Male–female differences in characteristics and early outcomes of patients undergoing tricuspid valve surgery: a national cohort study in the Netherlands

Kevin M. Veen, Mostafa M. Mokhles, Jerry Braun, Michel I.M. Versteegh, Ad J.J.C. Bogers and Johanna J.M. Takkenberg, on the behalf of the data registry committee of the Netherlands Association for Cardio-Thoracic Surgery

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ABSTRACT

Objectives

This study aims to explore male–female differences in baseline and procedural characteristics, and outcomes of patients undergoing isolated or concomitant tricuspid valve (TV) surgery.

Methods

All TV procedures registered between 2007 and 2016 in the database of the Netherlands Association for Cardio-Thoracic Surgery were analysed. Logistic regression analyses with interaction terms were used to determine whether sex was associated with hospital mortality.

Results

Five thousand five hundred and eighty-two patients underwent TV surgery [isolated: $N = 685$ (49% male), TV_{repair}: $N = 5286$ (50% male) and $TV_{replacement}$: $N = 250$ (46% male)]. In the TV_{repair} group, females were significantly older, had less prior percutaneous/surgical coronary interventions, less extracardiac arteriopathies, a lower prevalence of renal impairment, less endocarditis, a lower prevalence of preoperative critical condition, less recent myocardial infarction, less concomitant coronary artery bypass grafting (CABG) and, in case of concomitant mitral valve surgery, less concomitant mitral valve repair compared to males. In the $TV_{replacement}$ group, females more often had a history of prior valve surgery and less prior CABG. Hospital mortality for males and females was 7.0% ($N = 183$) and 6.1% ($N = 163$), $P = 0.241$ in the TV_{repair} group and 2.6% ($N = 3$) and 8.8% ($N = 12$), $P = 0.074$ in the $TV_{replacement}$ group. Sex was not associated with hospital mortality (odds ratio (OR) 1.14, 95% confidence interval (CI) 0.88–1.48; $P = 0.322$). Sex demonstrated a significant interaction with the parameter 'critical preoperative condition' (OR 0.44, 95% CI 0.22–0.90; $P = 0.026$).

Conclusions

Substantial differences in patient and procedural characteristics existed between male and female patients undergoing TV surgery, although sex was not a derterminant for hospital mortality. Nevertheless, sex interacted with a critical preoperative condition, indicating the usefulness of separate risk factor models for males and females requiring TV surgery.

Keywords

Tricuspid valve surgery • Sex differences

INTRODUCTION

Male–female differences in cardiac diseases are being increasingly recognized and incorporated in risk models [1]. Outcomes for female patients have been reported to be less favourable than those for male patients, especially regarding in-hospital mortality [2–4]. Most reported series have focused on male–female specific outcomes after coronary artery bypass grafting (CABG) or mitral valve surgery [2, 3, 5] and data on male–female specific outcomes after tricuspid valve (TV) surgery remain scarce. TV regurgitation is reported to be more prevalent in women [6] and, overall, TV surgery, especially TV replacement is predominantly performed in females [7, 8]. Elucidating sex differences and identifying sexspecific risk factors in patients undergoing TV surgery could lead to better insight in disease presentation, treatment differences and outcomes. Hence, we aimed to study male–female differences in baseline and procedural characteristics, and outcomes after TV surgery using data from a Dutch nationwide prospective database. Given the relationship between aetiology and choice of surgery (repair versus replacement), both groups were analysed separately. In addition, patients undergoing isolated TV surgery were analysed separately. The performance of logistic EuroSCORE I was tested in all the subgroups. It was investigated whether sex-specific risk models are necessary. Furthermore, it was investigated whether sex is associated with the probability of undergoing TV repair versus TV replacement, and undergoing isolated TV surgery versus multiple valve surgery.

METHODS

Data source

The national database of the Netherlands Association for Cardio- Thoracic Surgery is a prospective database that contains anonymized patient data on baseline a procedural characteristics, risk factors and outcomes. Risk factors were defined according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE I) model [9]. Specifically, a critical preoperative condition was defined as: ventricular tachycardia/ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative inotropes or intra-aortic balloon pump, preoperative acute renal failure (anuria or oliguria <10 ml/h) [9]. A detailed description of the database has been published previously [10]. Approval from the data registry committee of Netherlands Association for Cardio-Thoracic Surgery was obtained to analyse this dataset.

In total, 15 466 procedures involving a heart valve were registered in the Netherlands from 1 January 2007 to 31 December 2016, of which 5582 were isolated or concomitant TV repair or replacement. The type of TV surgery was not known in 46 patients, who were omitted in the analyses of the TV repair and replacement subgroups.

Missing values

The national database of the Netherlands Association for Cardio- Thoracic Surgery has an exceptionally high degree of completeness in regards to most variables. However, missing data were not clustered and the exclusion of incomplete cases would significantly reduce the dataset. Therefore, multiple imputation by chained equations was performed to impute missing values. Five imputed datasets were generated using this method using 5 iterations each. All baseline variables were imputed, except for atrium septum defect and left ventricular function, since >30% of the data was missing. Imputation was done based on the other baseline variables. The imputations were visually checked by strip plots and density plots. The imputed datasets were used for the logistic regression models and to test the performance of EuroSCORE I.

Statistical analyses

Variables were presented as mean ± standard deviation (Gaussian) and as median [interquartile range (IQR)] (non- Gaussian). Categorical data was presented as percentages. Normality was tested using the Shapiro–Wilk test. Comparisons were made with the Student's t-test or Mann–Whitney test, as appropriate. Categorical data were compared with the χ^2 test or Fisher's exact test, as appropriate. A *P*-value of <0.05 was considered statistically significant. Both univariable and multivariable logistic regressions were used to explore determinants of hospital mortality, TV replacement (versus repair) and isolated TV surgery (versus multiple valve surgery). Included variables are shown in Supplementary Material, Table S1. Two modelling strategies were applied for hospital mortality. Firstly, a risk factor modelling approach was applied, forcing all variables in a multivariable model, regardless of significance. Interaction terms of sex and other variables were explored and significant interaction terms were incorporated in the multivariable model. Secondly, modelling hospital mortality in the males and females separately, an approach using forwards and backwards elimination was applied (Supplementary Material, Fig. S1), in order to obtain most important determinants in these populations. The latter was also applied for TV replacement and isolated TV surgery. In addition, in the final multivariable models of TV replacement and isolated TV surgery, it was tested whether sex interacted with the remaining covariates. In case of highly correlated variables, variables with most clinical relevance were entered the multivariable model. Correlation was tested with the Pearson or the Spearman method, as appropriate. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Linearity of continuous variables in the logit was checked using fractional polynomials. Model discrimination was assessed with area under the curve and model calibration was tested using the Hosmer–Lemeshow test (10 categories). Performance of EuroSCORE I was tested in the same manner. Statistical analyses were done in R (R Foundation for Statistical Computing, Vienna, Austria, version 3.3.3) with the use of the 'glm', 'MICE' and 'mfp' package.

RESULTS

Isolated tricuspid valve surgery

In total, 685 patients underwent isolated TV surgery. Table 1 presents baseline characteristics of patients undergoing isolated TV surgery. The type of TV surgery was comparable between males and females (replacement: 21.6% in females and 18.9% in males, $P = 0.434$). In case of a valve replacement, valve type was comparable between males and females (biological valve: 54.8% in females vs 47.6% in males, $P = 0.507$). Male patients underwent concomitant CABG more frequently (21.8%, $N = 74$) compared to female patients (11.8%, $N = 41$, $P < 0.001$).

Hospital mortality was 5.8% ($N = 20$) in females and 7.1% ($N = 24$) in males ($P = 0.591$). Hospital stay was longer in males compared to females (10.5 days, IQR 7.00–24.75 vs 8 days, IQR 6.00–16.00; $P = 0.011$).

Tricuspid valve repair

TV repair was performed in the majority of patients ($N = 5286$), of whom 50.3% were female and 49.7% male ($P = 0.66$). Baseline characteristics are presented in Table 1 and procedural characteristics in Table 2.

Hospital mortality in males and females was 7.0% ($N = 183$) and 6.1% ($N = 163$) $P = 0.241$, respectively. In approximately half the population, hospital stay was reported, which did not differ between males and females (median 8 days, IQR 6–14 vs median 8 days, IQR 6–13; $P = 0.367$). Comparable hospital mortality was found in the different age groups (Fig. 1), which was also true for the subgroups TV repair and replacement.

Tricuspid valve replacement

TV replacement was performed in the minority of patients ($N = 250$), of whom 45.6% were male and 54.4% female. Female patients underwent more prior valve surgery of one or more heart valves (Table 1). Data specifying which valve had been previously operated on were not collected uniformly (222 missing of 250 patients). No differences in procedural characteristics were found, except for CABG, which was performed more frequently in males (Table 2). Valve type (biological versus mechanical) was comparable between sexes ($P = 0.513$).

Hospital mortality in males and females was 2.6% ($N = 3$) and 8.8% ($N = 12$) ($P = 0.074$). Median hospital stay was comparable (females 10, IQR 7–19 days vs males 12.5, IQR 7–21 days; $P = 0.329$).

Table 1: Patient characteristics of males and females undergoing tricuspid valve repair or replacement

		Isolated TVS			TV repair			TV replacement		
Characteristics	**Entire cohort**	**Male**	**Female**	***P*-value**	**Male**	**Female**	**P-value**	**Male**	**Female**	***P*-value**
N	5582	339	346		2627	2659		114	136	
Age (years), median (IQR)	70 (61–75)	62 (49–71)	63 (49–71)	0.675	69 (61–75)	71 (63–76)	<0.001	59.5 (46–68)	59.5 (48–69.25)	0.85
Prior PCI, *n* (%)	287 (6.9)	27 (11.1)	7 (3.3)	0.003	177 (9.0)	100 (5.0)	<0.001	2 (2.3)	5 (5.3)	0.446
Prior CABG, *n* (%)	275 (5.4)	31 (10.2)	13 (4.5)	0.012	163 (6.7)	100 (4.2)	<0.001	7 (6.9)	3 (2.5)	0.192
Prior valve surgery, *n* (%)	576 (11.3)	49 (16.1)	57 (19.5)	0.319	237 (9.8)	263 (10.9)	0.208	24 (23.5)	48 (39.7)	0.015
Prior aortic surgery, *n* (%)	42 (0.9)	3 (1.0)	3 (1.1)	1.000	23 (1.0)	16 (0.7)	0.342	1 (1.0)	2 (1.7)	0.999
ASD, *n* (%)	162 (5.4)	28 (13.4)	42 (21.3)	0.048	59 (4.1)	90 (6.5)	0.007	4 (5.3)	6 (6.8)	0.754
Chronic lung disease, *n* (%)	833 (15.0)	33 (9.8)	35 (10.2)	0.949	418 (15.9)	387 (14.6)	0.18	9 (7.9)	14 (10.4)	0.651
Extracardiac arteriopathy, *n* (%)	395 (7.1)	19 (5.6)	12 (3.5)	0.252	233 (8.9)	148 (5.6)	<0.001	7 (6.1)	4 (3.0)	0.354
Neurological dysfunction, *n* (%)	168 (3.0)	6 (1.8)	7 (2.0)	1.000	72 (2.7)	91 (3.4)	0.177	1 (0.9)	4 (3.0)	0.379
Renal impairment, *n* (%)	169 (3.1)	18 (5.4)	6 (1.8)	0.019	108 (4.2)	49 (1.9)	<0.001	4 (3.5)	4 (3.0)	0.999
Endocarditis, *n* (%)	227 (4.1)	35 (10.4)	17 (5.0)	0.012	122 (4.7)	72 (2.7)	<0.001	16 (14)	10 (7.4)	0.135
Critical preoperative condition *n* (%)	268 (4.8)	45 (13.3)	21 (6.1)	0.002	159 (6.1)	93 (3.5)	<0.001	5 (4.4)	8 (5.9)	0.796
Unstable AP, *n* (%)	34 (0.6)	4 (1.2)	7 (2.0)	0.560	18 (0.7)	13 (0.5)	0.45	0 (0.0)	1 (0.7)	0.999
Recent MI, *n* (%)	187 (3.4)	20 (5.9)	12 (3.5)	0.190	114 (4.3)	65 (2.5)	<0.001	1 (0.9)	1 (0.7)	0.999
Pulmonary hypertension, *n* (%)	721 (13.0)	25 (7.4)	17 (5.0)	0.244	334 (12.8)	364 (13.8)	0.299	7 (6.1)	12 (8.9)	0.479
Emergency operation, *n* (%)	109 (2.0)	14 (4.1)	18 (5.2)	0.617	46 (1.8)	48 (1.8)	0.966	5 (4.4)	4 (3.0)	0.736

Percentages excluded missing cases.

AP: angina pectoris; ASD: atrium septum defect; CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention; TVS: tricuspid valve surgery.

Table 2: Procedural characteristics of males and females undergoing tricuspid valve repair or replacement

		TV repair			TV replacement		
Characteristics	**Entire cohort, *n* (%)**	**Male, *n* (%)**	**Female, *n* (%)**	***P*-value**	**Male, *n* (%)**	**Female, *n* (%)**	**P-value**
N	5582	2627	2659		114	136	
CABG	1399 (25.1)	851 (32.4)	514 (19.3)	<0.001	12 (10.5)	5 (3.7)	0.043
Arterial graft/venous graft	652 (46.7)	436 (51.3)	204 (39.8)	<0.001	3 (25.0)	2 (40.0)	0.783
Arterial graft	373 (26.6)	213 (23.6)	155 (30.2)		7 (58.3)	2 (40.0)	
Venous graft	371 (26.7)	201 (25.1)	154 (30.0)		2 (16.7)	1 (20.0)	
Aortic valve surgery	112 (19.9)	514 (19.6)	557 (21.0)	0.219	11 (9.6)	19 (14.0)	0.394
Repair	57 (5.1)	21 (4.1)	33 (5.9)	0.220	2 (18.2)	1 (5.3)	0.537
Replacement	1056 (94.9)	494 (95.9)	524 (94.1)		9 (81.8)	18 (94.7)	
Bio	745 (70.5)	368 (74.4)	361 (68.9)	0.147	3 (33.3)	10 (55.6)	0.420
Mechanical	307 (29.1)	124 (25.2)	161 (30.7)		6 (66.7)	8 (44.4)	
Homograft	4 (0.4)	2 (0.4)	2 (0.4)		0 (0.0)	0	
Mitral valve surgery	4473 (80.1)	2200 (83.7)	2178 (81.9)	0.083	31 (27.2)	33 (24.3)	0.702
Repair	3273 (73.3)	1770 (80.6)	1463 (67.2)	<0.001	14 (45.2)	11 (33.3)	0.476
Replacement	1193 (26.7)	426 (19.4)	713 (32.8)		17 (54.8)	22 (66.7)	
Bio	469 (38.8)	158 (36.2	286 (39.8)	0.241	9 (52.9)	13 (59.1)	0.754
Mechanical	731 (61.2)	273 (63.8)	268 (60.2)		8 (47.1)	9 (40.9)	
Homograft	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Pulmonary valve surgery	88 (1.6)	25 (1.0)	31 (1.2)	0.529	13 (11.4)	18 (13.2)	0.806
Repair	7 (4.8)	6 (16.0)	1 (0.0)	0.086	0 (0.0)	0 (0.0)	1
Replacement	80 (95.2)	21 (84.0)	29 (100)		12 (100)	18 (100)	
Bio	20 (25.3)	5 (23.8)	6 (20.7)	0.258	6 (50.0)	3 (17.6)	0.106
Mechanical	22 (27.8)	2 (9.5)	1 (3.4)		6 (50.0)	13 (76.5)	
Homograft	37 (46.8)	14 (66.7)	22 (75.9)		0 (0)	1 (5.9)	

Table 2: Procedural characteristics of males and females undergoing tricuspid valve repair or replacement (continued)

		TV repair			TV replacement		
Tricuspid valve replacement	250 (4.5)	0 (0.0)	0 (0.0)		114 (100)	136 (100)	
Bio	134 (54.0)				58 (51.3)	76 (56.3)	0.513
Mechanical	114 (46.0)				55 (48.7)	59 (43.7)	
Isolated tricuspid valve surgery	12.2 (685)	270 (10.2)	268 (10.1)	0.180	63 (55.2)	74 (54.4)	0.999
Aortic surgery	176 (3.2)	95 (3.6)	75 (2.8)	0.120	0 (0.0)	3 (2.2)	0.253
Rhythm surgery	1464 (26.2)	713 (27.1)	730 (27.1)	0.810	7 (6.1)	7 (6.1)	0.787

Percentages excluded missing cases.
CABG: coronary artery bypass grafting; TV, tricuspid valve.

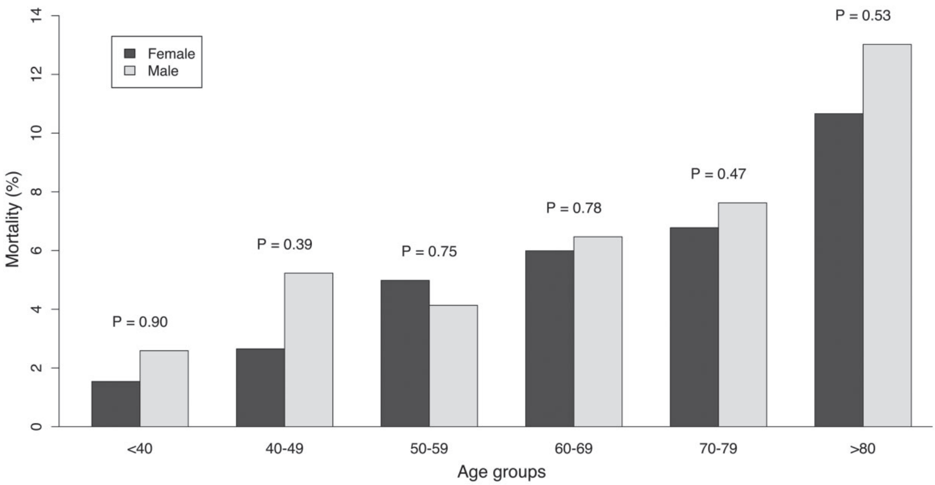

Figure 1: Hospital mortality in males and females of the entire cohort, stratified by age.

Performance of EuroSCORE I

Performance of EuroSCORE I is presented in Table 3. Observed/expected ratio was less than 1 in all groups (Supplementary Material, Tables S2–S7).

Determinants of hospital mortality

Determinants of hospital mortality were only explored in the TV repair subpopulation, because of limited number of events in the TV replacement and isolated TV subgroup (Supplementary Material, Table S8). Sex was not significantly associated with hospital mortality, even when adjusted for possible confounders (OR 1.15, 95% CI 0.88–1.49; *P* = 0.31). However, sex demonstrated a significant interaction with a critical preoperative condition (OR 0.44, 95% CI 0.22–0.90; *P* = 0.026) (Supplementary Material, Table S8). Table 4 presents determinants associated with hospital mortality for male and female patients separately. Age was associated with hospital mortality after TV repair in a linear fashion for females, but not for males. The determinant 'critical preoperative condition' weighted ~2.8 times heavier in females compared to males.

Table 3: Calibration and discrimination of EuroScore I in dif-ferent subgroups

Group	*N*	*P*-value Hosmer–Lemeshow test	AUC (95% CI)
Entire cohort	1517	<0.0001	0.73 (0.67–0.79)
Male	780	0.0001	0.72 (0.64–0.81)
Female	737	<0.0001	0.73 (0.65–0.82)
TV repair	1420	<0.0001	0.73 (0.67–0.79)
Male	736	0.0005	0.72 (0.64–0.81)
Female	684	<0.0001	0.74 (0.62–0.83)

AUC: area under the curve; CI: confidence interval; TV, tricuspid valve.

Table 4: Multivariable models of hospital mortality in the tricuspid valve repair group, stratified by sex

Characteristics	Multivariable male		Multivariable female	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age(FP for males)	1.00 (1.00–1.00)*	<0.001	1.05 (1.03–1.07)	<0.001
Prior CABG	2.08 (1.30–3.35)	0.003		
Chronic lung disease	1.90 (1.31–2.72)	0.001		
Creatinine > 200	3.90 (2.34–6.49)	<0.001	2.32 (1.02–5.26)	0.046
Critical preoperative condition	3.32 (2.10–5.31)	<0.001	9.30 (5.37–16.12)	<0.001
Concomitant CABG	1.90 (1.38–2.64)	<0.001	2.56 (1.79–3.67)	<0.001
AV repair			4.81 (1.67–13.87)	0.004
AV replacement	2.23 (1.60–3.13)	<0.001	2.75 (1.93–3.94)	<0.001
MV replacement	2.29 (1.60–3.29)	<0.001		
Endocarditis			2.94 (1.40–6.23)	0.005
Pulmonary hypertension			1.82 (1.21–2.75)	0.004
Area under curve	0.77 (0.74–0.81)		0.80 (0.76–0.83)	
P-value Hosmer–Lemeshow test	0.08		0.88	

FP male = $(age)^3$. *Due to the FP the estimates are small, resulting in a rounded hazard of 1.00.
AV: aortic valve; CABG: coronary artery bypass grafting; CI: confidence interval; FP, fractional polynomial; MV: mitral valve; OR: odds ratio.

Determinants of tricuspid valve replacement versus tricuspid valve repair

Sex was not a derterminant for the probability of undergoing TV replacement versus TV repair in univariable analyses (OR 0.86, 95% CI 0.67–1.11; *P* = 0.246). Determinants of the probability of undergoing TV replacement are presented in Table 5. The odds of requiring TV replacement increased from young age to midlife and decreased thereafter, with 2 fractional polynomials best describing this relationship. Sex did not interact significantly with the included variables. However, a trend was noted for the interaction between the term 'prior valve surgery' and sex (OR 0.53, 95% CI 0.28–1.01; *P* = 0.062) (Supplementary Material, Table S9).

Determinants of isolated tricuspid valve surgery versus multiple valve surgery

Sex was not a determinant for the probability of undergoing isolated TV surgery (OR 1.00, 95% CI 0.85–1.70; *P* = 0.996). Table 5 presents determinants of undergoing isolated TV surgery. Sex had a significant interaction with the term 'critical preoperative condition' (OR 2.44, 95% CI 1.21–4.90; *P* = 0.012), making it a stronger predictor in males (Supplementary Material, Table S10).

Table 5: Multivariable determinants of the probability of undergoing tricuspid valve replacement versus tricuspid valve repair and isolated tricuspid valve surgery versus multiple valve surgery

Characteristics	OR (95% CI)	*P*-value
Tricuspid valve replacement versus repair		
Age$_{(FP1)}$	0.88 (0.83–0.93)	<0.001
Age$_{(FP2)}$	0.02 (0.01–0.09)	<0.001
Prior valve surgery	2.11 (1.53–2.92)	<0.001
AV replacement	0.38 (0.25–0.6)	<0.001
MV repair	0.06 (0.04–0.09)	<0.001
MV replacement	0.17 (0.12–0.25)	<0.001
PV surgery	2.39 (1.41–4.05)	0.001
Rhythm surgery	0.29 (0.17–0.51)	<0.001
Aortic surgery	0.27 (0.08–0.9)	0.034
Other cardiac surgery	1.78 (1.21–2.62)	0.007
Endocarditis	1.83 (1.13–2.96)	0.014
AUC	0.88 (0.85–0.90)	
P-value Hosmer–Lemeshow	0.86	
Isolated tricuspid valve surgery versus multiple valve surgery		
Age	0.96 (0.95–0.96)	<0.001
TV replacement	7.39 (5.53–9.78)	<0.001
Rhythm surgery	0.57 (0.45–0.73)	<0.001
Critical preoperative condition	1.86 (1.32–2.59)	<0.001
Unstable angina pectoris	3.16 (1.38–7.32)	0.007
Pulmonary hypertension	0.41 (0.29–0.57)	<0.001
Postinfarct VSR	10.91 (3.78–31.5)	<0.002
AUC	0.74 (0.73–0.77)	
P-value Hosmer–Lemeshow	0.66	

$FP1 = \frac{1}{\left(\frac{age}{100}\right)^2}$, $FP2 = age/100$.

AUC: area under curve; AV: aortic valve; CI: confidence interval; MV: mitral valve; OR: odds ratio; PV: pulmonary valve; TV: tricuspid valve; VSR: ventricular septal rupture.

DISCUSSION

Significant male–female differences were found in both patient and procedural characteristics in patients undergoing TV surgery. Early mortality did not differ between males and females, even across the different age groups. Sex was not found to be a predictor of hospital mortality during TV repair. This is contrary to previous studies exploring male–female differences in other procedures [2, 11]. Nevertheless, these results are in agreement with previous studies focusing on isolated TV surgery [12, 13]. In addition, different determinants associated with hospital mortality in males and females were found. Sex interacted with determinants associated with TV replacement versus repair and isolated valve surgery versus multiple valve surgery.

Tricuspid valve repair

In TV repair surgery in the Netherlands, female patients presented at an older age, while male patients presented with more comorbidities. In case of concomitant mitral valve surgery, females received mitral valve replacement more often. This is in line with our previous study on isolated mitral valve surgery [5]. Unfortunately, the registry did not contain data on the aetiology of the valve disease. However, concomitant mitral and aortic valve surgery was performed frequently in this cohort and a recent systematic review found that in 85% of TV repair cases, the underlying aetiology was functional regurgitation [8]. In this respect, 2 other observations are interesting: in the general population, TV regurgitation is more prevalent in females [6] and female patients more frequently undergo TV interventions during mitral valve surgery [7]. These data raise 2 interesting questions: is it possible that female patients are more prone to TV regurgitation and does this occur earlier in the natural history of the disease compared to males? It has been reported that tricuspid annular circumference corrected for heart weight is larger in females compared to males and that the tricuspid annulus of females had a lesser degree of annular cellularity, which may lead to TR faster [14]. Furthermore, if females are more prone to TR, uncorrected TV regurgitation during left-sided valve surgery may be more progressive in females. Controversy exists as to whether sex is an independent predictor for progressive tricuspid regurgitation after left-sided valve surgery. Several studies found it to be predictive [15, 16], while others did not [17, 18]. Another explanation might be that confounding factors associated with TR, such as atrium septum defect with enlarged right atrium or atrial fibrillation [19], are more prevalent in females. This also seems to be partly the case in the cohort described by Vassileva et al. [7] analysing Medicare data, in which females underwent concomitant TV surgery more frequently, but also had a higher prevalence of atrial fibrillation. Further research on this topic is warranted, because if functional TR has a sex-dependent component, this may have major implications on the choice of whether or not to perform concomitant TV surgery.

Tricuspid valve replacement

TV replacement is performed rarely in the Netherlands. Contrary to the previous literature, TV replacement is approximately equally divided between males and females (46% males vs 54% females) [8]. Females undergoing TV replacement more frequently had prior heart valve surgery. These results match prior reported series in which the majority of patients undergoing TV operation after previous left-sided or TV surgery were females [20, 21]. Leviner et al. [22] noted that females undergoing TV replacement tended to have more previous surgery (P = 0.08) and were older (P = 0.04). Additionally, sex was not a predictor of late mortality in their cohort.

Isolated tricuspid valve surgery

Not surprisingly, length of hospital stay was longer in male patients because they were in a worse preoperative condition and underwent more concomitant CABG. Chandrashekar et al. [13] did not observe differences in length of stay between males and females when analysing the National Inpatient Sample database of the USA. However, they excluded patients with concomitant non-CABG surgery or endocarditis, which have been shown to be associated with longer hospital stay [23]. In this cohort, male patients had endocarditis more frequently (P = 0.012).

Determinants of hospital mortality after tricuspid valve repair

Sex was not a predictor of hospital mortality after TV repair, but mortality was, among others, associated with renal impairment, concomitant CABG and aortic valve replacement and a critical preoperative condition. Interestingly, while using the same modelling strategy, modelling of determinants of hospital mortality for males and females separately resulted in different models. This may indicate that some determinants were more predictive in either males or females. In this regard, sex-specific predictive models may be needed. Discrimination of EuroSCORE I was comparable between males and females and EuroSCORE I uniformly overpredicted mortality in this population. However, calibration was relatively better in males. Our group has previously shown that EuroSCORE I predicted hospital mortality relatively better in male patients undergoing isolated mitral valve surgery, both in terms of accuracy and calibration [5]. Furthermore, Massoudy et al. [24] showed that sex-specific weighting was needed to improve the predictability of EuroSCORE I in females. These findings support the need for sexspecific risk prediction models since some determinants have a more considerable impact on patient outcome based on sex.

Determinants of tricuspid valve replacement and isolated tricuspid valve surgery

The predictors associated with a higher chance of undergoing TV replacement rather than repair were endocarditis, other cardiac surgery and prior valve surgery, indicating that TV replacement was performed in case of structural valve damage or prior valve surgery. Additionally, pulmonary valve surgery was associated with TV replacement. In this case, the underlying aetiology may be carcinoid heart valve disease, because both pulmonary and TV are often affected simultaneously in patients with carcinoid heart valve disease [25]. Factors associated with a lower chance of undergoing TV replacement were concomitant mitral valve surgery, aortic valve surgery and aortic surgery, indicating that, in these patients, TV disease was secondary to left-sided valve disease and, therefore, functional in nature, for which a replacement of the valve was not necessary. Interestingly, a trend was found of sex interacting with prior valve surgery. Specifically, in females, prior valve surgery was more associated with TV replacement than in males, matching the observations by Leviner et al. [22]. In line with the reasoning above, this may indicate that females are more prone for recurrent tricuspid regurgitation. However, since it was not known which valve had been previously operated on, this could not be confirmed.

A critical preoperative condition and TV replacement were associated with a higher probability of undergoing isolated TV surgery, suggesting that isolated TV surgery was only performed when absolutely necessary and in the case that the underlying cause may be either primary TV disease or progression/recurrence of tricuspid regurgitation after prior valve surgery. Sex had a significant interaction with a preoperative critical condition, and was associated with a higher chance of undergoing isolated TV surgery in males.

Strengths and limitations

A major strength of this study is that we were able to use a nationwide database of adult cardiac surgery procedures, with exceptionally high degree of completeness. Nevertheless, TV replacement is performed rarely, which prohibits extensive modelling in this subpopulation. Another limitation was that this database does not record valve disease aetiology. Our modelling strategy may have caused some overfitting due to the 2 selection steps. Therefore, we expect that this model would not perform as well with external data. However, our aim was to explore which covariates were important in males compared to females, and whether this resulted in the same models, rather than to develop a prediction model in this subpopulation of mostly concomitant TV surgery. Furthermore, a prediction model will be mainly driven by initial indication, which is in most cases left-sided valve surgery. Due to multiple testing, especially of the baseline variables, it is possible that some differences were found by chance.

CONCLUSION

In TV surgery, substantial differences in patient and procedural characteristics exist between males and females. Sex is not a risk factor for hospital mortality or undergoing TV replacement versus TV repair. However, differences in the models for hospital death after TV repair were observed for females and males, characterized by a stronger effect of a preoperative critical condition in females. These observations indicate the need for separate risk factor models for males and females. Furthermore, sex interacted with preoperative critical condition, which in term was associated with undergoing isolated TV surgery versus multiple valve surgery (with a stronger effect in males), suggesting that the decision to perform isolated TV surgery may be sex-dependent.

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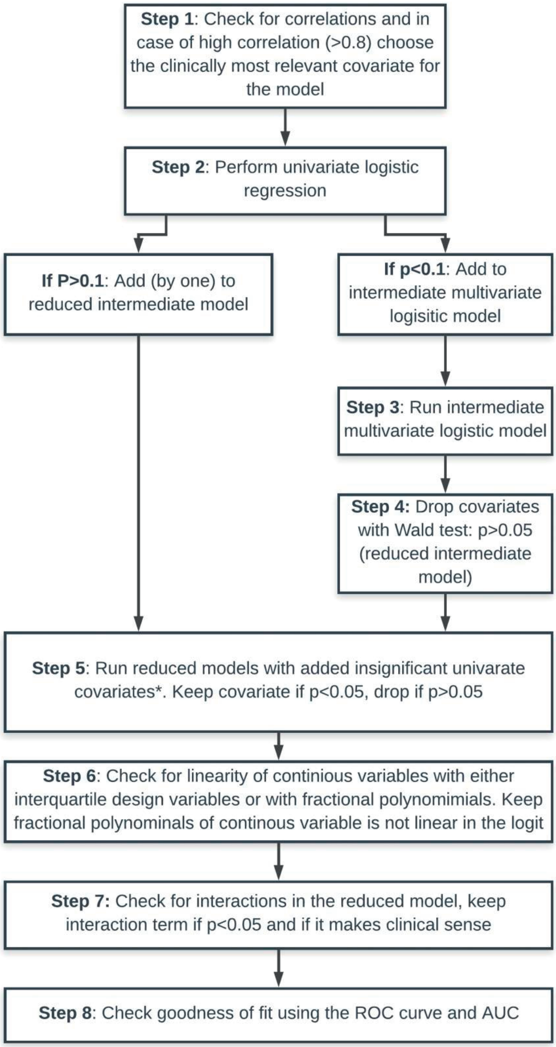
SUPPLEMENTARY MATERIAL

CONTENTS

Supplementary figure 1: Flow chart of modeling technique



Supplementary Table 1: Percentage missing per variables and variables used in analyses. *: indicates this variable was tested in univariable analyses. TVR: tricuspid valve replacement, TVS: tricuspid valve surgery

Characteristic	Percentage missing (%)	Univariable analyses mortality	Univariable analyses determinants TVR	Univariable analyses determinant isolated TVS
Age	0.00	*	*	*
Sex	0.00	*	*	*
Prior PCI	25.13	*	*	*
Prior CABG	8.81	*	*	*
Prior valve surgery	8.81	*	*	*
Prior aortic sugery	15.03	*	*	*
Concomitant CABG	0.02	*	*	*
Arterial graft	0.00			
Venous graft	0.00			
Aortic valve surgery	0.04			
Aortic valve procedure	0.56	*	*	
Aortic valve implant	0.56			
Mitral valve surgery	0.00			
Mitral valve procedure	0.32	*	*	
Mitral valve implant	0.23			
Pulmonary vavle surgery	0.04			
Pulmonary valve procedure	0.70	*	*	
Pulmonary valve implant	0.70			
Tricuspid valve surgery	0.00			
Tricuspid valve procedure	0.82		Dependent	*
Tricuspid valve implant	0.09			
Aortic surgery	0.04	*	*	*
Rythm surgery	0.04	*	*	*
ASD	46.01			
Chronic lung disease	0.21	*	*	*
Extracardiac ateriopathy	0.21	*	*	*
Neurlogical dysfunction	0.21	*	*	*
Creatinine >200	0.97	*	*	*
Endocarditis	0.23	*	*	*
Critical preoperative condition	0.21	*	*	*
Instable angina pectors	0.21	*	*	*
Recent MI	0.23	*	*	*
Pulmonary hypertension	0.91	*	*	*
Emergency surgery	0.21	*	*	*
Postinfarct VSR	0.20	*	*	*
Left ventricular function	72.0			
Isolated TVR	0.0			Dependent

Supplementary Table 2: Observed and expected frequencies in entire cohort. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	155.6	153.504	1	3,096	0,32
Quantile 2	148	144.659	1	4,341	0,23
Quantile 3	147	145.142	4	5,858	0,68
Quantile 4	164.8	159.572	3	8,228	0,36
Quantile 5	130.6	127.161	4,6	8,039	0,57
Quantile 6	144.2	139.943	6,4	10,657	0,60
Quantile 7	148	138.745	4	13,255	0,30
Quantile 8	142.4	134.513	9,6	17,487	0,55
Quantile 9	137.6	125.927	13,4	25,073	0,53
Quantile 10	133.8	99.571	18	52,229	0,34

Supplementary Table 3: Observed and expected frequencies in male subpopulation of the entire cohort. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	105	103.971	1	2	0,44
Quantile 2	50.2	49.859	1	1,341	0,75
Quantile 3	81.6	80.662	2	2,938	0,68
Quantile 4	70.6	68.524	1	3,076	0,33
Quantile 5	91.4	88.308	2	5,092	0,39
Quantile 6	63.6	62.166	3	4,434	0,68
Quantile 7	71.6	67.631	2	5,969	0,34
Quantile 8	73.4	69.698	5	8,702	0,57
Quantile 9	68.6	64.622	9	12,978	0,69
Quantile 10	69	49.379	9	28,621	0,31

Supplementary Table 4: Observed and expected frequencies in female subpopulation of the entire cohort. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	67,6	66,087	0	1.513	0,00
Quantile 2	80	78,303	1	2,697	0,37
Quantile 3	71,4	69,198	1	3,202	0,31
Quantile 4	82	78,404	1	4,596	0,22
Quantile 5	64,8	64,359	4	4,441	0,90
Quantile 6	67,8	64,409	2	5,391	0,37
Quantile 7	73,2	68,224	2	6,976	0,29
Quantile 8	66,6	63,08	5	8,52	0,59
Quantile 9	69,2	61,472	4,4	12,128	0,36
Quantile 10	64,4	50,383	9,6	23,617	0,41

Supplementary Table 5: Observed and expected frequencies in tricuspid valve repair group. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	141	139,19	1	2,81	0,36
Quantile 2	145	141,699	1	4,301	0,23
Quantile 3	141	139,288	4	5,712	0,70
Quantile 4	144	138,802	2	7,198	0,28
Quantile 5	126	123,176	5	7,824	0,64
Quantile 6	138	132,77	5	10,23	0,49
Quantile 7	137	128,591	4	12,409	0,32
Quantile 8	133	126,472	10	16,528	0,61
Quantile 9	129	117,508	12	23,492	0,51
Quantile 10	126	93,537	16	48,463	0,33

Supplementary Table 6: Observed and expected frequencies in the male subpopulation of the tricuspid valve repair group. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	96	95,14	1	1,86	0,54
Quantile 2	53	52,57	1	1,43	0,70
Quantile 3	73	72,331	2	2,669	0,75
Quantile 4	68	66,037	1	2,963	0,34
Quantile 5	81	78,48	2	4,52	0,44
Quantile 6	61	59,741	3	4,259	0,70
Quantile 7	71	67,915	3	6,085	0,49
Quantile 8	69	64,735	4	8,265	0,48
Quantile 9	64	60,803	9	12,197	0,74
Quantile 10	65	47,171	9	26,829	0,34

Supplementary Table 7: Observed and expected frequencies in the female subpopulation of the tricuspid valve repair group. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	59	57,682	0	1,318	0,00
Quantile 2	82	80,173	1	2,827	0,35
Quantile 3	73	69,64	0	3,36	0,00
Quantile 4	62	59,462	1	3,538	0,28
Quantile 5	61	59,862	3	4,138	0,72
Quantile 6	66	62,75	2	5,25	0,38
Quantile 7	68	63,515	2	6,485	0,31
Quantile 8	63	59,953	5	8,047	0,62
Quantile 9	63	55,906	4	11,094	0,36
Quantile 10	62	47,17	7	21,83	0,32

Supplementary table 8: Univariate and multivariable determinants of hospital mortality in patients undergoing tricuspid valve repair. PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, ASD: Atrium septum defect, AP: angina pectoris, MI: myocardial infarction. AV: aortic valve, MV: mitral valve, TV: tricuspid valve. VSR: Ventricular septum rupture. OR: odds ratio, CI: confidence interval.

Characteristics	Univariate		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age(per 1 year)	1.03 (1.02 – 1.04)	<0.001	1.04 (1.03 – 1.05)	<0.001
Sex (Female vs Male)	1.15 (0.92 – 1.43)	0.220	1.15 (0.88 – 1.49)	0.302
Prior PCI	1.65 (1.15 – 2.36)	0.007	1.03 (0.67 – 1.59)	0.900
Prior CABG	2.56 (1.80 – 3.63)	<0.001	2.24 (1.74 – 2.88)	<0.001
Prior valve surgery	1.77 (1.31 – 2.39)	<0.001	1.95 (1.3 – 2.94)	0.001
Prior aortic surgery	1.38 (0.52 – 3.63)	0.533	1.15 (0.78 – 1.69)	0.480
Prior other cardiac surgery	1.13 (0.70 – 1.84)	0.616	1.24 (0.40 – 3.85)	0.705
CABG	2.41 (1.93 – 30)	<0.001	1.41 (0.80 – 2.48)	0.238
AV repair	2.41 (1.02 – 5.7)	0.046	2.68 (1.07 – 6.70)	0.036
AV replacement	2.83 (2.25 – 3.56)	<0.001	2.20 (1.69 – 2.85)	<0.001
MV repair	0.61 (0.45 – 0.82)	0.001	0.76 (0.55 – 1.06)	0.103
MV replacement	1.38 (1.01 – 1.86)	0.046	1.66 (1.17 – 2.35)	0.005
PV surgery	0.53 (0.13 – 2.16)	0.373	1.85 (0.40 – 8.54)	0.431
Aortic surgery	2.08 (1.30 – 3.32)	0.002	1.51 (0.88 – 2.58)	0.134
Rhytm surgery	0.61 (0.46 – 0.8)	<0.001	0.90 (0.67 – 1.21)	0.482
Chronic lung disease	1.88 (1.45 – 2.44)	<0.001	1.56 (1.17 – 2.06)	0.002
Extracardiac ateriopathy	1.77 (1.25 – 2.48)	0.001	1.17 (0.80 – 1.72)	0.404
Neurlogical dysfunction	1.35 (0.77 – 2.36)	0.288	1.00 (0.54 – 1.86)	0.994
Renal impairment	4.95 (3.39 – 7.24)	<0.001	3.22 (2.06 – 5.04)	<0.001
Endocarditis	3.00 (2.01 – 4.48)	<0.001	1.67 (1.03 – 2.72)	0.039
Critical preoperative condition	5.70 (4.18 – 7.77)	<0.001	6.80 (3.79 – 12.21)	<0.001
Unstable AP	5.81 (2.66 – 12.68)	<0.001	2.13 (0.79 – 5.72)	0.134
Recent MI	2.89 (1.92 – 4.39)	<0.001	1.43 (0.63 – 3.24)	0.395
Pulmonary hypertension	1.82 (1.39 – 2.39)	<0.001	1.28 (0.95 – 1.74)	0.104
Emergency operation	5.81 (3.63 – 9.21)	<0.001	1.12 (0.58 – 2.16)	0.736
Postinfarct VSR	5.58 (1.97 – 15.64)	0.001	2.51 (0.42 – 14.89)	0.309
Interaction terms with seks				
Critical preoperative condition	0.49 (0.26 – 0.92)	0.026	0.44 (0.22 – 0.90)	0.026
Recent MI	0.40 (0.17 – 0.91)	0.031	0.69 (0.25 – 1.93)	0.481
Postinfarct VSR	0.09 (0.01 – 1.15)	0.065	0.18 (0.01 – 3.33)	0.248

Supplementary Table 9: Tricuspid valve replacement vs repair with interaction term between sex and prior valve surgery. AV: aortic valve, MV: mitral valve, PV: Pulmonary valve. * denotes the product between variables (interaction term)

Characteristic	OR (95% CI)	P value
	Tricuspid valve replacement vs repair	
MV repair	0,06 (0,04 to 0,09)	0
MV replacement	0,17 (0,12 to 0,25)	0
AV replacement	0,38 (0,25 to 0,59)	0
Rythm surgery	0,3 (0,17 to 0,52)	0
Prior valve surgery	2,75 (1,8 to 4,14)	0
Sex	1,06 (0,76 to 1,48)	0,737
PV surgery	2,36 (1,39 to 4,01)	0,001
$Age_{(FP1)}$	0,88 (0,83 to 0,93)	0
$Age_{(FP2)}$	0,02 (0,01 to 0,09)	0
Aortic surgery	0,26 (0,08 to 0,87)	0,029
Endocarditis	1,9 (1,17 to 3,06)	0,01
Sex* Prior valve surgery	0,53 (0,28 to 1,01)	0,062

Supplementary Table 10: Isolated tricuspid valve surgery vs multiple valve surgery with interaction term between sex and peropeative critical condition. AP: angina pectoris, TV: tricuspid valve, VSR: Ventricle septum rupture. * denotes the product between variables (interaction term)

Characteristic	OR (95% CI)	P value
	Isolated tricuspid valve surgery vs multiple valve surgery	
Age	0,96 (0,95 to 0,96)	<0,001
TV replacement	7,39 (5,58 to 9,87)	<0,001
Rythm surgery	0,57 (0,45 to 0,73)	<0,001
Critical preop condition	1,06 (0,59 to 1,9)	0,843
Unstable AP	3,35 (1,45 to 7,77)	0,005
Pulmonary hypertension	0,41 (0,29 to 0,57)	<0,001
Postinfarct VSR	12,3 (4,18 to 36,6)	<0,001
Sex	0,9 (0,75 to 1,07)	0,247
Sex* Critical preop condition	2,44 (1,21 to 4,9)	0,012