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FOCUS ON MITRAL AND TRICUSPID VALVES

Impact of Frailty on Outcomes in Patients Undergoing Percutaneous Mitral Valve Repair

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ABSTRACT

OBJECTIVES The aim of this study was to describe the impact of frailty in patients undergoing percutaneous mitral valve repair (PMVR).

BACKGROUND Frailty is common in elderly patients and those with comorbidities and is associated with adverse prognosis.

METHODS Frailty according to the Fried criteria was assessed in consecutive patients admitted for PMVR. Associations of frailty with 6-week (device success, changes in 6-min walking distance and Minnesota Living With Heart Failure Questionnaire and Short Form 36 physical and mental component scores, and improvement ≥1 New York Heart Association functional class) and long-term outcomes during a median follow-up period of 429 days were examined.

RESULTS Of 213 patients admitted for PMVR (median age 78 years; age range 50 to 95 years; 57.3% men), 45.5% were classified as frail. Compared with nonfrail patients, frail patients had a similar device success rate (81.4% vs. 84.5%; $p = 0.56$) and improvement in 6-min walking distance, New York Heart Association functional class, and Short Form-36 scores but a more pronounced improvement in Minnesota Living With Heart Failure Questionnaire score (mean change −15.9 vs. −11.2 points; $p = 0.002$). Mortality at 6 weeks was significantly higher in frail (8.3%) compared with nonfrail (1.7%) patients ($p = 0.03$). Hazards of death (hazard ratio: 3.06; 95% confidence interval: 1.54 to 6.07; $p = 0.001$) and death or heart failure decompensation (hazard ratio: 2.03; 95% confidence interval: 1.22 to 3.39; $p = 0.007$) were significantly increased in frail patients during long-term follow-up, which did not change relevantly after adjustment for European System for Cardiac Operative Risk Evaluation score and N-terminal pro-brain natriuretic peptide level.

CONCLUSIONS PMVR can be performed with equal efficacy and is associated with at least similar short-term functional improvement in frail patients. These results support the continued use of PMVR in frail elderly patients with the goal of palliation of heart failure symptoms and improvement in quality of life. (J Am Coll Cardiol Intv 2017;10:1920–9)

Catheter-based percutaneous mitral valve repair (PMVR) is increasingly used for the treatment of symptomatic mitral valve regurgitation (MR) in patients who are judged inoperable or at high surgical risk by the heart team (1). A comprehensive evaluation of such morbid patients is mandatory for an individualized risk-benefit analysis before the treatment decision

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is made. Traditional risk scores used in cardiac surgery are based mainly on the severity of cardiac disease and predict total mortality, which is insufficient to reflect the complexity of patients eligible for PMVR and the symptomatic objective of this treatment (2). Recent guidelines recommend extended patient evaluation, including holistic measures of patient performance such as the frailty syndrome (3). However, evidence supporting this approach is lacking.

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Frailty represents a complex clinical syndrome of increased vulnerability to stressors (4), which is associated with adverse health outcomes in many clinical scenarios, such as heart failure, cardiac surgery, and cardiovascular interventions (5–7). Various contributors to the frailty syndrome have been identified, such as age-related biological processes and cardiovascular and noncardiovascular morbidity. On the basis of the characteristics of patients undergoing PMVR, who have a mean age >75 years and have many comorbidities, including advanced cardiac disease, we hypothesized that frailty is common in these patients and might affect clinical outcomes. Furthermore, because frailty adversely affects quality of life and functional capacity (8–10), one might question whether frail patients show a reasonable extent of symptomatic improvement after PMVR compared with nonfrail patients.

The aim of this study was to test the hypotheses that frailty is common and has an adverse impact on clinical outcomes and functional benefit in patients undergoing PMVR. Frailty, defined by the validated Fried criteria, was assessed in consecutive patients undergoing PMVR at our center, and the impact on procedural outcomes, short-term functional changes, and long-term clinical outcomes was analyzed.

METHODS

PATIENTS. In this prospective, observational study, all consecutive patients admitted for PMVR to the Heart Centre of the University of Cologne between May 2014 and June 2016 were eligible for inclusion. Exclusion criteria were inability or denial to provide written informed consent and age <18 years. All patients had symptomatic grade 3 or 4 MR with indication for treatment according to current guidelines (11) and were discussed by the heart team, consisting of cardiothoracic surgeons and interventional and noninterventional cardiologists, who agreed on interventional treatment with the MitraClip system (Abbott Vascular, Santa Clara, California). There were no general clinical or morphological criteria precluding PMVR, but the decision on feasibility aligned with criteria defined in a recent consensus paper of the German Society of Cardiology (12). On an individual basis, the heart team assessed operative risk on the basis of validated scores and additional clinical variables, such as left ventricular function and cause of MR, as well as current guidelines on the treatment of valve disease.

The PMVR procedure was performed under general anesthesia, as comprehensively described elsewhere (12). All interventional cardiologists performing PMVR in this study had a minimum experience of 100 MitraClip procedures. All included patients gave written informed consent. The study was approved by the local ethics committee of the University of Cologne (13–15).

BASELINE ASSESSMENT. Baseline demographic and clinical characteristics were extracted from the patient record according to a prespecified protocol. The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) score was calculated using the online calculator (http://www.euroscore.org/calcold.html). Transthoracic echocardiography with quantification of MR was performed according to current guideline recommendations (13,16) by an experienced senior cardiologist before PMVR and, blinded to clinical parameters of the patient and the primary procedural result of PMVR, at discharge. Blood tests and electrocardiography were performed before the procedure as part of routine evaluation.

The functional assessment of the patients included 6-min walking distance (6MWD), New York Heart Association (NYHA) functional class, Minnesota Living With Heart Failure Questionnaire (MLWHFQ) score (14), and the generic, validated Medical Outcomes Study Short Form-36 (SF-36) (OptumInsight, Eden Prairie, Minnesota) (15,17) and was performed during the hospitalization 1 to 5 days before the procedure by a trained medical student, who was blinded to echocardiographic results.

The 6-min walking distance was assessed according to the standardized protocol of the American Thoracic Society (18). Briefly, in an internal, flat corridor 50 m in length, marked by 2 yellow stripes, the participants were given the following instructions: "Walk from end to end of the corridor at your own pace, in order to cover as much ground as

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

EuroSCORE = European System for Cardiac Operative Risk Evaluation

HR = hazard ratio

IQR = interquartile range

MCS = mental component score

MLWHFQ = Minnesota Living With Heart Failure Questionnaire

MR = mitral valve regurgitation

NT-proBNP = N-terminal pro-brain natriuretic peptide

NYHA = New York Heart Association

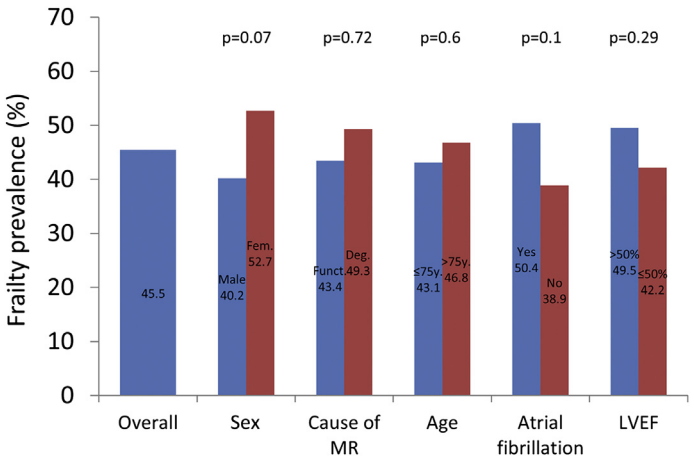
PCS = physical component score

PMVR = percutaneous mitral valve repair

SF-36 = Medical Outcomes Study Short Form-36

6MWD = 6-min walking distance

FIGURE 1 Prevalence of Frailty



Depicted for the total population and strata of age, sex, underlying pathology of mitral valve regurgitation (MR), atrial fibrillation, and left ventricular ejection fraction (LVEF). p Value for difference between strata. Deg. = degenerative; Fem. = female; Funct. = functional.

possible for 6 min, but don't run or jog." The distance covered during the test was recorded in meters. The SF-36 and MLWHFQ surveys were conducted by interview. Responses to the SF-36 applied to the patient's health over the previous 4 weeks and were graded and scored from 0 to 100, with a higher score reflecting better health-related quality of life. Two separate component summary scores are provided, distinguishing between physical (physical component score [PCS]) and mental (mental component score [MCS]) health.

Frailty was assessed according to the criteria defined by Fried et al. (19). Five components of the frailty syndrome were measured, and 1 point was scored for each criterion met to specification, with patients meeting at least 3 of the 5 criteria classified as frail and those meeting 1 or 2 of the 5 criteria classified as pre-frail: 1) unintentional weight loss of >5% of body weight or >4.5 kg in the past year; 2) weakness: grip strength of the dominant hand measured with a Jamar dynamometer and averaged from 3 measures <18 kg in women and <30 kg in men; 3) self-reported exhaustion: "In the last week (during 3 days or more) I felt everything I did was an effort and/or I was not able to brace myself up for anything"; 4) slowness: walking time for a separate 4.57-m walk test >6 s; and 5) low physical activity, derived from 1 question for reasons of practicality as a modification to the original Fried score, in which a physical activity questionnaire was used: "Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by making you sit or lie down to rest during the day?" answered as 4 or 5 (on a 6-point, Likert-type scale ranging from 0 = no to 5 = very much). Frailty was also judged clinically by the treating physician as 1 of several pre-specified causes for denial of surgery. A given patient might have more than 1 reason for denial of surgery.

FOLLOW-UP. Follow-up examination was assessed about 6 weeks after the initial procedure, including transthoracic echocardiography, blood tests, electrocardiography, and functional assessment, including 6MWD, NYHA functional class, MLWHFQ, and SF-36. We deliberately chose a follow-up period of 6 weeks because many patients were transferred to geriatric rehabilitation after the initial hospital stay, which would have precluded presentation at 30 days post-procedure in a substantial number of the patients. Pre-specified complications assessed according to the Mitral Valve Academic Research Consortium (20) after the procedure were cause-specific mortality, neurological events, heart failure-associated hospitalization, major access-related vascular complications, major cardiac structural complications related to access, and technical and device success. If the patient was not able to visit the clinic for follow-up because of long distance to the hospital or a medical condition, vital status and adverse events were evaluated by telephone with the patient, relatives, or the treating physician.

Long-term follow-up regarding vital status, cause of death, and hospitalization for heart failure decompensation was assessed by telephone with patients, relatives, or treating physicians, with validation of hospital stays through retrieval of discharge letters in December 2016.

STATISTICAL ANALYSIS. Patients fulfilling the Fried criteria for frailty were compared with those not fulfilling frailty criteria, including those with pre-frailty, with respect to baseline characteristics and outcomes. Continuous variables are expressed as mean ± SD or as median with interquartile range (IQR) if not normally distributed. The statistical significance of differences of continuous variables by subgroups was calculated using the Mann-Whitney *U* test if not normally distributed and the Student *t* test if normally distributed. Nominal and ordinal data are expressed as percentages, and the statistical significance of differences was calculated using the chi-square test. If the expected value in any of the cells was <5, the Fisher exact test was used. In addition to the absolute changes in functional parameters from baseline to 6 weeks, we also examined the rate of clinically relevant improvement according to cutoffs

recommended by the Mitral Valve Academic Research Consortium (20). Because no cutoff values defining clinically relevant improvement in MLWHFQ and SF-36 scores are validated in patients with PMVR, we used conservative cutoff levels suggesting at least moderate improvement: an increase of 5 or more points in SF-36 score and 50% of the SD of change in MLWHFQ score in our population (a decrease of 7.5 or more points). Adjusted analysis of the association between frailty and clinically relevant improvement was performed using multivariate logistic regression. Kaplan-Meier plots and univariate and multivariate Cox proportional hazard models were used to analyze the impact of frailty on long-term outcomes. Observations were censored at end of follow-up (December 2016), date of event (death or hospitalization), or date of last confirmed status alive, whichever was first. The proportional hazard assumption was tested visually using a log-log plot, without evidence of a violation. A p value <0.05 was considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS. Two hundred thirty patients were admitted for PMVR at our institution during the study period. Thirteen patients were excluded because they declined to participate (n = 4) or were incapable of giving consent because of a critical state of health in the intensive care unit (n = 9) (Online Figure 1). Four patients were excluded because frailty status could not be classified because of missing data on individual frailty criteria. Ultimately, 213 patients were included (mean age 78 ± 8 years, 57.3% men), with high estimated surgical risk (median logistic EuroSCORE 17.8%; IQR: 10.3% to 28.1%). The underlying pathology of MR was primary/degenerative in 35.2%, secondary/functional in 57.3%, and combined degenerative and functional in 7.5%.

Ninety-seven of the 213 patients (45.5%) were classified as frail according to the Fried criteria (**Figure 1**). The remaining 116 patients were regarded as the nonfrail comparison group, with 102 (87.9%) fulfilling criteria for pre-frailty. Similar prevalence rates of frailty were observed in strata of sex, age (>75 or ≤75 years), MR pathology (primary or secondary), atrial fibrillation, and ejection fraction (>50% or ≤50%) (**Figure 1**). Frail patients did not differ significantly from nonfrail patients regarding sex, pathology of MR, logistic EuroSCORE, echocardiographic parameters, and comorbidities but showed a significantly

TABLE 1 Baseline Characteristics of the Study Patients by Frailty Status

	Frail (n = 97)	Not Frail (n = 116)	p Value*
Male	49 (50.5)	73 (62.9)	0.07
Age, yrs	79 ± 7	76 ± 9	0.02
BMI, kg/m^2	26.2 ± 5.0	25.5 ± 4.6	0.33
Cause of MR			0.72
Functional MR	53 (54.6)	69 (59.5)	
Degenerative MR	37 (38.1)	38 (32.8)	
Combined pathology	7 (7.2)	9 (7.8)	
Structural cardiac disease			0.63
Ischemic cardiomyopathy	50 (51.5)	54 (46.6)	
Dilated cardiomyopathy	38 (39.1)	47 (40.5)	
None	9 (9.3)	15 (12.9)	
Logistic EuroSCORE, %	20.5 (12.1-33.7)	15.4 (9.8-25.8)	0.05
LVEF			0.37
>50%	48 (49.5)	49 (42.2)	
30%-50%	22 (22.7)	36 (31)	
<30%	27 (27.8)	31 (26.7)	
Reasons for denying surgery			
Surgical high risk	70 (72.2)	89 (76.7)	0.45
Old age	53 (54.6)	44 (37.9)	0.02
Frailty (clinical judgment of treating physician)	18 (18.6)	11 (9.5)	0.05
Inoperability	7 (7.2)	3 (2.6)	0.11
Patient's preference	6 (6.2)	8 (6.9)	0.83
Diabetes mellitus	34 (35.1)	27 (23.3)	0.06
Previous stroke	11 (11.3)	17 (14.7)	0.48
Previous myocardial infarction	31 (32)	36 (31)	0.89
Coronary artery disease	58 (59.8)	69 (59.5)	0.96
Previous cardiac surgery	27 (27.8)	50 (43.1)	0.02
Previous mitral valve surgery	3 (3.1)	9 (7.8)	0.14
Atrial fibrillation	62 (63.9)	61 ± 52.6	0.10
LV end-diastolic diameter, mm	55 ± 9	57 ± 9	0.23
LA volume index, ml/m^2	56 (42-72)	60 (44-83)	0.22
Tricuspid regurgitation			0.12
Grade 0/1	37 (39)	55 (49)	
Grade 2	31 (32.6)	38 (33.9)	
Grade 3/4	27 (28.4)	19 (17.0)	
RV systolic pressure, mm Hg	47 ± 13	44 ± 15	0.19
eGFR, ml/min	40 ± 20	51 ± 19	<0.001
NT-proBNP, ng/l	3,815 (1,946-9,515.25)	2,320 (1,426-5,038)	<0.001
NYHA functional class			<0.01
I or II	5 (5.2)	22 (19.0)	
III or IV	92 (94.8)	94 (81.0)	
6MWD, m	136 (20-217)	306.5 (205.25-373.75)	<0.001
MLWHFQ score	41 ± 15	29 ± 18	<0.001
SF-36			
Physical component score (range 0-100)	30 ± 7	40 ± 8	<0.001
Mental component score (range 0-100)	47 ± 11	51 ± 9	0.009

Values are n (%), mean ± SD, or median (interquartile range). *For comparison of frail and nonfrail patients.

BMI = body mass index; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LA = left atrial; LVEF = left ventricular ejection fraction; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; MR = mitral valve regurgitation; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; RV = right ventricular; SF-36 = Short Form 36; 6MWD = 6-min walking distance.

TABLE 2 Procedural Results

	Frail (n = 97)	Not Frail (n = 116)	p Value*
Deaths before procedure	2	0	
Technical success†	94 (99.0)	110 (94.8)	0.10
Technical success with pre-discharge reduction of MR to ≤2†	84 (88.4)	104 (89.7)	0.78
MitraClip not implanted for technical, morphological, or procedural reason	1 (1.1)	6 (5.2)	0.10
Number of clips implanted‡	1.7 (0.8)	1.6 (0.7)	0.72
Number of clips implanted in primary MR‡	1.5 (0.6)	1.6 (0.7)	
Number of clips implanted in secondary MR‡	1.8 (0.8)	1.7 (0.7)	
Major cardiac structural complications related to access			
Pericardial effusion necessitating pericardiocentesis	1 (1.0)	1 (0.9)	1.00
Major access-related vascular complication			
Vascular surgery at access site	0 (0.0)	1 (0.9)	1.00
Length of hospital stay, days‡	8 (6-12)	7 (5-9)	<0.01
Pre-discharge grade of MR			0.57
0–2	84 (91.3)	106 (93.8)	
3 or 4	8 (8.7)	7 (6.2)	
Discharge to a rehabilitation institution	48 (51.6)	59 (51.8)	0.98

Values are n, n (%). *For comparison of frail and nonfrail patients. †Referring to 211 patients who started the procedure. ‡n (SD) or n (interquartile range).
MR = mitral valve regurgitation.

higher age, a lower rate of previous cardiac surgery, and significantly worse renal function (Table 1). Also, frail patients showed significantly worse functional status at baseline compared with nonfrail patients regarding N-terminal pro-brain natriuretic peptide (NT-proBNP) level, NYHA functional class, 6MWD, SF-36 MCS and PCS, and MLWHFQ score.

TABLE 3 Outcome Parameters at 6 Weeks

	Frail (n = 97)	Not Frail (n = 116)	p Value*
Death	8 (8.3)	2 (1.7)	0.03
Pre-procedural	2	0	
Periprocedural (in-hospital or <30 days)	2	2	
Post-discharge or >30 days	4	0	
Death with cardiovascular cause	6	2	
Stroke	2 (2.1)	2 (1.7)	0.86
Immediate (<24 h)	0	0	
Periprocedural (in-hospital or <30 days)	2	1	
Post-discharge or >30 days	0	1	
Second intervention mitral valve	0 (0.0)	3 (2.6)	0.13
Partial clip detachment	2 (2.1)	3 (2.6)	0.80
Decompensation with rehospitalization	3 (3.1)	3 (2.6)	0.75
Device success	79 (81.4)	98 (84.5)	0.56
Functional outcomes			
Improvement in 6MWD ≥50 m	24/63 (38.0)	32/89 (36.0)	0.79
Improvement in PCS ≥5 points	47/71 (66.2)	47/99 (47.5)	0.02
Improvement in MCS ≥5 points	30/71 (42.2)	34/99 (34.3)	0.29
Improvement in MLWHFQ score ≥−7.5 points	54/71 (76.1)	51/99 (51.5)	0.001

Values are n (%), n, or n/N (%). *For comparison of frail and nonfrail patients.
MCS = mental component score; PCS = physical component score; other abbreviations as in Table 1.

PROCEDURAL RESULTS AND 6-WEEK OUTCOMES. Two patients did not undergo the scheduled PMVR procedure because they died of heart failure before the intervention and were not included in the analysis of technical success.

In 7 of 211 patients (3.3%) undergoing the PMVR procedure, the MitraClip could not be implanted for technical, procedural, or morphological reasons. Two of these patients died during the further hospital stay because of heart failure.

Technical success with reduction of MR to grade 2 or lower and other procedural outcome parameters were similar in frail and nonfrail patients (Table 2). No case of emergency cardiac surgery or procedural death occurred. Two patients with clips implanted died during the index hospital stay, 1 because of a cardiovascular cause not related to heart failure (nonfrail) and 1 because of a noncardiovascular cause (frail). The length of hospital stay was significantly longer in frail compared with nonfrail patients, whereas the rate of discharge to a rehabilitative institution did not differ significantly.

Two hundred two patients were discharged alive with at least one MitraClip implanted. Four frail patients died after discharge within 6 weeks, 3 of heart failure and one of a noncardiovascular cause. Overall mortality at 6 weeks was significantly higher in frail compared with nonfrail patients, whereas device failure, stroke rate, and hospitalization for heart failure decompensation did not differ significantly (Table 3, Figure 2).

The rate of patients with detailed functional assessment at the 6-week follow-up visit, defined by the availability of MLWHFQ data, was 86% (n = 171), mainly because of missed assessment during the visit or language restrictions (Online Figure 1). Available functional assessment was slightly lower in frail (n = 72 [81%]) compared with nonfrail (n = 99 [91%]) patients (p = 0.04). Patients with functional assessment at follow-up did not differ significantly from patients without functional assessment regarding baseline characteristics with the exception of higher body mass index and lower 6MWD (Online Table 1).

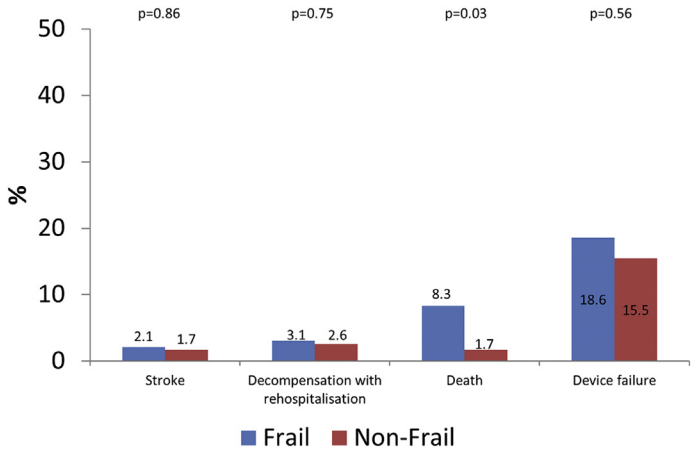
At 6-week follow-up, NT-proBNP levels had decreased by a median of 405 ng/l (IQR: −2,559 to 711 ng/l) in frail patients and by a median of 59 ng/l (IQR: −1,133 to 502 ng/l) in nonfrail patients, without a significant difference between groups (p = 0.27). Functional parameters (NYHA functional class, 6 MWD, MLWHFQ score, and SF-36 MCS and PCS) improved in both frail and nonfrail patients at

follow-up (Figure 3). The magnitude of improvement did not differ significantly between frail and nonfrail patients, with the exception of a significantly enhanced improvement in MLWHFQ score in frail patients. The rate of patients with clinically relevant improvement was similar in frail and nonfrail patients regarding 6MWD and SF-36 MCS and was significantly higher in frail patients for SF-36 PCS and MLWHFQ score (Table 3). The latter association between frailty and relevant improvement in MLWHFQ score remained statistically significant ($p = 0.003$) when adjusting for baseline parameters of heart failure severity (ejection fraction, NYHA functional class, and NT-proBNP).

In sensitivity analysis defining all frail patients without available MLWHFQ scores at follow-up as "not improved" and all nonfrail patients without available MLWHFQ scores at follow-up as "improved," frail and nonfrail patients showed the same rate of clinically relevant improvement (61% vs. 56%; $p = 0.50$). Additional sensitivity analysis was performed to account for the higher mortality in the frail group and the potentially resulting survival bias in functional outcomes. The endpoint of survival at 6 weeks with a relevant improvement in MLWHFQ score was examined in all patients who died or survived with serial MLWHFQ data available (total $n = 181$). Frail patients had a significantly higher rate of survival or relevant improvement in MLWHFQ score (68%) compared with nonfrail patients (50%) ($p = 0.01$).

LONG-TERM FOLLOW-UP. Median follow-up time was 429 days (IQR: 239 to 618 days), with 38 patients (17.8%) deceased since baseline assessment and 36 patients (16.9%) experiencing hospitalization for heart failure decompensation. Frail patients showed significantly lower survival and survival free of heart failure hospitalization compared with nonfrail patients (Figure 4). The estimated 1-year survival rate was 0.80 (95% confidence interval [CI]: 0.70 to 0.87) in frail patients and 0.96 (95% CI: 0.90 to 0.98) in nonfrail patients, and the estimated 1-year event-free survival rate was 0.71 (95% CI: 0.60 to 0.79) in frail patients and 0.85 (95% CI: 0.77 to 0.91) in nonfrail patients. The hazard ratio (HR) of death was 3.06 (95% CI: 1.54 to 6.07; $p = 0.001$), and the HR of death or heart failure hospitalization was 2.03 (95% CI: 1.22 to 3.39; $p = 0.007$), associated with frailty. Frailty remained significantly associated with risk for death (HR: 2.88; 95% CI: 1.45 to 5.73; $p = 0.003$) after adjustment for logistic EuroSCORE and with risk for death or heart failure hospitalization (HR: 1.98; 95% CI: 1.13 to 3.8; $p = 0.02$) after adjustment for logistic EuroSCORE and NT-proBNP level.

FIGURE 2 Outcomes at 6-Week Follow-Up



p value for difference between frail and nonfrail patients.

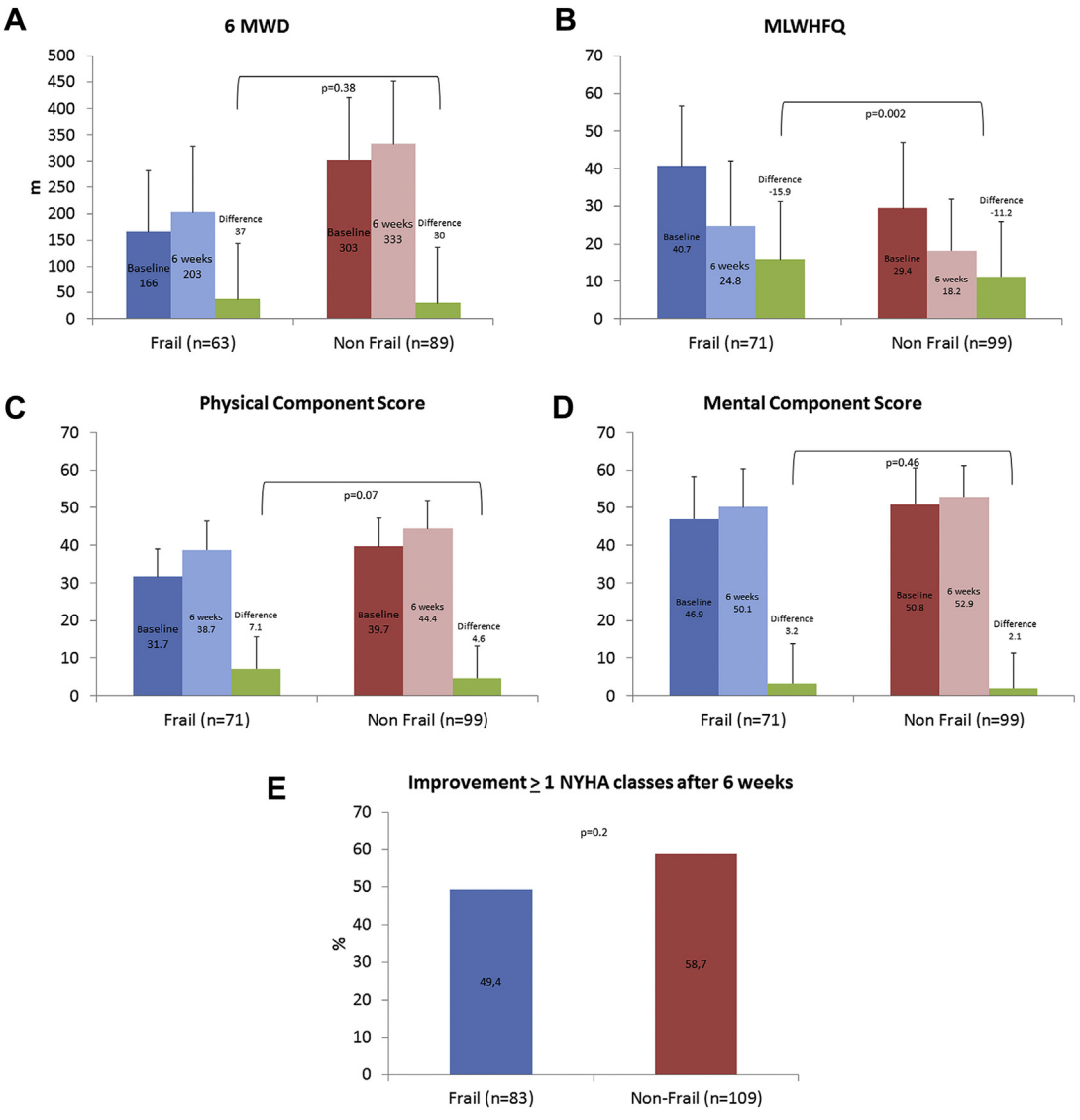
DISCUSSION

This prospective study is the first to examine the prevalence of frailty and its impact on efficacy, safety, functional changes, and long-term outcomes in PMVR.

Frailty diagnosed using the validated Fried criteria was found in 46% of patients, with a total of 94% of patients fulfilling the criteria for pre-frailty and frailty. The number of frail patients undergoing PMVR is 10 times higher than that of patients undergoing conventional cardiac surgery (5) and more than 4 times higher than that of community-dwelling older patients (21), confirming our hypothesis that frailty is a common condition in patients with PMVR that requires further attention.

The components used for the definition of frailty, such as physical exhaustion, slowness, and low physical activity, show marked overlap with characteristics of the heart failure syndrome, which might partly explain the high frailty prevalence in these patients (7). Heart failure might be a distinguished example for the generally established concept that individual morbidity per se can contribute to manifestation of frailty, and distinction as to whether heart failure or morbidity-independent processes drive development of frailty might not be possible. Importantly, we found only a weak or lacking association of frailty with baseline markers of heart failure. Furthermore, associations of frailty with our outcome parameters were independent of baseline heart failure markers, demonstrating that our

FIGURE 3 Changes in Functional Parameters From Baseline to 6 Weeks

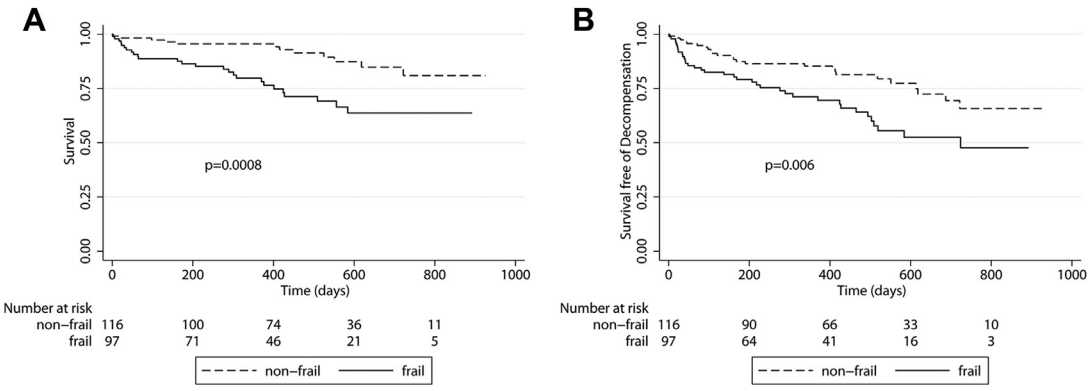


Depicted are baseline, 6-week, and absolute changes (delta) in 6-min walking distance (6MWD) **(A)**, Minnesota Living With Heart Failure Questionnaire (MLWHFQ) score (range 0 to 105; higher scores indicate worse quality of life) **(B)**, physical component **(C)** and mental component **(D)** scores (range 0 to 100; higher scores indicate better physical and mental status), and improvement of ≥1 New York Heart Association functional class at 6 weeks **(E)**. p Value for comparison of absolute changes between frail and nonfrail patients.

frailty measure comprises relevant health dimensions beyond heart failure severity. This is of major relevance when considering frailty a novel independent risk factor in patients undergoing PMVR.

On the basis of existing research on frailty in other cardiovascular interventions, we hypothesized that frailty might be of prognostic relevance in PMVR. Importantly however, technical success, 6-week device success, and immediate procedural adverse events were not significantly different between frail and nonfrail patients. Hence, PMVR can be performed effectively and safely also in frail patients, which is important to know for patients and relatives. Our data extend existing research on the feasibility of PMVR in distinct high-risk patients (22,23). However, our findings must be seen in the context of a very experienced team of operators, and immediate procedural results might differ between frail and nonfrail patients at less experienced centers. We observed significantly longer hospital stays in frail patients,

FIGURE 4 Kaplan-Meier Survival Plots for Mortality and Mortality or Heart Failure Hospitalization by Baseline Frailty Status



(A) Survival and **(B)** heart failure hospitalization free survival in frail and nonfrail patients; p value by log-rank test.

suggesting a prolonged recovery time or a higher rate of minor complications. However, this must be interpreted cautiously given that issues specific to national health care systems might determine length of hospital stay; for instance, in the United States, the duration of hospitalization after PMVR is less than one-half of that in Germany (24).

A major finding of this study is that frailty is a strong risk factor for adverse mid- to long-term outcomes in patients undergoing PMVR, with a 3-fold increased hazard of death and a 2-fold increased hazard of death or heart failure hospitalization. Importantly, the association of frailty with adverse outcomes was independent of logistic EuroSCORE and NT-proBNP as a marker of heart failure severity. These findings are of major relevance in showing that frailty, not only is a strong prognostic marker in patients undergoing PMVR, but provides additional, complementary information beyond traditional risk factors. This is of particular interest in the setting of PMVR, because there is a lack of validated risk scores, and the logistic EuroSCORE has only limited predictive value in these patients (25).

A further important finding of our study is that frail patients showed at least similar, and with regard to heart failure-associated symptoms, even enhanced, improvement in functional status after PMVR compared with nonfrail patients. Also, the rate of clinically relevant improvement of SF-36 PCS and MLWHFQ score was significantly higher in frail compared with nonfrail patients. This is of particular relevance for the informed treatment decision of patients, because it was unclear whether treatment of MR, which in this context is only 1 contributor to the complex frailty syndrome, might be able to improve the functional status of frail patients. However, despite the substantial functional improvement in frail patients after PMVR, the absolute levels of functional parameters were still lower in frail compared with nonfrail patients at 6 weeks, suggesting a persisting pathophysiological impact of frailty independently of MR.

STUDY LIMITATIONS. This was a monocentric study including patients from a high-volume referral center for interventional mitral valve therapy. Thus, more severely ill and compromised patients might have been included in our cohort compared with overall patients undergoing PMVR, which could lead to an overestimation of frailty prevalence. However, when considering usual markers of morbidity such as age, EuroSCORE, and cardiovascular comorbidity, as well as long-term outcomes, our cohort is comparable with recently published real-world registries of patients with PMVR (24,26-28). Nonetheless, confirmation of our estimates in an even larger multicenter cohort would strengthen the level of evidence to include frailty measures in guideline recommendations. Furthermore, frail patients more frequently had missing follow-up data on functional parameters. This was due partly to the higher death rate but also to difficulties to attend the follow-up survey because of long distance to hospital or dependency in traveling. Although patients without follow-up data had shorter 6MWDs compared with those with follow-up data, particularly MLWHFQ score did not differ at baseline between patients with and without follow-up data

available. Hence, we consider the risk for effect overestimation in frail patients resulting from selection bias to be low. Assuming a worst-case scenario with all frail patients with missing MLWHFQ scores having "not improved" and all nonfrail patients with missing MLWHFQ scores having "improved," frail and nonfrail patients at least showed the same rate of clinically relevant improvement at 6 weeks. Additionally, sensitivity analysis examining a combined endpoint of survival and clinically relevant improvement in MLWHFQ score still showed a better result for frail patients, suggesting no evidence for relevant survival bias.

CONCLUSIONS

Our data provide the first evidence that a validated diagnosis of frailty is common in patients undergoing PMVR and contributes important information regarding procedural safety and efficacy, functional short-term changes, and long-term outcomes in frail patients. Although frail patients are more likely to die after MitraClip implantation compared with nonfrail patients, our data demonstrate that frailty does not affect the procedural success and safety of MitraClip implantation and that frail patients derive at least as much benefit in functional status and quality of life as nonfrail patients. These results support the continued use of the MitraClip in frail elderly patients, in whom the goal is palliation of heart failure symptoms and improvement in quality of life.

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PERSPECTIVES

WHAT IS KNOWN? The risk-benefit assessment is insufficiently defined in patients undergoing interventional valve therapy such as PMVR. Frailty is common in elderly patients and in those with comorbidities and affects outcome and functionality.

WHAT IS NEW? Frailty assessed by a validated score is a strong prognostic marker with additive information compared with traditional risk markers in patients undergoing PMVR. The procedure itself can be performed equally safely and effectively, and functional short-term benefit is similar in frail patients.

WHAT IS NEXT? Objective measures of frailty might be assessed in patients eligible for mitral valve repair as a basis for individualized treatment decision making. Additional research is warranted to examine to impact of individual domains of frailty and distinct frailty assessments to further optimize patient selection and maximize outcomes.

REFERENCES

1. De Bonis M, Al-Attar N, Antunes M, et al. Surgical and interventional management of mitral valve regurgitation: a position statement from the European Society of Cardiology Working Groups on Cardiovascular Surgery and Valvular Heart Disease. Eur Heart J 2016;37:133–9.

2. Papachristofi O, Mackay JH, Powell SJ, Nashef SA, Sharples L. Impact of the anesthesiologist and surgeon on cardiac surgical outcomes. J Cardiothorac Vasc Anesth 2014;28:103–9.

3. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2438–88.

4. Strandberg TE, Pitkala KH. Frailty in elderly people. Lancet 2007;369:1328–9.

5. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation 2010;121:973–8.

6. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. J Am Coll Cardiol Intv 2012;5:974–81.

7. Vidan MT, Blaya-Novakova V, Sanchez E, Ortiz J, Serra-Rexach JA, Bueno H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. Eur J Heart Fail 2016;18:869–75.

8. Uchmanowicz I, Gobbens RJ. The relationship between frailty, anxiety and depression, and health-related quality of life in elderly patients with heart failure. Clin Interv Aging 2015;10:1595–600.

9. Gharacholou SM, Roger VL, Lennon RJ, et al. Comparison of frail patients versus nonfrail patients >= 65 years of age undergoing percutaneous coronary intervention. Am J Cardiol 2012;109:1569–75.

10. Schoenenberger AW, Stortecky S, Moser A, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). Eur Heart J 2012;33:587.

11. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012) The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Rev Esp Cardiol 2013;66:E1–42.

12. Boekstegers P, Hausleiter J, Baldus S, et al. Percutaneous interventional mitral regurgitation treatment using the Mitra-Clip system. Clin Res Cardiol 2014;103:85–96.

13. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–70.

14. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living With Heart Failure Questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled

trial of pimobendan. Pimobendan Multicenter Research Group. Am Heart J 1992;124:1017–25.

15. Lim DS, Reynolds MR, Feldman T, et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair. J Am Coll Cardiol 2014;64:182–92.

16. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1–44.

17. Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.

18. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.

19. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56.

20. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. Eur Heart J 2015;36:1878–91.

21. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012;60:1487–92.

22. Matsumoto T, Nakamura M, Yeow WL, et al. Impact of pulmonary hypertension on outcomes in patients with functional mitral regurgitation undergoing percutaneous edge-to-edge repair. Am J Cardiol 2014;114:1735–9.

23. Glower DD, Kar S, Trento A, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. J Am Coll Cardiol 2014;64:172–81.

24. Sorajja P, Mack M, Vemulapalli S, et al. Initial experience with commercial transcatheter mitral valve repair in the United States. J Am Coll Cardiol 2016;67:1129–40.

25. Triantafyllis AS, Kortlandt F, Bakker AL, et al. Long-term survival and preprocedural predictors of mortality in high surgical risk patients undergoing percutaneous mitral valve repair. Catheter Cardiovasc Interv 2016;87:467–75.

26. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol 2013;62:1052–61.

27. Puls M, Lubos E, Boekstegers P, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. Eur Heart J 2016;37:703–12.

28. Nickenig G, Estevez-Loureiro R, Franzen O, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011–2012 Pilot European Sentinel Registry. J Am Coll Cardiol 2014;64:875–84.

KEY WORDS frailty, MitraClip, percutaneous edge-to-edge mitral valve repair, quality of life

APPENDIX For a supplemental table and figure, please see the online version of this article.