

1 Supplemental material

Figure legends

Supplementary Figure 1: Right ventricular to pulmonary artery coupling in accordance with cluster assignment.

A) Scatter plot relating preprocedural TAPSE to sPAP levels. *R*: correlation coefficient by Pearson correlating TAPSE and sPAP levels. Colored line: linear regression line. Colored area: 95% confidence interval.

B) Bee swarm plot comparing preprocedural TAPSE/sPAP ratios in accordance with cluster assignment. sPAP: systolic pulmonary artery pressure (as assessed by echocardiography); TAPSE: tricuspid annular plane systolic excursion.

Supplementary Figure 2: Comparison of time from TAVR to follow-up echocardiography among clusters.

Supplementary Figure 3: Imputation of missing values. In total, 4.64% of the 2928 data points related to the enrolled 366 patients had missing values for those 8 variables required for allocating patients according to the modified sequential staging classification (Supplementary Figure 3.A), and the largest proportion of missing values was found for measurements of right midventricular diameter (10.9% of values missing) (Supplementary Figure 3.B). After imputing missing values, initially observed and later imputed values for right midventricular diameter displayed a similar distribution (29.5 ± 6.60 [95% CI: 28.8-30.2] mm vs. 27.9 ± 2.10 [95% CI: 27.2-28.6] mm, *p*-value: 0.1859) (Supplementary Figure 3.C-D).

A) Illustration of missing and observed values.

B) Bar plot showing the proportion of missing values per variable.

C) Density plot showing the distribution of right midventricular diameter as observed and imputed by a random forest algorithm.

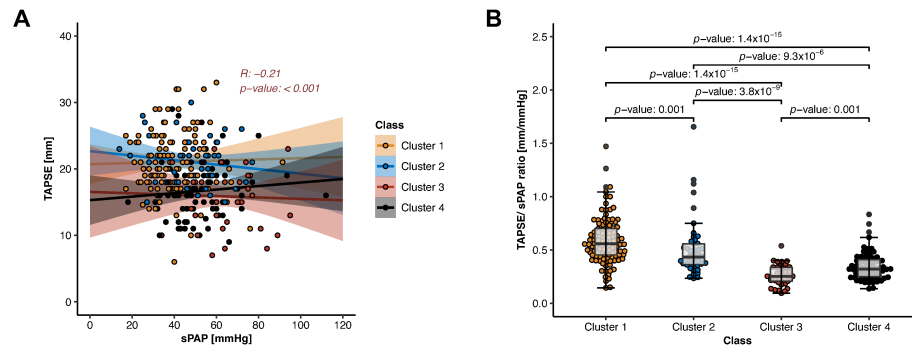
Supplemental material

2

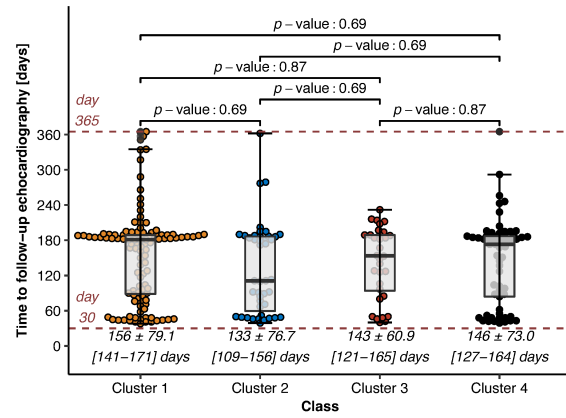
D) Bee swarm plot comparing right midventricular diameter as observed and imputed. Independent-samples Wilcoxon test was used for comparison.

LA area: left atrial area; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; mPAP: mean pulmonary artery pressure; MR: mitral regurgitation; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

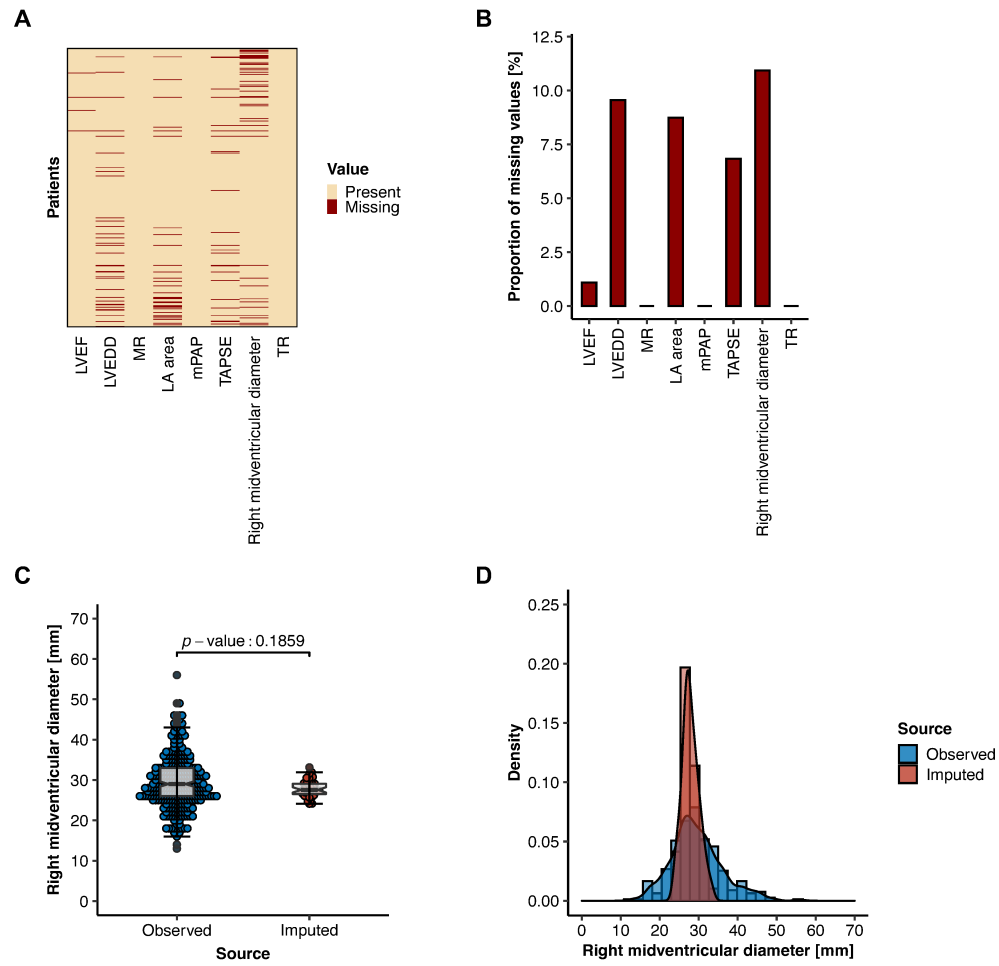
Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3



Supplementary Table 1: R packages employed in this study.

<i>Amelia</i>	<i>mlbench</i>
<i>base</i>	<i>purrr</i>
<i>circlize</i>	<i>randomForest</i>
<i>datasets</i>	<i>rcompanion</i>
<i>dplyr</i>	<i>Rcpp</i>
<i>forcats</i>	<i>readr</i>
<i>foreach</i>	<i>readxl</i>
<i>gcookbook</i>	<i>reshape2</i>
<i>ggbeeswarm</i>	<i>stats</i>
<i>ggExtra</i>	<i>stringr</i>
<i>ggplot2</i>	<i>survival</i>
<i>ggpubr</i>	<i>survminer</i>
<i>graphics</i>	<i>tibble</i>
<i>grDevices</i>	<i>tidyr</i>
<i>iterators</i>	<i>tidyverse</i>
<i>itertools</i>	<i>utils</i>
<i>methods</i>	<i>writexl</i>
<i>missForest</i>	

Supplemental material

7

Supplementary Table 2: Demographic and clinical characteristics in accordance with the modified staging classification from Généreux.

	Stage 0 (n = 76)	Stage 1 (n = 54)	Stage 2 (n = 110)	Stage 3 (n = 126)	p-value
Age, mean ± SD [95% CI], years	78.9 ± 6.11 [77.5-80.3]	81.0 ± 5.77 [79.4-82.6]	79.4 ± 6.42 [78.2-80.6]	80.1 ± 7.75 [78.7-81.4]	0.1075
Women, No. (%)	36 (47.4%)	15 (27.8%)	47 (42.7%)	48 (38.1%)	0.1319
BMI mean ± SD [95% CI], kg/m ²	26.0 ± 4.38 [25.0-27.0]	26.6 ± 4.26 [25.4-27.7]	27.4 ± 3.77 [26.6-28.1]	26.9 ± 5.04 [26.0-27.7]	0.0751
Arterial hypertension, No. (%)	62 (81.6%) ^(2,3)	48 (88.9%)	105 (95.5%) ⁽⁰⁾	119 (94.4%) ⁽⁰⁾	0.0117
Diabetes mellitus, No. (%)	20 (26.3%)	17 (31.5%)	29 (26.4%)	35 (27.8%)	0.9135
NYHA functional class, mean ± SD [95% CI]	2.34 ± 0.740 [2.17-2.51] ^(2,3)	2.52 ± 0.693 [2.33-2.71] ⁽³⁾	2.67 ± 0.718 [2.54-2.81] ^(1,3)	2.87 ± 0.737 [2.74-3.00] ^(0,1,2)	8.8x10 ⁻⁶
NYHA functional class III	38 (50.0%)	22 (40.7%)	57 (51.8%)	76 (60.3%)	0.0984
NYHA functional class IV	0 (0.0%) ^(1,2,3)	4 (7.41%) ⁽⁰⁾	11 (10.0%) ⁽⁰⁾	20 (15.9%) ⁽⁰⁾	0.0027
EuroSCORE, mean ± SD [95% CI], %	10.7 ± 7.14 [9.05-12.3] ^(2,3)	13.8 ± 8.88 [11.4-16.2] ⁽³⁾	16.6 ± 12.5 [14.2-18.9] ^(0,3)	25.1 ± 17.5 [22.0-28.1] ^(0,1,2)	1.0x10 ⁻¹⁰
eGFR, mean ± SD [95% CI], mL/min	66.7 ± 18.8 [62.4-71.0] ⁽³⁾	59.6 ± 18.2 [54.6-64.5]	62.7 ± 23.0 [58.3-67.0] ⁽³⁾	54.6 ± 20.2 [51.0-58.2] ^(0,2)	0.0006
CAD, No. (%)	57 (75.0%)	48 (88.9%)	97 (88.2%)	109 (86.5%)	0.0871
COPD, No. (%)	5 (6.58%) ⁽³⁾	3 (5.56%) ⁽³⁾	16 (14.5%)	25 (19.8%) ^(0,1)	0.0154
Atrial fibrillation and/ or flutter, No. (%)	14 (18.4%) ^(2,3)	16 (29.6%) ⁽³⁾	47 (42.7%) ^(0,3)	84 (66.7%) ^(0,1,2)	4.8x10 ⁻¹¹

Chi-square or Fisher's exact test were used to evaluate the association between categorical variables, and Kruskal-Wallis test in combination with pairwise Wilcoxon test with correction for multiple testing (Benjamini-Hochberg method) was used for comparison of continuous variables, as appropriate. Numbers in parentheses indicate between which stages significant differences (p -value ≤ 0.05) were detected.

Supplemental material

8

BMI: body mass index; CAD: coronary artery disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; SD: standard deviation.

Supplemental material

9

Supplementary Table 3: Comparison of preprocedural echocardiographic and hemodynamic characteristics in accordance with the modified staging classification from Généreux.

	Stage 0 (n = 76)	Stage 1 (n = 54)	Stage 2 (n = 110)	Stage 3 (n = 126)	p-value
AVA, mean ± SD [95% CI], cm ²	0.771 ± 0.199 [0.726-0.817]	0.804 ± 0.164 [0.759-0.848]	0.768 ± 0.215 [0.727-0.809]	0.784 ± 0.223 [0.744-0.823]	0.6664
AVG _{mean} , mean ± SD [95% CI], mmHg	43.4 ± 13.1 [40.4-46.5] ⁽³⁾	40.2 ± 13.5 [36.5-43.9] ⁽³⁾	44.6 ± 17.5 [41.3-48.0] ⁽³⁾	32.9 ± 14.2 [30.4-35.5] ^(0,1,2)	4.5x10 ⁻⁹
Cardiac output, mean ± SD [95% CI], L/min	4.99 ± 1.03 [4.76-5.23] ⁽³⁾	5.18 ± 1.12 [4.87-5.49] ⁽³⁾	5.10 ± 1.28 [4.86-5.34] ⁽³⁾	4.61 ± 1.30 [4.38-4.84] ^(0,1,2)	0.0007
LVEF, mean ± SD [95% CI], %	58.9 ± 2.87 [58.2-59.5] ^(1,2,3)	53.7 ± 9.89 [51.0-56.4] ^(0,3)	54.8 ± 8.70 [53.1-56.5] ^(0,3)	46.9 ± 13.6 [44.5-49.3] ^(0,1,2)	1.1x10 ⁻¹⁰
LVEDD, mean ± SD [95% CI], mm	41.9 ± 4.99 [40.7-43.1] ^(1,2,3)	46.5 ± 9.29 [43.8-49.1] ⁽⁰⁾	47.8 ± 7.34 [46.3-49.2] ⁽⁰⁾	49.4 ± 9.58 [47.6-51.1] ⁽⁰⁾	4.5x10 ⁻⁸
mPCWP, mean ± SD [95% CI], mmHg	10.3 ± 4.59 [9.24-11.3] ^(2,3)	11.3 ± 3.53 [10.3-12.2] ^(2,3)	21.8 ± 6.44 [20.6-23.0] ^(0,1)	20.7 ± 9.00 [19.1-22.3] ^(0,1)	< 2.2x10 ⁻¹⁶
mPAP, mean ± SD [95% CI], mmHg	17.7 ± 4.02 [16.7-18.6] ^(2,3)	18.8 ± 3.55 [17.8-19.8] ^(2,3)	34.9 ± 7.41 [33.5-36.3] ^(0,1,3)	32.9 ± 12.3 [30.7-35.0] ^(0,1,2)	< 2.2x10 ⁻¹⁶
sPAP (echocardiography), mean ± SD [95% CI], mmHg	35.7 ± 10.1 [32.8-38.6] ^(2,3)	39.6 ± 10.6 [36.3-43.0] ^(2,3)	50.8 ± 14.2 [47.7-53.9] ^(0,1)	52.8 ± 17.1 [49.5-56.1] ^(0,1)	1.9x10 ⁻¹²
PVR, mean ± SD [95% CI], WU	1.55 ± 0.704 [1.39-1.71] ^(2,3)	1.49 ± 0.726 [1.30-1.69] ^(2,3)	2.79 ± 1.46 [2.52-3.07] ^(0,1)	2.88 ± 1.84 [2.56-3.21] ^(0,1)	< 2.2x10 ⁻¹⁶
TAPSE, mean ± SD [95% CI], mm	22.0 ± 3.98 [21.0-22.9] ⁽³⁾	22.0 ± 3.97 [20.9-23.1] ⁽³⁾	21.4 ± 3.43 [20.7-22.0] ⁽³⁾	16.0 ± 4.95 [15.1-16.9] ^(0,1,2)	< 2.2x10 ⁻¹⁶
Right midventricular diameter, mean ± SD [95% CI], mm	26.6 ± 3.99 [25.6-27.6] ⁽³⁾	27.5 ± 4.90 [26.1-28.9] ⁽³⁾	27.6 ± 4.90 [26.6-28.6] ⁽³⁾	33.4 ± 7.65 [32.0-34.8] ^(0,1,2)	3.3x10 ⁻¹¹
LA area, mean ± SD [95% CI], cm ²	19.4 ± 3.58 [18.5-20.2] ^(1,2,3)	26.0 ± 6.14 [24.2-27.7] ^(0,3)	27.1 ± 7.71 [25.5-28.7] ^(0,3)	29.5 ± 9.15 [27.9-31.2] ^(0,1,2)	< 2.2x10 ⁻¹⁶
RA area, mean ± SD [95% CI], cm ²	15.2 ± 3.45 [14.3-16.0] ^(1,2,3)	19.3 ± 5.46 [17.8-20.8] ^(0,3)	19.8 ± 5.84 [18.7-21.0] ^(0,3)	24.6 ± 8.73 [23.0-26.2] ^(0,1,2)	1.4x10 ⁻¹⁵
"Classical" low-flow, low-gradient AS	0 (0.0%) ^(1,2,3)	8 (14.8%) ^(0,3)	12 (10.9%) ^(0,3)	40 (31.7%) ^(0,1,2)	1.9x10 ⁻⁸

Supplemental material

10

LV dysfunction (LVEF < 50%)	0 (0.0%) ^(1,2,3)	17 (31.5%) ⁽⁰⁾	23 (20.9%) ^(0,3)	60 (47.6%) ^(0,2)	3.7x10 ⁻¹²
PH (mPAP ≥ 25 mmHg)	0 (0.0%) ^(2,3)	0 (0.0%) ^(2,3)	110 (100%) ^(0,1,3)	88 (69.8%) ^(0,1,2)	< 2.2x10 ⁻¹⁶
RV dysfunction (TAPSE ≤ 16 mm)	0 (0.0%) ⁽³⁾	0 (0.0%) ⁽³⁾	0 (0.0%) ⁽³⁾	87 (69.0%) ^(0,1,2)	< 2.2x10 ⁻¹⁶
MR ≥ III/IV°, No (%)	0 (0.0%) ^(1,3)	5 (9.26%) ⁽⁰⁾	5 (4.55%) ⁽³⁾	24 (19.0%) ^(0,2)	1.6x10 ⁻⁵
TR ≥ III/IV°, No (%)	0 (0.0%) ⁽³⁾	0 (0.0%) ⁽³⁾	0 (0.0%) ⁽³⁾	33 (26.2%) ^(0,1,2)	8.6x10 ⁻¹⁶

Kruskal-Wallis test in combination with pairwise Wilcoxon test with correction for multiple testing (Benjamini-Hochberg method) was used for comparisons among clusters. Numbers in parentheses indicate between which stages significant differences (p -value ≤ 0.05) were detected.

AVA: aortic valve area; AVG_{mean} : mean aortic valve gradient; CI: confidence interval; LA area: left atrial area; LV dysfunction: left ventricular dysfunction; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; mPAP: mean pulmonary artery pressure; mPCWP: mean postcapillary wedge pressure; MR: mitral regurgitation; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RA area: right atrial area; RV dysfunction: right ventricular dysfunction; SD: standard deviation; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

Supplementary Table 4: Comparison of echocardiographic follow-up data in accordance with the modified staging classification from Généreux.

	Stage 0 (n = 48)	Stage 1 (n = 41)	Stage 2 (n = 71)	Stage 3 (n = 87)	p-value
LVEF, mean ± SD [95% CI], %	58.3 ± 4.16 [57.1-59.5] ^(1,2,3)	54.3 ± 7.92 [51.8-56.8] ^(0,3)	54.8 ± 7.55 [53.0-56.5] ^(0,3)	48.6 ± 12.4 [46.0-51.3] ^(0,1,2)	1.9x10 ⁻⁶
sPAP, mean ± SD [95% CI], mmHg	32.6 ± 8.64 [29.7-35.6] ^(1,2,3)	38.0 ± 10.2 [34.3-41.6] ^(0,2,3)	46.0 ± 16.7 [41.5-50.5] ^(0,1)	48.4 ± 14.9 [45.1-51.8] ^(0,1)	6.3x10 ⁻⁸
Right midventricular diameter, mean ± SD [95% CI], mm	29.3 ± 4.52 [27.7-30.8]	27.6 ± 4.04 [26.3-29.0] ⁽³⁾	28.8 ± 4.96 [27.5-30.1] ⁽³⁾	32.4 ± 7.42 [30.7-34.2] ^(1,2)	0.0017
TAPSE, mean ± SD [95% CI], mm	22.9 ± 5.03 [21.4-24.4] ^(2,3)	20.8 ± 4.04 [19.5-22.0] ⁽³⁾	20.6 ± 4.57 [19.5-21.7] ^(0,3)	17.2 ± 4.90 [16.1-18.2] ^(0,1,2)	4.5x10 ⁻⁹
LA area, mean ± SD [95% CI], cm ²	20.9 ± 7.26 [18.7-23.0] ^(1,2,3)	25.3 ± 6.37 [23.3-27.4] ^(0,3)	27.0 ± 6.81 [25.3-28.7] ⁽⁰⁾	29.1 ± 8.11 [27.3-30.8] ^(0,1)	8.7x10 ⁻⁸
RA area, mean ± SD [95% CI], cm ²	15.4 ± 4.43 [14.1-16.8] ^(1,2,3)	18.7 ± 5.53 [16.9-20.5] ^(0,2,3)	21.3 ± 6.47 [19.7-22.9] ^(0,1,3)	24.5 ± 9.31 [22.5-26.6] ^(0,1,2)	1.2x10 ⁻¹⁰
MR ≥ III/IV°, No (%)	0 (0.0%)	1 (2.44%)	2 (2.82%)	6 (6.90%)	0.2356
TR ≥ III/IV°, No (%)	1 (2.08%) ⁽³⁾	1 (2.44%) ⁽³⁾	4 (5.63%) ⁽³⁾	19 (21.8%) ^(0,1,2)	0.0002

Kruskal-Wallis test in combination with pairwise Wilcoxon test with correction for multiple testing (Benjamini-Hochberg method) was used for comparisons among clusters. Numbers in parentheses indicate between which stages significant differences (p -value ≤ 0.05) were detected.

CI: confidence interval; LA area: left atrial area; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; RA area: right atrial area; SD: standard deviation; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.