



Universiteit  
Leiden  
The Netherlands

## **Prognostic value of right ventricular remodelling in patients undergoing concomitant aortic and mitral valve surgery**

Tse, Y.K.; Li, H.L.; Yu, S.Y.; Wu, M.Z.; Ren, Q.W.; Huang, J.Y.; ... ; Yiu, K.H.

### **Citation**

Tse, Y. K., Li, H. L., Yu, S. Y., Wu, M. Z., Ren, Q. W., Huang, J. Y., ... Yiu, K. H. (2022). Prognostic value of right ventricular remodelling in patients undergoing concomitant aortic and mitral valve surgery. *European Heart Journal - Cardiovascular Imaging*, 24(5), 653-663. doi:10.1093/ehjci/jeac162



Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3567789>

**Note:** To cite this publication please use the final published version (if applicable).

# Prognostic value of right ventricular remodelling in patients undergoing concomitant aortic and mitral valve surgery

Yi-Kei Tse<sup>1,2</sup>, Hang-Long Li<sup>2</sup>, Si-Yeung Yu<sup>1,2</sup>, Mei-Zhen Wu<sup>1,2</sup> , Qing-Wen Ren<sup>1,2</sup>, Jiayi Huang<sup>1,2</sup>, Hung-Fat Tse<sup>1,2</sup>, Jeroen J. Bax<sup>3,4</sup>, and Kai-Hang Yiu<sup>1,2\*</sup> 

<sup>1</sup>Division of Cardiology, Department of Medicine, The University of Hong Kong Shenzhen Hospital, 518000 Shenzhen, China; <sup>2</sup>Division of Cardiology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, 000000 Hong Kong, China; <sup>3</sup>Department of Cardiology, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands; and <sup>4</sup>Department of Cardiology, Turku Heart Center, University of Turku and Turku University Hospital, 20521 Turku, Finland

Received 23 March 2022; accepted after revision 2 August 2022; online publish-ahead-of-print 22 August 2022

## Aims

Long-term risk stratification and surgical timing remain suboptimal in concomitant aortic and mitral (double) valve surgery. This study sought to examine the predictors, changes, and prognostic implications of right ventricular (RV) remodelling in patients undergoing double-valve surgery.

## Methods and results

In 152 patients undergoing double-valve surgery, four RV remodelling patterns were characterized using transthoracic echocardiography: normal RV size and systolic function (Pattern 1); dilated RV (tricuspid annulus diameter >35 mm) with normal systolic function (Pattern 2); normal RV size with systolic dysfunction (percentage RV fractional area change <35%; Pattern 3); and dilated RV with systolic dysfunction (Pattern 4). The primary endpoint was the composite of heart failure hospitalization and all-cause mortality. Patterns 1, 2, 3, and 4 RV remodelling were present in 41, 20, 23, and 16% of patients, respectively. Patients with Stage 4 RV remodelling had worse renal function, higher EuroSCORE II, and impaired left ventricular ejection fraction. During a 3.7-year median follow up, 45 adverse events occurred. Patterns 3 and 4 RV remodelling were associated with significantly higher adverse event rates compared with Pattern 1 (37 and 75% vs. 11%,  $P < 0.01$ ) and had incremental prognostic value when added to clinical parameters and EuroSCORE II ( $\chi^2$  increased from 30 to 66,  $P < 0.01$ ). At 1 year after surgery ( $n = 100$ ), Patterns 3 and 4 RV remodelling had a higher risk of adverse events compared with Pattern 1.

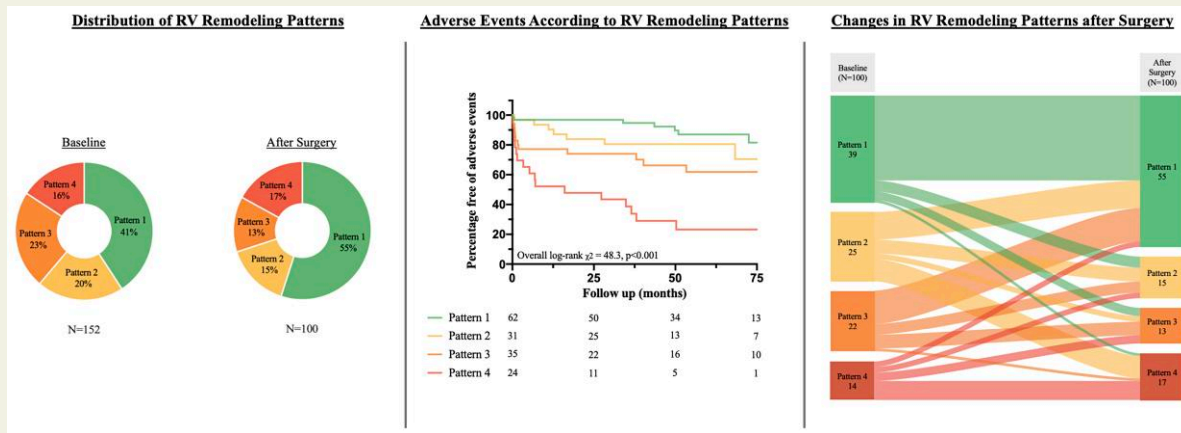
## Conclusion

Right ventricular remodelling was strongly related to adverse outcomes and deserves consideration as part of the risk and decision-making algorithms in double-valve surgery.

\* Corresponding author. Tel: +852 22553633; Fax: +852 28186304. E-mail: khkyiu@hku.hk

© The Author(s) 2022. Published by Oxford University Press on behalf of the European Society of Cardiology. All rights reserved. For permissions, please email: [journals.permissions@oup.com](mailto:journals.permissions@oup.com).

## Graphical Abstract



## Keywords

adverse outcome • concomitant aortic and mitral valve surgery • right ventricular remodelling • right ventricular function

## Introduction

Concomitant lesions of the aortic and mitral valves<sup>1</sup> can occur in up to 20% of patients with native valvular disease and the prevalence is expected to further increase due to global aging populations with degenerative valvular pathologies. This is reflected in part by growing volumes of double-valve surgery,<sup>2,3</sup> which represents the only definitive treatment to improve symptoms and survival.<sup>4</sup> Nonetheless, double-valve surgery is associated with dramatically higher mortality (~35% at 12 years) far exceeding that expected for isolated aortic or mitral valve surgery.<sup>5</sup> Their poor long-term outcomes may be attributed to an uncertain timing of intervention, whereby current guidelines remain ambiguous in defining surgical triggers for multiple valvular heart disease.<sup>4,6</sup> In particular, surgical indications are primarily based on symptoms, which could be subjective,<sup>5,7</sup> and left ventricular (LV) dilation and/or dysfunction that may not accurately reflect disease severity.<sup>5,8</sup> This conundrum has provided a crucial rationale to search for outcome markers that can improve surgical timing and risk stratification in this high-risk population.

Although long considered a passive bystander in left-sided valvular heart disease, the prognostic importance of right ventricular (RV) remodelling has recently been recognized.<sup>9–11</sup> RV remodelling reflects the downstream pathophysiological consequences of multiple valvular heart disease, whereby chronic pressure and volume overload induce RV dilation and dysfunction.<sup>9</sup> The RV remodelling process and its influence on clinical outcomes remain largely unexplored in double-valve surgery. The current study aimed to evaluate the prevalence and correlates of RV remodelling in patients with concomitant aortic and mitral valve disease and evaluate the prognostic value in patients undergoing double-valve surgery.

## Methods

## Study population

Between November 2012 and January 2020, 175 consecutive patients who underwent concomitant aortic and mitral (double) valve surgery

at Queen Mary Hospital (Hong Kong) were retrospectively evaluated. Double (concomitant aortic and mitral) valve replacement (DVR) was performed in 134 patients, and aortic valve replacement (AVR) with mitral valve repair (MV repair) was performed in 41 patients. Patients were excluded if they had congenital heart disease ( $n = 5$ ), missing echocardiograms ( $n = 10$ ), or if the images were not focused on the RV for a detailed geometry assessment ( $n = 8$ ). Hence, a total of 152 patients were included in this study (Figure 1).

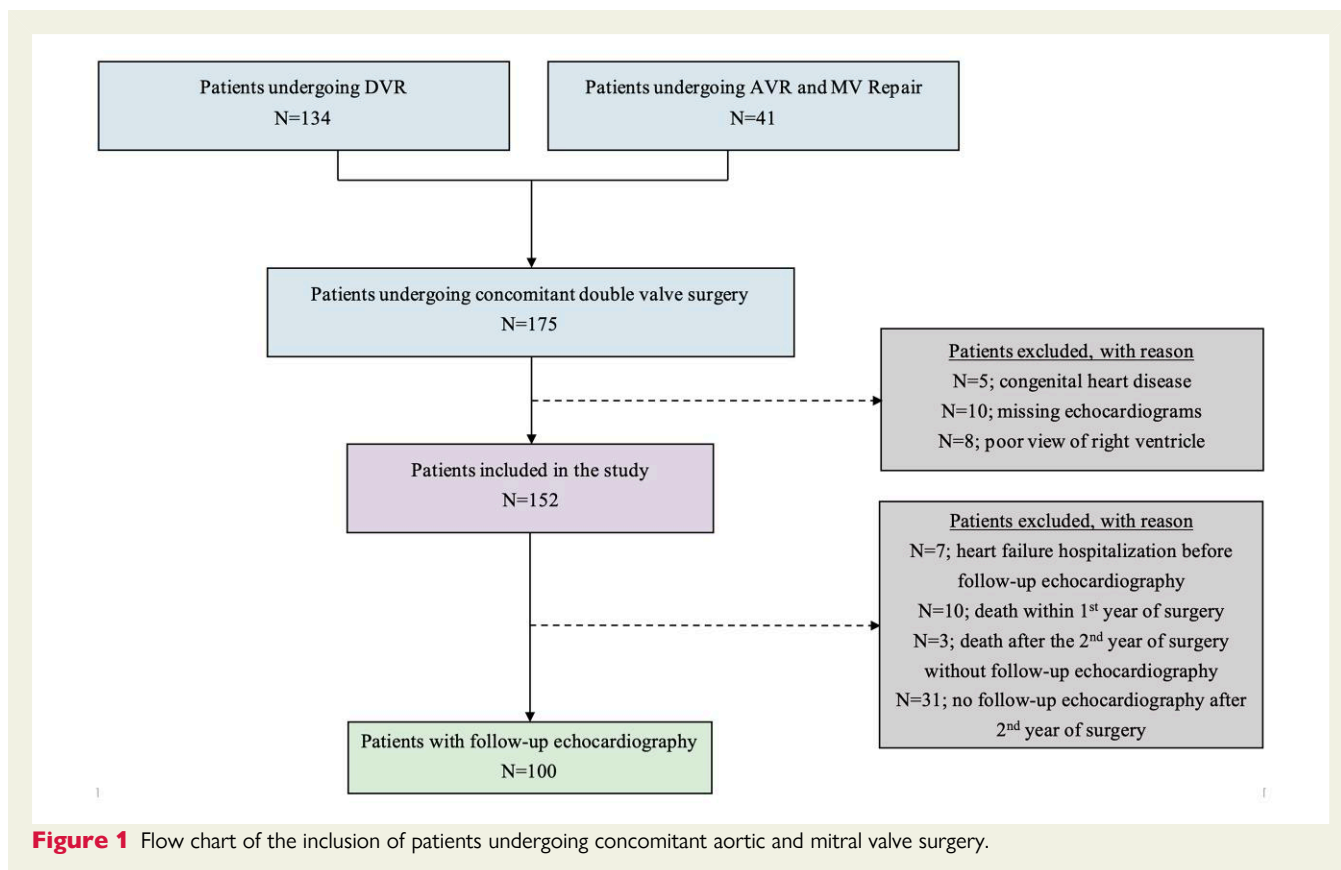
Adverse outcomes were defined as the composite of heart failure (HF) hospitalization and all-cause mortality. HF hospitalization was defined as having symptoms or signs of HF and being prescribed diuretics during hospitalization; HF must also be the primary reason for admission as recorded by the physician. Information on outcomes was retrieved from the centralized inter-hospital patient management system and follow up was complete for all patients. The study was part of the Chinese Valvular Heart Disease Study to evaluate the pattern of disease, pathophysiology, and clinical outcomes of valvular heart disease in Chinese patients.<sup>12</sup> The study was approved by the ethics committee of the West Cluster Hospital Authority of Hong Kong and all patients gave written informed consent.

## Clinical and laboratory parameters

Baseline demographic and clinical variables were evaluated at the time of pre-operative transthoracic echocardiography. Clinical characteristics included conventional cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, and smoking status), medical history (previous myocardial infarction and stroke), New York Heart Association (NYHA) functional class, and medication. Pre-operative laboratory data were based on the most recent analysis within 6 months before concomitant aortic and mitral valve surgery.

## Echocardiographic variables

All transthoracic echocardiography studies were performed by experienced sonographers using available ultrasound systems (Vingmed E9, General Electric Vingmed Ultrasound, Milwaukee, WI, USA; and iE33, Philips Medical Systems, Andover, MA, USA). The evaluation included



**Figure 1** Flow chart of the inclusion of patients undergoing concomitant aortic and mitral valve surgery.

M-mode, two-dimensional and colour, continuous- and pulsed-wave Doppler echocardiography according to current recommendations.<sup>13–15</sup> LV volumes were measured in the apical four- and two-chamber views and LV ejection fraction (LVEF) was derived using the biplane Simpson's method. Left atrial volumes were estimated by the biplane area-length method. RV end-systolic and end-diastolic areas were evaluated on RV-focused apical views. From the same view, tricuspid annulus (TA) diameter, measured at end-diastole from the insertion of the septal leaflet to the insertion of the anterior leaflet, was used to define RV dilation. Global RV systolic function was assessed by the percentage RV fractional area change (RVFAC), defined as  $(RV \text{ end-diastolic area} - RV \text{ end-systolic area}) / RV \text{ end-diastolic area} \times 100\%$ .<sup>16</sup> RVFAC was chosen as the primary measure of RV systolic function because of its superior correlation with cardiac magnetic resonance-derived RVEF compared with TA plane systolic excursion (TAPSE).<sup>17</sup> Prior studies in valvular surgery have likewise utilized RVFAC and demonstrated significant association with clinical outcomes that was not observed with TAPSE.<sup>18</sup> Pulmonary artery systolic pressure (PASP) was estimated from the peak tricuspid regurgitation (TR) velocity using the modified Bernoulli equation with the addition of 3, 8, or 15 mmHg based on the inferior vena cava diameter and collapsibility. All ventricular and atrial size measurements were indexed for body surface area. In patients with atrial fibrillation, the average of three beats was considered for RVFAC. Both baseline and post-operative echocardiographic data were obtained to evaluate changes in RV remodelling.

## Statistical analysis

Continuous data are expressed as mean  $\pm$  SD for normally distributed variables or as median with interquartile range for non-normally

distributed variables. Categorical variables are presented in frequencies and/or proportions. Based on current guidelines,<sup>14,16</sup> cut-off values of 35 mm for TA diameter and 35% for RVFAC were used to characterize four patterns of RV remodelling<sup>9</sup>:

- Pattern 1: normal RV size with normal systolic function
- Pattern 2: dilated RV with normal systolic function
- Pattern 3: normal RV size with systolic dysfunction
- Pattern 4: dilated RV with systolic dysfunction

Clinical and echocardiographic differences between four patterns of RV remodelling were analysed using the one-way analysis of variance and Kruskal–Wallis  $H$  test for continuous variables and the  $\chi^2$  test and Fisher's exact test for categorical variables. Changes in pre- and post-operative echocardiographic characteristics were evaluated using the paired  $t$ -test and Wilcoxon signed-rank test. Kaplan–Meier analyses with log-rank tests were conducted to compare adverse events across the four patterns of RV remodelling. Cox proportional hazards analysis was performed to evaluate the clinical, laboratory, and echocardiographic factors associated with adverse events. Variables with  $P < 0.05$  on univariate analysis were incorporated into multivariate regression models. To investigate the incremental prognostic value of RV remodelling over EuroSCORE II, multivariate stepwise block analysis was performed, and the  $\chi^2$  values of the models with and without the addition of RV remodelling patterns were compared. Formal risk reclassification analyses were conducted by calculating the continuous net reclassification improvement (NRI) for adverse outcomes. Decision curve analysis was used to estimate the net benefit of RV assessment in addition to guideline-based surgical indications as a decision tool.<sup>19</sup> All statistical analyses were performed using R version 4.0.3.  $P$ -values  $< 0.05$  denoted statistical significance.

## Results

### Patient characteristics

Among the 152 patients included in the study (mean age:  $64 \pm 8$  years; 49% men), 118 (78%) patients underwent DVR and 34 (22%) underwent AVR with MV repair. Tables 1 and 2 summarize the baseline characteristics of the overall population and according to different patterns of RV remodelling. The majority of patients (72%) had atrial fibrillation and the use of warfarin (67%) was high. Over 60% of patients had  $\geq$ moderate mitral stenosis,  $\geq$ moderate aortic stenosis, and  $\geq$ moderate aortic regurgitation, while 50% had  $\geq$ moderate mitral regurgitation and  $\geq$ moderate TR.

### RV remodelling patterns

The distribution of RV remodelling patterns in the overall population was as follows: 62 (41%) patients presented with Pattern 1 RV remodelling (no RV dilation, no RV dysfunction); 31 (20%) had Pattern 2 RV remodelling (RV dilation, no RV dysfunction); 35 (23%) showed Pattern 3 remodelling (no RV dilation, RV dysfunction); and 24 (16%) had Pattern 4 remodelling (RV dilation and dysfunction; Figure 2).

Patients with Pattern 4 RV remodelling were more commonly male, had worse renal function, and a higher EuroSCORE II when compared with those with Pattern 1. LV systolic function was decreased in advanced patterns of RV remodelling, and reduced LVEF (<40%) was more frequently observed in RV remodelling

**Table 1** Clinical and laboratory characteristics of patients undergoing concomitant aortic and mitral valve surgery and according to the pattern of right ventricular remodelling

Characteristics	Overall (n = 152)	Pattern 1 (n = 62)	Pattern 2 (n = 31)	Pattern 3 (n = 35)	Pattern 4 (n = 24)	P-value
Demographic characteristics						
Age, years	$64 \pm 8$	$64 \pm 7$	$63 \pm 9$	$62 \pm 7$	$67 \pm 10$	0.079
Male	74 (48.7)	23 (37.1)*	13 (41.9)	20 (57.1)	18 (75)**	0.008
NYHA Class III/IV	10 (6.6)	3 (4.8)	2 (6.5)	1 (2.9)	4 (16.7)	0.167
Clinical characteristics						
Hypertension	34 (22.4)	17 (27.4)	3 (9.7)	7 (20)	7 (29.2)	0.210
Diabetes mellitus	19 (12.5)	5 (8.1)	4 (12.9)	4 (11.4)	6 (25)	0.232
Dyslipidaemia	33 (21.7)	14 (22.6)	4 (12.9)	11 (31.4)	4 (16.7)	0.293
Smoking	28 (18.4)	11 (17.7)	2 (6.5)	10 (28.6)	5 (20.8)	0.126
Atrial fibrillation	109 (71.7)	38 (61.3)	25 (80.6)	25 (71.4)	21 (87.5)	0.057
Laboratory examination						
Interval between laboratory examination and surgery, months	2.8 (1.0–5.2)	2.9 (1.1–5.6)	3.7 (2.2–5.8)	3.0 (1.0–4.7)	1.8 (0.7–4.1)	0.151
Haemoglobin, g/dL	12.8 (11.5–14.0)	12.9 (11.9–13.5)	13.1 (11.5–14.2)	13.4 (11.6–14.5)*	11.4 (9.8–13.0)***	0.040
Creatinine, mg/dL	0.96 (0.78–1.16)	0.85 (0.72–1.04)*	0.90 (0.84–1.18)	1.00 (0.84–1.18)	1.13 (0.93–1.41)**	0.002
Medications						
Beta-blockers	66 (43.4)	28 (45.2)	11 (35.5)	16 (45.7)	11 (45.8)	0.810
Calcium channel blockers	26 (17.1)	11 (17.7)	4 (12.9)	4 (11.4)	7 (29.2)	0.344
Diuretics	22 (14.5)	6 (9.7)	6 (19.4)	4 (11.4)	6 (25)	0.239
Warfarin	102 (67.1)	39 (62.9)	26 (83.9)	23 (65.7)	14 (58.3)	0.155
Cardiac surgery risk-scoring system						
EuroSCORE II	2.51 (1.61–4.17)	2.27 (1.30–3.14)*	2.49 (1.79–3.59)	2.83 (1.93–4.95)	3.43 (2.32–6.69)**	0.016
Valvular surgery details						
Dual valve replacement	118 (77.6)	49 (79.0)	26 (83.9)	28 (80.0)	15 (62.5)	0.257
AVR and MV repair	34 (22.4)	13 (21.0)	5 (16.1)	7 (20.0)	9 (37.5)	0.265
Concomitant tricuspid annuloplasty	76 (50.0)	22 (35.5)*,****	22 (71.0)**,***	13 (37.1)*,****	19 (79.2)**,***	<0.001
Concomitant CABG	13 (8.6)	7 (11.3)	0 (0)	2 (5.7)	4 (16.7)	0.091
Outcomes						
In-hospital mortality	7 (4.6)	1 (1.6)*	1 (3.2)	1 (2.9)	4 (16.7)**	0.022

AVR, aortic valve replacement; CABG, coronary artery bypass grafting; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; MV repair, mitral valve repair; NYHA, New York Heart Association.

\* $P < 0.05$  vs. Pattern 4.

\*\* $P < 0.05$  vs. Pattern 1.

\*\*\* $P < 0.05$  vs. Pattern 3.

\*\*\*\* $P < 0.05$  vs. Pattern 2.

**Table 2** Echocardiographic characteristics of patients undergoing concomitant aortic and mitral valve surgery and according to the pattern of right ventricular remodelling

Characteristics	Overall (n = 152)	Pattern 1 (n = 62)	Pattern 2 (n = 31)	Pattern 3 (n = 35)	Pattern 4 (n = 24)	P-value
Aetiology of valvular heart disease						
CRHD	93 (61.2)	35 (56.5)	23 (74.2)	24 (68.6)	11 (45.8)	0.116
Degenerative	47 (30.9)	19 (30.6)	8 (25.8)	9 (25.7)	11 (45.8)	0.344
Mitral valve prolapse	4 (2.7)	3 (4.8)	0 (0.0)	1 (2.9)	0 (0.0)	0.445
Bicuspid aortic valve	3 (2.0)	2 (3.2)	0 (0.0)	1 (2.9)	0 (0.0)	0.626
Infective endocarditis	5 (3.3)	3 (4.8)	0 (0.0)	0 (0.0)	2 (8.3)	0.201
LV, LA, and left-sided valvular disease						
LVEDV, mL/m <sup>2</sup>	56 (40–79)	52 (40–72)	65 (40–81)	59 (44–82)	58 (41–78)	0.467
LVESV, mL/m <sup>2</sup>	23 (16–35)	19 (14–27)*	26 (17–42)	26 (19–47)**	26 (19–37)	0.014
LVEF, %	57 (49–63)	61 (57–65)***,****	56 (51–60)***	50 (41–59)**	54 (47–61)**	<0.001
LA volume index, mL/m <sup>2</sup>	103 (76–140)	93 (73–126)****	114 (85–159)	109 (71–139)	121 (90–176)**	0.022
MS ≥ moderate	93 (61.2)	39 (62.9)	20 (64.5)	23 (65.7)	11 (45.8)	0.691
MR ≥ moderate	77 (50.7)	29 (46.8)	13 (41.9)	20 (57.1)	15 (62.5)	0.362
AS ≥ moderate	97 (63.8)	41 (66.1)	19 (61.3)	21 (60)	16 (66.7)	0.879
AR ≥ moderate	94 (61.8)	39 (62.9)	21 (67.7)	18 (51.4)	16 (66.7)	0.511
RV, RA, and right-sided valvular disease						
TA diameter, mm	32 (27–38)	29 (26–31)***,****	38 (36–40)*,**	29 (26–32)***,****	39 (38–42)*,**	<0.001
RV basal diameter, mm/m <sup>2</sup>	22 (19–25)	21 (18–22)***,****	26 (23–29)*,**	20 (17–24)***,****	28 (25–29)*,**	<0.001
RV mid-cavity diameter, mm/m <sup>2</sup>	12 (10–15)	11 (9–13)***,****	14 (12–17)*,**	12 (10–13)***,****	15 (13–17)*,**	<0.001
RV end-diastolic area, cm <sup>2</sup> /m <sup>2</sup>	8 (7–11)	8 (7–9)***,****	11 (9–13)*,**	7 (7–9)***,****	11 (9–13)*,**	<0.001
RV end-systolic area, cm <sup>2</sup> /m <sup>2</sup>	5 (4–7)	4 (3–5)*,**,****	6 (5–8)*,**,****	6 (5–7)*,**,****	8 (7–10)*,**,****	<0.001
PASP, mmHg	42 (35–51)	40 (32–46)****	44 (38–53)	42 (35–50)	49 (39–59)**	0.003
RA end-systolic area, mm <sup>2</sup> /m <sup>2</sup>	13 (10–17)	11 (9–13)***,****	17 (14–22)*,**	13 (10–16)***,****	19 (16–23)*,**	<0.001
RVFAC, %	38 (32–47)	45 (41–48)***,****	44 (39–47)*,**	30 (24–33)***,****	31 (25–35)*,**	<0.001
RVFAC/PASP, %/mmHg	0.9 (0.7–1.3)	1.2 (0.9–1.6)*,**,****	1.0 (0.8–1.2)*,**,****	0.7 (0.5–0.9)*,**,****	0.7 (0.4–0.8)*,**,****	<0.001
TR ≥ moderate	82 (53.9)	22 (35.5)***,****	25 (80.6)*,**	14 (40)***,****	21 (87.5)*,**	<0.001

AR, aortic regurgitation; AS, aortic stenosis; CRHD, chronic rheumatic heart disease; FAC, fractional area change; LA, left atrium; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MS, mitral stenosis; PASP, pulmonary artery systolic pressure; RA, right atrium; RV, right ventricle; TA, tricuspid annulus; TR, tricuspid regurgitation.

\*P < 0.05 vs. Pattern 3.

\*\*P < 0.05 vs. Pattern 1.

\*\*\*P < 0.05 vs. Pattern 2.

\*\*\*\*P < 0.05 vs. Pattern 4.

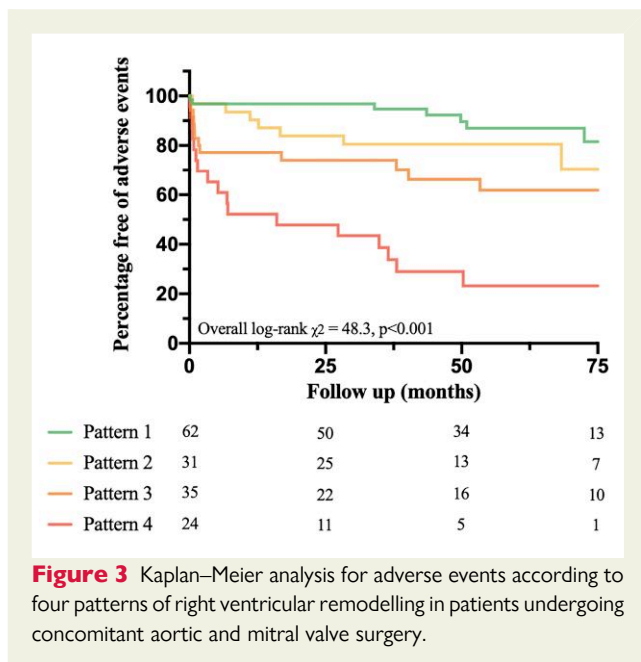
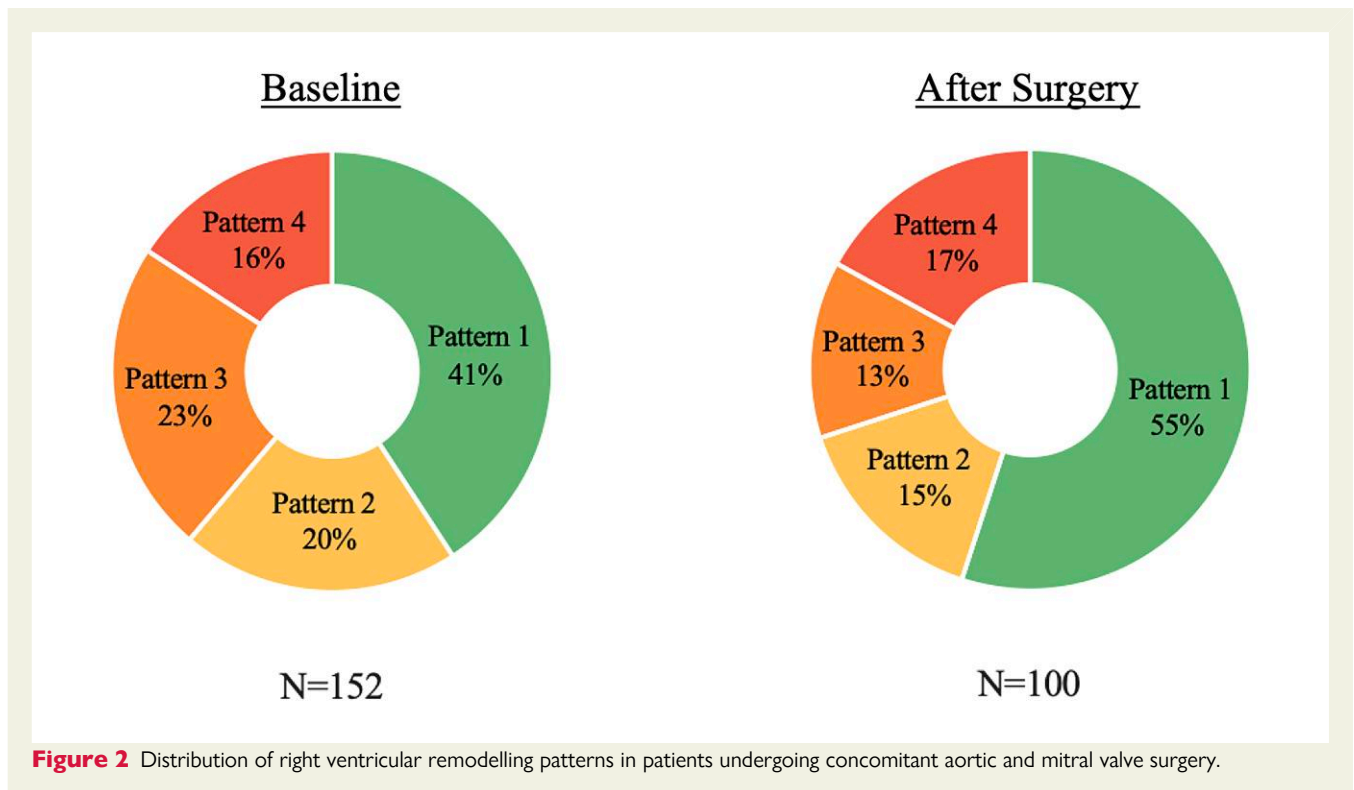
Patterns 3 and 4. RV dimensions (RV basal and mid-cavity diameter) were significantly larger in RV remodelling Patterns 2 and 4 than in Patterns 1 and 3, as were RV end-diastolic and end-systolic areas and right atrial area. Likewise, significant TR was more prevalent in patterns comprising RV dilation (Patterns 2 and 4). Higher PASP values were observed in patients with remodelling Pattern 4 when compared with Pattern 1. Patterns 3 and 4 remodelling exhibited significantly lower RVFAC/PASP than Patterns 1 and 2.

## Association between RV remodelling and adverse events

During a median follow up of 3.7 years (interquartile range: 1.8–5.8 years), 45 adverse events occurred [26 HF hospitalizations and 19 deaths (7 in-hospital deaths)]. Severe complications occurred in 10

(7%) patients, including 4 (3%) prosthetic valve thromboses, 4 (3%) endocarditis/abscess formations, and 2 (1%) cardiogenic shocks (see [Supplementary data online, Table S1](#)). Kaplan–Meier analysis revealed that Patterns 3 and 4 RV remodelling were associated with significantly higher adverse event rates compared with Pattern 1 (37 and 75 vs. 11%,  $P = 0.004$  and  $P < 0.001$ , respectively; [Figure 3](#)). Conversely, Pattern 4, but not Pattern 3 RV remodelling, had significantly higher rates of adverse events compared with Pattern 2 (75 and 37 vs. 24%,  $P < 0.001$  and  $P = 0.212$ ). When considering the presence of RV dilation or RV dysfunction only, patients with RV dilation or RV dysfunction had significantly worse adverse outcomes than their counterparts (see [Supplementary data online, Figure S1](#)).

Univariate Cox regression analysis showed that age, hypertension, HF, haemoglobin level, EuroSCORE II, LV end-systolic volume, LVEF, TA diameter, RV end-diastolic and end-systolic area, RVFAC, and RV



remodelling patterns were associated with adverse events. Notably,  $\geq$ moderate TR was not associated with adverse events on univariate analysis. At multivariable Cox regression analysis, RV remodelling patterns remained significantly associated with adverse events, whereby Patterns 3 and 4 RV remodelling conferred a 3.9- and 8.2-fold excess risk, respectively, independent of hypertension, HF, and EuroSCORE II (Table 3). These results remained consistent when all-cause mortality was defined as the endpoint (see

Supplementary data online, Table S2) and in subgroup analysis excluding patients with concomitant TA (see Supplementary data online, Table S3). Across the two types of valvular surgery, Pattern 4 RV remodelling was consistently associated with adverse outcomes after intervention (see Supplementary data online, Tables S4 and S5).

Right ventricular remodelling patterns improved risk prediction compared with traditional risk markers and guideline-based surgical triggers. In nested Cox regression models, the addition of RV remodelling patterns provided prognostic information beyond clinical variables (hypertension and HF) and EuroSCORE II (see Supplementary data online, Figure S2). Inclusion of RV assessment (TA diameter and RVFAC) provided a consistently positive and larger net clinical benefit over NYHA class, LV size (LV end-diastolic volume), and LV function (LVEF) alone (Figure 4). In particular, TA diameter and RVFAC led to significant NRI of 47% (95% CI, 8.65–86.2%,  $P = 0.017$ ) and 57% (95% CI, 20.8–92.5%,  $P = 0.002$ ) for adverse outcomes, respectively.

### Post-operative echocardiography

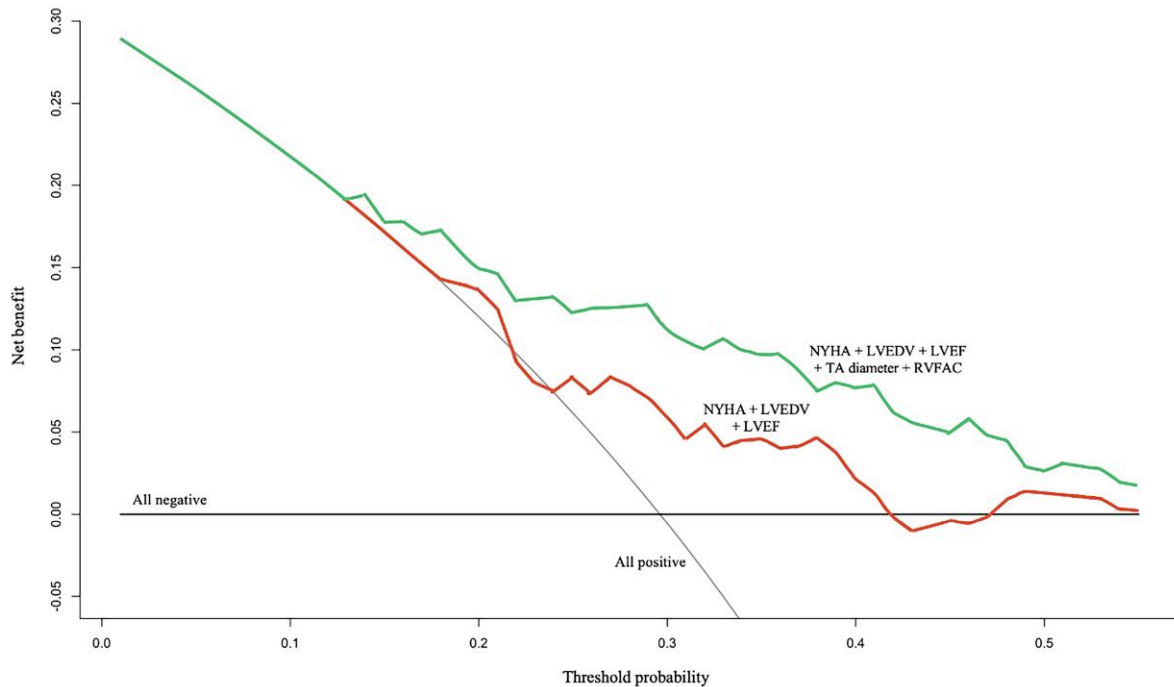
After double-valve surgery, transthoracic echocardiography was performed in 100 patients (median interval: 1.7 years; interquartile range: 1.2–2.5 years) after excluding those who had incurred an adverse event (HF hospitalization and all-cause mortality) or with no echocardiograms during follow up. Patients who underwent follow-up echocardiography had similar characteristics as the rest of the cohort (see Supplementary data online, Table S6). The distribution of post-operative RV remodelling patterns was as follows: Pattern 1 RV remodelling was found in 55 (55%) patients; Pattern 2 in 15 (15%) patients; Pattern 3 in 13 (13%) patients; and Pattern 4 in 17 (17%) patients (Figure 2). Patient flow

**Table 3** Univariate and multivariate cox proportional hazards regression models for adverse events for patients undergoing concomitant aortic and mitral valve surgery

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Demographic and anthropometric characteristics				
Age	1.063 (1.022–1.106)	0.002		
Male	1.627 (0.900–2.942)	0.107		
NYHA Class III/IV	0.865 (0.268–2.797)	0.809		
Cardiovascular risk factors and cardiovascular disease				
Hypertension	2.053 (1.114–3.783)	0.021	1.554 (0.781–3.094)	0.209
Diabetes mellitus	1.083 (0.458–2.560)	0.855		
Dyslipidaemia	1.306 (0.674–2.529)	0.429		
Smoking	1.112 (0.535–2.312)	0.776		
Atrial fibrillation	1.609 (0.795–3.254)	0.186		
Heart failure	3.444 (1.804–6.576)	<0.001	2.085 (1.036–4.195)	0.039
Laboratory assessment				
Haemoglobin, g/dL	0.805 (0.695–0.932)	0.004		
Creatinine, mg/dL	1.225 (0.994–1.511)	0.057		
Medications				
Beta-blockers	1.394 (0.389–1.321)	0.286		
Calcium channel blockers	1.455 (0.720–2.940)	0.296		
Diuretics	1.657 (0.797–3.445)	0.176		
Warfarin	0.781 (0.429–1.420)	0.417		
Cardiac surgery risk-stratification systems				
EuroSCORE II	1.043 (1.018–1.068)	<0.001	1.042 (1.008–1.077)	0.014
Procedural details				
Dual valve replacement	0.558 (0.300–1.038)	0.065		
AVR and MV repair	1.780 (0.957–3.309)	0.069		
Concomitant tricuspid annuloplasty	1.237 (0.688–2.222)	0.478		
Echocardiographic variables				
CRHD	0.679 (0.378–1.220)	0.196		
LVEDV, mL	1.003 (1.000–1.007)	0.089		
LVESV, mL	1.007 (1.001–1.013)	0.022		
LVEF, %	0.966 (0.943–0.990)	0.006		
MS ≥ moderate	0.740 (0.401–1.365)	0.335		
MR ≥ moderate	0.853 (0.474–1.532)	0.594		
AS ≥ moderate	1.030 (0.559–1.898)	0.925		
AR ≥ moderate	0.700 (0.389–1.261)	0.235		
PASP	1.02 (0.997–1.044)	0.084		
TA diameter, mm	1.08 (1.031–1.132)	0.001		
RV end-diastolic area, cm <sup>2</sup>	1.120 (1.058–1.185)	<0.001		
RV end-systolic area, cm <sup>2</sup>	1.203 (1.120–1.292)	<0.001		
RVFAC, %	0.951 (0.924–0.978)	<0.001		
TR ≥ moderate	1.730 (0.943–3.176)	0.077		
RV remodelling patterns		<0.001		<0.001
Pattern 1 vs. Pattern 2	2.162 (0.758–6.167)	0.149	1.921 (0.654–5.648)	0.235
Pattern 1 vs. Pattern 3	3.803 (1.516–9.541)	0.004	3.924 (1.519–10.141)	0.005
Pattern 1 vs. Pattern 4	11.750 (4.861–28.404)	<0.001	8.172 (3.194–20.906)	<0.001

Abbreviations as in Tables 1 and 2.





**Figure 4** Decision curve analysis of the EuroSCORE II and right ventricular remodelling patterns for risk prediction.

through patterns of RV remodelling before and after surgery is shown in *Figure 5*. Sequential echocardiographic measurements demonstrated significant improvements in LVEF, LV end-diastolic and end-systolic volumes, left atrial volume index, PASP, and right atrial areas following surgery. There were nonetheless no significant changes in TA diameters, RV dimensions, RV areas, and RVFAC (*Figure 6*). Correlates of post-operative Pattern 4 RV remodelling include RV end-diastolic and end-systolic area and  $\geq$ moderate TR before surgery (see [Supplementary data online, Table S7](#)).

After follow-up echocardiography (median: 2.1 years; interquartile range: 1.5–4.5 years), 24 adverse events occurred (19 HF hospitalizations and 5 deaths). Four (7%) adverse events occurred in Pattern 1 remodelling, 4 (27%) in Pattern 2, 6 (46%) in Pattern 3, and 10 (59%) in Pattern 4. The persistence of Patterns 3 and 4 RV remodelling after surgery conferred significantly worse long-term outcomes compared with Pattern 1 (77 and 59 vs. 4%,  $P < 0.001$  for both). On multivariate adjustment for EuroSCORE II, Patterns 3 and 4 RV remodelling remained associated with a higher risk of adverse events (see [Supplementary data online, Table S8](#)).

## Discussion

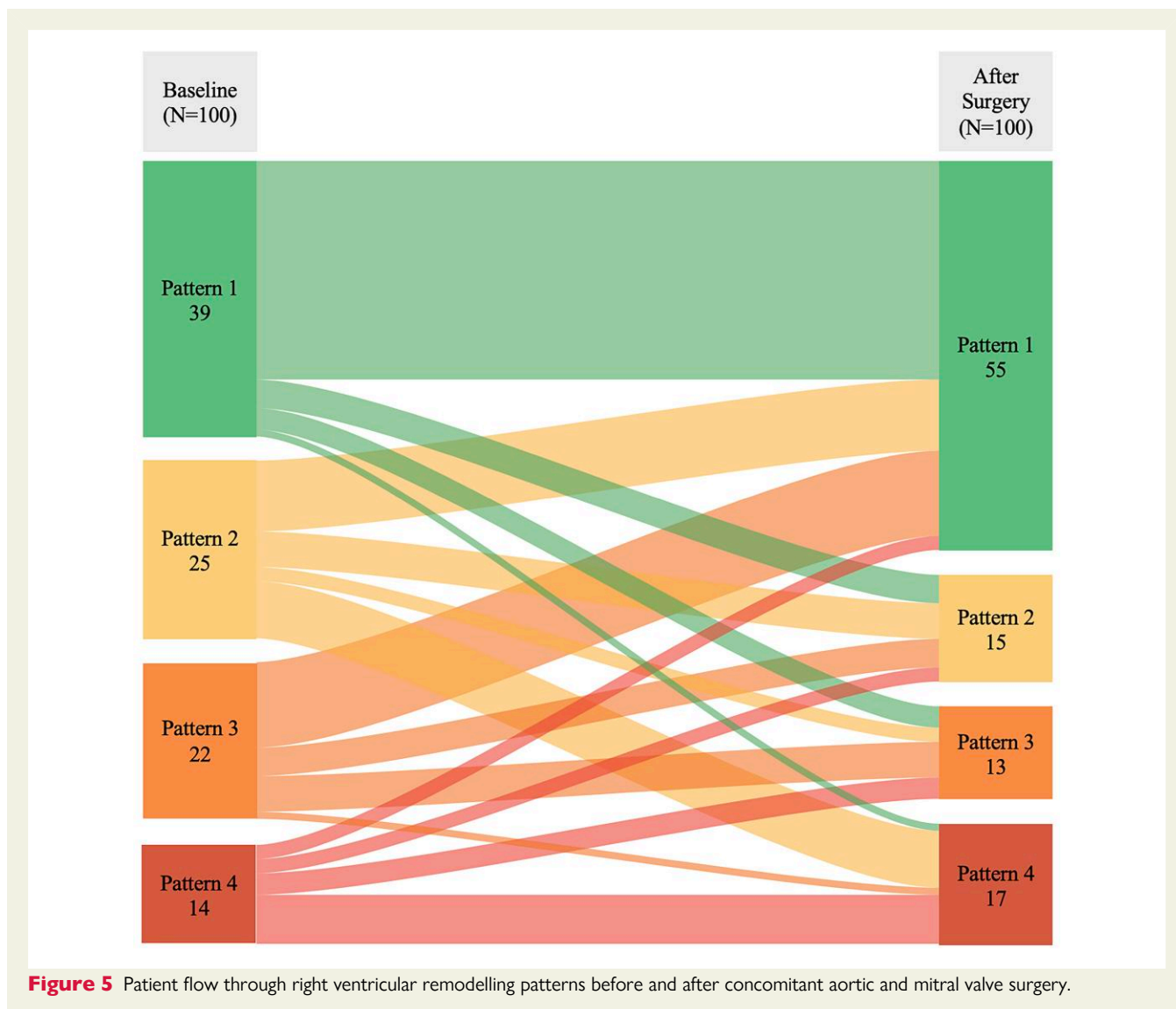
The current study reports on the prevalence, changes, and prognostic value of RV remodelling in patients undergoing concomitant aortic and mitral valve surgery. The principal findings are: (i) patients with multiple valvular heart disease had a high prevalence of RV dilation and dysfunction; (ii) RV remodelling was strongly linked to adverse outcomes following double-valve surgery, with concomitant RV

dilation and dysfunction exhibiting the highest excess risk; (iii) RV remodelling patterns provided incremental prognostic value over traditional risk markers (clinical variables and EuroSCORE II) and guideline-based surgical indications (symptoms and LV dilation and/or dysfunction); and (iv) RV dilation and dysfunction persisted in a substantial proportion of patients following surgery, which conferred a higher risk of adverse outcomes.

## RV remodelling in valvular heart disease

Ventricular dilation and dysfunction, as downstream pathophysiological consequences of valvular heart disease, represent key triggers for valvular intervention. RV dysfunction has been reported in 20–30% of patients with isolated aortic and mitral valve disease.<sup>10</sup> The prevalence of RV remodelling was likewise high in the present cohort of patients with concomitant aortic and mitral valve disease, with 59 and 39% developing RV dilation and RV dysfunction, respectively. The greater degree of adverse RV remodelling reflects the complexity of patients with multiple valve diseases that may relate to their poor outcome compared with those with isolated valve disease.

In the natural history of aortic and mitral valve disease, progressive LV remodelling with hypertrophy, dilation, and increased LV filling pressures can transmit to the left atrium and pulmonary circulation, resulting in RV pressure overload. This elevation of pulmonary artery pressure and RV afterload induces RV remodelling, leading to RV hypertrophy and dilation. Changes in RV geometry may result in TA dilation and subsequent TR.<sup>20</sup> Over time, chronic pressure overload and volume overload may impact RV coronary blood flow and contractility,<sup>21</sup> ultimately resulting in impaired RV function. Further, LV remodelling induced by left-sided valvular lesions can reduce the



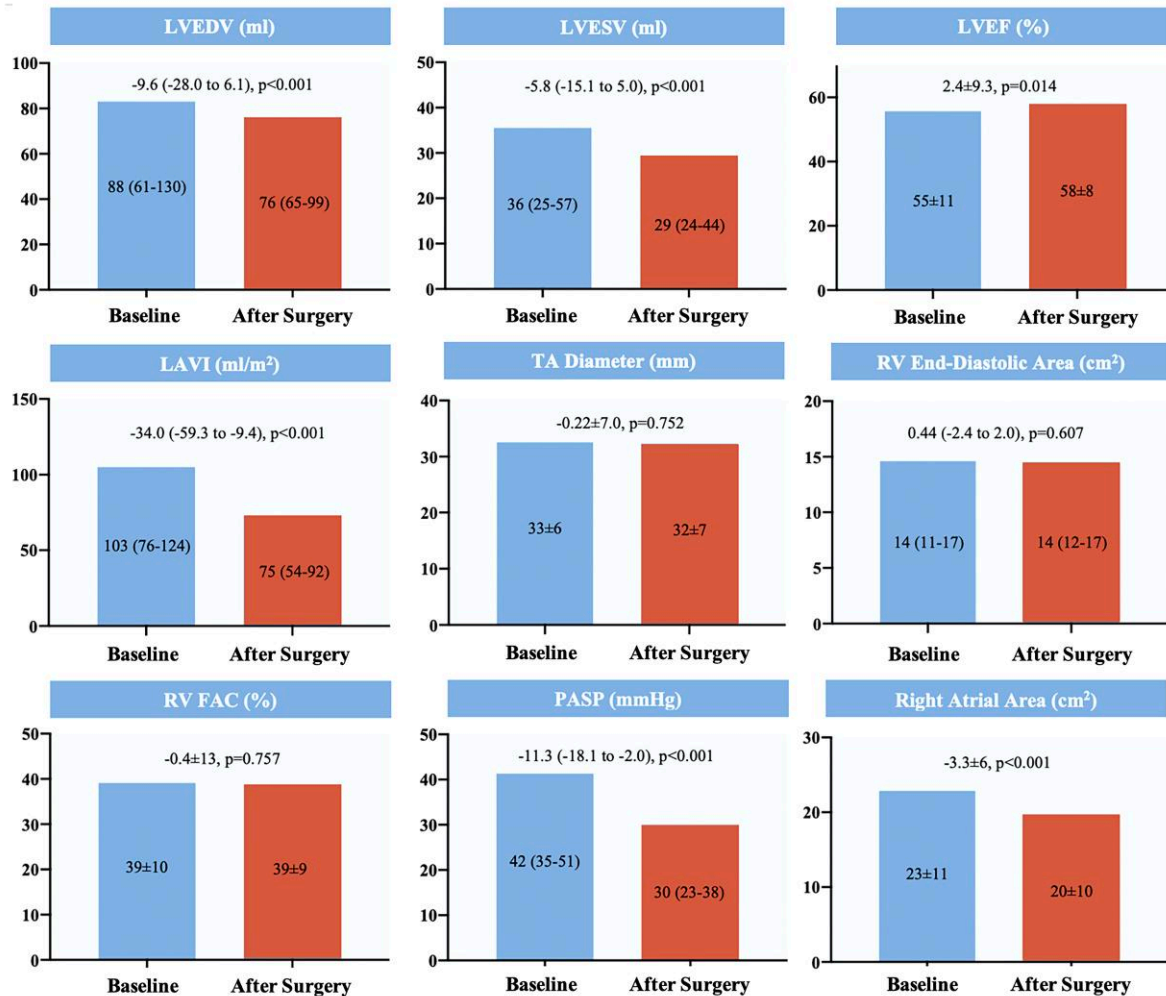
contractility of the interventricular septum with consequent RV dysfunction.<sup>22</sup> Clinically, RV dilation and dysfunction may manifest as worse symptomatic and functional status in isolated valvular disease.<sup>23</sup> The present data extend observations from isolated single valvular disease<sup>11,23</sup> and are the first to demonstrate that in those with concomitant aortic and mitral valve disease and demonstrate that advanced patterns of RV remodelling were characterized by worse clinical (higher EuroSCORE II, worse renal function) and echocardiographic parameters (lower LVEF, higher PASP, and lower RVFAC/PASP). Consequently, RV remodelling could reflect the clinical status and disease progression of patients with multiple valvular diseases.

### Prognostic value of RV remodelling in valvular surgery

While risk stratification in patients with left-sided heart valve disease has largely emphasized LV remodelling,<sup>4,6</sup> increasing attention is now directed towards the RV. In particular, RV dysfunction has emerged

as a strong prognosticator in patients with various valvular diseases<sup>9,11</sup> and valvular interventions. Kammerlander *et al.*,<sup>18</sup> using RVFAC, showed an association between RV systolic function and survival in left-sided valve surgery, but not RV dilation. Conversely, our group has previously shown that RV dilation was associated with adverse outcomes in patients undergoing TA.<sup>12</sup> While the discordant definitions of RV dilation and dysfunction can account for these diverting results, the general concept that RV remodelling confers significantly higher risk holds true independent of the method of assessment. Moreover, the gradient of risk associated with progressive RV remodelling highlights a potential interaction between RV dilation and dysfunction, which may potentiate each other to drive a heightened risk of adverse outcomes.

Interestingly, despite significant improvement in LV dimensions and function following double-valve surgery, RV size and systolic function stabilized in our cohort. While the possibility of RV recovery following cardiac surgery remains contentious,<sup>24,25</sup> prior studies suggest that normal ventricular size and function hold a greater potential for reverse remodelling.<sup>26</sup> Accordingly, the current study



**Figure 6** Longitudinal changes of echocardiographic parameters before and after concomitant aortic and mitral valve surgery.

demonstrates that pre-operative RV dilation may predict post-operative RV dysfunction. Thus, RV dysfunction conceivably represents a more advanced stage in the natural history of multiple valvular heart disease. These findings imply that an earlier surgery, before advanced LV and RV remodelling, may improve clinical outcomes and suggest a potential role for post-operative RV assessment in patients undergoing double-valve surgery.

## Clinical implications

Driven by aging populations, the prevalence of multiple valvular heart disease and the complexity of its management will continue to grow with escalating comorbidities, reinforcing the need for improved decision-making strategies. For these patients, surgery is the only definitive treatment and is indicated based on the consequences of valvular lesions, i.e. symptoms or LV dilatation or dysfunction.<sup>4,6</sup> However, subjective symptoms are difficult to interpret, and LV remodelling has been variably linked with adverse outcomes in patients with combined valvular lesions.<sup>5,8</sup> Thus, patients with multiple valvular diseases often experience delayed surgical treatment and suboptimal risk assessment.<sup>5,7,8</sup>

In this regard, outcome measures beyond that of the LV may be important for prognosis. The current study highlights the importance of RV remodelling in patients with multiple valvular heart disease, whereby RV dilation and dysfunction likely represent an advanced stage within its clinical spectrum. In turn, advanced RV remodelling portends an excess risk that may persist even after double-valve surgery. As such, beyond guideline-based surgical indications, RV assessment may provide unique insights into disease progression and prognosis in multiple valvular diseases. In particular, outcome prediction in double-valve surgery has long been hampered by the suboptimal performance of standard risk scores.<sup>27</sup> Accordingly, TA diameter and RVFAC may serve as pragmatic markers for risk stratification in double-valve surgery. Building on our findings, novel methods such as 3D echocardiography and cardiac magnetic resonance imaging that may better characterize RV remodelling merit future studies to determine their prognostic value.

## Limitations

This was a single-centre, retrospective study and was subject to limitations inherent to this type of study design. Our study included

patients with a heterogeneous mixture of valvular lesions and the role of the RV in specific combinations of dual valvular heart disease remains to be established. Nevertheless, RV remodelling was independently and incrementally linked to adverse events beyond clinical parameters and EuroSCORE II. While RVFAC has been well-validated against cardiac magnetic resonance and showed superior correlation compared with TAPSE,<sup>17</sup> it primarily measures radial contraction and neglects the contribution of the RV outflow tract to the overall RV systolic function. The implications of RV function, characterized by TAPSE, RV S', and RV ejection fraction, in patients undergoing concomitant aortic and mitral valve surgery requires further study. Finally, due to the limited number of patients with follow-up echocardiography, results are exploratory and warrant further confirmation in future studies.

## Conclusion

In patients undergoing double-valve surgery, RV remodelling (dilation and dysfunction), is frequent and associated with worse clinical status. At both baseline and 1 year following surgery, advanced patterns of RV remodelling were independently and incrementally linked to adverse outcomes. These findings emphasize the need to include RV assessment as part of the decision-making and risk assessment strategy in patients with multiple valvular heart disease.

## Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Imaging* online.

## Acknowledgements

The authors thank the medical and nursing staff of the Division of Cardiology, Queen Mary Hospital, for their help and support during this study.

## Funding

This study is supported by the Sanming Project of Medicine in Shenzhen, China (No. SZSM201911020) and HKU-SZH Fund for Shenzhen Key Medical Discipline (No. SZXK2020081).

**Conflict of interest:** None declared.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

## References

1. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003;**24**:1231–43.
2. Leavitt BJ, Baribeau YR, DiScipio AW, Ross CS, Quinn RD, Olmstead EM, et al. Outcomes of patients undergoing concomitant aortic and mitral valve surgery in northern new England. *Circulation* 2009;**120**(Suppl):S155–62.
3. Jamieson WR, Edwards FH, Schwartz M, Bero JW, Clark RE, Grover FL. Risk stratification for cardiac valve replacement. National Cardiac Surgery Database. Database Committee of the Society of Thoracic Surgeons. *Ann Thorac Surg* 1999;**67**:943–51.
4. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–91.
5. Gillinov AM, Blackstone EH, Cosgrove DM III, White J, Kerr P, Marullo A, et al. Mitral valve repair with aortic valve replacement is superior to double valve replacement. *J Thorac Cardiovasc Surg* 2003;**125**:1372–87.
6. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**:e521–643.
7. Connelly KA, Creati L, Lyon W, Yui M, Rosalion A, Wilson AC, et al. Early and late results of combined mitral-aortic valve surgery. *Heart Lung Circ* 2007;**16**:410–5.
8. Coutinho GF, Correia PM, Antunes MJ. Concomitant aortic and mitral surgery: to replace or repair the mitral valve? *J Thorac Cardiovasc Surg* 2014;**148**:1386–92.e1.
9. Dietz MF, Prihadi EA, van der Bijl P, Goedemans L, Mertens BJA, Gurosoy E, et al. Prognostic implications of right ventricular remodeling and function in patients with significant secondary tricuspid regurgitation. *Circulation* 2019;**140**:836–45.
10. Le Tourneau T, Deswarte G, Lamblin N, Foucher-Hosseine C, Fayad G, Richardson M, et al. Right ventricular systolic function in organic mitral regurgitation: impact of biventricular impairment. *Circulation* 2013;**127**:1597–608.
11. Boldt J, Zickmann B, Ballesteros M, Dapper F, Hempelmann G. Right ventricular function in patients with aortic stenosis undergoing aortic valve replacement. *J Cardiothorac Vasc Anesth* 1992;**6**:287–91.
12. Yiu KH, Wong A, Pu L, Chiang MF, Sit KY, Chan D, et al. Prognostic value of pre-operative right ventricular geometry and tricuspid valve tethering area in patients undergoing tricuspid annuloplasty. *Circulation* 2014;**129**:87–92.
13. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr* 2009;**10**:1–25.
14. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr* 2010;**11**:307–32.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;**7**:79–108.
16. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;**23**:685–713; quiz 86–8.
17. Anavekar NS, Gerson D, Skali H, Kwong RY, Yucel EK, Solomon SD. Two-dimensional assessment of right ventricular function: an echocardiographic-MRI correlative study. *Echocardiography* 2007;**24**:452–6.
18. Kammerlander AA, Marzluf BA, Graf A, Bachmann A, Kocher A, Bonderman D, et al. Right ventricular dysfunction, but not tricuspid regurgitation, is associated with outcome late after left heart valve procedure. *J Am Coll Cardiol* 2014;**64**:2633–42.
19. Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. *JAMA* 2015;**313**:409–10.
20. Dandel M, Hetzer R. Echocardiographic assessment of the right ventricle: impact of the distinctly load dependency of its size, geometry and performance. *Int J Cardiol* 2016;**221**:1132–42.
21. Westerhof BE, Saouti N, van der Laarse WJ, Westerhof N, Vonk Noordegraaf A. Treatment strategies for the right heart in pulmonary hypertension. *Cardiovasc Res* 2017;**113**:1465–73.
22. Nagel E, Stuber M, Hess OM. Importance of the right ventricle in valvular heart disease. *Eur Heart J* 1996;**17**:829–36.
23. Iacuzio L, Essayagh B, Civaia F, Dan Schouver E, Rusek S, Dommerc C, et al. Right-sided heart structural and functional remodeling in mitral regurgitation secondary to mitral valve prolapse. *Am J Cardiol* 2018;**122**:2095–103.
24. Mandoli GE, Cameli M, Novo G, Agricola E, Righini FM, Santoro C, et al. Right ventricular function after cardiac surgery: the diagnostic and prognostic role of echocardiography. *Heart Fail Rev* 2019;**24**:625–35.
25. Orde SR, Chung SY, Pulido JN, Suri RM, Stulak JM, Oh JK, et al. Changes in right ventricle function after mitral valve repair surgery. *Heart Lung Circ* 2020;**29**:785–92.
26. Suri RM, Schaff HV, Dearani JA, Sundt TM, Daly RC, Mullany CJ, et al. Recovery of left ventricular function after surgical correction of mitral regurgitation caused by leaflet prolapse. *J Thorac Cardiovasc Surg* 2009;**137**:1071–6.
27. Velicki L, Cemerlic-Adzic N, Pavlovic K, Mihajlovic BB, Bankovic D, Mihajlovic B, et al. Clinical performance of the EuroSCORE II compared with the previous EuroSCORE iterations. *Thorac Cardiovasc Surg* 2014;**62**:288–97.