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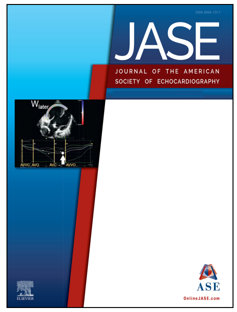

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Valentina Mantegazza, MD, Manuela Muratori, MD, Laura Fusini, MD, Anna Garlaschè, MD, Sarah Ghulam Ali, MD, Paola Gripari, MD, Cristina Ferrari, MD, Antonio L. Bartorelli, MD, Carlo Vignati, MD, Piergiuseppe Agostoni, MD, PhD, Gianluca Pontone, MD, PhD, Mauro Pepi, MD, Gloria Tamborini, MD

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Predictors of prognosis in patients with secondary mitral regurgitation undergoing mitral valve transcatheter edge-to-edge repair

Valentina Mantegazza, MD [a,b], Manuela Muratori, MD [a], Laura Fusini, MD [a,c], Anna Garlaschè, MD [a], Sarah Ghulam Ali, MD [a], Paola Gripari, MD [a], Cristina Ferrari, MD [a], Antonio L Bartorelli, MD [d], Carlo Vignati, MD [a,b], Piergiuseppe Agostoni, MD, PhD [a,b], Gianluca Pontone, MD, PhD [a], Mauro Pepi, MD [a], Gloria Tamborini, MD [a]

[a] Centro Cardiologico Monzino IRCCS, 20138, Milan, Italy

[b] Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, 20122, Milan, Italy

[c] Department of Electronics, Information and Bioengineering, Politecnico di Milano, 20133, Milan, Italy

[d] Department of Biomedical and Clinical Sciences, University of Milan, 20122, Milan, Italy

Address for correspondence: Dr. Valentina Mantegazza

Phone: +39 0258002152

Fax: +39 0258002287

E-mail: valentina.mantegazza@cardiologicomonzino.it

Treatment of secondary mitral regurgitation (SMR) in heart failure (HF) patients with left ventricular (LV) dysfunction is subject of debate.[1] The concept of disproportionate (d-SMR) and proportionate SMR (p-SMR) has been advocated, based on the ratio between the effective regurgitant orifice area (EROA) and LV end-diastolic volume (EDV).[2] A ratio ≥0.150 is supposed to identify d-SMR patients, who would benefit from transcatheter edge-to-edge repair (TEER) in adjunct to guideline-directed medical therapy.[2] We aimed to evaluate the prognostic role of EROA/LVEDV ratio, other two-dimensional (2D) and three-dimensional (3D) echocardiographic parameters, and clinical variables in patients with SMR undergoing TEER in our Center.

We enrolled consecutive patients with ≥moderate-to-severe SMR, undergoing MitraClip® implantation between 2011 and 2020, as clinically indicated. Informed consent was obtained from all subjects. The study complied with the Declaration of Helsinki and was approved by the local Ethics Committee (R1675/22–CCM1791). Patients underwent 2D and 3D transthoracic echocardiography (TTE) at baseline. 3D datasets were acquired from the apical view, in 4-beat full-volume or single-beat mode (according to heart rhythm). MR was graded by integrating qualitative, semi-quantitative, and quantitative criteria.[3] According to the European guidelines, SMR was defined as severe when EROA was ≥20 mm^2 or regurgitant volume ≥30 mL.[4] Patients were classified as d-SMR or p-SMR, as per EROA/LVEDV ratio ≥0.150 or <0.150, respectively. TEER was performed under general anesthesia, guided by fluoroscopy and transesophageal echocardiography. Residual MR grade after device deployment was quantified intraoperatively based on 2D and 3D anatomical assessment, color Doppler jet characteristics and pulmonary vein flow pattern.[5]

The endpoint of the study was a composite of all-cause death or hospitalization for HF within 12 months from the procedure. Follow-up was conducted through clinical visits, phone contact either with patients or their families, referring cardiologists or general practitioners. According to the occurrence or not of the endpoint (EP), patients were classified into 2 groups: EP+ and EP-, respectively. Descriptive and comparative statistics were used. To identify outcome predictors, univariable Cox proportional hazards model was conducted. Multivariable models were run including best subset selection with 3 predictor variables and were ranked by Akaike information criterion (AIC). The final model was identified by the lowest AIC value, and estimated regression coefficients were used to calculate the risk score for each patient. Kaplan-Meier analysis using the log-rank test was performed to compare the endpoint incidence. SPSS 27.0 (SPSS Inc., IL) and R 4.1.2 were used for statistical analysis.

Ninety-two patients with SMR were enrolled. 2DTTE, 2D and 3DTEE were available in all patients, whereas 3DTTE was missing in 4 patients. The follow-up was complete in all patients. Thirty-one patients met the endpoint: 24 hospitalizations for decompensated HF, 7 deaths (Table 1). No significant differences in comorbidities and anti-remodeling drugs were observed between p-SMR and d-SMR, nor between EP+ and EP-. d-SMR showed significantly higher LVEF and smaller LV dimensions vs. p-SMR patients (Table 1). No significant differences were observed in the number of implanted clips (2 clips: 58.8% in d-SMR vs. 51.2% in p-SMR), nor in residual MR grade after the procedure (respectively, 1.6±0.6 vs. 1.5±0.6) or EP incidence (33.3% vs. 34.1%). Compared with EP-, EP+ showed higher NYHA class and EuroScoreII values, had lower hemoglobin and higher BNP levels, and more often required inotropes before the procedure (35.5 vs. 13.1%); had significantly lower TAPSE, 3DLVEF and 3DRVEF (Table 1); were more frequently implanted with 2 clips (74.2% vs. 45.9%) and showed significantly higher post-implantation residual MR grade (1.9±0.6 vs. 1.3±0.5). The EROA/LVEDV ratio did not show prognostic value both at uni- and multivariable analysis. Statistically significant variables at univariable analysis were hemoglobin, EuroScoreII, TAPSE, 3DRVEF, and postprocedural residual MR grade. The model showing the smallest AIC included EuroScoreII, 3DRVEF, and residual MR grade (C-index = 0.762). From this model, a scoring algorithm was constructed to calculate the risk for all-cause mortality and hospitalization for HF at 12-months follow-up. Figure 1 shows the Kaplan-Meier curves stratified according to quartiles of score values.

Our data suggest that the proposed cut-off for EROA/LVEDV ratio may not apply to all real-world contexts.[6-7] Rather, the best candidates for TEER seem to be less clinically compromised patients, with a good RV function as assessed by 3DTTE, and a MV anatomy conducive to an optimal technical result. Arguably, a new scoring model, based on EuroScoreII, 3DRVEF and residual intraoperative MR grade, might predict the outcome of patients with SMR treated by TEER, and guide the clinician in planning an individualized follow-up.

This study is limited by its retrospective single-center nature and small sample size. Our results should be considered as preliminary, as they may not hold true for higher risk patients (e.g. extreme LV dysfunction and/or dilation). Although our study gives a further hint in the controversy on SMR treatment, especially regarding the RV role, further prospective studies are needed to confirm our findings.

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Declarations of interest

The authors have no conflicts of interest to disclose.

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References

1. Coats AJS, Anker SD, Baumbach A, et al. The management of secondary mitral regurgitation in patients with heart failure: a joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC. Eur Heart J. 2021;42(13):1254-1269. doi: 10.1093/eurheartj/ehab086.
2. Packer M, Grayburn PA. New Evidence Supporting a Novel Conceptual Framework for Distinguishing Proportionate and Disproportionate Functional Mitral Regurgitation. JAMA Cardiol. 2020;5(4):469-475. doi: 10.1001/jamacardio.2019.5971.
3. Lancellotti P, Pibarot P, Chambers J, et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. Eur Heart J Cardiovasc Imaging. 2022;23(5):e171-e232. doi: 10.1093/ehjci/jeab253.
4. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-2791. doi: 10.1093/eurheartj/ehx391.
5. Avenatti E, Mackensen GB, El-Tallawi KC, et al. Diagnostic Value of 3-Dimensional Vena Contracta Area for the Quantification of Residual Mitral Regurgitation After MitraClip Procedure. JACC Cardiovasc Interv. 2019;12(6):582-591. doi: 10.1016/j.jcin.2018.12.006.
6. Adamo M, Cani DS, Gavazzoni M, et al. Impact of disproportionate secondary mitral regurgitation in patients undergoing edge-to-edge percutaneous mitral valve repair. EuroIntervention. 2020;16(5):413-420. doi: 10.4244/EIJ-D-19-01114.
7. Ooms JF, Bouwmeester S, Debonnaire P, et al. Transcatheter Edge-to-Edge Repair in Proportionate Versus Disproportionate Functional Mitral Regurgitation. J Am Soc Echocardiogr. 2022;35(1):105-115.e8. doi: 10.1016/j.echo.2021.08.002.

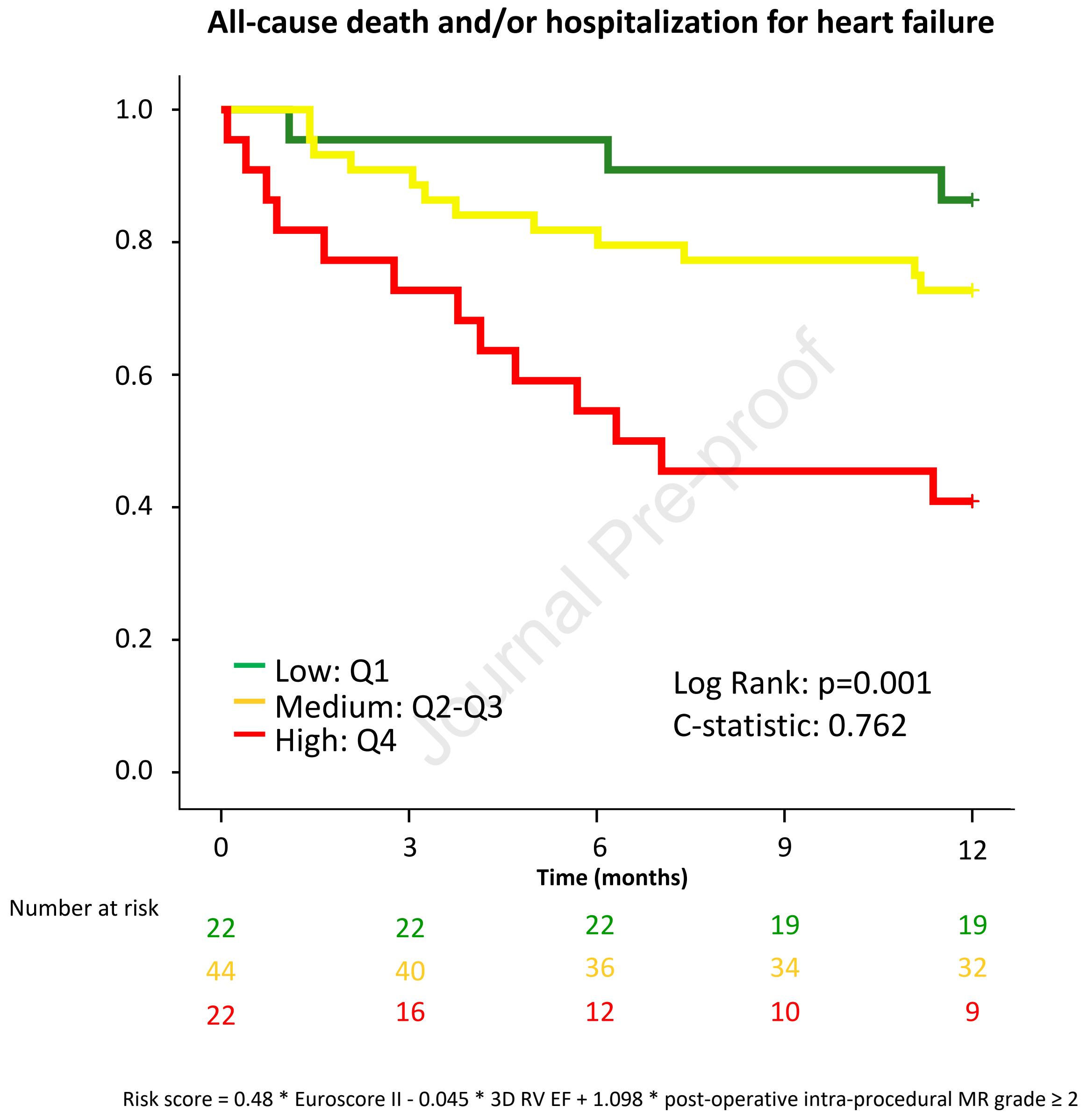
Figure legends

Figure 1. **Kaplan-Meyer curves for all-cause mortality and hospitalization for heart failure at 12-months follow-up in patients with secondary mitral regurgitation undergoing mitral valve transcatheter edge-to-edge repair, according to quartiles of the final scoring model**. 3D = three-dimensional; EF = ejection fraction; MR = mitral regurgitation; RV = right ventricular; TEER = transcatheter edge-to-edge repair.

Table 1 – Characteristics of study population

		SMR proportionality		Primary endpoint within 12MFU	
	All	**Proportionate**	**Disproportionate**	**Endpoint+**	**Endpoint-**
Demographics and clinical data	**n = 92**	**n = 41**	**n = 51**	**n = 31**	**n = 61**
Age (y)	73 ± 8	70 ± 8	75 ± 8*	74 ± 8	72 ± 8
Male (n, %)	72 (78.3)	32 (78.0)	40 (78.4)	26 (83.9)	46 (75.4)
EuroScore II (%)	7.0 [3.0-13.3]	6.3 [2.7-11.8]	7.8 [4.0-14.0]	12.2 [6.5-20.2]	5.2 [2.7-10.3]†
NYHA class (n, %)					
II	21 (22.8)	12 (29.3)	9 (17.6)	2 (6.5)	19 (31.1)†
III-IV	71 (77.2)	29 (70.7)	42 (82.4)	29 (93.5)	42 (68.9)†
Laboratory data	**n = 92**	**n = 41**	**n = 51**	**n = 31**	**n = 61**
Hemoglobin (mg/dL)	12.8 ± 1.6	13.1 ± 1.4	12.6 ± 1.7	12.2 ± 1.7	13.1 ± 1.5†
Creatinine clearance (mL/min)	51.0 ± 23.7	53.9 ± 25.4	48.7 ± 22.3	45.3 ± 21.3	53.9 ± 24.5
	n = 77	**n = 36**	**n = 41**	**n = 25**	**n = 52**
BNP (pg/mL)	500 [206-1162]	535 [190-1168]	500 [206-1056]	855 [426-1500]	357 [170-902]†
2D TTE	**n = 92**	**n = 41**	**n = 51**	**n = 31**	**n = 61**
LV EDD (mm)	68 ± 10	72 ± 10	66 ± 9*	70 ± 11	67 ± 9
LV ESD (mm)	55 ± 10	59 ± 9	52 ± 11*	57 ± 11	55 ± 10
2D LV EDV (mL)	193.8 ± 61.8	226.0 ± 60.7	167.9 ± 49.7*	189.3 ± 72.5	196.1 ± 56.1
2D LV EDVi (mL/m^2)	104.8 ± 31.4	121.3 ± 30.5	91.6 ± 25.6*	102.6 ± 37.4	106.0 ± 28.2
2D LV ESV (mL)	124.7 ± 51.8	153.6 ± 51.0	101.5 ± 39.6*	124.8 ± 59.3	124.7 ± 48.1
2D LV ESVi (mL/m^2)	67.4 ± 26.8	82.4 ± 25.7	55.3 ± 21.1*	67.5 ± 31.0	67.3 ± 24.6
2D LV EF (%)	37.3 ± 8.6	32.9 ± 5.5	40.9 ± 9.1*	36.0 ± 7.0	38.0 ± 9.3
LAd (mm)	53.4 ± 8.5	52.8 ± 6.6	54.0 ± 9.9	54.7 ± 9.1	52.8 ± 8.2
2D LAVi (mL/m^2)	71.9 ± 34.2	68.1 ± 23.3	75.0 ± 41.0	72.0 ± 23.3	71.9 ± 38.8
TR grade ≥ moderate (n, %)	31 (33.7)	12 (29.3)	19 (37.3)	9 (29.0)	22 (36.1)
TAPSE (mm)	19 ± 4	19 ± 5	19 ± 5	18 ± 4	20 ± 4†
PASP (mmHg)	45 ± 12	41 ± 11	49 ± 12*	46 ± 9	45 ± 13
Vena contracta (mm)	6.2 ± 1.5	6.1 ± 1.4	6.3 ± 1.5	6.6 ± 1.3	6.0 ± 1.5
EROA (mm^2)	30 ± 9	26 ± 6	33 ± 9*	30 ± 7	30 ± 9
EROA/LVEDV	0.165 ± 0.054	0.119 ± 0.021	0.202 ± 0.042*	0.174 ± 0.058	0.161 ± 0.052
Mitral regurgitant volume (mL)	45 ± 12	43 ± 10	47 ± 13	43 ± 10	46 ± 13
3D TTE	**n = 88**	**n = 39**	**n = 49**	**n = 29**	**n = 60**
3D LV EDV (mL)	201.3 ± 59.5	225.5 ± 56.7	178.8 ± 53.3*	197.2 ± 61.0	202.9 ± 59.3
3D LV EDVi (mL/m^2)	108.6 ± 29.7	121.3 ± 27.2	97.3 ± 27.5*	104.9 ± 29.8	110.2 ± 29.8
3D LV ESV (mL)	129.6 ± 50.8	154.3 ± 48.6	106.7 ± 41.6*	134.0 ± 55.2	127.8 ± 49.3
3D LV ESVi (mL/m^2)	69.7 ± 26.1	83.0 ± 23.8	58.0 ± 22.3*	70.3 ± 27.4	69.4 ± 25.7
3D LV EF (%)	37.2 ± 9.5	32.3 ± 6.5	41.6 ± 9.6*	34.4 ± 8.6	38.5 ± 9.7†
3D RV EDV (mL)	126.5 ± 45.8	130.8 ± 48.2	123.1 ± 44.0	133.5 ± 47.7	123.3 ± 44.9
3D RV EDVi (mL/m^2)	68.6 ± 23.1	69.8 ± 22.7	67.6 ± 23.6	72.1 ± 23.9	66.9 ± 22.7
3D RV ESV (mL)	70.3 ± 32.7	73.2 ± 35.5	68.0 ± 30.5	80.5 ± 36.8	65.5 ± 29.7
3D RV ESVi (mL/m^2)	37.9 ± 16.8	39.0 ± 17.8	37.1 ± 16.1	43.5 ± 19.0	35.3 ± 15.2†
3D RV EF (%)	45.8 ± 10.5	45.4 ± 10.0	46.0 ± 10.9	41.6 ± 9.2	47.7 ± 10.5†

12MFU=12-months follow-up; 2D=two-dimensional; 3D=three-dimensional; EDD=end-diastolic diameter; EDV=end-diastolic volume; EF=ejection fraction; EROA=effective regurgitant orifice area; ESD=end-systolic diameter; ESV=end-systolic volume; i=index; LAd=left atrial diameter; LAV=left atrial volume; LV=left ventricular; PASP=pulmonary artery systolic pressure; RV=right ventricular; SMR=secondary mitral regurgitation; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation.
* $p < 0.05$ disproportionate vs. proportionate; † $p < 0.05$ endpoint+ vs. endpoint-


All-cause death and/or hospitalization for heart failure
1.0
0.8
0.6
0.4
0.2
0.0
Low: Q1
Medium: Q2-Q3
High: Q4
Log Rank: p=0.001
C-statistic: 0.762
0
3
6
9
12
Time (months)
Number at risk
22 22 22 19 19
44 40 36 34 32
22 16 12 10 9
Risk score = 0.48 * Euroscore II - 0.045 * 3D RV EF + 1.098 * post-operative intra-procedural MR grade ≥ 2