Outcomes after tricuspid valve surgery concomitant with left ventricular assist device implantation in the EUROMACS registry: a propensity score matched analysis

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ABSTRACT

Objectives

Tricuspid regurgitation (TR) is common in patients receiving a left ventricular assist device (LVAD). Controversy exists as to whether concomitant tricuspid valve surgery (TVS) is beneficial in currently treated patients. Therefore, our goal was to investigate the effect of TVS concomitant with a LVAD implant.

Methods

The European Registry for Patients with Mechanical Circulatory Support was used to identify adult patients. Matched patients with and without concomitant TVS were compared using a propensity score matching strategy.

Results

In total, 3323 patients underwent LVAD implantation of which 299 (9%) had TVS. After matching, 258 patients without TVS were matched to 258 patients with TVS. In the matched population, hospital deaths, days on inotropic support, temporary right ventricular assist device implants and hospital stay were comparable, whereas stay in the intensive care unit was higher in the TVS cohort (11 vs 15 days; $P = 0.026$). Late deaths ($P = 0.17$), cumulative incidence of unexpected hospital readmission ($P = 0.15$) and right heart failure ($P = 0.55$) were comparable between patients with and without concomitant TVS. In the matched population, probability of moderate-to-severe TR immediately after surgery was lower in patients with concomitant TVS compared to patients without TVS (33% vs 70%; $P = 0.001$). Nevertheless, the probability of moderate-to-severe TR decreased more quickly in patients without TVS ($P = 0.030$), resulting in comparable probabilities of moderate-to-severe TR within 1.5 years of follow-up.

Conclusions

In matched patients, TVS concomitant with LVAD implant does not seem to be associated with better clinical outcomes. Concomitant TVS reduced TR significantly early after LVAD implant; however, differences in probability of TR disappeared during the follow-up period.

INTRODUCTION

Implantation of a left ventricular assist device (LVAD) improves survival, functional status and quality of life in patients with end-stage heart failure [1, 2]. In these patients tricuspid regurgitation (TR) is common [3], and current guidelines recommend consideration of tricuspid valve surgery (TVS) when moderate-to-severe TR is present [4]. Nevertheless, controversy exists whether concomitant TVS is associated with better outcomes, because contemporary studies are hampered by small sample sizes and are biased due to baseline differences [5]. In this study, we investigated the clinical outcomes after TVS concomitant with LVAD implantation compared to propensity score matched controls using the European Registry for Patients with Mechanical Circulatory Support (EUROMACS). Furthermore, we assessed the postoperative course of TR in patients with and without concomitant TVS.

METHODS

Study design

The EUROMACS is a registry of the European Association for Cardio-Thoracic Surgery. In this registry all relevant clinical, echocardiographic, haemodynamic and laboratory parameters of patients who require mechanical circulatory support have been collected prospectively since January 2011. Participating centres were allowed to enter data acquired before 2011 retrospectively, making this study an ambispective cohort study. Detailed descriptions of the database and the collection procedure were provided previously [6].

Patients

All patients operated on between 1995 and 2018 were identified. Patients <18 years old and with planned right ventricular (RV) or biventricular were excluded from analysis. Additionally, patients with single ventricle physiology were excluded (Supplementary Material, Fig. S1).

Study outcome

The main outcomes that were assessed were early (both 30-day and hospital deaths separately) and late deaths. A late death was defined as death after 30 days, regardless of hospital admission status. Furthermore, unplanned hospital readmission and right heart failure were assessed. Right heart failure was defined according to the INTERMACS adverse event definitions [7]. Patients were censored at heart transplant, death and when lost to follow-up. Lastly, the course of the probability of moderate-to-severe TR was evaluated in patients with and without TVS.

Missing values

Multiple imputation by chained equations using the statistical MICE package in R was used to impute missing values [8] Selected baseline variables with <55% missing values were imputed; >55% missing values was considered excessive missingness (Supplementary Material, Table S1). Nevertheless, 51 out of the 67 imputed variables (76%) had <30% missing values. An exception was made for the variable tricuspid annular plane systolic excursion (62% missing), because this variable is highly important in the setting of TVS, and it was reasonable to assume it could be imputed based on observed variables, such as the RV ejection fraction (missing mechanism: missing at random). Imputations were done based on the other baseline variables. In the case of highly correlated variables, the variable with the highest clinical value was chosen as the predictor (Supplementary Material, Table S2). Correlation was tested with Pearson R or Spearman rho, as appropriate. Five imputed datasets were generated with this method using 5 iterations each. The imputations were visually checked by strip plots and density plots, and no major deviations were noted between imputed data and complete data (e.g. tricuspid annular plane systolic excursion: Supplementary Material, Fig. S2). Analyses were done on each dataset separately and pooled according to Rubin's rules [9]. In baseline comparisons of the matched groups, continuous data were transformed to the approximate Gaussian distribution and were pooled according to Rubin's rules.

Statistical analyses

Continuous data are presented as mean ± standard deviation (Gaussian distribution) or median [interquartile range (IQR)] (non-Gaussian distribution). Categorical data are presented as frequencies (percentage). Comparisons among continuous variables were made with the Student's *t*-test or the Mann–Whitney test, as appropriate. Continuous data outside 3 standard deviations were considered erroneous and removed (Supplementary Material, Table S3). Comparisons of categorical variables were made with the χ^2 test or with the Fisher's exact test, as appropriate. Propensity score matching was used to balance baseline differences, because the main interest of this study is the treatment effect in a typical treated patient instead of a population level treatment effect [10]. The parsimonious propensity score model was developed using least absolute shrinkage and selection operator regression [11]. This machine learning analysis technique shrinks unimportant covariates to zero. The parsimonious model comprised all non-zero covariates. In total, 62 variables were offered to the least absolute shrinkage and selection operator model, which selected 15 variables (Supplementary Material, Table S4). Thereafter, 9 variables were added due to clinical significance and to achieve satisfactory balance (Supplementary Material, Table S5). The final propensity score model contained 24 variables (Supplementary Material, Tables S5 and S6). One-on-one matching without replacement was performed, and the caliper was set at 0.15. For the main outcome, a sensitivity analyses was performed with the caliper set at 0.001. Standard mean difference before and after matching was used to assess covariate balance. Late survival was calculated

and visualized with the Kaplan–Meier method; both cohorts were compared with the log-rank test. Because some patients had no recorded follow-up, a sensitivity analysis was performed to test the robustness of the log-rank test under different missing mechanisms. Unplanned hospital readmission and right heart failure were considered competing risks with death, and Fine and Gray competing risk models were used to calculate cumulative incidences. Gray's tests were used to quantify significant differences among cohorts. Generalized mixed models were used to analyse repeated echocardiograms. Further details regarding the mixed models are provided in Supplementary Material, Text S1. Follow-up completeness was calculated using the modified Clark C (C*) [12]. All analyses were done in R (R core team 2017, Vienna, Austria) with the use of statistical packages 'glmnet', 'Matching', 'survival', 'cmprsk', 'splines' and 'lme4'.

RESULTS

In total, 3323 procedures were included [3024 (91%) without TVS and 299 (9%) with TVS]. In the TVS cohort, 292 (97%) patients had a tricuspid valve repair, and 7 (3%) patients had a tricuspid valve replacement (6 mechanical and 1 biological). After propensity score matching, 258 procedures without TVS surgery were matched to 258 procedures with additional TVS. Density plots of the propensity score in the unmatched and matched cohorts are presented in Fig. 1. In patients who survived 30 days and had recorded late follow-up information, the mean follow-up time was 1.7 ± 1.5 years with a completeness of 86% (C*).

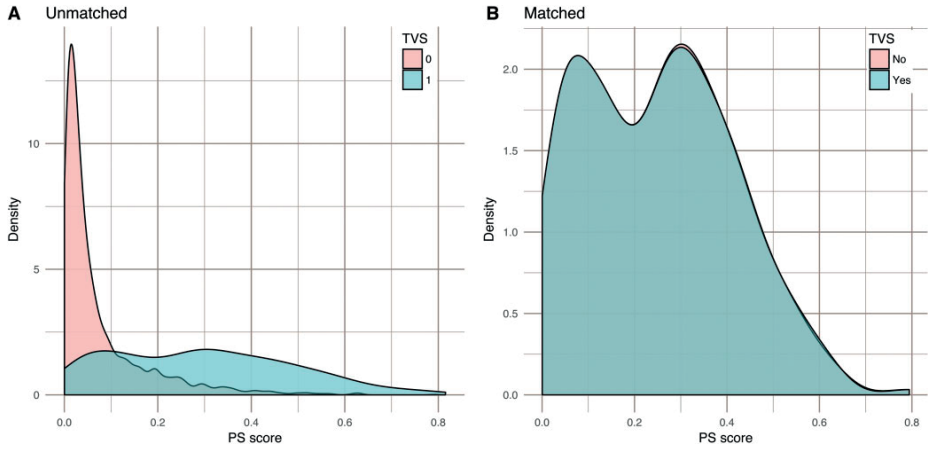

Figure 1: Density of propensity score in the (A) unmatched and (B) matched cohorts. PS: propensity score; TVS: tricuspid valve surgery.

Patient characteristics

Patient characteristics are presented in Table 1. In the unmatched cohort, patients who did not undergo TVS had, among others, significantly less TR, more ischaemic cardiomyopathy and better kidney and liver function. In the matched cohort, no significant differences in baseline characteristics were noted. In addition, the overall absolute standard mean difference before matching was 18.7 and after matching, it was 4.9 (Supplementary Material, Table S7).

Table 1: Characteristics of patients with or without concomitant tricuspid valve surgery in matched and unmatched cohorts

	Unmatched groups[a]			Matched groups[b]		
	No TVS	**TVS**	***P*-value**	**No TVS**	**TVS**	***P*-value**
n	3024	299		258	258	
Age (years), median (IQR)	56.00 (47.00–62.00)	57.00 (47.50–63.00)	0.044	56.00 (47.00–64.00)	57.00 (47.25–63.00)	0.74
Male sex, *n* (%)	2519 (83.3)	235 (78.6)	0.048	205 (79.5)	202 (78.3)	0.83
Body surface area (m^2), median (IQR)	1.96 (1.81–2.12)	1.96 (1.85–2.12)	0.80	1.94 (1.79–2.11)	1.96 (1.84–2.11)	0.75
White, *n* (%)	2271 (87.4)	248 (95.8)	0.003	247 (95.7)	245 (95.0)	>0.99
Aetiology (%), *n* (%)			<0.001			0.77
Coronary artery disease	252 (10.0)	24 (9.3)		20 (7.8)	26 (10.1)	
Idiopathic disease	614 (24.5)	100 (38.8)		95 (36.8)	97 (37.6)	
Ischaemic disease	1011 (40.3)	62 (24.0)		66 (25.6)	65 (25.2)	
Other	632 (25.2)	72 (27.9)		77 (29.8)	70 (27.1)	
≥2 Years since first diagnosis, *n* (%)	1546 (63.5)	188 (75.5)	0.001	190 (73.6)	192 (74.4)	0.90
Destination therapy, *n* (%)	467 (16.9)	47 (15.9)	0.72	42 (16.9)	43 (16.8)	>0.99
Ascites, *n* (%)	198 (10.3)	36 (18.0)	<0.001	55 (21.3)	56 (21.7)	0.90
Rhythm, *n* (%)			0.084			0.99
Sinus	1337 (55.4)	119 (47.8)		128 (49.6)	120 (46.5)	
Atrial fibrillation	397 (16.4)	44 (17.7)		45 (17.4)	49 (19.0)	
Paced	613 (25.4)	80 (32.1)		82 (31.8)	82 (31.8)	
Other	68 (2.8)	6 (2.4)		3 (1.2)	7 (2.7)	
INTERMACS class, *n* (%)			<0.001			0.90
1	427 (15.0)	19 (6.4)		17 (6.6)	20 (7.8)	
2	942 (33.2)	118 (40.0)		101 (39.1)	93 (36.0)	
3	738 (26.0)	92 (31.2)		80 (31.0)	80 (31.0)	
≥4	733 (25.8)	66 (22.4)		60 (23.3)	65 (25.2)	
IABP, *n* (%)	287 (11.3)	17 (6.6)	0.030	24 (9.3)	15 (5.8)	0.34

Table 1: Characteristics of patients with or without concomitant tricuspid valve surgery in matched and unmatched cohorts (continued)

	Unmatched groups[a]			Matched groups[b]		
ECMO, *n* (%)	306 (10.9)	22 (7.5)	0.097	18 (7.0)	19 (7.4)	>0.99
Ventilator (%), *n* (%)	377 (14.8)	19 (7.5)	0.002	18 (7.0)	26 (10.1)	>0.99
Medication, *n* (%)						
Loop diuretics, *n* (%)	1886 (80.5)	218 (86.9)	0.018	213 (82.6)	224 (86.8)	0.82
Use of ≥3 inotropes, *n* (%)	198 (10.5)	23 (11.2)	0.87	51 (19.8)	33 (12.8)	0.79
Laboratory values, median (IQR)						
Serum creatinine (mg/dl)	107.00 (83.00–150.00)	115.00 (90.50–150.00)	0.035	109.50 (84.00–152.75)	114.00 (88.00–150.00)	0.51
ASAT (U/l)	33.00 (23.00–75.00)	35.00 (25.00–57.00)	0.41	34.00 (24.00–67.75)	34.00 (25.00–55.00)	>0.99
Total bilirubin (mg/dl)	1.20 (0.78–2.00)	1.69 (1.14–2.50)	<0.001	1.50 (0.90–2.55)	1.53 (1.05–2.28)	0.92
Albumin (g/dl)	507.15 (420.21–579.60)	507.15 (449.91–574.16)	0.54	507.15 (405.72–579.60)	507.15 (434.70–579.60)	0.82
Haemoglobin (g/dl)	11.80 (10.20–13.60)	11.40 (10.07–13.03)	0.11	11.70 (9.83–13.20)	11.40 (10.00–13.28)	0.65
Haemodynamic values, median (IQR)						
RA pressure (mmHg)	10.00 (7.00–15.00)	13.00 (9.50–17.00)	<0.001	12.00 (8.00–16.00)	13.00 (9.00–16.00)	0.63
PCWP (mmHg)	24.00 (18.00–30.00)	25.00 (20.75–29.25)	0.085	24.00 (18.00–30.00)	24.50 (20.00–29.00)	0.21
PVR	231.50 (137.00–354.75)	267.00 (166.75–372.50)	0.11	262.00 (177.00–368.00)	276.50 (160.00–372.50)	0.71
SVR	1262.00 (896.25–1676.50)	1446.50 (1102.75–1908.00)	0.001	1317.00 (1021.00–1590.00)	1300.00 (1062.50–1858.00)	0.38
PAP, systolic (mmHg)	51.00 (39.00–64.00)	49.50 (40.00–63.00)	0.71	52.00 (40.00–63.00)	52.00 (40.00–65.00)	0.66
Echocardiographic results						
TAPSE (mm), median (IQR)	14.00 (12.00–17.00)	15.00 (12.00–18.00)	0.28	14.00 (11.00–17.00)	14.00 (12.00–17.00)	0.63
No aortic regurgitation, *n* (%)	1469 (63.5)	151 (55.7)	0.060	146 (56.6)	148 (57.4)	0.98
Severe mitral regurgitation, *n* (%)	392 (17.4)	77 (30.4)	<0.001	76 (29.5)	66 (25.6)	0.83

Table 1: Characteristics of patients with or without concomitant tricuspid valve surgery in matched and unmatched cohorts (continued)

	Unmatched groups[a]			Matched groups[b]		
Tricuspid regurgitation, *n* (%)			<0.001			0.79
None	286 (11.4)	4 (1.4)		8 (3.1)	4 (1.6)	
Trivial	504 (20.1)	14 (4.8)		15 (5.8)	15 (5.8)	
Mild	907 (36.2)	34 (11.7)		39 (15.1)	37 (14.3)	
Moderate	564 (22.5)	113 (38.8)		96 (37.2)	112 (43.4)	
Severe	243 (9.7)	126 (43.3)		100 (38.8)	90 (34.9)	
LVEF (%), median (IQR)	19.00 (15.00–23.00)	20.00 (15.00–25.00)	0.029	20.00 (15.00–24.00)	20.00 (15.00–23.00)	0.85
RVF, *n* (%)			<0.001			0.89
Normal	400 (22.1)	21 (10.7)		37 (14.3)	31 (12.0)	
Mild	460 (25.4)	44 (22.3)		45 (17.4)	52 (20.2)	
Moderate	700 (38.6)	96 (48.7)		124 (48.1)	114 (44.2)	
Severe	252 (13.9)	36 (18.3)		52 (20.2)	61 (23.6)	

[a]Data and tests on complete cases.

[b]Data from first imputed dataset; P-values from tests are derived from the pooled analyses.

ASAT: aspartate aminotransferase; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; IQR: interquartile range; LVEF: left ventricular ejection fraction; PAP: pulmonary atrial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RA: right atrium; RVF: right ventricle function.; SVR: systemic vascular resistance; TAPSE: tricuspid annular plane systolic excursion; TVS: tricuspid valve surgery.

Hospital outcome

Hospital outcomes are presented in Table 2. In the unmatched cohort, cardiopulmonary bypass time (80 vs 118 min; $P < 0.001$), intensive care unit (ICU) stay (10 vs 15 days; $P < 0.001$), hospital stay (30 vs 34; $P = 0.001$) and days on inotropic support (>14 days: 24.7% vs 32.4%) were longer in the patients who underwent TVS. In the matched cohorts, these variables were all comparable, except for cardiopulmonary bypass time (85 vs 116 min; $P < 0.001$) and ICU stay (11 vs 15 days; $P = 0.026$) (Table 2). Additionally, in the matched groups, the 30-day mortality risk [13.6%, 95% confidence interval (CI) 9.5–18.6 vs 10.0%, 95% CI 6.5–14.4; $P = 0.27$] and hospital mortality risk (20.2%, 95% CI 14.7–24.7 vs 16.5%, 95% CI 13.0–22.6; $P = 0.41$) were comparable between the patients with and without concomitant TVS. Sensitivity analyses with the caliper at 0.001 did not change point estimates greatly (Supplementary Material, Table S8).

Table 2: Hospital outcomes of patients with or without concomitant tricuspid valve surgery in matched and unmatched cohorts

	Unmatched groups			Matched groups		
	No TVS	**TVS**	***P*-value**	**No TVS**	**TVS**	***P*-value**
n	3024	299		258	258	
CPB time (min), median (IQR)	80 (58–111.5)	118 (94–157)	<0.001	84.50 (61.00–114.50)	115.50 (92.25–157.75)	<0.001
Device brand, *n* (%)			<0.001			0.93
HeartMate II	776 (27.4)	120 (40.4)		102 (39.5)	96 (37.2)	
HeartWare HVAD	1481 (52.3)	117 (39.4)		112 (43.4)	113 (43.8)	
HeartMate III	414 (14.6)	58 (19.5)		42 (16.3)	47 (18.2)	
Other	160 (5.7)	2 (0.7)		2 (0.8)	2 (0.8)	
Hospital deaths, *n* (%)	452 (15.2)	55 (18.8)	0.58	50 (20.2)	45 (16.5)	0.41
30-Day deaths, *n* (%)	306 (11.9)	32 (11.0)	0.72	32 (13.6)	25 (10.0)	0.27
Temporary RVAD support, *n* (%)	138 (4.5)	23 (7.7)	0.024	22	16	0.40
Days of inotropic support, *n* (%)			0.013			0.29
1–7	993 (56.6)	92 (48.2)		11 (7.0)	13 (7.7)	
8–13	321 (18.3)	37 (19.4)		85 (53.8)	85 (50.6)	
14–27	276 (15.7)	48 (25.1)		27 (17.1)	41 (24.4)	
>27	158 (9.0)	14 (7.3)		33 (20.9)	29 (17.3)	
Ongoing	6 (0.3)	0 (0.0)		2 (1.3)	0 (0.0)	
ICU/CCU stay, median (IQR)	10 (5–23)	15 (6–53)	<0.001	11.00 (5.00–24.00)	15.00 (6.00–31.00)	0.026
Hospital stay, median (IQR)	30 (21–46)	34 (25–53)	0.001	33.00 (22.00–54.00)	34.50 (24.75–52.25)	0.38

CCU: cardiac care unit; CPB: cardiopulmonary bypass; ICU: intensive care unit; IQR: interquartile range; RVAD: right ventricular assist device; TVS: tricuspid valve surgery.

Late outcome

In total, 2522 patients had recorded late follow-up and did not die within 30 days (no TVS: 2263 and TVS: 259 patients); 809 patients died during the follow-up period (Supplementary Material, Fig. S3). Kaplan–Meier survival curves are shown in Fig. 2A, B. Unmatched patients with and without concomitant TVS had comparable late survival rates ($P = 0.41$). Additionally, cumulative incidence plots are shown in Figs 3A and B and 4A and B. In unmatched patients, cumulative incidence of unplanned hospital readmission from any cause and cumulative incidence of right heart failure were higher in the TVS cohort (Figs 3A and 4A); *P*-value = 0.006 and *P*-value = 0.011, respectively.

In the matched cohort, 226 patients with TVS survived 30 days and had recorded late follow-up versus 204 matched controls, 128 of whom died during the follow-up period. Late

survival was comparable between patients with and without TVS (*P* = 0.17) (Fig. 2B). Notably, the curves diverged after ~1 year of follow-up with 2-year survival estimates of 75.6% (95% CI 69.3–82.5) in the no TVS cohort and 63.2% (95% CI 55.3–72.2) in the TVS cohort, but still with overlapping CIs. In total, 22 patients in the matched control group and 7 patients in the TVS cohort did not have recorded follow-up information. Sensitivity analyses revealed that only in the scenario in which all missing patients in the no TVS cohort survived and in which all in the TVS cohort died, the log-rank test results differed significantly (Supplementary Material, Table S9). Sensitivity analyses with the caliper set at 0.001 did not considerably change point estimates (Supplementary Material, Table S8). In the matched cohorts, cumulative incidence of unplanned hospital readmissions (*P* = 0.15) and right heart failure (*P* = 0.55) were comparable between patients with and without concomitant TVS (Figs 3B and 4B).

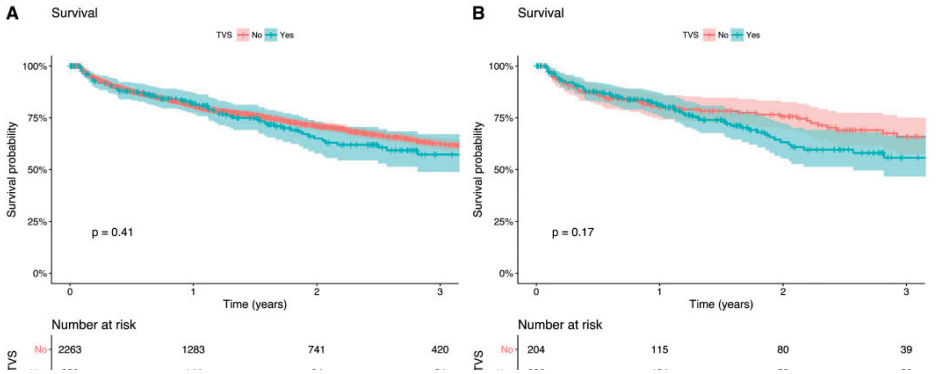

Figure 2: Kaplan–Meier curve of patients who survived 30 days in the (A) unmatched and (B) matched cohorts. TVS: tricuspid valve surgery.

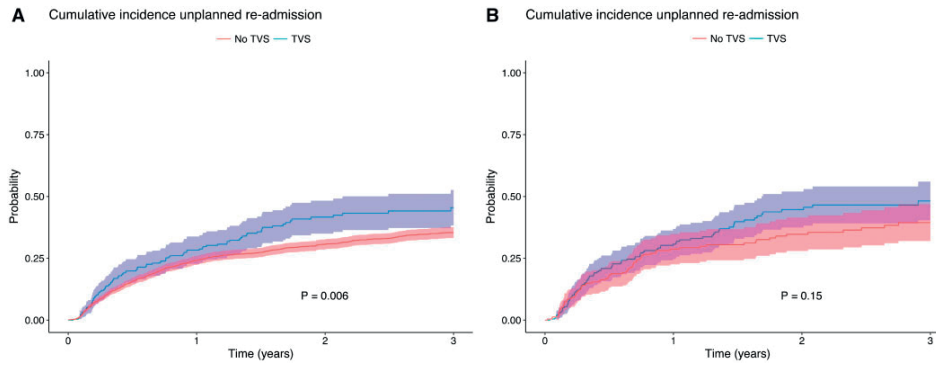

Figure 3: Cumulative incidence estimated by the Fine and Gray model with death as the competing risk of unexpected hospital readmission in the (A) unmatched and (B) matched cohorts. TVS: tricuspid valve surgery.

Evolution of tricuspid regurgitation

In total, 1219 patients had 3956 recorded echocardiograms during the follow-up period (mean: 3.2 echocardiograms, range: 1–28). Figure 5A presents the probability of moderate-to-severe TR over time in the unmatched cohorts. In the matched cohorts, 224 patients had 725 recorded echocardiograms (mean 3.2, range 1–21) that could be used in the mixed models. Immediately after LVAD implantation, patients who underwent TVS had a significantly lower probability of moderate-to-severe TR (33% vs 70%; *P* = 0.001) (Fig. 5B). Nevertheless, during follow-up, the probability of moderate-to-severe TR decreased more quickly in the no TVS cohort compared to the TVS cohort (*P* = 0.030), resulting in comparable probabilities within 1 year of follow-up.

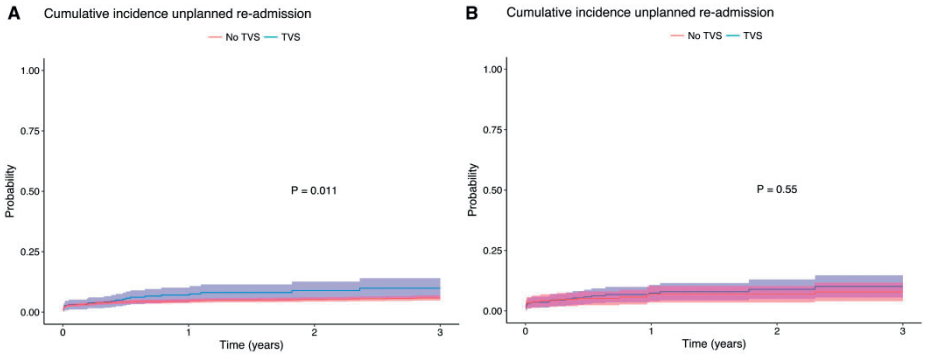

Figure 4: Cumulative incidence estimated by the Fine and Gray model with death as the competing risk of right heart failure in the (A) unmatched and (B) matched cohorts. TVS: tricuspid valve surgery.

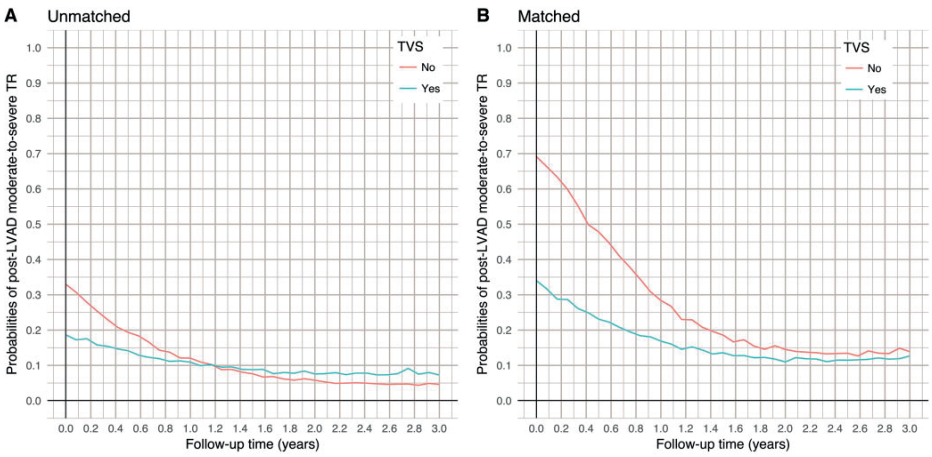

Figure 5: Course of the probability of moderate-to-severe tricuspid regurgitation over time in the (A) unmatched and (B) matched cohorts estimated by the mixed model. LVAD: left ventricular assist device; TR: tricuspid regurgitation; TVS: tricuspid valve surgery.

DISCUSSION

We evaluated outcomes of concomitant TVS during LVAD implantation in the largest European LVAD registry. In the matched cohort, comparable risks and rates of mortality, days on inotropic support, cumulative incidence of unexpected readmission and right heart failure were noted. Not surprisingly, cardiopulmonary bypass time was longer in the TVS cohort. Furthermore, patients who underwent concomitant TVS stayed longer in the ICU compared to patients who did not undergo TVS. Immediately after surgery the probability of moderate-to-severe TVS was significantly lower in the TVS cohort; however, this difference disappeared during the follow-up period.

Patients undergoing TVS are significantly different from patients without concomitant TVS. Patients undergoing TVS presented as less acute patients with a longer history of cardiac diagnosis and fewer ischaemic aetiologies (among others), which is also illustrated by different densities in propensity scores (Fig. 1). Hence, patients undergoing TVS seemed to be a select subgroup in the overall LVAD population. It has to be noted that conclusions regarding treatment effect in this study only apply to this subgroup and may not apply in other subgroups within the LVAD population.

Prior analyses of the Society of Thoracic Surgeons database and the INTERMACS database revealed results comparable to our results [13, 14]. Patients receiving TVS who were recorded in the Society of Thoracic Surgeons database stayed longer in the ICU. RV assist device implant and hospital mortality risks were comparable in this cohort [13].

The investigators of the INTERMACS database noted comparable rates of late survival in patients with preoperative moderate-to-severe TR with and without concomitant TVS [14]. Moreover, a recent systematic review, pooling mostly small retrospective studies, found no differences in early and late survival risks/rates [5]. Interestingly, both in retrospective studies and INTERMACS database studies, it was noted that pre-LVAD moderate-to-severe TR was associated with poorer late survival rates [3, 14, 15]. Regarding the latter observation, it seems peculiar that eliminating TR does not result in a better outcome. Two hypotheses may explain these paradoxical results. First, TVS may not sustainably reduce post-LVAD TR. Song et al. found a relatively high rate of recurrent TR in patients who received concomitant TR. Additionally, there are reports that LVAD support exacerbates TR due to a leftward shift of the interventricular septum and increased venous return [16, 17]. Nevertheless, our results support the idea that TVS reduces TR soon after the operation, but that in patients without concomitant TVS, TR also decreases in the following months. Second, it may be that TR does not cause death in most cases. It is known that TR is frequently caused by RV dilatation in response to elevated pulmonary pressures [18]. Therefore, TR may merely be a symptom or a marker of RV damage secondary to long-standing pulmonary hypertension or primary RV damage caused by the underlying ischaemic or cardiomyopathic diseases. By treating TR, one may be treating the symptom rather than the causing factor of mortality and morbidity (e.g. RV dysfunction). To

some extent, our findings support this theory because favourable RV remodelling is observed in patients with an LVAD implant without concomitant TVS [19, 20]. This finding would inherently be paired with a reduction of TR, even without an intervention, assuming that the TR is functional in nature.

In this respect, the cause of TR (primary or secondary) is important. Primary TR, caused by structural valve damage or interfering pacemaker/implantable cardioverter defibrillator leads, will certainly not reduce itself and may even cause RV dysfunction [21]. Therefore, we propose that this aspect be taken into account in the decision process whether to perform concomitant TVS. Robertson et al. [13] suggested that the decision to perform concomitant TVS should not be solely based on the pre-LVAD TR grade. Our data and reports in the current literature support this suggestion, because our results and multiple other studies were do not to show any benefit from concomitant TVS. Current guidelines suggest consideration of concomitant TVS in all patients with pre-LVAD moderate-to-severe TR, which may not be necessary. Nevertheless, if one follows the trends in concomitant TVS for functional TR during left-sided valve surgery, it has become clear that TR in some cases is not reduced or even becomes worse [22, 23]. The remaining challenge is now to adequately identify these patients in the LVAD population.

Strengths and limitations

The strength of this study is the relatively large sample size compared to those reported in the current literature. Additionally, the EUROMACS registry records serial echocardiograms, which made it possible to analyse the change in TR over time. In contrast to previous studies, we accounted for the within-patient correlations in our analyses of the postoperative course of TR over time using advanced statistical modelling. This study has several important limitations. First, the database is not designed to specifically address concomitant TVS in patients with LVAD implants. Therefore, important factors, such as the cause of TR or the reasons for intervention, were not collected. This lack may introduce selection bias, because these factors could not be captured in the propensity model. Furthermore, the surgeon and institutional preferences can introduce selection bias. Although the majority of variables of interest had below 30% missing values, we accepted up to 55% missing values. On the other side, the EUROMACS database collects many variables, making it more plausible that missing data could be predicted from the other observed variables, thereby strengthening the missing-at-random assumption. In addition, since last year, the EUROMACS investigators intensified their quality control measures to reduce missingness in the future [24]. Furthermore, assessing TR remains challenging: TR is subject to loading conditions, which means TR severity is highly dynamic [25]. Unfortunately, it was impossible to analyse patients receiving a tricuspid valve replacement compared to a tricuspid valve repair due to the small numbers. Some differences could be due to chance because of multiple testing. Propensity score matching reduces the sample size and therefore may reduce the power of the tests. Nevertheless, we utilized a matching technique because the main interest of this study was the effect of treatment in a typical treated patient. Some

patients in the matched population had no recorded follow-up information. Nevertheless, sensitivity analyses did not change the direction of the conclusions in most of the hypothetical missing scenarios.

CONCLUSIONS

Patients undergoing concomitant TVS differ significantly from patients without TVS. In matched patients, concomitant TVS during LVAD implant does not seem be associated with better clinical outcomes. Concomitant TVS reduced TR significantly early after LVAD implant; however, differences in probability of TR disappeared during the follow-up period. Using current selection criteria, TVS does not seem beneficial.

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SUPPLEMENTARY MATERIAL

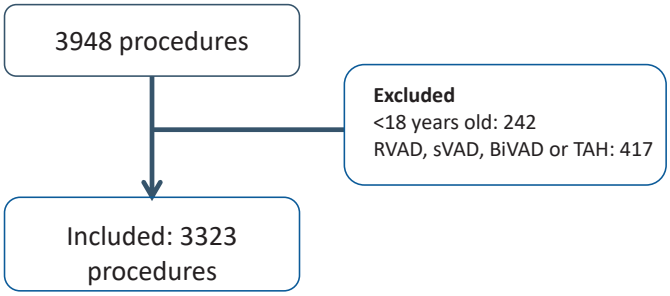
CONTENTS

SUPPLEMENTARY TEXT 1

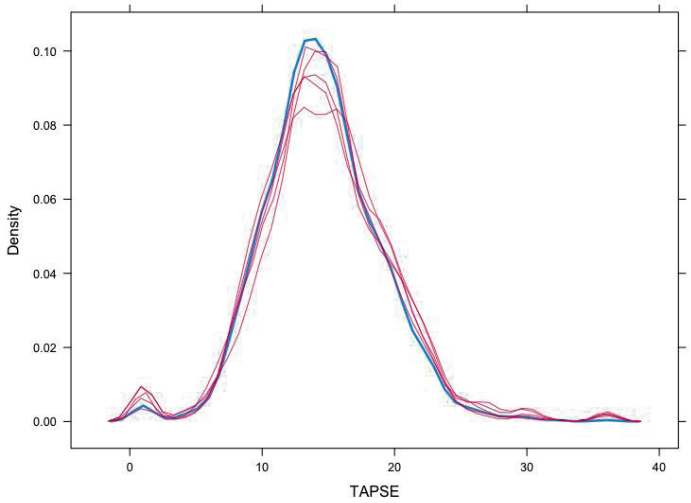
Generalized mixed-models

All models had random intercepts for patients. Natural cubic splines for time were added to establish flexibility over time. All models contained the following covariates: time (with splines), tricuspid valve surgery (yes/no) and the interaction between tricuspid valve surgery and time. The number of knots for the splines was determined using a backwards approach starting with 3 knots to 0 knots. Models were compared by likelihood ratio tests. One knots proved to be sufficient.

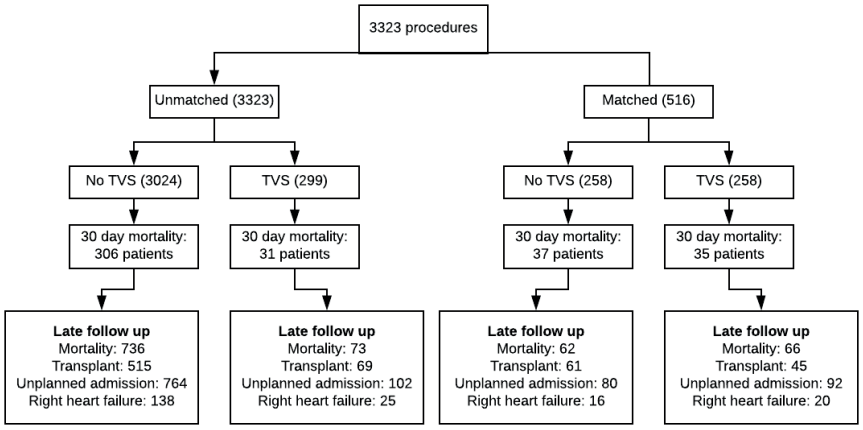
The marginal probabilities for the effect plot were obtained using a Monte Carlo sampling procedure. For each combination of follow-up time and covariate of interest 3000 patients are generated with random effect values coming from the normal distribution $N(0, \sigma_b^2)$, where σ_b^2 denotes the estimated variance of the random effects from the model. The mean of the 3000 calculated probabilities is taken as estimate.



Supplementary Figure 1: Flowchart of included patients



Supplementary Figure 2: Kernel density plot of complete data of tricuspid annular plane systolic excursion (blue line) and imputed data of the 5 imputed datasets (red lines).



Supplementary Figure 3: Flow diagram of mortality, transplants and events in unmatched and matched cohorts.

Supplementary Table 1: Missing data (alphabetic order)

Variable	Count missing	Precentage missing (%)
ACE inhibitors	737	22,2
Acenocoumarol	1608	48,4
Age	44	1,3
Albumin	1858	55,9
Aldosterone antagonist	1258	37,9
Amiodarone	813	24,5
Anticoagulant therapy	1302	39,2
Antiplatelet drugt herapy	822	24,7
Aortic regurgitation	738	22,2
ARB	805	24,2
Ascites	1218	36,7
Betablockers	776	23,4
Bicarbonat HCO3	1877	56,5
Bloodtype	18	0,5
Blood Urea Nitrogen	1013	30,5
Bosentan	1538	46,3
BSA	504	15,2
Cancer Other Than Local SkinCancer	539	16,2
Cardia cArrest	515	15,5
Cardiac Index	787	23,7
Cardiac Output	2009	60,5
Cardiac Surgery	506	15,2
Cholesterol	2506	75,4
Connective Tissue Or Inflammatory	581	17,5
COPD	516	15,5
CPB Time	399	12,0
Creatinine	923	27,8
CRPC reactive protein	778	23,4
Cumadine	2886	86,8
ICD	80	2,4
Diabetes	249	7,5
Dialysis	295	8,9
Diastolic BP	737	22,2
ECG rhythm	659	19,8
ECMO	212	6,4
Ethnic origin	465	14,0
Feeding Tube	614	18,5
Gender	0	0,0
Hemoglobin	633	19,0

Supplementary Table 1: Missing data (alphabetic order) (continued)

Variable	Count missing	Precentage missing (%)
History Of Neurological Event	557	16,8
History Of Previous Alcohol Abuse	1838	55,3
Hospital stay		
IABP	521	15,7
Iloprost	1540	46,3
INR	550	16,6
INTERMACS class	188	5,7
Intubation	508	15,3
Lactate	2275	68,5
LDH	1201	36,1
Loop diuretics	729	21,9
LVEDD2	947	28,5
LVEDV	2726	82,0
LvEf Percent	823	24,8
LVESD	1941	58,4
LVESV	2814	84,7
LVSF	2854	85,9
Major Infections	525	15,8
Major MI	515	15,5
Marcumar	2517	75,7
Marital status	1060	31,9
Mitral regurgitation	814	24,5
Neseritide	1247	37,5
Nitric Oxide	824	24,8
NT Pro BNP	2347	70,6
Number of inotropes	1233	37,1
Pa Capillary Wedge Pressure	3292	99,1
pH	1768	53,2
Phenprocoumon	1379	41,5
Platelet	720	21,7
Positive Blood Cultures	853	25,7
Potassium	730	22,0
Primary Diagnosis	556	16,7
PTT	803	24,2
Pulmonary artery diastolic pressure	1712	51,5
Pulmonary Artery Pressure Mean	1652	49,7
Pulmonary artery systolic pressure	1715	51,6
Pulmonary artery wedge pressure	1938	58,3
Pulmonary Regurgitation	1438	43,3

Supplementary Table 1: Missing data (alphabetic order) (continued)

Variable	Count missing	Precentage missing (%)
PVR	2405	72,4
RA pressure	1798	54,1
Reason For Admission	445	13,4
Reticulocytes	3032	91,2
Rhesusfactor	18	0,5
R value at peak	3298	99,2
RVEF	1314	39,5
ASAT	751	22,6
ALAT	1412	42,5
Sildenafil	1490	44,8
Smoking History	1466	44,1
Sodium	727	21,9
SVR	2499	75,2
Symptomatic Peripheral Vascular Disease	549	16,5
Systolic BP	1066	32,1
TAPSE	2061	62,0
Time since first cardiac diagnosis	638	19,2
Total bilirubin	881	26,5
Transfusion History	2074	62,4
Tricuspid regurgitation	528	15,9
Tricuspid valve surgery	0	0,0
Ultrafiltration	517	15,6
Ventilation	1019	30,7
Ventilator	529	15,9
Peripheral edema	865	26,0
VO max	3167	95,3
Warfarin	1577	47,5
WBC	545	16,4

Supplementary Table 2: Variables used in imputation

Imputed variables	
ACE inhibitors	Nitric Oxide
Age	Platelet
Albumin[1]	Positive Blood Cultures[1]
Aldosterone antagonist	Potassium
Amiodarone	Primary Diagnosis
Anticoagulant therapy drugs status	PTT
Aortic regurgitation	Pulmonary artery diastolic pressure[1]
ARB	Pulmonary Artery Pressure Mean

Supplementary Table 2: Variables used in imputation (continued)

Imputed variables	
Ascites	Pulmonary artery systolic pressure[1]
Betablockers	Pulmonary artery wedge pressure[1]
Bloodtype	Pulmonary Regurgitation
Blood Urea Nitrogen[1]	RA pressure
BSA	Rhesusfactor
Cancer Other Than Local Skin Cancer	RVEF
Cardiac Arrest	ASAT
Carotid Artery Disease	ALAT[1]
Connective Tissue Or In flammatory	Sodium
COPD	Symptomatic Peripheral Vascular Disease
Creatinine	Systolic BP
CRPC reactive protein	TAPSE[1]
ICD	Time since first cardiac diagnosis
Diabetes	Total bilirubi
Dialysis	Tricuspid regurgitation
Diastolic BP[1]	Volume Status peripheral edema
ECG rhythm	White blood cell count
ECMO	Mitral regurgitation
Ethnic origin	Multiple intropes
Feeding Tube[1]	Legend
Gender	1: not a predictor due to high correlation with other variables
Hemoglobin	
History Of Neurological Event	
IABP	
INR	
INTERMACS Patient Profile	
Intubation[1]	
LDH	
Loop diuretics	
LvEf Percent	
Major Infections	
Major MI	

Supplementary Table 3: Overview of data continuous outside 3 standard deviations

	Mean	Mean - 3SD	Mean + 3 SD	#removed variables
Age	53.53	16.88	90.19	0
LVSF	11.12	-8.97	31.2	6
TAPSE	15.93	-27.15	59	14
Systolic BP	100.44	50.02	150.86	20
Diastolic BP	64.69	27.65	101.73	22
BSA	2.22	-5.41	9.85	32
Pulmonary artery systolic pressure	52.52	-3.5	108.55	17
Pulmonary artery diastolic pressure	26.81	-23.52	77.13	5
RA pressure	11.65	-10.77	34.07	16
Pulmonary artery wedge pressure	24	-2.3	50.3	4
SVR	1337.62	-819.7	3494.93	7
PVR	279.27	-375.68	934.22	13
Cardiac Index	1.04	-3.08	5.16	6
Cardiac Output	4	-3.65	11.65	4
Sodium	131.67	39.67	223.68	6
Potassium	4.34	-12.4	21.07	6
Blood Urea Nitrogen	61.98	-68.71	192.68	26
Creatinine	204.02	-2823.53	3231.57	15
ALAT	226.42	-3847.52	4300.36	16
ASAT	346.72	-4170.23	4863.66	37
LDH	628	-3583.7	4839.69	32
Total bilirubin	2.14	-26.99	31.28	6
Albumin	623.23	-1629.7	2876.17	38
NT Pro-BNP	10047.39	-26451.64	46546.41	24
Cholesterol	3.75	-9.69	17.18	1
WBC	34.04	-1433.06	1501.14	7
Reticulocytes	10.79	-37.64	59.22	3
Hemoglobin	16.28	-88.56	121.11	66
Platelet	206.05	-55.82	467.92	26
INR	1.61	-3.17	6.4	11
PTT	41.09	-28.16	110.33	38
pH	12.21	-553.52	577.94	1
Lactate	4.57	-35.65	44.79	21
BicarbonatHCO3	24.23	10.84	37.61	17
CRPCreactiveprotein	51111614.32	-7685840681.11	7788063909.75	1
LVEDD2	64.88	-42.31	172.07	22
LVESD	58.12	-89.77	206.01	14
LVEDV	250.44	-69.98	570.86	4
LVESV	193.51	-89.48	476.5	3
LvEf Percent	18.65	-5.39	42.68	26
Pulmonary Artery Pressure Mean	35.86	-26.6	98.33	1
Pa Capillary Wedge Pressure	24.94	-0.73	50.6	0

Supplementary Table 4: All variables originally offered to the Lasso logistic model

Variable	Type
Bloodtype	Categorical
Rhesusfactor	Categorical
Age	Continuous
Gender	Categorical
Mitral regurgitation	Categorical
Tricuspid regurgitation	Categorical
Aortic regurgitation	Categorical
Systolic blood pressure	Continuous
Volume Status peripheral edema	Categorical
Cardiac rhythm	Categorical
BSA	Continuous
Neseritide	Categorical
ARB	Categorical
Amiodarone	Categorical
ACE inhibitors	Categorical
Betablockers	Categorical
Aldosteroneantagonist	Categorical
Loop diuretics	Categorical
Anticoagulant therapy drugs status	Categorical
Nitric Oxide	Categorical
Sodium	Continuous
Potassium	Continuous
Creatinine	Continuous
ASAT	Continuous
LDH	Continuous
Total bilirubin	Continuous
White blood cell count	Continuous
Hemoglobin	Continuous
Platelet	Continuous
INR	Continuous
PTT	Continuous
CRPC reactive protein	Continuous
Time since first cardiac diagnosis	Categorical
Ethnic origin	Categorical
Primary Diagnosis	Categorical
Current ICD Device	Categorical
Cardiac Arrest	Categorical
Dialysis	Categorical
Intubation	Categorical

Supplementary Table 4: All variables originally offered to the Lasso logistic model (continued)

Variable	Type
Major MI	Categorical
Positive Blood Cultures	Categorical
Major Infections	Categorical
IABP	Categorical
ECMO	Categorical
INTERMACS Patient Profile	Categorical
Diabetes	Categorical
COPD	Categorical
Symptomatic Peripheral Vascular Disease	Categorical
Connective Tissue Or Inflammatory Disease	Categorical
Carotid artery Disease	Categorical
History of Neurological Event	Categorical
Cancer Other than local skin cancer	Categorical
Device brand LVAD	Categorical
RVEF	Categorical
Ascites	Categorical
Pulmonary Regurgitation	Categorical
LvEf Percent	Continuous
Pulmonary Artery Pressure Mean	Continuous
RA pressure	Continuous
TAPSE	Continuous
Pulmonary artery wedge pressure	Continuous
Albumin	Continuous

Supplementary Table 5: Variables included in propensity score model

Variable	Type	Selection
Tricuspid regurgitation	Categorical, 5 levels	By Lasso
Systolic BP	Continuous, linear	By Lasso
Volume Status peripheral edema	Categorical, 3 levels	By Lasso
ACE inhibitors	Categorical, 2 levels	By Lasso
Beta blockers	Categorical, 2 levels	By Lasso
PTT	Continuous, linear	By Lasso
Ethnic origin	Categorical, 2 levels	By Lasso
Primary Diagnosis	Categorical, 4 levels	By Lasso
Current ICD Device In Place	Categorical, 2 levels	By Lasso
Intubation	Categorical, 2 levels	By Lasso
Major MI	Categorical, 2 levels	By Lasso
Device Brand LVAD	Categorical, 4 levels	By Lasso
Pulmonary Regurgitation	Categorical, 5 levels	By Lasso

Supplementary Table 5: Variables included in propensity score model (continued)

Variable	Type	Selection
RA pressure	Continuous, linear	By Lasso
Potassium	Continuous, linear	Due covariate imbalance
LVEF	Continuous, linear	Due covariate imbalance
INTERMACS Patient Profile	Categorical, 4 levels	Due clinical significance
Age	Continuous, linear	Due clinical significance
TAPSE	Continuous, linear	Due covariate imbalance
ECMO	Categorical, 2 levels	Due covariate imbalance
Albumin	Continuous, linear	Due clinical significance
ECG rhythm	Categorical, 4 levels	Due covariate imbalance
Total bilirubin	Continuous, multiple fractional polynomial: Total bilirubin^-2 +Total bilirubin^-1	Due covariate imbalance
BSA	Continuous, linear	Due covariate imbalance

Supplementary Table 6: Estimates of included variables in PS model

Characteristic	log(OR), [95% CI]
(Intercept)	-6,62 [-8,991 to -4,348]
Tricuspid regurgitation: Trivial	0,328 [-0,73 to 1,612]
Tricuspid regurgitation: Mild	0,436 [-0,526 to 1,67]
Tricuspid regurgitation: Moderate	2,126 [1,203 to 3,34]
Tricuspid regurgitation: Severe	3,058 [2,12 to 4,281]
Systolic blood pressure	-0,016 [-0,025 to -0,006]
Peripheral edema: Mild	-0,54 [-0,965 to -0,133]
Peripheral edema: Moderate	-0,022 [-0,411 to 0,357]
Peripheral edema: Severe	0,139 [-0,27 to 0,539]
ACE inhibitors	-0,375 [-0,702 to -0,056]
Beta blockers	-0,207 [-0,515 to 0,101]
PTT	0,012 [0,003 to 0,022]
Ethnic origin: Caucasian vs other	0,915 [0,346 to 1,55]
Primary Diagnosis: Idiopathic	0,188 [-0,332 to 0,733]
Primary Diagnosis: Ischemic	-0,326 [-0,858 to 0,226]
Primary Diagnosis: Other	0,08 [-0,461 to 0,642]
ICD	0,403 [0,058 to 0,755]
Intubation	-0,55 [-1,138 to -0,002]
Major MI	-0,599 [-1,169 to -0,072]
HeartWare HVAD	-0,635 [-0,951 to -0,319]
Other	-2,329 [-4,164 to -1,107]
Thoratec - HeartMate III	-0,145 [-0,546 to 0,248]
Pulmonary Regurgitation: Trivial	0,479 [0,143 to 0,815]

Supplementary Table 6: Estimates of included variables in PS model (continued)

Characteristic	log(OR), [95% CI]
Pulmonary Regurgitation: Mild	0,118 [-0,268 to 0,499]
Pulmonary Regurgitation: Moderate	-0,252 [-0,925 to 0,374]
Pulmonary Regurgitation: Severe	-1,432 [-2,882 to -0,366]
RA pressure	0,014 [-0,009 to 0,037]
Potassium	0,203 [0,055 to 0,36]
LvEf Percent	0,025 [0,004 to 0,046]
INTERMACS 2 - Progressive decline	0,734 [0,166 to 1,34]
INTERMACS 3- Stable but inotrope dependent	0,603 [0,01 to 1,232]
INTERMACS 4/7	0,54 [-0,098 to 1,208]
Age	0,017 [0,004 to 0,03]
TAPSE	0,014 [-0,018 to 0,046]
ECMO	0,207 [-0,435 to 0,823]
Albumin	0 [0 to 0,001]
ECG: Atrial fibrillation	0,059 [-0,335 to 0,444]
ECG: Other rhythm	-0,159 [-1,12 to 0,67]
ECG: Paced	-0,341 [-0,701 to 0,016]
I(Bilirubin^-2)	0,034 [0,017 to 0,054]
I(Bilirubin^-1)	-0,495 [-0,787 to -0,218]
BSA	0,234 [-0,33 to 0,809]

Supplementary Table 7: Standard mean differences before and after matching. *means of 5 imputed datasets

names	Standard mean difference before matching*	Standard mean difference after matching*
BSA	6,1	4,1
Age	15,3	4,4
Gender	11,8	2,8
Creatinine	6,3	3,7
Ascites	18,6	2,9
Loop diuretics	20,1	5,8
Multiple inotropes	2,4	10,0
ASAT	6,7	2,0
Total bilirubin	17,0	8,7
Hemoglobin	9,9	9,8
RA pressure	34,6	4,6
LVEF Percent	10,8	2,0
IABP	17,6	12,1
ECMO	12,8	2,3
Pulmonary artery systolic pressure	4,4	4,3
Asian	38,6	3,3

Supplementary Table 7: Standard mean differences before and after matching. *means of 5 imputed datasets (continued)

names	Standard mean difference before matching*	Standard mean difference after matching*
White	35,3	5,4
Other race	11,0	5,7
Idiopathic etiology	27,3	1,1
Ischemic etiology	34,1	6,8
Other etiology	6,3	10,2
History cardiac diagnosis one month to a year	30,4	1,4
History cardiac diagnosis one to two years	12,1	0,8
History cardiac diagnosis over two years	12,1	8,0
Atrial fibrillation	3,2	0,4
Other rhythm	3,4	6,4
Paced rhythm	14,1	0,4
INTERMACS class II	6,6	4,0
INTERMACS class III	24,7	5,9
INTERMACS class ≥IV	5,9	3,3
MR trivial	42,7	0,8
MR mild	21,7	4,3
MR moderate	8,1	7,4
MR severe	9,4	5,5
TR trivial	124,2	0,6
TR mild	55,3	8,5
TR moderate	14,0	10,5
TR severe	34,1	6,8
RVF mild	37,6	2,9
RVF moderate	12,3	7,2
RVF severe	12,7	3,4
AR trivial	7,7	0,9
AR mild	14,4	1,0
AR moderate	13,4	6,0
AR severe	1,4	9,2
TAPSE	3,2	6,0
Pulmonary artery wedge pressure	24,8	7,2
Albumin	1,1	2,5

Supplementary Table 8: Sensitivity analyses with caliper set at 0.001

	TVS (n=117)	No TVS (n=117)	p-value
30-day mortality	10.4% (5.3 to 17.9)	7.9% (3.4 to 14.3)	0.69
Hospital mortality	21.2% (10.2 to 24.4)	16.4% (13.6 to 30.6)	0.47
Late mortality $_{\text{KM estimate at 2 years}}$	68.3% (57.7 to 80.4)	60.3 (50.4 to 72.1)	0.18*

TVS: Tricuspid valve surgery. *Derived from log-rank test

Supplementary Table 9: Sensitivity analyses survival (matched patients)

Scenario	P-value log-rank
No TVS: all 22 missing survived 3 year *TVS*: all 7 patients survived 3 years	0.059
No TVS: all 22 missing died at 0.5 year *TVS*: all 7 patients died at 0.5 year	0.86
No TVS: all 22 missing died at 1 year *TVS*: all 7 patients died at 1 year	0.75
No TVS: all 22 missing died at 2 years *TVS*: all 7 patients died at 2 years	0.31
No TVS: all 22 missing died at random time points *TVS*: all 7 patients died at random time points	0.59
No TVS: all 22 missing survived at 3 years *TVS*: all 7 patients died at random time points	0.007*
No TVS: all 22 died at random time points *TVS*: all 7 patients survived at 3 years	0.77
No TVS: 11 patients of 22 died at random time points *TVS*: 3 patients of 7 died at random time points	0.28

In the matched cohort 22 patients without TVS and 7 patients with TVS did not had recorded follow-up. In order to test the robustness of the log-rank test of the kaplan-meier analyses different scenarios were tested under different missing mechanism including missing not at random. The linearized occurrence rate of death was calculated using the formula: number of events/ total patients years and was 19% patient-year.
Therefore: expected alive at 3 years no TVS: 22*0.81^3 ≈ 11 and in TVS cohort: 7*0.81^3 ≈ 4