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Sarrazyn, C.; Fortuni, F.; Laenens, D.; Chua, A.P.; Santi, M.P.L.; Myagmardorj, R.; ... ; Marsan, N.A.

Original research

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Camille Sarrazyn ,[1] Federico Fortuni,[1,2] Dorien Laenens,[1] Aileen Paula Chua,[1] Maria Pilar Lopez Santi,[1] Rinchyenkhand Myagmardorj,[1] Takeru Nabeta,[1] Maria Chiara Meucci,[1,3] Gurpreet Kaur Singh,[1] Bart Josephus Johannes Velders ,[4] Xavier Galloo ,[1,5] Jeroen Joost Bax,[1] Nina Ajmone Marsan [1]

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[1]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
[2]Cardiology, Ospedale Nuovo San Giovanni Battista, Foligno, Italy
[3]Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy
[4]Department of Cardio-Thoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands
[5]Department of Cardiology, UZ Brussel, Brussel, Belgium

Correspondence to
Dr Nina Ajmone Marsan; n.ajmone@lumc.nl

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ABSTRACT

Background Significant secondary mitral regurgitation (SMR) is known to be associated with worse prognosis. However, data focusing specifically on moderate SMR and associated risk factors are lacking. In the present study, clinical and echocardiographic parameters associated with outcomes were evaluated in a large cohort of patients with moderate SMR.

Methods Patients with moderate SMR were retrospectively included and stratified by New York Heart Association (NYHA) class and specific aetiology (atrial SMR (aSMR) or ventricular SMR (vSMR)) with a further classification of vSMR based on left ventricular ejection fraction (LVEF) ≥40% or <40%. The primary endpoint was all-cause mortality and the secondary endpoint was the composite of all-cause mortality and heart failure (HF) events.

Results Of the total 1061 patients with moderate SMR (age 69±11 years, 59% male) included, 854 (80%) were in NYHA class I–II and 207 (20%) were in NYHA class III–IV. Regarding the aetiology, 352 (33%) had aSMR and 709 (67%) had vSMR, of which 329 (46%) had LVEF ≥40% and 380 (54%) had LVEF <40%. During a median follow-up of 82 (IQR 55–115) months, 397 (37%) died and 539 (51%) patients had HF events or died. On multivariable analysis, NYHA class III–IV (HR 1.578; 95% CI 1.244 to 2.002, p<0.001) and SMR aetiology were independently associated with both endpoints. Specifically, compared to aSMR, vSMR with LVEF ≥40% had a HR of 1.528 (95% CI 1.108 to 2.106, p=0.010) and vSMR with LVEF <40% had a HR of 1.960 (95% CI 1.434 to 2.679, p<0.001). To further support these findings, patients were matched for (1) NYHA class and (2) SMR aetiology by propensity scores including age, sex, diabetes, chronic obstructive pulmonary disease, renal function, left atrial volume index, NYHA class (only for SMR aetiology matching), LVEF, SMR aetiology (only for NYHA class matching), tricuspid regurgitation severity and right ventricular pulmonary artery coupling index. After matching, NYHA class and SMR aetiology remained associated with both outcomes (for both: log rank p<0.050).

Conclusion In patients with moderate SMR, distinction in SMR aetiology and assessment of symptoms are important independent determinants of outcome.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Severe secondary mitral regurgitation (SMR) is associated with a high rate of adverse events and the underlying aetiology (atrial SMR vs ventricular SMR) has been shown to have different outcome and to require customised treatment strategy.
⇒ Currently, data specifically focussing on patients with moderate SMR are scarce, and little is known about how to effectively risk stratify this population.

WHAT THIS STUDY ADDS

⇒ In this large cohort of 1061 patients with moderate SMR, the determinants of outcome were for the first time assessed specifically in this population.
⇒ New York Heart Association (NYHA) functional class and SMR aetiology were associated with mortality and heart failure, independently of other clinical and echocardiographic characteristics.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The assessment of NYHA functional class and identification of the underlying SMR aetiology, already in moderate SMR, might be useful in clinical practice for patient management and timely treatment decisions.

INTRODUCTION

Secondary mitral regurgitation (SMR) is a common valvular heart disease, associated with poor clinical outcomes.[1–7] While having moderate SMR has been associated already with an increased risk of adverse events, most studies included an heterogeneous cohort of both moderate and severe SMR. Therefore, data specifically identifying risk factors within patients with moderate SMR are lacking, while it may help timely management of these patients.[8–13]

Therefore, the aim of the current study was to evaluate which clinical and echocardiographic factors are associated with long-term survival in a large cohort of patients with moderate SMR.

Particularly, patients were classified according to the two distinct SMR aetiologies proposed in recent literature: (1) atrial SMR (aSMR) due to mitral annular dilatation accompanied by left atrial (LA) remodelling but with normal left ventricular (LV) dimensions and systolic function and (2) ventricular SMR (vSMR) as a consequence of LV remodelling including chamber dilatation and/or dysfunction accompanied by significant mitral annular dilatation and leaflet tethering.[14 15]

Furthermore, the symptomatic status and the most relevant comorbidities were specifically taken into account in the analysis for the potential impact in the decision making and patient management.

METHODS

Patient population and data collection

Patients diagnosed with moderate SMR between January 2008 and December 2018 were identified from the departmental cardiology information system (EPD-Vision 12.9.9.3; Leiden University Medical Centre, Leiden, The Netherlands) and echocardiographic database. The entry point in this study was defined as the first echocardiogram showing moderate SMR in the absence of signs of congestion (peripheral oedema, ascites or jugular venous distention) as assessed at the outpatient clinic. In case of a previous acute coronary syndrome or a heart failure (HF) hospitalisation, patients should have been stable for at least 3 months. HF hospitalisation was defined as hospitalisation (>24 hours) due to symptoms and signs of HF.

Regarding cardiac resynchronisation therapy (CRT), a timeframe of at least 6 months after CRT implantation was respected. Also, for patients receiving CRT implantation within the first 6 months after selection, the first echocardiogram showing moderate SMR at least 6 months after implantation was considered as the entry point of the study. Patients with missing clinical data, congenital heart disease, hypertrophic obstructive cardiomyopathy, previous heart valve surgery or other (>mild) valvular heart disease (with the exception of secondary tricuspid regurgitation (TR)) were excluded (online supplemental figure 1).

Clinical variables

Baseline demographic and clinical variables were collected from the medical records. New York Heart Association (NYHA) class was assessed by the attending physician at the time of outpatient clinic. Coronary artery disease was defined as >50% stenosis on invasive angiography or a history of myocardial infarction or coronary revascularisation or coronary artery bypass grafting.

Echocardiography

Transthoracic echocardiography was performed, using a commercially available system (VIVID 7, E9 and E95; GE-Vingmed, Horten, Norway). Echocardiographic images were stored and analysed offline with a dedicated software (EchoPac V.204; GE-Vingmed, Horten Norway). M-mode, two-dimensional and colour, continuous-wave and pulsed-wave Doppler data were acquired from the parasternal, apical and subcostal views, according to current guidelines.[16] In atrial fibrillation (AF), average measurements of three consecutive cardiac cycles were obtained.

LV volumetric dimensions were obtained from the apical 2-chamber and 4-chamber views and indexed to body surface area (BSA). LV ejection fraction (LVEF) was calculated according to Simpson's biplane method. Pulsed-wave Doppler recordings of the transmitral flow were used to obtain peak early (E) and late (A) diastolic velocities.[17] Using tissue Doppler imaging of the mitral annulus in the apical 4-chamber view, e' was measured at the lateral and septal sides and averaged to calculate the E/e' ratio for estimation of LV filling pressures.[17] The end-systolic LA volume was obtained from the apical 2-chamber and 4-chamber views using Simpson's method of disks and indexed to BSA (left atrial volume index (LAVI)).[16]

Pulmonary artery systolic pressure (PASP) was calculated according to the Bernoulli equation derived from the TR jet peak velocity and the estimated right atrial pressure, derived from the diameter and collapse of the inferior vena cava. For the evaluation of the right ventricular systolic function, M-mode was applied to measure tricuspid annular plane systolic excursion (TAPSE).[18] The TAPSE/PASP ratio was used to assess the right ventricular-pulmonary artery coupling.[19]

Severity of SMR and TR was assessed according to current recommendations using a multiparametric approach including qualitative, semiquantitative and quantitative parameters.[20] Moderate SMR was defined as SMR with an effective regurgitant orifice area between 20 and 39 mm^2 with a regurgitation volume between 30 and 59 mL, obtained by flow convergence method, together with a vena contracta width between 3 and 6 mm (or 3–7 mm when biplane available). Adjunctive semiquantitative and quantitative parameters were used particularly in case of discordance between the quantified severity of SMR.[21]

SMR aetiology was further divided in aSMR or vSMR.[9–11] aSMR was defined in the presence of mitral annulus dilatation without leaflet abnormalities in normal LVEF (≥50%) and LV dimensions (indexed LV end-diastolic volume <71 mL/m^2 (women) or <79 mL/m^2 (men)), without regional wall motion abnormalities. Mitral annulus dilatation was defined by an anteroposterior diameter >35 mm or a ratio of annular diameter:anterior leaflet length >1.3 (assessed in end-diastole from the parasternal long-axis view).[21] vSMR was defined as tenting or restriction resulting in leaflet malcoaptation (without leaflet structural abnormalities) due to impaired LVEF (<50%), regional wall motion abnormalities and/or LV dilatation.[15 16]

Follow-up and outcomes

The primary outcome was all-cause mortality. The secondary outcome was a composite endpoint of HF events and all-cause mortality. HF events were defined as HF hospitalisation or the start or increasing dose of loop diuretics in an outpatient setting. Additionally, data were collected on CRT implantation and mitral valve intervention (MVI), including surgical therapy (MV repair or replacement) and transcatheter edge-to-edge (TEER) MV repair during follow-up. Mortality data were obtained from the departmental cardiology information system (EPD-Vision 12.9.9.3), which is directly linked to the governmental death registry and therefore complete for all patients.

Statistical analysis

Categorical data are presented as absolute numbers and percentages. Continuous data are presented as mean±SD when normally distributed or as median (IQR) when not normally distributed. Pearson's χ^2 test or the Fisher's exact test (categorical variables) and the unpaired Student's t-test or Mann-Whitney U test (continuous variables) were used to compare the baseline characteristics between two groups, as appropriate. For comparison between more than two groups, analysis of variance or Kruskal-Wallis test was performed, as appropriate, with post hoc Bonferroni correction.

Cumulative event-free survival rates were estimated using the Kaplan-Meier survival method. Additionally, a log-rank test was used to compare groups.

Cox proportional hazard regression analysis was performed to investigate the association between clinical and echocardiographic parameters with the primary and secondary endpoint. Complete case analyses were conducted for Cox regression analyses as data were complete in 1019 (96%) patients. Both MVI and CRT implantation during follow-up were introduced as time-dependent covariates. The definition to differentiate between aSMR versus vSMR included LVEF and LV dimensions. Due to collinearity, these variables were therefore not combined with SMR aetiology in the same multivariable Cox regression model. However, vSMR were further categorised according to LVEF: vSMR with LVEF ≥40% and vSMR with LVEF <40% to better characterise LV dysfunction.[22] The HRs and 95% CIs were calculated. Variables in the univariable Cox regression analysis with $p<0.05$ were considered for inclusion in the multivariable Cox regression analysis. Collinearity between all pairs of continuous variables included in the multivariable analysis was tested by a correlation factor analysis (correlation coefficient <0.7) and the proportional hazards assumption was verified by Schoenfeld residuals.

To further analyse the association between NYHA class, SMR aetiology and outcomes, propensity score (PS) matching was performed on all variables significantly associated with outcomes on univariable Cox regression analysis. The PS were calculated and a nearest-neighbour 1:1 matching was applied handling a calliper threshold of 0.2. Overlap in PS was illustrated in a mirrored histogram, and covariate balance was illustrated in a love plot. An absolute standardised mean difference <0.1 was considered to be a balanced matching. In total, two PS-matched analyses were performed resulting in two matched cohorts. In the first cohort, patients were matched for all significant variables on univariable Cox regression analysis, except for NYHA class. Subsequently, Kaplan-Meier survival analysis was performed to evaluate the association between NYHA class and both endpoints. A similar approach was applied for the second cohort, where patients were matched for the relevant variables, except for SMR aetiology. Kaplan-Meier survival analysis was performed to evaluate the association between SMR aetiology and both endpoints.

Additionally, a PS-adjusted Cox regression analysis for the entire cohort was performed, evaluating the association with both endpoints for NYHA class and SMR aetiology separately.

All hypothesis tests had a two-sided significance level of 0.05. Statistical analysis was performed using SPSS for Windows, V.29.0 (IBM Armonk, New York, USA) and R V.4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Baseline clinical and echocardiographic characteristics of the study population

	Total population N=1061
Clinical variables	
Age, years	69 (±11)
Male sex, n (%)	624 (59)
Arterial hypertension, n (%)	617 (58)
Diabetes, n (%)	179 (17)
Dyslipidaemia, n (%)	540 (51)
eGFR, mL/min/1.73 m²	70 (±25)
COPD, n (%)	142 (13)
Coronary artery disease, n (%)	483 (46)
Atrial fibrillation, n (%)	556 (52)
NYHA class III–IV, n (%)	207 (20)
Beta-blockers, n (%)	766 (72)
RAAS inhibitors, n (%)	720 (68)
MRA, n (%)	240 (23)
Loop diuretics, n (%)	487 (46)
CRT at baseline, n (%)	178 (17)
Echocardiographic variables	
LV end-diastolic volume index (mL/m²)	65 (50–87)
LV end-systolic volume index (mL/m²)	32 (22–56)
LV ejection fraction, (%)	45 (±14)
SMR aetiology, n (%)	
aSMR	352 (33)
vSMR, LVEF ≥40%	329 (31)
vSMR, LVEF <40%	380 (36)
Vena contracta, mm	4 (3–5)
EROA, mm	24 (±7)
Regurgitation volume, mL	39 (±11)
Regurgitation fraction, %	36 (±10)
LAVI (mL/m²)	38 (29–49)
E/e' ratio	14 (13–14)
E/A ratio*	1.2 (0.9–1.4)
Severe TR, n (%)	158 (15)
TR gradient, mm Hg	27 (20–34)
TAPSE/PASP, mm/mmHg	0.80 (±0.6)

Variables expressed as mean (±SD), median (IQR) or n (%).
*Only calculated for patients in sinus rhythm.
aSMR, atrial SMR; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RAAS, renin-angiotensin aldosterone system blockers; SMR, secondary mitral regurgitation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; vSMR, ventricular SMR.

RESULTS

Patient population

A total of 1061 patients (mean age 69±11 years, 59% men) with moderate SMR were included. Baseline characteristics are summarised in table 1. In the overall population, history of AF was present in 52% and 20% presented with NYHA class III–IV. Regarding echocardiographic characteristics, LV volumes were on average not dilated, mean LVEF was 45±14% and median LAVI was 38 (IQR 29–49) mL/m². The underlying SMR aetiology was classified as aSMR in 33% of patients, while 67% of patients were classified as vSMR. In vSMR, 46% had LVEF ≥40% and 54% had LVEF <40% (figure 1). The baseline clinical and echocardiographic characteristics according to NYHA class and SMR aetiology are displayed in online supplemental tables 1 and 2, respectively.

Follow-up and patient outcomes

During a median follow-up of 82 (IQR 55–115) months, 397 (37%) patients died. The mortality rates were 16%, 23% and 35%, respectively at 3, 5 and 10 years follow-up. Regarding the composite endpoint of HF event and all-cause mortality, 539 (51%) patients experienced HF events (343 (32%) patients) or died (196 (18%) patients) during a median follow-up of 78 (IQR 44–111) months.

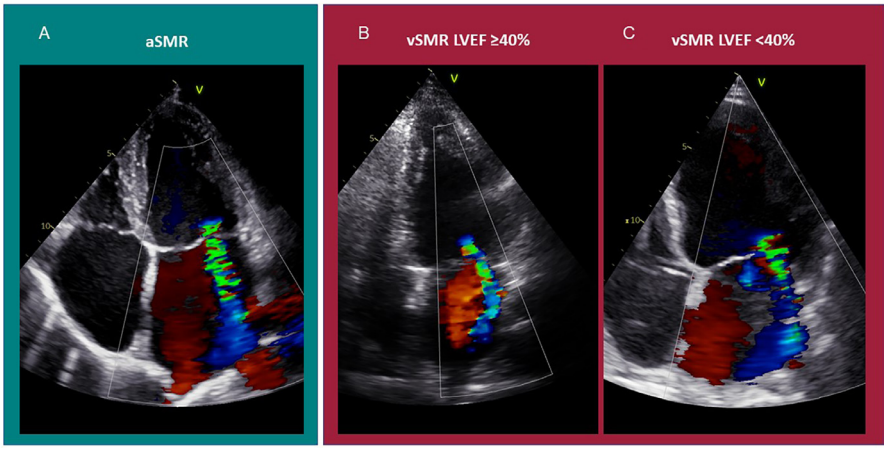

Figure 1 Examples of the underlying aetiology in patients with moderate SMR. (A) Echocardiographic image from a patient with moderate aSMR with leaflet malcoaptation due to annular dilatation, with normal LVEF (ie, ≥50%), no regional wall motion abnormalities and with normal LV dimensions. (B) Echocardiographic image of a patient with moderate vSMR and LVEF ≥40% with leaflet malcoaptation due to restriction of the posterior mitral valve leaflet in the presence of wall motion abnormalities after inferoposterior myocardial infarction. (C) Echocardiographic image of a patient with moderate vSMR and LVEF <40% with leaflet malcoaptation due to tethering in the presence of LV dysfunction and dilatation in dilated cardiomyopathy. aSMR, atrial SMR; LVEF, left ventricle ejection fraction; SMR, secondary mitral regurgitation; vSMR, ventricular SMR.

Table 2 summarises the univariable Cox regression analysis for the primary and secondary endpoint. SMR aetiology, together with several clinical and echocardiographic parameters, was associated with both endpoints. At the multivariable Cox regression analysis (table 3), vSMR regardless of LVEF was independently associated with worse outcomes as compared with aSMR, and together with age, male sex, diabetes, chronic obstructive pulmonary disease, renal function, NYHA class III–IV, LAVI, severe TR (only for all-cause mortality) and TAPSE/PASP. Moreover, both MVI and CRT implantation during follow-up were independently associated with worse outcomes.

Considering their independent association with the study endpoints and the clinical relevance, further analyses were performed according to NYHA class and SMR aetiology.

Association between NYHA class and outcomes

The Kaplan-Meier curves illustrated in figure 2 (panels A–B) show worse outcomes in patients with NYHA class III–IV (vs

Table 2 Univariable Cox regression analysis for both study endpoints

	All-cause mortality		Composite endpoint: heart failure events and all-cause mortality	
Variable	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Clinical variables				
Age, years	1.020 (1.018 to 1.038)	**<0.001**	1.022 (1.013 to 1.030)	**<0.001**
Male sex	1.874 (1.508 to 2.329)	**<0.001**	1.617 (1.352 to 1.935)	**<0.001**
Arterial hypertension	1.098 (0.897 to 1.345)	0.365	1.113 (0.936 to 1.324)	0.226
Diabetes	1.587 (1.248 to 2.018)	**<0.001**	1.656 (1.348 to 2.033)	**<0.001**
eGFR, mL/min/1.73 m²	0.981 (0.976 to 0.985)	**<0.001**	0.998 (0.997 to 0.999)	**<0.001**
COPD	1.976 (1.551 to 2.518)	**<0.001**	1.845 (1.486 to 2.290)	**<0.001**
Coronary artery disease	1.456 (1.194 to 1.775)	**<0.001**	1.413 (1.193 to 1.674)	**<0.001**
Atrial fibrillation	1.214 (0.995 to 1.481)	0.056	1.277 (1.077 to 1.514)	**0.006**
NYHA class III–IV	2.337 (1.889 to 2.892)	**<0.001**	2.014 (1.668 to 2.431)	**<0.001**
Echocardiographic variables				
SMR aetiology				
aSMR	Reference group	**<0.001**	Reference group	**<0.001**
vSMR, LVEF ≥40%	1.415 (1.064 to 1.882)	**0.017**	1.370 (1.370 to 1.736)	**0.009**
vSMR, LVEF <40%	2.546 (1.971 to 3.288)	**<0.001**	2.343 (1.891 to 2.903)	**<0.001**
LAVI, mL/m²	1.014 (1.010 to 1.018)	**<0.001**	1.014 (1.010 to 1.017)	**<0.001**
Severe TR	1.482 (1.144 to 1.919)	**0.003**	1.505 (1.204 to 1.880)	**<0.001**
TAPSE/PASP, mm/mm Hg	0.513 (0.395 to 0.667)	**<0.001**	0.520 (0.418 to 0.646)	**<0.001**
MVI (time-dependent)	2.075 (1.607 to 2.680)	**<0.001**	1.901 (1.515 to 2.386)	**<0.001**
CRT (time-dependent)	2.224 (1.687 to 2.933)	**<0.001**	2.122 (1.658 to 2.717)	**<0.001**

Significant values are marked in bold.
aSMR, atrial SMR; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; MVI, mitral valve intervention; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SMR, secondary mitral regurgitation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; vSMR, ventricular SMR.

Table 3 Multivariable Cox regression analysis for both study endpoints

	All-cause mortality		Composite endpoint: heart failure events and all-cause mortality	
Variable	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age, years	1.034 (1.023 to 1.045))	**<0.001**	1.022 (1.013 to 1.031)	**<0.001**
Male sex	1.698 (1.351 to 2.134)	**<0.001**	1.489 (1.230 to 1.802)	**<0.001**
Diabetes	1.406 (1.097 to 1.804)	**0.007**	1.491 (1.205 to 1.845)	**<0.001**
eGFR, mL/min/1.73 m²	0.999 (0.998 to 0.999)	**0.042**	0.999 (0.998 to 0.999)	**0.003**
COPD	1.362 (1.055 to 1.758)	**0.018**	1.261 (1.486 to 2.290)	**0.049**
Coronary artery disease	0.970 (0.770 to 1.223)	0.797	0.981 (0.804 to 1.196)	0.848
Atrial fibrillation			1.121 (0.918 to 1.367)	0.262
NYHA class III–IV	1.578 (1.244 to 2.002)	**<0.001**	1.365 (1.104 to 1.687)	**0.004**
SMR aetiology				
aSMR	Reference group	**<0.001**	Reference group	**<0.001**
vSMR, LVEF ≥40%	1.528 (1.108 to 2.106)	**0.010**	1.583 (1.198 to 2.093)	**0.001**
vSMR, LVEF <40%	1.960 (1.434 to 2.679)	**<0.001**	1.956 (1.498 to 2.553)	**<0.001**
LAVI, mL/m²	1.007 (1.001 to 1.012)	**0.013**	1.008 (1.003 to 1.012)	**0.001**
Severe TR	1.181 (1.096 to 1.557)	**0.030**	1.176 (0.925 to 1.495)	0.186
TAPSE/PASP, mm/mm Hg	0.797 (0.642 to 0.990)	**0.041**	0.762 (0.631 to 0.920)	**0.005**
MVI (time-dependent)	1.359 (1.026 to 1.800)	**0.032**	1.302 (1.017 to 1.668)	**0.037**
CRT (time-dependent)	1.389 (1.023 to 1.886)	**0.036**	1.328 (1.010 to 1.744)	**0.042**

Significant values are marked in bold.
aSMR, atrial SMR; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; MVI, mitral valve intervention; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SMR, secondary mitral regurgitation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; vSMR, ventricular SMR.

NYHA class I–II) for both endpoints (both p<0.001). To further demonstrate the association with outcomes of NYHA class, patients were matched for the following variables: age, sex, diabetes, chronic obstructive pulmonary disease, renal function, LAVI, TR severity, TAPSE/PASP ratio, together with SMR aetiology (without further distinction in vSMR LVEF ≥40% or <40% subgroups, but including LVEF as continuous variable). The PS matching was well-balanced with 396 patients remaining in the analysis and all included covariates reached an absolute mean difference of <0.10 after matching (online supplemental figure 2). Kaplan-Meier survival analysis in the matched cohort confirmed a significantly better survival for the group with NYHA class I–II (vs NYHA class III–IV, for the primary endpoint: p<0.001; for the secondary endpoint p=0.004) (figure 2, panels C–D). Additionally, the PS-adjusted Cox regression analysis for the entire cohort confirmed the independent association with both endpoints for NYHA class III–IV (vs NYHA class I−II; for the primary endpoint: HR 1.491; 95% CI 1.172 to 1.897, p=0.001; for the secondary endpoint: HR 2.079; 95% CI 1.720 to 2.513, p<0.001).

Association between SMR aetiology and outcomes

The Kaplan-Meier survival curves presented in figure 3 (panels A–B) show significantly worse outcomes for patients with vSMR as compared with patients with aSMR, with the worst outcome for patients with vSMR with LVEF <40% when considering the primary and secondary endpoint (both p<0.001). To further demonstrate the association with outcomes of SMR aetiology, patients were matched for the following variables: age, sex, diabetes, chronic obstructive pulmonary disease, renal function, LAVI, TR severity, TAPSE/PASP ratio, together with NYHA class III–IV (vs NYHA class I−II) and with LVEF as continuous variable). The PS-matching was well-balanced with 236 patients remaining in the analysis and all included covariates reached an absolute mean difference of <0.10 after matching (online supplemental figure 3). Kaplan-Meier survival analysis in the matched cohort confirmed a significantly better survival for the group with aSMR (vs vSMR, for both endpoints p=0.001) (figure 3, panels C–D). Additionally, the PS-adjusted Cox regression analysis for the entire cohort confirmed the independent association with both endpoints for aSMR (vs vSMR; for the primary endpoint: HR 0.586; 95% CI 0.410 to 0.839, p=0.003; for the secondary endpoint: HR 0.482, 95% CI 0.381 to 0.609, p<0.001).

DISCUSSION

The current study focused uniquely on moderate SMR including a large cohort of patients, and showed the following main findings: (1) moderate SMR is associated with high rates of HF events and mortality during long-term follow-up; (2) severe HF symptoms (NYHA class III–IV) are associated with a significantly increased risk of adverse events in these patients, even after adjusting for relevant clinical and echocardiographic variables; (3) already in moderate SMR, identification of SMR aetiology becomes important since vSMR has significantly worse outcomes as compared with aSMR, independently of LVEF, NYHA class and relevant comorbidities.

Outcomes of patients with moderate SMR

Previous studies showed the highest rates of adverse events in patients with severe SMR, although patients with moderate SMR already experienced worse event-free survival as compared with mild SMR.[4 13 23] Therefore, moderate SMR should be considered as a stage in the continuum risk of the SMR spectrum of severity. Specifically, initial studies on outcome in patients with moderate SMR reported a 5-year overall survival between 59% and 66%, which is lower than the 5-year survival of 77% observed in the current study. However, previous studies either included patients with reduced LVEF (<50%), or, if LVEF was preserved,

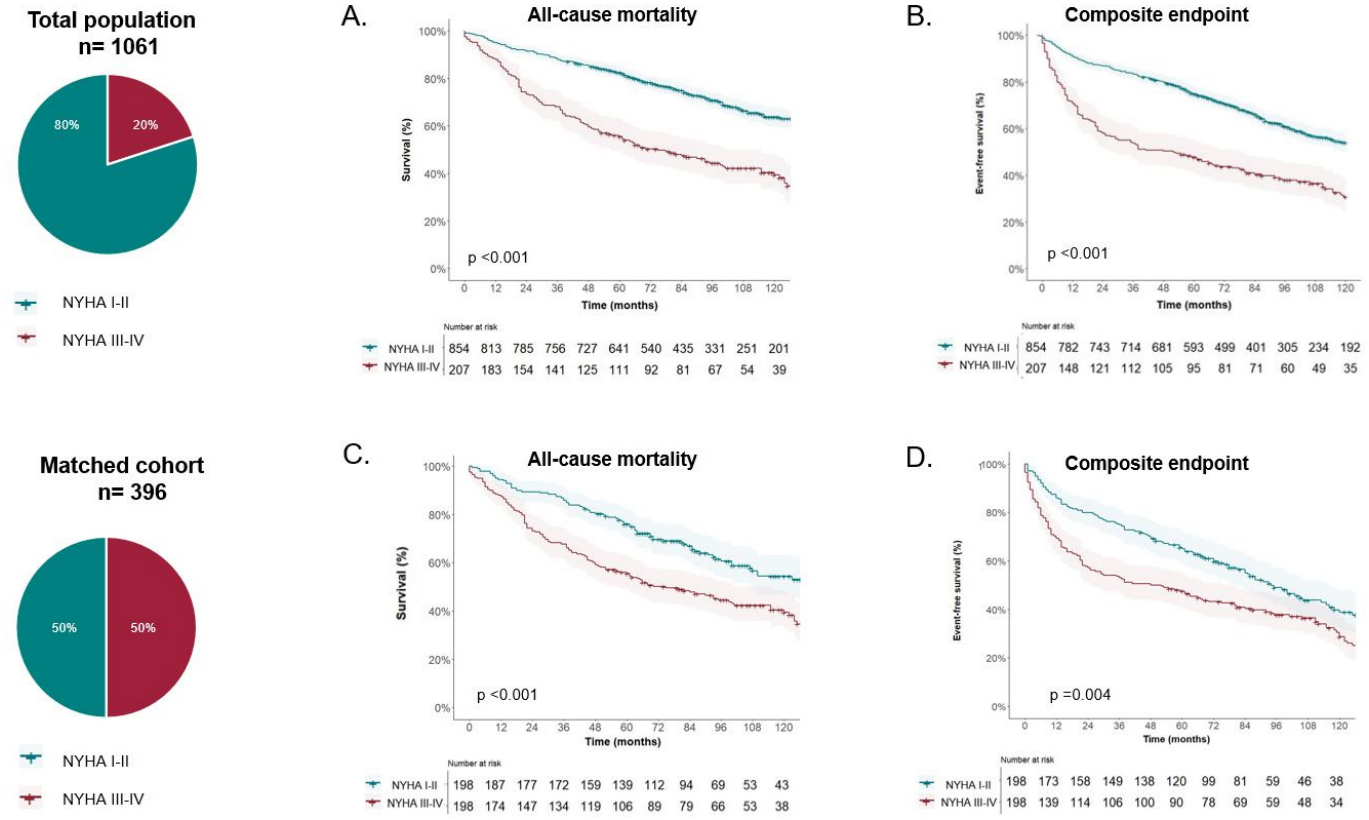

Figure 2 Kaplan-Meier curves according to NYHA functional class (NYHA class I–II versus NYHA class III–IV). Top panels consider the total study population for all-cause mortality (panel A) and for the composite endpoint of death and heart failure (panel B). Bottom panels below considered the matched cohort for all-cause mortality (panel C) and for the composite endpoint of death and heart failure event (panel D). Patients were matched for the following variables: age, sex, diabetes, chronic obstructive pulmonary disease, renal function, LAVI, TR severity, TAPSE/PASP ratio, together with SMR aetiology (without further distinction in vSMR LVEF ≥40% or <40% subgroups but with LVEF as a continuous variable). LAVI, left atrial volume index; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SMR, secondary mitral regurgitation; TR, tricuspid regurgitation; TAPSE, tricuspid annular plane systolic excursion; vSMR, ventricular SMR.

the patients presented with signs/symptoms of HF.[4 6 13 24] In the present study, a large cohort of patients was evaluated covering the entire spectrum of LVEF and irrespective of the presence of HF, which may explain the slightly better survival rates. Also, the management of SMR has evolved significantly over the past decade including new medical therapy, changes in surgical indications and extended implementation of TEER with potential impact on survival rates.[14] However, mortality and HF events were still high, demonstrating that moderate SMR should not be considered as a benign condition.[25] Accordingly, identification of characteristics associated with adverse outcomes in patients with moderate SMR is of clinical importance to optimise their follow-up and therapeutic management.

NYHA class and outcomes

By imposing a chronic volume overload on the LV, LA and pulmonary circulation, SMR contributes significantly to the development of HF. Accordingly, the prevalence of HF symptoms (assessed by NYHA class) has been reported to be higher in patients with increased SMR severity, and with progressively impaired LVEF.[3 4 6 23] Therefore in patients with moderate SMR, HF symptoms can be present, but might be difficult to determine whether these symptoms are related to the SMR or the LV dysfunction.

When considering outcomes, previous studies in patients with SMR have shown a significant association between NYHA class and mortality, independent of SMR severity, LVEF and comorbidities. These studies however included patients with moderate and severe SMR with reduced LVEF (<50%).[4 6 23]

The current study is the first to demonstrate the prognostic importance of NYHA class in a large cohort of pure moderate SMR covering the entire LVEF spectrum, and confirmed the independent association with both endpoints at long-term follow-up. Importantly, this independent association was further supported by the analysis in a matched cohort. This observation highlights the importance of assessing HF symptoms in patients with moderate SMR, especially beyond LVEF, in order to possibly implement a prompt customised treatment.

SMR aetiology and outcomes

The clinical importance of distinguishing between atrial and ventricular aetiology in severe SMR is widely recognised, as treatment strategies may differ with a focus on early restoration of sinus rhythm in aSMR versus the optimisation of HF treatment in vSMR.[14] With the advent of novel medical treatment, such as sacubitril/valsartan and sodium-glucose cotransporter-2 inhibitors, and the expanded use of TEER, this distinction may become even more important, particularly in moderate SMR.

Regarding aSMR, higher event rates have been described per increasing degree of aSMR. For example, an earlier study showed that in patients with AF, mild MR was associated with higher event rates as compared with patients without aSMR.[7] Naser *et al* extended this finding by demonstrating in a larger cohort of patients in both sinus rhythm and (new-onset) AF that

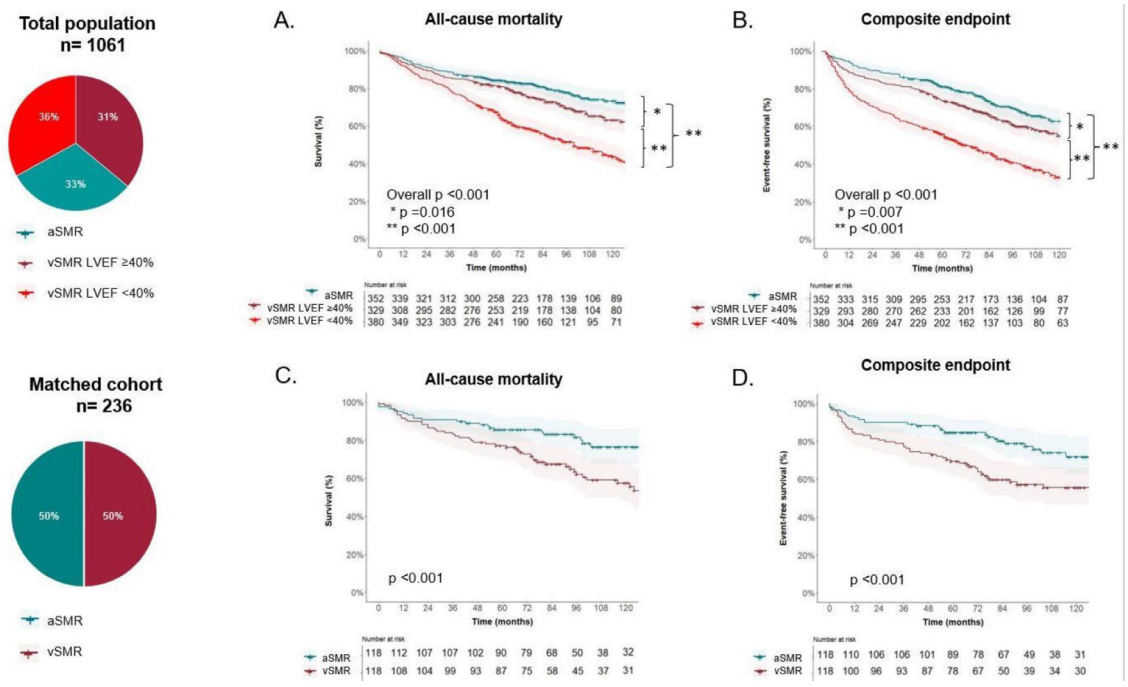

Figure 3 Kaplan-Meier curves according to SMR aetiology. Top panels consider the total study population for all-cause mortality (panel A) and for the composite endpoint of death and heart failure (panel B). Bottom panels below considered the matched cohort for all-cause mortality (panel C) and for the composite endpoint of death and heart failure events (panel D). Patients were matched for the following variables: age, sex, diabetes, chronic obstructive pulmonary disease, renal function, LAVI, TR severity, TAPSE/PASP ratio, NYHA functional class III–IV (vs NYHA functional class I–II) and with LVEF as a continuous variable. aSMR, atrial SMR; LAVI, left atrial volume index; LVEF, left ventricle ejection fraction; NYHA, NewYork Heart Association; PASP, pulmonary artery systolic pressure; SMR, secondary mitral regurgitation; TR, tricuspid regurgitation; TAPSE, tricuspid annular plane systolic excursion; vSMR, ventricular SMR.

mortality rate was higher in patients who developed more severe aSMR during follow-up.[26] The current study reported 5-year survival of 84% and 5-year HF-free survival of 81% for patients with aSMR, which are remarkably better than the survival rates reported in previous studies, namely 50%–70% and 56%, respectively.[9 11 12 27] This difference may be explained by the inclusion of both moderate and severe aSMR in all previous studies, together with some inconsistency in the definition of aSMR. For example, only severe LA dilatation was used to define aSMR, resulting in a patient cohort with a more advanced stage of the disease.[9 11]

Regarding vSMR, Benfari *et al* and Malagoli *et al* reported significantly higher mortality rates per increasing degree of SMR severity, both including patients with the entire spectrum of SMR severity and in reduced LVEF.[28 29] However, studies focussing specifically on moderate SMR are scarce. Goliash *et al* reported a 5-year survival rate of 64% in patients with moderate vSMR and LVEF <40%, which is comparable to the 67% in patients vSMR with LVEF <40% in the current study.[6]

Finally, only few studies have compared the difference in outcomes between aSMR and vSMR side by side.[8–12] Kim *et al* demonstrated superior prognosis in patients with aSMR (only unadjusted survival analysis).[12] Mori *et al* confirmed this finding in a large cohort after matching for comorbidities, but not for LVEF.[10] Thus far, this is the first study including only moderate SMR and demonstrating the independent association of SMR aetiology with outcomes at long-term follow-up after adjusting for LVEF and relevant comorbidities. It highlights that an early distinction in SMR aetiology, already in moderate SMR, may help in decision making, including closer monitoring and/or timely aetiology-targeted treatment strategies.

Study limitations

The current study is limited by its retrospective observational design from a single tertiary centre and the results need to be confirmed in multicentre prospective cohorts. Furthermore, considering the long inclusion period, the understanding of MR pathophysiology and its treatment has evolved and therefore may have affected the outcomes. Especially with the introduction of sodium-glucose cotransporter-2 and sacubitril/valsartan, medical treatment across the spectrum of HF has extended. During the study period, more insights were acquired for refining patient selection for TEER implementation. However, patients were treated according to the guidelines at time of inclusion and outcome analyses were corrected for interventions. Advanced echocardiographic measures such as longitudinal strain by two-dimensional speckle tracking echocardiography were not evaluated for the current analysis. N-terminal pro b-type natriuretic peptide as a marker of volume overload was not systematically available and therefore could not be included in the analysis. Although exercise testing may be of additional value in assessing patients with moderate SMR, it was unfortunately not performed in the majority of patients. Also information on change in medications during follow-up was not available, but analyses were corrected for MVI and CRT as time-dependent covariates. Finally, sequential echocardiograms were not systematically available to assess potential changes during follow-up.

CONCLUSION

Moderate SMR is characterised by a high rate of adverse events. Assessment of NYHA class and early identification of SMR aetiology are important independent associates of outcome and

might be useful in clinical practice to optimise patient management and timely therapeutic decisions.

X Xavier Galloo @XGalloo

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ORCID iDs
Camille Sarrazyn http://orcid.org/0000-0002-5382-5140
Bart Josephus Johannes Velders http://orcid.org/0000-0002-3999-4220
Xavier Galloo http://orcid.org/0000-0002-6294-7668
Nina Ajmone Marsan http://orcid.org/0000-0001-7208-5769

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