# Invasive hemodynamics and cardiac biomarkers to predict outcomes after percutaneous edge-to-edge mitral valve repair in patients with severe heart failure

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## Abstract

**Background** Percutaneous mitral valve repair (PMVR) via MitraClip implantation is a therapeutic option for high-risk or non-surgical candidates with severe mitral regurgitation (MR) and advanced stages of heart failure (HF). However, these patients have a high mortality despite PMVR, and predictors for outcomes are not well established. Here, we evaluated invasive hemodynamics, echocardiography parameters, and biomarkers to predict outcomes after PMVR in severe HF patients.

**Methods** Patients with reduced ejection fraction (EF) and severe and moderate-to-severe MR undergoing PMVR at our centre between September 2009 and January 2016 were analysed retrospectively. Inclusion criteria were: left ventricular EF < 45%, preoperative right heart catheterization, successful MitraClip deployment ("technical success"), and follow-up for at least 1 year after the procedure. Data from preoperative right heart catheterization, echocardiography, and biomarkers were assessed. Primary endpoint was all-cause mortality at 1 year after PMVR. We performed univariate and multivariate Cox regression analyses and generated a risk score to predict outcomes.

**Results** Of 174 patients with PMVR and severe HF, 79.9% had functional MR. Mean EF was 25% (17.2; 30.7) and advanced New York Heart Association functional class was prevalent (class II: 13%; class III: 70%; and class IV: 17%). The cumulative incidences of all-cause death were 6.9% and 17.8% at 30 days and 1 year, respectively. In the Cox multivariate model, high-sensitive troponin T [hsTnT; hazard ratio (HR) 1.01; confidence interval (CI) 1.01–1.02; $p < 0.0001$] and mixed venous $O_2$-saturation (HR 0.92; CI 0.89–0.96; $p < 0.0001$) were found to significantly and independently predict outcomes. A simple risk score including these two parameters was sufficient to discriminate between low- and high-risk patients (HR 7.22; CI 3.4–15.5; $p < 0.001$).

**Conclusion** In a cohort of patients with severe HF undergoing PMVR, patients with elevated hsTnT and reduced mixed venous $O_2$-saturation carried the worst prognosis. A simple risk score including these two parameters may improve patient selection and outcomes after PMVR.

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## Introduction

In recent years, edge-to-edge percutaneous mitral valve repair (PMVR) via MitraClip (Abbott Vascular, North Chicago, Illinois, USA) implantation has emerged as a therapeutic option for patients with severe mitral regurgitation (MR) and high surgical risk or judged as inoperable [1–5]. Recently, the first randomized controlled study, the Endovascular Valve Edge-to Edge Repair Study (EVEREST II), demonstrated that PMVR has a superior safety compared to surgical mitral valve repair and similarly improves clinical outcomes despite inferior clinical efficacy [2]. Although the EVEREST patient cohort had low-to-moderate surgical risk, older patients with multiple comorbidities and heart failure (HF) are thought to be particularly eligible for non-surgical techniques [6–8]. Of particular high risk for surgical operations are patients with advanced stages of HF, who often display severe MR [9–11]. However, patients with severe HF have a high mortality with or without PMVR, and predictors for outcomes after PMVR in these patients are not well established [3, 12]. Here, we evaluated invasive hemodynamics, echocardiography parameters, and cardiac biomarkers to predict outcomes after PMVR in a single-centre cohort of severe HF patients, consequently generating a risk score aiming to improve future patient selection prior MitraClip implantation in patients with severe HF.

## Methods

The study conforms with the principles outlined in the *Declaration of Helsinki* [13]. The study was performed in a retrospective approach. The medical decision for MitraClip implantation was provided by cardiologists and cardiac surgeons in the heart team [14, 15]. All patients were informed about specific risks and alternatives of MitraClip therapy, as well as the options for continued medical treatment and high-risk surgical mitral valve repair and gave informed written consent to the procedure. The study protocol was in accordance with the local ethics committee.

### Patient population

From September 2009 to January 2016, 339 consecutive high surgical risk or non-surgical candidates with severe and moderate-to-severe symptomatic MR were treated with the MitraClip device at our institution. Of these, only patients with complete invasive hemodynamic workup with right heart catheterization and moderate-to-severely reduced left ventricular (LV) function [ejection fraction (EF) < 45%], successful MitraClip deployment (technical success), and follow-up until death or for at least 1 year after the procedure were included in the present analysis ($n = 174$; Fig. 1). All patients were on stable (at least 4 months) optimized individual target HF medication and were treated with percutaneous coronary angioplasty and stent implantation,

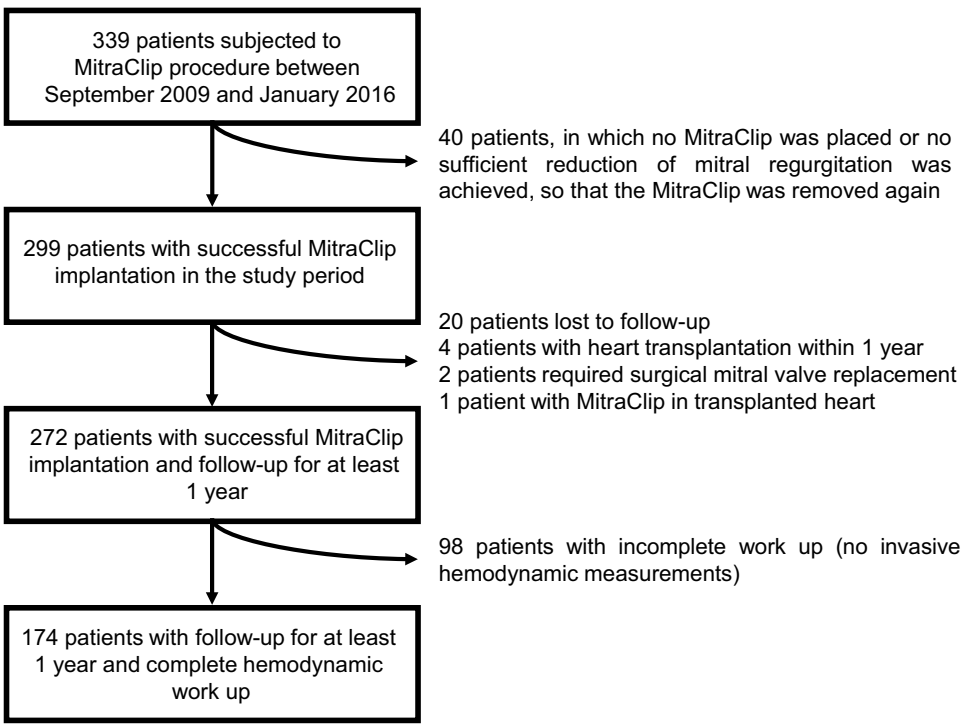


**Fig. 1** Study protocol. Flow chart indicating reasons for exclusion of patients from the study. Only patients with successful MitraClip deployment ("technical success"), follow-up until death or for at least 1 year and complete hemodynamic assessment were included in the study

implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy (CRT) devices prior MitraClip implantation, if applicable. All patients met the following inclusion criteria: (1) severe or moderate-to-severe MR; (2) dyspnoea New York Heart Association (NYHA) functional classes II–IV; and (3) reduced LV function. Patients either presented LVEF < 30% or an LVEF between 30 and 45% combined with a high estimated surgical risk documented by Society of Thoracic Surgeon's (STS) score, logistic EuroSCORE, and EuroSCORE II. The main exclusion criteria were morphological properties of the mitral valve that would make successful MitraClip implantation unlikely or impossible, as published previously [16].

## Pre-interventional workup

Pre-interventional workup included the patient's medical history, careful clinical assessment, determining NYHA class, and a 6-min walk test (6-MWT) [17]. Furthermore, complete laboratory workup including high-sensitive troponin T (hsTnT), N-terminal-pro-brain-natriuretic peptide (NT-proBNP), and serum creatinine was done in all patients [18]. Glomerular filtration rate (GFR) was calculated using the MDRD (Modification of Diet in Renal Disease) formula. Mitral regurgitation and mitral valve morphology were determined by transthoracic and transoesophageal echocardiography (TTE and TEE), performed and assessed by an experienced examiner unaware of the study [9, 19, 20]. LVEF was estimated using the Simpson biplane method and right atrial (RA) pressure was estimated by the diameter of the inferior vena cava and its variability during inspiration as described before [21–23]. MR was graded according to the American Society of Echocardiography guidelines [24]. Since the prevalence of restrictive leaflet motion and eccentric MR in the study population was high, the method of the proximal isovelocity surface area (PISA) for grading of MR was not employed. Effective regurgitation orifice area (EROA) or regurgitation volume quantifying techniques underestimate the severity of MR in highly eccentric jets of mitral valve regurgitation [25] and may be inappropriate for patients with functional MR [26]. This lack of quantitative MR data may be limiting; however, MR was graded according to current guidelines [24, 27] in a semi-quantitative manner with colour Doppler and assessment of the width of the vena contracta instead. Moreover, severity of MR was quantified in each patient by invasive measurements in the cathlab using LV angiogram, pulmonary artery (PA) pressure and v-wave. Right heart catheterizations via a femoral venous approach were performed in all included patients in a stable and compensated condition before MitraClip implantation to determine cardiac index, PA pressures and resistance and mixed venous $O_2$-saturation (mixed $SO_2$). Cardiac index was determined by saturation measurement according to the Fick principle. Pulmonary artery pressures, pulmonary capillary wedge pressure (PCWP), and right ventricular (RV) and RA pressures were measured during breath hold in baseline over at least three heart cycles [28, 29]. Mean pulmonary artery pressure was calculated by integration of the pressure curve by the Metek software (Metek GmbH, Roetgen, Germany). Pulmonary artery resistance was derived from pulmonary artery resistance = (mean PA pressure − PCWP)/cardiac output. All shown data were taken from the latest available visit for each patient before MitraClip implantation.

## MitraClip implantation procedure and follow-up

MitraClip procedures were performed under general anaesthesia [30–32]—monitored by a cardiac anaesthesiologist—and were guided by TEE and fluoroscopy in the cardiac catheterization laboratory, as previously described [33]. In brief, MitraClip system was introduced into the left atrium via transseptal puncture and steered until it was aligned over the origin of the regurgitant jet and advanced into the LV. The mitral leaflets were grasped, and the device was closed to approximate the leaflets. Grading criteria for postprocedural MR were adapted from Foster et al. [34]. Applied parameters comprised colour flow Doppler jet characteristics and pulmonary vein flow patterns as well as vena contracta width. Once the resulting MR reduction was deemed satisfactory, the clip was deployed. A second clip was placed if the reduction of MR was inadequate. Intraprocedural anticoagulation with heparin was adjusted to an activated clotting time (ACT) of 250–300 s. Access site closure was achieved by applying one ProGlide SH closure device (Abbott Vascular, North Chicago, IL, USA) using the preclosure technique. All patients received prophylactic antibiotic therapy for 3 days after MitraClip implantation. Patients were transferred to our intensive care, coronary care or advanced heart failure unit after the procedure (for at least 24 h). Post procedure, patients were seen in our outpatient clinic at 1, 6, and 12 months after PMVR. Study endpoint was defined as death from cardiovascular or non-cardiovascular cause. Technical, device, and procedural success were defined according to the Mitral Valve Academic Research Consortium (MVARC) [35] (for details, see Suppl. Table).

## Statistical methods

Continuous data are expressed as median values and 25% and 75% percentiles (Q1; Q3). Categorical variables are expressed as absolute numbers and percentages. Baseline characteristics were compared between groups using the Mann–Whitney test for quantitative variables and the Chi-square test for qualitative variables. Survival data were summarized by Kaplan–Meier survival curves and unadjusted survival rates were compared using the log-rank

test. Multivariable Cox regression using stepwise forward selection was performed to analyse the influence of relevant variables on 1-year (all-cause) mortality. Effects that proved to be statistically significant in univariable analysis were further subjected to multivariable Cox regression analysis. Optimal cut-off values for hsTnT and mixed $SO_2$ were determined using a freely available online tool (Cutoff Finder; http://molpath.charite.de/cutoff) [36]. It offers five methods for cut-off determination from which we chose significance of correlation with survival variable. The optimal cutoff is defined as the point with the most significant log-rank test split. As a complementary method, ROC (receiver operating characteristic) curve analysis was performed using SPSS. Proportion between hsTnT, mixed $SO_2$, and post-interventional MR grade was analysed by logistic regression. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS statistical software package (SPSS Inc., IBM company, Chicago, IL, USA) and GraphPad Prism (GraphPad Software, La Jolla, CA, USA).

## Results

### Patient population and procedural outcomes

From September 2009 to the end of January 2016 (study period), a total of 339 patients underwent MitraClip procedure (including demanding anatomies outside the EVEREST criteria [16] very early on). In 40 of these patients (11.8%), no MitraClip was placed or no sufficient MR reduction was achieved, so that the MitraClip was removed again (technical success at our centre 88.2%). As technical success was an inclusion criterion for the present study, in all patients, the deployment of the clip was successful ($n = 174$; technical success 100%; see Fig. 1 and Suppl. Table). Device success was 94.3% and procedural success was 90.2% according to MVARC [35]. Procedural data are summarized in the Suppl. Table. Demographic and clinical characteristics of the 174 included patients are given in detail in Table 1. All patients were highly symptomatic with a median walking distance in the 6-MWT of only 305 m (210; 417) and with a median NYHA class of 2.96 ($\pm 0.5$; class II: 13%; class III: 70%; and class IV: 17%), pointing to overall severe HF in these patients. One-year follow-up was completed by 143 patients (82.2%); 31 patients (17.8%) died within 1 year after MitraClip implantation. Short-term mortality at 30 days after PMVR was 6.9% (12 patients).

### Pre-procedural echocardiographic and hemodynamic assessment

Careful assessment of standard echocardiographic parameters was performed in all patients prior MitraClip implantation (Table 2). Of these, LV end diastolic and systolic diameters (LVESD, LVEDD) as well as highly impaired LVEF [25% (17.2; 30.1)] constrain a severely impaired LV function in patients undergoing PMVR. Furthermore, RV function was highly decreased as shown by reduced longitudinal RV shortening [tricuspid annular plane systolic excursion (TAPSE); 1.32 cm (1.0; 1.6)] and enlarged RV and right atrium (RA) (see Table 2). All patients who were analysed in the present study underwent invasive hemodynamic assessment before MitraClip implantation (Table 3). Severe hemodynamic impairment was documented by elevated RA pressure, systolic RV pressure, mean PA pressure, and PCWP. Moreover, cardiac index [2.07 l/min/$m^2$ (1.75; 2.40)] and mixed $SO_2$ [59% (52; 62)] were markedly reduced.

### Cardiac biomarkers and renal function

Kidney function was reduced to a median GFR of 60.4 ml/min (44.3; 74.5), measured by the MDRD formula. As cardiac biomarkers, hsTnT as well as NT-proBNP were measured. Whereas hsTnT was only slightly elevated (reference < 14 pg/ml; 14–50 pg/ml observational zone; >50 pg/ml elevated) with a median of 29 pg/ml (17.7; 49.2), NT-proBNP was markedly increased [4504 ng/l (1625; 10,725)], reflecting severe HF in these patients. Other potential biomarkers for HF were not tested in the present study [37–41].

### Univariate analysis of predictors of mortality

To identify baseline risk factors for 1-year mortality, preoperatively assessed parameters from right heart catheterization and echocardiography, as well as clinical characteristics and lab parameters were compared between patients who died within 1 year after PMVR and those who did not (Tables 1, 2, 3, 4). In these univariate analyses, we found the absence of arterial hypertension (lower blood pressure, possibly as an indicator of more advanced HF) and higher NYHA functional class to be associated with 1-year mortality, pointing to a more advanced HF in patients who died within 1 year (Table 1). Although cardiac indices were not significantly reduced in non-survivors, mixed $SO_2$ was markedly lowered [59% (53; 64) vs. 51% (45; 60); $p = 0.002$; Table 3]. Moreover, the cardiac biomarkers NT-proBNP and hsTnT were strikingly increased in the non-survivor group (Table 4). Of note, there was a trend towards younger age in the patients who did not survive 1 year after PMVR. Comorbidities as coronary artery disease, diabetes or history of stroke were not significantly different, only kidney function was reduced in the non-survivor group (Table 4). Other risk factors validated in different PMVR cohorts by others, as such as right ventricular function (TAPSE) or atrial fibrillation were not significantly altered between survivors and non-survivors in our

**Table 1** Patients' characteristics

| | Total ($n=174$) | Survivors ($n=143$) | Non-survivors ($n=31$) | $p$ value | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| Age at implantation (a) | 75.2 (64.9; 81.0) | 76.9 (66.2; 82.3) | 69.0 (59.8; 77.7) | 0.083 | 0.978 (0.954/1.003) |
| Sex | | | | | |
| Male | 121 (69.5%) | 101 (70.6%) | 20 (64.5%) | 0.536 | 1.261 (0.604/2.633) |
| Female | 53 (30.5%) | 42 (29.4%) | 11 (35.5%) | | |
| NYHA class (I–IV) | 2.96 (SD ± 0.50) | 2.9 (SD ± 0.48) | 3.23 (SD ± 0.53) | **0.001*** | 3.525 (1.622/7.662) |
| 6-MWT (m) | 305 (210; 417) | 306 (277; 362) | 302 (200.5; 421) | 0.887 | 1,000 (0.996/1.004) |
| STS score (%) | 14.7 (6.2; 22.7) | 14.7 (6.2; 22.5) | 13.5 (6.2; 25.5) | 0.381 | 1.014 (0.983/1.045) |
| Log. EuroSCORE (%) | 24.4 (15.4; 37.6) | 23.8 (14.3; 37.0) | 24.8 (20.5; 42.5) | 0.311 | 1.009 (0.992/1.027) |
| EuroSCORE II (%) | 5.7 (3.8; 11.6) | 5.4 (3.6; 11.2) | 7.3 (4.7; 13.6) | 0.184 | 1.024 (0.998/1.061) |
| Etiology of MR | | | | | 1.836 (0.643/5.255) |
| Degenerative | 35 (20.1%) | 31 (21.7%) | 4 (12.9%) | 0.256 | |
| Functional | 139 (79.9%) | 112 (78.3%) | 27 (87.1%) | | |
| Functional MR[a] | | | | 0.6422 | 0.83 (0.379/1.819) |
| DCMP | 65 (48.5%) | 52 (47.7%) | 13 (52%) | | |
| ICMP | 69 (51.5%) | 57 (52.3%) | 12 (48%) | | |
| Device therapy | | | | | |
| Pacemaker | 10 (5.7%) | 10 (7%) | | | |
| ICD | 39 (22.4%) | 29 (20.3%) | 10 (32.3%) | 0.077 | 1.276 (0.974/1.673) |
| CRT | 22 (12.5%) | 15 (10.5%) | 7 (22.6%) | **0.040*** | 1.609 (0.449/2.051) |
| Heart failure medication | | | | | |
| Betablocker | 150 (86.0%) | 125 (87.4%) | 25 (80.6%) | 0.817 | 1.186 (0.281/5.006) |
| ACE-I/ARB | 146 (83.9%) | 122 (85.3%) | 24 (77.4%) | 0.951 | 1.039 (0.313/3.449) |
| Aldosterone-antagonist | 94 (54.0%) | 79 (55.2%) | 15 (48.4%) | 0.916 | 0.960 (0.697/1.538) |
| CAD | | | | 0.256 | 0.749 (0.455/1.234) |
| No CAD | 17 (9.8%) | 11 (7.7%) | 6 (19.4%) | | |
| CAD—not significant | 57 (32.8%) | 49 (34.3%) | 8 (25.8%) | | |
| CAD—significant | 100 (57.5%) | 83 (58.0%) | 17 (54.8%) | | |
| Atrial fibrillation | | | | 0.864 | 1.035 (0.697/1.538) |
| No AF | 75 (43.1%) | 62 (43.4%) | 13 (41.9%) | | |
| Paroxysmal AF | 36 (20.7%) | 30 (21.0%) | 6 (19.4%) | | |
| Permanent AF | 63 (36.2%) | 51 (35.7%) | 12 (38.7%) | | |
| Hypertension | 131 (75.3%) | 112 (78.3%) | 19 (61.3%) | **0.049*** | 0.484 (0.235/0.998) |
| Hyperlipidemia | 99 (56.9%) | 84 (58.7%) | 15 (48.4%) | 0.306 | 0.692 (0.342/1.400) |
| Diabetes mellitus | 51 (29.3%) | 41 (28.7%) | 21 (67.7%) | 0.689 | 1.166 (0.549/2.477) |
| Stroke | 24 (13.8%) | 17 (11.9%) | 7 (22.6%) | 0.155 | 1.843 (0.794/4.278) |
| COPD | 33 (19.0%) | 28 (19.6%) | 5 (16.1%) | 0.656 | 0.804 (0.309/1.095) |
| Malignant disease | 18 (10.3%) | 15 (10.5%) | 3 (9.7%) | 0.852 | 0.893 (0.272/2.938) |

All data were taken from before MitraClip implantation and follow-up was performed for 1 year after MitraClip. Patients were separated in patients who survived the first year after the procedure (survivors) and patients who did not survive 1 year after MitraClip implantation (non-survivors). Data are given as median (25–75 percentiles) or absolute number (%). Univariate analysis was performed using Cox regression

*NYHA* New York Heart Association, *6-MWT* 6-min walk test, *STS* Society of Thoracic Surgeons, *MR* mitral regurgitation, *DCMP* dilative cardiomyopathy, *ICMP* ischemic cardiomyopathy, *ICD* implantable cardioverter/defibrillator, *CRT* cardiac resynchronization therapy, *ACE-I* angiotensin conversing enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CAD* coronary artery disease, *AF* atrial fibrillation, *COPD* chronic obstructive pulmonary disease

*Bold text represents $p$ values $<0.05$. Hazard ratio is given as 95% confidence interval (CI)

[a]Five patients were classified as "mixed etiology/other"

patient cohort. Whereas number of implanted clips was not different between survivors and non-survivors (one single clip was sufficient in 69.9% (survivors) vs. 67.7% (non-survivors); $p=0.765$, [hazard ratio (HR) 1.122], we could confirm data from others [42] that residual MR grade after the procedure is important for outcome [1.2 (1; 1.5) (survivors) vs. 1.5 (1; 2) (non-survivors); HR 1.831; $p=0.033$].

**Table 2** Data assessed by echocardiography

| | Total ($n=174$) | Survivors ($n=143$) | Non- survivors ($n=31$) | $p$ value | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| LA diameter (mm) | 49 (46; 54) | 49 (46; 54) | 49 (46; 55) | 0.79 | 1.008 (0.953/1.065) |
| LVESD (mm) | 47.5 (36; 58) | 47 (36; 57) | 51.5 (41.75; 64.25) | **0.029*** | 1.030 (1.003/1.057) |
| LVEDD (mm) | 59 (51; 67) | 59 (51; 67) | 60 (50; 68) | 0.494 | 1.012 (0.979/1.045) |
| EF (%) | 25 (17.25; 30.75) | 25 (18.75; 30.75) | 24.5 (15.75; 36.75) | 0.837 | 1.004 (0.964/1.046) |
| MR (I.–III. grade) | 2.76 (SD ± 0.39) | 2.76 (SD ± 0.32) | 2.76 (SD ± 0.40) | 0.960 | 0.976 (0.372/2.557) |
| RA area (cm) | 20.9 (16.4; 25.65) | 20.45 (16.4; 25.6) | 21.6 (17.1; 27.6) | 0.974 | 1.001 (0.956/1.048) |
| TAPSE (cm) | 1.32 (1; 1.61) | 1.3 (1; 1.62) | 1.4 (0.86; 1.6) | 0.891 | 0.947 (0.432/2.077) |
| RV factor (mm) | 33.21 (23.65; 38.72) | 33.44 (23.99; 38.24) | 32.43 (19.41; 39.64) | 0.721 | 0.994 (0.961/1.028) |
| RV diameter (mm) | 42 (37.58; 47.5) | 42.5 (37.5; 47.5) | 44.3 (37.7; 47.5) | 0.757 | 1.007 (0.961/1.056) |
| RAP (mmHg) | 10 (5; 15) | 10 (5; 15) | 15 (10; 20) | **0.045*** | 1.063 (1.001/1.129) |
| sPA pressure (mmHg) | 52.5 (43; 62) | 53 (43; 60) | 50 (43; 66.5) | 0.885 | 1.003 (0.975/1.032) |
| Vena cava diameter (mm) | 21 (18; 26) | 20 (18; 25.25) | 23 (18.75; 26) | 0.153 | 1.052 (0.981/1.128) |
| Vena cava variability | | | | 0.079 | 0.460 (0.194/1.095) |
| No | 84 (48.3%) | 65 (45.5%) | 19 (61.3%) | | |
| Yes | 65 (37.4%) | 58 (40.6%) | 7 (22.6%) | | |
| N/A | 25 (14.4%) | 20 (14.0%) | 5 (16.1%) | | |
| TR (I.–III. grade) | 1.74 (SD ± 0.76) | 1.7 (SD ± 0.75) | 1.92 (SD ± 0.77) | 0.212 | 1.405 (0.823/2.396) |

All data were taken from before MitraClip implantation and follow-up was performed for 1 year after MitraClip. Patients were separated in patients who survived the first year after the procedure (survivors) and patients who did not survive 1 year after MitraClip implantation (non-survivors). Data are given as median (25–75 percentiles) or absolute number (%). Univariate analysis was performed using Cox regression

*LA* left atrium, *LVESD* left ventricular end systolic diameter, *LVEDD* left ventricular end systolic diameter, *EF* ejection fraction, *MR* mitral regurgitation, *RA* right atrium, *TAPSE* tricuspid annular plane systolic excursion, *RV* right ventricle, *RAP* right atrial pressure, *sPA* systolic pulmonary artery, *TR* tricuspid regurgitation

*Bold text represents $p$ values $<0.05$. Hazard ratio is given as 95% confidence interval (CI)

**Table 3** Invasive hemodynamic data

| | Total ($n=174$) | Survivors ($n=143$) | Non- survivors ($n=31$) | $p$ value | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| Cardiac index (l/min/m$^2$) | 2.07 (1.75; 2.4) | 2.07 (1.77; 2.4) | 2.1 (1.67; 2.3) | 0.999 | 0.999 (0.559/1.788) |
| Cardiac output (l/min) | 3.8 (3.1; 4.8) | 3.9 (3.2; 4.8) | 3.5 (2.8; 4.6) | 0.531 | 0.901 (0.651/1.248) |
| Mixed $SO_2$ (%) | 59 (52; 64) | 59 (53; 64) | 51.5 (45; 60) | **0.002*** | 0.947 (0.915/0.980) |
| mPA pressure (mmHg) | 36 (30; 42) | 35 (28; 42) | 40 (35; 45) | 0.176 | 1.027 (0.988/1.067) |
| RA pressure (mmHg) | 11 (8; 15) | 11 (8; 14) | 13 (10; 18) | **0.031*** | 1.083 (1.007/1.164) |
| sRV pressure (mmHg) | 55 (45; 65) | 55 (43; 65) | 60 (50; 65) | 0.191 | 1.017 (0.991/1.044) |
| dRV pressure (mmHg) | 12 (8; 16) | 12 (8; 16) | 14 (10; 19) | 0.052 | 1.077 (1.001/1.160) |
| PCWP (mmHg) | 25 (19; 30) | 25 (19; 30) | 26 (22; 30) | 0.253 | 1.023 (0.984/1.064) |
| TPG (mmHg) | 10 (8; 14) | 10 (8; 14) | 10 (7; 15) | 0.807 | 1.006 (0.958/1.057) |
| PAR (dyn × s × cm$^{-5}$) | 230 (152; 323) | 213.5 (150; 328.5) | 257.5 (168; 317) | 0.977 | 1.000 (0.998/1.002) |

All data were taken from before MitraClip implantation and follow-up was performed for 1 year after MitraClip. Patients were separated in patients who survived the first year after the procedure (survivors) and patients who did not survive 1 year after MitraClip implantation (non-survivors). Data are given as median (25–75 percentiles) or absolute number (%). Univariate analysis was performed using Cox regression

*Mixed $SO_2$* mixed venous $O_2$-saturation, *mPA* mean pulmonary artery, *RA* right atrium, *sRV* end-systolic right ventricular, *dRV* end-diastolic right ventricular, *PCWP* pulmonary capillary wedge pressure, *TPG* transpulmonary gradient, *PAR* pulmonary artery resistance

*Bold text represents $p$ values $<0.05$. Hazard ratio is given as 95% confidence interval (CI)

## Multivariate analysis of predictors of mortality

Parameters that proved to be statistically significant in univariate analysis were further subjected to Cox proportional hazards analysis. Tested parameters were: LVESD, NYHA class, renal function, NT-proBNP, hsTnT, RA pressure measured by catheter and mixed $SO_2$. In this analysis, the best predictors of all-cause mortality at 1 year were hsTnT ($p=0.001$; HR 1.012; Fig. 2) and mixed $SO_2$ ($p=0.008$; HR 0.945; Fig. 3). When procedural data that

**Table 4** Renal function and cardiac biomarkers

| | Total ($n=174$) | Survivors ($n=143$) | Non-survivors ($n=31$) | $p$ value | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| Creatinine (mg/dl) | 1.17 (0.9; 1.55) | 1.15 (0.89; 1.51) | 1.31 (1.05; 1.95) | 0.1 | 1.192 (0.967/1.469) |
| GFR (ml/min) | 60.42 (44.35; 74.49) | 62.83 (45.52; 76.08) | 50.56 (32.77; 62.57) | **0.027*** | 0.983 (0.969/0.998) |
| hsTnT (pg/ml) | 29 (17.75; 49.25) | 25 (16; 43) | 76 (30; 110) | **<0.001*** | 1.01 (1.006/1.013) |
| NT-proBNP (ng/l) | 4504 (1625; 10,725) | 3507 (1472; 8725) | 8775 (5298; 18,103) | **0.002*** | 1.011 (1.004/1.017) |

All data were taken from before MitraClip implantation and follow-up was performed for 1 year after MitraClip. Patients were separated in patients who survived the first year after the procedure (survivors) and patients who did not survive 1 year after MitraClip implantation (non-survivors). Data are given as median (25–75 percentiles) or absolute number (%). Univariate analysis was performed using Cox regression

*GFR* glomerular filtration rate calculated by MDRD (modification of diet in renal disease) formula, *hsTnT* high sensitive Troponin T, *NT-proBNP* N-terminal pro-brain natriuretic peptide

*Bold text represents $p$ values < 0.05. Hazard ratio is given as 95% confidence interval (CI)

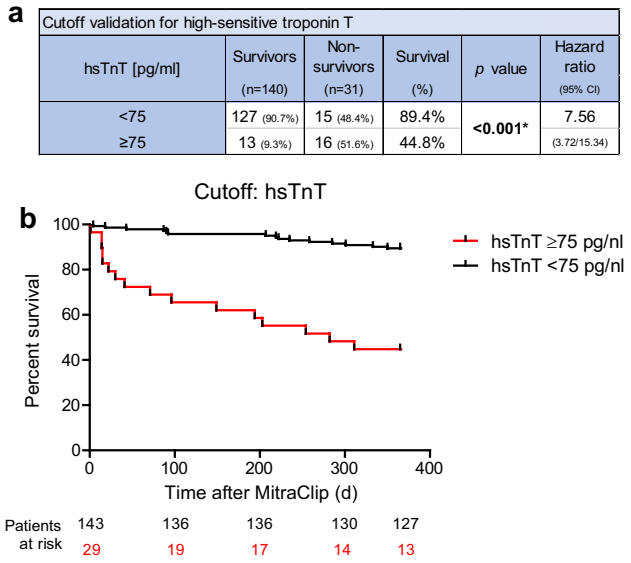


**Fig. 2** High-sensitive Troponin T (hsTnT) as predictor of 1-year mortality. **a** hsTnT was measured prior MitraClip implantation. Patients were separated into two groups: patients with hsTnT < 75 pg/ml and patients with hsTnT ≥ 75 pg/ml. Groups were separated for patients who survived the first year after MitraClip implantation (survivors) and patients who did not (non-survivors). Survival rates are given for both groups. Differences in survival between patients with hsTnT < 75 pg/ml and hsTnT ≥ 75 pg/ml were tested by the log-rank test; $p$ value and 95% confidence interval (CI) are given. **b** Kaplan–Meier estimated curve stratified for hsTnT. One-year survival of patients after MitraClip with pre-interventional serum hsTnT < 75 pg/ml (black curve; $n=142$) is compared to 1-year survival of patients with serum hsTnT ≥ 75 pg/ml (red curve; $n=29$). Vertical bars represent censored events

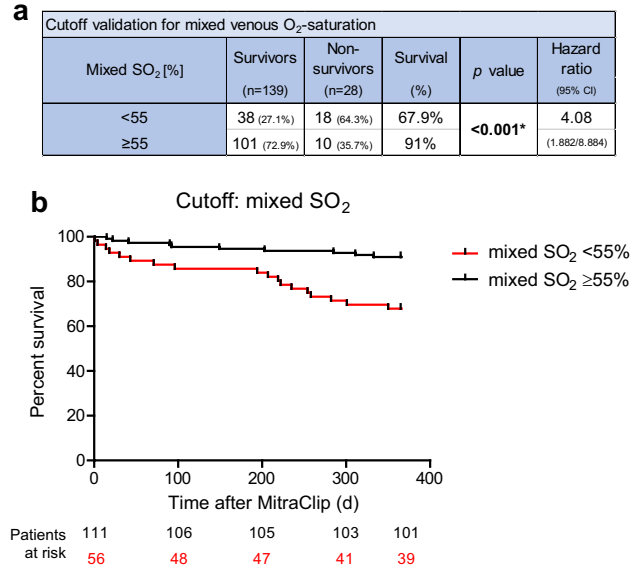


**Fig. 3** Mixed venous $O_2$-saturation (mixed $SO_2$) as predictor of 1-year mortality. **a** Mixed $SO_2$ was measured by right heart catheterization prior MitraClip implantation. Patients were separated into two groups: patients with mixed $SO_2 \geq 55\%$ and patients with mixed $SO_2 < 55\%$. Groups were separated for patients who survived the first year after MitraClip implantation (survivors) and patients who did not (non-survivors). Survival rates are given for both groups. Differences in survival between patients with mixed $SO_2 \geq 55\%$ and $< 55\%$ were tested by the log-rank test; $p$ value and 95% confidence interval (CI) are given. **b** Kaplan–Meier estimated curve stratified for mixed $SO_2$. One-year survival of patients after MitraClip with pre-interventional mixed $SO_2 \geq 55\%$ measured by right heart catheterization (black curve; $n=111$) is compared to 1-year survival of patients with mixed $SO_2 < 55\%$ (red curve; $n=56$). Vertical bars represent censored events

were significantly different between survivors and non-survivors (MR grade post MitraClip, intraprocedural complications, see Suppl. Table) were additionally included in the multivariant Cox regression analysis, hsTnT and mixed $SO_2$ remained the strongest predictors for 1-year survival after MitraClip procedure after stepwise forward selection (hsTnT: HR 1.0129; $p < 0.0001$; mixed $SO_2$: HR 0.9238; $p < 0.0001$). To further define the clinical relevance of

these findings, cut-off values for mixed $SO_2$ and hsTnT were determined as follows.

### Cut-off values for hsTroponin T and mixed venous $O_2$-saturation

We used an online tool to determine cut-off values published by Budczies and colleagues [36], based on a bundle of parameters as such as the distribution of the distinct parameter in the sample cohort, and the correlation with survival. Thereby, we determined optimal cut-off values for hsTnT and mixed $SO_2$ (see Figs. 2, 3). By doing so, we found the best cut-off value for hsTnT ≥ 75 pg/nl (HR 7.6; CI 3.7–15.3; $p < 0.001$). The best cut-off value for mixed $SO_2$ was < 55% (HR 4.1; CI 1.8–8.9; $p < 0.001$). When we performed conventional ROC curve analysis, similar results for hsTnT (cutoff ≥ 75 ng/l; AUC 0.766; $p < 0.001$; sensitivity 50%; specificity 91.2%) and mixed $SO_2$ (cut-off < 55%; AUC 0.730; $p < 0.001$; sensitivity 75%; specificity 70%) were found. At Kaplan–Meier analysis, 1-year survival was 89% in patients with hsTnT < 75 pg/nl vs. 45% in patients with hsTnT ≥ 75 pg/nl (log rank $p < 0.001$) and 91% in patients with mixed $SO_2$ ≥ 55% vs. 68% in patients with mixed $SO_2$ < 55% (log rank $p < 0.001$). Of note, neither hsTnT nor mixed $SO_2$ were related to post-interventional MR grade [hsTnT: odds ratio (OR) 1.0048; confidence interval (CI) 0.9928–1.0169; $p = 0.4385$; mixed $SO_2$: OR 0.9789; CI 0.9321 − 1.0820; $p = 0.3924$], demonstrating that albeit a clear correlation to survival, those parameters were not related to device success.

### A novel score system to predict mortality

We applied these cut-off values to create a novel simple risk score for patients with severe HF undergoing PMVR. Based on the cut-off values for hsTnT and mixed $SO_2$, risk groups were defined as follows: "low risk": hsTnT < 75 pg/ml and mixed $SO_2$ ≥ 55%; "high risk": hsTnT ≥ 75 pg/ml and/or mixed $SO_2$ < 55%. This risk score identified patients at risk for mortality within 1 year with a sensitivity of 80% and a specificity of 61.5%, resulting in a positive predictive value of 30.4% and a negative predictive value of 93.6%. At Kaplan–Meier analysis, 1-year survival was 95.8% in "low risk" patients and only 66.6% in "high risk" patients (Fig. 4). Patients who met both criteria (hsTnT ≥ 75 pg/ml and mixed $SO_2$ < 55%) had an even lower 1-year survival of only 20%.

**a**

| Risk score analysis | | | | | |
|---|---|---|---|---|---|
| Risk score | Survivors (n=139) | Non-survivors (n=28) | Survival (%) | *p* value | Hazard ratio (95% CI) |
| Low risk | 91 (65.5%) | 4 (14.3%) | 95.8% | <0.001* | 7.220 |
| High risk | 48 (34.5%) | 24 (57.1%) | 66.6% | | (3.374/15.456) |

**b**

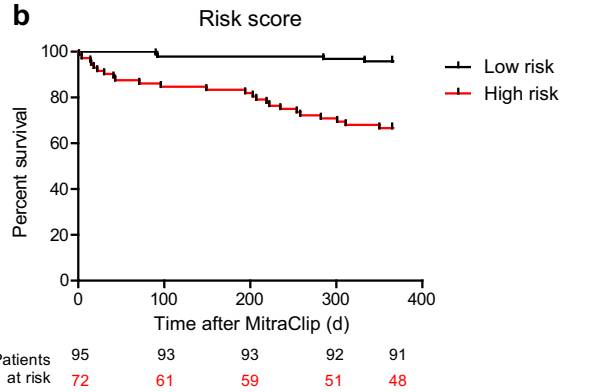


**Fig. 4** Scoring system for risk stratification after MitraClip in severe heart failure patients. Patients were classified as follows: low risk ($n = 95$): high-sensitive Troponin T (hsTnT) < 75 pg/ml and mixed venous $O_2$-saturation (mixed $SO_2$) ≥ 55%; high risk ($n = 72$) hsTnT ≥ 75 pg/ml and/or mixed $SO_2$ < 55%. **a** Numbers of patients and survival rates in low- and high-risk groups. Differences in survival between groups were tested by the log-rank test; *p* value and 95% confidence interval (CI) are given. **b** Kaplan–Meier estimated 1-year survival of patients after MitraClip, stratified for low and high risks. Vertical bars represent censored events. Survival is compared between the two groups using log-rank test. *$p < 0.001$

## Discussion

Functional moderate-to-severe or severe MR is a frequent finding in HF patients and comprises independent prognostic relevance [8, 11, 43]. Percutaneous edge-to-edge mitral valve repair with MitraClip implantation has emerged as a low-risk treatment option especially in patients with HF, resulting in improved quality of life and reduced symptoms [9, 20, 44, 45]. Prospective randomized data on hard clinical endpoints (mortality and HF rehospitalisation) in patients with severe MR and HF treated with a MitraClip are awaited in the near future. To our best knowledge, there is limited data on parameters for pre-interventional risk assessment in severe HF patients undergoing MitraClip implantation. The present study shows, for the first time, that a mixed venous $O_2$-saturation (mixed $SO_2$) < 55%, measured by right heart catheterization, is a strong and independent predictor of outcomes in patients with severe HF and higher grade MR undergoing PMVR via MitraClip. Moreover, we demonstrate that a simple score system based on mixed $SO_2$ and a cardiac biomarker (hsTnT) may predict outcome in this particular patient population with severe HF and moderate-to-severe or severe MR. Although our study was performed in a small and dedicated patient cohort at a single centre, our results may help to identify MitraClip candidates at exceptional risk.

## Mitral valve repair in a severe heart failure population

The degree of severe HF in the present study is unique compared to previously published results in EVEREST II, TRAMI, ACCESS-EU, TCVT, and GRASP [2, 46–49]. The average EF in our study population was 25%, and 65.3% showed an EF < 30%. In the EVEREST II trial the average EF in the MitraClip group was 60%, in ACCESS-EU approximately 1/3 of patients had an EF < 30%, and in TRAMI one-third of patients revealed an EF > 50% [46, 47, 49]. Current guidelines recommend MitraClip therapy for patients with high surgical risk remaining symptomatic under optimal medical therapy only with an IIB recommendation [6]. However, due to the high surgical risk in HF patients with functional MR, MitraClip is predominantly considered for this group. As such, 79.9% of our overall study population had secondary, functional MR, which is comparable to TRAMI (71.3%) and ACCESS-EU (77.1%); in EVEREST II only 27.0% had functional MR [2]. When we applied data analysis only to the functional MR subgroup (data not shown), we obtained comparable results for hsTnT and mixed $SO_2$. A separate analysis for the primary MR group ($n = 35$) was not performed due to the small number of patients. However, as the latter patients also displayed severe HF, comparable results may be hypothesized. Overall, the analysed patients in our current study presented with true severe HF, further advanced compared to previously published results [2, 46–48]. Our data were compiled to establish a risk score for this specific patient group.

## Predictors of 1-year survival

Overall 1-year mortality in our study population was 17.8%. Interestingly, despite severe HF in our patient population, the mortality was comparable to 15.8% after an average of 310 days in a recently published meta-analysis from 16 trials including 2980 patients undergoing MitraClip implantation [50]. Furthermore, 1-year mortality was 20.3% in TRAMI, 15.3% in TCVT, and 17.3% in ACCESS-EU, as such all comparable to our results [42, 47, 49].

In univariate analysis, the following parameters could differentiate survivors and non-survivors: NYHA class, LVESD, RA pressure, NT-proBNP, hsTnT (higher values associated with non-survivors), GFR, mixed $SO_2$ (lower values associated with non-survivors) as well as CRT, absence of arterial hypertension and procedural failure measured by immediate MR grade after the procedure (all associated with non-survivors). The latter strongly predicted outcomes after MitraClip in, e.g., the TRAMI registry, and we could confirm this relevance in our study. However, MR grade was not among the strongest predictors in our hands. The result that CRT was more frequent in the non-survivor group could be a potential confounder of the study, although all patients with indication to guidelines were implanted prior MitraClip implantation.

In accordance with the literature, non-survivors showed higher NYHA class [42, 51, 52]. However, in contrast to the previous studies, parameters as such as surgical risk scores (STS score, logistic EuroSCORE, or EuroSCORE II) [51, 53–55], LVEF [42], PA pressures, transpulmonary gradients or pulmonary resistance [56, 57], and tricuspid regurgitation [42] or TAPSE [53] were not predictive for 1-year survival in our severe HF patients. These findings implicate that in patients with severe HF, a specifically tailored risk stratification prior PMVR needs to be applied. Regarding cardiac biomarkers, NTpro-BNP, and hsTnT were both predictive in univariate analysis in accordance with the previous literature [58]. Prior to the present study, the predictive capacity of hemodynamics prior to MitraClip implantation was unclear, as hemodynamic evaluation is not routinely performed in all centres. In our patient population, due to severe HF, hemodynamics were severely worsened with an average cardiac index of 2.07 l/min/$m^2$. However, the only highly predictive parameter measured by right heart catheter was mixed $SO_2$, with low values associated with higher mortality.

## Development of a novel risk score

We could demonstrate that, among the tested parameters, hsTnT and mixed $SO_2$ revealed the highest predictive capacity in our population in multivariate analysis. Why are these parameters so important? Cardiac troponins are components of the thin filament of the sarcomere and are released in cardiac diseases due to a number of putative pathomechanisms including volume overload, biventricular strain, myocardial ischaemia, and an increased rate of myocardial cell turnover with cell death or apoptosis [59–62]. For hsTnT, already concentrations near the 99th percentile value predicted risk of death or hospitalisation for HF [63]. Reduced mixed $SO_2$ in HF patients reflects the fact that the cardiac output is insufficient to meet systemic requirements and was shown to be predictive in severe HF [64, 65]. Thus, altered hsTnT and mixed $SO_2$ in our patient cohort may simply reflect the severity of HF in the patients at risk.

Using the combination of both parameters appears to be an attractive risk score for patients with severe HF undergoing MitraClip procedure, reflected by the high negative predictive value of 93.6%. This underscores that patients with low hsTnT and high mixed $SO_2$ may be optimal candidates and possibly implies that an early procedure for non-surgical candidates should be performed before deterioration. Identification of patients at high risk with this simple risk score, in combination with modern concepts of HF patient care, e.g., heart nurse and/or ambulant hemodynamic monitoring

[66–68], could help to direct a personalized therapy to patients with severe MR and severe HF.

## Conclusion

In summary, we have compiled a novel risk score for pre-interventional assessment of patients with moderate-to-severe or severe MR and severe HF undergoing MitraClip therapy. The score combines the biomarker hsTnT and mixed $SO_2$ derived from right heart catheterization. Future studies should clarify if patients at high risk may benefit from intensified post-interventional and post-discharge care or if the risk score may help to avoid futile invasive interventions or to better select patients with severe HF who benefit from PMVR interventions at earlier stages of the disease.

## Limitations

The data were retrieved from a single centre in a retrospective approach and data calculation was not realized by a core lab. MR grading was performed by a semi-quantitative method and not by EROA and PISA quantification. Furthermore, altogether 20 patients (of 299) were lost to follow-up during the 1-year study period. However, our retrospective study comprises the first larger series of patients with true severe HF undergoing MitraClip implantation and thorough statistical testing was deployed to avoid overfitting. Furthermore, the score includes mixed $SO_2$ derived from invasive hemodynamics, as such the presented risk score is only applicable in patients undergoing right heart catheterization. Another limitation of the study is that we focused only on severe HF patients, whereas the variables could also predict outcome in an overall population of MitraClip candidates. Finally, this study was performed in a dedicated patient cohort, and, to produce more substantial data, the novel risk score needs to be validated prospectively in an independent patient population.

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### Compliance with ethical standards

**Conflict of interest** S. T. P., R. B., and P. W. R. received speaker honoraria from Abbott Vascular. M. M. K., N. G., R. B., and P. W. R. are investigators in the RESHAPE-HF (A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) study. S.P. received research grants from Abbott. All other authors have no conflicts of interest to disclose.

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