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Prevalence and prognostic implications of different aetiologies of low flow aortic stenosis

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Abstract

Background The prevalence and prognostic implications of low-flow (LF) aetiologies in aortic stenosis (AS) are unknown. This study aimed to characterize the specific causes of LF, their prevalence, and prognostic significance.

Methods In 408 patients with severe LFAS included, the aetiology of LF was identified. The primary endpoint was the composite of all-cause death and hospitalizations for heart failure (HF) up to 36 months. Secondary endpoints included individual components of the primary endpoint and cardiovascular mortality.

Results The most common LF cause was reduced LVEF ($n=228$, 55.9%), while preserved LVEF included five aetiologies: (1)mixed aetiologies ($n=65$, 36.1%), (2)small LV cavity ($n=58$, 32.2%), (3)significant isolated mitral regurgitation ($n=39$, 21.7%), (4)significant isolated tricuspid regurgitation ($n=13$, 7.2%), (5)significant isolated mitral stenosis ($n=5$, 2.8%). Over a median follow-up of 15 (IQR 6 – 36) months obtained in 302 patients, 159 (52.6%) reached the primary composite endpoint, 108 (35.8%) died and 91 (30.8%) were hospitalized due to HF. LF aetiology was not associated with outcomes. Independent predictors of the primary endpoint were severe MR (adj.HR 1.71, $p=0.04$) and TR (adj.HR 1.47, $p=0.04$). Aortic valve replacement (adj.HR 0.76, $p<0.001$) and mean transvalvular gradient ≥ 40 mmHg (adj.HR 0.39, $p<0.001$) were protective.

Conclusions The main cause of LFAS is reduced LVEF, while in preserved LVEF mixed causes and small LV volume prevailed, without association with the outcome. Severe mitral and tricuspid regurgitation were strongly associated with worse outcomes, while valve replacement and mean transvalvular gradient ≥ 40 mmHg emerged as protective factors.

Keywords Aortic stenosis, Concentric remodeling, Tricuspid regurgitation, Aortic valve replacement, Paradoxical low flow

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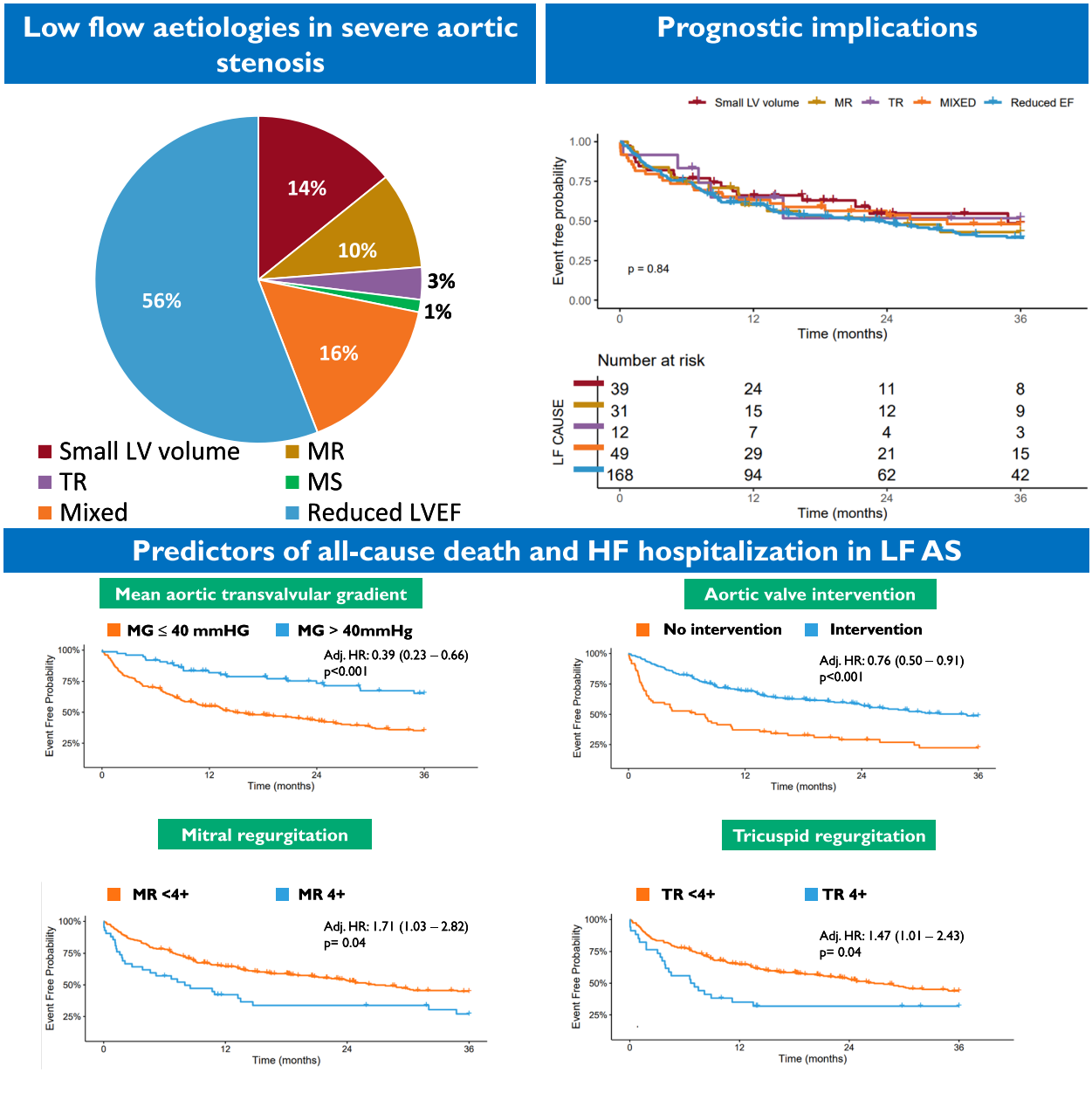
Graphical abstract

This study aimed to address unanswered questions in low-flow aortic stenosis (LF AS). In patients with preserved LVEF (paradoxical low flow), five aetiological factors were identified, with different prevalence. Survival curves showed no significant difference in the occurrence of the primary endpoint according to the LF cause. Factors independently associated with a higher risk of HF hospitalizations and all-cause mortality in LF AS were severe (4+) mitral regurgitation (MR), severe (4+) tricuspid regurgitation (TR), mean transvalvular gradient ≥40mmHg (MG, protective factor) and aortic valve intervention (protective factor). *LV: left ventricular; MR: mitral regurgitation; TR: tricuspid regurgitation; MS: mitral stenosis; LVEF: left ventricular ejection fraction*



Introduction

Aortic stenosis (AS) is the most common valvular heart disease and the most frequent cause of valve procedure, with a significant burden on global healthcare systems due to its epidemiology, adverse clinical outcomes, and increasing incidence with aging populations [1]. While

many patients with severe AS exhibit preserved left ventricular (LV) ejection fraction (EF) and high transvalvular flow rates, a distinct subset of individuals presents with low flow (LF) aortic stenosis [2, 3]. LF does not necessarily imply the presence of low transvalvular gradient as some patients with severe AS may have high transvalvular gradient (mean gradient ≥ 40 mmHg) despite the LF status. A LF condition is usually associated to a reduced LVEF (< 50%), (*i.e.,* "classical" low flow), but it may also occur with preserved LVEF (≥ 50%) (*i.e.*, "paradoxical" low flow) [4]. The presence of LF, both with reduced and preserved left ventricular function, has been associated with worse clinical outcomes and higher peri-procedural mortality due to higher rate of comorbidities, less efficient ventricular-arterial coupling, higher sensitivity to afterload, a high rate of clinical or subclinical ventricular disfunction and a more advanced stage of the disease [5–8]. The underlying mechanisms contributing to a reduced transvalvular flow in the presence of preserved LVEF are multifactorial and complex and they often interplay together to determinate the LF status despite the apparent preserved contractile LV function. Although several factors have been identified as potential contributors (concentric remodelling with decreased LV cavity size, impaired diastolic filling, valvular diseases, elevated arterial impedance, severe right ventricular dysfunction etc. [9]), the actual prevalence of this etiological determinants in aortic stenosis and their impact on outcome is not known.

The aims of the present study were to characterize the specific etiological factors contributing to LF, describe their prevalence and assess their prognostic implications.

Methods

Study design and patient population

Retrospective observational cohort study including consecutive patients aged ≥ 18 years with echocardiographic diagnosis of LF severe AS who underwent transthoracic echocardiography at a referral center for valve disease (San Raffaele University Hospital, Milan), between November 1st, 2016 to October, 31th, 2022. Patients with previous AV interventions were excluded (supplementary Fig. 1). Clinical data and echocardiographic data for each patient were systematically extracted from electronic health records and stored in a specialized database. Severe LF AS was defined as aortic valve area (AVA) ≤ 1 cm^2 (or ≤ 0.6 cm^2/m^2) and a stroke volume index (SVi) ≤ 35 ml/m^2 according to current recommendations [2]. Patients were classified as having "classical" severe LF AS with reduced LVEF (< 50%) or "paradoxical" severe LF-AS with preserved LVEF (≥ 50%). In cases of severe MR, which causes overestimation of LVEF, the same LVEF cut-off (≥ 50%) was used according to current recommendation [2, 3] to avoid confusion, and patients were categorized as "preserved LVEF" despite potentially subclinically impaired systolic function. Patients with preserved LVEF were additionally sub-classified based on the prevalent cause of LF, including severe MR, as described below. After the index evaluation, therapeutic management (either interventional or conservative) was determined by Heart Team discussion. Coronary angiography or coronary computed tomography angiography (CCTA) were performed when clinically indicated according to current recommendation. Coronary artery disease (CAD) was defined as any prior history of obstructive coronary stenosis, myocardial

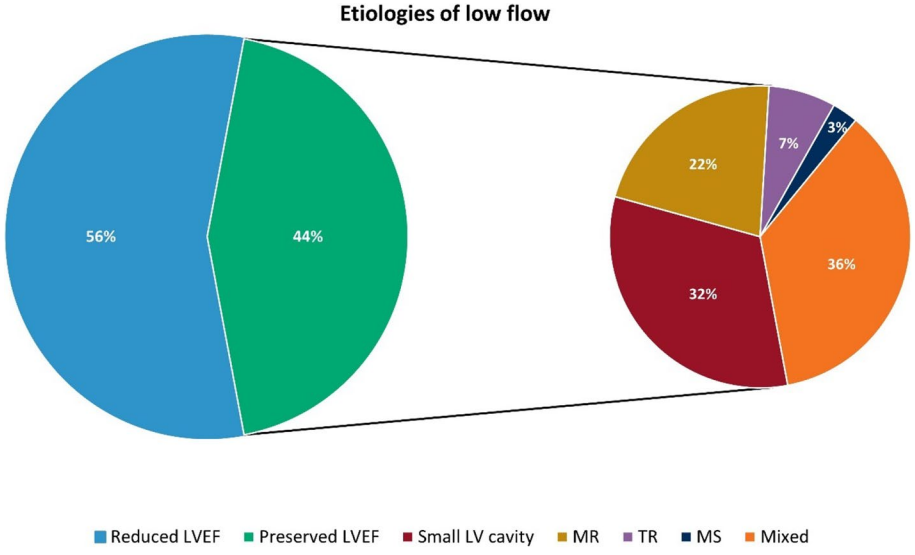


Fig. 1 Prevalence of different low flow aetiologies. The pie chart shows the proportion of patients with reduced and preserved LVEF as cause of LF. The right-side pie highlights the single specific aetiologies of low flow in the group of patients with preserved LVEF

revascularization or myocardial infarction or evidence at the angiography of significant coronary disease. The study protocol was approved by the internal review board (MILDPVL-TAVI). The study was conducted according to institutional guidelines and legal requirements.

Echocardiographic evaluation

Comprehensive transthoracic examination was performed according to current recommendations [10], using commercially available equipment: GE Vivid E9 and E95 (GE Healthcare, Milwaukee, Wisconsin, USA) and Philips EPIQ 7 (Philips Medical Systems, Philips Healthcare, Andover, MA) ultrasound systems. The grading of AS was based on the multiparametric approach suggested by current recommendations [3, 11], including at least the peak transaortic flow velocity, mean transvalvular pressure gradient, and AVA calculation by the continuity equation. Stroke volume indexed to body surface area (SVi) was calculated using left ventricular outflow tract diameter, obtained from the parasternal long-axis view, and left ventricular outflow tract velocity time integral. Mitral regurgitation (MR) and tricuspid regurgitation (TR) were graded as absent/trivial (grade 0), mild (grade 1 +), moderate (grade 2 +), moderate-to-severe (grade 3 +), and severe (grade 4 +) according with current recommendations [12]. Right ventricular systolic function was evaluated by the tricuspid annular plane systolic excursion (TAPSE), measured by aligning the M-mode linear cursor to the lateral tricuspid annulus in the apical 4-chamber focused RV view, by tissue-Doppler imaging of RV lateral annulus (S'TDI) and fractional area change (FAC). RV dysfunction was defined as the presence of at least two of the following: TAPSE < 16 mm, S'TDI < 10 cm/s, FAC < 35% [13]. Pulmonary artery systolic pressure (PASP) was estimated by a sum of tricuspid regurgitation jet gradient and estimated right atrial pressure derived from analysis of the inferior vena cava (IVC) dimensions and response to inspiration.

Low flow aetiology adjudication

In patients with preserved LVEF the main aetiology of low flow was attributed to each case by two experienced echocardiographers, blinded to each other's assessment, as follows. Disagreement was resolved by consensus after unblinding. Inter-observer agreement was quantified using Cohen's κ (95% CI).

(1) *Small LV cavity*: defined as relative wall thickness (RWT) above 0.43 together with LV end-diastolic volume index (LVEDVi) ≤ 40 ml/m^2 obtained from the apical four-chamber view and the apical two-chamber view using Simpson's biplane method and adjusted to patient's body surface area (BSA) [14]. We considered that LVEDVi below 40 ml/m^2, added to signs of concentric remodeling (RWT > 0.43), could reflect the inability of a little LV cavity to guarantee normal flow status.
(2) *Significant isolated mitral regurgitation*: defined as significant MR (≥ grade 3 +) judged sufficient to exclusively justify the low flow condition.
(3) *Significant isolated tricuspid regurgitation*: defined as significant TR (≥ grade 3 +) judged sufficient to exclusively justify the low flow condition.
(4) *Significant isolated mitral stenosis*: defined as hemodynamically significant MS judged sufficient to exclusively justify the low flow condition.
(5) *Mixed aetiologies*: when concomitant factors coexisted and no single predominant cause of low flow could be established (*i.e.*, coexisting moderate MR with moderate TR; RV dysfunction with atrial fibrillation, small LV ventricle with moderate mitral stenosis etc..).

Follow-up and clinical outcome

The primary endpoint of this study was the composite of all-cause death and hospitalizations for heart failure up to 36 months. The single secondary endpoints were hospitalizations for heart failure, all-cause death, and cardiovascular death.

Clinical follow-up was retrospectively obtained and data on event rate were collected through revision of medical software systems records and via phone-calls. In case of no response a second attempt was made with a time lag of at least 7 days. If no response was obtained and no data were retrieved from the institutional medical software records, the patient was considered lost to follow-up. Patients with follow-up time < 6 months were excluded from the study follow-up. HF hospitalization was defined as hospital or emergency department admission where HF was the primary diagnosis based on official clinical records or through report from the patient or its referring physician.

Statistical analysis

Continuous data are presented as either the mean ± SD or median (interquartile range), depending on the normality of distribution, which was evaluated through the Shapiro–Wilk test. Categorical data are represented by number and percentage. For comparison purposes, the Student's t-test or the Wilcoxon rank sum test was used for continuous variables and the Chi-square test or Fisher exact test were utilized for categorical variables, as deemed appropriate. Time-to-event data were collected starting from the baseline echocardiographic date. Kaplan–Meier method with the log-rank test were employed to analyse survival free from the study endpoints. Pairwise comparisons among groups were performed with Bonferroni-adjusted log-rank tests. Patients

Table 1 Patients' clinical data

	Total population (*n* = 408)	Reduced EF (*n* = 228)	Preserved EF (*n* = 180)	*p*-value
Age (years)	80 ± 8	79 ± 9	82 ± 8	**0.001**
Female (*n*, %)	194 (47.6%)	73 (32.0%)	121 (67.2%)	**< 0.0001**
BSA (m^2)	1.76 ± 0.20	1.80 ± 0.20	1.71 ± 0.20	**< 0.0001**
Atrial fibrillation (*n*, %)	139 (34%)	70 (31%)	69 (38%)	0.19
Smoking (*n*, %)	64 (15.7%)	37 (16.2%)	27 (15%)	0.8
Hypertension (*n*, %)	337 (82.6%)	199 (87.3%)	138 (76.7%)	**0.015**
Dyslipidemia (*n*, %)	226 (55.4%)	135 (59.2%)	91 (50.6%)	0.11
Diabetes (*n*, %)	151 (37.0%)	98 (42.9%)	53 (29.4%)	**0.01**
CAD (*n*, %)	213 (52.2%)	139 (60.9%)	74 (41.1%)	**0.0004**
Previous MI (*n*, %)	95 (23.3%)	72 (31.6%)	23 (12.8%)	**0.03**
NYHA Class (I; II; III; IV)(%)	3.8%; 42.3%; 44.9%; 8.9%	4.4%; 36.8%; 47.3%; 11.6%	3.2%; 48.7%; 42.3%; 5.8%	0.08
CKD (*n*, %)	320 (78.4%)	178 (78.1%)	142 (78.9%)	0.66

Data are expressed as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. *BSA: body surface area according to Mosteller formula. CAD: coronary artery disease. CKD: chronic kidney disease defined as eGFR < 60 ml/min/1.73m² according to Cockcroft-Gault formula. MI: myocardial infarction*

Table 2 Echocardiographic data

	Total population (*n* = 408)	Reduced EF (*n* = 228)	Preserved EF (*n* = 180)	*p*-value
EF (%)	46% ± 15	34 ± 8	60 ± 6	**< 0.001**
LVEDVi (ml/m^2)	65 ± 30	83 ± 29	45 ± 14	**< 0.001**
LVESVi (ml/m^2)	38 ± 26	55 ± 25	18 ± 7	**< 0.001**
LAVi (ml/m^2)	52 ± 18	51 ± 16	52 ± 21	0.60
IVS diast (mm)	12 ± 2	12 ± 3	13 ± 2	0.77
LVPW diast (mm)	11 ± 3	11 ± 2	11 ± 3	0.06
RWT	0.48 ± 0.15	0.44 ± 0.15	0.54 ± 0.15	**0.005**
LV mass indexed (g/m^2)	121 ± 42	123 ± 37	118 ± 47	0.45
E/e' lat	14 ± 5	14 ± 5	14 ± 6	0.78
Aortic Mean Gradient (mmHg)	32 ± 14	30 ± 13	35 ± 15	0.70
Aortic Mean Gradient ≥ 40 mmHg	102 (25%)	47 (20.6%)	55 (30.6%)	**0.03**
Aortic Vmax	3.5 ± 0.6	3.4 ± 0.6	3.5 ± 0.7	0.6
AVA (cm^2)	0.75 ± 0.2	0.74 ± 0.2	0.76 ± 0.2	0.53
AVAi (cm^2/m^2)	0.4 ± 0.1	0.4 ± 0.2	0.4 ± 0.1	0.5
SVi (ml/m^2)	30 ± 4	30 ± 4	29 ± 4	0.65
MR grade ≥ 3 + (n, %)	116 (28.4%)	53 (23.3%)	63 (35%)	**0.01**
TR grade ≥ 3 + (n, %)	72 (17.6%)	31 (13.6%)	41 (22.8%)	**0.02**
PASP (mmHg)	43 ± 15	44 ± 14	43 ± 16	0.45
TAPSE (mm)	19 ± 4	19 ± 4	20 ± 3	**0.005**

EF ejection fraction, *IVS* inter-ventricular septum, *LVPW* left ventricle posterior wall, *LVEDVi/LVESVi* left ventricle end-diastolic/end-systolic volume index, *LAVi* left atrial volume index, *AVA* aortic valve area, *SVi* left ventricular outflow tract stroke volume indexed per body surface area, *MR* mitral regurgitation, *TR* tricuspid regurgitation, *PASP* pulmonary artery systolic pressure, *TAPSE* tricuspid annular plane excursion

were censored at the time of last available follow-up up to 36 months. Time-to-event outcomes were analysed using Cox proportional hazards and Fine–Gray competing-risks models. For the primary composite endpoint and mortality, standard and time-dependent Cox models were applied, with AVR included as a time-dependent covariate to account for the risk of immortal-time bias. For heart failure hospitalization, we accounted for death as a competing event. The cause-specific hazard was assessed using cause-specific Cox regression (death treated as censoring), while the subdistribution hazard was estimated using the Fine–Gray model. Subdistribution hazard ratios (sHR) and 95% confidence intervals were derived, alongside the cause-specific HRs for comparison. The proportional-hazards assumption was checked with the use of Schoenfeld residuals. For the primary endpoint, variables significantly associated with events at univariate analysis (p value < 0.05) were entered into a multiple logistic regression model to determine independent parameters. A 1:1 nearest-neighbor matching based on age (tolerance ± 3 years) was performed to identify a control group of patients with normal-flow, high-gradient aortic stenosis from the same institution, in order to assess differences in outcomes and key clinical characteristics. A p-value of < 0.05 was considered statistically significant. Statistical analyses were carried out using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the study population

Patients' clinical and echocardiographic characteristics are reported in Tables 1 and 2. The study population consisted of 408 patients (mean age 80 ± 8 years, 47.5% female) with severe LF AS. As expected, patients exhibited a high burden of comorbidities and cardiovascular risks factors. Almost all patients were symptomatic at the time of the first evaluation, with functional NYHA II and NYHA III classes being highly represented (42% and 45%, respectively). The most common cause of low flow was reduced LVEF (n = 228, 55.9%, mean LVEF of 34 ± 8%) (Fig. 1). Patient with preserved LVEF were older, more commonly female (n = 121, 67.2% vs n = 73, 32.0%, p < 0.001), with a lower body surface area (1.71 ± 0.20 cm^2 vs 1.80 ± 0.20 cm^2, p < 0.001) and higher prevalence of ≥ Grade 3 + atrioventricular valves regurgitation. Conversely, patients with reduced LVEF showed a higher prevalence of coronary artery disease (n = 139, 61% vs

n = 74, 41.1%, *p* < 0.001), previous myocardial infarction (*n* = 72, 31.6% vs *n* = 23, 12.8%, *p* = 0.03), diabetes (*n* = 98, 43% vs *n* = 53, 29.4%, *p* > 0.01) and hypertension (*n* = 199, 87.3% vs n = 138, 76.7%, *p* = 0.015).

Aetiology of low flow in patients with preserved LVEF

In patients with preserved LVEF (*n* = 180, 44.1%, mean LVEF 60 ± 6%) the following five aetiologies were observed (Fig. 1):

(1) *Mixed aetiologies* (*n* = 65, 36.1%).
(2) *Small LV cavity* (*n* = 58, 32.2%).
(3) *Significant isolated mitral regurgitation* (*n* = 39, 21.7%).
(4) *Significant isolated tricuspid regurgitation* (*n* = 13, 7.2%).
(5) *Significant isolated mitral stenosis* (*n* = 5, 2.8%).

Among the two reviewers who classified low-flow aetiologies, inter-observer agreement was almost perfect, with a raw accuracy of 95.6% and an unweighted Cohen's κ = 0.94 (95% CI 0.91–0.98; p < 0.001). Interestingly, the main disagreement occurred for the "mixed aetiologies" category, likely due to overlapping features with the other groups.

Table 3 Predictors of the primary composite endpoint at the univariate and multivariate analysis (adjusted for age, sex and significant (*p* < 0.05) predictors at univariate analysis). AVR was modeled as a time-dependent covariate. Variables with p < 0.05 at univariate analysis were entered into the multivariable model; for MR and TR only the more significant threshold was retained

Determinants of primary endpoint	Univariate analysis		Multivariate analysis	
	HR	*p*-value	Adj. HR	*p*-value
Age	1.02 (1.00–1.04)	**0.04**	1.01 (0.99–1.03)	1
Female sex	0.84 (0.61–1.15)	0.3	0.88 (0.64–1.20)	0.1
BMI	1.02 (1.00–1.04)	0.06		
Smoking	0.66 (0.43–1.1)	0.1		
Hypertension	1.01 (0.62–1.66)	0.95		
Dyslipidemia	1 (0.78–1.48)	0.7		
DM	1.26 (0.91–1.74)	0.17		
CAD	1.20 (0.86–1.67)	0.28		
NYHA Class > 2	1.47 (1.02–2.11)	**0.04**	1.48 (1.01–2.15)	**0.03**
CKD	1.18 (0.78–1.77)	0.44		
AV Intervention	0.59 (0.42–0.84)	**< 0.001**	0.76 (0.50–0.91)	**< 0.001**
• TAVR	0.68 (0.50–0.93)	**0.01**		
• SAVR	0.56 (0.34–0.91)	**< 0.001**		
LVEF ≥ 50%	0.86 (0.63–1.19)	0.4		
LVEF < 50%	1.16 (0.84–1.59)			
MR ≥ 3 +	1.38 (0.99–1–92)	0.05		
MR 4 +	1.85 (1.19–2.85)	**0.003**	1.71 (1.03–2.82)	**0.04**
TR ≥ 3 +	1.53 (1.03–2.29)	**0.04**		
TR 4 +	1.79 (1.10–2.94)	**0.02**	1.47 (1.01–2.43)	**0.04**
RV dysfunction	1.21 (0.87–1.68)	0.26		
MG ≥ 40	0.37 (0.24–0.57)	**< 0.001**	0.39 (0.23–0.66)	**< 0.001**

BMI Body mass index, *CAD* Coronary artery disease, *CKD* Chronic kidney disease, *DM* Diabetes mellitus, *LVEF* Left ventricular ejection fraction, *MR* Mitral regurgitation, *TR* Tricuspid regurgitation, *AV* Aortic valve, *RV* Right ventricle, *MG* Mean aortic transvalvular gradient

Outcomes

Among the study population, 302 (74%) patients underwent invasive treatment, of whom 245 (60%) transcatheter aortic valve replacement (TAVR, all by femoral approach) and 57 (14%) surgical aortic valve replacement (SAVR). Ninety-one patients (22.3%) were left untreated while no data were available for 15 patients (3.7%). Patients with a mean aortic transvalvular gradient ≥ 40 mmHg were more likely to undergo invasive treatment (supplementary Table 3, *p* < 0.01). Clinical follow-up was completed for 302 (70.6%) patients (230 who underwent AVR and 72 who were left untreated, *p* = 0.3), while the remaining patients were excluded from follow-up because of a follow-up time below 6 months or inability to obtain information (lost to follow-up).

Primary endpoint (central illustration)

At a median follow-up of 15 (IQR 6–36) months, 159 (52.6%) patients reached the primary composite endpoint, all-cause death was reported in 108 patients (35.7%, *n* = 67 cardiovascular and *n* = 41 non-cardiovascular) and HF hospitalization in 93 (30.8%) patients. At the univariate analysis, predictors of the primary composite endpoint were age, NYHA class > 2, severe (grade 4 +) MR, moderate-to-severe (Grade 3 +) and severe (Grade 4 +) TR (Table 3). Conversely, protective factors for the primary endpoint were invasive treatment (both TAVR and SAVR, supplementary Fig. 2) and a mean aortic valve gradient ≥ 40 mmHg, both in the subgroups of reduced and preserved LVEF (Fig. 2 and supplementary Fig. 3). At multivariate analysis, adjusted for age, sex and all variables statistically significant at univariable Cox regression analysis, NYHA class > 2, grade 4 + MR, grade 4 + TR, invasive treatment strategy and the mean aortic transvalvular gradient ≥ 40 mmHg maintained their independent association with the occurrence of the primary endpoint. Among the LF aetiologies, the rate of survival free from the primary endpoint was similar in patients with preserved LVEF and reduced LVEF (HR for LVEF < 50%: 1.16 [0.84–1.59], log-rank *p* = 0.4). Similarly, in the group of patients with preserved LVEF, no differences in the

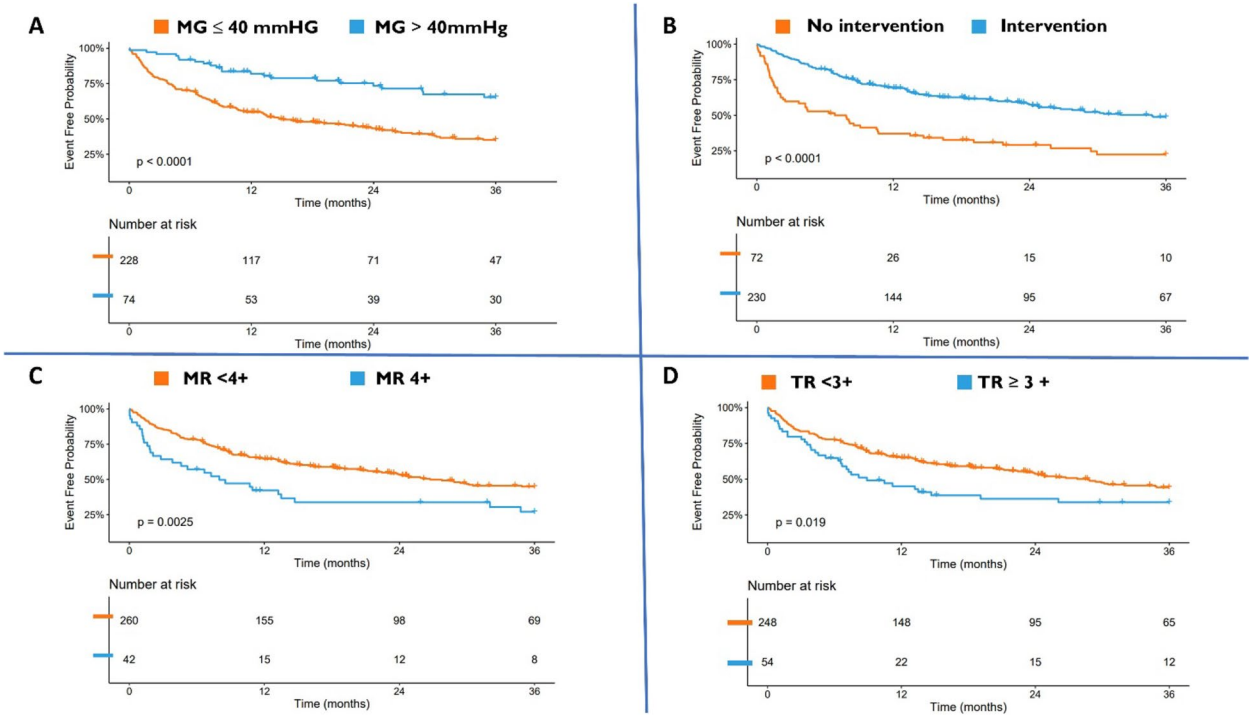


Fig. 2 Kaplan–Meier curves for the survival free from the primary endpoint according to: **A** mean gradient (MG) ≥ 40 mmHg vs < 40 mmHg; **B**: AV intervention vs no AV intervention; **C** MR 4 + vs MR < 4 +; **D** TR > 2 + vs TR ≤ 2 +. All log-rank $p < 0.05$. *AV: aortic valve; MR: mitral regurgitation; TR: tricuspid regurgitation*

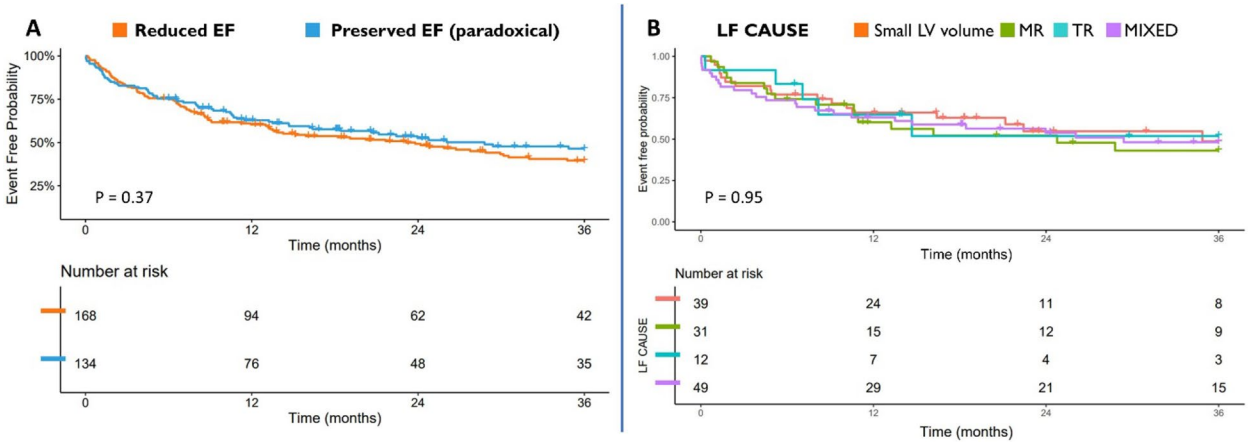


Fig. 3 Kaplan–Meier Curves for the survival free from the primary endpoint according to the LF aetiology: **A** Reduced LVEF vs Preserved LVEF; **B**: cumulative event-free survival of the specific LF aetiologies in patients with preserved LVEF. All log rank $p > 0.05$. *EF: left ventricular ejection fraction; LV: left ventricle; MR: mitral regurgitation; TR: tricuspid regurgitation. Note that mitral stenosis is not depicted in the figure due to the very low number of patients at follow-up*

survival free from the primary endpoint was observed between the single aetiologies (log-rank $p = 0.95$) (Fig. 3).

Secondary endpoints

Mortality

At the median follow-up of 15 (6–36) months, a high rate of all-cause mortality was observed (35.7%), with cardiovascular mortality being the most frequent. Predictors of mortality are reported in the supplementary Table 1. Invasive treatment was associated with a lower risk of all-cause mortality (HR 0.32 [0.24–0.42], $p < 0.001$) and cardiovascular mortality (HR 0.34 [0.24–0.47], $p < 0.001$). Both TAVR and SAVR were associated with a lower all-cause mortality against the conservative treatment (supplementary Fig. 2). RV dysfunction and TR ≥ grade 3 + were associated with a higher all-cause mortality (HR 1.78 [1.21–2.60], $p < 0.01$ and HR 1.66 [1.06–2.59], $p = 0.03$, respectively). No differences in all cause and cardiovascular mortality were observed between the

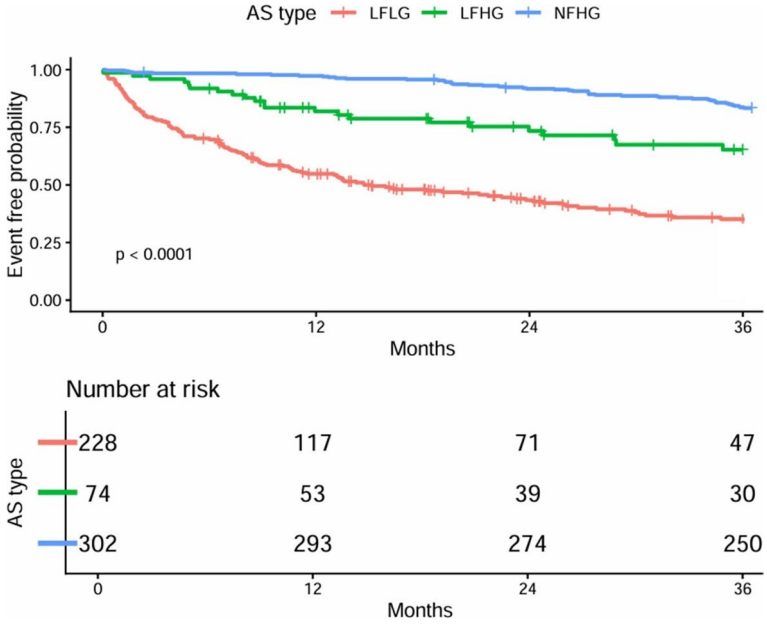


Fig. 4 Kaplan Meier curves of the survival free from the primary endpoint including an age-matched population of normal flow high gradient AS patients (NFHG). The log-rank analysis confirmed the prognostic role of both SVi and transvavular gradient, delineating three groups with progressively worse prognosis: (i) normal-flow/high-gradient, (ii) low-flow/high-gradient (LFHG) and low-flow/low-gradient (LFLG), all $p < 0.001$

reduced and preserved LVEF groups (HR for LVEF < 50%: 1.38 [0.93–2.05], log-rank $p = 0.1$).

HF hospitalizations

Predictors of HF hospitalization are reported in supplementary Table 2. As death is a competing event for HF hospitalizations, both cause-specific Cox and Fine–Gray competing-risk analyses were reported. AV intervention and higher mean gradient were associated with a lower risk of HF hospitalization [sHR: 0.48 (0.36–0.64), supplementary Fig. 7, and 0.32 (0.24–0.43), respectively], whereas severe MR was consistently associated with increased risk [sHR: 1.97 (1.68–2.30)]. Notably, severe TR (4 +) reached statistical significance only in the Fine–Gray model [sHR: 1.61 (1.30–2.00)]. Interestingly, among the group receiving invasive treatment, SAVR but not TAVR demonstrated a reduced risk of HF hospitalization.

Prognostic role of SVi and mean transvalvular gradient

To assess the prognostic role of SVi, 302 1:1 age-matched patients with normal-flow (> 35 ml/m^2) high-gradient (mean gradient ≥ 40 mmHg) aortic stenosis were included. As depicted in the Kaplan–Meier curves (Fig. 4), the risk of the primary endpoint was the lowest in normal-flow high-gradient patients, the higher in low-flow low-gradient patients and intermediate in patients with low flow but a mean transvalvular gradient ≥ 40 mmHg (all $p < 0.001$). Patients with normal-flow/high-gradient AS had a lower burden of coronary artery disease, atrioventricular valve pathology and RV dysfunction and were less symptomatic (supplementary Table 6).

Discussion

The main findings of this study are: (i) in the subgroup of patients with preserved LVEF, mixed aetiologies and small LV cavity are the most common causes of LF; (ii) LF AS patients are characterized by a high rate of adverse events irrespective of the specific aetiology of LF; (iii) in the general population of LF AS, severe MR, severe TR, NYHA class > 2 are associated with worst outcome whereas AV intervention and a mean transvalvular gradient ≥ 40 mmHg ("concordant-gradient severe AS") carry a better prognosis; (v); age-matched patients with normal-flow high-gradient severe aortic stenosis have the best prognosis.

Aetiologies of low flow

Although several aetiologies of LF in AS have been reported, there are no previous studies specifically clarifying their prevalence and prognostic association. In this novel analysis, we were able to assess the specific low-flow aetiologies in our population and whether they were associated with outcomes. Our results showed that in patients with preserved LVEF ("paradoxical"), the most prevalent was a "mixed" aetiology. This multifactorial condition is the result of a multiple cardiac involvement *(i.e.*, AF, RV dysfunction, moderate atrio-ventricular valvopathies), as no single factor could solely account for the stroke volume reduction. Furthermore, a large proportion of patients with preserved LVEF showed significant concentric remodeling with reduced LV volume as the specific cause of low flow. These patients usually exhibit

impaired LV filling, altered myocardial longitudinal function and elevated afterload, all of which are the pathophysiological consequences of AS in association with elevated arterial impedance [4, 6]. Interestingly, in the survival analysis, we observed no difference in the occurrence of the primary and secondary endpoints for any single cause, including the LVEF spectrum, suggesting that in these patients the low flow condition is the main prognostic determinant, overshadowing the influence of its specific aetiology.

Clinical implications of including low flow aetiology in the echocardiographic report

In clinical practice, patients with low flow despite preserved LVEF are often classified as having 'paradoxical low flow' without a thorough pathophysiological explanation. Although our analysis did not find an association with outcomes, we recommend including the underlying mechanism for SVi reduction in a comprehensive echocardiographic report, as this would both give consistence to echocardiographic findings and impact patient management and follow-up. For those with significant atrioventricular valve regurgitation, addressing the valve disease may reverse the low-flow status, while in cases of structural abnormalities (e.g., concentric remodeling with small LV volumes), reducing the afterload from aortic stenosis may take months to achieve flow improvement.

Role of intervention

According to our results, AV intervention (either TAVR or SAVR) showed to be a strong protective factor against the occurrence of the primary composite endpoint, HF hospitalizations, all-cause and cardiovascular mortality suggesting that in this high-risk population an invasive strategy should be considered whenever feasible (supplementary Table 5). Most of the patients included in our study underwent TAVR, given that this was an elderly population with high surgical risk and significant burden of comorbidities. We observed no differences between TAVR and SAVR for the occurrence of the primary outcome, while SAVR was associated with a lower risk of HF hospitalizations (supplementary Table 2). However, it is important to note that these results may be influenced by the fact that patients who underwent AV intervention were potentially in better clinical status than those who were excluded. Nevertheless, no clinical or echocardiographic data can accurately highlight this distinction (as reported in supplementary Table 4). Furthermore, an examination of the survival curves reveals a high rate of events and non-cardiovascular mortality even in treated patients, underscoring the potential risk of futility, which should always be taken into account before treating this high-risk population. These findings emphasize the need for a comprehensive evaluation when determining the appropriateness of the intervention and for a holistic approach, aimed at the screening and treatment of both cardiovascular and non-cardiovascular comorbidities to improve patient symptoms and outcomes.

Transvalvular gradient

Interestingly, we found that in the subgroup of patients with a mean transvalvular gradient ≥ 40 mmHg ("low-flow/high-gradient" or "concordant gradient severe AS") the rate of events was substantially lower than in patients with gradient < 40 mmHg ("low-flow/low-gradient"). These results are concordant with a recent study on moderate aortic stenosis, in which "discordant gradient moderate AS" was associated with an increased risk of mortality compared with "concordant gradient moderate AS" [15]. This could be explained by the fact that a high mean transvalvular gradient, even in the presence of reduced SVi, reflects an earlier stage of the disease, with more efficient ventricular function and ventricular-arterial coupling with reduced ventricular-valvular afterload, ensuring the preservation of transvalvular flow rate. Barasch et al. reported that in patients with severe AS, the presence of a reduced transvalvular gradient is associated with almost a 50% lower referral rate to surgery and led to a twofold increase in mortality compared to patients with higher gradients [6]. Indeed, in our population, only 5.1% of patients with "low-flow/high-gradient" AS were left untreated, while the rate of untreated patients in the "low-flow/low-gradient" group was considerably higher (29.2%, $p < 0.001$, supplementary Table 3). Despite this difference in the management of patients, the multivariable analysis, that included AV intervention as covariate, confirmed the independent protective effect of a mean transvalvular gradient ≥ 40 mmHg, thereby confirming the aforementioned pathophysiological considerations. Finally, in the comparison of an age-matched population with normal-flow/high-gradient AS, the outcome analysis confirmed the prognostic role of both SVi and transvavular gradient, delineating a spectrum of three groups with progressively worse prognosis: (i) normal-flow/high gradient, (ii) low-flow/high gradient and (iii) low-flow/low gradient (Fig. 4). It is noteworthy that the age-matched population had significantly less extravalvular cardiac damage which may explain why the poorer outcome in LF patients – representing a population with more advanced disease – was driven by the LF status rather than its specific cause [19].

Role of mitral valve and tricuspid valve pathology (supplementary Figs. 4–5)

Although no single specific aetiology of low flow was associated with outcomes in our analysis, considering the entire population of the study, both severe MR and TR were linked to worse outcomes. Similarly, a recent study

demonstrated that the presence of moderate-to-severe MR in patients with low flow low gradient AS undergoing TAVR portends a worse clinical outcome at 1 year [16]. Considering the secondary endpoints, we observed a higher rate of all-cause mortality in patients with moderate-to-severe TR, while no impact of mortality was observed for MR. This is consistent with the recent proposed cardiac damage staging classification for AS, where pulmonary vasculature or tricuspid valve involvement is associated with higher mortality compared to left atrial or mitral valve involvement [8, 17]. Conversely, when considering HF hospitalizations, this result partially reverses, with severe MR associated with a higher risk of events during follow-up. It is important to underline that the phenotype of atrioventricular valve pathology, although not specifically evaluated in our study, might delineate different risk profiles. Indeed, patients with functional MR and TR could benefit from AV intervention, as the reduction of afterload, left ventricular end diastolic pressure and wedge pressure can lead to a significant improvement in the degree of atrioventricular valve regurgitation, with potential prognostic implication [16, 18]. Differently, in patients with organic/degenerative disease, in which MR is not the consequence of AS damage, minimal or no improvement is expected after AV intervention; therefore, the prognosis of these patients may be purely trailed by the mixed valvular disease rather than AS alone, with the risk of futility. As a result, it is crucial for the optimal management of these patients to identify and report the aetiology of atrioventricular valve disease. In patients with functional aetiology, a tailored approach involving AVR as the first/only therapeutic step, followed by targeted treatment of MR or TR, if still significant, is reasonable. For those with a degenerative aetiology, a double valve intervention should be considered when evaluating the risk–benefit ratio, also influencing the choice between TAVR and SAVR.

Study limitations

Some limitations should be acknowledged when interpreting the results of our study. Firstly, this is a retrospectively enrolled population of a single referral center for heart valve disease (*i.e.*, population and selection bias) limiting the generalizability of the results to other settings. Secondly, the rate of patients lost to follow-up was relatively high, although most patients were excluded because of a follow-up time below six months. Baseline characteristics of patients with and without follow-up were broadly comparable (Supplementary Table 8), indicating that missing follow-up was unlikely to have introduced major selection bias. Furthermore, although the severity of AS was carefully assessed according to current recommendations, including cardiac CT and/or dobutamine test as needed, we lacked access to data regarding calcium score or dobutamine test for a significant proportion of patients, as many of them underwent these tests in other centers. The small sample size of each subgroup of low flow might not have been sufficient to detect differences in outcomes between groups. We did not report the prevalence of cardiac amyloidosis or other cardiomyopathies in the study cohort, as this could be influenced by reporting bias and underdiagnosis during the index echocardiography, given the retrospective nature of the study and the high rate of undiagnosed cardiac amyloidosis in the elderly population with aortic stenosis. We did not collect re-hospitalization, precluding us to perform a recurrent-event analysis. Finally, the control cohort of patients with normal-flow/high-gradient was similar only for age rather than other demographic or echocardiographic factors, reflecting a similar population from the same institution, highlighting differences in cardiovascular risk factors and extra valvular cardiac damage that might be overlooked with extensive propensity matching. The comparison with this age-matched cohort should be interpreted as purely exploratory, due to the above limitations. Finally, in the reduced LVEF group, we did not provide the cause of impaired systolic function, which could have further characterized the prognosis of this population.

Conclusion

Low flow severe AS is an advanced stage valvular disease characterized by a high rate of adverse events regardless of the low flow aetiology. In patients with preserved LVEF, the most common aetiologies of low flow are mixed causes and altered left ventricular geometry with small volumes. In the general population of LF AS, severe MR and TR were strongly associated with the occurrence of the primary endpoint, while invasive treatment (SAVR or TAVR) and a mean transvalvular gradient ≥ 40 mmHg emerged as protective factors.

Abbreviations

LF	Low flow
AS	Aortic stenosis
AVA	Aortic valve area
LVEF	Left ventricular ejection fraction
MR	Mitral regurgitation
TR	Tricuspid regurgitation
TAVR	Transcatheter aortic valve replacement
SAVR	Surgical aortic valve replacement
HR	Hazard ratio

Supplementary Information

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Supplementary Material 1.

Disclosures
The Authors have no conflicts of interest to declare.

Authors' contributions
G.F. wrote the main manuscript text. F.B. wrote and reviewed the manuscript. M.F., P.C., M.M., M.G., contributed to data collection. G.I., F.A., S.S., M.B., D.M. reviewed the manuscript. A.C., M.M, F.M. supervised the work. E.A. conceived and supervised the work. All authors reviewed the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the internal ethics review board (MILDPVL-TAVI). The study was conducted according to institutional guidelines and legal requirements and according to the Declaration of Helsinki. All involved patients signed informed consent for the potential use of their anonymized clinical data for research purpose.

Competing interests
The authors declare no competing interests.

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