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

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Abstract: COMPERA 2.0 risk stratification has been demonstrated to be useful in patients with precapillary pulmonary hypertension (PH). However, its suitability for patients at risk for post-capillary PH or PH associated with left heart disease (PH-LHD) is unclear. To investigate the use of COMPERA 2.0 in patients with severe aortic stenosis (SAS) undergoing transcatheter aortic valve replacement (TAVR), who are at risk for post-capillary PH, a total of 327 eligible SAS patients undergoing TAVR at our institution between September 2015 and November 2020 were included in the study. Patients were classified into four strata before and after TAVR 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 hazards regression model. 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 (1 mmHg=0.133 kPa) 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 $P<0.001$); each 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 (eGFR), hemoglobin, albumin, and valve type (HR 1.76, 95% CI 1.01–3.07, $P=0.047$). Similar results were observed at 30 d after TAVR. COMPERA 2.0 can serve as a useful tool for risk stratification in patients with SAS undergoing TAVR, indicating its potential application in the management of 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 classification (FC), 6-minute walking distance (6MWD), and B type natriuretic peptide (BNP) or N-terminal fragment of pro-BNP (NT-proBNP). COMPERA 2.0 has been validated for the prediction of outcomes for patients with precapillary pulmonary hypertension (PH), i.e., group 1 PH and group 4 PH (Boucly et al., 2022; Hoeper et al., 2022; Stubbs et al., 2022; Humbert et al., 2023). However, its applicability in patients at risk for post-capillary PH, 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

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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 Society of Thoracic Surgeons (STS) risk score constitutes the most important risk assessment tool for SAS (Otto et al., 2021; Writing Committee Members 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 that 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, and BNP or NT-proBNP levels are available at baseline before TAVR and at the first follow-up around 30 d after TAVR. Patients who could not perform 6MWD due to the severity of SAS were included and recorded as 6MWD< 165 m, while they were excluded if they had a stroke, disability, or other unknown disease. The flow diagram of the study is shown in Fig. 1.

2.2 COMPERA 2.0 risk assessment

A 4-stratum risk assessment was performed with NYHA FC, 6MWD, and BNP/NT-proBNP cut-offs according to the COMPERA 2.0 algorithm (Table 1). In brief, for each component, a score of 1 was assigned for low risk, 2 for intermediate–low risk, 3 for intermediate–high risk, and 4 for high risk. An average score was calculated with a value of <1.50 classified as low risk, 1.50–2.49 as intermediate–low, 2.50–3.49 as intermediate–high, and ⩾3.50 as high (Boucly et al., 2022; Hoeper et al., 2022). The overall survival was assessed according to the four strata at baseline before TAVR and at the first follow-up of around 30 d after TAVR. A Sankey plot was used to present the changes in risk strata before and after TAVR.

2.3 BNP/NT-proBNP level measurement

Blood samples at the baseline and first follow-up were drawn into ethylenediaminetetraacetic acid (EDTA) tubes and analyzed immediately in the central laboratory. The level of NT-proBNP was measured by the Elecsys proBNP II STAT assay using ROCHE COBAS E601 and E411 (Mannheim, Germany) with a detection range

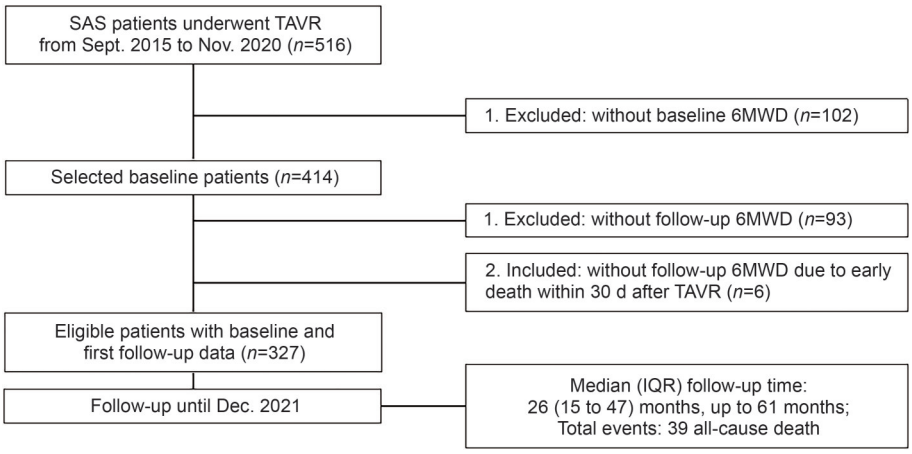

Fig.1 Study flow diagram. SAS: severe aortic stenosis; TAVR: transcatheter aortic valve replacement; 6MWD: 6-minute walking distance; IQR: interquartile range.

Table 1 COMPERA 2.0 risk assessment model

Score	NYHA FC	6MWD (m)	BNP (ng/L)	NT-proBNP (ng/L)	Risk strata	Average score
1	I/II	>440	<50	<300	Low	<1.50
2		320–440	50–199	300–649	Intermediate–low	1.50–2.49
3	III	165–319	200–800	650–1100	Intermediate–high	2.50–3.49
4	IV	<165	>800	>1100	High	⩾3.50

NYHA FC: New York Heart Association functional classification; 6MWD: 6-minute walking distance; BNP: B type natriuretic peptide; NT-proBNP: N-terminal fragment of pro-BNP.

of 10 to 35 000 pg/mL. The level of BNP was determined by the Atellica® IM BNP assay using the Atellica® IM Analyzer (Massachusetts, USA) with a detection range of 2 to 5000 pg/mL.

2.4 Primary endpoint and follow-up

The primary endpoint of this study was all-cause death. Patients were first followed up at around 30 d and then generally at intervals of half a year. The follow-up period of this project was censored at Dec. 25, 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.

2.5 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 using Student's *t*-test or Mann-Whitney *U* test between two groups, and one-way analysis of variance (ANOVA) or Kruskal-Wallis test among three or more groups. Comparisons of categorical variables (e.g., sex, NYHA FC) were performed using the Chi-square test. Survival analysis was conducted using Kaplan-Meier curves and the log-rank test. These were done for the entire group and 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 the risk stratum level on survival were evaluated using the Cox proportional hazards regression model with calculated hazard ratio (HR) and 95% confidence interval (CI). A *P*-value less than 0.05 was considered statistically significant. All statistical analyses and figure 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 (1 mmHg= 0.133 kPa) at baseline before TAVR. Notably, there was no difference between the 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 (15–47) months was 11.9% (39/327). The in-hospital, 30-d, and at 1-year mortality rates were 1.5% (5/327), 1.8% (6/327), and 3.7% (12/327), respectively. The estimated 3-year and 5-year survival rates were 84% and 78%, respectively, and the estimated mean (95% CI) survival time was 54.6 (52.7–56.5) months (Fig. 2).

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 (26%) 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 an increase in the risk stratum level (Table 3).

The Kaplan-Meier estimated survival rates at 3-year and 5-year 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;

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

Characteristics	All	Survivors	Non-survivors	*P* value
n (%)	327 (100)	288 (88)	39 (12)	
Age (years)	76 (70, 80)	75 (70, 80)	80 (76, 83)	<0.001
Female (*n* (%))	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 per 1.73 m^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 (*n* (%))	191 (58)	167 (58)	24 (62)	0.731
Diabetes (*n* (%))	66 (20)	57 (20)	9 (23)	0.671
Lung disease (*n* (%))	125 (38)	108 (38)	17 (44)	0.486
Prior MI (*n* (%))	4 (1)	4 (1)	0	1.000
Prior CABG (*n* (%))	2 (0.6)	2 (0.7)	0	1.000
Prior PCI (*n* (%))	41 (13)	37 (13)	4 (10)	0.800
Prior AF or AFL (*n* (%))	58 (18)	48 (17)	10 (26)	0.181
Prior stroke (*n* (%))	17 (5)	14 (5)	3 (8)	0.439
Moderate–severe MR (*n* (%))	65 (20)	50 (17)	15 (39)	0.002
Moderate–severe TR (*n* (%))	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 (*n* (%))				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 (*n* (%))				<0.001
Low	113 (35)	108 (38)	5 (13)	
Intermediate	117 (46)	107 (37)	10 (26)	
High	97 (30)	73 (25)	24 (62)	
Transfemoral (*n* (%))	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 (*n* (%))				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, 12 053)	<0.001

Data were presented as number (percentage) or mean (interquartile range). Comparisons were performed using the Mann-Whitney *U* test or the Chi-square test. Three patients had no valve area data, 42 patients had no tricuspid regurgitation in which PASP was reported as normal without an absolute value, 66 patients were adjudicated with 6MWD less than 165 m without an exact value, and 8 patients had B type natriuretic peptide (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 arterial systolic pressure; 6MWD: 6-minute walking distance; NT-proBNP: N-terminal fragment of pro-BNP. 1 mmHg=0.133 kPa.

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

Characteristics	Low	Intermediate–low	Intermediate–high	High	*P* value
n (%)	14 (4)	80 (25)	148 (45)	85 (26)	
Age (years)	69 (65, 74)	72 (67, 76)	76 (71, 80)	79 (74, 82)	<0.001
Female (*n* (%))	6 (43)	37 (46)	61 (41)	38 (45)	0.894
BMI (kg/m^2)	23 (22, 26)	23 (21, 25)	23 (21, 26)	23 (19, 25)	0.222
eGFR (mL/min per 1.73m^2)	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 (*n* (%))	8 (57)	49 (61)	84 (57)	50 (59)	0.930
Diabetes (*n* (%))	3 (21)	11 (14)	28 (19)	24 (28)	0.131
Lung disease (*n* (%))	2 (14)	32 (40)	58 (39)	33 (39)	0.311
Prior MI (*n* (%))	0	0	1 (1)	3 (4)	0.153
Prior CABG (*n* (%))	0	0	2 (1)	0	0.487
Prior PCI (*n* (%))	0	7 (9)	19 (13)	15 (18)	0.165
Prior AF or AFL (*n* (%))	1 (7)	9 (11)	31 (21)	17 (20)	0.193
Prior stroke (*n* (%))	0	3 (4)	6 (4)	8 (9)	0.207
Moderate–severe MR (*n* (%))	1 (7)	10 (13)	23 (16)	31 (37)	<0.001
Moderate–severe TR (*n* (%))	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 (cm^2)	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 (*n* (%))					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	
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)	<0.001
STS risk (*n* (%))					<0.001
Low	13 (93)	48 (60)	45 (30)	7 (8)	
Intermediate	1 (7)	25 (31)	60 (41)	31 (37)	
High	0	7 (9)	43 (29)	47 (55)	
Transfemoral (*n* (%))	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 (*n* (%))					<0.001
I/II	14 (100)	33 (41)	9 (6)	0	
III	0	39 (49)	97 (66)	22 (26)	
IV	0	8 (10)	42 (28)	63 (74)	
6MWD (m)	427 (389, 501)	399 (335, 445)	340 (276, 377)	222 (160, 293)	<0.001
NT-proBNP (ng/L)	191 (102, 250)	357 (128, 828)	2200 (921, 3782)	5581 (2559, 15582)	<0.001
All-cause mortality (*n* (%))	0	2 (3)	16 (11)	21 (25)	<0.001
In-hospital mortality (*n* (%))	0	0	2 (1)	3 (4)	0.066
30-d mortality (*n* (%))	0	0	2 (1)	4 (5)	0.026
One-year mortality (*n* (%))	0	0	4 (3)	8 (9)	0.002

Data were presented as number (percentage) or mean (interquartile range). Comparisons were performed using the Mann-Whitney *U* test or the Chi-square test. Three patients had no valve area data, 42 patients had no tricuspid regurgitation in which PASP was reported as normal without an absolute value, 66 patients were adjudicated with 6MWD less than 165 m without an exact value, and 8 patients had B type natriuretic peptide (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 arterial systolic pressure; 6MWD: 6-minute walking distance; NT-proBNP: N-terminal fragment of pro-BNP. 1 mmHg=0.133 kPa.

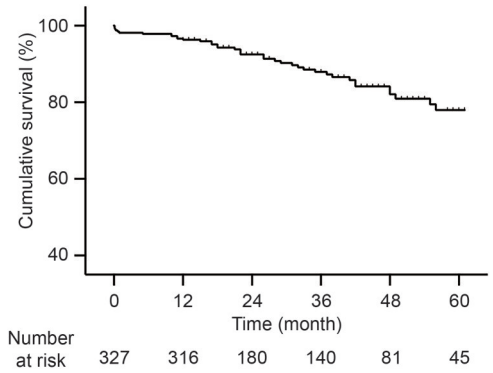

Fig. 2 Overall survival.

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, estimated glomerular filtration rate (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 left ventricular ejection fraction (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).

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) d. 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).

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

Changes in the risk strata were shown by a Sankey plot (n=321; Fig. 4). Among 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

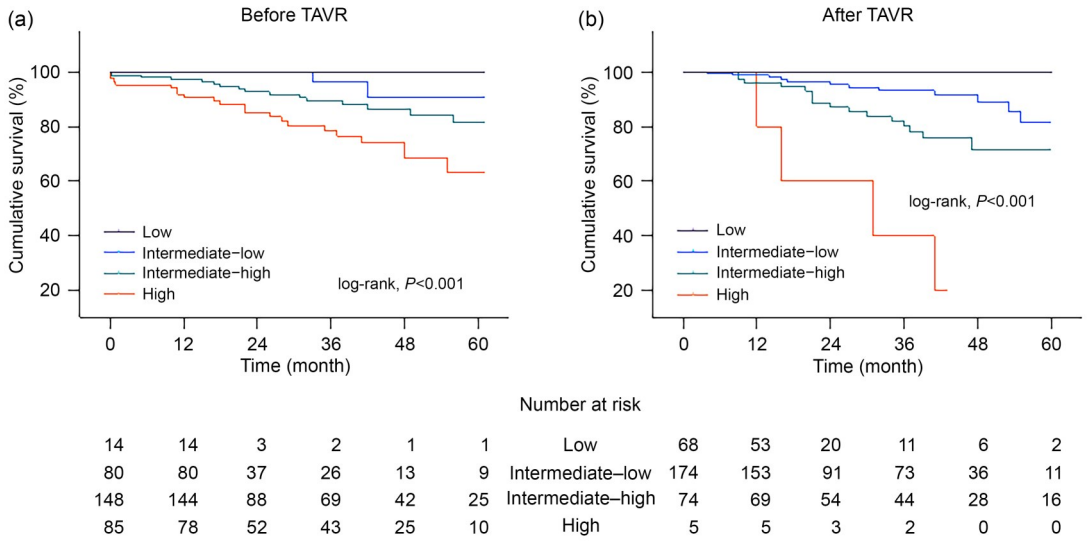

Fig. 3 Survival based on COMPERA 2.0 before (a) and after (b) transcatheter aortic valve replacement (TAVR).

Table 4 Cox regression before and after transcatheter aortic valve replacement (TAVR)

Cox regression	HR (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

Multi-variables: 1, Adjustment for age, sex, estimated glomerular filtration rate (eGFR), hemoglobin, albumin, and valve types; 2, Adjustment for age, sex, eGFR, hemoglobin, albumin, valve types, and the Society of Thoracic Surgeons (STS) score; 3, Adjustment for STS score; 4, Adjustment for pulmonary arterial systolic pressure (PASP) and left ventricular ejection fraction (LVEF). HR: hazard ratio; CI: confidential interval.

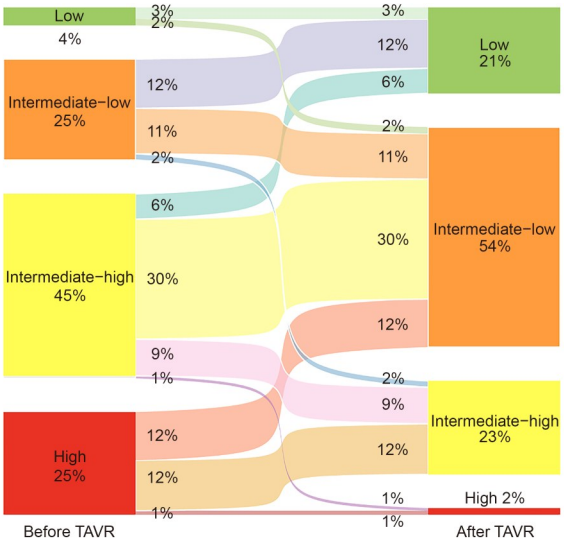

Fig. 4 Risk changes in Sankey plot. TAVR: transcatheter aortic valve replacement.

baseline, 45% (36/80) remained in the intermediate–low-risk stratum, 49% (39/80) improved to the low-risk one, and 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, 65% (95/146) at intermediate–low risk, 20% (29/146) remained at intermediate–high risk, and 1% (2/146) worsened to high risk and suffered from death during follow-up. Additionally, two patients died before the first follow-up. For patients with high risk at baseline, 47% (38/81) improved to being at intermediate–low risk, 49% (40/81) to intermediate–high risk, and 4% (3/81) remained at high risk and two of them suffered from death during follow-up. Another four 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.

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 can 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-LHD, group 2 PH, or post-capillary PH.

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

4.2 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; Vachiéry et al., 2019). In a multicenter, double-blind, randomized clinical trial, sildenafil for secondary pulmonary hypertension due to valvular disease (SIOVAC, NCT00862043) 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 committed 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 high 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 Cardio Micro-Electro-Mechanical System (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.

5 Conclusions

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.

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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. Dao ZHOU, Hanyi DAI, Abuduwufuer YIDILISI, Lin DENG, Yuchao GUO, Jiaqi FAN, Qifeng ZHU, and Yuxin HE worked with interpretating the study data and results. Jian'an WANG contributed to the study design and 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

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All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethical approval institution is The Second Affiliated Hospital of Zhejiang University School of Medicine (Nos. 2014-159 and 2016-038). Informed consent was obtained from all patients being included in the study.

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