[Title]: Secondary mitral regurgitation: keeping coherence with the ASE grading guidelines, which proportionality concept best predicts prognosis in the real-world?

[Título]: Regurgitação mitral secundária: qual o conceito de proporcionalidade que melhor prevê diagnóstico sendo coerente com as guidelines da ASE?

[Short Title]: Prognosis of Proportionality in sMR

[Authors]: João Presume[1], Pedro Lopes[1], Pedro Freitas[1], Francisco Albuquerque[1], Carla Reis[1], Eduarda Horta[1], Liliana Marta[1], Sara Guerreiro[1], Marisa Trabulo[1], João Abecasis[1], Pedro de Araújo Gonçalves[1], Manuel Almeida[1], Manuel Canada[1]; Miguel Mendes[1], Maria João Andrade[1], Regina Ribeiras[1]

[**Institutional Affiliations**]: [1] Cardiology Department, Hospital de Santa Cruz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal;

[Author Contribution]: conception and design (JP, PL, PF, FA, RR), data collection (JP, PL, PF, FA, CR, EH, MT, JA, PAG, MA, MJA, RR), data analysis (JP, PL, PF, FA, LM, SG, RR), drafting (JP, PL, PF, FA, RR), revising (JP, PL, PF, FA, CR, EH, LM, SG, MT, JA, PAG, MA, MJA, MM, RR). All authors read and approved the final manuscript.

[Key Words]: Secondary mitral regurgitation; Prognosis; Heart Failure; Echocardiography

[Corresponding Author]
[Name]: João Presume
[Telephone]: +351 21 043 1000 | [Fax]: +351 21 043 15 89
[E-mail]: joaopresume@hotmail.com

[Address]: [1,2] Av. Prof. Dr. Reinaldo dos Santos, 2790-134 Carnaxide, Lisbon, Portugal
[Word Count]: 3112 words.
[Declarations of interest]: none.
[Funding sources]: none

Abstract

Introduction:

Proportionality of secondary mitral regurgitation (sMR) may be a key factor to decide whether a patient might benefit from mitral intervention. The aim of this study was to evaluate the prognostic value of two different concepts of proportionality and assess their ability to improve MR stratification proposed by the ASE guidelines.

Methods:

We conducted a retrospective analysis in patients with reduced LVEF (<50%) and at least mild sMR. Proportionality status was calculated using formulas proposed by: a) Grayburn, *et al.* – disproportionate sMR defined as $\frac{EROA}{LVEDV} > 0.14$; b) Lopes, *et al.* – disproportionate sMR whenever measured EROA > theoretical EROA (determined as $\frac{50\% \times \text{LVEF} \times \text{LVEDV}}{\text{Mitral VTI}}$). Primary endpoint was all-cause mortality.

Results:

A total of 572 patients (69±12 years; 76% male) were included. Mean LVEF was 33±9%, with a median LVEDV of 174 mL [136;220] and a median EROA of 14mm^2 [8;22]. During a mean follow-up of 4.1±2.7 years, there were 254 deaths. Considerable disagreement ($p<0.001$) existed between both formulas: amongst 96 patients with disproportionate sMR by Lopes' criteria, 46 (48%) were considered proportionate by Grayburn's; and among 62 patients with disproportionate sMR by Grayburn's, 12 (19%) were considered proportionate by Lopes'.

On multivariate analysis, only Lopes' definition of disproportionate sMR maintained independent prognostic value (HR 1.5; 95%CI 1.07–2.1, p=0.018) and improved the risk stratification of ASE sMR classification.

Conclusion:

Amongst the two available formulas to define disproportionate sMR, Lopes' model emerged as the only one with independent prognostic value while improving the risk stratification proposed by the ASE guidelines.

Abstract *- Português*

Introdução:

A proporcionalidade da regurgitação mitral secundária (sMR) pode ser um fator chave na decisão de que doentes podem beneficiar de intervenção mitral. O objetivo deste estudo foi de avaliar o valor prognóstico de dois modelos de proporcionalidade e aferir a sua capacidade para melhorar a estratificação da regurgitação mitral proposta pelas guidelines da ASE.

Methods:

Realizamos um estudo retrospetivo com doentes com LVEF reduzida (<50%) e pelo menos sMR ligeira. O status de proporcionalidade foi calculado usando as fórmulas propostas por: a) Grayburn, *et al.* – sMR desproporcional definida por $\frac{EROA}{LVEDV} > 0.14$; b) Lopes, *et al.* – sMR desproporcional quando o EROA medido > EROA teórico (determinado por $\frac{50\% \times \text{LVEF} \times \text{LVEDV}}{\text{Mitral VTI}}$). O endpoint primário foi mortalidade por qualquer causa.

Results:

Um total de 572 pacientes (69±12 anos; 76% sexo masculino) foram incluídos. LVEF média foi de 33±9%, com um LVEDV mediano de 174 mL [136;220] e um EROA mediano de 14mm^2 [8;22]. Após um follow-up médio de 4.1±2.7 anos, ocorreram 254 mortes. Verificou-se marcada discordância (p<0.001) entre ambas as fórmulas: de entre 96 doentes com sMR desproporcional pelo modelo de Lopes, 46 (48%) foram considerados proporcionais pela fórmula de Grayburn; de entre os 62 doentes com sMR desproporcional pelo modelo de Grayburn, 12 (19%) foram considerados proporcionais pelo modelo de Lopes.

Em análise multivariável, apenas a definição de desproporcionalidade descrita por Lopes manteve valor prognóstico independente (HR 1.5; 95%CI 1.07–2.1, p=0.018) e melhorou a estratificação de risco pela classificação da sMR da ASE.

Conclusion:

De entre as duas fórmulas disponíveis para definição sMR desproporcional, apenas o modelo de Lopes demonstrou valor prognóstico independente e melhorou a estratificação de risco proposta pelas guidelines da ASE.

[Acronyms]:

ACEi – Angiotensin converting enzyme inhibitor;

ARB – Angiotensin II receptor blocker;

ASE – American Society of Echocardiography;

CRT – Cardiac resynchronization therapy;

COAPT – Cardiovascular Outcomes Assessment of the Mitraclip Percutaneous Therapy for Heart Failure Patients with Severe Secondary Mitral Regurgitation

EROA – Effective regurgitant orifice area;

sMR – secondary mitral regurgitation;

HF – Heart failure;

ICD – Implantable cardiac defibrillator;

LV – Left ventricle;

LVEF – Left ventricular ejection fraction;

LVEDV – Left ventricular end-diastolic volume;

MITRA-FR – Multicentre Study of Percutaneous Mitral Valve Repair Mitraclip Device in Patients With Severe Secondary Mitral Regurgitation;

MRA – Mineralocorticoid receptor antagonist;

NYHA – New York Heart Association;

RF – Regurgitant fraction;

RVol – Regurgitant volume;

PASP – Pulmonary artery systolic pressure;

TAPSE – Tricuspid annular plane systolic excursion;

TEER – Trancatheter edge-to-edge repair;

VTI – Velocity time integral;

Introduction

Secondary mitral regurgitation (sMR) most commonly results from abnormal left ventricular size, shape, or function.[1,2] Its manifestation in patients with reduced left ventricular ejection fraction (LVEF) is associated with worse prognosis.[1,2] Two recent landmark randomized clinical trials (MITRA-FR and COAPT) evaluating the role of transcatheter mitral edge-to-edge repair (TEER) in sMR showed conflicting results.[3,4] While MITRA-FR failed to show any benefit from intervention, the COAPT trial revealed a lower rate of HF hospitalization and all-cause mortality. While several reasons may account for the discrepancies found, the concept of sMR disproportionality has been suggested as an important one.

Grayburn, *et al.* were the first to introduce the concept of MR disproportionality as an elegant way to interpret the severity of sMR in line with LV dilation and dysfunction, assuming that sMR is hemodynamically significant when regurgitant fraction (RF) is at least 50%.[5] The model proposed by these authors assumes different lines of proportionality (whose slope varies according to the LVEF) that relate effective regurgitant orifice area (EROA) or regurgitant volume (RVol) to the LV end diastolic volume (LVEDV). As such, patients with MR EROA or RVol below the line of proportionality are considered to have non-severe / proportionate sMR, while patients above the line have disproportionate sMR. However, the only $\frac{EROA}{LVEDV}$ published cutoff by Grayburn *et al.* is 0.14 which is only valid for a RF of 50% and a LVEF of 30%.[6] Consequently, the clinical applicability of this cutoff is seriously compromised whenever LVEF is different from 30%.

Recently, Lopes *et al.* built upon the original concept of Grayburn *et al.* and emerged with a patient-individualized formula where a patient-specific theoretical cutoff of EROA / RVol is established according to individual LVEDV and LVEF (assuming also that hemodynamically significant sMR occurs when RF is at least 50%).[7] Therefore, the model by Lopes *et al.* has the advantage of being versatile and applicable to any patient. Whenever the Doppler measured EROA / RVol is superior to the established patient-specific theoretical cutoff, then sMR is considered disproportionate.

At its core, both authors theorize that mitral intervention can achieve better outcomes when applied to patients with disproportionate SMR. However, it remains to be established which is the best way to assess sMR proportionality. The aim of this study was to evaluate the prognostic value of both proportionality concepts and assess their ability to improve MR stratification on top of the American Society of Echocardiography (ASE) grading guidelines.[8]

Methods

Study population and patient assessment

We studied a single-center retrospective cohort of patients who underwent transthoracic echocardiography from 2010 until 2018 and were found to have at least mild sMR and reduced LVEF (defined as <50%). Patients had to be ambulatory and on guideline-directed heart failure therapy for at least 3 months before being included. Patients with age <18 years, hospitalization for decompensated HF in the previous 3 months, at least moderate aortic valve disease, previous valve intervention, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, left ventricular non-compaction cardiomyopathy or renal transplant were excluded. The study protocol was reviewed and approved by the local ethics committee, which waived the need for informed consent.

Transthoracic echocardiographic examinations were conducted with equipment by GE-Healthcare (Chicago, IL, USA). Data was retrieved from EchoPAC software (GE-Healthcare) for retrospective evaluation. Two-dimensional, M-mode and Doppler measurements (including MR quantification) were employed based on the criteria of the ASE.

During follow-up, patients had regular medical visits. Therapy adjustments were left at the discretion of the assistant physician. The primary endpoint was all-cause mortality.

Proportionality evaluation

Two frameworks for the evaluation of MR disproportionality were evaluated on this cohort.

According to Lopes, *et al.*, proportionality was determined based on calculation of an individualized theoretical EROA cutoff determined by the formula: $\frac{50\% \times \text{LVEF} \times \text{LVEDV}}{\text{Mitral VTI}}$.[7] Measured EROA by the PISA method was then compared with this theoretical cutoff.[7] Briefly, if measured EROA > individualized theoretical EROA the patient was considered to have disproportionate sMR.[7] If not, sMR was considered proportionate/non-severe.[7]

In order to determine disproportionality according to Grayburn, *et al.*, $\frac{EROA}{LVEDV}$ ratio was calculated.[5] The proportionality cutoff used was 0.14, according to published data (line of proportionality).[6] Even though this cutoff was established specifically for patients with a LVEF of 30% at a RF of 50% we considered that a ratio > 0.14 identified disproportionate sMR, whereas a ratio ≤ 0.14 was categorized as non-severe / proportionate.

Mitral regurgitation severity was classified according to the EROA cutoffs proposed by the ASE classification in order to allow meaningful comparisons between the two above mentioned formulas of sMR proportionality (grade I [mild] if EROA < $0.2cm^2$; grade II [moderate] if EROA 0.2-$0.29cm^2$; grade III [moderate-severe] if EROA 0.3-$0.39cm^2$; and grade IV [severe] if EROA ≥ $0.4cm^2$)[8].

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as mean and standard deviation, or median and interquartile range for variables with skewed distributions. Differences among groups were evaluated with the use of Pearson's Chi-squared test, Mann-Whitney U, and independent samples *t*-test, where appropriate. κ statistic was used to assess agreement between proportionality formulas. Kaplan-Meier survival curves were plotted for each group of patients. Patients were censured if mitral intervention or heart transplant/left ventricular assist device was performed. The log-rank test was used to assess for significant differences in time to endpoint between groups. Univariate and multivariate analysis with Cox regression were applied to evaluate the association between studied variables and all-cause mortality. Variables with a p-value < 0.05 were included in the multivariable model. Net reclassification index (categorical NRI) was used to ascertain if proportionality enhances prognostic value of MR grade stratification by ASE guidelines. All reported p-values are two-tailed, with a p-value of 0.05 indicating statistical significance. Analysis was performed using IBM SPSS Statistics software, version 25 (2017).

Results

Study population and follow-up

A total of 572 patients (mean age 69 ± 12 years; 76% male) were included. The majority of patients were in class II (55.8%) or III (33.4%) of New York Heart Association (NYHA). There were 526 (92.0%) patients treated with beta-blockers, 525 (91.8%) with angiotensin converting enzyme inhibitor / angiotensin II receptor blocker (ACEi/ARB), 235 (41.1%) with mineralocorticoid receptor antagonist (MRA), 170 (29.7%) had an implantable cardiac defibrillator (ICD), and 167 (29.2%) were under cardiac resynchronization therapy (CRT). Mean LVEF was 33 ± 9%, with a median LVEDV of 174 mL [IQR: 136 – 220], and a median EROA of 14mm^2 [IQR: 8 – 22]. According to ASE guidelines sMR was classified as mild (grade I) in 418 (73%) patients, moderate (grade II) in 109 (19%), moderate-to-severe (grade III) in 33 (6%) and severe (grade IV) in 12 (2%). Other clinical characteristics and echocardiographic parameters are further described in **Table 1**.

Discordance between SMR proportionality frameworks

According to Grayburn's model, 62 patients (11%) were classified as disproportionate, and 510 (89%) as non-severe/proportionate. On the other hand, Lopes' model categorized 96 (17%) patients as disproportionate and 476 (83%) as non-severe/proportionate. Amongst the 96 patients with disproportionate sMR by Lopes' formula, 46 (48%) were considered proportionate by the Grayburn's formula; and amongst the 62 patients with disproportionate sMR by Grayburn's, 12 (19%) were considered proportionate by Lopes' (meaning only a moderate agreement between the two frameworks as depicted by Cohen's $\kappa = 0.58$; $p < 0.001$).

Different SMR proportionality frameworks with different prognostic value

During a mean follow-up of 4.1 ± 2.7 years, there were 254 (44.4%) deaths. Kaplan-Meier survival curves for both models showed significant association between the presence of disproportionality and all-cause mortality (**Figures 1 and 2**). However, and after adjusting for several confounding variables associated with prognosis (namely, age, sex, creatinine, hypertension, atrial fibrillation, ischemic etiology, NYHA functional class, beta-blockers, ACEi/ARB, diuretics, ICD, CRT, LVEDV, LVEF, E, E/e', LAVI, SPAP, TAPSE and TR ≥ moderate), only Lopes' formula maintained independent prognostic impact (adjusted HR 1.5 [95% CI 1.07 – 2.1], $p = 0.018$; versus Grayburn's formula: adjusted HR 1.0 [95% CI 0.67 – 1.5], $p = 0.998$) – **Table 2**.

Reclassification of SMR severity

The reclassification of ASE SMR severity is presented in **Figure 3** and **Table 3.** Only Lopes' model was able to distinguish lower and higher risk subsets of patients according to the proportionality status when added to ASE SMR classification (NRI = 0.129; $p < 0.001$). Grayburn's model for disproportionality showed a non-significant NRI of 0.003 ($p = 0.455$) when added to the ASE sMR classification and was not able to improve risk prediction.

Discussion

Classifying sMR remains challenging, not only due to the morphology of the regurgitant orifice, but also owing to its dependence on loading conditions, its dynamic nature and its variation during the cardiac cycle. To the best of our knowledge, this is the first study that compared two different frameworks proposed to define sMR disproportionality. In this cohort, only Lopes' model of disproportionate sMR was independently associated with all-cause mortality and showed improvement in risk stratification when added to the ASE classification.

Whether MR acts as a "bystander" or a "contributor" in heart failure patients with reduced LVEF has always been questioned. This debate increased with the conflicting results of the two landmark trials of TEER in sMR. While MITRA-FR results suggest that sMR is just a "bystander", COAPT findings seem to indicate that there is a subgroup of patients where sMR is a "contributor" of the disease that when managed can lead to better outcomes.[9,10] It became paramount to understand why both trials revealed conflicting results in a somewhat identical population of heart failure patients.[3,4,9] Amongst the several explanations proposed by different investigators, the most striking one was the difference noted in mean EROA and LVEDV: MITRA-FR enrolled patients with smaller mean EROA and larger mean LVEDV when compared to COAPT.[11] The concept of disproportionate sMR (which simultaneously accounts for the severity of MR and LVEDV) emerged as a potential identifier of patients where sMR is the primary driver (or "contributor") for the progression of HF that might benefit the most from TEER.[5–7]

In this observational study, we sought to compare the prognostic impact of two published disproportionate sMR models and assess if they could improve our current method of sMR classification. Even though various retrospective studies have been published showing prognostic impact of Grayburn's model ([6,12–14]), our data suggests that the comparison of theorical EROA vs. measured EROA (Lopes' formula model) has greater association with all-cause mortality than the framework proposed by Grayburn. Two main reasons may justify these discrepancies: the cutoff of 0.14 proposed by Grayburn *et al.* only applies to patients with LVEF of 30%; Lopes' model uses an individualized formula that is more versatile and can be applied to any patient irrespective of their LVEF (which is accounted for in the original formula).

Our study also shows that including proportionality status significantly improved the risk stratification of ASE sMR classification. While the presence of disproportionate sMR by Lopes' formula showed a higher mortality risk for every ASE subgroup, this did not happen with Grayburn's model. This finding is particularly important for patients with at least moderate sMR, in whom the hemodynamic severity of the regurgitant lesion might not be accurately reflected by EROA and/or RVol alone. The inclusion of proportionality evaluation (which integrates LV size, LVEF and sMR grading) as an additional tool on a multiparametric assessment of sMR could be an important upgrade to identify patients at higher risk of events during follow-up. Nevertheless, it remains to be established (for example by a randomized clinical trial) if patients with disproportionate sMR are indeed the subgroup that will benefit most from mitral intervention.

Limitations

Our study has some limitations that should be acknowledged. This was a retrospective, single center study, and our conclusions should be viewed as hypothesis generating due to the possible presence of unmeasured confounding factors and selection bias, and should be further validated in prospective studies. Also, the method used for evaluation of MR severity was 2D echocardiography, which has various limitations and imperfect concordance of severity between measured parameters.[15,16] The regurgitant orifice in sMR is frequently semilunar or elliptical, affecting measurements leading to possible underestimation of the EROA by 2D PISA method. Furthermore, since volume status and blood pressure was not readily available on electronic records, it was not taken into account in the interpretation of sMR severity, which is notoriously dynamic. Moreover, caution should be taken when this concept is applied to patients with mild MR where measurement errors may be present.

Conclusion

In this study, the presence of disproportionate sMR was associated with lower survival during long term follow-up. Despite the existence of two formulas to define sMR proportionality status, only Lopes *et al.* model maintained independent prognostic impact and was able to improve risk stratification of sMR severity according to the ASE criteria.

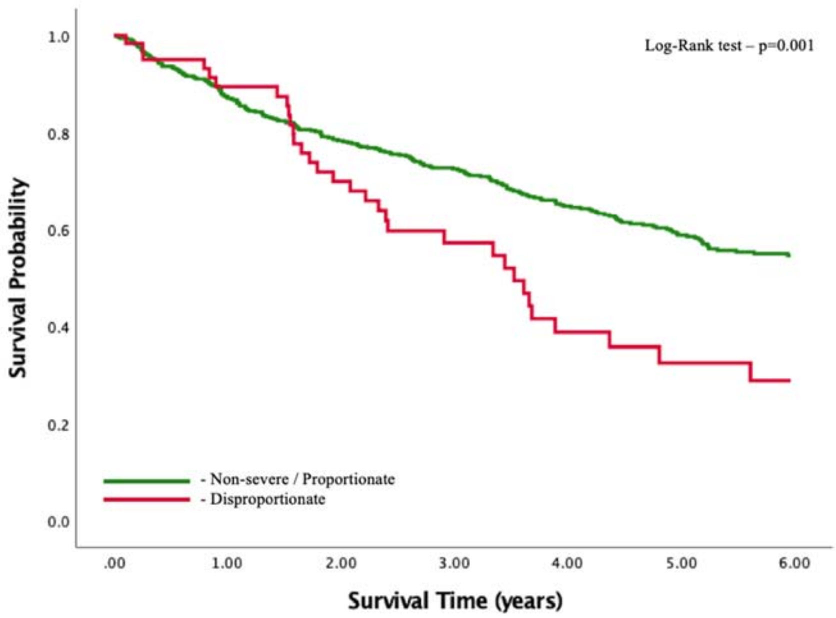
References

1. O'Gara; PT, Mack MJ. Secondary Mitral Regurgitation. N Engl J Med 2020;383:1458–67.
2. Chehab O, Roberts-Thomson R, Ng Yin Ling C, et al. Secondary mitral regurgitation: Pathophysiology, proportionality and prognosis. Heart 2020;106(10):716–23.
3. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med 2018;379(24):2307–18.
4. Obadia J-F, Messika-Zeitoun D, Leurent G, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. N Engl J Med 2018;379(24):2297–306.
5. Grayburn PA, Sannino A, Packer M. Proportionate and Disproportionate Functional Mitral Regurgitation: A New Conceptual Framework That Reconciles the Results of the MITRA-FR and COAPT Trials. JACC Cardiovasc Imaging [Internet] 2019;12(2):353–62. Available from: https://doi.org/10.1016/j.jcmg.2018.11.006
6. Packer M, Grayburn PA. New Evidence Supporting a Novel Conceptual Framework for Distinguishing Proportionate and Disproportionate Functional Mitral Regurgitation. JAMA Cardiol 2020;5(4):469–75.
7. Lopes PM, Albuquerque F, Freitas P, et al. Assessing proportionate and disproportionate functional mitral regurgitation with individualized thresholds. Eur Hear J - Cardiovasc Imaging 2021;351:1–10.
8. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr [Internet] 2017;30(4):303–71. Available from: http://dx.doi.org/10.1016/j.echo.2017.01.007
9. Pibarot P, Delgado V, Bax JJ. MITRA-FR vs. COAPT: Lessons from two trials with diametrically opposed results. Eur Heart J Cardiovasc Imaging 2019;20(6):620–4.
10. Packer M. Disproportionate functional mitral regurgitation: a new therapeutic target in patients with heart failure and a reduced ejection fraction. Eur J Heart Fail 2020;22(1):23–5.
11. Atianzar K, Zhang M, Newhart Z, Gafoor S. Why did coapt win while mitra-FR failed? Defining the appropriate patient population for MitraClip. Interv Cardiol Rev 2019;14(1):45–7.
12. Lindenfeld J, Abraham WT, Grayburn PA, et al. Association of Effective

Regurgitation Orifice Area to Left Ventricular End-Diastolic Volume Ratio With Transcatether Mitral Valve Repais Outcomes. JAMA Cardiol 2021;6(4):427–36.
13. Berrill M, Beeton I, Fluck D, et al. Disproportionate Mitral Regurgitation Determines Survival in Acute Heart Failure. Front Cardiovasc Med 2021;8(December):1–12.
14. Namazi F, van der Bijl P, Fortuni F, et al. Regurgitant Volume/Left Ventricular End-Diastolic Volume Ratio: Prognostic Value in Patients With Secondary Mitral Regurgitation. JACC Cardiovasc Imaging 2021;14(4):730–9.
15. Biner S, Rafique A, Rafii F, et al. Reproducibility of Proximal Isovelocity Surface Area, Vena Contracta, and Regurgitant Jet Area for Assessment of Mitral Regurgitation Severity. JACC Cardiovasc Imaging [Internet] 2010;3(3):235–43. Available from: http://dx.doi.org/10.1016/j.jcmg.2009.09.029
16. Uretsky S, Aldaia L, Marcoff L, et al. Concordance and Discordance of Echocardiographic Parameters Recommended for Assessing the Severity of Mitral Regurgitation. Circ Cardiovasc Imaging 2020;13(5):1–10.

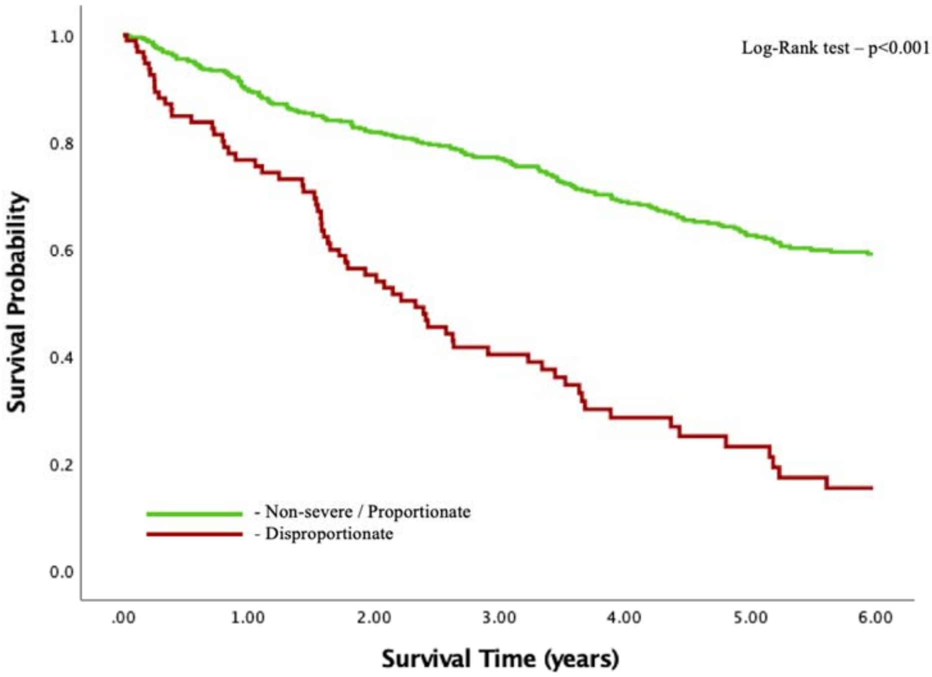
Figures and Tables

Figure 1 – Kaplan-Meier survival curves for Grayburn’s framework subgroups



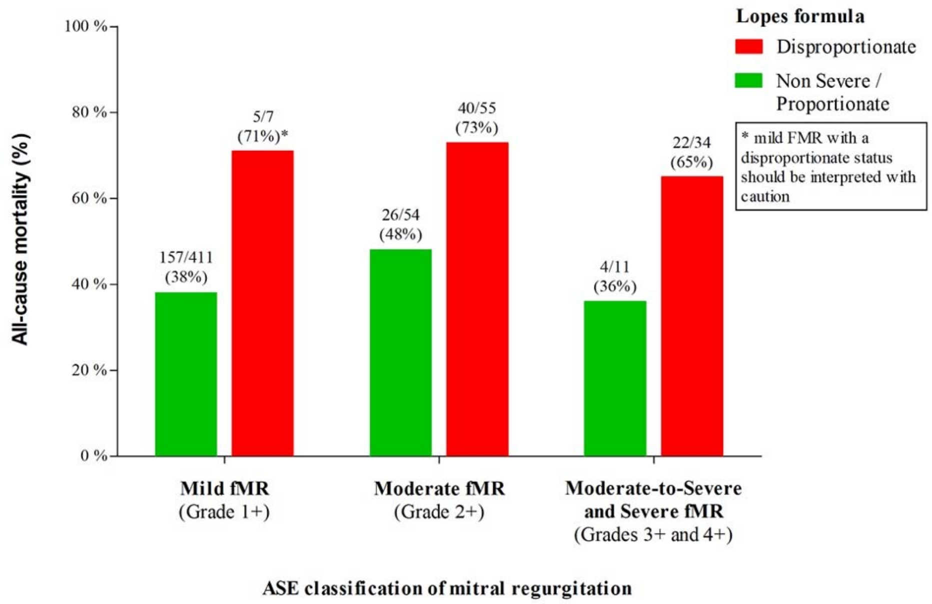
No at risk				
Non-severe / Proportionate	510	373	256	141
Disproportionate	62	35	13	8

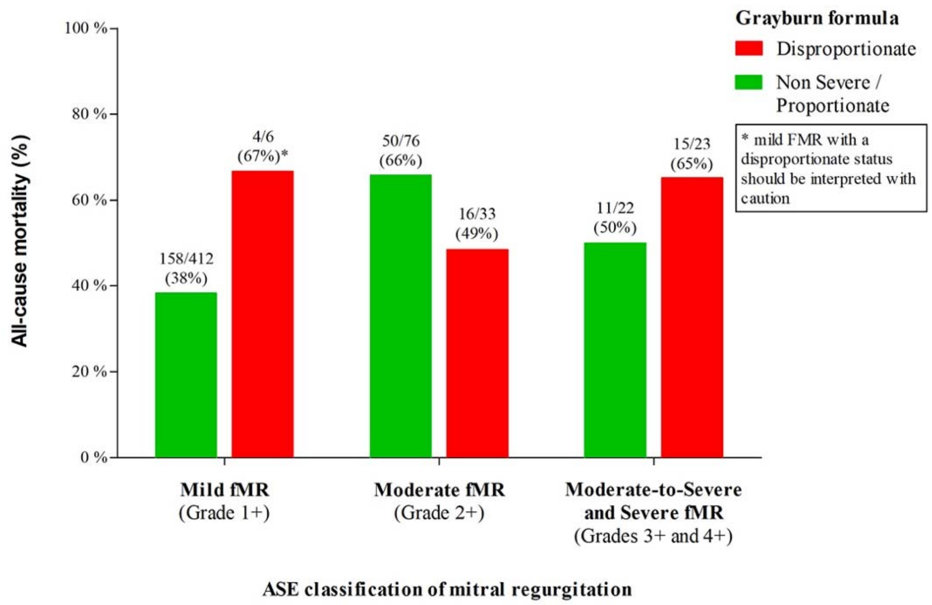
Figure 2 – Kaplan-Meier survival curves for Lopes' framework subgroups



No at risk				
Non-severe / Proportionate	476	362	252	141
Disproportionate	96	46	17	8

Figure 3 - a) Distribution and mortality of ASE MR classification stratified according to proportionality sub-groups for both frameworks;





ASE – American Society of Echocardiography; fMR – secondary/functional mitral regurgitation;

Table 1 – Clinical characteristics at baseline

Clinical characteristics	***Total population (n=572)***	***Non-Events (n=318)***	***Events (n=254)***	***p-value***
Age	69 ± 12	65 ± 12	72 ± 11	**<0.001**
Male	434 (76)	231 (73)	203 (80)	**0.043**
Atrial fibrillation	245 (43)	113 (36)	132 (52)	**<0.001**
Hypertension	414 (72)	213 (67)	201 (79)	**0.001**
Diabetes mellitus	178 (31)	95 (30)	83 (33)	0.472
Creatinine (mg/dL)	1.17 [0.92-1.82]	1.07 [0.88–1.45]	1.44 [1.02-2.59]	**<0.001**
NYHA				**<0.001**
I	55 (9.6)	45 (14)	10 (4)	
II	319 (55.8)	188 (59)	131 (52)	
III	191(33.4)	82 (26)	109 (43)	
IV	7 (1.2)	3 (1)	4 (2)	
Etiology				
Ischemic	350 (61.2)	182 (57)	86 (66)	**0.030**
Non-ischemic	222 (38.8)	136 (61)	86 (39)	**0.030**
Therapeutics				
ACEi/ARB	525 (91.8)	305 (96)	220 (87)	**<0.001**
Beta-blockers	526 (92.0)	299 (94)	227 (89)	**0.042**
MRA	235 (41.1)	134 (42)	101 (40)	0.566
Diuretics	368 (64)	184 (58)	184 (72)	**<0.001**
ICD	170 (29.7)	113 (36)	57 (22)	**0.001**

CRT-D/P	167 (29.2)	76 (24)	91 (36)	**0.002**
Echocardiographic findings				
LVEDV (mL)	169 [132-215]	169 [131-216]	178 [140-223]	**0.020**
LVEF (%)	35 [28-40]	36 [29-42]	32 [24-38]	**<0.001**
EROA (mm^2)	14 [8-22]	12 [7-19]	16 [10-24]	**<0.001**
RVol (mL)	23 [12-34]	19 [11-30]	27 [16-37]	**<0.001**
RF (%)	40 [22-60]	34 [18-51]	47 [31-70]	**<0.001**
E	0.84 [0.66-1.04]	0.85 [0.69-1.00]	0.94 [0.72-1.10]	**<0.001**
E/e'	13 [10-17]	12 [10-17]	14 [11-18]	**0.007**
LAVI	53 [41-70]	50 [39-66]	62 [51-76]	**<0.001**
SPAP (mmHg)	39 [33-49]	38 [32-45]	46 [37-57]	**<0.001**
TAPSE (mm)	19 [15-21]	20 [17-22]	17 [15-20]	**<0.001**
TR ≥ moderate	93 (16.3)	34 (11)	59 (23)	**<0.001**
ASE sMR classification				**<0.001**
Grade I	418 (73)	256 (80)	162 (64)	
Grade II	109 (19)	43 (14)	66 (26)	
Grade III	33 (6)	16 (5)	17 (7)	
Grade IV	12 (2)	3 (1)	9 (3)	

ACEi – Angiotensin converting enzyme inhibitor; ARB – Angiotensin II receptor blocker; ASE – American Society of Echocardiography; CRT – Cardiac resynchronization therapy; EROA – Effective regurgitant orifice area; sMR – secondary mitral regurgitation; ICD – Implantable cardiac defibrillator; LVEF – Left ventricular ejection fraction; LVEDV – Left ventricular end-diastolic volume; MRA – Mineralocorticoid receptor antagonist; NYHA – New York Heart Association; RF – Regurgitant fraction; RVol – Regurgitant volume; SPAP – Systolic pulmonary artery pressure; TAPSE – Tricuspid annular plane systolic excursion;

Table 2 - Hazard ratios (univariate and multivariate analysis) for the primary outcome

	Hazard Ratio (95% CI)	p-value
Grayburn Model		
Disproportionate sMR (univariate analysis)	1.846 (1.289-2.643)	**0.001**
Disproportionate sMR (multivariate analysis*)	0.999 (0.669-1.493)	0.998
Lopes Model		
Disproportionate sMR (univariate analysis)	3.174 (2.390-4.216)	**<0.001**
Disproportionate sMR (multivariate analysis*)	1.499 (1.072-2.097)	**0.018**

*Adjusted for Age, Sex, Serum Creatinine, Hypertension, Atrial fibrillation, Ischemic etiology, NYHA functional class, Beta-blockers, ACEi/ARB, Diuretics, ICD, CRT, LVEDV, LVEF, E, E/e’, LAVI, SPAP, TAPSE, TR ≥ moderate;
CI – Confidence interval; sMR – secondary mitral regurgitation

Table 2 – Net reclassification index of American Society of Echocardiography mitral regurgitation classification by: a) Grayburn, *et al* formula; b) Lopes, *et al* formula

a)

		Proportionate/Non-severe sMR	Disproportionate sMR
No event	Grade I-II by ASE classification	267	12
	Grade III-IV by ASE classification	5	1
Death	Grade I-II by ASE classification	207	19
	Grade III-IV by ASE classification	12	16

Event NRI = 0.003
P =0.45

b)

		Proportionate/Non-severe sMR	Disproportionate sMR
No event	Grade I-II by ASE classification	269	10
	Grade III-IV by ASE classification	3	3
Death	Grade I-II by ASE classification	182	44
	Grade III-IV by ASE classification	5	23

Event NRI = 0.129
P < 0.001

ASE – American Society of Echocardiography; sMR – secondary/functional mitral regurgitation.