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Clinical Outcomes of Transcatheter Aortic Valve Replacement in Patients with Various Flow-Gradient and Ejection Fraction Profiles

ABSTRACT

Background: To compare the clinical outcomes of transcatheter aortic valve replacement (TAVR) for severe aortic stenosis (AS) in patients with different flow-gradient and left ventricular ejection fraction (EF) profiles.

Methods: Patients with severe AS who underwent TAVR with newer generation valves (Sapien3/3 Ultra, Evolut Pro/Pro+/FX) were retrospectively analyzed. Patients were divided into 5 groups: normal-flow high-gradient (NF-HG) AS (stroke volume index ≥ 35 mL/m^2 and mean pressure gradient ≥ 40 mm Hg), low-flow high-gradient (LF-HG) with preserved EF (pEF, ≥ 50%), LF-HG with reduced EF (rEF), low-flow low-gradient (LF-LG) with pEF, and LF-LG with rEF.

Results: A total of 846 patients were included in this study (NF-HG, n = 458; LF-HG with pEF, n = 142; LF-HG with rEF, n = 50; LF-LG with pEF, n = 113; LF-LG with rEF, n = 83). For the entire cohort, the median age was 82 years, and the periprocedural mortality rate was 2.1% with the highest rate in the LF-LG with rEF AS (7.2%). The 1-year and 5-year mortality rates were 13% and 51%, respectively. Multivariable Cox regression analysis showed higher all-cause mortality in the LF-HG with pEF (hazard ratio 1.42 [95% CI: 1.02-1.98]), LF-LG with pEF (1.84 [1.32-2.55]), and LF-LG with rEF (1.78 [1.22-2.61]) groups compared with the NF-HG group. Cardiovascular death rates were significantly higher in the LF-LG groups, but not in the LF-HG groups.

Conclusion: In addition to both LF-LG with pEF and rEF AS, LF-HG with pEF AS had a higher all-cause mortality rate after TAVR compared to NF-HG AS.

Keywords: Aortic stenosis, aortic valve replacement, echocardiography

INTRODUCTION

Transcatheter Aortic Valve Replacement (TAVR) is an established therapeutic approach for patients with severe aortic stenosis (AS).[1-3] Severe AS is generally defined by an aortic valve area of ≤ 1.0 cm^2 (or an indexed aortic valve area of ≤ 0.6 cm^2/m^2), alongside a transaortic peak velocity of ≥ 4 m/s or a mean pressure gradient of ≥ 40 mm Hg.[4] However, certain patients with AS exhibit low stroke volume, leading to a low-gradient profile despite having an aortic valve area of ≤ 1.0 cm. This specific scenario is referred to as low-flow low-gradient (LF-LG) AS. The primary underlying causes of LF-LG AS include reduced left ventricular (LV) ejection fraction (EF) and small LV cavity caused by concentric LV hypertrophy, even in the presence of preserved left ventricular ejection fraction (LVEF).[5] Transcatheter aortic valve replacement is also considered beneficial for patients with LF-LG AS; however, it is widely acknowledged that these patients experience less favorable clinical outcomes compared to patients with high-gradient AS, especially in patients with LF-LG with rEF AS.[6,7] On the other hand, low stroke volume or low-flow status may itself be a predictor of TAVR outcomes.[8,9] While Muratori et al[6] reported that patients with LF-LG with preserved EF (pEF) had similar survival rates than patients with normal-flow high-gradient (NF-HG), A report from the SwissTAVI registry[7] showed that patients with LF-LG with preserved EF (pEF) had higher mortality rates than patients with high-gradient AS but lower mortality rates than patients with LF-LG with rEF AS. In addition, Maréchaux et al[9] reported

ORIGINAL INVESTIGATION

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that asymptomatic or minimally symptomatic patients with LF-HG with pEF AS have a considerable increased risk of mortality during follow-up compared with patients with NH-HG with pEF AS. Consequently, the prognostic impact of low-flow high-gradient (LF-HG) AS compared to NF-HG or LF-LG AS remains unclear. In addition, the difference in TAVR outcomes between LF-LG with pEF and LF-LG with rEF AS is controversial. Clarification of the prognostic differences based on flow-gradient and LVEF status is crucial for enhancing the strategies in risk stratification and patient management. The aim of this study was to compare the clinical outcomes of TAVR for severe AS in patients with different flow-gradient and LVEF profiles.

METHODS

Patients

This single-center retrospective study focused on patients with severe native aortic valve stenosis and rEF who underwent TAVR between January 2018 and December 2022. A total of 1170 TAVR procedures were performed during this time period. Of these, 846 patients who underwent TAVR with newer generation transcatheter heart valves (Sapien 3/3 Ultra [Edwards Lifesciences, Irvine, CA, USA] or Evolut Pro/Pro+/FX [Medtronic Inc., Minneapolis, MN, USA]) for severe AS qualified for inclusion in the study. This study excluded patients who TAVR using older generation valves, or valve-in-valve TAVR for failed bioprostheses. In addition, patients with normal-flow low-gradient AS or unknown flow status, as well as cases involving unsuccessful delivery or conversion to open surgery, were excluded in the analysis. Figure 1 shows the flowchart of patient selection. The choice between balloon-expandable and self-expanding valves for TAVR was primarily made at the discretion of the interventionist, taking into account multiple factors such as the presence of coronary artery disease and the anatomy of the aortic root complex—including annular size and the extent of valve or root calcification. For instance, self-expanding valves were generally preferred in patients with small aortic annuli, whereas balloon-expandable valves were favored in those with coronary artery disease due to improved post-TAVR access to the coronary ostia. During the study period, the cusp overlap technique with controlled pacing was employed for Evolut valve implantation, while rapid pacing was used for Sapien valve implantation.

These patients were divided into 5 groups: NF-HG AS (stroke volume index ≥ 35 mL/m^2 and mean pressure gradient ≥ 40 mm Hg), LF-HG with pEF (stroke volume index < 35 mL/m^2, mean pressure gradient ≥ 40 mm Hg, and LVEF ≥ 50%), LF-HG with rEF (LVEF < 50%), LF-LG with pEF (stroke volume index < 35 mL/m^2, mean pressure gradient < 40 mm Hg, and LVEF ≥ 50%), and LF-LG with rEF. Stroke volume was obtained by transthoracic echocardiography using the LV outflow tract area and the LV outflow tract time-velocity integral. The time-velocity integral was averaged over 3 cardiac cycles for patients in sinus rhythm and 5 cycles for patients in atrial fibrillation. The stroke volume was then indexed to body surface area. Low-flow low-gradient severe AS was comprehensively assessed using dobutamine stress echocardiography and/or computed-tomography aortic valve calcium scoring.[10]

The primary outcomes of interest were all-cause mortality, cardiovascular death, and composite of all-cause mortality and rehospitalization for heart failure. Other outcomes of interest included periprocedural outcomes. Definitions, terminology, and reported outcomes were consistent with the Society of Thoracic Surgeons (STS)/American College of Cardiology Transcatheter Valve Therapies Registry and the Valve Academic Research Consortium 3 (VARC-3) criteria.[11] The decision for the TAVR procedure was made by a dedicated heart team, primarily based on age and surgical risk according to the STS Predicted Risk of Mortality (STS-PROM), as well as patient anatomy and patient-specific factors such as frailty. The study protocol was approved by the Institutional Review Board (IRB 45CFR164.512). Individual patient consent was waived due to the retrospective nature of the study. This study did not involve the use of artificial intelligence-assisted technologies in the production of this work.

Statistical Analysis

Continuous values are presented as median (interquartile range) unless otherwise noted, and the Kruskal-Wallis test was used to compare between groups for these values. Categorical values are reported as numbers (percentages), and the chi-squared test or Fisher's exact test was used to compare groups. Kaplan-Meier curves with log-rank *P* values were constructed to estimate event-free rates for follow-up outcomes, and Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% CIs. Forward selection multivariable Cox proportional hazards models were used to assess predictors of follow-up outcomes. The variables listed in Table 1, as well as flow-gradient and LVEF status, were included in the multivariable analysis, and the final model was selected based on the model with the lowest Akaike Information Criterion. Because of the covariance of flow-gradient and LVEF status, LVEF, transaortic mean pressure gradient, and stroke volume index were excluded as variables from multivariable analysis. All *P* values were two-sided and a 5% level was considered significant. All analyses were conducted using

HIGHLIGHTS

- This single-center retrospective study evaluates the impact of different flow-gradient profiles and left ventricular ejection fraction (EF) on transcatheter aortic valve replacement (TAVR) outcomes.
- Higher mid-term all-cause mortality was observed in patients with low-flow high-gradient aortic stenosis (AS) and preserved EF, in addition to findings in low-flow low-gradient AS with preserved and reduced EF.
- Detailed stratification of flow-gradient profiles plays a key role in assessing risk and prognosis in patients undergoing TAVR for severe AS.

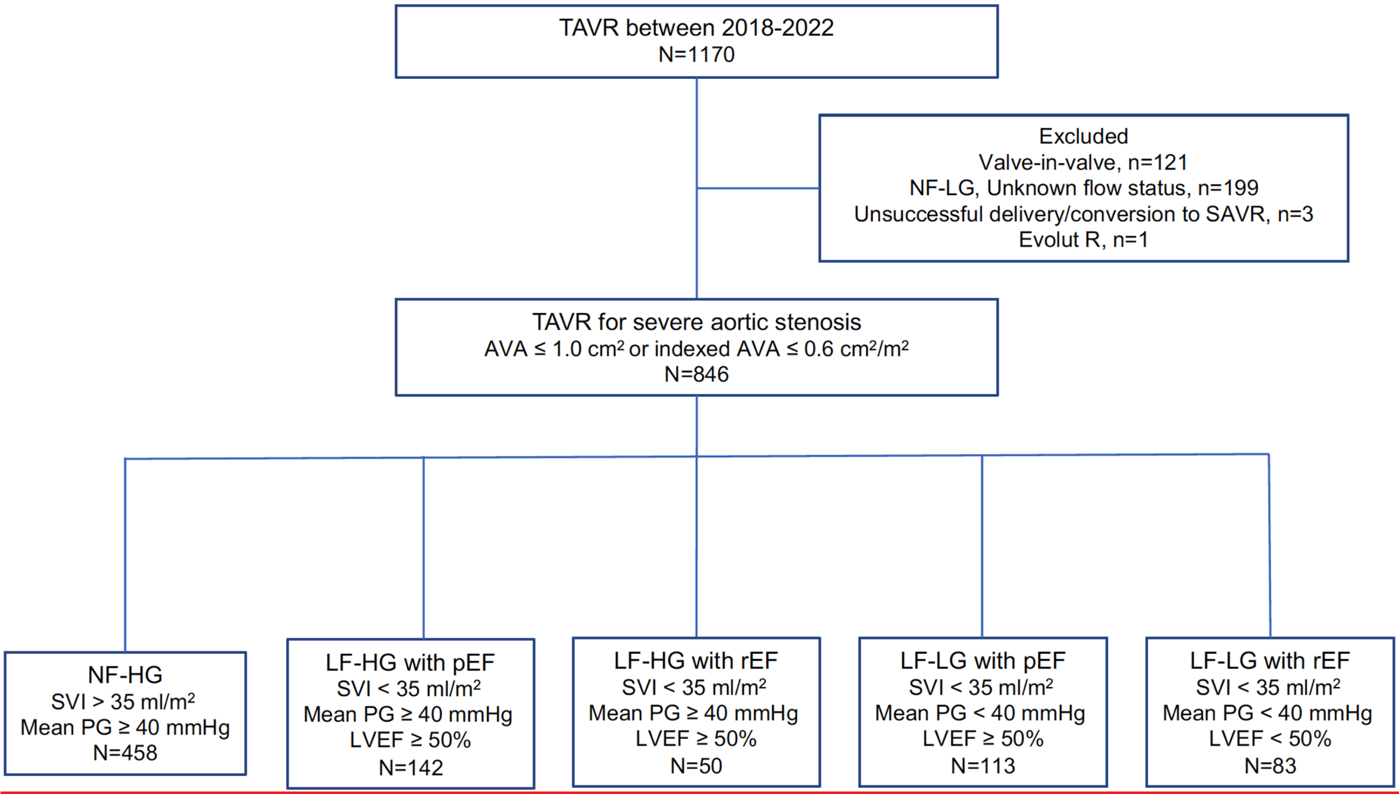

Figure 1. Flowchart of patient selection. AVA, aortic valve area; LF-HG, low-flow low-gradient; LF-LG, low-flow low-gradient; LVEF, left ventricular ejection fraction; NF-LG, normal-flow low-gradient; NF-NG, normal-flow normal-gradient; pEF, preserved ejection fraction; PG, pressure gradient; rEF, reduced ejection fraction; SAVR, surgical aortic valve replacement; SVI, stroke volume index; TAVR, transcatheter aortic valve replacement.

the R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Patient Characteristics

Of the 846 patients, 388 patients (46%) had low flow status. After further subdivision, there were 142, 50, 113, and 83 patients in the LF-HG with pEF, LF-HG with rEF, LF-LG with pEF, and LF-LG with rEF groups, respectively. The median age for the entire cohort was 82 years. Baseline and procedural characteristics are shown in Table 1, suggesting substantial differences between groups. Notably, patients in the NF-HG group were more likely to be female and had the lowest rates of prior coronary revascularization, atrial fibrillation, and prior pacemaker/defibrillator, whereas the LF-LG with rEF group had the highest rates. Society of Thoracic Surgeons-Predicted Risk of Mortality scores were higher in the LH-HG with pEF and LF-LG groups. The rates of New York Heart Association III/IV and non-elective procedures, and creatinine levels were higher in patients with rEF.

Periprocedural Outcomes

The overall periprocedural mortality rate was 2.1% with the highest rate in the LF-LG with rEF AS (7.2%, $P = .046$). The periprocedural permanent pacemaker implantation rate was also significantly different between groups with the lowest rate in the NF-HG group and the highest rate in the LF-HG with rEF and LF-LG with pEF groups. Consequently, the early safety rate was lowest in the LF-HG with rEF group. The indexed effective orifice area was smallest in this group as well. Other clinical and echocardiographic outcomes, including device success rate, were comparable between groups (Table 2).

Mid-Term Outcomes

The median follow-up period was 24 (range 0-72) months, and the overall 1- and 5-year all-cause mortality rates were 13% and 51%, respectively. Figure 2 shows Kaplan-Meier curves with log-rank *P* values for the follow-up outcomes of interest, and Table 3 presents the outcomes of both univariable and multivariable Cox regression analyses, focusing on the influence of flow-gradient and LVEF status on endpoints. In the crude analysis, LF-LG with pEF and rEF AS were associated with all-cause mortality, cardiovascular death, and composite of all-cause mortality and rehospitalization for heart failure compared with NF-HG AS, whereas LF-HG with pEF AS was associated with the composite outcome. Multivariable analysis showed that the rates of all-cause mortality and the composite outcome were significantly higher in the LH-HG with pEF, LF-LG with pEF, and LF-LG with rEF AS compared with NF-HG AS. In addition, LF-LG with pEF and rEF AS were also associated with cardiovascular death. The results of multivariable analysis are shown in Supplementary Table 1.

Table 1. Baseline and Procedural Characteristics

	NF-HG n = 458	LF-HG with pEF n = 142	LF-HG with rEF n = 50	LF-LG with pEF n = 113	LF-LG with rEF n = 83	*P*
Baseline characteristics						
Age, years	82 (77-87)	80 (76-86)	79 (71-86)	82 (77-88)	83 (79-87)	.02
Female	256 (56)	55 (39)	20 (40)	46 (40)	22 (27)	<.001
Body surface area, m^2	1.9 (1.7-2.0)	2.0 (1.8-2.2)	2.1 (1.8-2.2)	1.9 (1.8-2.1)	1.9 (1.8-2.0)	<.001
Body mass index, kg/m^2	27 (23-32)	29 (24-32)	28 (25-34)	28 (24-32)	26 (25-30)	.03
NYHA III/IV	203 (44)	80 (56)	35 (70)	63 (56)	59 (71)	<.001
STS score	3.3 (2.1-4.9)	3.2 (2.2-4.9)	3.9 (2.6-7.8)	4.0 (2.5-6.0)	3.9 (2.6-7.8)	<.001
Diabetes	136 (30)	49 (35)	26 (52)	44 (39)	34 (41)	.007
Moderate/severe chronic lung disease	36 (7.9)	16 (11)	4 (8.0)	15 (13)	8 (9.6)	.39
Creatinine, mg/dL	1.1 (0.8-1.4)	1.1 (0.9-1.5)	1.3 (1.0-1.5)	1.1 (0.9-1.5)	1.3 (1.0-1.7)	<.001
Prior stroke	47 (10)	23 (19)	7 (14)	17 (15)	12 (14)	.30
Peripheral artery disease	93 (20)	35 (25)	11 (22)	29 (26)	21 (25)	.61
Prior coronary revascularization	169 (37)	63 (44)	23 (46)	61 (54)	50 (60)	<.001
Atrial fibrillation	117 (26)	67 (47)	22 (44)	63 (56)	59 (71)	<.001
Prior pacemaker/defibrillator	43 (9.4)	25 (18)	8 (16)	21 (19)	24 (29)	<.001
LVEF, %	65 (60-70)	62 (58-65)	33 (20-40)	63 (55-68)	38 (30-40)	<.001
Aortic valve area, cm^2	0.8 (0.6-0.9)	0.7 (0.6-0.8)	0.6 (0.4-0.7)	0.7 (0.6-0.8)	0.7 (0.6-0.8)	<.001
Transaortic mean PG, mm Hg	47 (42-55)	46 (42-53)	47 (42-54)	33 (29-36)	29 (23-34)	<.001
Stroke volume index, mL/m^2	46 (40-53)	30 (27-32)	28 (24-31)	29 (26-32)	27 (23-30)	<.001
Mitral regurgitation ≥ moderate	40 (8.7)	15 (11)	12 (24)	15 (13)	27 (33)	<.001
Tricuspid regurgitation ≥ moderate	46 (10)	10 (7.0)	8 (16)	23 (20)	20 (24)	<.001
Procedural characteristics						
Non-elective procedure	33 (7.2)	15 (11)	12 (24)	10 (8.8)	15 (18)	<.001
Transfemoral access	419 (91)	133 (94)	46 (92)	99 (88)	80 (96)	.23
Self-expanding valve	228 (50)	53 (37)	23 (46)	51 (45)	25 (30)	.005
Pre-balloon dilation	157 (34)	54 (38)	14 (28)	44 (39)	20 (24)	.15
Post-baloon dilation	26 (5.6)	11 (7.7)	1 (2.0)	7 (6.2)	2 (2.4)	.44

Median (interquartile range), or n (%).
LF-HG, low-flow high-gradient; LF-LG, low-flow low-gradient; LVEF, left ventricular ejection fraction; NF-HG, normal-flow high-gradient; NYHA, New York Heart Association; pEF, preserved ejection fraction; PG, pressure gradient; rEF, reduced ejection fraction; STS, Society of Thoracic Surgeons.

DISCUSSION

In this study, outcomes after TAVR in patients were compared with severe AS according to flow-gradient and LVEF status, and observed the following major findings: 1) 46% of the patients had low-flow status determined as a stroke volume index of < 35 mL/m^2, 2) both LF-LG with pEF and rEF AS had similarly worse clinical outcomes compared to NF-HG AS (adjusted HRs of 1.98 [95% CI 1.47-2.65] and 2.21 [1.59-3.07] for all-cause mortality, respectively), 3) In addition, LF-HG with pEF was associated with higher all-cause mortality and a composite of all-cause mortality and rehospitalization for heart failure compared to NF-HG AS. The overall periprocedural, 1-year, and 5-year mortality rates (2.1%, 13%, and 51%, respectively) in this study are consistent with recent reports on TAVR outcomes.[12,13] In addition, the rate of low-flow status is also in line with previous studies.[14]

To date, considerable attention has been paid to the outcomes of TAVR in patients with LF-LG AS, and LF-LG with rEF appears to be associated with worse outcomes compared to high-gradient AS.[6-8,15,16] However, there is controversy regarding the difference in outcomes between LF-LG with pEF and high-gradient AS or between LF-LG with pEF and rEF AS. Muratori et al[6] reported that patients with LF-LG with pEF had similar survival rates than patients with NF-HG, whereas LF-LG with rEF was associated with a twofold increased risk of mortality at 5-year follow-up. On the other hand, data from the multicenter SwissTAVI registry showed all-cause mortality rates of 44% in high-gradient AS, 52% in LF-LG with pEF (HR 1.35, 95% confidence interval 1.23-1.48), and 63% in LF-LG with rEF (HR 1.7, 95% confidence interval 1.54-1.88), suggesting that patients with LF-LG with pEF had higher mortality rates than patients with high-gradient AS but lower mortality rates than patients with LF-LG with rEF AS.[7] In a meta-analysis, Osman et al[15] showed that patients with both LF-LG with pEF and rEF AS had increased mid-term all-cause mortality compared to those with high-gradient AS, whereas LF-LG with pEF and rEF had similar mid-term all-cause mortality with an odds ratio of 0.81 and 95% confidence interval of 0.51-1.28. These results were consistent with this meta-analysis. In addition, worse all-cause mortality was shown in LF-HG with pEF AS compared to NF-HG AS. This study also showed that patients with

Table 2. Periprocedural Outcomes

	NF-HG n = 458	LF-HG with pEF n = 142	LF-HG with rEF n = 50	LF-LG with pEF n = 113	LF-LG with rEF n = 83	*P*
Mortality*	7 (1.5)	2 (1.4)	1 (2.0)	2 (1.8)	6 (7.2)	.046
Acute stroke	8 (1.7)	2 (1.4)	4 (8.0)	4 (3.5)	2 (2.4)	.08
Major cardiac structural complication	6 (1.3)	2 (1.4)	0	2 (1.8)	0	.88
Major vascular complication	3 (0.7)	2 (1.4)	0	4 (3.5)	2 (2.4)	.08
Valve malposition	1 (0.2)	0	0	0	0	>.99
Need for second valve	3 (0.7)	0	0	0	0	>.99
Acute kidney injury ≥ stage 2	6 (1.3)	3 (2.1)	1 (2.0)	4 (3.5)	2 (2.4)	.47
New permanent pacemaker implantation*	53/415 (13)	18/117 (15)	10/42 (24)	22/92 (24)	10/59 (17)	.048
Transaortic mean PG ≥ 20 mm Hg*	22 (4.8)	6 (4.2)	0	1 (0.9)	1 (1.2)	.12
Indexed effective orifice area, cm^2/m^2	0.99 (0.77-1.25)	0.94 (0.71-1.07)	0.84 (0.66-1.04)	0.92 (0.80-1.17)	0.89 (0.70-1.08)	<.001
Aortic regurgitation*						.32
Mild	87 (19)	33 (23)	10 (20)	21 (19)	10 (12)	
Moderate/severe	9 (2.0)	0	1 (2.0)	1 (8.8)	0	
Device success	414 (90)	125 (88)	47 (94)	98 (87)	73 (88)	.57
Early safety	379 (83)	118 (83)	34 (68)	82 (73)	63 (76)	<.001

Median (interquartile range), or n (%).
LF-HG, low-flow high-gradient; LF-LG, low-flow low-gradient; NF-HG, normal-flow high-gradient; pEF, preserved ejection fraction; PG, pressure gradient; rEF, reduced ejection fraction.
*30-day data or in-hospital data if 30-day data is not available.

LF-LG with rEF AS experienced higher rates of periprocedural mortality. However, the incidence of major procedural complications did not significantly differ from other groups. This may suggest that the observed outcome differences more likely reflect the high-risk baseline characteristics commonly present in the LF-LG with rEF cohort, including advanced comorbidities and impaired ventricular function.

To date, studies focusing on the effects of LF-HG AS are limited. However, Maréchaux et al[9] showed that LF-HG status displayed considerable mortality risk during follow-up compared with NF-HG status in patients with asymptomatic or minimally severe AS with pEF. In addition, Mangner et al[14] observed higher all-cause mortality in patients with LF-HG AS compared to NF-HG AS at 3 years after TAVR (38% versus 25%). The results, which focus solely on newer-generation valves, are likely to reinforce these earlier findings and more closely reflect current practice. In the Simvastatin Ezetimibe in Aortic Stenosis study,[17] they suggested that patients with low-flow AS exhibit a higher global LV load and a higher

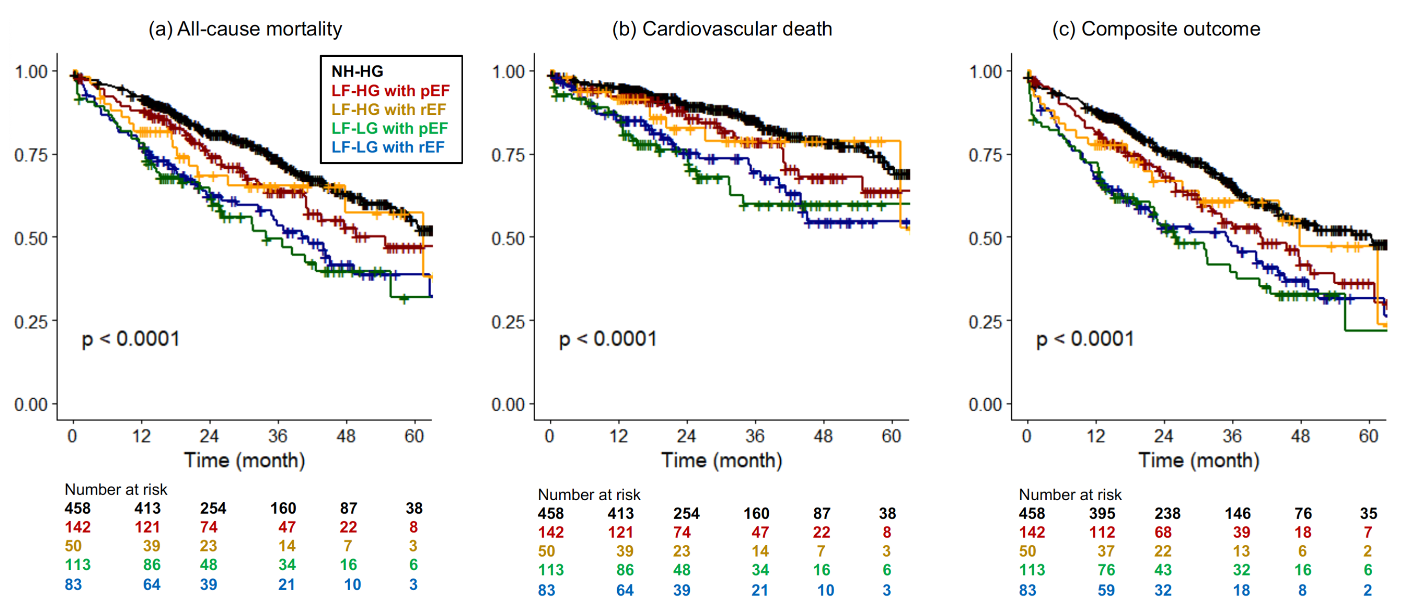

Figure 2. Kaplan–Meier curves for mid-term outcomes of interest. CI, confidence interval; HR, hazard ratio; LF-HG, low-flow low-gradient; LF-LG, low-flow low-gradient; NF-HG, normal-flow high-gradient; pEF, preserved ejection fraction; rEF, reduced ejection fraction.

Table 3. Results of Univariable and Multivariable Cox Proportional Hazards Models for Follow-Up Outcomes

		Crude HR (95%CI)	Adjusted HR (95%CI)
All-cause mortality	LF-HG with pEF versus NF-HG	1.38 (0.99-1.92)	**1.42 (1.02-1.98)**
	LF-HG with rEF versus NF-HG	1.40 (0.84-2.32)	1.15 (0.68-1.95)
	LF-LG with pEF versus NF-HG	**2.03 (1.47-2.81)**	**1.84 (1.32-2.55)**
	LF-LG with rEF versus NF-HG	**2.25 (1.58-3.20)**	**1.78 (1.22-2.61)**
Cardiovascular death	LF-HG with pEF versus NF-HG	1.44 (0.92-2.23)	1.40 (0.89-2.19)
	LF-HG with rEF versus NF-HG	1.36 (0.68-2.73)	**1.95 (1.27-3.00)**
	LF-LG with pEF versus NF-HG	**2.26 (1.48-3.44)**	**1.94 (1.19-3.18)**
	LF-LG with rEF versus NF-HG	**2.53 (1.60-4.00)**	1.04 (0.50-2.16)
Composite outcome*	LF-HG with pEF versus NF-HG	**1.45 (1.08-1.95)**	**1.41 (1.05-1.91)**
	LF-HG with rEF versus NF-HG	1.34 (0.84-2.14)	1.07 (0.66-1.74)
	LF-LG with pEF versus NF-HG	**1.98 (1.47-2.65)**	**1.77 (1.31-2.38)**
	LF-LG with rEF versus NF-HG	**2.21 (1.59-3.07)**	**1.66 (1.17-2.35)**

CI, confidence interval; HG, high gradient; HR, hazard ratio; LF-HG, low-flow high-gradient; LF-LG, low-flow low-gradient; NF-HG, normal-flow high-gradient; pEF, preserved ejection fraction; rEF, reduced ejection fraction.
*Composite of all-cause mortality and rehospitalization for heart failure. Bold: $P < .05$

prevalence of myocardial systolic dysfunction, which cannot be predicted by assessing LVEF alone. The combination of increased global LV afterload and decreased cardiac output in the low-flow group suggests diminished cardiac reserve. Chronic exposure to elevated afterload eventually exceeds the limit of compensatory capacity of the LV, leading to intrinsic impairment of myocardial function and reduced cardiac output.[5] This pathophysiologic mechanism may help explain the worse prognosis observed in low-flow patients in the present study. This study highlights the essential role of detailed flow-gradient status stratification in risk and prognosis assessment for TAVR in patients with severe AS, including the introduction of the "LF-HG AS" concept. Adopting this approach could lead to the development of more tailored treatment strategies. On the other hand, this study found no significant prognostic differences between LF-HG with rEF and NF-HG AS. It is unclear whether this suggests that reduced stroke volume due to a smaller LV cavity, rather than due to rEF, has a more detrimental effect on TAVR outcomes, or whether this observation is simply due to lack of statistical power resulting from the small sample size of patients with LF-HG AS and rEF. In addition, conflicting results were suggested by Alkhalil et al,[8] who reported that low flow was an independent predictor of adverse events in the rEF subgroup, but not the pEF subgroup, in patients with high-gradient AS. Further research with larger cohorts is needed to accurately assess the true impact in this specific patient population.

According to current American College of Cardiology/American Heart Association guidelines, aortic valve intervention is recommended only for symptomatic patients with AS and pEF or LF-LG AS, and for asymptomatic patients with severe AS and pEF under certain conditions such as very severe AS and low surgical risk.[4] It is critical to consider the timing of the intervention in terms of both procedural risks and long-term benefits. In this study, a higher periprocedural mortality was found in the LF-LG with rEF group, whereas similar periprocedural mortality were observed in the LF-HG and LF-LG with pEF AS compared to the NF-HG AS. Given the potentially worse follow-up mortality in the LF-HG with pEF and LF-LG AS, the optimal timing of the intervention should also be reconsidered. It has also been reported that patients with LF-HG AS are less likely to undergo aortic valve intervention than patients with high-gradient AS,[18] and these patients typically have more delayed referral for interventional evaluation, which may contribute to worse outcomes.[10] In addition, Ludwig et al[19] reported that among patients with non-severe LF-LG AS and rEF, TAVR represents a major predictor of superior survival compared with those on medical management. Further research is needed to investigate whether earlier detection, referral, and intervention for these conditions could lead to beneficial outcomes.

Study Limitations

This study is constrained by several notable limitations. Firstly, being a single-center retrospective study with a relatively small patient cohort, there are concerns regarding the statistical power and overall robustness of the findings. It may also limit the generalizability of the findings to other institutions with different patient populations or procedural strategies. Although several clinical and procedural variables were adjusted for, unmeasured confounders such as frailty, the severity of prior heart failure, or other comorbidities, were not captured in this dataset and may have influenced the outcomes. In addition, there are recognized technical difficulties in performing accurate echocardiographic assessments, for example, in measuring the calcified LV outflow tract in cases of severe AS,[20] which may lead to misclassification of flow status. Another limitation is the absence of data on the preoperative waiting period and follow-up reverse flow data from echocardiography, which restricts the ability to perform a more comprehensive analysis incorporating these aspects. Furthermore, the choice of transcatheter heart valve type (balloon-expandable vs. self-expanding) was at the discretion of the interventionist, which may have introduced a treatment selection bias. Although valve type in the multivariable analysis was adjusted for and no significant impact on the endpoints was found, unmeasured confounding related to device selection cannot be completely excluded. Despite these challenges, this study is still clinically significant as it highlights the utility of non-invasive and commonly assessed parameters in predicting mid-term outcomes.

CONCLUSION

This single-center retrospective study showed that, in addition to both LF-LG with pEF and rEF AS, LF-HG with pEF AS had a higher all-cause mortality rate after TAVR compared to NF-HG AS.

Ethics Committee Approval: The study protocol was approved by the Main Line Health Hospitals Institutional Review Board (IRB 45CFR164.512) on November 11, 2020.

Informed Consent: Individual patient consent was waived due to the retrospective nature of the study.Peer-review: Externally peer-reviewed.

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Supplementary Table 1. Results of forward selection multivariable Cox proportional hazards models for follow-up outcomes.			
	All-cause mortality	**Cardiovascular death**	**Composite outcome***
		HR (95%CI)	
LF-HG with pEF versus NF-HG	**1.42 (1.02-1.98)**	1.40 (0.89-2.19)	**1.41 (1.05-1.91)**
LF-HG with rEF versus NF-HG	1.15 (0.68-1.95)	1.04 (0.50-2.16)	1.07 (0.66-1.74)
LF-LG with pEF versus NF-HG	**1.84 (1.32-2.55)**	**1.95 (1.27-3.00)**	**1.77 (1.31-2.38)**
LF-LG with rEF versus NF-HG	**1.78 (1.22-2.61)**	**1.94 (1.19-3.18)**	**1.66 (1.17-2.35)**
Age, years	**1.04 (1.02-1.06)**	**1.04 (1.01-1.06)**	**1.03 (1.01-1.04)**
Female	Not selected	Not selected	Not selected
Body surface area, m^2	Not selected	Not selected	Not selected
Body mass index, kg/m^2	Not selected	Not selected	Not selected
NYHA III/IV	Not selected	Not selected	Not selected
STS score	**1.04 (1.01-1.08)**	1.05 (0.99-1.10)	**1.06 (1.02-1.09)**
Diabetes	1.28 (0.99-1.64)	**1.49 (1.07-2.06)**	**1.30 (1.04-1.64)**
Moderate/severe chronic lung disease	**1.82 (1.26-2.61)**	**2.47 (1.59-3.84)**	**1.85 (1.34-2.56)**
Creatinine, mg/dl	**1.11 (1.04-1.20)**	1.08 (0.98-1.20)	**1.09 (1.02-1.16)**
Prior stroke	**1.59 (1.14-2.22)**	**2.05 (1.35-3.09)**	1.79 (1.33-2.38)
Peripheral artery disease	Not selected	Not selected	Not selected
Prior coronary revascularization	Not selected	Not selected	Not selected
Atrial fibrillation	Not selected	Not selected	Not selected
Prior pacemaker/defibrillator	Not selected	Not selected	Not selected
Aortic valve area, cm^2	Not selected	Not selected	Not selected
Mitral regurgitation ≥ moderate	Not selected	Not selected	Not selected
Tricuspid regurgitation ≥ moderate	**1.81 (1.32-2.46)**	**1.67 (1.10-2.51)**	**1.65 (1.23-2.21)**
Non-elective procedure	**2.18 (1.56-3.01)**	**2.29 (1.48-3.55)**	**1.90 (1.39-2.61)**
Transfemoral access	0.73 (0.49-1.08)	**0.60 (0.37-0/98)**	Not selected
Self-expanding valve	1.22 (0.96-1.55)	Not selected	1.21 (0.97-1.51)

Median (interquartile range), or n (%). LF-HG: low-flow high-gradient, LF-LG: low-flow low-gradient, LVEF: left ventricular ejection fraction, NF-HG: normal-flow high-gradient, NYHA: New York Heart Association, pEF: preserved ejection fraction, PG: pressure gradient, rEF: reduced ejection fraction, STS: Society of Thoracic Surgeons. **Bold:** $P < .05$.