Relevance of Functional Mitral Regurgitation in Aortic Valve Stenosis

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The clinical relevance of functional-mitral-regurgitation (FMR) in patients with aortic valve stenosis (AS) has been poorly studied using a quantitative approach. In addition, FMR prognostic value has mostly been analyzed after aortic valve replacement. Between 2010 and 2014 the echocardiograms of consecutive AS patients were retrospectively reviewed. Inclusion criteria were calcified aortic valve with transaortic-velocity >2.5 m/s and calculated mitral effective regurgitant orifice area (ERO) in the presence of mitral regurgitation. Organic mitral valve disease was an exclusion-criteria. Primary endpoint was heart failure or death under medical management. Secondary endpoint was heart failure or death. Eligible patients were 189, age 79 ± 8 years, 61% NYHA I/II, indexed aortic valve area (AVA) 0.55 ± 0.17 cm^2/m^2. Mitral ERO was 7.6 ± 4.2 mm^2 (>10 mm^2 in 30% of patients). Longitudinal function (by S'-TDI) was associated with mitral ERO independently of ejection fraction and ventricular volumes (p = 0.01). Mitral ERO greater than 10 mm^2 (threshold identified by spline survival-modeling) was associated with severe symptoms (Odds ratio [OR] 3.1 [1.6 to 6.0]; p = 0.0006) and higher pulmonary-arterial-pressure (OR 3.0 [1.4 to 5.9]; p = 0.002). Follow-up was completed for 175 patients. After 4.7 [1.4 to 7.2] years, 87 (50%) patients underwent AVR, 66 (38%) had heart-failure, 64 (37%) died. No procedure on FMR was required. Mitral ERO was independently associated with primary and secondary endpoints both as continuous variable (Hazard ratio [HR] 1.15 [1.00 to 1.30]; p = 0.04 and HR 1.23 [1.05 to 1.43]; p = 0.01 per 5 mm^2 ERO increase) or as ERO> versus ≤10 mm^2. Adjustment for S'-TDI or subgroup-analysis did not affect results. The analysis by AVA revealed the incremental prognostic role of mitral ERO over AS severity. In conclusion, AS patients with concomitant FMR >10 mm^2 holds a higher risk during medical follow-up. FMR quantitation, even for volumetrically modest regurgitation, provides incremental prognostic information over AS severity. **(Am J Cardiol 2020;136:115−121)**

Patients with aortic valve stenosis (AS) frequently present some degree of functional-mitral-regurgitation (FMR).[1,2] The prevalence of this combination is heterogeneous and is reported in up to 60% of patients.[3] When quantified, FMR seems to be mild in the majority of cases, but, nonetheless, held relevant hemodynamic[4] and clinical consequences.[5] The studies demonstrating the association between mitral regurgitation and morbidity and mortality in patients with AS have mostly analyzed the outcome after aortic valve replacement (AVR).[6−9] Therefore, the impact of quantitatively assessed FMR during the medical follow-up of patients with AS remains almost unexplored. In the era of expanding indication for aortic valve intervention, it is crucial to focus on the entire patients' natural history[10,11] rather than on the preoperative assessment at the time of referral for AVR.[12,13] The aim of the present study was to assess the clinical impact and outcome under medical management (before AVR) of quantified by mitral effective regurgitant orifice area (ERO) in patients with significant AS and associated FMR.

Methods

Consecutive echocardiograms performed at the echocardiographic laboratory of the University of Verona between January 2010 and December 2014 were retrospectively reviewed. Inclusion criteria were calcified aortic valve cusps with transaortic velocity >2.5 m/s and mitral ERO quantification when mitral regurgitation was present. Exclusion criteria were organic mitral valve disease, mitral valve prosthesis, and the presence of subaortic obstruction (which precludes a correct quantification of aortic valve disease). All patients were included in our institution's Valve Registry, approved by the Institution Review Board.

Transthoracic echocardiograms were obtained using a uniform acquisition protocol for imaging, performed by a single cardiologist (AR), with commercially available ultrasound systems. Apical-4 chamber and 2-chamber views were used for calculation of left ventricular (LV) volumes and ejection fraction (EF) by Simpson's biplane method.

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For assessment of AS, multiple transducer positions were used to record peak aortic jet velocities, always including the right parasternal view.[14] The highest velocity signal obtained was used to calculate peak and mean gradients. In patients with atrial fibrillation, 5 consecutive beats were averaged. Left ventricular outflow tract was measured at the base of the valve leaflets from a parasternal long-axis view in mid-systole and used to calculate aortic valve area (AVA) by the continuity equation[15] and was indexed for body surface area. Stroke volume was measured by pulsed wave Doppler in the left ventricular outflow tract and indexed for body surface area. Tissue Doppler velocities of the mitral annuli were recorded at medial and lateral level, and the measures were averaged.

In the presence of mitral regurgitation, ERO was quantified using the proximal velocity surface area (PISA) method. In order to exclude mitral regurgitation with organic etiology, it was defined as the presence of intrinsic anatomic abnormalities affecting the mitral valve or its subvalvular apparatus (for instance, rheumatic, prolapse, or congenital disease); on the opposite, the presence of annulus calcification without calcium infiltration of the mitral leaflet was not considered sufficient to classify the mitral regurgitation as organic, reflecting its little or no impact on mitral valve function.[16,17]

Follow-up information was obtained from chart review or direct interviews with patients or their relatives and was completed in 93% of patients. Information regarding valve intervention and mortality was obtained. Primary endpoint was defined as heart failure hospitalization or death under medical management (censoring on AVR). Secondary endpoint included any heart failure hospitalization or death.

Continuous variables are presented as means ± standard deviation. Categorical variables are expressed as absolute numbers and percentages. Differences between groups were analyzed using unpaired *t* test, $\chi^{2,}$ or analysis of variance, as appropriate. Correlations between variables were evaluated with Pearson or Spearman's coefficients. Associations between variables were assessed using regression analysis. The cohort has been divided into 2 groups: significant FMR versus others; the threshold was selected analyzing the spline knotted model for the primary endpoint using mitral ERO as continuous covariate (Supplementary Figure 1). Cox Proportional Hazards Model was used to calculate hazards for the endpoints. Only variables that were found to be significant in univariate analyses were included in multivariate analyses. *p* Value <0.05 was considered statistically significant.

Results

Based on inclusion criteria, 189 patients formed the study population (Table 1). Twenty-six percent had EF <50%, and 39% were highly symptomatic. AS was graded as severe (i.e., indexed AVA <0.6 cm^2/m^2) in 60% patients (with average indexed AVA 0.55 ± 0.17 cm^2/m^2). Spline curve modeling for primary endpoint prediction at 3 years revealed a steep increase in event-rate at about ERO of 10 mm^2, steadily increasing with higher ERO values, as displayed in Supplementary Figure 1; this threshold was thus chosen to subdivide our population. A total of 133 (70%) patients presented no-FMR or minimal FMR (ERO ≤10 mm^2), while 56 (30%) had mitral ERO >10 mm^2. In only 2 cases, the mitral ERO exceeded 30 mm^2. Patients with higher mitral ERO presented more frequently with NYHA class III/IV larger end-diastolic volume and left atrial volume, lower EF, higher E/e', and higher systolic pulmonary artery pressure in comparison with patients with ERO ≤10 mm^2.

Clinical and echocardiographic determinants of ERO are displayed in Table 2. Indexed end-diastolic volume, EF, and mitral annular peak systolic velocity at Tissue Doppler (S'-TDI) were significantly associated with higher ERO. In a comprehensive multivariate model, only S'-TDI (chi-square 6.2; p = 0.01) maintained an independent association with ERO >10 mm^2, whereas ventricular volumes and EF lost significance. Using EF instead of end-diastolic volume in the model did not alter the significance of S'-TDI.

Regarding the clinical consequences, FMR was associated with higher pulmonary arterial pressure (>45 mmHg) (OR for ERO>10 mm^2: 3.0 [1.4-5.9]; p = 0.002), lower indexed stroke volume (<35 ml/m^2) (OR for ERO>10 mm^2: 2.6 [1.3-5.1]; p = 0.008) and more severe symptoms (OR for ERO>10 mm^2: 3.1 [1.6-6.0]; p = 0.0006).

Median follow-up was 4.7 [IQR: 1.4 to 7.2] years, during which 87 (50%) patients underwent AVR (39 transcatheter AVR and 48 surgical AVR), and 64 (37%) patients died, 41 (23%) under medical management (primary endpoint) and 23 (13%) after AVR. No procedure on FMR was performed. Furthermore, 66 (38%) patients had a hospitalization for heart failure (46 during medical follow-up and 20 post-AVR).

Time course for primary endpoint is displayed by Kaplan Meier curves in Figure 1; the curves show an early separation and progressive divergence resulting in a notably different 2- and 4-year event rate: 38 ± 5% and 47 ± 6% for ERO ≤10 mm^2 and 59 ± 7% and 90 ± 5% for ERO >10 mm^2 (p <0.0001). The number of overall and medical events by ERO groups are shown in Supplementary Table 1.

Cox proportional hazard models are presented in Table 3-left column. ERO greater than 10 mm^2 was significantly associated with events occurring during the medical follow-up (HR 2.75 [1.81 to 4.19]; p <0.0001), even after adjusting for age, left ventricular EF, and AVA (HR: 2.17 [1.39 to 3.37]; p = 0.0006). Using mitral ERO as continuous variable, HR was 1.21 [1.08 to 1.35]; p = 0.002 for each 5 mm^2 increase unadjusted. Significance persisted after multivariable adjustments (HR 1.15 [1.00 to 1.30]; p = 0.04 for 5 mm^2 ERO increase).

Kaplan Meier curves for secondary endpoint were similar (Figure 1), and ERO >10 mm^2 was associated with overall events univariably (HR 3.74 [2.44 to 5.73]; p <0.0001) and in multivariable analysis (HR 2.72 [1.68 to 4.38]; p <0.0001), as shown in Table 3-right column. Using mitral ERO as continuous variable, the positive association with secondary endpoint was confirmed (HR 1.23 [1.05 to 1.43]; p = 0.01 per 5 mm^2 ERO increase after multivariable adjustment).

Further adjustment for S'-TDI did not affect results: adjusted HR for ERO >10 mm^2 was 2.05 [1.27 to 3.33]; p = 0.004 for the primary endpoint, and 2.52 [1.50 to 4.24]; p = 0.0005 for the secondary endpoint.

Table 1
Clinical and echocardiographic characteristics of overall population and according to two ERO subgroups (ERO 0−10 mm^2 and ERO >10 mm^2)

Variable	Overall population (n = 189)	Effective regurgitation orifice		p Value
		0−10 mm^2 (n = 133)	>10 mm^2 (n = 56)	
Age (years)	79 ± 8	78 ± 9	81 ± 6	0.03
Men	95 (50%)	65 (49%)	30 (54%)	0.6
Body surface area (m^2)	1.75 ± 0.2	1.77 ± 0.2	1.72 ± 0.2	0.1
NYHA class III-IV	73 (39%)	41 (31%)	32 (59%)	0.0006
Systolic blood pressure (mmHg)	133 ± 23	136 ± 23	128 ± 23	0.09
Diastolic blood pressure (mmHg)	77 ± 12	79 ± 10	72 ± 14	0.004
Atrial fibrillation	45 (24%)	28 (21%)	17 (30%)	0.2
Arterial hypertension	156 (83%)	107 (81%)	49 (87%)	0.4
Dyslipidemia	127 (67%)	88 (66%)	39 (70%)	0.2
Type 2 Diabetes	48 (25%)	33 (25%)	15 (27%)	0.9
Smoker	35 (19%)	27 (20%)	8 (14%)	0.5
Family history of CV disease	25 (13%)	18 (14%)	7 (13%)	0.9
End-diastolic volume index (ml/m^2)	72 ± 22	66 ± 18	87 ± 27	<0.0001
End-systolic volume index (ml/m^2)	34 ± 20	29 ± 17	45 ± 28	<0.0001
Ejection fraction (%)	56 ± 14	59 ± 13	50 ± 17	<0.0001
Ventricular septum (mm)	14.6 ± 3	14.6 ± 3	14.6 ± 3	0.9
Stroke volume index (ml/m^2)	42 ± 11	42 ± 10	41 ± 12	0.4
Peak gradient (mm Hg)	54 ± 23	55 ± 24	53 ± 21	0.7
Mean gradient (mm Hg)	32 ± 14	33 ± 15	32 ± 13	0.7
Aortic valve area (cm^2)	0.95 ± 0.33	0.97 ± 0.32	0.92 ± 0.35	0.4
Aortic valve area index (cm^2/m^2)	0.55 ± 0.17	0.55 ± 0.16	0.54 ± 0.19	0.7
E (cm/s)	84 ± 27	79 ± 27	96 ± 30	0.0006
A (cm/s)	90 ± 30	93 ± 29	80 ± 34	0.05
DTE (ms)	199 ± 71	210 ± 75	172 ± 57	0.004
S'-TDI (cm/s)	6 ± 1	6 ± 1	5 ± 1	<0.0001
E/e'	13± 6	12 ± 6	16 ± 7	0.001
sPAP (mmHg)	43 ± 11	40 ± 8	49 ± 15	<0.0001
Left atrial volume index (ml/m^2)	44 ± 17	41 ± 18	51 ± 15	0.0008
Mitral ERO (mm^2)	7.6 ± 4.2	3.4 ± 3.3	17.6 ± 5.7	<0.0001

Abbreviations: CV = cardiovascular; DTE = deceleration time of E wave; E/e' = ratio between E wave velocity and early diastolic velocity of the mitral annulus; ERO = effective regurgitant orifice; NYHA = New York Heart Association functional class; S'-TDI = systolic velocity of the mitral annulus; sPAP = systolic pulmonary artery pressure.

Table 2
Clinical and echocardiographic determinants of ERO >10 mm^2

	Univariate determinants of ERO >10 mm^2		Multivariate determinants of ERO >10 mm^2	
	Chi-square	p	Chi-square	p
Age (years)	5.5	0.02	3.0	0.08
Men (n)	0.3	0.55		
Systolic Blood Pressure (mmHg)	3.1	0.07		
Diastolic blood pressure (mmHg)	8.4	0.004	3.1	0.08
Interventricular septum (mm)	0.1	0.9		
End diastolic volume (mL)	22.7	<0.0001	3.4	0.07
Ejection fraction (%)	16.4	<0.0001		
AVA (cm^2)	0.8	0.37		
E (cm/s)	11.9	0.0006		
A (cm/s)	4	0.04		
S'-TDI (cm/s)	21.8	<0.0001	6.2	0.01
E/e'	9.4	0.002	0.4	0.5
LAV (ml)	12.3	0.0004	0.1	0.7

Abbreviations: AVA = aortic valve area; E/e' = ratio between E wave velocity and early diastolic velocity of the mitral annulus; ERO = effective regurgitant orifice; LAV = left atrial volume; S'-TDI = systolic velocity of the mitral annulus.

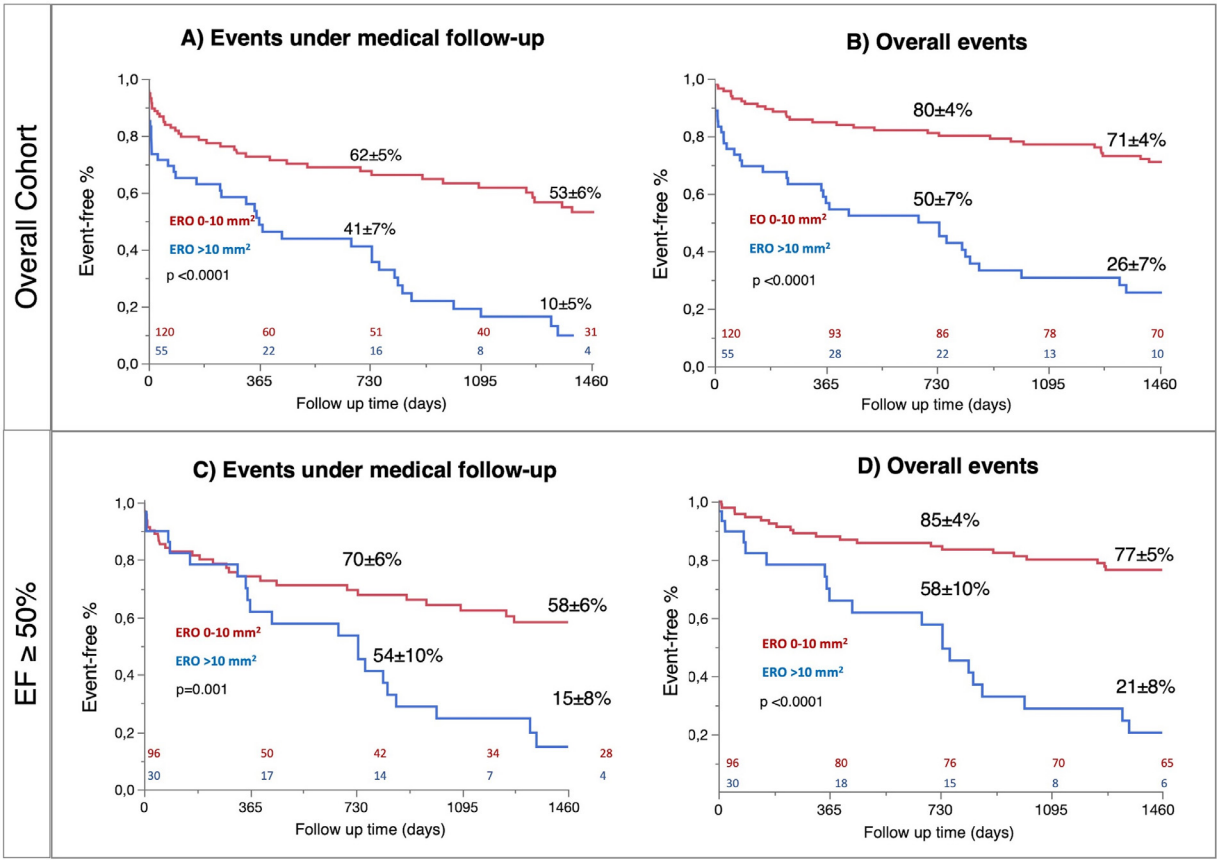

Figure 1. Central illustration. Kaplan-Meier curves for events under medical follow-up (A and C) and overall events (B and D) according to the severity of concomitant mitral regurgitation. Figures A and B represent the overall study cohort. Figure C and D represent the subgroup of patients with preserved EF (≥50%) Abbreviations: EF = ejection fraction; ERO = effective regurgitant orifice.

Table 3
Cox proportional hazard regression model for primary (heart failure or death under medical management) and secondary endpoint (overall heart failure or death). Models are presented for ERO as categorical variable as well as for 5 mm^2 continuous increase

	Primary endpoint		Secondary endpoint	
	Unadjusted	Adjusted for age, EF, AVA	Unadjusted	Adjusted for age, EF, AVA
HR [95%CI] for ERO >10 mm^2	2.75 [1.81−4.19]; p <0.0001	2.17 [1.39−3.37]; p =0.0006	3.74 [2.44−5.73]; p <0.0001	2.72 [1.68−4.38]; p <0.0001
HR [95%CI] for ERO 5 mm^2 increase	1.21 [1.08−1.35]; p = 0.002	1.15 [1.00−1.30]; p =0.04	1.33 [1.19−1.49]; p <0.0001	1.23 [1.05−1.43]; p =0.01

Abbreviations: AVA = aortic valve area; CI = Confidence Interval; EF = ejection fraction; ERO = effective regurgitant orifice; HR = hazard ratio.

A Forest plot of HRs for the primary endpoint in patients with ERO >10 mm^2 is presented in Figure 2. ERO greater than 10 mm^2 confirmed to impact the outcome in each subgroup of patients with the only noticeable exception of patients with elevated pulmonary pressure level (≥45 mm Hg, p for interaction <0.0001). The analysis was then focused on the subgroup of patients with EF ≥50%. This group was composed of 140 patients (mean age 79 ± 8 years; male 46%); 94 of these (67%) had FMR (mean ERO of 9 ± 7 mm^2). As shown in Figure 1, FMR was overall associated with higher event rate in patients under medical follow-up: event rate at 4 years were 85 ± 8% versus 42 ± 6% in patients with ERO above versus below 10 mm^2. On note, in patients with preserved EF, the separation between the 2 curves began after approximately 1 year. Secondary endpoint was also significantly worse in patients with more FMR and followed a similar pattern: event rate at 4 years were 79 ± 8% versus 23 ± 5% in patients with ERO above versus below 10 mm^2. Hazards for primary endpoint were 2.31 [1.97 to 3.91]; p = 0.002 for ERO >10 mm^2 unadjusted, and 1.92 [1.11 to 3.32]; p = 0.02 for ERO >10 mm^2 after adjustments for age and AVA. Significance for ERO >10 mm^2 was maintained in secondary endpoint analysis (HR 4.26 [2.49 to 7.30]; p < 0.0001 unadjusted model and HR 3.87 [1.17 to 6.89]; p <0.0001 in multivariate model).

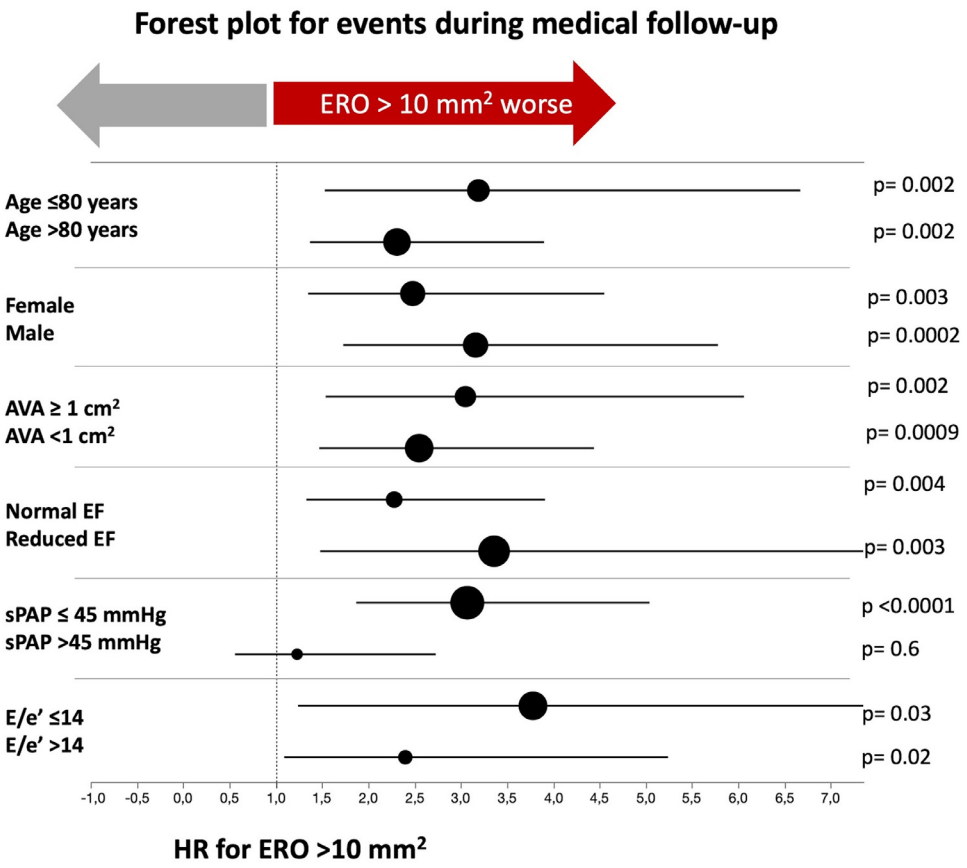

Figure 2. Subgroup analysis showing the impact of ERO >10 mm^2 on events during medical follow-up. Abbreviations: AVA = aortic valve area; E/e' = ratio between E wave velocity and early diastolic velocity of the mitral annulus; EF = ejection fraction; ERO = effective regurgitant orifice; HR = hazard ratio; sPAP = systolic pulmonary artery pressure.

Combining AS severity with FMR quantification, the Kaplan Maier curves for primary endpoint (Supplementary Figure 2) show that patients with severe AS and ERO >10 mm^2 had the worse outcome (2-year event rate 57 ± 9%), while patients with moderate AS and no/trivial MR the best (2-year event rate 19 ± 6%). Prognosis during medical follow-up was not different comparing patients with moderate AS associated with ERO >10 mm^2, with patients with severe AS but without significant FMR (2-year event rate 46 ± 8 and 50 ± 11%).

Discussion

The main findings of the present study are:

1. AS patients presenting with concomitant FMR of at least 10 mm^2 holds a considerably higher risk of heart failure or death, particularly during the medical follow-up.
2. Among AS patients with preserved EF, the presence and quantitation of FMR identify the risk of events, particularly after the first year of medical follow-up.
3. FMR quantitation, even of relatively modest amount, provides incremental prognostic information over the AS severity itself.

Despite some contrasting results,[18,19] it is currently accepted that the presence of moderate or severe mitral regurgitation identifies an advanced stage of AS, and the patients present considerably worse prognosis after treatment.[20] This combination of aortic and mitral valve disease has intrinsic pathophysiological complexity.[21] First of all, FMR in AS patients has different determinants versus the more common FMR found in heart failure patients.[22] In the present study, the FMR associated echocardiographic features were LV remodeling and loss of systolic longitudinal shortening rather than the conventional FMR determinants (tenting area and coaptation depth).[3] Longitudinal function estimated by S'-TDI may reflect the burden of LV remodeling, during which longitudinal performance is lost, and circumferential function is gained to compensate.[3,23,24] Second, regarding the etiology, FMR seems more prone to improve after AVR as compared with organic mitral regurgitation.[25] Third, another distinguishing feature of FMR in AS patients is the commonly modest quantitative amount of regurgitation. This aspect, detectable only by a quantitative approach, is shown by our study where the average regurgitant volume is about 21 ± 12 ml per beat, which corresponds to 11 ± 7 mm^2 of mitral ERO. This raises the doubt on how a small regurgitant volume could hold such a dismal prognosis. The reason can be found in the pathophysiology of AS, which usually presents with relatively small ventricles and concentric hypertrophy, generating high end-diastolic intraventricular pressure.[26] In this scenario, even a modest mitral regurgitation can significantly reduce the

forward stroke volume as well as increase the left atrial pressure or promote left atrial dysfunction, and ultimately activate neurohormonal signals which are known to contribute the remodeling and the worse natural history, similarly to what has been described for heart failure with preserved EF.[27] Although this hypothesis will require further evidence, it is corroborated by the remarkable association between FMR with NYHA class and pulmonary pressure level in our study.

As mentioned, the FMR in AS has rarely been studied in a quantitative manner, and this is one strength of our study. Indeed, without a homogeneous quantification method, it would be impossible to stratify the individual patients' risk linked to FMR, and most of the regurgitations would fall in the mild or moderate grade at most, without gaining much attention.

From a spline modeling of the risk in Supplementary Figure 1 we inferred that excess mortality due to FMR begins at about ERO 10 mm^2. It is not surprising that this value does not correspond to current guidelines' threshold for mitral regurgitation severity, as AS patients or combined valve disease, in general, are not adopted to generate recommendation.[15]

Another strength of our study is the focus on outcome during the medical management. Indeed, the majority of the study in literature, particularly from referral centers, investigates the pre-AVR period and the subsequent follow-up; little data are available for the long natural history of this progressive disease,[28] before the development indication for AVR. Furthermore, during 5 years of medical follow-up, only 46% of our cohort received an indication for percutaneous or surgical AVR. This highlights considerable undertreatment of the disease, similar to what is seen for other valve diseases.[29–31] This undertreatment, combined with the high event rate under medical management, reveals the need for early detection and better risk stratification of the patients followed in the echocardiography laboratory.

Forest plot analysis shows that the negative impact of ERO >10 mm^2 appears in all subgroups (male vs female, older vs younger patients, non-severe vs severe AS, and different grades of diastolic dysfunction); only higher systolic pulmonary artery pressure leads to worse prognosis, per se, identifying a further stage that should not be reached.[20] Additionally, the prognostic impact of concomitant FMR is confirmed in patients with EF ≥50% and emerged after about 1 year of follow-up, as shown by the separation of the Kaplan Meier curve. Noteworthy, asymptomatic patients with severe AS at baseline and EF less than 60% have increased risks of all-cause and cardiovascular mortality even after AVR.[32] Moreover, others demonstrated that EF <60% in the presence of moderate AS predicts further deterioration of EF and appears to represent abnormal EF in AS.[33] We suggest that a concomitant FMR might be a further clue of abnormal LV function at this stage.

The small size of the study population and the single-center, retrospective design are the main limitations of our study. Also, we do not have the power to define a precise mitral ERO cutoff for excess mortality, and our proposed analysis should be considered as a pilot experience that will need further validation. Another limitation is that we did not have details on the cardiovascular cause of death. We decided to study the events under medical management in terms of combined endpoint of heart failure and all-cause of mortality. Besides, it is often difficult to define the actual cause of death in this cohort of relatively old patients, which could be valve-related even in the presence of non-severe AS. We did not have speckle tracking analysis available for all the patients to study longitudinal LV function; however, we measured and averaged S'TDI at medial and lateral level in all the patients.

Current guidelines encourage to find criteria for identification of patients with asymptomatic severe AS who would benefit the most from early AVR and recommend risk stratification of patients with AS using the integration of a constellation of different variables; however, there is not yet a specific mention for concomitant FMR.[2] As a clinical implication of the present study, in asymptomatic patients with moderate-to-severe AS and normal EF, a concomitant FMR should trigger the clinician towards a more objective assessment of functional capacity (treadmill test or, preferably, cardiopulmonary exercise test).[11] Similarly, unclear symptoms in patients with non-severe AS and concomitant FMR should be judge as non-valve related with extreme caution. Cardiologists' attention directed to both AS severity, and FMR quantification, may contribute to improve the individual patient's management, not only at the time of referral but also during the − frequently long − medical follow-up.

Authors Contribution

Giovanni Benfari: conceptualization, writing - review & editing, writing - original draft, supervision; Martina Setti: writing - review & editing, writing - original draft; Stefano Nistri: writing - review & editing, writing - original draft; Diego Fanti: methodology, writing - review & editing, writing - original draft; Caterina Maffeis: writing - review & editing, writing - original draft; Elvin Tafciu: conceptualization; michele pighi: conceptualization; Mariantonietta Cicoira: supervision; Flavio L Ribichini: supervision; Andrea Rossi: supervision, conceptualization, methodology.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Nothing to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.09.016.

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