







Cite this article as: Veen KM, Mokhles MM, Soliman O, de By TMMH, Mohacsi P, Schoenrath F *et al.* Clinical impact and 'natural' course of uncorrected tricuspid regurgitation after implantation of a left ventricular assist device: an analysis of the European Registry for Patients with Mechanical Circulatory Support (EUROMACS). *Eur J Cardiothorac Surg* 2021;59:207–16.

# Clinical impact and 'natural' course of uncorrected tricuspid regurgitation after implantation of a left ventricular assist device: an analysis of the European Registry for Patients with Mechanical Circulatory Support (EUROMACS)

Kevin M. Veen <sup>a</sup>, Mostafa M. Mokhles<sup>a</sup>, Osama Soliman<sup>b</sup>, Theo M.M.H. de By <sup>c</sup>, Paul Mohacsi<sup>d</sup>, Felix Schoenrath <sup>e,f</sup>, Lech Paluszkiwicz <sup>g</sup>, Ivan Netuka<sup>h,i</sup>, Ad J.J.C. Bogers<sup>a</sup>, Johanna J.M. Takkenberg <sup>a</sup> and Kadir Caliskan <sup>b,\*</sup>, on behalf of the EUROMACS Investigators

<sup>a</sup> Department of Cardiothoracic Surgery, Erasmus MC, Rotterdam, Netherlands

<sup>b</sup> Department of Cardiology, Erasmus MC, Rotterdam, Netherlands

<sup>c</sup> EUROMACS Registry, EACTS, Windsor, UK

<sup>d</sup> Department of Cardiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

<sup>e</sup> Department of Cardiothoracic and Vascular Surgery, German Heart Center Berlin, Berlin, Germany

<sup>f</sup> DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany

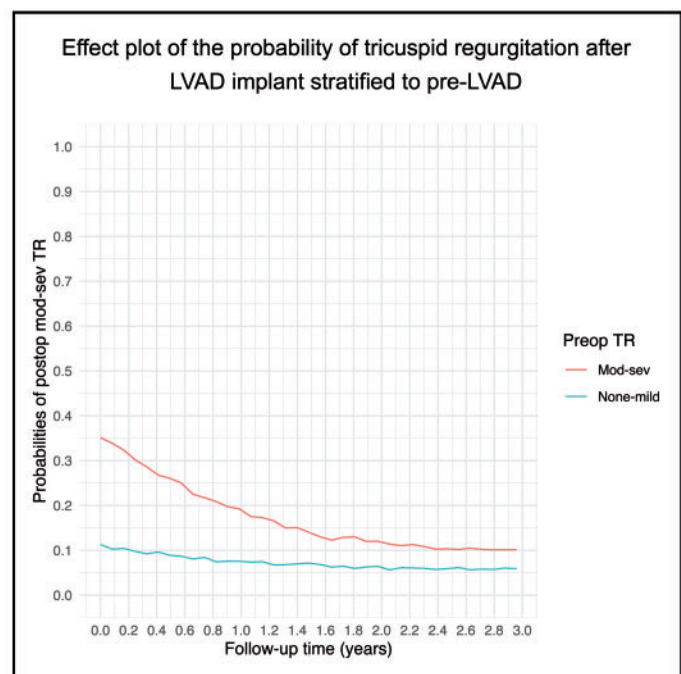
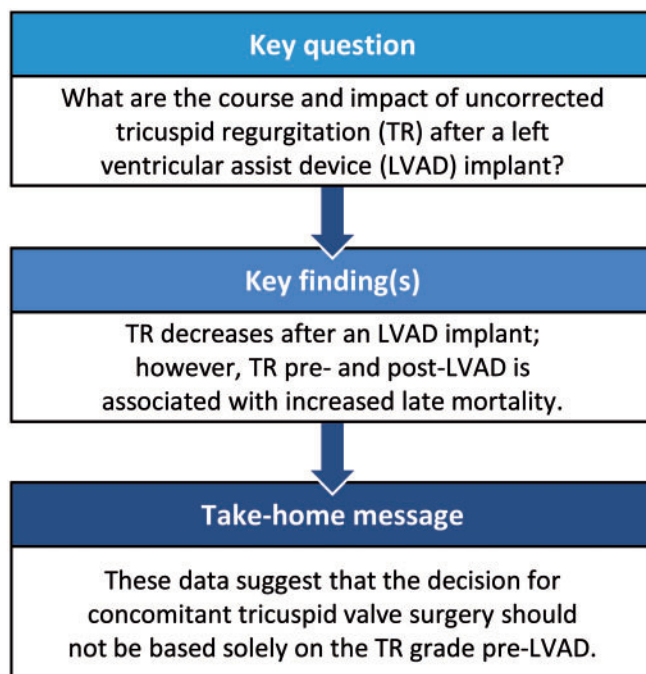
<sup>g</sup> Department for Thoracic and Cardiovascular Surgery, Heart and Diabetes Centre NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany

<sup>h</sup> Department of Cardiothoracic Surgery, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

<sup>i</sup> Department of Cardiovascular Surgery, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

\* Corresponding author. Department of Cardiology, Erasmus MC, Rg-431, Dr. Molewaterplein 40, 3015 GD Rotterdam, Netherlands. Tel: +31 10 704 0704; e-mail: k.caliskan@erasmusmc.nl (K. Caliskan).

Received 21 March 2020; received in revised form 15 June 2020; accepted 27 June 2020



## Abstract

**OBJECTIVES:** Data on the impact and course of uncorrected tricuspid regurgitation (TR) during left ventricular assist device (LVAD) implantation are scarce and inconsistent. This study explores the clinical impact and natural course of uncorrected TR in patients after LVAD implantation.

**METHODS:** The European Registry for Patients with Mechanical Circulatory Support was used to identify adult patients with LVAD implants without concomitant tricuspid valve surgery. A mediation model was developed to assess the association of TR with 30-day mortality via other risk factors. Generalized mixed models were used to model the course of post-LVAD TR. Joint models were used to perform sensitivity analyses.

**RESULTS:** A total of 2496 procedures were included (median age: 56 years; men: 83%). TR was not directly associated with higher 30-day mortality, but mediation analyses suggested an indirect association via preoperative elevated right atrial pressure and creatinine ( $P = 0.035$ ) and bilirubin ( $P = 0.027$ ) levels. Post-LVAD TR was also associated with increased late mortality [hazard ratio 1.16 (1.06–1.3);  $P = 0.001$ ]. On average, uncorrected TR diminished after LVAD implantation. The probability of having moderate-to-severe TR immediately after an implant in patients with none-to-mild TR pre-LVAD was 10%; in patients with moderate-to-severe TR pre-LVAD, it was 35% and continued to decrease in patients with moderate-to-severe TR pre-LVAD, regardless of pre-LVAD right ventricular failure or pulmonary hypertension.

**CONCLUSIONS:** Uncorrected TR pre-LVAD and post-LVAD is associated with increased early and late mortality. Nevertheless, on average, TR diminishes progressively without intervention after an LVAD implant. Therefore, these data suggest that patient selection for concomitant tricuspid valve surgery should not be based solely on TR grade.

**Keywords:** Left ventricular assist device • Tricuspid regurgitation • Mortality • Natural course

### ABBREVIATIONS

|          |  |
|----------|--|
| CI       | Confidence interval  |
| EUROMACS | European Registry for Patients with Mechanical Circulatory Support |
| LVAD     | Left ventricular assist device                                     |
| RA       | Right atrium   |
| RV       | Right ventricular  |
| RVF      | Right ventricular function   |
| SEM      | Structural equation model  |
| TR       | Tricuspid regurgitation  |

## INTRODUCTION

Tricuspid regurgitation (TR) is common in patients with end-stage heart failure undergoing left ventricular assist device (LVAD) implant [1]. Most studies addressing TR after an LVAD implant focus on comparing patients with and without tricuspid valve surgery concomitant with an LVAD implant [2]. However, it is still unclear what the 'natural' course of post-LVAD TR is, and which patients will potentially benefit most from concomitant tricuspid valve surgery. TR has been reported to decrease after an LVAD implant [3–5], but it is not known whether this occurs in all patients uniformly or only in subgroups. Assessing the course and clinical impact of TR after LVAD is important, because it may provide a rationale to perform, or to refrain from performing, tricuspid valve surgery during LVAD implantation. Therefore, this study explores the evolution of TR after an LVAD implant in patients who did not undergo concomitant tricuspid valve surgery. Furthermore, we explored the impact of the preoperative and postoperative TR grade on early (30-day) and late mortality using the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) database. We hypothesized that pre-LVAD TR is part of an interplay with other risk factors [e.g. right ventricular (RV) failure, pulmonary hypertension, renal and/or liver function] and that TR may be

associated with 30-day mortality by increasing these risk factors. Therefore, we performed a mediation analysis. To account for the dynamic nature of TR after LVAD implantation and potential survival bias, the longitudinal evolution of TR was modelled and linked to survival under the joint modelling framework.

## METHODS

### Data source

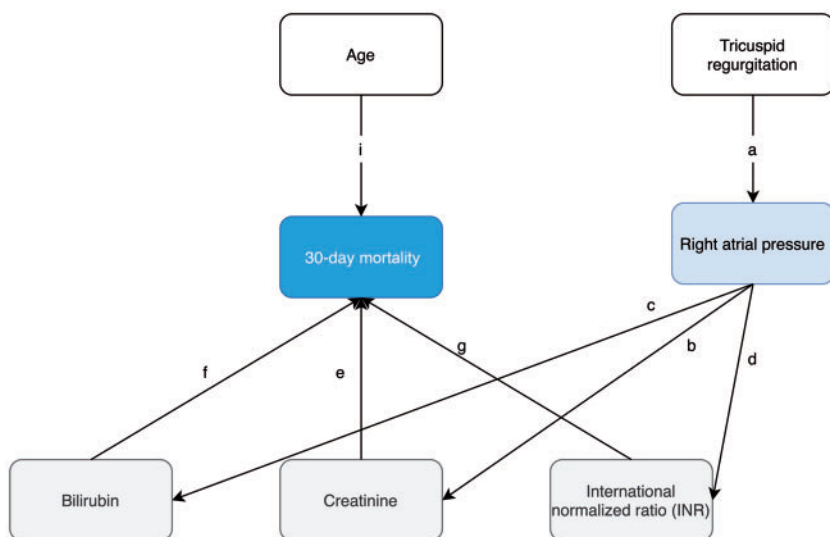
EUROMACS is a registry of the European Association for Cardio-Thoracic Surgery. In this registry, all relevant clinical, echocardiographic haemodynamic and laboratory parameters of patients who require mechanical circulatory support have been collected prospectively since January 2011. Participating centres (Supplementary Material, Table S1) were allowed to enter data before 2011 retrospectively. Detailed descriptions of the database and collection procedure were provided previously [6].

### Patients

All patients operated between 2005 and 2018 were identified. Patients under 18 years of age, with no recorded pre-LVAD TR grade and with concomitant tricuspid valve surgery were excluded from analysis (Supplementary Material, Fig. S1). Additionally, we excluded patients with a planned durable RV assist device, biventricular assist device or total artificial heart implant. Patients were followed until death or the end of the study. Patients were censored at heart transplant or explant.

### Outcome

The main outcomes that were assessed were 30-day mortality, late mortality (defined as death after 30 days) and TR grade (5-point system: none–trivial–mild–moderate–severe).



**Figure 1:** Path diagram of the structural equation model with table of regressions. Paths are indicated by labels a–h, which correspond to the labels in Table 3. Arrows denote the direction of the regression [e.g. tricuspid regurgitation predicts right atrial pressure (path a), which in turn predicts creatinine level (path b)]. INR: internationalized normal ratio.

## Statistical analyses

Continuous data are presented as mean (standard deviation) (Gaussian distribution) or median (interquartile range) (non-Gaussian distribution). Categorical data are presented as frequencies (percentage). Comparisons among continuous variables were made with the one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Continuous data outside 3 standard deviations were considered erroneous and removed (Supplementary Material, Table S2). Comparisons of categorical variables were made with the  $\chi^2$  test or with the Fisher's exact test, as appropriate. Due to multiple testing (34 tests), a Bonferroni correction was applied, considering  $P = 0.0014$  as significantly different. Data with <50% missing values were imputed using multiple imputation (Supplementary Material, Text S1 and Tables S3 and S4).

Univariable and multivariable ordinal proportional odds regression models were used to explore determinants associated with TR at baseline. A forwards stepwise modelling strategy was applied in which all covariates with  $P$ -value <0.10 were entered into the multivariable model.

We hypothesized that the effect of TR on 30-day mortality was mediated by well-known risk factors. Therefore, mediation analysis with a structural equation model (SEM) was performed. The selected variables incorporated into the model included right atrial pressure, creatinine and bilirubin levels and the international normalized ratio (all were incorporated as continuous variables), and were based on previous literature [7–9]. Using SEM, one can compute direct and indirect associations (associations via other variables) on outcomes by specifying a pathway. The conceptual pathways are shown in Fig. 1. A comprehensive explanation of mediation analyses with SEM is provided in Supplementary Material, Text S1. Late mortality was calculated and visualized using the Kaplan–Meier method, and a log-rank test was performed to compare strata. Modified Clark's C, denoted as C\*, was used to calculate completeness of follow-up [10].

## Evolution of tricuspid regurgitation

Logistic mixed models were used to assess longitudinal evolution of TR grade over time (Supplementary Material, Text S1). Subgroup analysis was done for patients with moderate-to-severe TR pre-LVAD. In these patients, separate models containing RV ejection fraction impairment, pulmonary hypertension, pre-LVAD mitral regurgitation, pre-LVAD rhythm, duration of cardiac diagnosis (time elapsed since first cardiac diagnosis) and pre-LVAD right atrium (RA) pressure were developed to investigate the association of these variables with the course of post-LVAD TR. All analyses were done in R (version 3.6.3) (R Project for Statistical Computing: <https://www.r-project.org/>).

## Sensitivity analyses

It is possible that a portion of the dropout of patients is caused by deaths due to TR, resulting in informative censoring (survival bias). In this case, the dropout is not random, thus leading to bias in the mixed model results. Therefore, a sensitivity analysis was performed in which the dynamic longitudinal evolution of TR was inserted into a Cox model under the joint modelling framework. Modelling these entities together alleviates possible bias due to missing values that are missing not at random (i.e. survival bias). The other baseline covariates inserted in the Cox model were based on information from previously published articles; only the current value parameterization of TR was investigated [11, 12]. Several other sensitivity analyses were conducted to test the robustness of the model estimates. These analyses included: exclusion of patients with pre-LVAD extracorporeal membrane oxygenation and patients with postoperative durable RV assist device. Additionally, centre heterogeneity was accounted for in the random effects by performing a mixed model with patients nested in hospitals.

## RESULTS

The database contained 3948 procedures. After applying the exclusion criteria, 2411 patients undergoing 2496 procedures were included (Supplementary Material, Fig. S1). In total, 1892 patients had recorded late follow-up (>30 days) with a median of 1.3 interquartile range (0.5–2.6) years, with a completeness of 85% (C\*).

### Baseline characteristics

Baseline characteristics stratified to TR grade are presented in Table 1. Nearly all the baseline characteristics differed significantly between patients with none-to-mild TR compared to those with moderate-to-severe TR, even after the Bonferroni

correction. Seventy-three potential determinants were tested in univariable ordinal regression models, and 12 determinants remained significant in multivariable analyses. Among others, a higher TR grade at baseline was significantly associated with more peripheral oedema, other pulmonary and mitral valve dysfunction, higher RA pressure, more loop diuretics and worse right ventricular function (RVF) (Supplementary Material, Table S5).

### Pre-left ventricular device tricuspid regurgitation and early mortality

In total, 271 (10.9%) patients died within 30 days. The 30-day mortality was comparable between patients with none-to-mild

**Table 1:** Baseline characteristics stratified to pre-left ventricular assist device TR grade

|   | None-to-mild TR        | Moderate-to-severe TR  | P-value |
|---|------------------------|------------------------|---------|
| <b>Demographics</b>                       |                        |                        |         |
| <i>n</i>                                  | 1690                   | 806                    |         |
| Age (years)                               | 56.00 (47.00–62.00)    | 56.00 (46.00–62.00)    | 0.71    |
| Male gender, <i>n</i> (%)                 | 1416 (83.8)            | 657 (81.5)             | 0.17    |
| Body surface area (m <sup>2</sup> )       | 1.99 (1.83–2.12)       | 1.92 (1.78–2.08)       | <0.001  |
| White race, <i>n</i> (%)                  | 1234 (86.3)            | 626 (86.2)             | 0.97    |
| Ischaemic aetiology HF, <i>n</i> (%)      | 620 (43.3)             | 251 (35.2)             | <0.001  |
| ≥2 Years since first diagnosis            | 811 (60.3)             | 494 (70.4)             | <0.001  |
| Destination therapy                       | 294 (17.5)             | 128 (15.9)             | 0.36    |
| Ascites                                   | 96 (8.5)               | 94 (16.9)              | <0.001  |
| Rhythm, <i>n</i> (%)                      |                        |                        | 0.001   |
| Sinus                                     | 796 (58.1)             | 341 (49.6)             |         |
| Atrial fibrillation                       | 225 (16.4)             | 130 (18.9)             |         |
| Paced                                     | 28 (2.0)               | 28 (4.1)               |         |
| Other                                     | 322 (23.5)             | 189 (27.5)             |         |
| INTERMACS profile, <i>n</i> (%)           |                        |                        | <0.001  |
| 1   | 238 (14.7)             | 79 (10.1)              |         |
| 2   | 538 (33.3)             | 259 (33.2)             |         |
| 3   | 457 (28.3)             | 205 (26.3)             |         |
| ≥4  | 384 (23.7)             | 237 (30.4)             |         |
| IABP, <i>n</i> (%)                        | 173 (12.0)             | 58 (8.1)               | 0.008   |
| ECMO, <i>n</i> (%)                        | 183 (11.2)             | 50 (6.5)               | <0.001  |
| Ventilator (%)                            | 224 (15.6)             | 52 (7.3)               | <0.001  |
| Medication, <i>n</i> (%)                  |                        |                        |         |
| Loop diuretics                            | 1060 (78.8)            | 588 (86.7)             | <0.001  |
| Use of ≥3 inotropes                       | 182 (13.0)             | 93 (13.3)              | 0.91    |
| <b>Laboratory values</b>                  |                        |                        |         |
| Serum creatinine (mg/dl)                  | 106.00 (84.00–146.00)  | 106.00 (82.00–144.00)  | 0.43    |
| ASAT (U/l)                                | 33.00 (22.00–70.00)    | 30.00 (21.00–55.00)    | 0.002   |
| Total bilirubin (mg/dl)                   | 1.18 (0.74–1.90)       | 1.40 (0.90–2.27)       | <0.001  |
| Albumin (g/dl)                            | 499.91 (410.07–579.60) | 521.64 (440.50–579.60) | 0.010   |
| Haemoglobin (g/dl)                        | 12.00 (10.30–13.60)    | 11.75 (10.20–13.30)    | 0.17    |
| <b>Haemodynamics</b>                      |                        |                        |         |
| RA pressure (mmHg)                        | 10.00 (6.00–14.00)     | 11.00 (8.00–16.00)     | <0.001  |
| PCWP (mmHg)                               | 24.00 (17.00–30.00)    | 25.00 (20.00–30.00)    | 0.005   |
| PAP, systolic (mmHg)                      | 51.00 (38.00–62.00)    | 53.00 (41.75–65.00)    | 0.003   |
| <b>Echocardiography</b>                   |                        |                        |         |
| TAPSE (mm)                                | 15.00 (12.00–17.00)    | 14.00 (11.00–16.00)    | <0.001  |
| No aortic regurgitation, <i>n</i> (%)     | 1043 (67.8)            | 397 (54.8)             | <0.001  |
| Severe mitral regurgitation, <i>n</i> (%) | 162 (11.1)             | 223 (30.3)             | <0.001  |
| LVEF grade <20%, <i>n</i> (%)             | 779 (57.2)             | 431 (64.2)             | 0.010   |
| <b>RVF</b>                                |                        |                        |         |
| Normal                                    | 279 (24.4)             | 89 (15.6)              |         |
| Mild                                      | 334 (29.2)             | 105 (18.4)             |         |
| Moderate                                  | 389 (34.1)             | 274 (48.1)             |         |
| Severe                                    | 140 (12.3)             | 102 (17.9)             |         |

Normally distributed variables are presented as means (standard deviations) and not normally distributed variables are medians (interquartile range).

ASAT: aspartate aminotransferase; ECMO: extracorporeal membrane oxygenation; HF: heart failure; IABP: intra-aortic balloon pump; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; LVEF: left ventricular ejection fraction; PAP: pulmonary atrial pressure; PCWP: pulmonary capillary wedge pressure; RA: right atrium; RVF: right ventricular function; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

TR versus moderate-to-severe TR (10.8% vs 10.9%;  $P=0.99$ ). Procedural and hospital outcomes in patients with none-to-mild and moderate-to-severe TR are presented in Table 2.

The conceptual paths of the SEM are shown in Fig. 1 and the regression estimates and significance, in Table 3. Overall, the model fitted well, as indicated by the fit indices in Table 3. Although the total effect of TR on 30-day mortality was

insignificant, the path TR to RA pressure to creatinine was significantly associated with 30-day mortality ( $P=0.035$ ) (Table 3). Additionally, the path TR to RA pressure to bilirubin was significantly associated with 30-day mortality ( $P=0.027$ ) (Table 3). However, the path TR to RA pressure to international normalized ratio was not associated with 30-day mortality ( $P=0.057$ ) (Table 3).

**Table 2:** Procedural characteristics and early outcomes

|  | None-to-mild TR      | Moderate-to-severe TR | P-value |
|--|----------------------|-----------------------|---------|
| Device                                     |                      |                       | 0.005   |
| HeartMate II LVAS                          | 484 (29.5)           | 186 (24.2)            |         |
| HeartWare HVAD                             | 841 (51.3)           | 452 (58.8)            |         |
| HeartMate3                                 | 241 (14.7)           | 95 (12.4)             |         |
| Other                                      | 74 (4.5)             | 36 (4.7)              |         |
| CPB time                                   | 79.00 (58.00–108.00) | 80.00 (60.00–111.00)  | 0.22    |
| ICU/CCU stay (days)                        | 10.00 (5.00–23.00)   | 10.00 (5.00–22.00)    | 0.81    |
| Hospital stay (days)                       | 29.00 (21.00–43.00)  | 31.00 (21.00–44.00)   | 0.18    |
| Discontinuation of IV inotropes (days) (%) |                      |                       | 0.30    |
| 1–7  | 558 (55.0)           | 295 (58.4)            |         |
| 8–13                                       | 184 (18.1)           | 97 (19.2)             |         |
| 14–27                                      | 168 (16.6)           | 73 (14.5)             |         |
| >27  | 103 (10.1)           | 38 (7.5)              |         |
| Temporary RVAD                             | 66 (3.9)             | 39 (4.8)              | 0.32    |
| 30-Day mortality, <i>n</i> (%)             | 184 (10.9)           | 87 (10.8)             | >0.99   |

Normally distributed variables are presented as means (standard deviations) and not normally distributed variables are medians (interquartile ranges).

CCU: coronary care unit; CPB: cardiopulmonary bypass; ICU: intensive care unit; IV: intravenous; LVAS: left ventricular assist system; RVAD: right ventricular assist device; TR: tricuspid regurgitation.

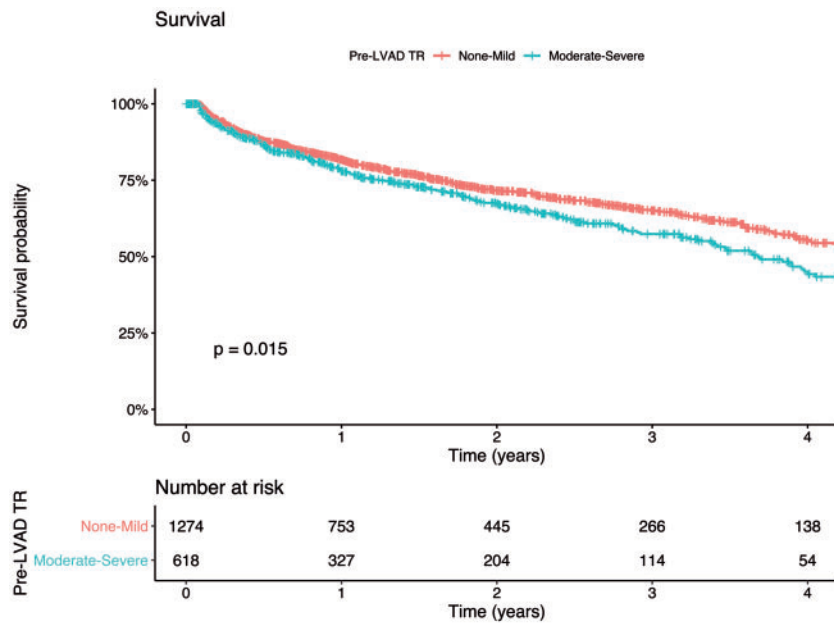
**Table 3:** Estimates of the paths of the structural equation model

| Regressions                                      | Path <sup>a</sup> | $\beta$ -Estimate (95% CI) | P-value |
|--|-------------------|----------------------------|---------|
| Mortality ~                                      |                   |                            |         |
| Bilirubin  | f                 | 0.056 (0.003–0.080)        | >0.001  |
| Creatinine                                       | e                 | 0.001 (0.001–0.001)        | >0.001  |
| INR  | g                 | 0.121 (0.033–0.209)        | 0.007   |
| Age  | i                 | 0.016 (0.010–0.021)        | >0.001  |
| TR per 1 grade                                   | h                 | -0.047 (-0.101 to 0.007)   | 0.087   |
| RA pressure ~                                    |                   |                            |         |
| TR   | a                 | 0.805 (0.464–1.146)        | >0.001  |
| Bilirubin ~                                      |                   |                            |         |
| RA pressure                                      | c                 | 0.048 (0.023–0.072)        | 0.002   |
| Creatinine ~                                     |                   |                            |         |
| RA pressure                                      | b                 | 1.159 (0.341–1.977)        | 0.015   |
| INR ~  |                   |                            |         |
| RA pressure                                      | d                 | 0.011 (0.003–0.019)        | 0.011   |
| Indirect effects of TR                           |                   |                            |         |
| Direct effect                                    | h                 | -0.047 (-0.101 to 0.007)   | 0.087   |
| RA pressure–creatinine                           | a–b–e             | 0.001 (0.001–0.001)        | 0.035   |
| RA pressure–bilirubin                            | a–c–f             | 0.002 (0.001–0.003)        | 0.027   |
| RA pressure–INR                                  | a–d–g             | 0.001 (0.000–0.001)        | 0.058   |
| Total effect                                     |                   | -0.043 (-0.098 to 0.012)   | 0.12    |
| Fit measures                                     |                   |                            |         |
| $\chi^2$   |                   | >0.001                     |         |
| Non-normed fit index                             |                   | 0.95                       |         |
| Comparative fit index                            |                   | 0.98                       |         |
| Root mean square error of approximation (95% CI) |                   | 0.051 (0.037–0.065)        |         |
| Standardized root mean square residual           |                   | 0.065                      |         |

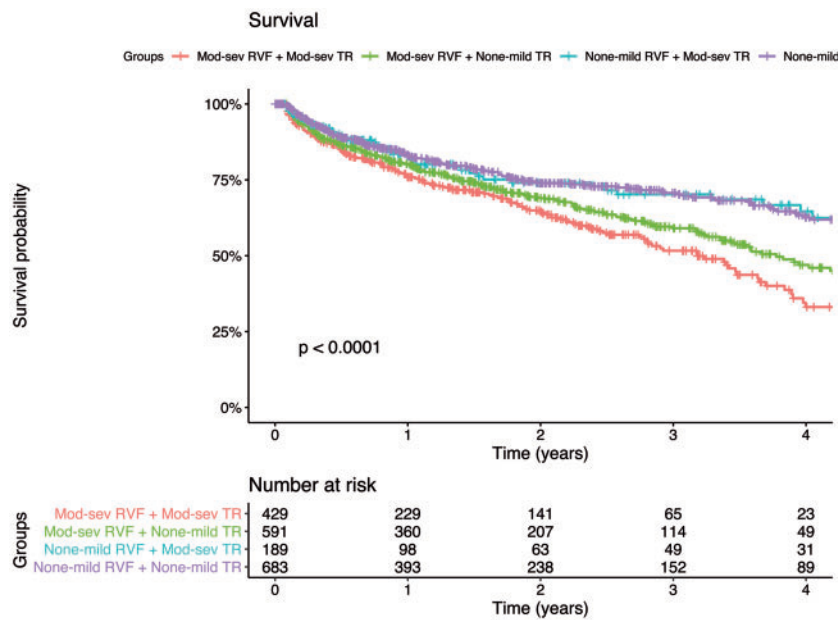
<sup>a</sup>Paths correspond to the paths specified in Fig. 1.

CI: confidence interval; INR: internationalized normal ratio; RA: right atrium; TR: tricuspid regurgitation.





**Figure 2:** Kaplan–Meier curve of late survival (includes only 30-day survivors) after LVAD implant stratified to pre-LVAD TR grade. LVAD: left ventricular assist device; TR: tricuspid regurgitation.



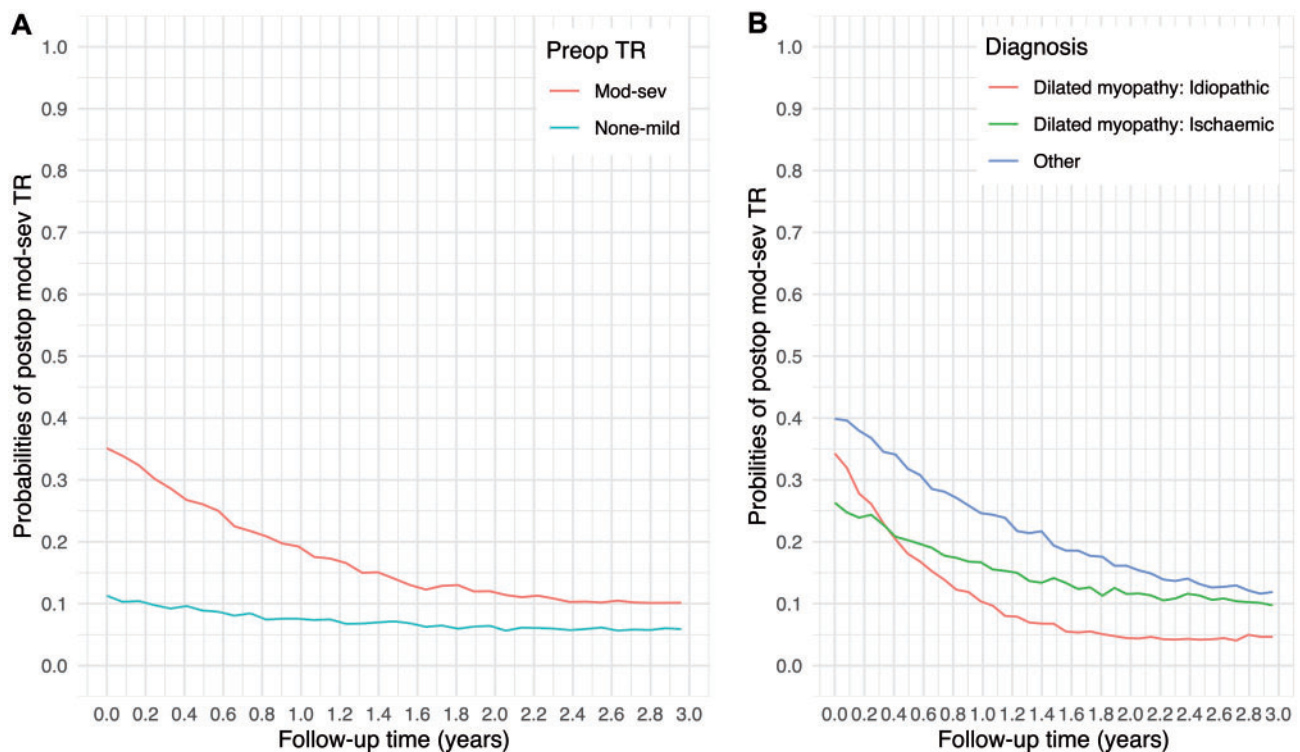
**Figure 3:** Kaplan–Meier curve of late survival (includes only 30-day survivors) after left ventricular assist device implant stratified to pre-left ventricular assist device TR grade with or without right ventricular dysfunction. Of note, data from the first imputed data set are used. RVF: right ventricular failure, mod: moderate; sev: severe; TR: tricuspid regurgitation.

### Pre-left ventricular assist device tricuspid regurgitation and late mortality

A total of 626 of 2410 thirty-day survivors died during the long-term (>30 days) follow-up period. Survival after 30 days, stratified to none-to-mild TR versus moderate-to-severe TR at baseline, is presented in Fig. 2 and differed significantly between strata ( $P=0.015$ ).

The Spearman correlation between pre-LVAD TR and pre-LVAD RVF was 0.22 ( $P < 0.001$ ). Therefore, these variables were

combined into 1 variable. In Fig. 3 the population is stratified to different levels of right ventricle dysfunction with or without significant TR. Three years after implant, the Kaplan–Meier survival estimate was lower in patients with both moderate-to-severe TR and RVF [54%, 95% confidence interval (CI) 47–61] compared to patients with good RVF and none-to-mild TR (68%, 95% CI 64–73). In a sensitivity analysis with only complete cases, the group with both moderate-to-severe TR and RVF pre-LVAD had survival and hazard ratios comparable to those of patients with none-to-mild TR and moderate-to-severe RVF pre-LVAD ([Supplementary](#)



**Figure 4:** (A) Effects plot of the probability of TR after left ventricular assist device (LVAD) implant stratified to pre-LVAD. (B) Effects plot of the evolution of TR after LVAD (in patients with moderate-to-severe TR pre-LVAD). TR: mod-sev: moderate to severe; postop: postoperative; preop: preoperative; TR: tricuspid regurgitation.

Material, Figs S2 and S3). RVF did seem to be conditionally missing based on observed variables (Supplementary Material, Table S6).

### Evolution of tricuspid regurgitation

During the follow-up period, 914 (48%) patients had 1 or more echocardiograms, with 3113 echocardiograms in total (mean 3.4, range 1–8) (Supplementary Material, Fig. S4). Figure 4A presents the probabilities of having moderate-to-severe TR after an LVAD implant, stratified to pre-LVAD TR severity. The odds of moderate-to-severe TR after an LVAD implant decreased over time and became comparable after ~1.4 years in patients with moderate-to-severe TR pre-LVAD versus patients with none-to-mild TR pre-LVAD.

In patients with moderate-to-severe TR pre-LVAD, no significant differences were observed in the course of TR post-LVAD among different levels of pre-LVAD RV ejection fraction impairment, pre-LVAD pulmonary hypertension, pre-LVAD mitral regurgitation, pre-LVAD rhythm, duration of cardiac diagnoses, an implantable cardioverter-defibrillator or pre-LVAD RA pressure (Supplementary Material, Figs S5–S11), except for patients with idiopathic dilated myopathy. In these patients post-LVAD TR decreased faster compared to patients with other diagnoses (Fig. 4B), but the odds of moderate-to-severe TR became comparable after ~2.5 years. The difference in the odds of moderate-to-severe TR was observed predominantly in patients with other diagnoses (e.g. myocarditis and toxic or postpartum myopathy) compared to patients with idiopathic dilated myopathy (Fig. 4B). To gain insight into the possibility of informative censoring (survival bias), the longitudinal evolution of TR was jointly modelled

with a survival model and compared with the estimates of the mixed model (Supplementary Material, Table S7). Some sensitivity was observed in both the effect size and standard errors (Supplementary Material, Table S8); however, the direction of the effect did not change, nor did the significance. Hence, the decrease in the probability of TR after LVAD cannot be solely explained by survival bias.

### Post-left ventricular assist device tricuspid regurgitation and mortality

Moderate-to-severe TR post-LVAD was associated with increased mortality (hazard ratio 1.16, 95% CI 1.06–1.30;  $P=0.001$ ), as estimated by the joint model adjusted for several baseline variables including RV dysfunction (Supplementary Material, Table S7).

### Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the outcomes. Estimates of the evolution of TR did not change considerably if patients with pre-LVAD ECMO were excluded (Supplementary Material, Tables S9 and S10). Including the centre as a random effect did not change estimates (Supplementary Material, Table S11). Furthermore, centres that tended to repair the tricuspid valve in the setting of moderate-to-severe TR pre-LVAD had similar evolutions of post-LVAD TR in patients without tricuspid valve intervention compared to centres that were not inclined to repair the tricuspid valve (Supplementary Material, Fig. S12). Excluding patients with an RV assist device implant during the follow-up period did not

considerably change the estimates of the longitudinal evolution or of survival (Supplementary Material, Tables S12 and S13).

## DISCUSSION

This study explores the clinical impact of pre-LVAD and post-LVAD TR on 30-day and late mortality and the course of post-LVAD TR in the survivors. Interesting observations were noted: both pre- and post-LVAD TR seemed to be associated with reduced survival. Nevertheless, on average, TR resolved 'spontaneously' after an LVAD implant, which was not solely due to survival bias.

### Early and late mortality

We hypothesized that TR is part of an entire pathway that may lead to higher 30-day mortality, i.e. mediated by other variables. To gain insight in this hypothesis, we developed a conceptual model with several paths (Fig. 1). When this model was tested, it fit well, suggesting that TR may not be directly related to 30-day mortality but that by increasing other risk factors it is indirectly associated with 30-day mortality. Notably, we did not include RVF in the pathways because of the circular relation with the severity of TR, which cannot be modelled. The impaired RVF can lead to TR due to RV/annulus dilation, but also the other way around due to volume or pressure overload [7]. Furthermore, TR was chosen in the model because TR is associated with renal dysfunction in the literature [9].

The investigators of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) found TR to be associated with reduced late survival [13]. Assessing the Kaplan–Meier curve of the combined variables, it seems that pre-LVAD-impaired RVF is the driving factor in late mortality after an LVAD implant; however, impaired RVF accompanied by TR resulted in an even worse survival. These data may suggest that pre-LVAD TR in the setting of impaired RVF adds extra late risk, which can partly be explained by the negative spiral that ensues when TR is present in the setting of impaired RVF, leading to more dysfunction. Furthermore, TR together with impaired RVF is associated more with renal failure than with isolated TR or impaired RVF alone [14, 15]. Nevertheless, it has to be noted that confounding may be present here, and, in a sensitivity analysis with complete cases, pre-LVAD RVF did seem to be the driving factor regardless of pre-LVAD TR. RVF was conditionally missing upon other observed baseline variables, suggesting the missing at random mechanism. Multiple imputation is more valid in missing-at-random scenarios [16].

### Evolution of tricuspid regurgitation

TR decreases without intervention after an LVAD implant, and this decrease is not solely based on patients dying of TR. Overall, an immediate decrease of ~65% is observed from moderate-to-severe TR to non-to-mild TR in patients with moderate-to-severe TR pre-LVAD. Other studies comparing point estimates over time noted comparable results [1, 4]. The decrease in TR may be explained by the fact that LVAD support reduces pulmonary pressures, subsequently reducing the pressure overload of the right ventricle, which leads to right ventricle remodelling and

regression of the tricuspid valve annulus dilatation. The remodelling in turn leads to resolution of functional TR.

Furthermore, it seems that TR decreases more quickly in patients with idiopathic cardiomyopathy compared to other cardiomyopathies. However, later in the follow-up period, this difference disappears. Furthermore, these results can be explained by confounding because the models were univariable, and some misclassifications in TR grade will be present, which can bias outcome in the small subgroups.

### Clinical implications and rationale for eventual tricuspid valve surgery

The observations of this study in respect to concomitant tricuspid valve surgery can be interpreted in 2 ways. First, one can argue that concomitant surgery of the tricuspid valve is warranted, because both preoperative and postoperative TR are associated with increased mortality. It has to be noted that this study by design cannot establish a causal relationship between TR and mortality, and TR may just be a marker of significant RVF. Second, one can argue that a less aggressive strategy is warranted because, on average, the TR will resolve after LVAD implantation without any further intervention.

Current guidelines advise consideration of tricuspid valve surgery in the presence of moderate or severe TR at baseline. Current practice notwithstanding, we may be overtreating patients with unnecessary concomitant tricuspid valve surgery if we follow the guidelines. This deficit also may explain why previous studies comparing patients with and without concomitant tricuspid valve surgery were unable to find an effect [2]. Some patients will not benefit because TR will resolve without an intervention. Therefore, the key point seems to be appropriate patient selection, taking into account the aetiology of TR, the severity of RV dysfunction and the underlying myocardial disease when deciding to perform concomitant surgery. Anwer *et al.* [17] proposed that atrial fibrillation should be included in this decision process. We were not able to show a significant effect of pre-LVAD atrial fibrillation on the odds of significant TR post-LVAD with the subgroup analyses, but there were only a few patients in the atrial fibrillation group. Functional TR has a chance to reduce spontaneously, whereas primary TR (e.g. caused by a pacemaker or an implantable cardioverter-defibrillator lead) probably will not. Furthermore, functional TR has not only been caused by tricuspid valve annular dilatation but also by valve tethering [18]. In the case of severe tethering, tricuspid annuloplasty may not be enough to reduce TR [19].

### Future perspectives

Future studies should focus on understanding the different mechanisms and concomitant factors contributing to significant TR and finding the appropriate predictors of TR after LVAD implantation, preferably in a longitudinal prospective dedicated data set encompassing RV functional and dimensional, pulmonary and haemodynamic parameters. Therefore, we recently set up the Serial Multiparametric Evaluation of Right Ventricular Function After Left Ventricular Assist Device Implantation (EuroEchoVAD) study (see [clinicaltrials.org](http://clinicaltrials.org), NCT03552679) to investigate the evolution of RVF, TR and other echocardiographic parameters before and after LVAD implantation. The findings of the study will enhance the prediction of the early and late development of



postoperative RVF, the course of TR severity and the subsequent mortality and morbidity. Furthermore, novel transcatheter devices to treat tricuspid valve regurgitation are on the horizon. These devices have the potential to become interesting addenda in the treatment of functional TR in the setting of LVAD implantation. However, several challenges need to be addressed before they can enter daily clinical practice [20].

## Limitations

This study has several limitations common to retrospective registry analyses. EUROMACS is not designed to address the specific questions in this study. Therefore, there is a limited amount of data collected with a focus on the right ventricle, or these data are not uniformly collected. Furthermore, it has to be emphasized that misspecification may be present in a registry and that follow-up is suboptimal, which can introduce bias. We prevented more loss of data by imputation of the missing data in order to generate more power in the analysis. Nevertheless, some variables could not be imputed due to excessive missingness, and we could not use the longitudinal trajectory of TR in the imputation model. Additionally, follow-up data on TR were not collected at prespecified, regular intervals and assessing TR remains challenging [21]. However, we used mixed models, which can handle these unstructured data sets, and TR was dichotomized in these models to create a more robust measurement. Unfortunately, in some subgroups, the sample size was small, and it was not known if patients had tricuspid valve surgery during the follow-up period. Advanced path models are used to shed some light on the impact of TR on 30-day mortality via other variables. However, due to the circular relationship with RVF, the true effect of TR on mortality may be impossible to estimate. Thereafter, the mechanism of TR was not recorded in the registry. Presumably, most of the TR is functional in nature, supported by the fact that TR is associated with RVF and its symptoms/treatment.

## CONCLUSIONS

Moderate-to-severe TR pre-LVAD is positively correlated with worse RVF pre-LVAD and is associated with worse late mortality. However, overall, TR decreases after the LVAD is implanted, regardless of pre-LVAD pulmonary hypertension or right ventricle function. Hence, in the majority of the patients, additional tricuspid valve surgery may be redundant. Therefore, patient selection for concomitant tricuspid valve surgery should not be based solely on TR grade alone. Further studies are urgently needed to tackle this clinical dilemma in the era of durable mechanical circulatory support.

## SUPPLEMENTARY MATERIAL

[Supplementary material](#) is available at *EJCTS* online.

**Conflict of interest:** none declared.

## Author contributions

**Kevin M. Veen:** Conceptualization; Formal analysis; Methodology; Writing—original draft. **Mostafa M. Mokhles:** Conceptualization; Supervision;

Writing—review & editing. **Osama Soliman:** Supervision; Writing—review & editing. **Theo M.M.H. de By:** Data curation; Writing—original draft. **Paul Mohacsi:** Supervision; Writing—review & editing. **Felix Schoenrath:** Writing—review & editing. **Lech Paluszkiwicz:** Writing—review & editing. **Ivan Netuka:** Writing—review & editing. **Ad J.J.C. Bogers:** Conceptualization; Supervision; Writing—review & editing. **Johanna J.M. Takkenberg:** Conceptualization; Methodology; Writing—review & editing. **Kadir Caliskan:** Conceptualization; Supervision; Writing—review & editing.

## Reviewer information

European Journal of Cardio-Thoracic Surgery thanks Paul Kurlansky, Roberto Lorusso, Davide Pacini and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

## REFERENCES

- [1] Piacentino V 3rd, Williams ML, Depp T, Garcia-Huerta K, Blue L, Lodge AJ *et al.* Impact of tricuspid valve regurgitation in patients treated with implantable left ventricular assist devices. *Ann Thorac Surg* 2011;91:1342–6; discussion 6–7.
- [2] Veen KM, Etnel JRG, Takkenberg J. Tricuspid valve disease: surgical outcome. In: Soliman OI, ten Cate FJ (eds). *Practical Manual of Tricuspid Valve Diseases*. Cham: Springer International Publishing, 2018, 305–27.
- [3] Morgan JA, Paone G, Nemeš HW, Murthy R, Williams CT, Lanfear DE *et al.* Impact of continuous-flow left ventricular assist device support on right ventricular function. *J Heart Lung Transplant* 2013;32:398–403.
- [4] Atluri P, Fairman AS, MacArthur JW, Goldstone AB, Cohen JE, Howard JL *et al.* Continuous flow left ventricular assist device implant significantly improves pulmonary hypertension, right ventricular contractility, and tricuspid valve competence. *J Card Surg* 2013;28:770–5.
- [5] Lee S, Kamdar F, Madlon-Kay R, Boyle A, Colvin-Adams M, Pritzker M *et al.* Effects of the HeartMate II continuous-flow left ventricular assist device on right ventricular function. *J Heart Lung Transplant* 2010;29:209–15.
- [6] de By TM, Mohacsi P, Gummert J, Bushnaq H, Krabatsch T, Gustafsson F *et al.* The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): first annual report. *Eur J Cardiothorac Surg* 2015;47:770–6; discussion 6–7.
- [7] Deo SV, Daly RC, Altarabsheh SE, Hasin T, Zhao Y, Shah IK *et al.* Predictive value of the model for end-stage liver disease score in patients undergoing left ventricular assist device implantation. *ASAIO J* 2013;59:57–62.
- [8] Cowger J, Sundareswaran K, Rogers JG, Park SJ, Pagani FD, Bhat G *et al.* Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. *J Am Coll Cardiol* 2013;61:313–21.
- [9] Maeder MT, Holst DP, Kaye DM. Tricuspid regurgitation contributes to renal dysfunction in patients with heart failure. *J Card Fail* 2008;14:824–30.
- [10] Wu Y, Takkenberg JJ, Grunkemeier GL. Measuring follow-up completeness. *Ann Thorac Surg* 2008;85:1155–7.
- [11] Rizopoulos D. *Joint Models for Longitudinal and Time-to-Event Data: With Applications in R*. New York: Chapman and Hall/CRC, 2012.
- [12] Kirklin JK, Xie R, Cowger J, de By T, Nakatani T, Schueler S *et al.* Second annual report from the ISHLT Mechanically Assisted Circulatory Support Registry. *J Heart Lung Transplant* 2018;37:685–91.
- [13] Song HK, Gelow JM, Mudd J, Chien C, Tibayan FA, Hollifield K *et al.* Limited utility of tricuspid valve repair at the time of left ventricular assist device implantation. *Ann Thorac Surg* 2016;101:2168–75.
- [14] Fender EA, Zack CJ, Nishimura RA. Isolated tricuspid regurgitation: outcomes and therapeutic interventions. *Heart* 2018;104:798–806.
- [15] Agricola E, Marini C, Stella S, Monello A, Fiscicaro A, Tufaro V *et al.* Effects of functional tricuspid regurgitation on renal function and long-term prognosis in patients with heart failure. *J Cardiovasc Med (Hagerstown)* 2017;18:60–8.
- [16] Papageorgiou G, Grant SW, Takkenberg JJM, Mokhles MM. Statistical primer: how to deal with missing data in scientific research? *Interact CardioVasc Thorac Surg* 2018;27:153–8.
- [17] Anwer LA, Tchanchaleishvili V, Poddi S, Daly RC, Joyce LD, Kushwaha SS *et al.* Atrial fibrillation should guide prophylactic tricuspid procedures

- during left ventricular assist device implantation. *ASAIO J* 2018;64: 586-93.
- [18] Tornos Mas P, Rodriguez-Palomares JF, Antunes MJ. Secondary tricuspid valve regurgitation: a forgotten entity. *Heart* 2015;101:1840-8.
- [19] Fukuda S, Song JM, Gillinov AM, McCarthy PM, Daimon M, Kongsarepong V *et al.* Tricuspid valve tethering predicts residual tricuspid regurgitation after tricuspid annuloplasty. *Circulation* 2005;111: 975-9.
- [20] Chang CC, Veen KM, Hahn RT, Bogers A, Latib A, Oei FBS *et al.* Uncertainties and challenges in surgical and transcatheter tricuspid valve therapy: a state-of-the-art expert review. *Eur Heart J* 2020;41: 1932-40.
- [21] Grant AD, Thavendiranathan P, Rodriguez LL, Kwon D, Marwick TH. Development of a consensus algorithm to improve interobserver agreement and accuracy in the determination of tricuspid regurgitation severity. *J Am Soc Echocardiogr* 2014;27:277-84.