Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) *in press*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Research Article

https://doi.org/10.1631/jzus.B2400057

COMPERA 2.0 risk stratification in patients with severe aortic stenosis: implication for group 2 pulmonary hypertension

Zongye CAI[1,2,3,*], Xinrui QI[1,2,3,*], Dao ZHOU[1,2,3], Hanyi DAI[1,2,3], Abuduwufuer YIDILISI[1,2,3], Ming ZHONG[4], Lin DENG[5], Yuchao GUO[1,2,3], Jiaqi FAN[1,2,3], Qifeng ZHU[1,2,3], Yuxin HE[1,2,3], Cheng LI[1,2,3], Xianbao LIU[1,2,3], Jianan WANG[1,2,3,#]✉

[1]*Department of Cardiology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310009, China*
[2]*State Key Laboratory of Transvascular Implantation Devices, Hangzhou, 310009, China*
[3]*Heart Regeneration and Repair Key Laboratory of Zhejiang province, Hangzhou, 310009, China*
[4]*Department of Nephrology, Center of Kidney and Urology, the Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, 518107, China*
[5]*Department of Cardiology, The Eighth Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong, 518033, China*

Unedited

Abstract: Background: COMPERA 2.0 risk stratification has been demonstrated to be useful in patients with precapillary pulmonary hypertension (PH). However, its suitability for patients at a risk for post-capillary PH, or PH associated with left heart disease (PH-LHD), is unclear. Aims: To investigate the use of COMPERA 2.0 in patients with severe aortic stenosis (SAS) undergoing transcatheter aortic valve replacement (TAVR), which are at risk for post-capillary PH. Methods: 327 eligible SAS patients undergoing TAVR between September 2015 to November 2020 in our institute were included. Patients before and after TAVR were classed into four strata using the COMPERA 2.0 risk score. The primary endpoint was all-cause mortality. Survival analysis was performed using Kaplan-Meier curves, log-rank test, and Cox proportional hazard models. Results: The study cohort had a median (interquartile range) age of 76 (70-80) years and a pulmonary arterial systolic pressure of 33 (27-43) mmHg before TAVR. The overall mortality was 11.9% during 26 (15-47) months of follow-up. Before TAVR, cumulative mortality was higher with an increase in the risk stratum level (Log-rank, both $P < 0.001$); one increase in the risk stratum level resulted in an increased risk of death (Hazard Ratio, HR 2.53, 95% confidential interval, CI 1.54 - 4.18, $P < 0.001$), which was independent of age, sex, estimated glomerular filtration rate, hemoglobin, albumin, and valve type (HR 1.76, 95% CI 1.01 - 3.07, $P = 0.047$). Similar results were found at 30 days after TAVR.Conclusions: COMPERA 2.0 can be a useful tool for risk stratification in patients with SAS undergoing TAVR, indicating its potential use in PH-LHD. Further validation is needed in patients with confirmed post-capillary PH by right heart catheterization.

Key words: COMPERA 2.0; Mortality; Aortic stenosis; Pulmonary hypertension

1 Introduction

COMPERA 2.0 is a 4-stratum risk assessment model that includes a combination of three simple and commonly used parameters in clinical practice: New York Heart Association (NYHA) Functional class (FC), 6-minute walking distance (6MWD), and brain natriuretic peptide (BNP) or N-terminal fragment of pro-BNP

✉ Jian'an WANG, wangjianan 111@zju.edu.cn
[*] The two authors contributed equally to this work
Jian'an WANG, https://orcid.org/0000-0002-4583-3204

Received Jan. 30, 2024; Revision accepted July 8, 2024;
Crosschecked xxx. xx, 20xx; Published online xxx. xx, 20xx

© Zhejiang University Press 2024

(NT-proBNP). COMPERA 2.0 has been validated for the prediction of outcomes for patients with precapillary PH, i.e., group 1 and group 4 pulmonary hypertension (PH) (Boucly et al., 2021; Hoeper et al., 2021; Humbert et al., 2022a,2022b; Stubbs et al., 2022). However, its applicability in patients at risk for post-capillary PH, or PH associated with left heart disease (PH-LHD), or group 2 PH, remains to be clarified.

Group 2 PH is very common among valvular heart diseases, especially severe aortic stenosis (SAS); the prevalence of PH was reported to be 32% to 100% in patients with SAS (Maeder et al., 2022; Miyamoto et al., 2022) and more than 50% even after transcatheter aortic valve replacement (TAVR) (Schewel et al., 2019). PH was also found to be an independent predictor of long-term mortality in patients with SAS undergoing TAVR (Schewel, et al., 2019). NYHA FC, 6MWD, and BNP or NT-proBNP have also been demonstrated as independent predictors of clinical outcomes in patients with SAS undergoing TAVR (Sigvardsen et al., 2017; Sato et al., 2019; O'leary et al., 2020; Hadziselimovic et al., 2022; Tuttle et al., 2022). Therefore, we speculated that COMPERA 2.0 could be utilized as a risk assessment tool in patients with SAS undergoing TAVR. Nowadays, the STS score constitutes the most important risk assessment tool for SAS (Otto et al., 2021; Writing Committee et al., 2021; Vahanian et al., 2022; Xu et al., 2022); however, this score comprises a lot of parameters, making it challenging to use for all physicians taking care of patients. On the other hand, COMPERA 2.0 is an easy-to-use assessment tool, which will benefit a broad spectrum of physicians in clinical practice. To test our hypothesis, we included patients with SAS undergoing TAVR to investigate the utility of the COMPERA 2.0 risk assessment model.

2 Methods

2.1 Study population

The patients included in this study were consecutive symptomatic patients with SAS at low, intermediate, high, or prohibitive risk for surgery who underwent TAVR from September 2015 to November 2020 at The Second Affiliated Hospital of Zhejiang University School of Medicine (TORCH Registry, Transcatheter Aortic Valve Replacement Single Center Registry in Chinese Population, ClinicalTrials.gov Identifier: NCT02803294), Hangzhou, China. The inclusion criteria were as follows: NYHA FC, 6MWD, BNP or NT-proBNP level available at baseline before TAVR and at the first follow-up around 30 days after TAVR. Patients who could not perform 6MWD due to the severity of SAS were included and recorded as 6MWD < 165m, while they were excluded if they had stroke or disability or other unknown disease. The flow diagram of the study is shown in Fig. 1.

unedited

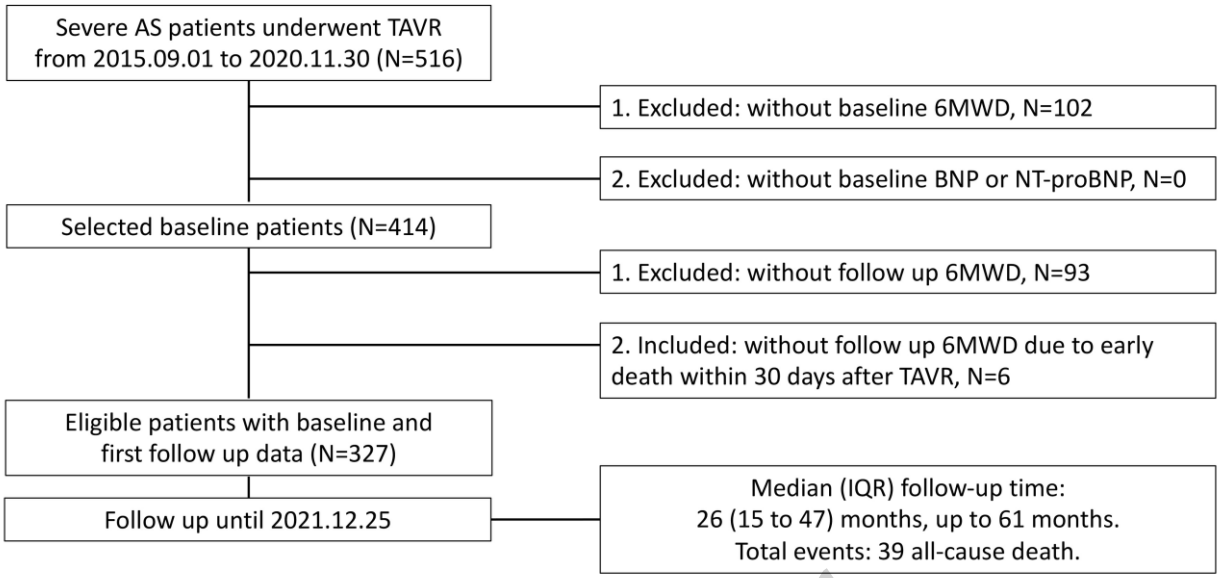

Fig. 1 Study flow diagram

Unedited

2.2 Ethics guidelines

The study complied with the Declaration of Helsinki, and the protocol was approved by the institutional review board of The Second Affiliated Hospital Zhejiang University School of Medicine. All patients provided written informed consent.

2.3 COMPERA 2.0 risk assessment

A four-stratum risk assessment was performed with NYHA FC, 6MWD, and BNP/NT-proBNP cut-offs according to the COMPERA 2.0 algorithm (Table 1) (Boucly, et al., 2021; Hoeper, et al., 2021). In brief, for each component, a score of 1 was assigned for low risk, 2 for intermediate-low, 3 for intermediate-high, and 4 for high risk, then an average score was calculated with a value of < 1.5 classified as low risk, 1.5-2.49 as intermediate-low risk, 2.5-3.49 as intermediate-high risk, and ≥3.5 as high risk (Boucly, et al., 2021; Hoeper, et al., 2021). The overall survival was assessed according to the four strata at baseline before TAVR and at the first follow-up of around 30 days after TAVR. Sankey plot was used to present changes in risk strata before and after TAVR.

Table 1 COMPERA 2.0 risk assessment model

Score	**1**	**2**	**3**	4
NYHA FC	I/II	-	III	IV
6MWD, m	＞440	320-440	165-319	< 165
BNP, ng/L	< 50	50-199	200-800	＞800
Or NT-ProBNP, ng/L	＜300	300-649	650-1100	＞1100
Risk-Strata	**Low**	**Intermediate-low**	**Intermediate-high**	**High**
Average score	＜1.5	1.5-2.49	2.5-3.49	≥3.5

*NYHA FC: New York Heart Association functional class, 6MWD: 6-minute walking distance, BNP: B type natriuretic peptide, NT-ProBNP: N-terminal of pro-B type natriuretic peptide.

unedited

2.4 BNP/NT-proBNP level measurement

Blood samples at the baseline and first follow-up were drawn into EDTA tubes and analyzed immediately in the central laboratory. The level of NT-proBNP (Elecsys proBNP II STAT) was measured by ROCHE COBAS E601 and E411 with a detection range of 10 to 35000 pg/mL. The level of BNP (ADVIA Centaur® BNP) was determined by SIEMENS Atellica with a detection range of 2 to 5000 pg/mL.

2.5 Primary endpoint and follow-up

The primary endpoint of this study was all-cause death. Patients were first followed up at around 30 days, then generally at an interval of half a year. The follow-up period of this project was censored at Dec 25th, 2021. Vital status was ascertained by on-site visits or shared medical system searching or phone calls to the patients or their relatives. Patients who were lost to follow-up were censored at the date of the last contact.

2.6 Statistical Analysis

Continuous data were presented as median and interquartile range (IQR) or mean ± standard deviation (SD) according to the data distribution, and categorical data were presented as number and percentage. Comparisons of continuous variables (e.g., age, 6MWD) were performed by using Student's t-test or Mann-Whitney U test between two groups, and one-way ANOVA or Kruskal-Wallis Test among three or more groups. Comparisons of categorical variables (e.g., sex, NYHA) were performed by using the chi-square test. Survival analysis was conducted using Kaplan-Meier curves and log-rank test. These were done for the entire group and also for subgroups of patients according to the four risk strata at baseline and first follow-up (with survival time starting at first follow-up for later analysis). The effects of risk stratum level on survival were evaluated using the Cox regression model with calculated hazard ratios (HR) and 95% confidence intervals (CI). A *P*-value less than 0.05 was considered statistically significant. All statistical analyses and Fig. plotting were performed using Prism 9.1.0, SPSS Version 28.0, or R 4.0.

3 Results

3.1 Baseline characteristics and follow-up

In total, 327 patients with SAS undergoing TAVR were included, whose baseline characteristics were listed in Table 2. The pulmonary arterial systolic pressure (PASP) of the cohort was 33 (27-43) mmHg at baseline before TAVR. Notably, there was no difference between survivors and non-survivors (Table 2), while PASP was gradually increased along with an increase in the risk stratum level (Table 3). The absolute mortality during a median (IQR) follow-up period of 26 (15 to 47) months was 11.9 % (39/327). The in-hospital mortality, mortality at 30 days, and at 1 year were 1.5% (5/327), 1.8% (6/327), and 3.7% (12/327), respectively. The estimated 3-year and 5-year survival was 84% and 78%, respectively, and the estimated mean (95% CI) survival time was 54.6 (52.7 to 56.5) months (Fig. 2).

unedited

Table 2 Baseline characteristics of the cohort and difference between survivors and non-survivors.

	All	Survivors	Non-survivors	P Value
N, No. (%)	327 (100)	288 (88)	39 (12)	
Age, y	76 (70, 80)	75 (70, 80)	80 (76, 83)	<0.001
Female, No. (%)	142 (43)	130 (45)	12 (31)	0.121
BMI, kg/m^2	23 (21, 25)	23 (21, 25)	22 (19, 25)	0.521
eGFR, mL/min/1.73m^2	79 (62, 89)	80 (64, 89)	70 (52, 83)	0.008
Haemoglobin, g/L	126 (115, 136)	127 (116, 136)	118 (95, 128)	0.004
Albumin, g/L	37.2 (35.0, 39.8)	37.5 (35.3, 40.0)	35.0 (31.8, 37.6)	<0.001
Hypertension, No. (%)	191 (58)	167 (58)	24 (62)	0.731
Diabetes, No. (%)	66 (20)	57 (20)	9 (23)	0.671
Lung disease, No. (%)	125 (38)	108 (38)	17 (44)	0.486
Prior MI, No. (%)	4 (1)	4 (1)	0 (0)	1.000
Prior CABG, No. (%)	2 (0.6)	2 (0.7)	0 (0)	1.000
Prior PCI, No. (%)	41 (13)	37 (13)	4 (10)	0.800
Prior AF or AFL, No. (%)	58 (18)	48 (17)	10 (26)	0.181
Prior stroke, No. (%)	17 (5)	14 (5)	3 (8)	0.439
Moderate-severe MR, No. (%)	65 (20)	50 (17)	15 (39)	0.002
Moderate-severe TR, No. (%)	42 (13)	33 (12)	9 (23)	0.042
Mean PG, mmHg	51 (41, 64)	51 (42, 67)	46 (37, 58)	0.016
Peak TV, cm/s	4.7 (4.2, 5.2)	4.7 (4.2, 5.4)	4.4 (4.2, 5.0)	0.010
Valve area*, cm^2	0.60 (0.47, 0.77)	0.59 (0.46, 0.76)	0.67 (0.53, 0.80)	0.155
Valve types, No. (%)				0.004
BAV	164 (50)	154 (54)	10 (26)	
TAV	159 (49)	131 (46)	28 (72)	
VIV	4 (1)	3 (1)	1 (3)	
STS score, % (%)	4.9 (3.2, 8.7)	4.6 (3.0, 8.0)	8.7 (4.9, 11.0)	<0.001
STS risk, No. (%)				<0.001
Low risk	113 (35)	108 (38)	5 (13)	

unedited

Intermediate risk	117 (46)	107 (37)	10 (26)	
High risk	97 (30)	73 (25)	24 (62)	
Transfemoral, No. (%)	314 (96)	276 (96)	38 (97)	1.000
LVEF, %	59.8 (47.4, 65.5)	60.1 (50.4, 65.5)	55.1 (40.1, 64.7)	0.075
PASP*, mmHg	33 (27, 43)	33 (27, 42)	34 (28, 49)	0.305
Functional class, No. (%)				0.002
I/II	56 (17)	54 (19)	2 (5)	
III	158 (48)	145 (50)	13 (33)	
IV	113 (35)	89 (31)	24 (62)	
6MWD*, m	346 (276, 400)	353 (289, 408)	268 (213, 331)	<0.001
NT-ProBNP*, pg/mL	1863 (528, 4705)	1613 (453, 4045)	3277 (1653, 12053)	<0.001

*Data was presented as number (percentage) or mean (interquartile range). Comparisons were performed using Mann-Whitney U test or chi-square test. 3 patients without Valve area data, 42 patients had no tricuspid regurgitation that PASP were reported as normal without an absolute value, 66 patients were adjudicated with 6MWD less than 165m without an exact value, 8 patients with BNP measurement.

BMI: body mass index, eGFR: estimated glomerular filtration rate, MI: myocardial Infarction, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, AF: atrial fibrillation, ALF: atrial flutter, MR: mitral regurgitation; TR: tricuspid regurgitation; PG: aortic pressure gradient, TV: aortic transvalvular velocity, BAV: bicuspid aortic valve, TAV: tricuspid aortic valve, VIV: valve in valve, STS: Society of Thoracic Surgeons, LVEF: left ventricular ejection fraction, PASP: pulmonary artery systolic pressure, 6MWD: 6-minute walking distance, NT-ProBNP: N-terminal of pro-B type natriuretic peptide

unedited

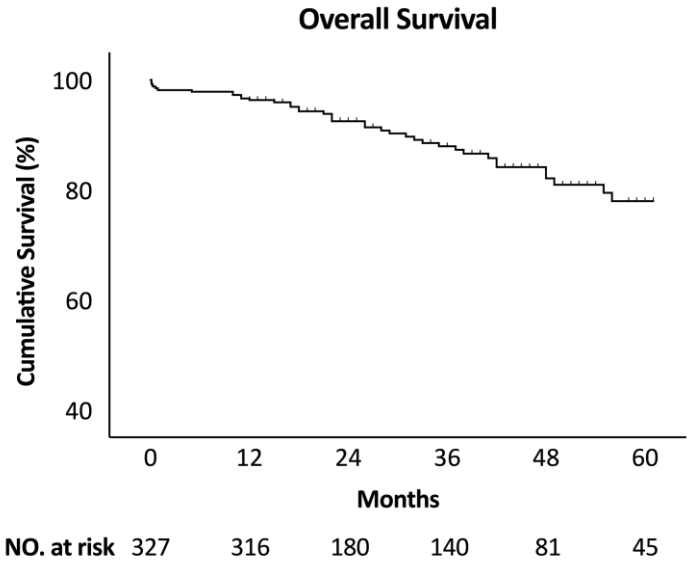

Fig. 2 Overall survival

3.2 COMPERA 2.0 risk strata at baseline before TAVR and survival

According to the COMPERA 2.0 risk strata, 14 (4%) SAS patients were classified as being at low risk, 80 (25%) at intermediate-low risk, 148 (45%) at intermediate-high risk, and 85 (25%) at high risk at baseline before TAVR (Table 3). One-year mortality (0%, 0%, 3%, and 9%, respectively, P = 0.002) and long-term mortality (0%, 3%, 11%, and 25%, respectively, P < 0.001) were significantly increased with the increase in the risk stratum level (Table 3).

The Kaplan-Meier estimated survival rates at 3 and 5 years from baseline before TAVR for the low risk group were both 100%, those for the intermediate-low risk group were both 92%, those for the intermediate-high risk group were 87% and 82%, respectively, and those for the high risk group were 74% and 62%, respectively (P < 0.001, Log Rank, Fig. 3A). A one-step increase in the risk stratum level resulted in an increased risk of death (HR 2.53, 95% CI 1.54 - 4.18, P < 0.001, Table 4), which was independent of age, sex, eGFR, hemoglobin, albumin, and valve type (HR 1.76, 95% CI 1.01 - 3.07, P = 0.047, Table 4), as well as PASP and LVEF (HR 2.47, 95% CI 1.41 – 4.35, P = 0.002, Table 4), but not independent when including STS score (HR 1.50, 95% CI 0.84 – 2.67, P = 0. 169, Table 4). Nevertheless, this was independent of STS score alone (HR 1.99, 95% CI 1.18 - 3.35, P = 0.010, Table 4).

unedited

Table 3 Baseline characteristics and mortality based on COMPRERA 2.0 risk stratification

	Low	Intermediate-low	Intermediate-high	High	P Value
N, No. (%)	14 (4%)	80 (25%)	148 (45%)	85 (26%)	
Age, y	69 (65, 74)	72 (67, 76)	76 (71, 80)	79 (74, 82)	<0.001
Female, No. (%)	6 (43)	37 (46)	61 (41)	38 (45)	0.894
BMI, kg/m²	23 (22, 26)	23 (21, 25)	23 (21, 26)	23 (19, 25)	0.222
eGFR, mL/min/1.73m²	85 (70, 93)	86 (74, 92)	78 (61, 88)	68 (53, 83)	<0.001
Haemoglobin, g/L	136 (131, 147)	127 (119, 135)	127 (115, 138)	121 (106, 131)	<0.001
Albumin, g/L	38.1 (36.6, 40.7)	38.3 (36.9, 41.1)	36.7 (34.7, 39.8)	36.0 (34.2, 38.3)	<0.001
Hypertension, No. (%)	8 (57)	49 (61)	84 (57)	50 (59)	0.930
Diabetes, No. (%)	3 (21)	11 (14)	28 (19)	24 (28)	0.131
Lung disease, No. (%)	2 (14)	32 (40)	58 (39)	33 (39)	0.311
Prior MI, No. (%)	0 (0)	0 (0)	1 (1)	3 (4)	0.153
Prior CABG, No. (%)	0 (0)	0 (0)	2 (1)	0 (0)	0.487
Prior PCI, No. (%)	0 (0)	7 (9)	19 (13)	15 (18)	0.165
Prior AF or AFL, No. (%)	1 (7)	9 (11)	31 (21)	17 (20)	0.193
Prior stroke, No. (%)	0 (0)	3 (4)	6 (4)	8 (9)	0.207
Moderate-severe MR, No. (%)	1 (7)	10 (13)	23 (16)	31 (37)	<0.001
Moderate-severe TR, No. (%)	1 (7)	3 (4)	19 (13)	19 (22)	0.004
Mean PG, mmHg	48 (37, 55)	45 (39, 59)	53 (43, 66)	52 (41, 66)	0.060
Peak TV, cm/s	4.7 (4.3, 5.1)	4.4 (4.1, 5.1)	4.8 (4.4, 5.4)	4.7 (4.2, 5.3)	0.063
Valve area*, cm²	0.59 (0.50, 0.75)	0.73 (0.56, 0.87)	0.58 (0.47, 0.75)	0.54 (0.42, 0.66)	<0.001
Valve types, No. (%)					0.223
BAV	8 (57)	45 (56)	73 (49)	38 (45)	
TAV	5 (36)	34 (43)	74 (49)	47 (55)	
VIV	1 (7)	1 (1)	2 (1)	0 (0)	
STS score, % (%)	2.24 (1.59, 3.39)	3.27 (2.12, 5.09)	4.92 (3.54, 8.53)	8.72 (5.24, 10.97)	0.000
STS risk, No. (%)					<0.001
Low risk	13 (93)	48 (60)	45 (30)	7 (8)	
Intermediate risk	1 (7)	25 (31)	60 (41)	31 (37)	

unedited

High risk	0 (0)	7 (9)	43 (29)	47 (55)	
Transfemoral, No. (%)	14 (100)	75 (94)	145 (98)	80 (94)	0.267
LVEF, %	63.3 (60.8, 69.1)	61.6 (58.3, 68.3)	60.8 (52.2, 66.1)	46.8 (34.6, 59.5)	<0.001
PASP*, mmHg	28.0 (24.0, 32.5)	32.0 (27.0, 36.8)	34.0 (28.0, 42.0)	38.0 (27.0, 54.0)	0.002
Functional class, No. (%)					<0.001
I/II	14 (100)	33 (41)	9 (6)	0 (0)	
III	0 (0)	39 (49)	97 (66)	22 (26)	
IV	0 (0)	8 (10)	42 (28)	63 (74)	
6MWD*, m	427 (389, 501)	399 (335, 445)	340 (276, 377)	222 (160, 293)	0.000
NT-ProBNP*, ng/L	191 (102, 250)	357 (128, 828)	2200 (921, 3782)	5581 (2559, 15582)	0.000
All-cause mortality, No. (%)	0 (0)	2 (3)	16 (11)	21 (25)	<0.001
In-hospital mortality, No. (%)	0 (0)	0 (0)	2 (1)	3 (4)	0.066
30 days mortality, No. (%)	0 (0)	0 (0)	2 (1)	4 (5)	0.026
One-year mortality, No. (%)	0 (0)	0 (0)	4 (3)	8 (9)	0.002

**Data was presented as number (percentage) or mean (interquartile range). Comparisons were performed using Mann-Whitney U test or chi-square test. 3 patients without Valve area data, 42 patients had no tricuspid regurgitation that PASP were reported as normal without an absolute value, 66 patients were adjudicated with 6MWD less than 165m without an exact value, 8 patients with BNP measurement.

BMI: body mass index, eGFR: estimated glomerular filtration rate, MI: myocardial Infarction, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, AF: atrial fibrillation, ALF: atrial flutter, PG: aortic pressure gradient, TV: aortic transvalvular velocity, BAV: bicuspid aortic valve, TAV: tricuspid aortic valve, VIV: valve in valve, STS: Society of Thoracic Surgeons, LVEF: left ventricular ejection fraction, PASP: pulmonary artery systolic pressure, 6MWD: 6-minute walking distance, NT-ProBNP: N-terminal of pro-B type natriuretic peptide.

unedited

Table 4 Cox regression before and after TAVR

Cox regression	Hazard ratio (95% CI)	*P* value
Baseline before TAVR		
Uni-variable	2.53 (1.54 - 4.18)	< 0.001
Multi-variables 1	1.76 (1.01 - 3.07)	0.047
Multi-variables 2	1.50 (0.84 – 2.67)	0.169
Multi-variables 3	1.99 (1.18 - 3.35)	0.010
Multi-variables 4	2.47 (1.41 – 4.35)	0.002
First follow-up after TAVR		
Uni-variable	3.46 (2.03 – 5.89)	0.002
Multi-variables 1	2.65 (1.54 - 4.58)	< 0.001
Multi-variables 2	2.66 (1.54 – 4.60)	< 0.001
Multi-variables 3	3.10 (1.80 – 5.36)	< 0.001

*1. Adjustment for age, sex, eGFR, hemoglobin, albumin, and valve types. 2. Adjustment for age, sex, eGFR, hemoglobin, albumin, and valve types, and STS score. 3. Adjustment for STS score. 4. Adjustment for PASP and LVEF. TAVR: transcatheter aortic valve replacement, PASP: pulmonary artery systolic pressure, LVEF: left ventricular ejection fraction.

Unedited

3.3 COMPERA 2.0 risk strata at first follow-up after TAVR and survival

The median (IQR) time to first follow-up after TAVR was 32 (20-35) days. Six patients died before the first follow-up, leaving a total of 321 patients for the first follow-up analysis. A total of 68 (21%) patients were classified as being at low risk, 174 (54%) at intermediate-low risk, 74 (23%) at intermediate-high risk, and 5 (2%) at high risk. Long-term mortality during follow up was elevated with an increase in the risk stratum level (0/68, 0%; 12/174, 7%; 17/74, 23%; and 4/5, 80%, respectively, $P < 0.001$).

The Kaplan-Meier estimated survival rates at 1, 3 and 5 years from the first follow-up after TAVR for the low-risk group were all 100%; those for the intermediate-low-risk group were 96%, 91% and 80%, respectively; those for the intermediate-high-risk group were 88%, 71% and 71%, respectively; and those at 1 year and 3 years for the high-risk group were 60% and 13%, respectively ($P < 0.001$, Log Rank, Fig. 3B). One increase in the risk stratum level yielded an increased risk of death (HR 3.46, 95% CI 2.03 - 5.89, $P = 0.002$, Table 4), which was independent of the mentioned baseline confounders (HR 2.65, 95% CI 1.54 – 4.58, $P < 0.001$, Table 4), even when including baseline STS score (HR 2.66, 95% CI 1.54 – 4.60, $P < 0.001$, Table 4), and it was independent of baseline STS score alone (HR 3.10, 95% CI 1.80 – 5.36, $P < 0.001$, Table 4).

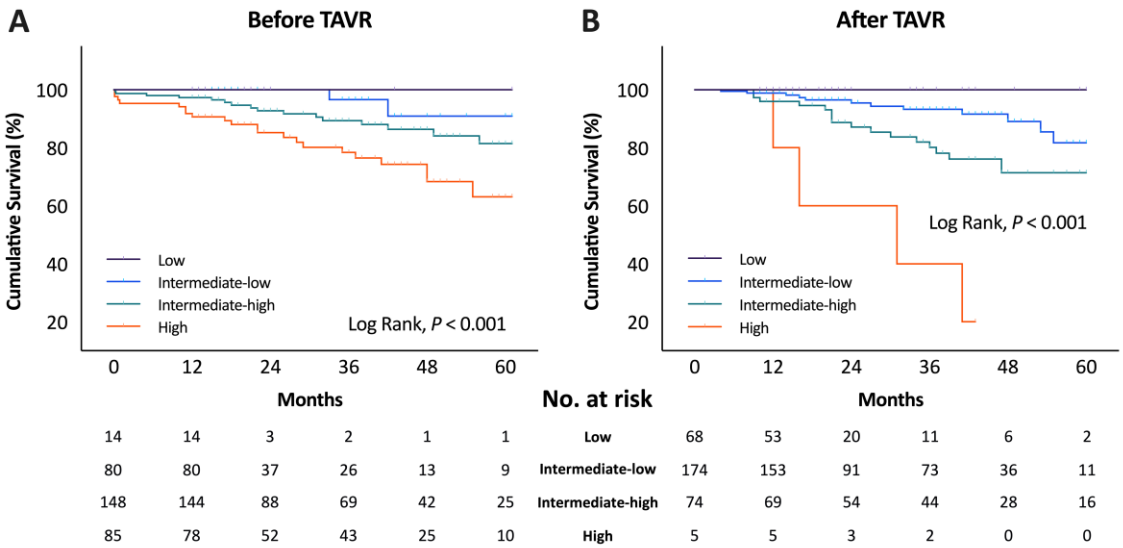

Fig. 3 Survival based on COMPERA 2.0

3.4 Changes in risk stratum from baseline to first follow-up and survival

Changes in the risk strata were shown by a Sankey plot (N = 321, Fig. 4). In patients with low risk at baseline, 64% (9/14) remained in the low risk stratum and 36% (5/14) switched to intermediate-low risk after TAVR. In patients with intermediate-low risk at baseline, 45% (36/80) remained in the intermediate-low risk stratum and 49% (39/80) improved to the low-risk one, while 6% (5/80) worsened to intermediate-high-risk. Among the patients with intermediate-high risk at baseline, 14% (20/146) improved to being at low risk and 65% (95/146) at intermediate-low risk, while 20% (29/146) remained at intermediate-high risk, 1% (2/146) worsened to high risk and suffered from death during follow up, and another 2 patients died before the first follow-up. For patients with high risk at baseline, 47% (38/81) improved to being at intermediate-low risk and 49% (40/81) to intermediate-high risk, while 4% (3/81) remained at high risk and 2 of them suffered from death during follow up. Another 4 patients died before the first follow-up. Altogether, changes in the risk strata before and after TAVR indicate that TAVR is an effective intervention for patients with SAS.

unedited

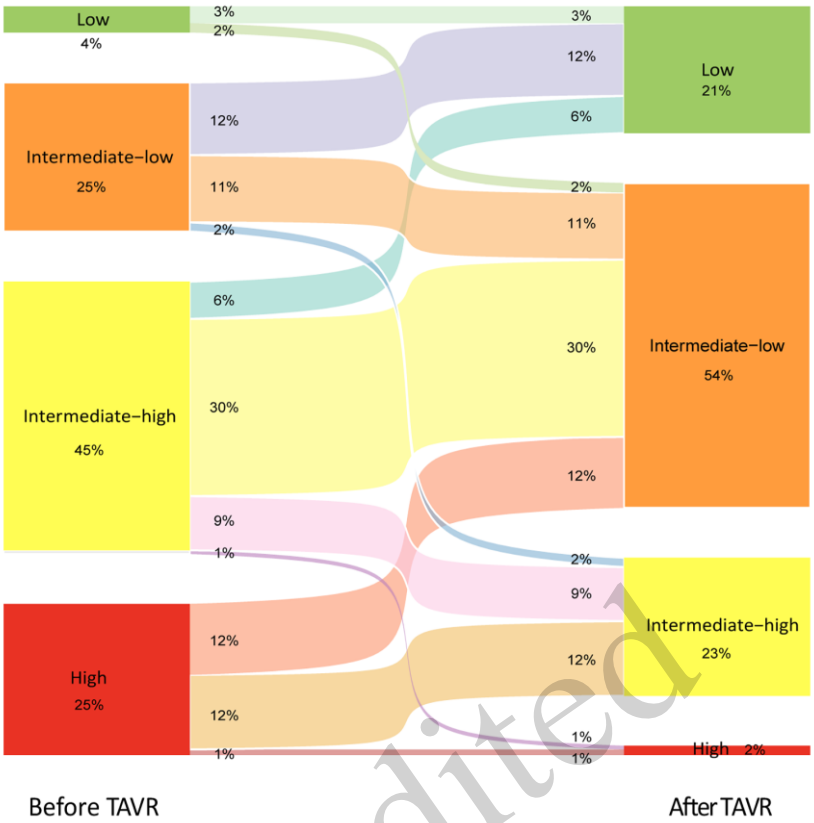

Fig. 4 Risk change Sankey plot

unedited

4 Discussion

In the current study, we investigated the use of COMPERA 2.0 in predicting the survival of patients with SAS undergoing TAVR. The main findings indicate that: COMPERA 2.0 risk assessment was able to predict long-term all-cause mortality in patients with SAS undergoing TAVR, with a higher risk stratum level associated with increased risk of death. This confirms that COMPERA 2.0 might be useful in patients at risk for PH associated with left heart disease or group 2 PH or postcapillary PH.

3.1 Prediction of long-term survival

The current study demonstrated the capability of COMPERA 2.0 to predict long-term mortality in patients with SAS undergoing TAVR. COMPERA 2.0 was designed to assess the mortality in group 1 PH, i.e., pulmonary arterial hypertension (PAH), from a reduction of a complex risk assessment algorithm (Galie et al., 2016), and incorporated FC, 6MWD and BNP/NT-proBNP in the final version since these parameters at follow-up are independent prognostic predictors (Hoeper et al., 2017). All three parameters are commonly used in clinical practice for follow up, not only in PAH but also heart failure or other pulmonary diseases. Indeed, each of them showed significance in the assessment of SAS patients undergoing TAVR. Although the cutoff for each parameter was not adjusted to fit the optimal prognostic values, COMPERA 2.0 still performed well. Furthermore, the 1-year mortality and estimated 5-years mortality were lower in our cohort when compared to other cohorts (Mack et al., 2015; Thyregod et al., 2019; Makkar et al., 2020), which might be due to the younger age and low STS score of our cohort. Nevertheless, COMPERA 2.0 could still clearly discriminate patients with a significant separation of the survival curves before and after TAVR in such a low-mortality population. Moreover, COMPERA 2.0 is independent of other prognostic factors, including age, advance

chronic kidney disease, hemoglobin, albumin, and valve type. Although it is not independent when including the STS score, STS score itself, including a long list of parameters, it is much easier to use and is more time and resource effective. Taken together, COMPERA 2.0 is a simple and feasible risk assessment calculator for the survival prediction of patients with SAS undergoing TAVR.

3.2 Potential use in PH-LHD

PH-LHD is the most common type of PH, with no pulmonary vasodilators currently recommended for use in those patients (Simonneau et al., 2019; Vachiery et al., 2019). In a multicenter, double-blind, randomized clinical trial, SIOVAC investigators found no benefit of sildenafil in patients with persistent PH after correction of the underlying valvular heart disease (Bermejo et al., 2018). The limitations of the SIOVAC study were the heterogeneity in the types of valvular heart disease (low proportion of isolated aortic valve replacement) and that most patients showed combined pre- and post-capillary PH (Bermejo, et al., 2018). PH confirmed by right heart catheterization is often present in patients with SAS before and after TAVR; 10%-20% of these patients showed pre-capillary PH that could hardly be reversed after TAVR. (O'sullivan et al., 2015; Schewel, et al., 2019) These patients might potentially benefit from pulmonary vasodilators and need further clinical trials. For patients with residual isolated post-capillary PH or combined pre- and post-capillary PH after TAVR, the potential causes should be investigated, such as insufficient guideline-directed medical therapy for heart failure or commitment mitral stenosis. In the current study, PASP was slightly increased in the whole population, while it was significantly increased in high-risk patients, indicating the highly probability of PH as a consequence of SAS in these patients. The significantly increased PASP in high-risk patients with poor mortality observed in this study is consistent with previous studies, that is, PH is an independent predictor of outcomes in patients with SAS undergoing TAVR (O'sullivan, et al., 2015; Schewel, et al., 2019). Indirectly, an improved risk stratum after TAVR might indicate the potential mitigation or reversal of PH in high-risk patients, while for patients who failed to improve after TAVR, right heart catheterization assessment or CardioMEMS implantation (Radhoe et al., 2021) might be useful to monitor hemodynamic changes in response to TAVR and medical therapies, so that the modifiable factors contributing to the risk of death can be differentiated and the outcomes can be optimized.

unedited

5 Conclusion

The COMPERA 2.0 algorithm, a combination assessment of NYHA FC, 6MWD and BNP/NT-proBNP, is a feasible tool for patients with SAS undergoing TAVR who are at risk of PH-LHD. Further validation is warranted in patients with confirmed post-capillary PH by right heart catheterization.

Data availability statement

Data sharing requests will be considered from researchers who submit a relevant study protocol and an appropriate statistical plan.

Acknowledgments

This project was supported by National Key R&D Program of China (2019YFA0110400 and 2016YFC13010204 for Jianan Wang), National Natural Science Foundation of China (81870292 for Jianan Wang, 81570233 and 81770252 for Xianbao Liu, 82100060 for Zongye Cai), China Postdoctoral Science Foundation (2020M680079 and 2021T140598 for Zongye Cai), Zhejiang Province Science and Technology Department Key R&D Program (2021C03097 and 2022C03063 for Jianan Wang), and Natural Science Foundation of Zhejiang Province of China (LQ21H020005 for Yuchao Guo).

Author contributions

Zongye Cai, Xinrui Qi, and Xianbao Liu designed the study. Zongye Cai and Xinrui Qi performed the data analysis and wrote the first manuscript of this study. Zongye Cai and Ming Zhong performed the Sankey-plot. Cheng Li collected the study

data. Jian'an Wang contributed to the study design, reviewing and checking the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Zongye Cai, Xinrui Qi, Dao Zhou, Hanyi Dai, Abuduwufuer Yidilisi, Ming Zhong, Lin Deng, Yuchao Guo, Jiaqi Fan, Qifeng Zhu, Yuxin He, Cheng Li, Xianbao Liu, and Jianan Wang declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration. The ethical approval institution is the Second Affiliated Hospital of Zhejiang University School of Medicine (2014-159 & 2016-038). Informed consent was obtained from the patient for being included in the report.

References

Bermejo J, Yotti R, Garcia-Orta R, et al., 2018. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: A multicenter, double-blind, randomized clinical trial. *Eur Heart J*, 39(15):1255-1264. https://doi.org/10.1093/eurheartj/ehx700

Boucly A, Weatherald J, Savale L, et al., 2021. External validation of a refined 4-strata risk assessment score from the french pulmonary hypertension registry. *Eur Respir J*, https://doi.org/10.1183/13993003.02419-2021

Galie N, Humbert M, Vachiery JL, et al., 2016. 2015 esc/ers guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (esc) and the european respiratory society (ers): Endorsed by: Association for european paediatric and congenital cardiology (aepc), international society for heart and lung transplantation (ishlt). *Eur Heart J*, 37(1):67-119. https://doi.org/10.1093/eurheartj/ehv317

Hadziselimovic E, Greve AM, Sajadieh A, et al., 2022. Association of annual n-terminal pro-brain natriuretic peptide measurements with clinical events in patients with asymptomatic nonsevere aortic stenosis: A post hoc substudy of the seas trial. *JAMA Cardiol*, 7(4):435-444. https://doi.org/10.1001/jamacardio.2021.5916

Hoeper MM, Kramer T, Pan Z, et al., 2017. Mortality in pulmonary arterial hypertension: Prediction by the 2015 european pulmonary hypertension guidelines risk stratification model. *Eur Respir J*, 50(2) https://doi.org/10.1183/13993003.00740-2017

Hoeper MM, Pausch C, Olsson KM, et al., 2021. Compera 2.0: A refined 4-strata risk assessment model for pulmonary arterial hypertension. *Eur Respir J*, https://doi.org/10.1183/13993003.02311-2021

Humbert M, Kovacs G, Hoeper MM, et al., 2022a. 2022 esc/ers guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*, https://doi.org/10.1183/13993003.00879-2022

Humbert M, Kovacs G, Hoeper MM, et al., 2022b. 2022 esc/ers guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*, 43(38):3618-3731. https://doi.org/10.1093/eurheartj/ehac237

Mack MJ, Leon MB, Smith CR, et al., 2015. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (partner 1): A randomised controlled trial. *Lancet*, 385(9986):2477-2484. https://doi.org/10.1016/S0140-6736(15)60308-7

Maeder MT, Weber L, Rickli H, 2022. Pulmonary hypertension in aortic valve stenosis. *Trends Cardiovasc Med*, 32(2):73-81. https://doi.org/10.1016/j.tcm.2020.12.005

Makkar RR, Thourani VH, Mack MJ, et al., 2020. Five-year outcomes of transcatheter or surgical aortic-valve replacement. *N Engl J Med*, 382(9):799-809. https://doi.org/10.1056/NEJMoa1910555

Miyamoto J, Ohno Y, Kamioka N, et al., 2022. Impact of periprocedural pulmonary hypertension on outcomes after transcatheter aortic valve replacement. *J Am Coll Cardiol*, 80(17):1601-1613. https://doi.org/10.1016/j.jacc.2022.08.757

O'leary JM, Clavel MA, Chen S, et al., 2020. Association of natriuretic peptide levels after transcatheter aortic valve replacement with subsequent clinical outcomes. *JAMA Cardiol*, 5(10):1113-1123. https://doi.org/10.1001/jamacardio.2020.2614

O'sullivan CJ, Wenaweser P, Ceylan O, et al., 2015. Effect of pulmonary hypertension hemodynamic presentation on clinical outcomes in patients with severe symptomatic aortic valve stenosis undergoing transcatheter aortic valve implantation: Insights from the new proposed pulmonary hypertension classification. *Circ Cardiovasc Interv*, 8(7):e002358. https://doi.org/10.1161/CIRCINTERVENTIONS.114.002358

Otto CM, Nishimura RA, Bonow RO, et al., 2021. 2020 acc/aha guideline for the management of patients with valvular heart disease: A report of the american college of cardiology/american heart association joint committee on clinical practice

Unedited

guidelines. *Circulation*, 143(5):e72-e227. https://doi.org/10.1161/CIR.0000000000000923

Radhoe SP, Veenis JF, Van Mieghem NM, et al., 2021. The effect of transcatheter aortic valve implantation on pulmonary artery pressures in a patient suffering from chronic heart failure: A case report. *Eur Heart J Case Rep*, 5(4):ytab112. https://doi.org/10.1093/ehjcr/ytab112

Sato K, Kumar A, Krishnaswamy A, et al., 2019. B-type natriuretic peptide is associated with remodeling and exercise capacity after transcatheter aortic valve replacement for aortic stenosis. *Clin Cardiol*, 42(2):270-276. https://doi.org/10.1002/clc.23138

Schewel J, Schmidt T, Kuck KH, et al., 2019. Impact of pulmonary hypertension hemodynamic status on long-term outcome after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*, 12(21):2155-2168. https://doi.org/10.1016/j.jcin.2019.08.031

Sigvardsen PE, Larsen LH, Carstensen HG, et al., 2017. Six-minute walking test and long term prognosis in patients with asymptomatic aortic valve stenosis. *Int J Cardiol*, 249:334-339. https://doi.org/10.1016/j.ijcard.2017.09.183

Simonneau G, Montani D, Celermajer DS, et al., 2019. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*, 53(1) https://doi.org/10.1183/13993003.01913-2018

Stubbs H, Lua S, Brewis M, et al., 2022. Compera 2.0 risk stratification in medically managed chronic thromboembolic pulmonary hypertension. *Eur Respir J*, 60(3) https://doi.org/10.1183/13993003.00313-2022

Thyregod HGH, Ihlemann N, Jorgensen TH, et al., 2019. Five-year clinical and echocardiographic outcomes from the nordic aortic valve intervention (notion) randomized clinical trial in lower surgical risk patients. *Circulation*, https://doi.org/10.1161/CIRCULATIONAHA.118.036606

Tuttle MK, Kiaii B, Van Mieghem NM, et al., 2022. Functional status after transcatheter and surgical aortic valve replacement: 2-year analysis from the surtavi trial. *JACC Cardiovasc Interv*, 15(7):728-738. https://doi.org/10.1016/j.jcin.2022.01.284

Vachiery JL, Tedford RJ, Rosenkranz S, et al., 2019. Pulmonary hypertension due to left heart disease. *Eur Respir J*, 53(1) https://doi.org/10.1183/13993003.01897-2018

Vahanian A, Beyersdorf F, Praz F, et al., 2022. 2021 esc/eacts guidelines for the management of valvular heart disease. *Eur Heart J*, 43(7):561-632. https://doi.org/10.1093/eurheartj/ehab395

Writing Committee M, Otto CM, Nishimura RA, et al., 2021. 2020 acc/aha guideline for the management of patients with valvular heart disease: A report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *J Am Coll Cardiol*, 77(4):e25-e197. https://doi.org/10.1016/j.jacc.2020.11.018

Xu H, Liu Q, Cao K, et al., 2022. Distribution, characteristics, and management of older patients with valvular heart disease in china. *JACC: Asia*, 2(3):354-365. https://doi.org/10.1016/j.jacasi.2021.11.013

unedited