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ORIGINAL RESEARCH ARTICLE

Prognostic value of the H_2FPEF score in patients undergoing transcatheter aortic valve implantation

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Abstract

Aims The aim of this study was to assess the prognostic value of the H_2FPEF score in patients undergoing transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS) and preserved left ventricular ejection fraction (EF).

Methods and results In this multicentre study, a total of 832 patients from two German high-volume centres, who received TAVI for severe AS and preserved EF (≥50%), were identified for calculation of the H_2FPEF score. Patients were dichotomized according to low (0–5 points; n = 570) and high (6–9 points; n = 262) H_2FPEF scores. Kaplan–Meier and Cox regression analyses were applied to assess the prognostic impact of the H_2FPEF score. We observed a decrease in stroke volume index (-2.04 mL/m^2/point) and mean transvalvular gradients (-1.14 mmHg/point) with increasing H_2FPEF score translating into a higher prevalence of paradoxical low-flow, low-gradient AS among patients with high H_2FPEF score. One year after TAVI, the rates of all-cause (low vs. high H_2FPEF score: 8.0% vs. 19.4%, $P < 0.0001$) and cardiovascular (CV) mortality (1.9% vs. 9.0%, $P < 0.0001$) as well as the rate of CV mortality or rehospitalization for congestive heart failure (6.4% vs. 23.2%, $P < 0.0001$) were higher in patients with high H_2FPEF score compared with those with low H_2FPEF score. After multivariable analysis, a high H_2FPEF score remained independently predictive of all-cause mortality [hazard ratio 1.59 (1.28–2.35), $P = 0.018$] and CV mortality or rehospitalization for congestive heart failure [hazard ratio 2.92 (1.65–5.15), $P < 0.001$]. Among the H_2FPEF score variables, atrial fibrillation, pulmonary hypertension, and elevated left ventricular filling pressure were the strongest outcome predictors.

Conclusions The H_2FPEF score serves as an independent predictor of adverse CV and heart failure outcome among TAVI patients with preserved EF. A high H_2FPEF score is associated with the presence of paradoxical low-flow, low-gradient AS, the HFpEF in patients with AS. By identifying patients in advanced stages of HFpEF, the H_2FPEF score might be useful as a risk prediction tool in patients with preserved EF scheduled for TAVI.

Keywords H_2FPEF score; HFpEF; Paradoxical low gradient; Aortic stenosis; TAVI

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Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) has increased over the last decades, and affected patients suffer from impaired prognosis.[1–4] Although the diagnosis of HFpEF leads to a similar rehospitalization burden compared with heart failure with reduced ejection fraction (HFrEF), its fatal impact still remains widely unrecognized and, thus, the condition itself underdiagnosed.[5–8] To overcome this shortcoming, the so-called H_2FPEF score has recently been published enabling the diagnosis of HFpEF with high accuracy using simple demographic, clinical, and

echocardiographic parameters.[9] Moreover, it has been demonstrated that the H_2FPEF score is able to predict adverse outcome in heart failure patients.[10–13]

Aortic stenosis (AS) is a frequent finding, especially among elderly patients, and severe AS is associated with dismal outcome if left untreated.[14,15] Pathophysiologically, left ventricular (LV) pressure overload due to obstructed outflow through the calcified aortic valve is usually associated with concentric LV hypertrophy.[16] In more advanced stages of the disease, the persistent pressure load promotes further structural LV alterations, very similar compared with those in HFpEF patients, leading to, for example, diastolic dysfunction, atrial fibrillation, and mitral (MR) or tricuspid regurgitation (TR).[17] As a consequence, these alterations may result in reduced stroke volume and—although LV ejection fraction (EF) is still preserved—in a 'paradoxical' low transvalvular gradient, a state defined as paradoxical low-flow, low-gradient AS (PLF-LG AS).[18] Thus, it has been suggested that PLF-LG AS is equal to HFpEF in patients with AS.[19–21] Compared with patients with high-gradient AS (HG-AS), these patients are known to have notably worse outcome after transcatheter aortic valve implantation (TAVI).[22,23] Yet in AS patients with preserved EF undergoing TAVI, especially in those with PLF-LG AS, only few baseline parameters have been identified as predictors of outcome.

The aim of this multicentre study was to assess the prognostic impact of the H_2FPEF score on adverse outcome in patients with preserved EF undergoing TAVI for severe AS. We hypothesized that a high H_2FPEF score is associated with a high prevalence of PLF-LG AS and, thus, with adverse outcome in patients undergoing TAVI.

Methods

Study design and data acquisition

The study is designed as a retrospective, multicentre analysis of data derived from TAVI registries of two German high-volume centres (University Heart and Vascular Centre Hamburg, Germany; German Heart Centre Munich, Germany). All clinical endpoints were adjudicated according to current Valve Academic Research Consortium 2 (VARC-2) criteria after 30 days. Survival data were obtained, as part of clinical routine, from either in-house data or telephone follow-up of the patient or the referring physician. The investigation conforms to the principles outlined in the Declaration of Helsinki.[24]

Patient population

Between 2013 and 2018, a total of 3852 patients underwent TAVI for severe AS at both centres. Decision to perform TAVI was made by an interdisciplinary heart team for all patients. After exclusion of patients with EF $<$ 50%, severe aortic regurgitation, valve-in-valve procedures, and combined percutaneous mitral valve treatment, 1555 patients fulfilled criteria for potential study inclusion. Of these, 832 patients with severe AS and preserved EF had available data for all six H_2FPEF score variables and, thus, formed the final study population. Median follow-up for these patients was 1.08 [95% confidence interval (CI) 1.06–1.11] years. A comparison of baseline characteristics between excluded and included patients is given in Supporting Information, *Table S1*.

H_2FPEF score calculation

The original H_2FPEF score comprises six weighted variables: obesity (defined as body mass index $>$30 kg/m^2), atrial fibrillation, age $>$60 years, arterial hypertension (defined as treatment with $\geq$2 antihypertensives), elevated LV filling pressures (defined as echocardiographic E/e' ratio $>$9), and echocardiographically derived systolic pulmonary artery pressure $>$35 mmHg. According to Reddy *et al.*, the probability for the diagnosis of *HFpEF* is $>$90%, if a patient reaches $\geq$6 score points.[9] In the present study, calculation of the score was modified adapting to common TAVI registry parameters. Arterial hypertension was defined based on the diagnosis of hypertension according to patient history, and elevated filling pressures were defined as invasively measured pre-procedural LV end-diastolic pressure (LVEDP) $\geq$15 mmHg. In accordance with the original publication, all variables were weighted equally (1 point) with the exception of obesity (2 points) and atrial fibrillation (3 points).[9]

Definition of aortic stenosis subtypes

Severity of AS and classification in HG-AS, PLF-LG AS, or normal-flow, low-gradient (NF-LG) AS were assessed by means of resting transthoracic echocardiography at baseline according to the current *European Society of Cardiology* and *European Association for Cardio-Thoracic Surgery* guidelines.[18] HG-AS was defined as an effective orifice area (EOA) $\leq$1.0 cm^2 and mean transvalvular gradient (Pmean) $>$40 mmHg. Severe PLF-LG AS was defined as an EOA $\leq$ 1.0 cm^2, Pmean $<$ 40 mmHg, and stroke volume index (SVI) $\leq$35 mL/m^2 and NF-LG AS as EOA $\leq$ 1.0 cm^2, Pmean $<$ 40 mmHg, and SVI $>$ 35 mL/m^2. EF was $\geq$50% in all patients. All parameters for AS subtype classification were available in 751 patients; 81 patients were not classified because of missing data.

Statistical analysis

The median follow-up time as well as the percentages of deaths were estimated by the Kaplan–Meier potential follow-up estimator.[25] Binary variables were shown as absolute numbers and percentages and were compared by

using χ^2 test. Continuous variables were shown as mean ± standard deviation or as median (25th percentile, 75th percentile), and for between-group comparisons, the Mann–Whitney *U* test was used. Unadjusted spline analyses were performed. Survival curves were produced using the Kaplan–Meier method, and curve differences were tested by the log-rank test. For the univariable and multivariable analyses, the following set of variables was used: age, male sex, body mass index, prior stroke, atrial fibrillation, hypertension, prior myocardial infarction, coronary artery disease, diabetes, chronic obstructive pulmonary disease (COPD), systolic pulmonary artery pressure in the categories ≤35 (reference), 36–55, and >55 mmHg, TR ≥ 2, MR ≥ 2, New York Heart Association (NYHA) stage, glomerular filtration rate <60 mL/min, non-transfemoral access, LVEDP, and H_2FPEF score with the low score (0–5 points) as reference. Variables that showed *P*-values <0.25 in the univariable Cox regression analyses were used in a forward selection process based on Akaike information criterion. We performed two different multivariable regressions: one with the H_2FPEF score and without the variables, which were used in the score and the other one vice versa. *C*-indices were calculated for the continuous H_2FPEF score and several endpoints. All statistical analyses were performed using R Version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical baseline characteristics and distribution of score variables

Figure 1 shows the H_2FPEF score distribution among the study population. Mean H_2FPEF score was 4.38. For further analyses, patients were dichotomized according to low [0–5 points, *n* = 570/832 (69%)] and high H_2FPEF score [6–9 points, *n* = 262/832 (31%)]. Clinical and echocardiographic baseline characteristics as well as the distribution of score variables among patients with low and high H_2FPEF scores are presented in *Table 1*. In patients with high H_2FPEF score, there was a higher prevalence of diabetes and COPD compared with those with low H_2FPEF score. Moreover, patients with high H_2FPEF score presented with worse renal function, advanced NYHA stages, and higher estimated surgical risk. There were no differences between both groups regarding age and sex. The prevalence of all other score variables was higher in patients with high H_2FPEF score.

Echocardiographic findings

In patients with high H_2FPEF score, the prevalence of both moderate or severe TR and moderate or severe MR was higher compared with those patients with low H_2FPEF score. Moreover, patients with high H_2FPEF score presented with significantly lower Pmean and lower SVI. *Figure 2* shows spline analyses for the association of the H_2FPEF score with Pmean, SVI, and with probabilities of prevalent PLF-LG AS and NF-LG AS. *Figure 2A* demonstrates spline analysis for the inverse association between Pmean and increasing H_2FPEF score revealing a 1.14 mmHg decrease in Pmean per 1-point increase of the H_2FPEF score. A similar inverse interrelation was observed for the H_2FPEF score and SVI (*Figure 2B*). Excluding H_2FPEF score 1–3, SVI decreased by 2.04 mL/m^2 with each H_2FPEF score point increase.

Distribution of aortic stenosis subtypes according to H_2FPEF score

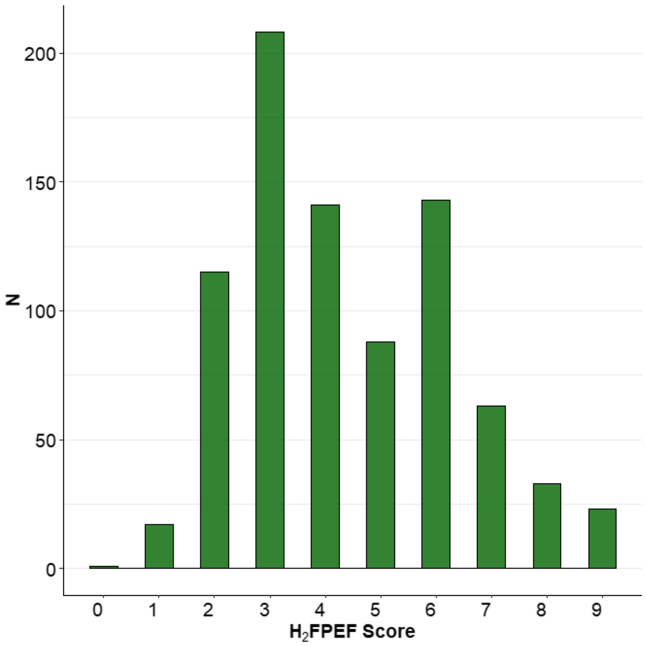
Regarding the distribution of AS subtypes, the proportion of HG-AS was significantly higher in patients with low H_2FPEF score (57.5%) compared with those with high H_2FPEF score (45.1%). Conversely, patients with high H_2FPEF score had a higher prevalence of PLF-LG AS (30.5%) compared with patients with low H_2FPEF score (13.9%). With regard to NF-LG AS, there was no statistical difference between both groups. However, the proportion of NF-LG AS was numerically higher in patients with high H_2FPEF score. *Figure 2C* and *2D* depicts spline analyses for the interrelations of increasing H_2FPEF score with the probability of prevalent PLG-LG AS or NF-LG AS among the subset of patients with low-gradient AS (Pmean < 40 mmHg) (*N* = 328). With the exception of H_2FPEF score 1–3, the probability of prevalent PLF-LG AS increased by 8% per 1-point increase of the H_2FPEF score while decreasing by 8% for the probability of NF-LG AS.

Outcome according to H_2FPEF score

Over the mean follow-up time of 1.08 years (95% CI 1.06–1.11), all-cause mortality occurred in 113 (54.6%) patients (H_2FPEF score 0–5: *N* = 55; H_2FPEF score 6–9: *N* = 58).

Procedural and 30 day VARC-2 outcome is shown in Supporting Information, *Table S2*. No differences were found between low and high H_2FPEF scores regarding TAVI access, transcatheter heart valve types, or any 30 day VARC-2 endpoints [i.e. disabling stroke, myocardial infarction, major or life-threatening bleeding, and renal failure (Acute Kidney Injury Network >2), new permanent pacemaker implantation, and more than mild paravalvular leakage]. However, 30 day all-cause mortality was significantly higher in patients with high H_2FPEF score compared with those with low H_2FPEF score (0.9% vs. 5.4%, *P* < 0.001). *Figure 3* shows Kaplan–Meier survival estimates according to low and high H_2FPEF scores for all-cause mortality (*Figure 3A*), cardiovascular (CV) mortality (*Figure 3B*), rehospitalization for congestive heart failure (CHF) (*Figure 3C*), and the combined endpoint of CV mortality and rehospitalization for CHF (*Figure 3D*) at

Figure 1 H_2FPEF score distribution among the study population.



1 year after TAVI. The rates of all-cause (low vs. high H_2FPEF score: 8.0% vs. 19.4%, $P < 0.0001$) and CV mortality (1.9% vs. 9.0%, $P < 0.0001$), rehospitalization for CHF (4.3% vs. 14.5%, $P = 0.00069$), and CV mortality or rehospitalization for CHF (6.4% vs. 23.2%, $P < 0.0001$) were significantly higher in patients with high H_2FPEF score compared with those with low H_2FPEF score.

Prognostic impact of H_2FPEF score

The prognostic impact of, both, a high H_2FPEF score (6–9 points) (I) and of the single score variables (II) was assessed by multivariable analysis for all-cause mortality (*Table 2*) and for the combined endpoint of CV mortality or rehospitalization for CHF (*Table 3*).

Multivariable analyses (I) determined a high H_2FPEF score as a strong independent predictor of all-cause mortality [hazard ratio (HR) 1.59, 95% CI 1.08–2.35, $P = 0.018$] and of CV mortality or rehospitalization for CHF (HR 2.92, 95% CI 1.65–5.15, $P < 0.001$). In separate multivariable analyses (II) with all score variables, but without the score itself, atrial fibrillation was the score variable with the strongest association with all-cause mortality (HR 1.99, 95% CI 1.34–2.95, $P < 0.001$) (*Table 2*). Pulmonary artery hypertension >55 mmHg (HR 3.02, 95% CI 1.22–7.47, $P = 0.017$), atrial fibrillation (HR 2.01, 95% CI 1.10–3.67, $P = 0.023$), and elevated LV filling pressure (HR 1.66, 95% CI 0.92–2.97, $P = 0.09$) showed the strongest association with CV mortality or rehospitalization for CHF (*Table 3*) among all score variables.

Moderate or severe TR, chronic renal failure, and non-transfemoral access were further independent predictors of all-cause mortality, while moderate or severe MR and NYHA stage were independently associated with CV mortality or rehospitalization for CHF.

The predictive value of the H_2FPEF score was assessed using *C*-statistics for all endpoints 1 year after TAVI resulting in *C*-indices of 0.66 for all-cause mortality, 0.78 for CV mortality, 0.64 for rehospitalization for CHF, and 0.69 for the combined endpoint of CV mortality or rehospitalization for CHF.

Discussion

The present multicentre study assessed the prognostic impact of the H_2FPEF score in 832 patients with preserved EF who received TAVI for severe AS. The main findings of this study are as follows. Among TAVI patients with preserved EF:

i A high H_2FPEF score (6–9 points) is associated with a higher prevalence of co-morbidities and a higher estimated surgical risk.
ii A high H_2FPEF score is associated with lower Pmean and lower SVI resulting in a higher probability of prevalent PLF-LG AS.
iii Rates of all-cause mortality, CV mortality, rehospitalization for CHF, and the combined endpoint of CV mortality or

Table 1 Clinical and echocardiographic baseline characteristics

	All patients (N = 832)	H_2FPEF score 0–5 (N = 570)	H_2FPEF score 6–9 (N = 262)	P-value
Clinical baseline characteristics				
Male sex	359 (43.1)	255 (44.7)	104 (39.7)	0.20
STS PROM	4.1 (2.8, 5.7)	3.9 (2.7, 5.4)	4.3 (3.0, 6.6)	0.036
EuroSCORE II	3.6 (2.3, 5.8)	3.4 (2.2, 5.5)	4.2 (2.6, 7.0)	<0.001
Diabetes	221 (26.6)	131 (23.0)	90 (34.4)	<0.001
COPD	116 (13.9)	69 (12.1)	47 (17.9)	0.032
GFR (CKD-EPI)	62.3 (46.8, 76.6)	65.1 (49.2, 78.7)	57.4 (41.8, 70.1)	<0.001
CAD	603 (72.8)	419 (73.8)	184 (70.8)	0.41
Prior MI	63 (7.6)	48 (8.4)	15 (5.7)	0.22
Prior CABG	70 (8.4)	50 (8.8)	20 (7.6)	0.68
Prior PCI	303 (36.5)	213 (37.4)	90 (34.4)	0.44
Prior stroke	111 (13.3)	67 (11.8)	44 (16.8)	0.061
Prior PM	29 (6.9)	28 (9.6)	1 (0.8)	0.0019
NYHA III/IV	589 (71.0)	382 (67.3)	207 (79.3)	<0.001
H_2FPEF score variables				
BMI (kg/m^2)	26.2 (23.5, 29.4)	25.7 (23.4, 28.7)	27.6 (24.1, 31.2)	<0.001
Hypertension	755 (90.7)	499 (87.5)	256 (97.7)	<0.001
Atrial fibrillation	266 (32.0)	32 (5.6)	234 (89.3)	<0.001
Moderate PHT (sPAP 36–55 mmHg)	502 (60.3)	321 (56.3)	181 (69.1)	<0.001
Severe PHT (sPAP > 55 mmHg)	113 (13.6)	51 (8.9)	62 (23.7)	<0.001
Age (years)	81.9 (78.0, 85.1)	81.6 (77.6, 85.1)	82.3 (78.8, 85.2)	0.18
LVEDP (mmHg)	12.0 (9.0, 18.0)	12.0 (8.0, 17.0)	14.0 (10.0, 20.0)	<0.001
Echocardiographic baseline parameters				
Moderate or severe TR	134 (16.1)	63 (11.1)	71 (27.1)	<0.001
Moderate or severe MR	179 (21.5)	99 (17.4)	80 (30.5)	<0.001
Pmean (mmHg)	42.0 (31.0, 51.0)	43.0 (33.7, 53.0)	39.0 (28.0, 48.7)	<0.001
Stroke volume index (mL/m^2)	39.0 (32.0, 46.8)	40.7 (34.4, 48.4)	35.2 (28.8, 43.7)	<0.001
HG-AS	423 (53.5)	309 (57.5)	114 (45.1)	0.0013
NF-LG AS	187 (25.4)	135 (26.8)	52 (22.3)	0.22
PLF-LG AS	141 (19.2)	70 (13.9)	71 (30.5)	<0.001
Procedural parameters				
TF access	783 (94.1)	536 (94.0)	247 (94.3)	1.00
TA access	33 (4.0)	22 (3.9)	11 (4.2)	0.97
TAX access	15 (1.8)	11 (1.9)	4 (1.5)	0.90
Other access	1 (0.1)	1 (0.2)	0 (0)	1.00

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HG-AS, high-gradient aortic stenosis; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction; MR, mitral regurgitation; NF-LG AS, normal-flow, low-gradient aortic stenosis; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PHT, pulmonary hypertension; PLF-LG AS, paradoxical low-flow, low-gradient aortic stenosis; PM, permanent pacemaker; Pmean, mean transvalvular pressure gradient; STS PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TA, transapical; TAX, transaxillary; TF, transfemoral; TR, tricuspid regurgitation.
Data presented are the number (percentage) of patients for categorical variables or median values (25th percentile, 75th percentile) for continuous variables.

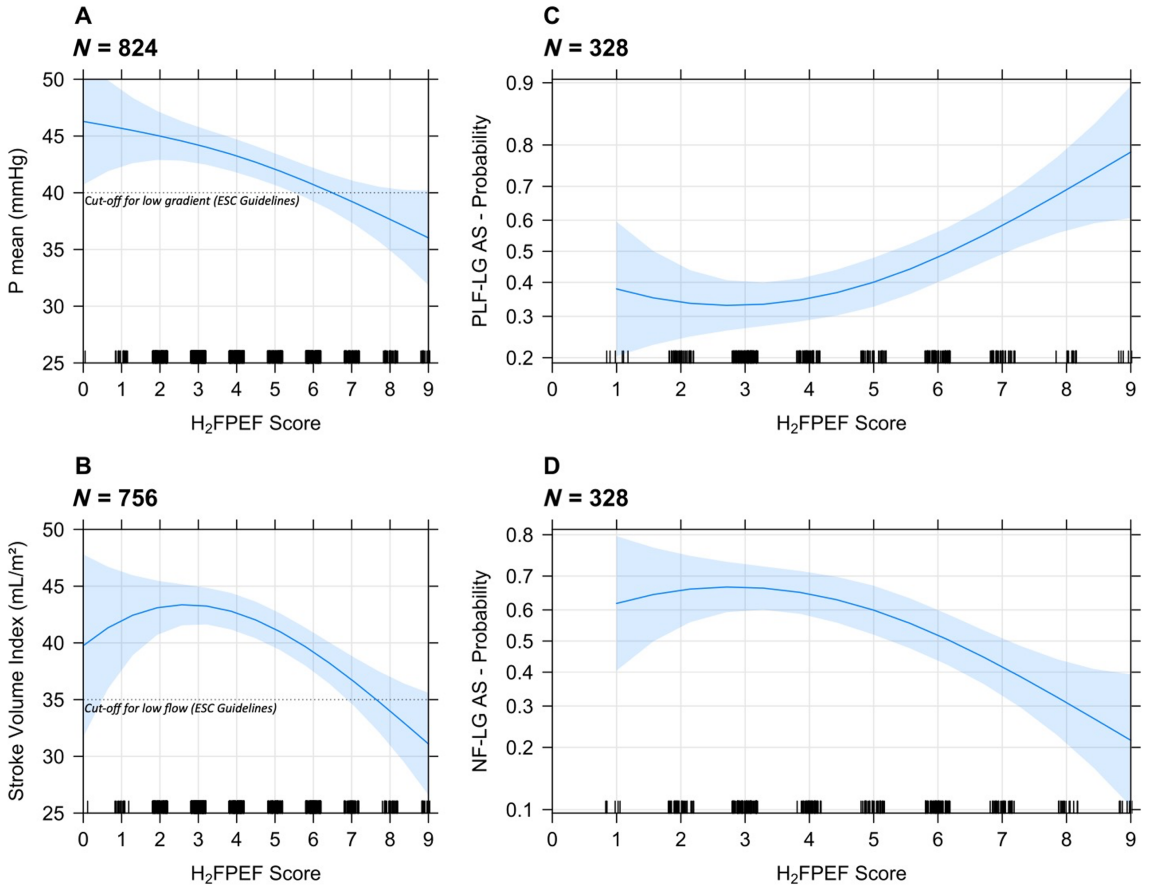
rehospitalization for CHF were significantly higher in patients with high H_2FPEF score compared with those with low H_2FPEF score 1 year after TAVI.

iv A high H_2FPEF score is an independent predictor of all-cause mortality and CV mortality or rehospitalization for CHF after TAVI.

The coexistence of severe AS and HFpEF is a common, yet underrecognized phenomenon. In a recent analysis of the US National Inpatient Sample registry, 37.0% of all patients receiving TAVI for severe AS and 67.4% of those with known heart failure were diagnosed with HFpEF.[26] In the present study, we investigated characteristics and outcomes of this subset of patients with AS and concomitant HFpEF as diagnosed by the H_2FPEF score. Compared with patients with HFrEF, patients with HFpEF are usually older, more commonly female, more likely to be hypertensive, and less likely to suffer from coronary artery disease.[2] Moreover, HFpEF is associated with co-morbidities that contribute to the progress of diastolic heart failure, such as atrial fibrillation, diabetes, obesity, chronic renal failure, pulmonary hypertension, and COPD.[27,28] In line with these findings, co-morbidities that were not comprised by the H_2FPEF score, such as diabetes, COPD, and impaired renal function, were associated with a high H_2FPEF score in our study. Thus, our results demonstrate that the H_2FPEF score may well be extended to patients with valvular heart disease as it seems to identify typical HFpEF phenotypes.

Among patients with AS, there seems to be a significant overlap of these HFpEF phenotypes with PLF-LG AS, which

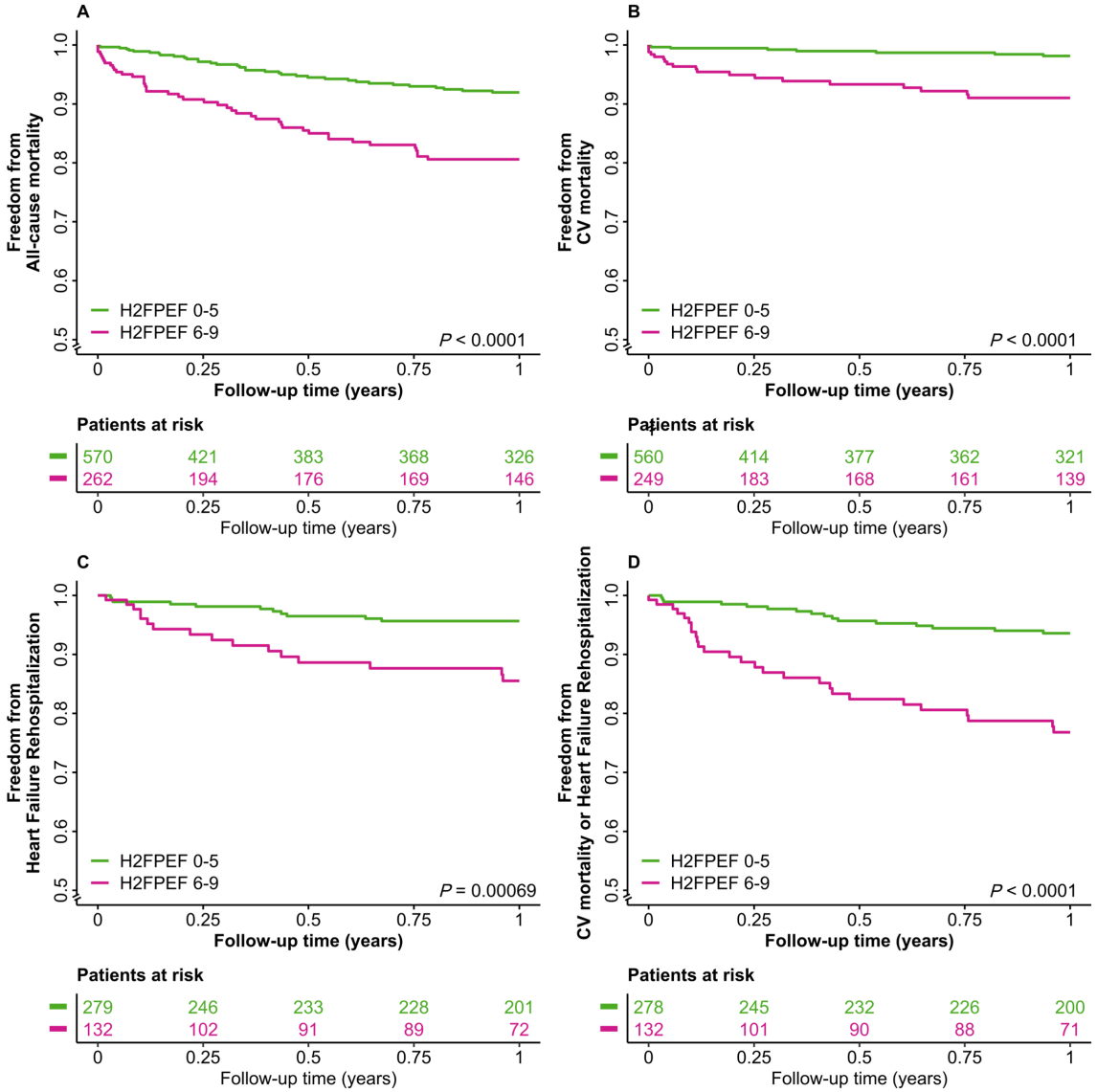
Figure 2 Unadjusted spline analyses for the association of the H_2FPEF score with (A) mean transvalvular pressure gradient (Pmean), (B) stroke volume index (SVI), (C) paradoxical low-flow, low-gradient aortic stenosis (PLF-LG AS), and (D) normal-flow, low-gradient aortic stenosis (NF-LG AS). Only patients with low-gradient AS (Pmean $<$ 40 mmHg) were included in PLF-LG AS and NF-LG AS. ESC, European Society of Cardiology.



is found in approximately 5–15% of AS patients.[29] Similar to HFpEF, PLF-LG AS is mostly found in elderly patients and typically associated with small ventricular size, LV hypertrophy, and a history of hypertension.[29] Presence of impaired diastolic filling, atrial fibrillation, pulmonary hypertension, and mitral and tricuspid regurgitation in advanced stages of AS result in a reduced stroke volume in these patients.[17] Taking these parallels into account, recent studies proposed to refer to PLF-LG AS as the *HFpEF of AS*.[19–21] This is strongly supported by the current study, as we demonstrate that Pmean and SVI decrease with increasing H_2FPEF score, and thus, a high proportion of AS patients with high H_2FPEF score, in fact, fulfil European Society of Cardiology guideline criteria for PLF-LG AS.

The negative prognostic role of reduced SVI has been well described for both HFpEF patients and patients receiving TAVI for severe AS.[30,31] Moreover, it has been shown that diastolic dysfunction, a key pathological mechanism in HFpEF, is associated with increased mortality in TAVI patients.[32] However, there was so far no data regarding prognostic implications of HFpEF itself in TAVI patients. Our results suggest that HFpEF, as diagnosed by a high H_2FPEF score, is in fact associated with higher risk for all-cause mortality and, even more, for CV mortality and heart failure events after TAVI among patients with severe AS and preserved EF. Thereby, the reduction of SVI and the presence of PLF-LG AS, as an expression of advanced diastolic dysfunction, may well be a driving force for the adverse impact of HFpEF in TAVI patients. In some of these patients, AS represents the sole cause of HFpEF, which may persist even after the resolution of AS by TAVI in those at advanced stages of the disease. In others, however, the evolution of AS may parallel the existence of HFpEF due to pathophysiological processes independent from AS with significant impact on symptoms and outcomes in these patients following AS treatment. Among the individual score variables, the main predictors for CV

Figure 3 Kaplan–Meier estimates according to low and high H_2FPEF scores for (A) all-cause mortality, (B) cardiovascular (CV) mortality, (C) heart failure rehospitalization, and (D) the combined endpoint of CV mortality or heart failure rehospitalization.



death and heart failure events in the present study were atrial fibrillation, pulmonary hypertension, and elevated LV filling pressure. Interestingly, these exact variables are also included in a staging classification of AS-induced cardiac damage, established by Généreux *et al.*, as indicators of advanced and potentially irreversible structural alterations of the heart.[17] Thus, the presented results strengthen the hypothesis that the H_2FPEF score may identify a subset of AS patients with preserved EF that suffers from poor prognosis even after AS treatment due to advanced, irreversible HFpEF, either caused by or coexistent to AS. Especially with regard to the prediction of CV and heart failure outcomes, calculation of the H_2FPEF score may enhance clinical decision making compared with single and dichotomous parameters (e.g. atrial fibrillation).

Study limitations

Some limitations of the present study have to be addressed. First, the retrospective design of the present study puts constraints on any drawn conclusions. Second, for the purpose of the current study, H_2FPEF score variables were slightly modified as we used invasively measured LVEDP compared with

Table 2 Univariable and multivariable analyses for all-cause mortality after TAVI

All-cause mortality						
	Univariable analysis		Multivariable analysis (with H_2FPEF score) (N = 832)		Multivariable analysis (with H_2FPEF score variables) (N = 832)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.06 (1.02–1.09)	0.0022	1.03 (0.99–1.06)	0.18	1.03 (0.99–1.07)	0.20
Male sex	0.98 (0.68–1.42)	0.91				
BMI	0.96 (0.92–1.00)	0.047			0.98 (0.93–1.02)	0.30
Prior stroke	1.32 (0.80–2.16)	0.28				
Atrial fibrillation	2.74 (1.89–3.97)	<0.001			1.99 (1.34–2.95)	<0.001
Hypertension	0.81 (0.45–1.48)	0.50			0.77 (0.41–1.44)	0.41
Prior MI	0.62 (0.25–1.51)	0.29				
CAD	0.81 (0.54–1.21)	0.30				
Diabetes	1.21 (0.81–1.79)	0.35				
COPD	1.30 (0.79–2.13)	0.30				
PHT						
≤35 mmHg	1 (reference)					
36–55 mmHg	1.66 (1.01–2.74)	0.047			1.06 (0.63–1.80)	0.81
>55 mmHg	3.31 (1.85–5.91)	<0.001			1.29 (0.67–2.50)	0.44
TR ≥ 2	3.55 (2.44–5.17)	<0.001	2.45 (1.61–3.71)	<0.001	2.27 (1.46–3.53)	<0.001
MR ≥ 2	2.34 (1.59–3.43)	<0.001				
NYHA	1.89 (1.40–2.56)	<0.001	1.30 (0.95–1.78)	0.098		
GFR < 60 mL/min	2.12 (1.45–3.11)	<0.001	1.80 (1.21–2.66)	0.0034	1.87 (1.26–2.79)	0.0021
Non-TF access	2.51 (1.49–4.23)	<0.001	2.24 (1.31–3.83)	0.0032	2.06 (1.19–3.59)	0.010
LVEDP > 15 mmHg	1.42 (0.98–2.07)	0.063			1.17 (0.79–1.73)	0.43
H_2FPEF score						
H_2FPEF score 0–5	1 (reference)					
H_2FPEF score 6–9	2.27 (1.57–3.29)	<0.001	1.59 (1.08–2.35)	0.018		

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PHT, pulmonary hypertension; TAVI, transcatheter aortic valve implantation; TF, transfemoral; TR, tricuspid regurgitation.
Score variables were highlighted.

Table 3 Univariable and multivariable analyses for the combined endpoint of cardiovascular mortality or rehospitalization for congestive heart failure after TAVI

Cardiovascular mortality or rehospitalization for congestive heart failure						
	Univariable analysis		Multivariable analysis (with H_2FPEF score) (N = 410)		Multivariable analysis (with H_2FPEF score variables) (N = 410)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.05 (0.99–1.10)	0.078	1.01 (0.96–1.06)	0.75	1.02 (0.96–1.08)	0.52
Male sex	0.76 (0.44–1.33)	0.34				
BMI	1.01 (0.95–1.07)	0.74			1.02 (0.96–1.09)	0.53
Prior stroke	1.55 (0.75–3.18)	0.23				
Atrial fibrillation	3.03 (1.74–5.30)	<0.001			2.01 (1.10–3.67)	0.023
Hypertension	0.79 (0.31–1.98)	0.61			0.65 (0.25–1.68)	0.37
Prior MI	1.44 (0.57–3.62)	0.44				
CAD	0.83 (0.39–1.77)	0.63				
Diabetes	1.04 (0.56–1.92)	0.91				
COPD	1.41 (0.69–2.91)	0.34				
PHT						
≤35 mmHg	1 (reference)					
36–55 mmHg	2.22 (1.04–4.75)	0.039			1.71 (0.78–3.72)	0.18
>55 mmHg	6.32 (2.79–14.32)	<0.001			3.02 (1.22–7.47)	0.017
TR ≥ 2	3.67 (1.88–7.15)	<0.001				
MR ≥ 2	3.32 (1.87–5.90)	<0.001	2.27 (1.24–4.13)	0.0075	1.87 (0.99–3.55)	0.055
NYHA	1.93 (1.25–2.99)	0.0030	1.65 (1.04–2.63)	0.034		
GFR < 60 mL/min	1.92 (1.10–3.35)	0.021	1.58 (0.90–2.80)	0.11	1.59 (0.89–2.82)	0.12
Non-TF access	0.00 (0–inf)	1.00				
LVEDP > 15 mmHg	2.10 (1.19–3.71)	0.011			1.66 (0.92–2.97)	0.090
H_2FPEF score						
H_2FPEF score 0–5	1 (reference)					
H_2FPEF score 6–9	3.52 (2.01–6.14)	<0.001	2.92 (1.65–5.15)	<0.001		

Abbreviations as in *Table 2*.
Score variables were highlighted.

echocardiographically derived measurements (E/e') that are included in the original score. Nevertheless, invasively measured LVEDP is considered a more precise method for the assessment of LV filling pressures as compared with echocardiographic E/e'.[33] Third, invasive assessment of LVEDP may have been influenced by general anaesthesia in patients with non-transfemoral access.

Conclusion

Among patients with severe AS and preserved EF undergoing TAVI, the H_2FPEF score serves as an independent predictor of adverse outcome. A high H_2FPEF score is further associated with lower Pmean and lower SVI translating into a higher rate of PLF-LG AS. Thus, by identifying patients with PLF-LG AS, the *HFpEF of AS*, the H_2FPEF score might be useful as a risk prediction tool for TAVI patients.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison of baseline characteristics between excluded and included patients
Table S2. Procedural parameters and VARC2 30-day outcome

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