





Peak atrial longitudinal strain and risk stratification in moderate and severe aortic stenosis

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Aims

We sought to investigate the association of left atrial strain with the outcome in a large cohort of patients with at least moderate aortic stenosis (AS).

Methods and results

We analysed 467 patients (mean age 80.6 ± 8.2 years; 51% men) with at least moderate AS and sinus rhythm. The primary study endpoint was the composite of all-cause mortality and hospitalizations for heart failure. After a median follow-up of 19.2 (inter-quartile range 12.5–24.4) months, 96 events occurred. Using the receiver operator characteristic curve analysis, the cut-off value of peak atrial longitudinal strain (PALS) more strongly associated with outcome was $<16\%$ {area under the curve (AUC) 0.70 [95% confidence interval (CI): 0.63–0.78], $P < 0.001$ }. The Kaplan–Meier curves demonstrated a higher rate of events for patients with PALS $< 16\%$ (log-rank $P < 0.001$). On multivariable analysis, PALS [adjusted HR (aHR) 0.95 (95% CI 0.91–0.99), $P = 0.017$] and age were the only variables independently associated with the combined endpoint. PALS provided incremental prognostic value over left ventricular (LV) global longitudinal strain, LV ejection fraction, and right ventricular function. Subgroup analysis revealed that impaired PALS was also independently associated with outcome in the subgroups of paucisymptomatic patients [aHR 0.98 (95% CI 0.97–0.98), $P = 0.048$], moderate AS [aHR 0.92, (95% CI 0.86–0.98), $P = 0.016$], and low-flow AS [aHR 0.90 (95% CI 0.83–0.98), $P = 0.020$].

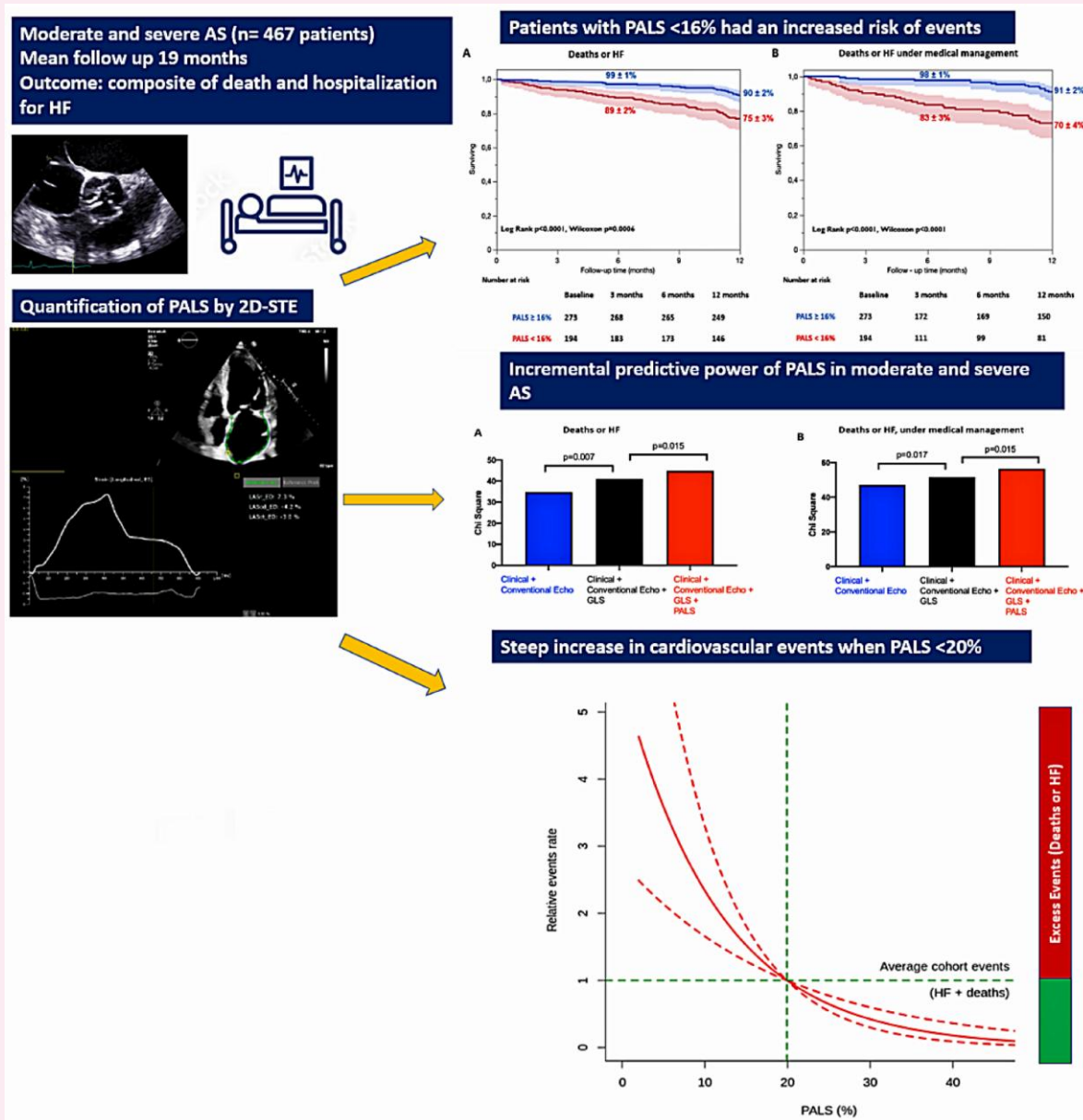
Conclusion

In our patients with at least moderate AS, PALS was independently associated with outcome. In asymptomatic patients, PALS could be a potential marker of sub-clinical damage, leading to better risk stratification and, potentially, earlier treatment.

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Graphical Abstract



In patients with moderate and severe AS, lower PALS by 2D strain echocardiography (a cut-off of <16%) was associated with an increased risk of experiencing events, incremental over left ventricular GLS. AS, aortic stenosis; GLS, global longitudinal strain; HF, heart failure; PALS, peak atrial longitudinal strain.

Keywords

aortic stenosis • speckle-tracking echocardiography • outcome • left atrium • peak atrial longitudinal strain

Introduction

Aortic stenosis (AS) is the most common valvular heart disease requiring intervention.¹ Untreated symptomatic severe AS is associated with a dismal prognosis.^{2,3} Recent data on excess mortality, associated even with moderate AS,⁴ the evidence of the beneficial effect of early surgical aortic valve replacement (AVR),⁵ and the technical advancements of transcatheter AVR,⁶ have sparked interest in broadening the criteria for managing AS patients. Consequently, identifying markers

of sub-clinical cardiac damage related to AS has become a key to appropriately prompt earlier treatment.⁷

Beyond the known effect of the pressure overload on the left ventricle (LV),⁸ the haemodynamic load imposed by AS may specifically determine the functional and structural remodelling of the left atrium (LA).⁹

Recently, peak atrial longitudinal strain (PALS), a sensitive echocardiographic parameter for assessing LA function, has demonstrated its ability to refine the prognostic stratification of patients with heart

failure (HF) and mitral regurgitation (MR).^{10–12} However, in the setting of AS, only modestly sized studies are available, with contradictory results on the independent association of PALS with outcome.^{13,14}

Hence, the aim of the present study was to examine the association of PALS with outcome in a large cohort of patients with AS. Moreover, we wanted to define whether PALS can provide incremental clinical and outcome information over conventional echocardiographic measures of valvular and ventricular functions, including LV global longitudinal strain (GLS).

Methods

To identify the patients to include in this study, we have interrogated the electronic echocardiographic database at two academic centres (Istituto Auxologico Italiano, San Luca Hospital, Milan, and University Hospital of Verona). The eligibility criteria were as follows:

- outpatients who had their transthoracic echocardiogram performed between January 2019 and June 2022 and
- at least moderate AS by quantitative echocardiographic criteria¹⁵ [peak aortic jet velocity ≥ 3 m/s or transaortic mean gradient ≥ 30 mmHg or aortic valve area (AVA) ≤ 1.5 cm²].

Exclusion criteria were as follows: moderate-to-severe mitral stenosis, severe aortic regurgitation (AR), previous aortic valve surgery/transcatheter interventions, any established diagnosis of cardiomyopathy, missing relevant clinical data, and poor-quality echocardiographic study unsuitable for a speckle-tracking evaluation. Atrial fibrillation was also an exclusion criterion as it independently impacts LA mechanics. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of both centres. The need for patient's written informed consent was waived due to the retrospective nature of the study.

Baseline clinical assessment

Baseline demographic and clinical features, including cardiovascular risk factors and comorbidities, were collected using the hospital database and patient information systems to retrieve a comprehensive clinical evaluation closely related to the echocardiographic assessment.

Echocardiographic evaluation

All patients underwent a standard transthoracic echocardiography using either an E95/E80 (GE Healthcare, Milwaukee, WI, USA) or an Epiq 7 (Philips Medical Systems, Andover, MA, USA) ultrasound system. Images stored were re-analysed offline using Image Arena TTA2 (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) by three experienced researchers (P.S., A.C., and S.M.) blinded to the medical history of the patients.

The quantification of LV and right ventricular (RV) sizes and functions, LV mass, and LA and right atrial (RA) dimensions followed the current recommendations.¹⁶ RV dysfunction was defined by at least one parameter among the following: tricuspid annulus plane systolic excursion (TAPSE) < 17 mm, RV free-wall S' velocity < 9.5 cm/s, or fractional area change $< 35\%$.^{16,17} MR and tricuspid regurgitation (TR) severity were graded as mild, moderate, or severe using the recommended multi-parametric approach.¹⁸

Pulmonary artery systolic pressure was derived from the TR jet velocity using the simplified Bernoulli equation combined with an estimate of the RA pressure obtained by examining the dimensions and collapsibility of the inferior vena cava.¹⁹

Maximum AS jet velocity was obtained by measuring the highest velocity recorded through the aortic valve using the continuous-wave Doppler from multiple acoustic windows (apical, suprasternal, and right parasternal views).¹⁵ The simplified Bernoulli equation was used to derive the peak transaortic pressure gradient from the maximum jet velocity. The mean pressure gradient across the aortic valve was

estimated by averaging the instantaneous gradients over the ejection period. The LV outflow tract diameter (LVOTd) was measured from a zoomed parasternal long-axis view in mid-systole parallel to the aortic valve plane. The LV outflow tract velocity–time integral (VTI) was measured on the pulsed-wave Doppler trace acquired from the LV apical three-chamber or five-chamber views with the sample volume located on the LV side of the aortic valve. LVOTd and VTI were used to calculate stroke volume (SV) and AVA using the continuity equation. The AS severity grading followed the current recommendations.¹⁵

Advanced speckle-tracking echocardiography (STE) was performed using the TomTec Autostrain® software package by different operators (P.S., A.C., and S.M.) for the assessments of LV GLS and PALS.^{20–22} All longitudinal strain parameters were expressed as absolute values.

PALS was obtained from dedicated apical four-chamber views, to avoid the foreshortening of the LA, and by initializing three reference points: medial mitral annulus, lateral mitral annulus, and the LA roof. The region of interest was delineated by the software package and eventually optimized by manual adjustments when needed.^{21,22}

STE parameters, AS quantification parameters, and LV ejection fraction (LVEF) values were obtained by averaging values derived from at least three consecutive cardiac cycles.

Clinical follow-up

The clinical follow-up of the enrolled patients was done by visits or telephone contacts directly to the patients or with a strictly familiar figure. The primary endpoint of the study was the composite of all-cause mortality or hospitalizations for HF after the index echocardiographic assessment. The secondary endpoint was mortality or HF under medical management, obtained by censoring AVR. HF was defined according to international guidelines as the evidence of central and/or peripheral congestion and/or peripheral hypoperfusion requiring hospitalization for appropriate therapy.²³ The assignment of clinical events was performed by physicians who were unaware of the patients' echocardiographic and clinical characteristics.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation or as median and inter-quartile range (IQR) as appropriate. Categorical variables are expressed as percentages. The comparison between them was computed using Student's *t*-test, Wilcoxon–Mann–Whitney test, or χ^2 test as appropriate. Receiver operator characteristic (ROC) curves were used to identify the optimal cut-off values, specificity, and sensitivity of the LV GLS and PALS associated with the composite endpoint, using Youden's Index. The Kaplan–Meier curves were used to estimate the event-free survival rates, and the differences between groups were analysed using the log-rank and Wilcoxon tests. Multivariable Cox proportional hazard regression was used to test the correlation of several clinical and echocardiography variables with the combined endpoint. For multivariable analysis, the statistical power of possible confounders was tested, and they were chosen based on their correlation and clinical relevance, after the computation of Pearson coefficient and variance inflation factor, considering the values between 1 and 10 as absence of collinearity. The results are presented as hazard ratio (HR) with the corresponding 95% confidence interval (CI). Moreover, the relationship between the spectrum of PALS values and the risk of events was illustrated by a spline curve.

Three subgroup analyses were also conducted defining groups as follows: (i) paucisymptomatic group: in the presence of New York Heart Association (NYHA) Class I or II, LVEF $> 50\%$, and non-severe MR; (ii) low-flow AS: defined as an LV stroke volume index (SVi) < 35 mL/min^{2.4}; and (iii) moderate AS: defined as an AVA between 1.0 and 1.5 cm².^{25–27}

To evaluate inter-observer and intra-observer variabilities, 20 random patients were selected, PALS and LV GLS were measured at two different time points by the same investigator, and a second analysis was completed by another investigator blinded to the previous results. Intraclass correlation coefficient (ICC) was used to assess inter-observer and intra-observer

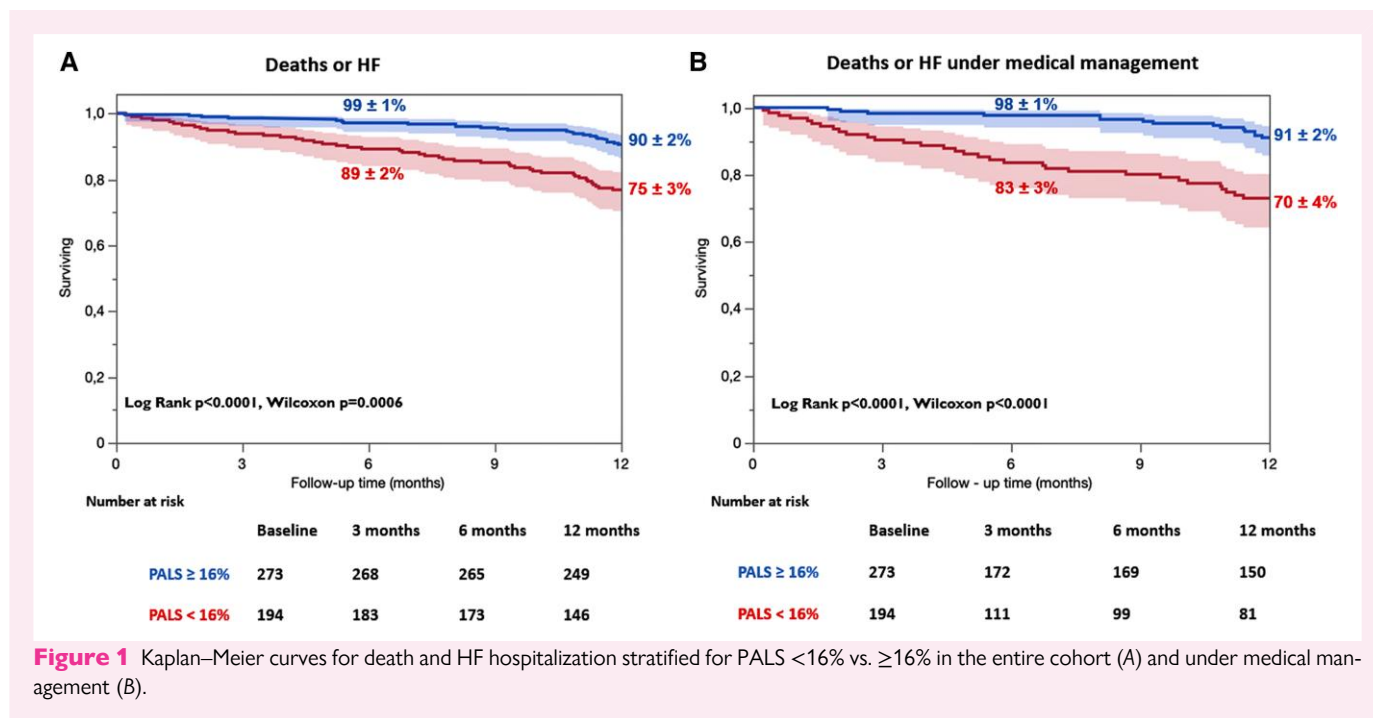
Table 1 Echocardiographic and clinical parameters (whole study cohort)

| | Overall population (n = 467) | Endpoint– (n = 371) | Endpoint + (n = 96) | P-value ^a |
|------------------------------------|------------------------------|---------------------|---------------------|----------------------|
| Age (years) | 80.6 ± 8.2 | 80.1 ± 8.4 | 82.8 ± 7.0 | 0.001 |
| Sex male | 237 (50.7%) | 191 (51.5%) | 46 (47.9%) | 0.53 |
| Body mass index, kg/m ² | 25.1 ± 5.0 | 26.4 ± 5.0 | 25.1 ± 5.0 | 0.02 |
| SBP (mmHg) | 137 ± 21.0 | 138.3 ± 18.1 | 136.0 ± 18.0 | 0.42 |
| DBP (mmHg) | 75 ± 11.7 | 76.1 ± 11.1 | 74.5 ± 11.1 | 0.23 |
| Previous AHF, n (%) | 82 (17.5) | 53 (14.3) | 29 (30.2) | 0.0005 |
| Previous syncope | 36 (7.7%) | 32 (8.6%) | 4 (4%) | 0.11 |
| Angina | 90 (19.3%) | 66 (17.8%) | 24 (25%) | 0.36 |
| NYHA Class ≥3 | 144 (30.8%) | 99 (26.7%) | 45 (46.9%) | 0.0002 |
| Hypertension | 295 (63.1%) | 217 (58.4%) | 78 (81.2%) | <0.0001 |
| Dyslipidaemia | 268 (57.4%) | 218 (58.7%) | 50 (52.0%) | 0.24 |
| Diabetes | 133 (28.5%) | 104 (28.0%) | 29 (30.2%) | 0.67 |
| COPD | 40 (15.0%) | 29 (7.8%) | 11 (11.4%) | 0.27 |
| History of smoking | 119 (25.5%) | 93 (25.1%) | 26 (27.6%) | 0.51 |
| CAD | 153 (32.8%) | 119 (32.1%) | 34 (35.4%) | 0.53 |
| PAD | 150 (32.1%) | 125 (33.7%) | 25 (26.0%) | 0.14 |
| History of MI | 85 (18.2%) | 61 (16.4%) | 24 (25%) | 0.06 |
| eGFR (mL/min/mq) | 57.2 ± 25.9 | 60.0 ± 25.9 | 47.1 ± 23.5 | <0.0001 |
| AVA (cmq) | 0.91 ± 0.29 | 0.92 ± 0.29 | 0.85 ± 0.31 | 0.04 |
| G. mean (mmHg) | 32 ± 16 | 32.3 ± 16.6 | 31.0 ± 15.8 | 0.76 |
| V. max (m/s) | 3.5 ± 0.9 | 3.5 ± 0.8 | 3.4 ± 0.8 | 0.25 |
| SVi (mL/mq) | 38.4 ± 8.6 | 39.1 ± 8.3 | 35.5 ± 9.3 | 0.001 |
| EDVI (mL/mq) | 64.3 ± 19.7 | 63.0 ± 18.5 | 69.2 ± 23.2 | 0.008 |
| LVMI (g/mq) | 115 ± 36 | 113 ± 34 | 120 ± 42 | 0.067 |
| RWT | 0.51 ± 0.22 | 0.51 ± 0.24 | 0.46 ± 0.14 | 0.84 |
| LAVI (mL/mq) | 46.9 ± 15.2 | 45.8 ± 14.7 | 51.4 ± 16.1 | 0.002 |
| LVEF (%) | 57.7 ± 12.1 | 58.9 ± 11.1 | 53.2 ± 14.8 | 0.0006 |
| TAPSE (mm) | 22 ± 4 | 22 ± 3 | 21 ± 3 | 0.04 |
| RV-FAC (%) | 45 ± 7 | 46 ± 7 | 43 ± 7 | 0.03 |
| E/A ratio | 1.02 ± 0.7 | 1.02 ± 0.50 | 1.05 ± 0.52 | 0.39 |
| E' TDI wave (cm/s) | 6.5 ± 2.0 | 6.6 ± 2.0 | 5.9 ± 1.8 | 0.01 |
| E/e' | 13.8 ± 5.4 | 13.4 ± 5.2 | 15.5 ± 6.8 | 0.01 |
| sPAP (mmHg) | 38 ± 13 | 36 ± 11 | 46 ± 16 | <0.001 |
| PALS (%) | 20.0 ± 9.3 | 21.1 ± 9.0 | 15.8 ± 9.2 | <0.001 |
| LACd (%) | 11.2 ± 5.9 | 9.4 ± 5.1 | 8.1 ± 5.2 | 0.019 |
| LaCt (%) | 9.1 ± 5.1 | 11.9 ± 6.8 | 8.2 ± 6.7 | <0.001 |
| LV GLS (%) | 14.7 ± 4.4 | 15.2 ± 4.2 | 12.7 ± 4.8 | <0.001 |
| Moderate or severe MR | 95 (20.3%) | 53 (14.3%) | 42 (43.7%) | <0.001 |
| Moderate or severe TR | 75 (16.0%) | 48 (12.9%) | 27 (28.1%) | 0.01 |
| Moderate AR | 52 (11.1%) | 35 (9.4%) | 17 (17.7%) | 0.037 |

Data are expressed as mean ± standard deviation. Bold values represent $p < 0.05$ (statistical significant).

^aObtained by using t-test or Wilcoxon–Mann–Whitney test for continuous variables as appropriate or χ^2 test for categorical variables.

AHF, acute HF; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; EDVI, end-diastolic volume index; eGFR, estimated glomerular filtration rate (Cockcroft–Gault formula); G. mean, aortic mean gradient; LaCd, LA conduit; LaCt, LA contraction; LAVI, LA volume index; LVMI, LV mass index; MI, myocardial infarction; PAD, peripheral artery disease; RV-FAC, RV fractional area change; RWT, relative wall thickness; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; TDI, tissue doppler imaging; V. max, aortic maximum velocity.



variabilities. Statistical analyses were performed using JMP 15 (SAS Institute Inc.) and R4.3.1 (R Foundation for Statistical Computing). A two-tailed P-value <0.05 was considered significant.

Results

Clinical and echocardiographic characteristics of the study cohort

A total of 467 patients were included in the final analysis (see [Supplementary data online, Figure S1](#)). Baseline clinical and echocardiographic characteristics of the enrolled patients are summarized in [Table 1](#). On average, patients were old, with a balanced representation of men and women, with severe AS and preserved LV function. Three hundred fifty-two patients (75.4%) were symptomatic. Dyspnoea was the commonest symptom (68.5%), followed by angina (19.3%) and syncope (7.7%). Moreover, 17.5% had at least one prior in-hospital admission for HF. Patients who experienced the combined endpoint were older, were more symptomatic (NYHA III and IV), and had a higher prevalence of hypertension and moderate-to-severe chronic kidney disease (CKD) [estimated glomerular filtration rate (eGFR) <30 mL/min/m²]. Moreover, they had a higher prevalence of more than moderate MR and TR and more than mild AR. Patients who met the study endpoint had smaller AVA (*P* = 0.04), lower SVi (*P* = 0.001) and LVEF (*P* = 0.0006), and more impaired RV function and pulmonary vasculature. Finally, the patients who experienced the outcome presented worse values of LV GLS and PALS.

Two hundred seven patients were classified in the moderate AS group, 276 in the paucisymptomatic AS group, and 179 in the low-flow AS group. Overlapping between groups was reported in [Supplementary data](#).

Association with the primary endpoint in the whole cohort

The median follow-up of the cohort was 19.2 (IQR 12.5–24.4) months. Ninety-six patients (20.5%) met the primary endpoint (33 hospitalizations for HF and 63 deaths for any cause without prior HF admission

during the follow-up). Fifty-three (11.4%) deaths occurred during the first year of the follow-up. Two hundred fifteen (46%) patients underwent AVR during the follow-up period: 197 (42.1%) transcatheter AVR and 18 (3.9%) surgical AVR.

Using the ROC curve, the best cut-off values associated with the outcome were 14% for LV GLS [AUC (95% CI: 0.68–0.79), *P* < 0.001] and 16% for PALS [AUC (95% CI: 0.63–0.78), *P* < 0.001] (see [Supplementary data online, Figure S2](#)). The Kaplan-Meier curves for the PALS threshold demonstrated a higher rate of events for patients with PALS < 16% (event-free rate at 1 year 75 ± 3% vs. 90 ± 2%, log-rank *P* < 0.001; [Figure 1A](#)). These results were maintained even after censoring for AVR (event-free rate at 1 year 70 ± 4% vs. 91 ± 2%, log-rank *P* < 0.001; [Figure 1B](#)).

By PALS tertiles ([Figure 2](#)), patients in the lowest one (PALS <15%) presented a higher rate of events compared with the other two groups (event-free rate at 1 year 67 ± 4% vs. 88 ± 3% vs. 91 ± 2%, log-rank *P* = 0.003). In addition, when dividing the cohort into three groups according to PALS and/or LV GLS reduction ([Figure 3](#)), we found higher cumulative event rates in patients with both PALS and GLS reduced values (log-rank *P* < 0.001), highlighting the additive value and interaction between PALS and the outcome link of GLS (*P* for interaction = 0.04). Results were confirmed at multivariable survival analysis [HR for either PALS or LV GLS reduced vs. preserved 3.1 (1.7–5.5) *P* = 0.002 and HR for both PALS and GLS reduced vs. preserved 4.1 (2.2–7.7) *P* < 0.03, adjusted for age, NYHA Class ≥3, transaortic mean gradient, LVEF, presence of RV dysfunction, and LV GLS].

The parameters associated with the primary endpoint at the univariate Cox regression analysis are shown in [Table 2](#).

The additive prognostic value of PALS was evaluated along with previously reported clinical and echocardiographic parameters using a hierarchical model χ^2 analysis ([Tables 3 and 4](#)). The addition of PALS to a model including age, NYHA Class ≥3, transaortic mean gradient, LVEF, RV dysfunction, and LV GLS improved the model, strengthening the association with the occurrence of death or hospitalization for HF both in the overall population and after excluding patients who underwent AVR ([Figure 4](#)). On multivariable analysis including the main clinical and conventional echocardiographic parameters and LV GLS, only

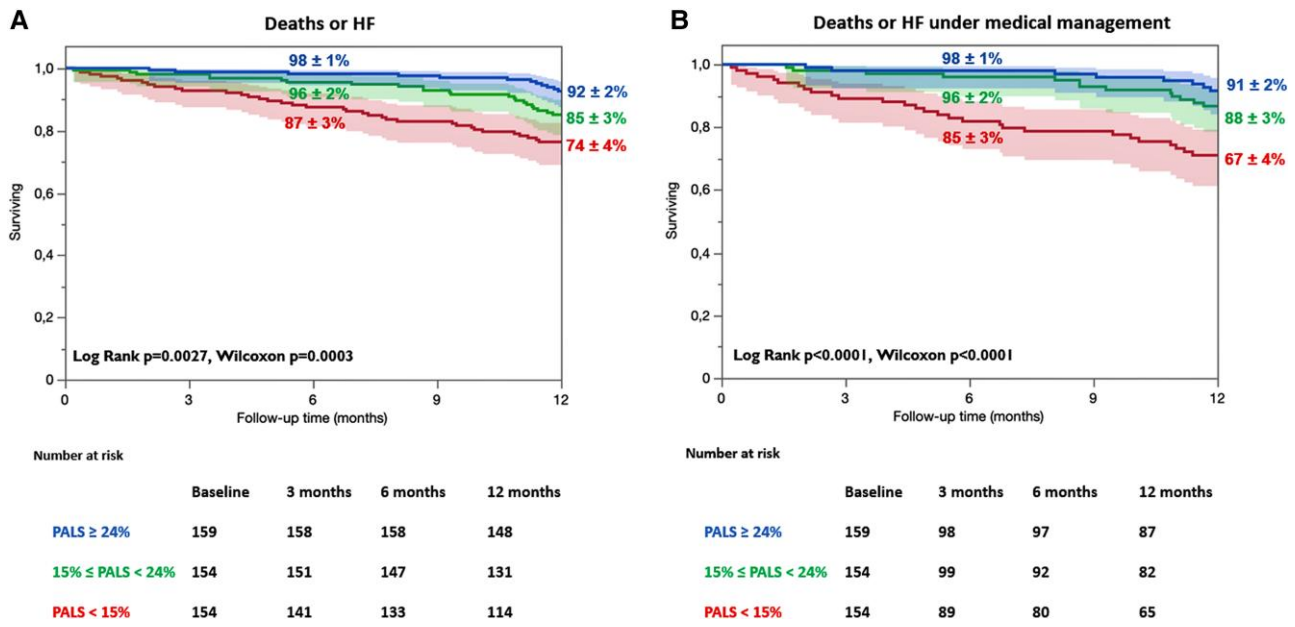


Figure 2 Kaplan–Meier curves for death and HF hospitalization stratified for PALS tertiles in the entire cohort (A) and under medical management (B).

PALS was found to be independently associated with the combined endpoint [aHR 0.95 (95% CI 0.91–0.99), $P = 0.017$].

The spline curve of mortality risk within the AS cohort (relative risk 1 represents the average mortality of the AS cohort) vs. PALS (continuous variable) shows that with progressive impairment of PALS, the events rate increases exponentially (Figure 5). The value of PALS where the excess events rate grows is represented by the threshold of <20% in the whole cohort; however, the risk becomes noteworthy at 16%.

Association with the outcome of LV GLS and PALS in different subgroups

The forest plot in [Supplementary data online, Figure S4](#) displays the effect of the PALS and GLS patterns according to severity AS, symptoms, and flow strata.

Furthermore, three groups of particular interest were illustrated in Kaplan–Meier curve analysis (moderate AS, low-flow AS, and

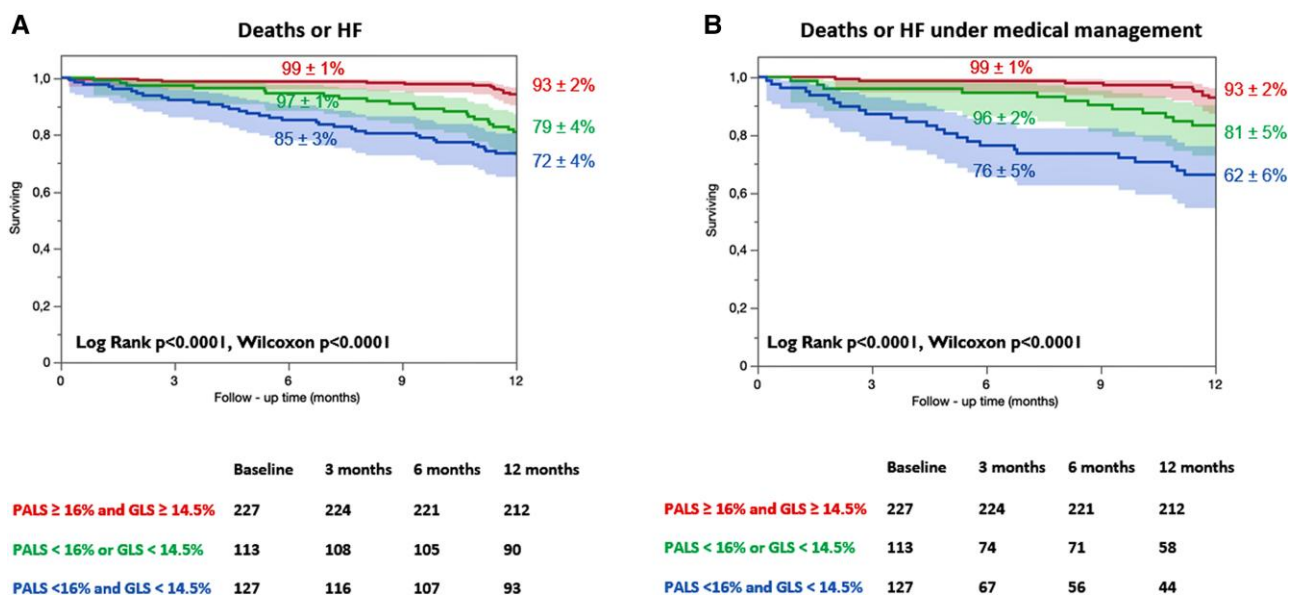


Figure 3 Kaplan–Meier curves for death and HF hospitalization stratified for PALS and GLS in the entire cohort (A) and under medical management (B).

Table 2 Univariate Cox regression analysis (whole study cohort)

| | HR (95% CI) | P-value |
|-----------------------|------------------|------------------|
| Age | 1.04 (1.02–1.07) | 0.002 |
| Previous AHF | 2.0 (1.4–2.9) | <0.001 |
| NYHA Class ≥ 3 | 2.4 (1.7–3.4) | <0.001 |
| Hypertension | 1.31 (0.92–1.88) | 0.131 |
| Severe CKD | 1.42 (1.00–1.84) | 0.049 |
| Moderate or severe MR | 1.82 (1.27–2.61) | 0.001 |
| LVMI | 1.01 (1.01–1.02) | 0.004 |
| LVEDVI | 1.02 (1.01–1.02) | <0.001 |
| LAVI | 1.02 (1.01–1.03) | <0.001 |
| LVEF | 0.97 (0.96–0.98) | <0.001 |
| Mean gradient | 1.01 (1.01–1.02) | 0.043 |
| e/e' | 1.06 (1.02–1.10) | 0.001 |
| SVI | 0.96 (0.94–0.98) | <0.001 |
| RV dysfunction | 1.6 (1.05–2.6) | 0.03 |
| sPAP | 1.03 (1.02–1.05) | <0.001 |
| PALS | 0.95 (0.93–0.98) | <0.001 |
| LV GLS | 0.46 (0.26–0.83) | 0.009 |
| LA conduit | 0.95 (0.92–0.99) | 0.013 |
| LA contraction | 0.96 (0.94–0.98) | 0.003 |

Bold values represent $p < 0.05$ (statistical significant).
 AHF, acute HF; LAVI, LA volume index; LVEDVI, LV end-diastolic volume index; LVMI, LV mass index; sPAP, systolic pulmonary artery pressure.

Table 3 Cox multivariable models—deaths or HF in patients under medical management

| | aHR (95% CI) | P-value |
|---|------------------|--------------|
| Model clinical + conventional echo $\chi^2 = 47.1$; $P < 0.001$ | | |
| Age | 1.04 (1.01–1.08) | 0.024 |
| NYHA Class ≥ 3 | 1.55 (1.12–3.69) | 0.019 |
| Mean gradient | 1.03 (1.01–1.04) | 0.002 |
| LVEF | 0.97 (0.96–0.99) | 0.027 |
| RV dysfunction | 1.43 (0.71–2.8) | 0.316 |
| Model clinical + conventional echo + LV GLS $\chi^2 = 51.6$; $P < 0.001$ | | |
| Age | 1.04 (1.01–1.08) | 0.02 |
| NYHA Class ≥ 3 | 1.72 (0.96–3.1) | 0.068 |
| Mean gradient | 1.02 (1.01–1.04) | 0.016 |
| LVEF | 0.98 (0.97–1.02) | 0.955 |
| RV dysfunction | 0.61 (0.39–2.5) | 0.556 |
| LV GLS | 0.95 (0.88–1.03) | 0.015 |
| Model clinical + conventional echo + LV GLS + PALS $\chi^2 = 56.4$; $P < 0.001$ | | |
| Age | 1.04 (1.01–1.08) | 0.104 |
| NYHA Class ≥ 3 | 1.72 (0.94–2.9) | 0.098 |
| Mean gradient | 1.02 (1.01–1.04) | 0.008 |
| LVEF | 0.99 (0.97–1.02) | 0.671 |
| RV dysfunction | 1.16 (0.57–2.4) | 0.629 |
| LV GLS | 0.95 (0.86–1.05) | 0.311 |
| PALS | 0.95 (0.91–0.99) | 0.017 |

Bold values represent $p < 0.05$ (statistical significant).
 aHR, adjusted hazard ratio; LV GLS, left ventricle global longitudinal strain; LVEF, left ventricle ejection fraction; NYHA, New York heart association; PALS, peak atrial longitudinal strain; RV, right ventricle.

paucisymptomatic AS; see [Supplementary data online, Table S2](#) and [Figures S5–S7](#)).

At Cox regression analysis, PALS was independently associated with outcome in the three groups: in the low-flow AS [aHR 0.90, 95% CI (0.83–0.98), $P = 0.020$], in the moderate AS [aHR 0.92, 95% CI (0.86–0.98), $P = 0.016$], and in the paucisymptomatic AS [aHR 0.98, 95% CI (0.97–0.98), $P = 0.048$].

Inter-observer and intra-observer variabilities

The ICCs for inter-observer variability were 0.941 [95% CI (0.857–0.976), $P < 0.001$] for GLS and 0.976 [95% CI (0.940–0.990), $P < 0.001$] for PALS. Additionally, the ICCs for intra-observer variability were 0.972 [95% CI (0.931–0.989), $P < 0.001$] for GLS and 0.982 [95% CI (0.954–0.993), $P < 0.001$] for PALS.

Discussion

The main findings of our study performed in patients with at least moderate AS can be summarized as follows: (i) PALS was independently associated with the composite outcome of HF hospitalization and death; (ii) PALS revealed an incremental value over clinical, conventional echocardiography parameters of LV function and AS severity, and LV GLS; (iii) the association with the outcome of PALS was maintained even when tested in patient subgroups, such as paucisymptomatic patients, moderate AS, and low-flow AS.

Insights into LA dysfunction in AS

Over time, the chronic pressure overload caused by AS may determine LV concentric hypertrophy.²⁸ Although this compensatory mechanism is intended to maintain the cardiac performance by decreasing LV afterload, the increase of both the LV filling pressures and the LA pressures may induce LA dysfunction and enlargement.⁹ This phenomenon, recently identified as atrial cardiomyopathy,²⁹ is sustained by molecular, cellular, and neurohormonal interlinked pathways resulting in chronic inflammation, atrial fibrosis, and electrophysiological changes.³⁰ This atrial remodelling determined by AS was confirmed on a murine experimental model of increased afterload simulating AS, which produced LA hypertrophy and fibrosis. Atrial remodelling in AS can serve as a substrate for atrial fibrillation³¹ and may correlate to the presence of cardiac injury and the development of HF symptoms in AS.^{32,33} In a multi-centre prospective observational study enrolling 745 patients with HF,¹⁰ PALS was independently associated with LV GLS among HF stages, thus reflecting the ability of PALS to stratify patient's clinical status and identify the haemodynamic consequences of LV dysfunction. Moreover, a recent study in moderate-to-severe AS demonstrated that PALS yielded an incremental prognostic power over *n*-terminal pro-B-type natriuretic peptide (NT-proBNP) and clinical variables.³⁴ The PALS $< 16\%$ cut-off in our study was close to the threshold reported to identify elevated LV filling pressures and severe LV diastolic dysfunction in patients with HF and preserved ejection fraction (HFpEF).¹¹

Table 4 Cox multivariable models—deaths or HF

| | aHR (95% CI) | P-value |
|--|------------------|--------------|
| Model clinical + echo conventional $\chi^2 = 34.7$; P < 0.001 | | |
| Age | 1.05 (1.01–1.08) | 0.006 |
| NYHA Class ≥ 3 | 1.72 (1.08–2.75) | 0.02 |
| Mean gradient | 1.00 (0.98–1.01) | 0.694 |
| LVEF | 0.98 (0.96–0.99) | 0.010 |
| RV dysfunction | 0.88 (0.47–1.64) | 0.696 |
| Model clinical + echo conventional + LV GLS $\chi^2 = 41.0$; P < 0.001 | | |
| Age | 1.04 (1.01–1.08) | 0.008 |
| NYHA Class ≥ 3 | 1.55 (0.93–2.40) | 0.095 |
| Mean gradient | 0.99 (0.98–1.01) | 0.538 |
| LVEF | 1.00 (0.99–1.01) | 0.820 |
| RV dysfunction | 0.78 (0.42–1.45) | 0.424 |
| LV GLS | 0.90 (0.85–0.97) | 0.007 |
| Model clinical + echo conventional + LV GLS + PALS $\chi^2 = 44.9$; P < 0.001 | | |
| Age | 1.04 (1.01–1.07) | 0.03 |
| NYHA Class ≥ 3 | 1.42 (0.89–2.23) | 0.095 |
| Mean gradient | 0.99 (0.98–1.01) | 0.538 |
| LVEF | 0.99 (0.97–1.01) | 0.820 |
| RV dysfunction | 0.72 (0.39–1.34) | 0.291 |
| LV GLS | 0.95 (0.88–1.03) | 0.299 |
| PALS | 0.96 (0.93–0.99) | 0.031 |

Bold values represent $p < 0.05$ (statistical significant).
 aHR, adjusted hazard ratio; LV GLS, left ventricle global longitudinal strain; LVEF, left ventricle ejection fraction; NYHA, New York heart association; PALS, peak atrial longitudinal strain; RV, right ventricle.

Furthermore, in patients with severe AS and HFpEF, PALS correlated to pulmonary hypertension.³⁵ In our study, we confirmed the significant association of PALS with outcome after adjustment for age, NYHA

class, LVEF, LV GLS, and RV dysfunction supporting its role as a surrogate marker of overall cardiac damage in AS. Therefore, we hypothesize that PALS could be interpreted as a sensitive marker of cardiac damage in patients with AS, and its incremental value, encompassing several pathophysiological determinants of cardiac damage in AS, may go beyond the merely LA function.¹⁰ Of note, PALS incorporates the haemodynamic consequences of LV systolic and diastolic dysfunctions, along with the haemodynamic role of AS and MR, effectively resulting in a 'barometric index' of cardiac function. Thus, it synthesizes the complex interplay between LA and LV into a single feasible value.³⁶

The association of PALS with outcome in AS

Limited and sometimes controversial evidence exists for the potential prognostic value of assessing LA mechanics using 2D STE in patients with AS. In a preliminary study¹⁴ of 89 asymptomatic, severe AS patients, those with LV GLS $\leq 16.8\%$ and PALS $\leq 19.8\%$ had a higher incidence of symptom-related events or death. However, only LV GLS remained prognostically significant in the multivariate analysis. Conversely, Galli et al.³⁷ studied 128 patients with severe AS in sinus rhythm, a quarter of whom underwent transcatheter AVR, and found that PALS $< 21\%$ was a significant predictor of overall death and HF. Another study, examining 102 moderate-to-severe AS patients, found that PALS and LA distensibility were independently associated with events, adjusting for the Charlson index but not LV GLS. Similar to our findings, these authors identified PALS $\leq 17\%$ as event-associated.³³

A recent study by Tan et al.³⁴ included 173 patients with at least moderate AS and normal LVEF, followed for 2.7 years. Patients with PALS $< 20\%$ experienced worse outcomes. Interestingly, PALS outperformed other echocardiographic indices, providing incremental information to established risk markers like LV GLS, LA volume index, and NT-proBNP.

In line with the previous paper, in our study, PALS had an incremental prognostic power over LV GLS and the conventional echocardiographic parameters of LV function and AS severity both in the overall cohort of the enrolled patients and in the subgroup analyses. We found a lower cut-off value of PALS (16%) compared with the other studies. However, we observed a progressive increase in the relative risk of experiencing events starting from a PALS $< 20\%$, which is similar to the previous studies. PALS also identified higher risk subsets of patients

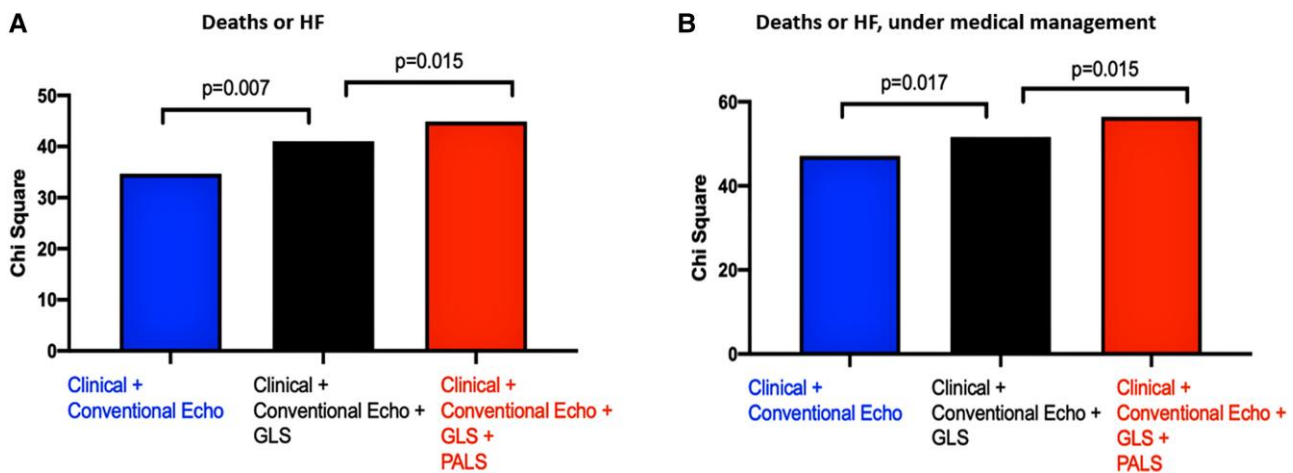


Figure 4 Hierarchical Cox regression analysis for the composite endpoint in the entire cohort (A) and under medical management (B).

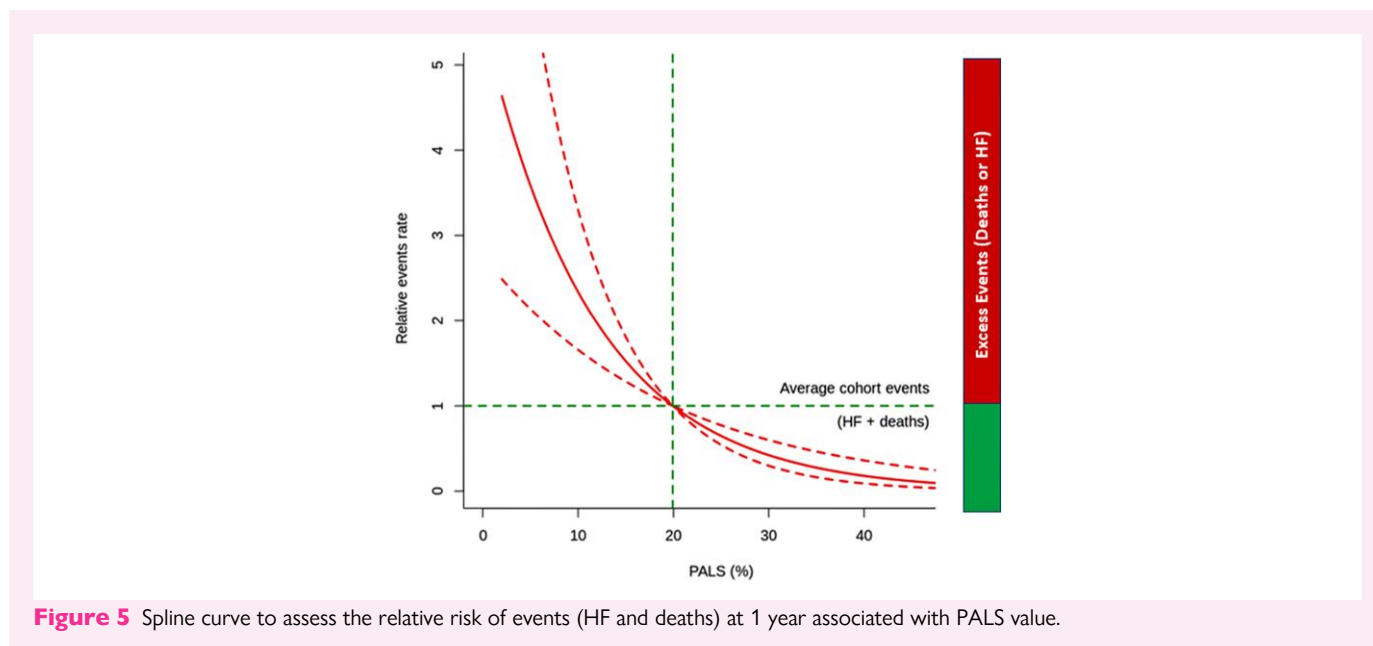


Figure 5 Spline curve to assess the relative risk of events (HF and deaths) at 1 year associated with PALS value.

with asymptomatic/mild symptomatic AS or moderate AS, according to Sonaglioni *et al.*'s³⁸ findings. Remarkably, no prior reports addressed low-flow status. In our study, PALS also added clinical value over LV GLS in this subgroup of patients with AS.

Extravalvular cardiac damage and AS

Concerning extravalvular cardiac damage and AS, a new staging classification considers extravalvular damage progression. The extent of cardiac damage was associated with the 1-year mortality rate after AVR. Patients with LA enlargement, atrial fibrillation, or significant MR (Stage 2) faced higher event incidence than LV damage or absence of cardiac damage, reinforcing atrial cardiomyopathy clinical impact.³⁹ This staging system, initially based on conventional parameters, was refined and validated using LV GLS in asymptomatic patients with severe AS⁴⁰ and severe AS patients undergoing transcatheter aortic valve replacement.⁴¹

LV GLS application in severe AS is supported by studies correlating it with myocardial fibrosis documented with cardiac magnetic resonance (CMR)⁴² and patient outcomes.⁴³ However, the afterload-mediated hypertrophic remodelling of the LV during AS may determine *per se* a reduction of the LV GLS.⁴⁴ Furthermore, LV GLS is not strongly related to early myocardial remodelling in the form of expansion of the extracellular matrix determined by CMR.⁴⁵ These data associated with the results of our study showing the incremental prognostic value of PALS over LV GLS identify PALS as an additional sensitive variable to refine the assessment of extravalvular damage in AS. Further research should explore whether the addition of PALS may enhance this staging classification.

Clinical implications

The results of the present study including a large cohort of patients with at least moderate AS showed that PALS was the echocardiographic parameter more strongly associated with outcome even after censoring for AVR. The measurement of PALS may therefore improve the risk stratification of patients with moderate-to-severe AS and identify those who might benefit from closer follow-up or an early pre-intervention evaluation.

Moreover, PALS has proven to stratify patients' risk in special subgroups of patients such as moderate AS, low-flow AS, and asymptomatic/mild symptomatic AS. In a hypothetical clinical flowchart, reduced PALS could act as a red flag, potentially prompting the implementation of the algorithm based on current guidelines in these specific subgroups.

Limitations

Our retrospective study, while analysing a substantial AS patient cohort, has limitations. We have selected our patients using strict eligibility criteria. Accordingly, the generalizability of the proposed PALS cut-off value to the wider population needs to be assessed. PALS values have shown significant intervendor variability, and the applicability of our threshold values to different STE software packages remains to be tested. To partially overcome this limitation, we used a vendor-independent software package to measure PALS using images obtained from multiple echocardiographic systems. We selected only patients in sinus rhythm, since atrial fibrillation impacts PALS measurements. Accordingly, our results do not apply to patients with atrial fibrillation.

Finally, multi-imaging data (cardiac Computed tomography or stress echocardiography) were not available to differentiate pseudo-severe from severe AS.

Conclusion

Our data showed that, in patients with at least moderate AS, PALS was more strongly associated with the outcome than conventional echocardiographic parameters of LV function, AS severity, and LV GLS, including patients with low-flow states, moderate AS, and paucisymptomatic AS. PALS may improve the clinical management of patients, identifying patients at higher risk who may benefit from closer follow-up and an earlier treatment.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data are available as appropriate request to the authors.

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