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ORIGINAL RESEARCH

Gender-Dependent Association of Pulmonary Hypertension with Adverse Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement

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Background: The relationship between pulmonary hypertension (PH) and outcomes after transcatheter aortic valve replacement (TAVR) has been shown to be unfavorable. The impact of gender on TAVR outcomes remains controversial. There have been no studies evaluating the simultaneous effects of both factors on TAVR outcomes.

Methods: We retrospectively analyzed a prospective cohort of patients who underwent TAVR between January 2016 and December 2022. The patients were stratified by gender and the presence of PH. The primary outcome of the study was all-cause mortality. Secondary outcome was a composite of all-cause mortality and heart failure hospitalization.

Results: We identified a total of 133 female patients without PH, 179 males without PH, 87 females with PH, and 122 males with PH. The median follow-up period was 18 months. Female patients without PH demonstrated a lower cumulative mortality rate compared to those with male gender and/or PH. Adjusted multivariate Cox proportional hazard analyses revealed that male gender and PH status, either individually or in combination, were independently associated with long-term mortality when compared to female patients without PH. Specifically, females with PH (HR 6.80, 95% confidence interval (CI): 1.49–31.12, P=0.013), males without PH (HR 6.45, 95% CI: 1.47–28.22, P=0.013), and males with PH (HR 7.2, 95% CI: 1.63–31.81, P=0.009) demonstrated significantly higher risk for mortality.

Conclusion: Patients who were male or had PH status had a higher risk of mortality. However, there was no synergistic effect between being male and having PH on the prognosis after TAVR.

Keywords: transcatheter aortic valve replacement, gender, pulmonary hypertension, outcome

Introduction

Transcatheter aortic valve replacement (TAVR) has evolved as an alternative treatment option for patients with severe aortic stenosis across the risk spectrum.[1–3] However, it is important to consider the presence of pulmonary hypertension (PH) in these patients, as it is a common complication of aortic stenosis and indicates a decompensated state of the disease with compensatory mechanisms of the left ventricle due to AS-related "cardiac damage".[4,5] Studies have reported a prevalence of PH in severe aortic stenosis patients ranging from 48% to 75%, and this condition has been associated with a poorer prognosis following aortic valve replacement.[6–8]

PH can be detected indirectly by non-invasive techniques such as echocardiography by estimating systolic pulmonary artery pressure from the maximum tricuspid regurgitation velocity. Right heart catheterization was the gold standard method for detecting PH and allowed assessment of the underlying haemodynamic mechanisms of PH. The most common type of PH was isolated post-capillary PH which was driven by elevated left-sided filling pressures with an elevated mean pulmonary artery pressure but normal vascular resistance. In patients undergoing aortic valve replacement

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for AS, 60% of PH was isolated post-capillary PH, while 28% was combined pre- and post-capillary PH, characterised by increased filling pressures, mean pulmonary artery wedge pressure and pulmonary vascular resistance.[7]

The impact of gender differences on outcomes in cardiovascular disease has been extensively studied. This includes conditions such as PH, AS, and even in individuals who have undergone TAVR. It has been observed that females are more susceptible to developing PH, but interestingly, they tend to have better survival rates compared to males.[9] However, there is inconsistency in the results regarding the impact of gender on TAVR patients.[10–12] While several studies have separately evaluated the effects of PH and gender on outcomes after TAVR, none have yet examined these two factors simultaneously. Therefore, the aim of the current study is to assess whether the prognostic influence of gender and PH is synergistic in patients after TAVR, with the goal of identifying subgroups at increased risk.

Materials and Methods

Patient Cohort

This study is a retrospective analysis of prospective single-center registry database of patients who underwent TAVR at Guangdong provincial people's hospital, approved by the Research Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2019384H). Our study complied with the Declaration of Helsinki. The current study enrolled patients who underwent TAVR between January 2016 and December 2022. No exclusion criteria were applied. Baseline clinical and echocardiographic characteristics, procedural data and outcome data were prospectively collected. Follow-up was performed 30 days, 6 months, 12 months and annually after TAVR. Written informed consent was obtained from all participants for this registry.

Echocardiography

All patients underwent transthoracic echocardiography evaluation pre-operation. The estimation of PASP is based on the sum of the right atrial pressure (RAP) and the peak tricuspid regurgitation (TR) velocity, as described by the modified Bernoulli equation. Estimation is based on the diameter and respiratory excursions of the inferior vena cava, as previously described.[13] Tricuspid regurgitation (TR) velocity >2.8 m/s, which is a well-defined cutoff value to diagnose PH according to American and European guidelines, is known to correspond to systolic pulmonary artery pressure (sPAP) of 36 mm Hg.[13,14] Furthermore, a cutoff value of sPAP of 36 mm Hg has been used and validated in previous studies.[15,16] Therefore, sPAP > 36 mm Hg was used as a cutoff for PH in current study. Patients were divided into no PH by sPAP≤ 36mmHg, mild PH by sPAP 37–50 mmHg, moderate PH by sPAP 51–70mmHg and severe PH by sPAP > 70mmHg. Any decrease of at least 1 degree at discharge was considered an improvement in PH severity, while an increase of at least 1 degree at discharge was considered a worsening in PH severity.

Procedure Details

According to the center expertise and device availability, self-expanding valve such as VenusA, VenusA-Pro, VenusA-Plus valve (Venus Medtech), Taurusone valve (Peijia Medical), ScienCrown valve (Lepu medical), Vitaflow (Microport), balloon-expanding valve such as Edwards Sapien (Edwards Lifesciences) were implanted. Decisions about TAVI, device type and size were made by consensus by a dedicated heart team consisting of cardiac surgeons, interventional cardiologists and cardiac imaging specialists.

Endpoint

The primary endpoint was defined as all-cause mortality after TAVR. All-cause mortality was sub-divided into cardiovascular and non-cardiovascular mortality according to the definition of Valve Academic Research Consortium-3 (VARC-3). The secondary endpoint was the composite of all-cause mortality and heart failure hospitalization. In-hospital mortality, stroke, permanent pacemaker implantation, major vascular complication and life-threatening bleeding were also recorded according to VARC-3.[17]

Statistical Analysis

Categorical variables were presented as numbers and percentages and were compared using Chi-square or Fisher exact testing. Continuous data were expressed as median with the 25th and 75th quartile and were compared using *t* test or Mann–Whitney *U*-test for two group comparisons based on the distribution of the variables. Kolmogorov–Smirnov test was used to test for normality. For more than two group comparisons, an analysis of variance test was performed for normally distributed variables, whereas a Kruskal–Wallis test was performed for skewed variables, respectively. Unadjusted Kaplan-Meier analysis was used to evaluate the incidence of clinical outcomes at maximal follow-up and the log rank test was used for group comparisons. Adjusted hazard ratios (HRs) were calculated in multivariable Cox-regressions including baseline clinical and echocardiographic characteristics known to affect patient outcomes after TAVR [age (a continuous variable), body mass index>30Kg/m2, New York Heart Association (NYHA) functional class > II, hypertension, diabetes mellitus, coronary artery disease, previous myocardial infarction, percutaneous coronary intervention (PCI), peripheral artery disease, previous stroke, chronic obstructive pulmonary disease (COPD), chronic kidney disease stage ≥ 3, atrial fibrillation, left ventricular ejection fraction< 50% and STS score≥ 10. Proportional assumptions hazard was tested based on Schoenfeld residuals. All statistical analyses were performed with SPSS version 26 (IBM Corporation, Armonk, New York).

Results

Baseline Clinical, Echocardiographic and Procedural Characteristics

In total, 521 patients were enrolled and retrospectively analyzed. Of these, 209 (40.1%) had PH, and 312 (59.9%) were non-PH. Among the patients, 220 (42.2%) were female, and 301 (57.8%) were male. Baseline clinical and echocardiographic characteristics are shown in Table 1. The patients' ages were similar among females and males, both with and without PH. Among patients with PH, the comorbidities such as prior myocardial infarction, atrial fibrillation, and

Table 1 Pre-Procedural Clinical and Echocardiographic Characteristics Stratified by Pulmonary Hypertension Status and Gender

Variables	No Pulmonary Hypertension [n=312(59.9%)]		Pulmonary Hypertension [n=209(40.1%)]		p value for Four-group Comparison	p value for Two-group within Females Comparison	p value for Two-group within Males Comparison
Gender, n(%)	Female [133 (25.5%)]	Male [179 (34.4%)]	Female [87 (16.7%)]	Male [122 (23.4%)]			
Age (years)	73.0 (68.0; 76.5)	71.0 (68.0; 76.0)	73.0 (69.0; 76.0)	73.0 (69.8; 76.3)	0.391	0.965	0.086
BMI (kg/m^2)	22.9 (20.3; 25.8)	23.5 (20.9; 25.8)	21.4 (19.7; 24.9)	21.8 (20.2; 24.1)	**0.001**	**0.030**	**0.001**
Hypertension, n(%)	77(57.9%)	96(53.6%)	43(49.4%)	53(43.4%)	0.121	0.217	0.083
DM, n(%)	37(27.8%)	42(23.5%)	14(16.1%)	22(18.0%)	0.126	0.044	0.258
CAD, n(%)	35(26.3%)	68(38.0%)	31(35.6%)	42(34.4%)	0.180	0.140	0.529
Prior MI, n(%)	4(3.0%)	9(5.0%)	9(10.3%)	14(11.5%)	**0.021**	**0.024**	**0.039**
Prior PCI, n(%)	20(15.0%)	34(19.0%)	20(23.0%)	16(13.1%)	0.231	0.135	0.178
Prior CABG, n(%)	0(0%)	1(0.6%)	0(0%)	2(1.6%)	0.297	-	0.568
PMI, n(%)	1(0.8%)	0(0%)	3(3.4%)	1(0.8%)	0.058	0.303	0.405
Atrial fibrillation or flutter, n(%)	15(11.3%)	18(10.1%)	18(20.7%)	33(27.0%)	**0.000**	0.056	**0.000**
Prior stroke, n(%)	9(6.8%)	20(11.2%)	2(2.3%)	11(9.0%)	0.083	0.207	0.546
CKD, n(%)	37(27.8%)	54(30.2%)	39(44.8%)	60(49.2%)	**0.000**	**0.009**	**0.001**
PAD, n(%)	15(11.3%)	20(11.2%)	9(10.3%)	20(16.4%)	0.467	0.828	0.190
COPD, n(%)	2(1.5%)	12(6.7%)	3(3.4%)	11(9.0%)	**0.039**	0.386	0.458
Hemodialysis, n(%)	2(1.5%)	2(1.1%)	3(3.4%)	1(0.8%)	0.436	0.386	1.000
Malignancy, n(%)	10(7.5%)	11(6.1%)	10(11.5%)	11(9.0%)	0.480	0.316	0.347
Heart valve surgery, n(%)	4(3.0%)	6(3.4%)	9(10.3%)	5(4.1%)	**0.046**	**0.024**	0.762
NYHA III/IV, n(%)	71(53.4%)	84(46.9%)	59(67.8%)	84(68.9%)	**0.000**	**0.033**	**0.000**
STS score	2.6 (1.8; 3.7)	1.6 (1.2; 2.8)	4.4 (2.5; 6.9)	2.5 (1.5; 4.6)	**0.000**	**0.000**	**0.000**

(*Continued*)

Table 1 (Continued).

Variables	No Pulmonary Hypertension [n=312(59.9%)]		Pulmonary Hypertension [n=209(40.1%)]		p value for Four-group Comparison	p value for Two-group within Females Comparison	p value for Two-group within Males Comparison
Echocardiography							
Mean gradient (mmHg)	56.0 (43.0; 66.0)	60.0 (48.0; 67.0)	57.1 (45.0; 69.0)	50.0 (39.8; 61.2)	**0.034**	0.517	**0.025**
Max velocity (m/s)	4.8 (4.3; 5.3)	4.7 (4.2; 5.3)	4.9 (4.4; 5.3)	4.4 (4.1; 5.0)	**0.012**	0.291	0.070
LVEF (%)	64.0 (58.0; 68.0)	55.0 (44.0; 67.0)	50.0 (34.0; 65.0)	47.0 (34.9; 61.0)	**0.000**	**0.000**	**0.000**
Moderate or severe AR, n(%)	47(35.3%)	85(47.5%)	39(44.8%)	74(60.7%)	**0.001**	0.158	**0.025**
Moderate or severe MR, n(%)	23(17.3%)	45(25.1%)	53(60.9%)	83(68.0%)	**0.000**	**0.000**	**0.000**
Moderate or severe TR, n(%)	7(5.3%)	15(8.4%)	47(54.0%)	62(50.8%)	**0.000**	**0.000**	**0.000**

Notes: Bold values indicate significant associations. Values are presented as n (%) or median (interquartile range).

Abbreviations: BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; PAD, peripheral artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; MI, myocardial infarction; STS score, the Society of Thoracic Surgery risk score; eGFR, estimated glomerular filtration rate; NYHA class, New York Heart Association Functional classification; LVEF, left ventricular ejection fraction; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation.

chronic kidney disease (CKD) were significantly higher than in patients without PH, regardless of gender. Consistently, the ratio of tricuspid regurgitation and mitral regurgitation being moderate or greater was higher, but the left ventricular ejection fraction (LVEF) was lower in patients with PH. Moreover, the mortality risk associated with surgery and NYHA function were significantly worse in patients with pulmonary hypertension (PH) compared to those without PH. When analyzing patients by gender and PH, it was observed that the left ventricular ejection fraction (LVEF) decreased in the following order: female without PH, female with PH, male without PH, and male with PH. Similarly, the ratio of chronic kidney disease (CKD) and moderate or greater mitral regurgitation increased in the same order. Furthermore, the procedure characteristics were found to be comparable among patients when divided by gender and PH (Table 2). Only two patients had a history of targeted drug treatment for pulmonary hypertension before procedure.

Table 2 Procedural Parameters and Outcomes After TAVR per Pulmonary Hypertension Status and Gender

	No Pulmonary Hypertension [n=312(59.9%)]		Pulmonary Hypertension [n=209(40.1%)]		p value for Four-group Comparison	p value for Two-group within Females Comparison	p value for Two-group within Males Comparison
Gender, n(%)	Female [133 (25.5%)]	Male [179 (34.4%)]	Female [87 (16.7%)]	Male [122 (23.4%)]			
Procedural parameters							
Self-expandable Valve, n(%)	129(97.0%)	177(98.9%)	84(96.6%)	121(99.2%)	0.346	1.000	1.000
Balloon pre-dilatation, n(%)	124(93.2%)	164(91.6%)	80(92.0%)	112(91.8%)	0.958	0.721	0.955
Balloon post-dilatation, n(%)	46(34.6%)	85(47.5%)	39(44.8%)	47(38.5%)	0.107	0.127	0.124
Valve in valve, n(%)	5(3.8%)	25(14.0%)	5(5.7%)	11(9.0%)	**0.011**	0.522	0.194
Procedural outcomes							
In-hospital mortality, n(%)	0(0%)	0(0%)	4(4.6%)	4(3.3%)	**0.005**	**0.023**	**0.026**
Stroke, n(%)	1(0.8%)	3(1.7%)	2(2.3%)	2(1.6%)	0.824	0.564	1.000
Life-threatening bleeding, n(%)	11(8.3%)	10(5.6%)	17(19.5%)	9(7.4%)	**0.002**	**0.014**	0.531
New pacemaker, n(%)	8(6.0%)	9(5.0%)	6(6.9%)	5(4.1%)	0.817	0.793	0.707
Acute kidney injury, n(%)	4(3.0%)	10(5.6%)	5(5.7%)	9(7.4%)	0.481	0.323	0.531
Follow up							
All-cause mortality, n(%)	2(1.5%)	16(8.9%)	15(17.2%)	18(14.8%)	**<0.001**	**0.000**	0.118
Cardiovascular mortality, n(%)	2(1.5%)	8(4.5%)	12(13.8%)	9(7.4%)	**0.001**	**0.000**	0.283
Composited endpoint, n(%)	2(0%)	21(11.7%)	15(17.2%)	18(14.8%)	**<0.001**	**<0.001**	0.443

Notes: Bold values indicate significant associations. Values are presented as n (%) or median (interquartile range).

In-Hospital and Follow-Up Outcomes After TAVR According to Gender and PH

In-hospital and follow-up outcomes are summarized in Table 2. A total of 8 patients died in-hospital after the procedure, and all of these patients had PH. Furthermore, there was no significant difference in the rate of in-hospital mortality between genders. Regarding the incidence of life-threatening bleeding, it varied among patients when divided by gender and PH. Specifically, it was highest (19.5%) in female patients with PH and lowest (5.6%) in males without PH, while females without PH and males with PH fell in between. However, there was no gender or PH difference in the rate of stroke, permanent pacemaker, and acute kidney injury.

A total of 505 patients underwent transthoracic echocardiography at discharge in the entire cohort. Of these, 149 (29.3%) exhibited an improvement in the severity of pulmonary hypertension (PH), 319 (63.2%) demonstrated no change, and 38 (7.5%) exhibited a worsening of PH. There was no significant difference in the severity change of PH reverse between female and male patients (P=0.943) (Figure 1a). In patients with PH before TAVR (n=199), 148 (74.4%) patients have an improvement in PH, and there was comparable in reverse PH severity between female and male (P=0.859) (Figure 1b).

During a median follow-up period of 18 (interquartile range: 8.5–31.5) months, the study found that 51 (9.8%) patients died for any cause and 31 (6.0%) died due to cardiovascular causes in the entire cohort. There was no significant difference in all-cause mortality or cardiovascular mortality between genders, but higher rate of composited endpoint in male patients (Log rank P=0.12, Log rank P=0.88 and Log rank P=0.04, respectively) (Supplementary Figure 1). However, when patients were divided by pulmonary hypertension (PH) status, those with PH had significantly higher rate of all-cause mortality, cardiovascular mortality and composited endpoint compared to those without PH (Log rank P<0.001, Log rank P=0.0018 and Log rank P=0.0045, respectively) (Supplementary Figure 2). Interestingly, this difference between patients with and without PH was observed only in female patients, not male patients (Figure 2). Moreover, when patients were divided by both gender and PH status, unadjusted Kaplan-Meier analysis consistently showed lower all-cause, cardiovascular mortality and composited endpoints of mortality and heart failure hospitalization rates in females without PH compared to males without PH, males with PH, and females with PH after a 2-year follow-up (all-cause mortality: 1.5% vs 8.9% vs 14.8% vs 17.2%, Log rank P<0.001; cardiovascular mortality: 1.5% vs 4.5% vs 7.4% vs 13.8%, Log rank P=0.0029; composited endpoint: 1.5% vs 11.7% vs 14.8% vs 17.2%) (Figure 3).

In the unadjusted Cox proportional hazard regression analysis, several factors were found to be associated with an increased risk of all-cause mortality, including females with pulmonary hypertension (PH), males without PH, males with PH, NYHA III or IV functional status, prior stroke, chronic kidney disease (CKD), and a STS risk score≥10 (Table 3). However, after adjusting for baseline characteristics, only females with PH (HR 6.80, 95% confidence interval (CI): 1.49–31.12, P=0.013), males without PH (HR 6.45, 95% CI: 1.47–28.22, P=0.013), males with PH (HR 7.2, 95% CI: 1.63–31.81, P=0.009), prior stroke (HR 2.53, 95% CI: 1.15–5.60, P=0.022), and a STS risk score≥10 (HR 5.66, 95% CI: 2.45–12.89, P=0.001) remained as independent predictors for all-cause mortality.

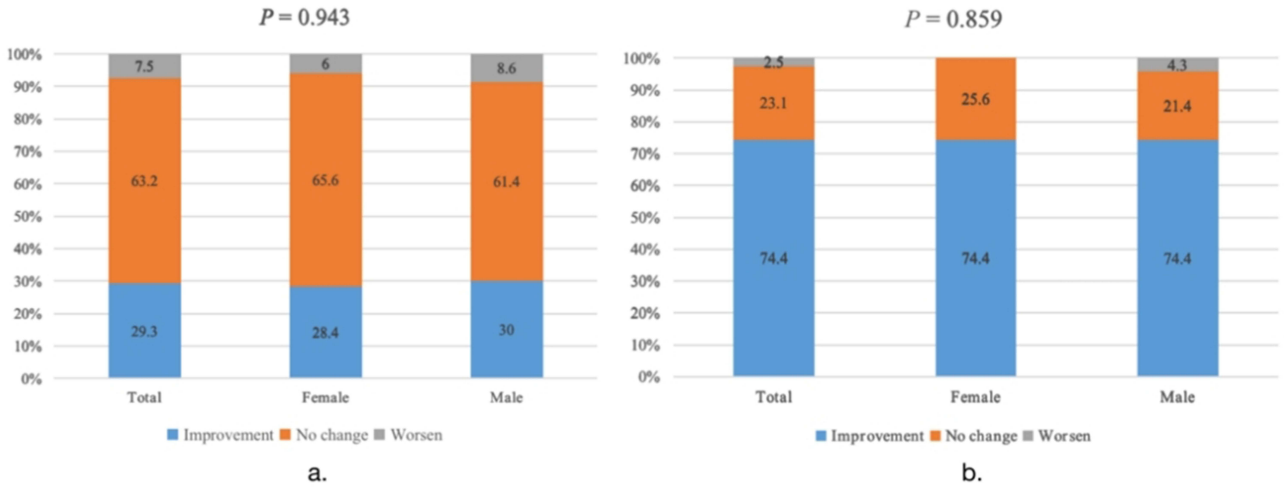

Figure 1 Pulmonary hypertension reversible at discharge in all patients (**a**) and patients with pulmonary hypertension (**b**).

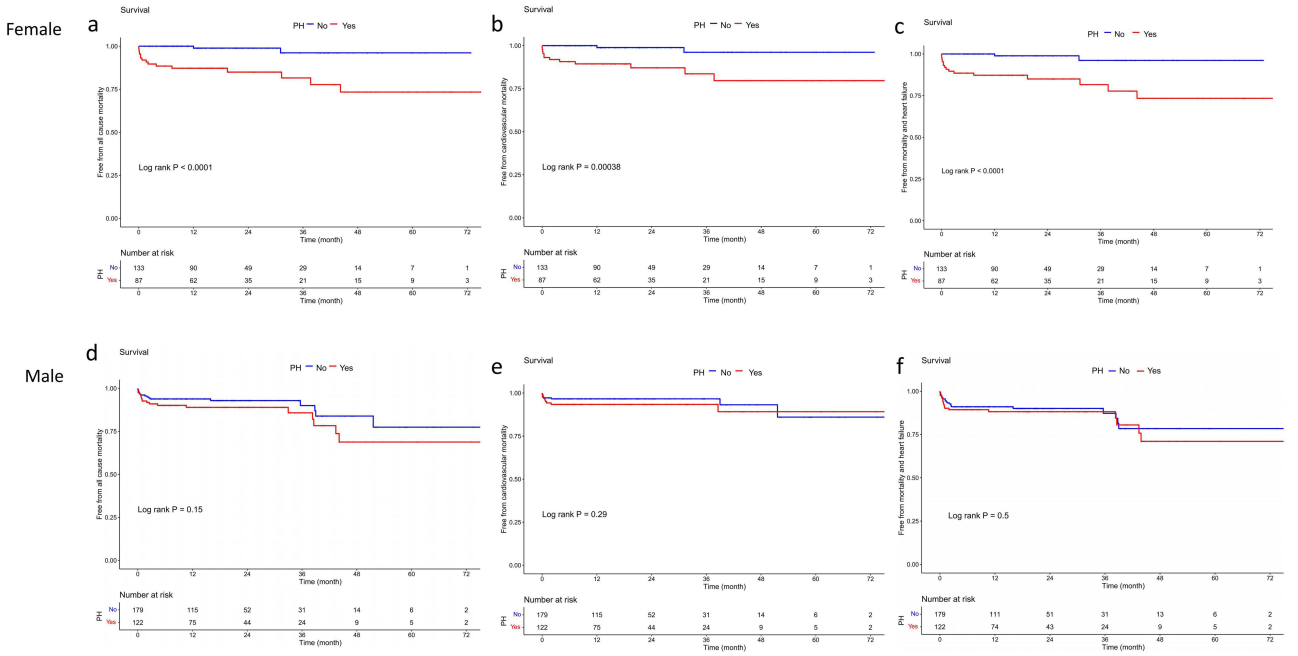

Figure 2 Follow-up clinical outcomes compared between patients with and without pulmonary hypertension in female (**a-c**) and male (**d-f**). All-cause mortality (**a** and **d**), cardiovascular mortality (**b** and **e**) and composited endpoints of mortality and heart failure (**c** and **f**).

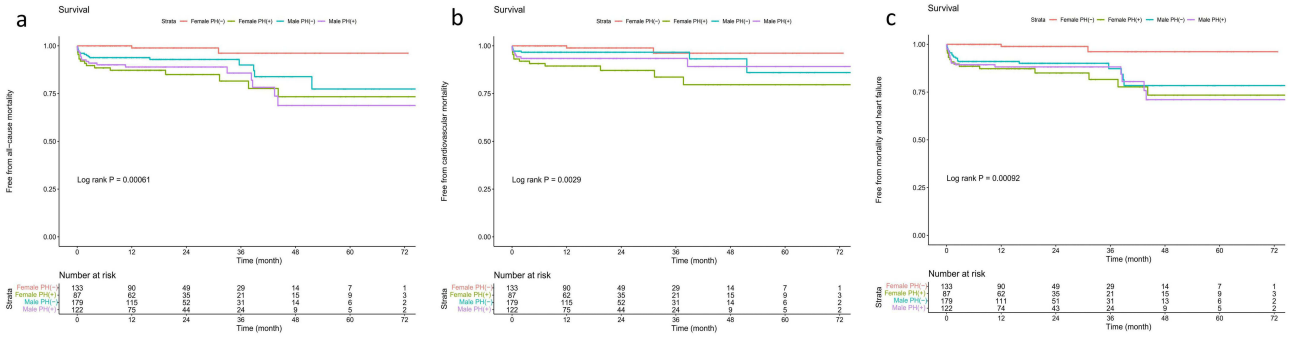

Figure 3 Follow-up clinical outcomes compared among patients divided by pulmonary hypertension and genders. All-cause mortality (**a**), cardiovascular mortality (**b**) and composited endpoints of mortality and heart failure (**c**).

Discussion

This study aimed to assess the outcomes of patients undergoing TAVR, specifically focusing on the impact of gender and PH. The primary findings are as follows: (1) Perioperative complications, except for life-threatening bleeding, were similar regardless of gender or the presence of pulmonary hypertension, while in-hospital mortality was slightly higher in patients with pulmonary hypertension; (2) The rates of all-cause mortality and cardiovascular mortality were significantly higher in patients with pulmonary hypertension compared to those without it. Interestingly, when stratified by gender, pulmonary hypertension was associated with all-cause mortality only in female patients, but not in male patients; (3) Additionally, when evaluating the combined impact of gender and pre-procedural PH on outcomes following TAVR, it was observed that the incidence of all-cause mortality was lowest in female patients without PH. The incidence was similar among female patients with PH and male patients with or without PH. (4) Further analysis using multivariate Cox proportional hazard models revealed a significantly increased risk of all-cause mortality in patients who were male, had

Table 3 Pulmonary Hypertension Gender Interaction Cox Proportional Hazard Analysis of Predictors of All-Cause Mortality

	Alive [n=469(91.4%)]	Dead [n=43(8.4%)]	Unadjusted HRs Univariate model	p value	Adjusted HRs Multivariate Model	p value
Female PH(-)			1.00(reference)		1.00(reference)	
Female PH(+)			8.223(1.821; 37.136)	0.006	6.805(1.488; 31.123)	0.013
Male PH(-)			6.486(1.491; 28.217)	0.013	6.449(1.474; 28.220)	0.013
Male PH(+)			8.281(1.882; 36.442)	0.005	7.203(1.631; 31.810)	0.009
Pre-procedural						
Age per 1 year increase			1.042 (0.997; 1.089)	0.068	-	-
Male, n(%)	266(56.7%)	30(69.8%)	1.857 (0.968; 3.564)	0.063		
BMI>30 kg/m2, n(%)	12(2.6%)	3(7.0%)	2.317 (0.715; 7.507)	0.161	-	-
NYHA III/IV, n(%)	258(55.0%)	32(74.4%)	2.213 (1.115; 4.391)	0.023	-	-
Hypertension, n(%)	248(52.9%)	16(37.2%)	0.547 (0.295; 1.016)	0.056	-	-
DM, n(%)	107(22.8%)	8(18.6%)	0.781 (0.362; 1.684)	0.529	-	-
CAD, n(%)	158(33.7%)	14(32.6%)	0.774 (0.406; 1.473)	0.434	-	-
Prior MI, n(%)	31 (6.6%)	4(9.3%)	1.618 (0.577; 4.538)	0.360	-	-
Prior PCI, n(%)	81(17.3%)	7(16.3%)	0.828 (0.368; 1.864)	0.648	-	-
Prior CABG, n(%)	3(0.6%)	0(0.0%)	0.049 (0.000; 153,598.185)	0.693		
PMI, n(%)	5(1.1%)	0(0.0%)	0.048 (0.000; 3897.118)	0.599		
Atrial fibrillation or flutter, n(%)	71(15.1%)	11(25.6%)	1.698 (0.855; 3.370)	0.130	-	-
Prior stroke, n(%)	34(7.2%)	8(18.6%)	2.435 (1.127; 5.260)	0.024	2.533(1.147; 5.596)	0.022
PAD, n(%)	53(11.3%)	10(23.3%)	1.886 (0.928; 3.833)	0.080	-	-
COPD, n(%)	23(4.9%)	5(11.6%)	2.293 (0.902; 5.828)	0.081	-	-
Hemodialysis, n(%)	6(1.3%)	1(2.3%)	2.456 (0.335; 18.032)	0.377		
Malignancy, n(%)	36(7.7%)	4(9.3%)	0.992 (0.354; 2.780)	0.987		
Heart valve surgery, n(%)	21(4.5%)	3(7.0%)	1.819 (0.562; 5.896)	0.318		
CKD, n(%)	159(33.9%)	25(58.1%)	2.410 (1.314; 4.420)	0.004	-	-
Mean gradient > 40 mmHg, n(%)	369(78.7%)	30(69.8%)	0.640 (0.334; 1.228)	0.180		
Max velocity > 4 m/s, n(%)	379(80.8%)	33(76.7%)	0.759 (0.374; 1.541)	0.446		
LVEF < 50%, n(%)	156(33.3%)	21(48.8%)	1.687 (0.927; 3.070)	0.087	-	-
Moderate or severe AR, n(%)	219(46.7%)	22(51.2%)	1.206 (0.663; 2.194)	0.539		
Moderate or severe MR, n(%)	178(38.0%)	20(46.5%)	1.401 (0.769; 2.551)	0.271		
Moderate or severe TR, n(%)	108(23.0%)	16(37.2%)	1.843 (0.993; 3.422)	0.053	-	-
STS score ≥ 10, n(%)	4(0.9%)	6(14.0%)	6.055(2.793; 13.127)	0.001	5.662(2.488; 12.886)	0.001

Notes: Values are presented as n (%).

Abbreviations: PH, pulmonary hypertension; BMI, body mass index; NYHA, New York Heart Association Functional classification; DM, diabetes mellitus; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PMI, permanent pacemaker implantation; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; CKD, Chronic kidney disease; LVEF, left ventricular ejection fraction; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; STS score, the Society of Thoracic Surgery risk score.

PH, or both. However, there was no evidence of a synergistic effect, indicating that having both factors did not further elevate the risk.

The presence of PH may be a marker of advanced aortic stenosis. PH is taken into consideration when calculating the baseline risk for cardiac surgery,[18] and it is an established risk factor for mortality in patients undergoing both surgical[15] and transcatheter aortic valve replacement.[19] A retrospective study conducted by Luçon et al involving 2435 patients who underwent TAVR reported that PH was associated with increased 1-year mortality, although it did not correlate with increased 30-day mortality.[19] Furthermore, Miyamoto et al confirmed in a multicenter registry study that the development of new-onset PH after TAVR was also associated with worse long-term survival.[16] In our study, the overall prevalence of preoperative PH was 40%, which is consistent with previous studies, which have reported a range from 30% to 75%.[16,20] Additionally, we found that the incidence of PH was similar between genders. This finding aligns with a study by Conrotto et al, which reported comparable systolic pulmonary arterial pressure between female and male patients undergoing TAVR.[21] However, our study discovered that the impact of pulmonary hypertension (PH) on all-cause mortality and cardiovascular mortality was significant in female patients,

but not in male patients. This suggests that there may be a gender difference in the prognostic impact of PH after TAVR. Previous studies have separately analyzed the prognostic effect of gender and PH on early and long-term outcomes, but none have assessed these two factors simultaneously. In our study, we found that being male and having PH were independently associated with all-cause mortality after TAVR. Interestingly, the presence of both factors did not increase the risk beyond that of being male and having PH alone. There was no synergistic effect between being male and having PH on the prognosis after TAVR. The present study may provide a suggestion for the patient's selection for TAVR. Female patients may attain much more benefit from the procedure before pulmonary hypertension occurs. Furthermore, for male patients with AS and pulmonary hypertension, TAVR should not be considered contraindicated.

In the context of aortic stenosis, PH often occurs as a result of chronic elevation of left ventricular pressure and concurrent mitral regurgitation, or preoperative comorbidities, or both problems. The most common type of PH is postcapillary PH secondary to left-sided heart disease, which may improve after treatment. In the present study, 74.4% of patients with PH before procedure had an improvement at discharge, with no difference between genders. Recently, Miyamoto et al demonstrated in a multicenter registry study that in patients with baseline PH, defined as pre-TAVR sPAP >36 mmHg,45.5% experienced normalization of PH at discharge.[16] Similarly, Alushi et al showed that 46% patients had a significant regression of PH after TAVR.[22] The rate of PH regression in our study was higher than the previous studies, and this might be explained by different definition of PH and PH improvement after TAVR. Of those patients without PH regression, pulmonary irreversible remodeling due to advanced stage of aortic stenosis or baseline comorbidities was the potential mechanism.

The impact of gender difference on short- and long-term outcomes after TAVR has been extensively studied, but it remains a controversial topic. Some studies have reported a worse long-term survival rate in female patients,[10,23] while others have shown similar or better survival rates compared to males.[12,24] In line with previous studies,[25,26] the present study revealed an increased incidence of procedure complications, such as life-threatening bleeding, after TAVR in females. One possible explanation for this finding is that the rate of major vascular complications was significantly higher in female patients, and they also had smaller vascular access sizes.[27] Our study revealed similar in-hospital mortality and long-term survival rates between genders, with a noticeable trend towards increasing long-term mortality in male patients. These findings contradict previous studies that suggested higher in-hospital mortality among female patients following TAVR, potentially due to a higher incidence of periprocedural complications.[28,29]

In the Cox proportional hazard model, the presence of male gender and/or complications from PH were found to be significantly associated with a higher risk of all-cause mortality. These factors were identified as independent risk factors when compared to females without PH. With the rapid expansion of TAVR indications to low surgical risk patients, the need for accurate long-term prognosis risk prediction after TAVR has become more crucial than ever before. Traditional risk scores like STS PROM and EuroSCORE, originally developed for cardiac surgery, are time-consuming and may not be suitable for TAVR patients. Thus, there is a lack of a specific risk stratification method for individuals undergoing TAVR. To the best of our knowledge, this study is the first to simultaneously evaluate gender and PH in TAVR patients. In the present study, we found that the simultaneous evaluation of gender and pulmonary hypertension status can independently predict long-term survival, even after adjusting for the STS risk score, which incorporates gender and PH status as covariates.

Limitations

There were several limitations in the present study that need to be noted. First, the study is a single-center study and has limited numbers of samples. The retrospective nature of the study may cause potential confounding factors that were not recorded and considered. Second, right heart catheterization, which is considered the gold standard for diagnosing pulmonary hypertension, was not routinely performed in patients undergoing TAVR in our institution. However, the wide availability and non-invasiveness make echocardiography an accepted method for evaluation of pulmonary hypertension. Moreover, pulmonary hypertension defined by echocardiography was also significantly associated with prognosis after TAVR.[15,16] Third, as the majority of patients died at home or in other medical facilities, there is a paucity of

echocardiographic data. Consequently, it is not feasible to determine whether patients who expired during the follow-up period still had pulmonary hypertension.

Conclusion

The retrospective study indicated that being male and having baseline PH were associated with an increased risk of mortality after TAVR. However, the present study did not find a synergistic effect between these two factors on the prognosis after TAVR. Instead, the findings suggest that intervention should be performed in patients with aortic stenosis before the development of pulmonary hypertension, particularly in female patients.

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Disclosure

The authors report no conflicts of interest in this work.

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