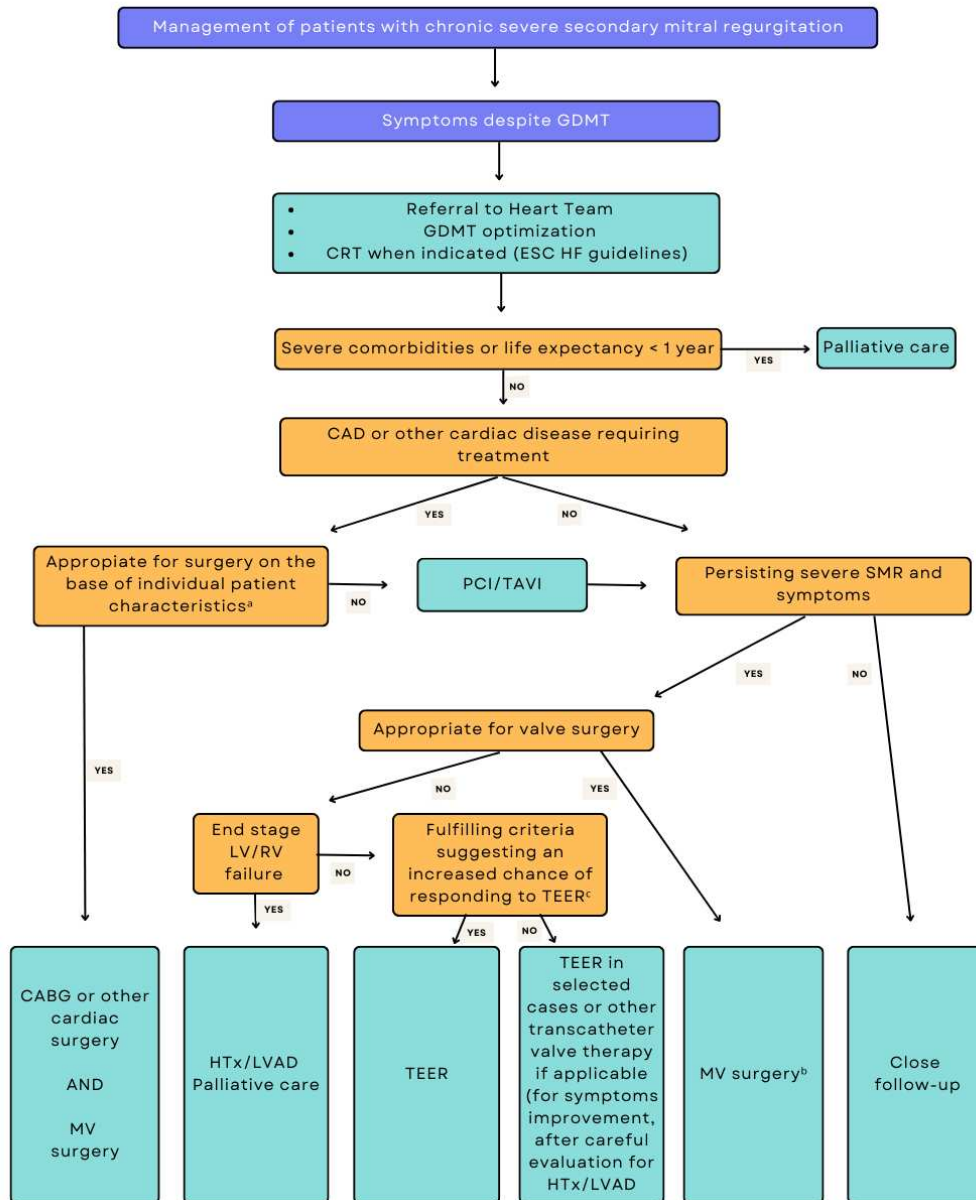


Figure 2. Management of patients with severe secondary mitral regurgitation. AD = coronary artery disease; CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; HF = heart failure; HTx = heart transplantation; LVAD = left ventricular assist devices; LV = left ventricle/left ventricular; LVEF = left ventricular ejection fraction; MV = mitral valve; PCI = percutaneous coronary intervention; RV = right ventricle/right ventricular; SMR = secondary mitral regurgitation; TAVI = transcatheter aortic valve implantation; TEER: transcatheter edge-to-edge repair. ^aLVEF, predicted surgical risk, amount of myocardial viability, coronary anatomy/target vessels, type of concomitant procedure needed, TEER eligibility, likelihood of durable surgical repair, need of surgical mitral replacement, local expertise. ^bParticularly when concomitant tricuspid valve surgery is needed.

COAPT criteria (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation)

Source: 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS).

Available from:

<https://academic.oup.com/eurheartj/article/43/7/561/6358470?login=false#364291409> (last accessed 13.08.2023).

1.4.2 Surgical approach

Individuals experiencing acute severe mitral regurgitation should undergo urgent surgery. Valve replacement is usually indicated when papillary muscle rupture is the underlying condition. Figure 3 presents the indications for undergoing surgery in case of severe chronic PMR. Depending on the Heart Team's decision, surgery is indicated for those with symptomatic severe PMR along with an acceptable surgical risk (6). LVEF of $\leq 60\%$, a left ventricular end-systolic diameter (LVESD) of ≥ 40 mm, LA volume of ≥ 60 mL/m² or diameter of ≥ 55 mm, systolic pulmonary arterial pressure (SPAP) greater than 50 mmHg, and AF are all linked to poorer outcomes and are regarded triggers for intervention regardless of symptomatology (65–72). In the absence of these requirements, watchful waiting in a hospital setting is an appropriate approach in asymptomatic patients diagnosed with severe PMR (6).

Mitral valve repair appears to be the preferred intervention when its outcomes are likely to be durable, as it is associated with greater survival than mitral valve replacement (73, 74). PMR caused by segmental valve prolapse has a low risk of relapse and therefore reoperation (74–76). It is a greater challenge to repair rheumatic lesions, significant valve prolapses, and especially cases of leaflet calcification or extensive annular calcification (77, 78). Patients, in whom a more complex repair is expected, should choose well-established repair centers with a track record of high success rates in repairs, low operative mortality, and a history of producing long-lasting outcomes. When repair is not an option, replacement of the mitral valve with subvalvular apparatus preservation is recommended (6).

Complete cardiopulmonary bypass (CPB) and ischemia arrest are used in standard mitral valve repair (MVr). There are several surgical techniques, involving median sternotomy, right thoracotomy, or even robot-assisted surgery. The essential concepts of MVr remain the same regardless of incisional approach: the goal is to establish a functional mitral valve with appropriate coaptation extent, ring annuloplasty, as well as prevention of systolic anterior motion.

The surgical procedures for MVr by median sternotomy are described here. This method is required for patients who require additional concomitant surgeries such as coronary artery bypass grafting (CABG), ascending aortic intervention, or extra/multiple valve intervention. CPB cannulation is accomplished through the ascending aorta together with bicaval venous cannulation. Antegrade and retrograde pathways are used to achieve cardioplegic arrest. The interatrial groove is uncovered after aortic crossclamping and an appropriate diastolic cardioplegic arrest. A left atriotomy is carried out from the pulmonary veins. An alternative method would be the transseptal approach by performing a right atriotomy and cutting the septum through the fossa ovalis. For exposure, appropriate retractors are used. The valve is then methodically evaluated using saline injection together with visual examination of each segment. The choice of repair technique will be determined according to the results of valve pathology. For all repairs, ring annuloplasty is recommended. Sutures are wrapped tightly around the annulus, alongside measurement of the anterior leaflet height. The size of the ring can vary, depending on the type of mitral regurgitation pathology (primary vs. secondary, ischemic vs. non-ischemic), with options ranging from a true-sized to an undersized ring. It is crucial to evaluate the valve regarding its coaptation depth, with 1 cm being appropriate. It is also essential to avoid severe ring undersizing, which might result in systolic anterior motion (SAM) (79).

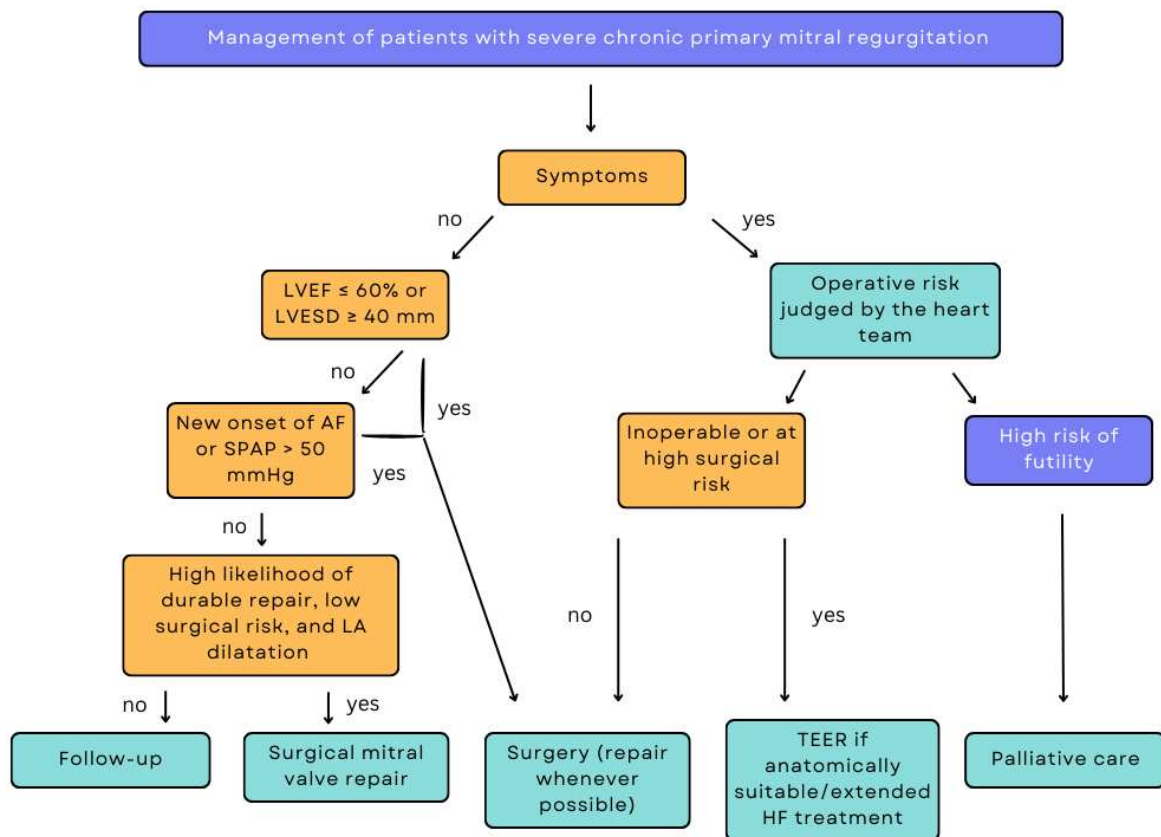


Figure 3. Management of patients with severe chronic primary mitral regurgitation. AF = atrial fibrillation; HF = heart failure; LA = left atrium/left atrial; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SPAP = systolic pulmonary arterial pressure; TEER = transcatheter edge-to-edge repair.

Source: 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS).

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<https://academic.oup.com/eurheartj/article/43/7/561/6358470?login=false#364291409> (last accessed 02.08.2023).

1.4.3 Transcatheter mitral valve replacement and repair

Transcatheter MV replacement with specific transcatheter mitral prostheses has come to be an effective treatment option for severe MR in high-risk patients with challenging native MV anatomy (80). Out of several transcatheter heart valve systems for the MV, transapical transcatheter MV replacement using the Tendyne device (Abbott) has been the most applied with over 800 patients all over the world (81). Nevertheless, this approach is in the early stages of its development.

Catheter-supported edge-to-edge therapy (transcatheter edge-to-edge repair, TEER), with transcatheter edge-to-edge repair (TEER) being an alternative, new term for transcatheter mitral valve repair (TMVR), has emerged as a safe and effective treatment modality for mitral valve insufficiency in the past few years (82,83). In 2018, the randomized controlled COAPT study has shown for the first time that patients diagnosed with secondary mitral regurgitation (SMR) had a survival benefit following TEER, when compared to sole pharmacologic therapy for heart failure (83). In 2013, the Food and Drug Administration (FDA) gave their approval for TEER with the MitraClip system (Abbott) for interventional therapy of patients suffering from symptomatic severe primary MR characterized by a high surgical risk. In 2019, the approval was extended for patients diagnosed with moderate-to-severe or severe secondary MR who continue to experience heart failure symptoms despite receiving optimal pharmacotherapy.

Recently, the PASCAL TEER system (Edwards Lifesciences) received FDA approval for individuals with primary MR and a high surgical risk (84). Disadvantageously, full remission and avoidance of further MR advancement cannot always be achieved, also a persisting MR of $\geq 2+$ is not rare (85). Additionally, structural characteristics, such as calcified leaflets, valve areas that are smaller in size, and shortened posterior leaflets, may limit adequate TEER outcomes (86). As a result, there is a current need for advancements in transcatheter technology to produce optimal and long-term results across a greater range of MV anatomies (84).

2. OBJECTIVES

2.1 Aims of the study

The aim of this study is to find out if and how the Covid-19 pandemic affected cardiologic patients undergoing TEER, specifically MitraClip, at the Regiomed clinic in Coburg regarding their state of health before the intervention and further the therapeutic outcome.

2.2 Hypothesis

Pandemic-related delays in healthcare delivery and potential concerns about infection in the hospital setting have an unfavorable impact on patients undergoing transcatheter mitral valve repair.

3. MATERIAL AND METHODS

3.1 Study design

The study design was a retrospective analysis of a database containing all TEER procedures performed with the MitraClip within two independent groups. The first group (group A) includes all TEER procedures between January 2019 and January 2020, whereas the second group (group B) does so between March 2020 and March 2021.

3.2 Data Collection

The required data was acquired by using the clinic's information system Orbis powered by Dedalus. The relevant set of patients was gained by using the inbuilt search and filter option. All consecutive patients undergoing a TEER procedure with the MitraClip at the Regimed clinic Coburg in the two already in 3.1 mentioned timespans were included in the data base. Data is anonymized, patient ID is not provided, and patients cannot be traced back.

3.3 Variables

All the following variables were determined in all patients and compared between the two groups:

Sociodemographic characteristics: sex, age at day of intervention, body mass index (BMI), duration of hospital stay in days, personal history of coronary artery disease (CAD), non-ST-segment elevation myocardial infarction (NSTEMI)/ST-segment elevation myocardial infarction (STEMI)/angina pectoris, chronic renal insufficiency, anemia, obesity, diabetes mellitus, bradycardia/sick sinus, chronic obstructive pulmonary disease (COPD)/asthma, stroke, pacemaker, arterial hypertension, reanimation, atrial fibrillation and death.

The New York Heart Association (NYHA) classification is used to categorize heart failure into four different degrees of severity, enabling the estimation of patient prognosis and facilitating the selection of appropriate treatment.

Class I: Asymptomatic cardiac disease without physical limitations. Routine physical exertion does not result in undue fatigue, arrhythmias, dyspnea, or angina pectoris.
Class II: Mildly symptomatic cardiac disease with slight impairment of exercise tolerance.

No symptoms at rest or with mild exertion. More strenuous physical activity (e.g., walking uphill or climbing stairs) causes fatigue, arrhythmias, dyspnea, or angina pectoris. Class III: Moderately severe cardiac disease with marked impairment of exercise tolerance during ordinary activity. No symptoms at rest. Mild physical activity (e.g., walking on level ground) induces fatigue, arrhythmias, dyspnea, or angina pectoris. Class IV: Severe cardiac disease with symptoms exhibited during all physical activities and at rest, leading to bed confinement. (<https://www.leitlinien.de/themen/herzinsuffizienz/3-auflage/kapitel-1#tab4>, last accessed 19.07.23)

Echocardiography parameters:

Ejection fraction (EF), degree of mitral regurgitation before and after the intervention. Skilled echocardiographers classified the intensity of MR as absent (0), mild (1+), moderate (2+), moderate to severe (3+), or severe (4+).

Laboratory parameters:

Creatinine in $\mu\text{mol/l}$, eGFR in ml/min and Troponin T in ng/ml . N-terminal pro-brain natriuretic peptide (NT-pro BNP) was later excluded from data analysis due to small sample size.

Anticoagulant pharmacotherapy at admission:

It was grouped into the following categories: vitamin-k-antagonists (VKA) including phenprocoumon, warfarin and enoxaparin, platelet aggregation inhibitors including acetylsalicylic acid, clopidogrel, ticagrelor and prasugrel, and lastly direct oral anticoagulants (DOAC) including dabigatran, apixaban and edoxaban.

The gathered data has been collected during the hospital stay for TMVR and there were no follow up examinations. The grade of MR was evaluated before and after the intervention, as well as the different laboratory parameters, if given, closest to the day of admission and discharge each. EF, NYHA class, medical diagnoses, BMI, and anticoagulant pre-medication were evaluated at admission only.

3.4 Procedural Characteristics

The MitraClip® system (Abbott Laboratories, Menlo Park, California, USA), as can be seen in Figure 4, is a device for percutaneous edge-to-edge repair of the mitral valve in patients diagnosed with severe mitral regurgitation who are at high surgical risk. This tool has shown to be therapeutically effective for both degenerative and functional mitral regurgitation.

The MitraClip intervention has minimal peri-procedural complication rates, a considerable reduction in mitral regurgitation, as well as a rise in functional capacity and, most importantly, quality of life. Similarly to the Alfieri technique, the middle scallops of the anterior and posterior leaflets of the regurgitant mitral valve are linked together (87). Also trial data from EVEREST and additionally registry results show that the MitraClip technique is viable and safe (88–90). It has been shown that the proficiency of the operator has a direct impact on the success of procedures (91). ACCESS-EU (the Amsterdam Center for Contemporary European Studies - A Two-Phase Observational trial of the MitraClip System in Europe), an extensive prospective, nonrandomized European trial, reported 81.8% survival at 1 year and 78.9% absence of severe MR (92). Certain morphological criteria must be met to ensure the clip's safe positioning (87). Beneficial are a coaptation length greater than 2 mm, a coaptation depth less than 11 mm, and, in presence of a degenerative condition, a flail gap below 10 mm and a flail width lower than 15 mm (93). The MitraClip system is comprised of a steerable guide catheter which is inserted transfemorally and later is delivered transseptally into the left atrium utilizing echocardiographic supervision. The clip delivery system, which can be seen in Figure 4, is inserted via the guide catheter (87).

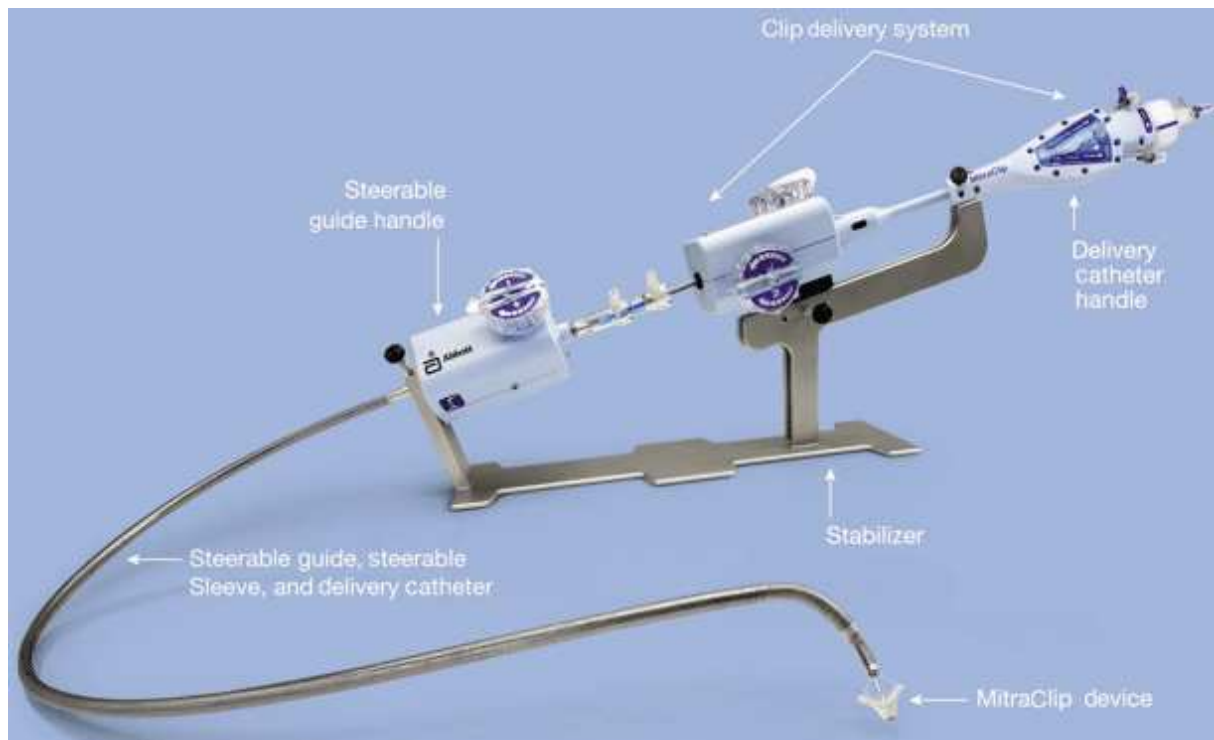


Figure 4. Components of the MitraClip system (Images provided and adapted from Abbott Laboratories, Menlo Park, California, USA).

Source: Sherif MA, Paranskaya L, Yuecel S, Kische S, Thiele O, D'Ancona G et al. MitraClip step by step; how to simplify the procedure. *Neth Heart J.* 2017 Feb;25(2):125-130.

Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5260622/> (last accessed 03.08.2023)

The intervention is typically carried out with the patient being under general anesthesia while closely monitoring their vital signs and using specific medical equipment (invasive arterial blood pressure measurement, central venous catheter, pulse oximetry). The main method of guiding the MitraClip® intervention involves a combination of 2D and 3D transesophageal echocardiography. Additionally, fluoroscopy is used to provide extra information during various steps of the procedure (87, 94). Ideally, the venous puncture is done on the right femoral vein. From that starting point, the guidewire and the Brockenbrough catheter are advanced into the superior vena cava, followed by guidewire removal and insertion of Brockenbrough needle. The actual MitraClip intervention begins with the transeptal puncture, with proper location of the puncture site being the crucial key to a successful procedure. The transesophageal echocardiography (TEE) guidance allows a safe performance of the puncture (94).

Assisted by fluoroscopy and TEE, the steerable guide catheter together with the dilator is gently moved into the left atrium using a guidewire which is placed in the left upper pulmonary vein. As soon as the catheter is in the right place, the guidewire and the dilator are removed. Now the clip delivery system can be guided towards the left upper pulmonary vein via a steerable catheter under fluoroscopic view. After placing the system above the mitral valve, clip adjustments are observed in a 2D and 3D view (87). In standard practice, it is advised to insert the opened clip into the left ventricle (95). Correct orientation and proper alignment of the clip are crucial for a successful grasp of the mitral valve leaflets (87). Post-procedurally, according to the German Cardiac Society (DGK), patients without an indication for oral anticoagulation (OAC) should receive antiplatelet therapy with 100 mg/day of acetylsalicylic acid (ASA) (alternatively 75 mg/day of clopidogrel) for at least half a year after edge-to-edge interventions and annuloplasty procedures. Additionally, for the first (up to 3) months, dual antiplatelet therapy (DAPT) is recommended in line with most studies (96).

3.5 Ethical Approval

The previously prepared research plan was sent to the institutional review board (IRB) of the Medical School Regiomed Coburg. Based on §2 of the statutes of the IRB, there are no objections to the implantation of the research project. The study was performed in accordance with the declaration of Helsinki.

3.6 Statistical Analysis

Microsoft Excel and MedCalc were used to analyze the collected data. The mean and standard deviation were calculated using Microsoft Excel. Frequencies and percentages were used to present categorical information. Unpaired categorical data were compared using the chi-square test.

A two-sided student t test was employed to test for significant differences in the means of variables between group A and group B. The statistical significance was tested at the 5% level ($P = 0.05$). The P -values were calculated using MedCalc.

4. Results

4.1 Patient baseline characteristics and comorbidities

The current study comprised 216 patients with severe MR who underwent TEER using the MitraClip technique. Group A, the pre-Covid group, included 117 patients (54.2%) whereas group B, the Covid group, included 99 patients (45.8%). In total, 112 of the 216 patients were female (51.9%). 62 patients (53.0%) were female in group A, whereas in group B 50 patients were of female sex (50.5%) (Table 1). The mean total age at day of intervention was 79.19 years. In group A, the mean age was 78.80 ± 6.47 years, whereas in group B it was 79.65 ± 6.52 years. There was no statistically significant difference in sex distribution ($P = 0.716$) or age ($P = 0.339$). The mean length of hospital stay in both groups was 10.20 days. In group A it was 8.83 ± 8.77 days and in group B 11.83 ± 10.11 days, at $P = 0.020$ indicating a statistically significant difference in length of hospital stay, with a longer stay in Group B. No significant difference existed between the mean of NYHA classes in both groups, with $P = 0.987$. The mean NYHA class was 2.95, so close to NYHA III, in all patients. In Group A it was 2.95 ± 0.54 and in group B 2.95 ± 0.53 . Before the procedure, the mean EF in all evaluated patients was 46.2%. In group A it was $48.5 \pm 14.7\%$. In group B it was $43.4 \pm 14.5\%$ which shows a statistically significant difference at $P = 0.011$, with group B having the smaller EF. In total, 123 patients out of 216 patients (56.9%) were diagnosed with CAD. In group A there were 66 (56.4%) and in group B 57 patients (57.6%). There was no statistically relevant difference with $P = 0.864$. Either STEMI, NSTEMI or angina pectoris (AP) were diagnosed in 32 of total 216 patients (14.8%). In group A there were 18 (15.4%) and in group B 14 patients (14.1%). There was no statistically relevant difference with $P = 0.798$. Chronic kidney disease (CKD) was diagnosed in 77 out of 216 patients (35.7%). Interestingly, 49 of these patients were found in group A (41.9%) and 28 patients in group B (28.3%), at $P = 0.038$ indicating a statistically significant difference. Anemia affected 30 out of 216 total patients (13.9%). In group A 19 (16.2%) and 11 patients in group B (11.1%). There was no statistically relevant difference with $P = 0.278$. 83 out of 216 patients were obese (38.4%). Counted as obese were those patients who had a body mass index (BMI) ≥ 30 . In group A there are 50 (42.7%) and in group B 33 patients (33.3%). There was no statistically relevant difference with $P = 0.157$. The mean BMI in all patients was 28.92. In group A it was 29.98 and in group B 27.96, at $P = 0.013$ indicating a statistically significant difference. Diabetes mellitus was diagnosed in 71 out of 216 total patients (32.9%). In group A 39 (33.3%) and in group B 32 patients (32.3%). There was no statistically relevant difference with $P = 0.875$.

Bradycardia due to sick sinus syndrome was found in 14 out of 216 total patients (6.5%). In group A 10 (8.6%) and in group B 4 patients (4.0%). There was no statistically relevant difference with $P = 0.180$. COPD and asthma affected 28 out of 216 total patients (13.0%). In group A 20 (17.1%) and in group B 8 patients (8.1%), at $P = 0.049$ indicating a statistically significant difference. 22 out of 216 patients (10.2%) experienced a stroke. In group A 12 (10.3%) and in group B 10 patients (10.1%). There was no statistically relevant difference with $P = 0.970$. A pacemaker was present in 52 out of 216 patients (24.1%). In group A 28 (23.9%) and in group B 24 patients (24.2%) had one. There was no statistically relevant difference with $P = 0.958$. Arterial hypertension was present in 150 out of 216 patients (69.4%). In group A 82 (70.1%) and in group B 68 patients (68.7%) had it. There was no statistically relevant difference with $P = 0.824$. In total, 8 out of 216 patients (3.7%) needed to undergo reanimation. In group A 3 (2.6%) and in group B 5 patients (5.1%). There was no statistically relevant difference with $P = 0.335$. Atrial fibrillation was found in 141 of 216 patients (65.3%). In group A 75 (64.1%) and in group B 66 patients (66.7%) had been diagnosed with it. There was no statistically relevant difference with $P = 0.693$. For a visualization of the most common morbidities in these patient groups, see Figure 5.

Table 1. Baseline characteristics & Comorbidities

Variable	Total N = 216	Group A N = 117	Group B N = 99	<i>P</i>
Age, y±SD	79.19±4.49	78.80±6.47	79.65±6.52	0.339 [†]
Female sex, n (%)	112 (51.6)	62 (53.0)	50 (50.5)	0.716*
BMI ^a , kg/m ² ±SD	28.92±5.93	29.98±5.99	27.96±5.86	0.013 [†]
Hospitalization in days ±SD	10.20±9.41	8.83±8.77	11.83±10.11	0.020 [†]

Comorbidities				
CAD ^b , n (%)	123 (56.9)	66 (56.4)	57 (57.6)	0.864*
STEMI ^c , NSTEMI ^d , AP ^e , n (%)	32 (14.8)	18 (15.4)	14 (14.1)	0.798*
CKD ^f , n (%)	77 (35.7)	49 (41.9)	28 (28.3)	0.038*
Anemia, n (%)	30 (13.9)	19 (16.2)	11 (11.1)	0.278*
Obesity, n (%)	83 (38.4)	50 (42.7)	33 (33.3)	0.157*
DM ^g , n (%)	71(32.9)	39 (33.3)	32 (32.3)	0.875*
Bradycardia, n (%)	14(6.5)	10 (8.6)	4 (4.0)	0.180*
COPD ^h , Asthma, n (%)	28 (13)	20 (17.1)	8 (8.1)	0.049*
Stroke, n (%)	22 (10.2)	12 (10.3)	10 (10.1)	0.970*
Pacemaker, n (%)	52 (24.1)	28 (23.9)	24 (24.2)	0.958*
Arterial hypertension, n (%)	150 (69.4)	82 (70.1)	68 (68.7)	0.824*
Reanimation, n (%)	8 (3.7)	3 (2.6)	5 (5.1)	0.335*
AF ⁱ , n (%)	141 (65.3)	75 (64.1)	66 (66.7)	0.693*
NYHA ^j class ±SD	2.95±0.54	2.95±0.54	2.95±0.53	0.987 †
EF ^k (%) ±SD	46.2±14.58	48.5±14.67	43.4±14.47	0.011†

Data are presented as mean±standard deviation or as number (%)

* Chi-square test

† Two-sided student t test

^a Body mass index

^b Coronary artery disease

^c ST elevation myocardial infarction

^d Non-ST elevation myocardial infarction

^e Angina pectoris

^f Chronic kidney disease

^g Diabetes mellitus

^h Chronic pulmonary disease

ⁱ Atrial fibrillation

^j New York Heart Association classification

^k Ejection fraction

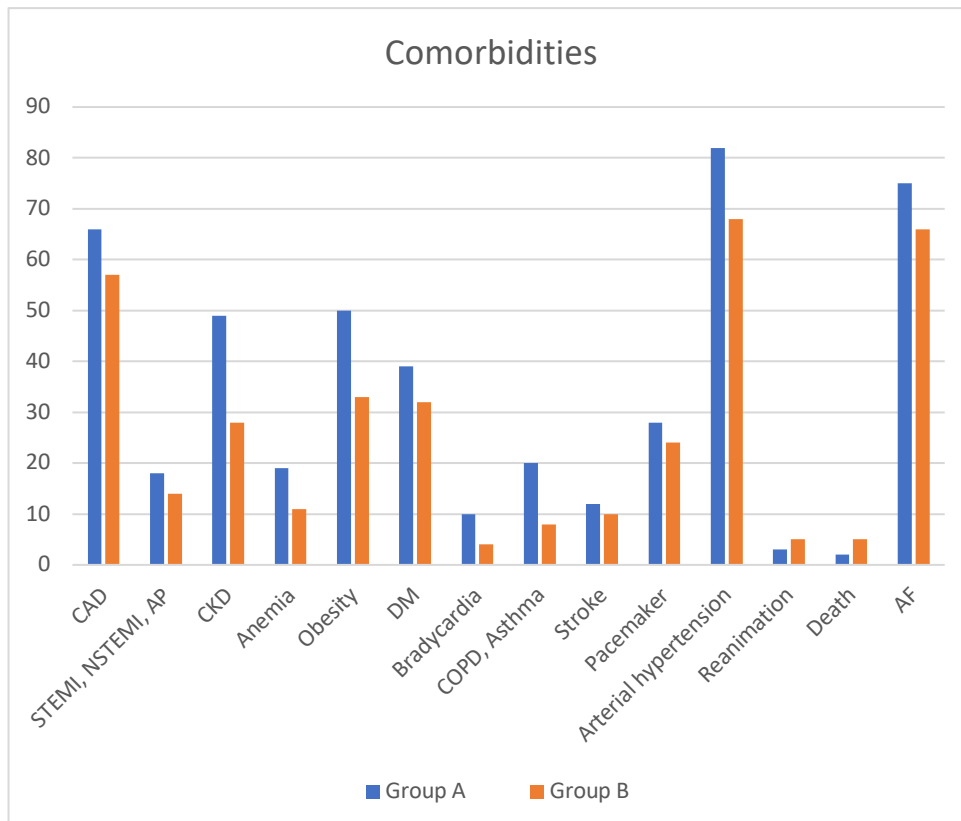


Figure 5. Comorbidities

CAD: Coronary artery disease, STEMI: ST elevation myocardial infarction, NSTEMI: Non-ST elevation myocardial infarction, AP: Angina pectoris, CKD: Chronic kidney disease, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, AF: Atrial fibrillation.

4.2 Acute outcome of the procedure

The procedure was considered successful, if postprocedural MR was <2. In group A, this was the case in 91 out of 117 patients (77.8%). In group B, 83 out of 99 procedures were successful (83.8%). In total, 174 out of 216 procedures (80.6%) were successful. The results do not significantly differ at $P = 0.263$. It is noteworthy, that the acute interventional outcomes were highly satisfactory both prior to and during the pandemic. In hospital-mortality affected 7 out of 216 total patients (3.2%). In group A, 2 patients (1.7%) died, while in group B it was 5 patients (5.1%) (Table 2, Figure 6). There was no statistically significant difference between the two groups ($P = 0.167$).

Table 2. Pre- and post-procedural MR.

Variable	Total N = 216	Group A N = 117	Group B N = 99	<i>P</i> *
MR pre-procedural ± SD	3.26±0.45	3.23±0.46	3.30±0.43	0.252
MR post-procedural ± SD	1.26±0.55	1.24±0.56	1.28±0.54	0.596

* Two-sided student t test

^a Mitral regurgitation

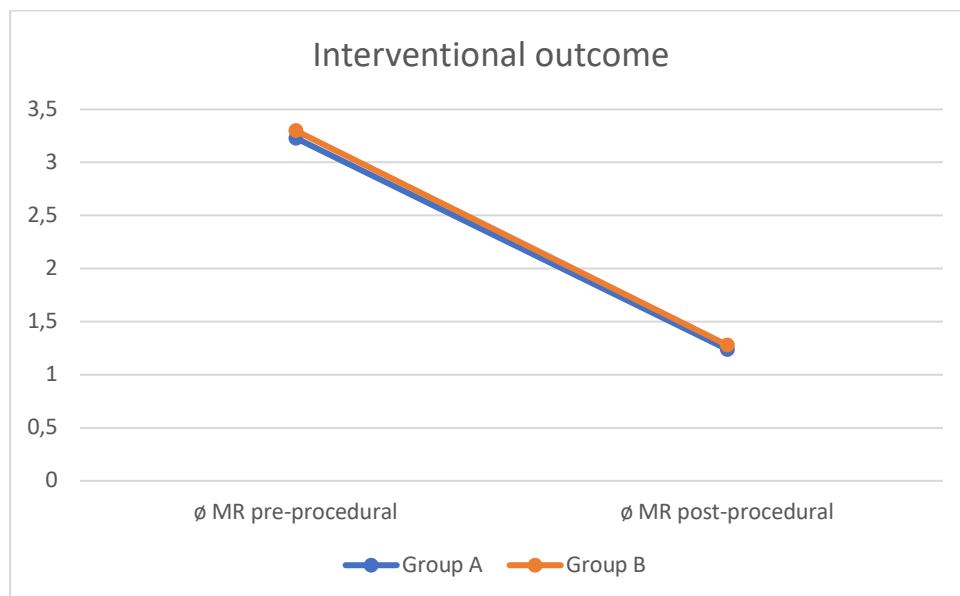


Figure 6. Interventional outcome

4.3 Laboratory diagnostics

To compare the two patient groups even better, different serum markers were evaluated, such as creatinine (Cr), the estimated glomerular filtration rate (eGFR) and troponin T (Trop). As already said in 3.3, some markers had to be excluded due to insufficient sample size. None of the serum markers showed a statistically significant difference in means.

Table 3. Serum markers.

Variable	Total N = 216	Group A N = 117	Group B N = 99	<i>P</i> *
Cr ^a (pre-procedural), mg/dl ± SD	125.27±52.16	122.47±47.79	132.39±56.90	0.165
Cr (post-procedural), mg/dl ± SD	117.16±54.36	117.95±61.87	116.24±45.64	0.820
eGFR ^b (pre-procedural), ml/min ± SD	50.28±18.74	51.49±18.48	49.36±19.05	0.406
eGFR (post-procedural), ml/min ± SD	56.02±21.97	55.77±21.07	56.32±22.99	0.855
Trop T ^c (pre-procedural), ng/ml ± SD	0.044±0.06	0.041±0.06	0.048±0.06	0.394

* Two-sided student t test

^a Creatinine

^b estimated glomerular filtration rate

^c Troponin C

4.4 Premedication

201 out of 216 total patients had already been under anticoagulant or platelet aggregation inhibitor therapy at the time of their admission. 15 patients on the other hand had been without that kind of medication at that time. 7 patients out of these 15 were in group A (5.98%), whereas 8 patients were in group B (8.1%). There was no statistically significant difference in means between the two groups ($P = 0.546$). Starting with the total number of patients, the most often prescribed drug had been inhibitors of platelet aggregation with 103 patients taking them (47.7%). Secondly, DOAC were taken by 85 patients (39.4%). Lastly, 39 patients had been undergoing VKA therapy (18.1%). For an overview, see Figure 7. In group A, 54 patients (46.2%) took inhibitors of platelet aggregation at the time of their admission. In group B, it was 49 patients (49.5%). There was no statistically significant difference in means between the two groups ($P = 0.624$). In group A, 49 patients (41.9%) took DOAC. In group B, 36 patients (36.4%) took them at the time of their admission. There was no statistically significant difference in means between the two groups ($P = 0.408$). At the time of admission, VKA were taken by 20 patients (17.1%) in group A and 19 patients (19.2%) in group B.

There was no statistically significant difference in means between the two groups ($P = 0.699$). Some patients were taking more than one drug of the three groups at once.

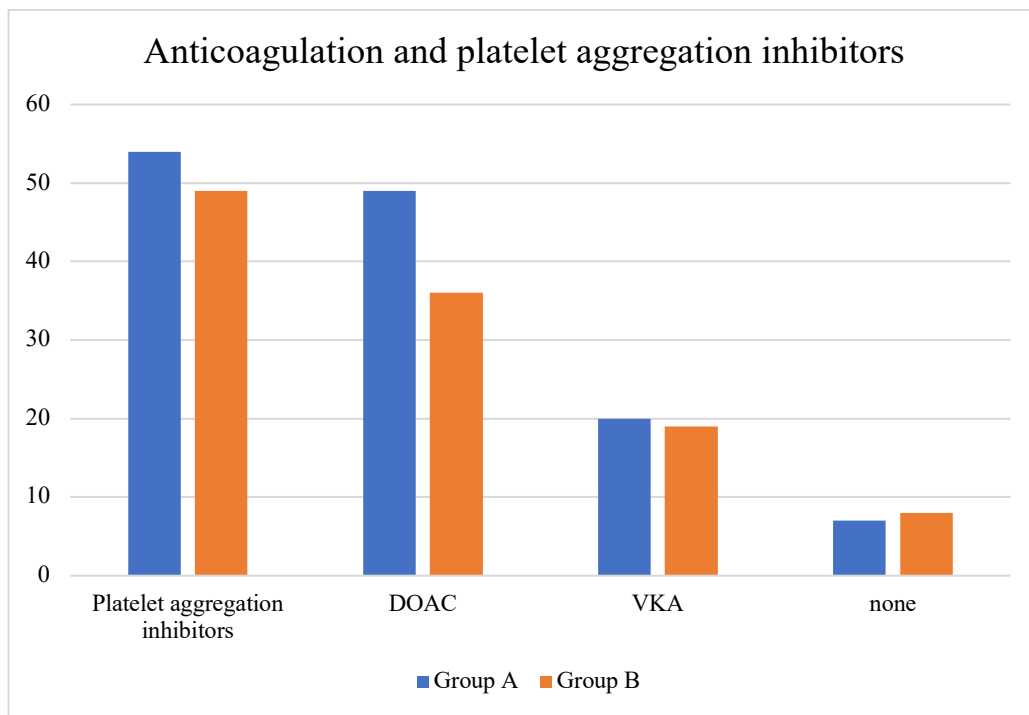


Figure 7. Anticoagulation and platelet aggregation inhibitors

5. Discussion

MR is a common cardiovascular disease, affecting especially the elderly population. MitraClip, which is a transcatheter mitral valve repair system designed for MR, is suitable for high-risk and thus inoperable, often elderly patient groups (97). The vast majority of participants of this study exhibited several comorbidities and an average heart failure severity of nearly NYHA class III was observed. After comparing the two independent patient groups, most baseline characteristics and overall, TEER outcome were similar. Contrary to the aim of a shortened hospitalization to conserve medical resources, the pandemic-related delays in healthcare delivery did significantly prolong the length of hospital stay and patients had a significantly smaller ejection fraction. In group B, the pandemic group, significantly fewer patients had chronic kidney disease or chronic pulmonary disease. Also, the average body mass index was significantly lower. These results could be explained by the absence of elective programs for cardiologic patients during the pandemic. Only emergency cases were treated, and these patients were commonly in a worse overall health condition than the typical elective patient for TEER, which explains the prolonged hospital stay and the decreased ejection fraction.

The decreased body mass index can be attributed to cardiac cachexia. The lower incidence of patients with chronic kidney disease and chronic pulmonary disease in Group B could reasonably stem from the cautiousness exhibited by these vulnerable patient populations regarding the potential for infection during their hospitalization. The results of this study are in line with the research by Andress *et al.*, indicating that deferring treatment for patients with severe valvular disease could lead to increased collateral damage. This is evident, particularly in the extended length of hospitalization observed in this study (98). Although this study does neither exhibit significant differences in preprocedural severity of heart failure according to the NYHA classification, nor in the short-term outcome of mitral valve insufficiency treatment, the study conducted by Andress *et al.* does demonstrate a remarkable, statistically significant difference within the one-year follow-up period. Within the initial year following the intervention, their study group experienced either emergency hospitalization or death in 65.3% of cases, whereas this occurred in 10.4% of cases within the control group ($P < 0.001$). At this point, it is important to note that both transcatheter aortic valve implantation (TAVI) patients and non-emergency percutaneous mitral valve repair (PMVR) interventions were examined in this context.

Observed in the context of the research done by Andress *et al.*, it would be of great interest to conduct a one-year follow up of the patients in this Regimed study to evaluate further significant differences, especially regarding long-term outcome (98).

Limitations:

Due to its design (retrospective, single-center, observational), the outcomes of this study must be interpreted within certain limitations. Owing to its single-center design, the participation of only 216 patients over a complete two-year timeline has resulted in the infrequent manifestation of certain events, such as death. The restricted sample size in this context prevents a statistically substantial comparison of these rarer events. To facilitate a better comparison, one potential approach could involve the analysis of laboratory samples taken at precisely defined times before and after the intervention. Future studies could expand the range of quantitative and objective parameters that are subject to evaluation.

6. Conclusion

Even though there were pandemic-related delays in healthcare delivery, the overall outcome of TEER procedures was similar in both groups. However, the pandemic demonstrated its influence on other parameters, such as the length of hospital stay, EF, the number of patients with certain comorbidities, and the BMI.

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8. Summary

Background:

With mitral regurgitation being the most common valve disease in the industrialized world, it affects roughly 10% of elderly over the age of 75 years. Due to demographic changes, its prevalence is thought to even increase in the future. TEER, particularly the MitraClip® system, is a suitable option for patients with an increased surgical risk. This thesis addresses the question of how the strained healthcare system during the pandemic has affected cardiological patients with mitral valve insufficiency, particularly TEER patients at the REGIOMED hospital in Coburg.

Methods:

The study design involved a retrospective analysis of a database containing all TEER procedures performed using the MitraClip® system within two independent groups. The first group (group A) included all TEER procedures between January 2019 and January 2020, while the second group (group B) included all procedures between March 2020 and March 2021. The study included a total of 216 patients, with 117 individuals in group A and 99 in group B. The data collected encompassed echocardiographic parameters (ejection fraction, degree of mitral valve insufficiency before and after the procedure), laboratory parameters (creatinine, estimated glomerular filtration rate, Troponin-T), premedication regarding anticoagulation, sociodemographic characteristics (gender, age at the time of the procedure, BMI, length of hospital stay, comorbidities), and the severity of heart failure according to the NYHA classification.

Results:

After comparing the two independent patient groups, most baseline characteristics and overall outcome were almost comparable. Still, the results showed statistically significant longer length of hospital stay in group B (11.83 vs. 8.83 days, $P = 0.020$). Ejection fraction was significantly smaller in group B (43.4% vs. 46.2%, $P = 0.011$). Significantly fewer patients had chronic kidney disease in group B (28.3% vs. 41.9%, $P = 0.038$). Also, a significantly smaller proportion of patients had chronic pulmonary disease in group B (8.1% vs. 17.1%, $P = 0.049$). The average BMI was significantly lower in group B (27.96 vs. 29.98 kg/m², $P = 0.013$).

Conclusion:

The results can largely be explained by the absence of elective programs for cardiological patients during the pandemic. Only emergency cases were treated, and they were commonly in a worse overall health condition than the typical elective patient for TEER.

9. Croatian summary

Ciljevi:

S obzirom na to da je mitralna regurgitacija najčešća bolest srčanog zaliska u industrializiranom svijetu, pogađa otprilike 10% starijih osoba starijih od 75 godina. Zbog demografskih promjena, smatra se da će njezina prevalencija čak i rasti u budućnosti. TEER, posebno sustav MitraClip®, prikladna je opcija za pacijente s povećanim kirurškim rizikom. Ovaj diplomski rad bavi se pitanjem kako je napregnuti zdravstveni sustav tijekom pandemije utjecao na kardiološke pacijente s nedostatnošću mitralnog zaliska, posebno na pacijente podvrgnute TEER-u u bolnici REGIOMED u Coburgu.

Metode:

Dizajn studije uključivao je retrospektivnu analizu baze podataka koja sadrži sve postupke TEER-a izvedene pomoću sustava MitraClip® unutar dvije neovisne skupine. Prva skupina (skupina A) obuhvaćala je sve postupke TEER-a od siječnja 2019. do siječnja 2020., dok je druga skupina (skupina B) obuhvaćala sve postupke od ožujka 2020. do ožujka 2021. U studiju je bilo uključeno ukupno 216 pacijenata, s 117 osoba u skupini A i 99 u skupini B. Prikupljeni podaci obuhvaćali su ehokardiografske parametre (frakcija izbacivanja, stupanj nedostatnosti mitralnog zaliska prije i nakon postupka), laboratorijske parametre (kreatinin, procijenjena glomerularna filtracija, Troponin-T), premedikaciju u vezi s antikoagulacijom, sociodemografske karakteristike (spol, dob u vrijeme postupka, BMI, duljina boravka u bolnici, komorbiditeti) te težinu zatajenja srca prema NYHA klasifikaciji.

Rezultati:

Nakon usporedbe dviju neovisnih skupina pacijenata, većina početnih karakteristika i ukupni ishod bili su gotovo usporedivi. Ipak, rezultati su pokazali statistički značajno dulje trajanje boravka u bolnici u skupini B (11,83 naspram 8,83 dana, $P = 0,020$). Frakcija izbacivanja bila je značajno manja u skupini B (43,4% naspram 46,2%, $P = 0,011$). Značajno manji broj pacijenata imao je kroničnu bolest bubrega u skupini B (28,28% naspram 41,88%, $P = 0,038$). Također, značajno manji broj pacijenata imao je kroničnu plućnu bolest u skupini B (8,08% naspram 17,09%, $P = 0,049$). Prosječni indeks tjelesne mase bio je značajno niži u skupini B (27,96 naspram 29,98 kg/m², $P = 0,013$).

Zaključak:

Rezultate se uglavnom može objasniti nedostatkom izbornih programa za kardiološke pacijente tijekom pandemije. Tretirani su samo hitni slučajevi, koji su često imali lošije opće zdravstveno stanje od tipičnih izbornih pacijenata za TEER postupak.