The clinical impact of tricuspid regurgitation in patients with a biatrial orthotopic heart transplant

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ABSTRACT

Introduction

Tricuspid regurgitation (TR) is common in patients with after biatrial orthotopic heart transplant (OHT). Nevertheless, the clinical impact and long-term sequel of TR remains unclear. In this study, we aim to elucidate the clinical impact and long-term course of TR, taking into account its dynamic nature.

Methods

All consecutive adult patients undergoing biatrial OHT (1984-2017) and with an available follow-up echocardiogram were included in this study. Mixed-models were used to model the evolution of TR. Thereafter, the mixed-model was inserted into a Cox model, under the joint-model framework, in order to address the association of the dynamic TR with mortality.

Results

In total, 572 patients were included (median age: 50 years, males:74.9%). Approximately 32% of patients had moderate-to-severe TR immediately after surgery. However, this declined to approximately 11% at 5 years and 9% at 10 years after of surgery, adjusted for survival bias. Pre-implant mechanical support was associated with less TR during follow-up, whereas concurrent LV dysfunction was significantly associated with more TR during follow-up. Survival at 1, 5, 10, 20 years was 97±1%, 88±1%, 66±2% and 23±2%, respectively. The presence of moderate-to-severe TR during follow-up was associated with higher mortality (HR:1.07,95%CI[1.02-1.12],p=0.006). The course of TR was positively correlated with the course of creatinine (R=0.45).

Conclusion

TR during follow-up is significantly associated with higher mortality and worse renal function. Nevertheless, probability of TR is the highest immediately after OHT and decreases thereafter. Therefore, it may be reasonable to refrain from surgical intervention for TR during earlier phase after OHT.

INTRODUCTION

Tricuspid regurgitation (TR) is common in patients post biatrial orthotopic heart transplant (OHT) (1). Risk factors for TR after OHT include endomyocardial biopsies, allograft rejection, mismatch between the donor heart size and pericardial cavity dimensions (2-4). Additionally, several studies identified a biatrial anastomoses technique (vs a bicaval anastomoses) as independent risk factor for TR after OHT (3, 5, 6). Nevertheless, the clinical impact of TR remains unclear, partly because post-OHT TR is a dynamic disease that changes over time in individual patients. Due to these complex characteristics the clinical impact of post-OHT TR cannot be approached using traditional statistical tools. In this study, we aim to elucidate the clinical impact and long-term course of TR, taking into account its dynamic nature, by using novel statistical models to link the course of post-OHT TR to survival and renal function.

METHODS

Patients

Consecutive patients that underwent biatrial OHT from 1984 to 2016 in Erasmus MC were included in this retrospective cohort study (n=687). Patients whom echocardiograms results were not retrievable or had recorded echocardiograms without TR measurements were excluded (n=115) resulting in 572 patients eligible for analyses. Of note, most patients that died within 30 days did not have a TR measurement on echocardiogram and, therefore, were excluded. (Supplementary Figure 1). None of the patients received tricuspid valve interventions during follow-up. Approval from the local Medical Ethical Committee was obtained to conduct this study (MEC-2017-421).

Data collection

Baseline characteristics were extracted from our institutional OHT database. Additionally, all echocardiographic measurements and creatinine measurements were collected longitudinally via automated extraction from the electronic patient records. Furthermore, echocardiographic measurements were supplemented with data acquired from paper patient records. The Dutch municipal civil registry was checked for the survival status.

Study outcome

The main outcome of this study is mortality in relation to the changing TR severity over time. Secondary outcomes include: the evolution of post-OHT TR grade and the evolution of post-OHT creatinine in relation to the changing TR severity.

Operation

All patients were operated with the biatrial anastomoses technique described in 1960 by Lower and Shumway (7). This technique entails an incision in the right atrium from the inferior vena cava toward the right atrial appendage to avoid sino-atrial node injury.

Statistics

Continuous data are presented as mean ± standard deviation (Gaussian distribution) or median [interquartile range (IQR)] (nonGaussian distribution). Categorical data are presented as frequencies (percentage).

Logistic mixed-effect models were used to assess probability of TR over time and investigate determinants of the longitudinal evolution over time. These models included random intercept and slope effects to capture the correlation of the repeated measurements in each patient. Natural splines with 2 knots placed at the 1st and 3rd quartiles were used to allow for flexibility of the subject-specific trajectories over time. Splines allow for non-linear trajectories over time. This is achieved by allowing a different spline-coefficient for each time interval defined by the knots (e.g. two knots define 3 such intervals). Survival probabilities were estimated and visualized by the Kaplan-Meier method. A joint model was developed to investigate determinants of mortality. More specifically, the mixed-effects model of TR and a relative risk model for the hazard of death (e.g. Cox model) were jointly modelled using shared-random effects. The subject-specific estimated longitudinal profiles were included in the relative risk model as predictors. Joint modelling has several benefits, such as the appropriate inclusion of endogenous covariates in relative risk models (TR), reduced bias and increased efficiency, while it can be used to derive dynamic predictions (8). At time point *t* one can investigate the effect of the current value of TR, the effect of the slope of TR (at which speed probability of TR is changing at time point *t*) and the cumulative effect of TR. Predictors were selected based upon clinical knowledge and availability. Left ventricle function, pacemaker, dialysis and number of rejection episodes after one year were included as exogenous time-varying covariates.

Global-local shrinkage priors were used for the regression coefficients of the relative risk sub-model for the selection of the current value of TR as predictor and this is presented in the article (Supplementary Table 1-3).

The longitudinal evolution of TR probability was correlated to the longitudinal evolution of creatinine by multivariate (multiple outcomes) mixed modelling. Correlation tests were done on the random effects D matrix.

Sensitivity analyses including both the mixed-effect model for right ventricle function and TR as predictors in the joint model and a model including year of surgery were performed in order the these the robustness of the estimates.

Missing baseline data used in the analyses was considered completely at random, and complete case analyses was performed. Creatinine at baseline had highest missing values (n=29, 5%). A. p-value <0.05 was considered statistically significant. Statistical analyses were done in

R (R core team 2017, Vienna, Austria) with the use of statistical packages "GLMMadaptive", "splines", "JointAI", "survival" and "JMbayes".

RESULTS

In total, 572 patients were included in this study. Baseline characteristics are presented in Table 1. Given the dynamic character of TR over time, baseline characteristics are not stratified on post-OHT TR grade. On average patients were 50 years old and 74.9% was male. Most frequently cyclosporine / prednisone (26.4%) and tacrolimus / prednisone (21.3%) are prescribed as immunosuppressive maintenance therapy. Median follow-up was 10.4 years (IQR: 6.4-15.3). Two patients were lost in follow-up, resulting in a completeness of 99.5% (C).

Table 1: Pre-, peri-, postoperative characteristics

Characteristics	N=572
Recipient Age (median, IQR)	50.23 [41.87, 56.32]
Donor age (median, IQR)	33.00 [22.00, 44.00]
Receiver female sex (n,%)	143 (25.1)
Donor female sex (n,%)	277 (49.0)
Primary diagnosis (n,%)	
Non ischemic	275 (49.4)
Ischemic	254 (45.6)
Other	28 (5.0)
Creatinine (median [IQR])	114.00 [93.00, 136.00]
Immunosuppression (n,%)	
Cyclosporine + azathioprine + prednisone	70 (12.3)
Cyclo+ MMF+ prednisone	32 (5.6)
Cyclosporine + prednisone	150 (26.4)
Tacrolimus+prednisone	121 (21.3)
tacrolimus+MMF	21 (3.7)
Other	175 (30.8)
Number of prior cardiac operations (n,%)	
0	415 (72.8)
1	125 (21.9)
2	26 (4.6)
3	4 (0.7)
Urgency (n,%)	
0	370 (65.1)
1	99 (17.4)
2	93 (16.4)

Table 1: Pre-, peri-, postoperative characteristics (continued)

Characteristics	N=572
3	6 (1.1)
Pre HTx diabetes (n,%)	35 (6.4)
Pre HTx mechical assistance (%)	
None	517 (92.8)
LVAD	33 (5.9)
ECMO	2 (0.4)
IABP	5 (0.9)
Ischemia time (median [IQR])	170.00 [143.00, 203.00]
Re-exploration for bleeding (n,%)	77 (13.5)
Dialysis* (%)	94 (16.8)
Pacemaker* (%)	70 (12.5)
Number rejection first year 1(median [IQR])	1.00 [1.00, 2.00]

*Number of patients that received a pacemaker or dialysis during follow up

Tricuspid regurgitation evolution

In total, 8826 echocardiograms were collected (range: 1-50, mean: 15.4) and all echocardiograms are used in the analyses. The model predicting the evolution of TR over time is presented in Table 2. Probability of TR changed over time, as indicated by the significant times estimates (Table 2). The evolution of the probability of moderate-to-severe TR over time, as estimated by the mixed-model, is presented in Figure 1. On average, approximately 32% of patients have moderate-to-severe TR immediately after surgery. However, this declines to approximately 11% after 5 years and 9% after 10 years of surgery. Pre-implant mechanical support was significantly associated with lower probability of moderate-to-severe TR during follow-up (Table 2). Additionally, a worse LV function at the time of the TR measurement was significantly associated with a higher probability of moderate-to-severe TR (Table 2). Strikingly, the number of rejections in the first year was not associated with a higher probability of moderate-to-severe TR.

Table 2: Estimates of logistic mixed-model part of the joint model to predict moderate-to-severe TR over time.

Variable	OR	95% CI	P value
Intercept	0.10	(0.01; 1.35)	0.090
Spline 1 of time[1]	0.23	(0.09; 0.56)	<0.001
Spline 2 of time[1]	0.03	(0.01; 0.13)	<0.001
Spline 3 of time[1]	0.18	(0.02; 1.22)	0.080
Receiver age	0.98	(0.95; 1.01)	0.138
Donor age	1.02	(0.99; 1.05)	0.114
Receiver female sex	0.77	(0.36; 1.59)	0.466
Donor female sex	1.66	(0.86; 3.18)	0.130

Table 2: Estimates of logistic mixed-model part of the joint model to predict moderate-to-severe TR over time. (continued)

Variable	OR	95% CI	P value
Ischemia time	0.96	(0.89; 1.04)	0.344
Cardiac reoperation	0.99	(0.56; 1.76)	0.952
Urgency 1 vs 0	1.40	(0.56; 3.55)	0.456
Urgency 2/3 vs 0	0.63	(0.27; 1.46)	0.322
No mechanical assistance prior HTx	6.29	(1.47; 27.31)	0.014
Pre HTx diabetes	0.60	(0.19; 1.94)	0.394
Number rejection first year	1.02	(0.88; 1.19)	0.742
Mildly impaired LV function vs normal[2]	1.73	(1.32; 2.31)	<0.001
Moderately impaired LV function vs normal[2]	4.03	(2.29; 7.18)	<0.001
Severely impaired LV function vs normal[2]	9.54	(2.82; 38.46)	<0.001
Pacemaker[2]	1.12	(0.59; 2.07)	0.718
Creatinine	1.00	(1; 1.01)	0.374

1: Time was modelled in an non-linear way with a spline function. CI: confidence interval, OR: odds ratio. 2: At the time of TR measurment (time-varying covariate)

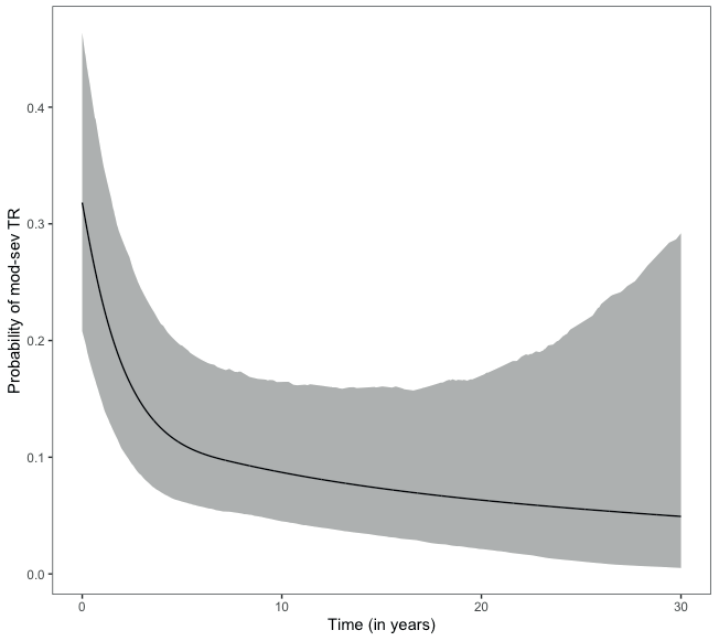

Figure 1: The marginal probability of moderate-to-severe TR during follow-up for an average patient.

Mortality

During follow-up 357 patients died of which 5 (0.9%) within 30 days. Survival at 1, 5, 10, 20 years was 97±1%, 88±1%, 66±2% and 23±2%, respectively (Figure 2). The presence of moderate-to-severe TR during follow-up was associated with higher mortality (Table 3). Table 3 presents the estimates of the joint model. A higher age, the presence of pre-OHT diabetes, recipient female sex and dialysis were significantly associated with mortality during follow-up. Moderate-to-severe TR remained significant a sensitivity analyses in which left ventricular dysfunction was incorporated in the Cox model as time-varying covariate (Supplementary Table 4).

Figure 3ab presents a dynamic survival probability plot for two patients. The first patients developed moderate-to-severe TR after approximately 3 years. At this moment, the survival probability of 10 years later is estimated to be 77% (Figure 3a). The second patient did not develop moderate-to-severe TR at 3 years, and the survival probability of 10 years later for this patients is estimated to be 81% (Figure 3b).

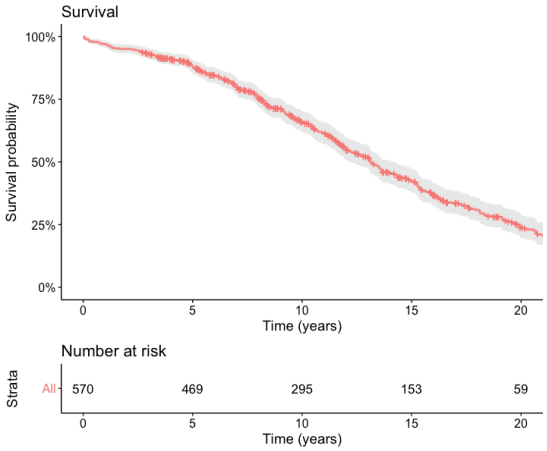

Figure 2: A Kaplan-Meier curve of overall survival.

Table 3: Estimates of the joint-model survival part

Variable	HR	95% CI	P value
Receiver age	1.04	(1.03; 1.06)	<0.001
Receiver female sex	1.44	(1.02; 2.03)	0.046
Donor female sex	1.05	(0.78; 1.44)	0.768
Ischemia time	1.00	(1; 1.01)	0.064
Cardiac reoperation	1.22	(0.91; 1.6)	0.174
Urgency1 vs 0	0.90	(0.61; 1.31)	0.590
Urgency2 vs 0	0.78	(0.48; 1.22)	0.270
Urgency3 vs 0	12.26	(2.32; 55.12)	0.012
No mechanical assistance prior HTx	0.75	(0.28; 2.19)	0.580

Table 3: Estimates of the joint-model survival part (continued)

Variable	HR	95% CI	P value
Donor Age	0.99	(0.98; 1.01)	0.372
Non-ischemic CMP vs ischemic	1.17	(0.82; 1.66)	0.364
Other diagnosis vs ischemic	1.15	(0.55; 2.15)	0.668
Pre HTx diabetes	2.30	(1.3; 3.8)	<0.001
Creatinine	1.00	(1.00; 1)	0.096
Pacemaker[1]	1.00	(0.64; 1.52)	0.972
Dialysis[1]	1.81	(1.27; 2.5)	0.002
Mod-sev TR	1.07	(1.02; 1.13)	0.006

1: Time-varying covariate

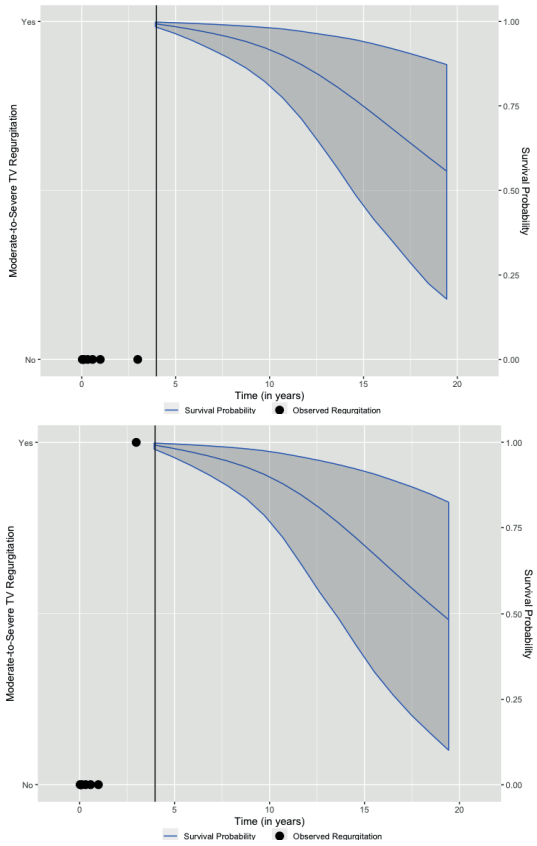

Figure 3ab: A dynamic plot of two patients (A and B). Patient A develops TR after 3 years and patient B does not develop TR after 3 years.

Kidney function

Creatinine was collected at 4426 times simultaneously with an echocardiogram. The longitudinal evolution of creatinine is presented in Figure 4 as estimated by a mixed-model containing only the variable time with a spline function.

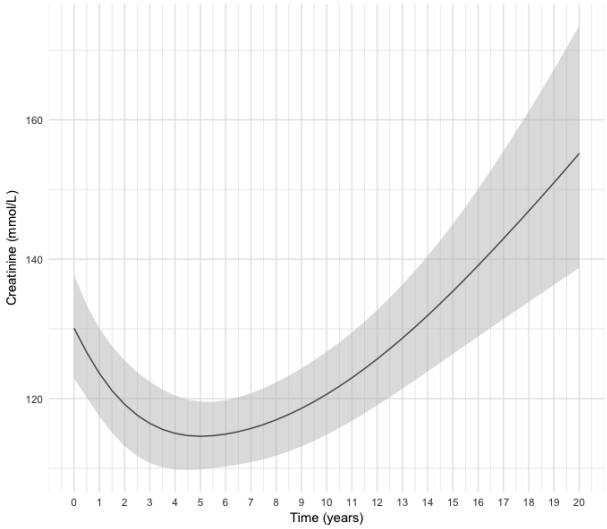

Figure 4: The predicted evolution of creatinine after HTx

The random slope of moderate-to-severe TR was highly positively correlated to the slope of creatinine (R = 0.45), meaning that if the probability moderate-to-severe TR increases, creatinine levels also increase in an individual patient. The intercept (starting point) of TR was not highly correlated the intercept (starting point) of creatinine (R = 0.04). The correlation matrix is shown in Supplementary Table 5.

The current value of post-OHT moderate-to-severe TR was found to be predictive for dialysis dependence (HR 1.21 95% CI [1.04 to 1.44], *P* = 0.012) as estimated by a simple joint-model adjusting for baseline creatinine, sex and age (Supplementary Table 6).

Sensitivity analyses

In a multivariate joint model including both the longitudinal evolution of dichotomized right ventricle function and of moderate-to-severe TR, only moderate-to-severe TR was found to be a significant predictor of mortality, whereas right ventricle function was not. It has to be noted that right ventricle function was only recorded in 1216 of 8826 echocardiograms leaving relatively little data for the analyses (Supplementary Table 7-8). Including year of surgery in the model of longitudinal evolution and Cox model did not change the significance or estimate of the longitudinal predictor of moderate-to-severe TR for mortality (Supplementary Table 9 – 10).

DISCUSSION

This study investigated the long-term course of moderate-to-severe TR and its impact on mortality and renal function. We found that moderate-to-severe TR during follow-up was associated with higher mortality and progressive decline of renal function. Specifically, moderate-to-severe TR was found to be a risk factor for dialysis. To the authors knowledge, this is the first study that accounts for the dynamic nature of TR during follow-up.

TR evolution

The etiology of TR after OHT is multifactorial in nature (3). In older studies higher pulmonary pressures after OHT and endomyocardial biopsies were mainly found to be associated with TR (3, 9-11). Furthermore, the biatrial surgical technique is found to be associated with more TR in multiple studies (12).

In our study, left ventricular dysfunction at the time of TR measurement was significantly associated with the higher probabilities of moderate-to-severe TR, probably because worse LV function causes higher pulmonary pressures, subsequently leading to RV dysfunction and dilatation, leading to functional TR. Moreover, we noted that patients who have mechanical assistance (LVAD, ECMO, IABP) prior OHT have a lower probability of post-OHT moderate-to-severe TR. It has been observed that left ventricular assist devices effectively unload the left ventricle and reduce pulmonary pressures (13). Hence, patients with pre-OHT mechanical assistance will probably have lower pulmonary pressures, resulting in less right ventricle dysfunction, annulus dilation and, secondary TR immediately after OHT.

Other studies noted initially a decrease in TR severity after OHT, but a relative increase later in follow up, or even a gradual increase in TR over time (5, 11, 14). This study did not replicate these results. Nevertheless, change over time was not significantly decreasing over time later in follow-up. The results of prior studies can partly be explained by the used methodology, which does not take into account the correlations within patients vs between patients nor does take into account the dropout of patients (either due to death or censoring), whereas the joint modeling framework does take these phenomena into account.

Mortality & Morbidity

In this cohort we only included patients with a follow-up echocardiogram, as the focus was on evolution of TR. Previously we reported the outcomes of the entire cohort (15). In patient who die early an echocardiogram may not be performed or TR in this echocardiogram is not recorded, explaining the low 30-day mortality (0.9%) in this subset of the entire cohort (Supplementary Figure 1).

Previous studies noted that TR at discharge was associated with impaired late morality (5, 16). Two other studies examined late TR and noted contradicting results in regard to the association with mortality (14, 17). This study models the dynamic nature of TR over time and

the association with mortality. During follow-up developing TR is associated with higher probability of mortality. The dynamic predictions estimated that developing TR at 3 years after OHT is paired with a 4% reduction in survival 10 years later compared to a patient who does not develop TR, given that all the other variables are similar.

The observed association of TR with mortality does not inherently imply a causal association. An important factor in in this interplay is right ventricular dysfunction. In a sensitivity analyses right ventricle function was not found to be a significant predictor of mortality. However, eyeballing the right ventricle function is difficult and the analyses be underpowered to detect differences. Moreover, it is complicated to make causal inference in regard to right ventricular dysfunction and TR due to their circular relationship; TR leads to right ventricular dysfunction, which leads to dilatation, in turn leading to more TR. One needs to backtrack which phenomena starts first and starts the negative spiral, which is difficult to do in retrospective studies. Nevertheless, previous studies claim that it is the TR that may lead to right ventricular dysfunction (1, 14, 18).

Moreover, we could also link the longitudinal evolution of TR probabilities to the longitudinal evolution of creatinine. Previous studies also found an association between renal function and TR (17). It is still debatable whether it is the TR or right ventricular dysfunction causing the renal dysfunction, however TR may contribute to renal dysfunction by increasing venous congestion (19) and the combination of TR and right ventricular dysfunction is found to predictive of impaired renal function (20). Furthermore, in a recent study Karam et al. noted stabilization of renal function and improvement of liver function in patients undergoing transcatheter tricuspid valve repair, suggesting a beneficial effect of eliminating TR (21).

Clinical implications

In most cases symptomatic TR is managed with usual heart failure treatments, but in refractory cases a surgical intervention becomes necessary (1). Literature regarding surgery for TR after OHT is scarce. Nevertheless, it has been shown that surgery in these patients can be performed safely (22, 23). The authors who linked discharge TR to impaired survival suggest to surgically intervene if TR is not resolved by discharge (5). However, our data shows that it may be reasonable to wait longer, as probability of TR continues to decrease after discharge, and TR usually remains asymptomatic for years (4). Notwithstanding, our data shows that after approximately five years post-OHT the decrease probability of moderate-to-severe TR negates. In patients with persistent TR at five years post-OHT surgical intervention may be most beneficial, assuming the association of TR and mortality / renal function is causal in nature.

A small randomized clinical trial (n=60) in which patients received either prophylactic tricuspid annuloplasty vs. no annuloplasty concomitant to OHT noted a better cardiac survival in the annuloplasty groups, if they combined early and late deaths (18). No overall survival difference was noted. Furthermore, opportunities arise with emerging trans-catheter devices to treat TR, since this population may be an interesting potential target population for trans-

catheter approaches (25). However, these devices still need to be validated in this complex subgroup of patients. Other authors advocate the use of bicaval anastomosis by default to prevent TR in the first place (6, 24).

Strengths and limitations

The major advantage of this study is that we were able to collect 8826 echocardiograms, enabling us to use advanced statistical methods to model the dynamic nature of TR and making less biased inference of the impact of TR during follow-up on mortality. Several limitations apply to this study common in retrospective analyses. We did not consider cardiac allograft vasculopathy (CAV) explicitly in this study since CAV is diagnosed by coronary angiography and, therefore, there is a delay between development and diagnosis of CAV. Nevertheless, CAV manifests as LV dysfunction, which we were able to analyze, hence CAV is implicitly considered. Patients who died without an TR measurement on echocardiogram were excluded, which can introduce selection bias. Assessing TR remains challenging, but we dichotomized this variable to create a more robust measurement. Moreover, we it was not possible to determine the cause of TR (e.g. biopsy related vs functional). Lastly, LV function, pacemaker and dialyses were incorporated in the models as a time-varying exogenous variable, while in fact these variables are more likely to be endogenous.

Conclusions

TR during follow-up is significantly associated with higher mortality and progressive decline of renal function / end-stage renal failure. Nevertheless, probability of TR is the highest immediately after OHT and decreases thereafter. Therefore, it may be reasonable to refrain from surgical intervention during early phase after OHT with bi-atrial anastomoses.

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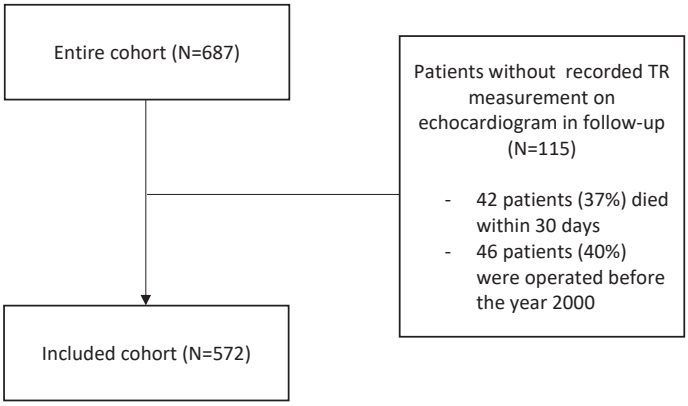
SUPPLEMENTARY MATERIAL

CONTENTS



Supplementary Figure 1: Flowchart of included patients.

Supplementary table 1: Estimates of the relative hazard model (cox) in the joint-model using the horseshoe global-local shrinkage prior and value, slope and area under the curve association structures.

Variable	HR	95% CI	P value
Receiver age	1.01	(1.00; 1.03)	0.050
Receiver female sex	1.25	(0.95; 1.77)	0.186
Donor female sex	1.03	(0.86; 1.26)	0.820
Ischemia time	1.00	(1; 1.01)	0.036
Cardiac reoperation	1.17	(0.95; 1.53)	0.198
Urgency1 vs 0	0.98	(0.73; 1.22)	0.870
Urgency2 vs 0	0.89	(0.56; 1.18)	0.544
Urgency3 vs 0	6.98	(1.02; 26.60)	0.042
No mechanical assistance prior HTx	0.83	(0.32; 1.23)	0.608
Donor Age	0.99	(0.98; 1.01)	0.404
Non-ischemic CMP vs ischemic	1.05	(0.86; 1.38)	0.656
Other diagnosis vs ischemic	1.09	(0.81; 1.75)	0.710
Pre HTx diabetes	2.17	(1.16; 3.79)	0.010
Creatinine	1.00	(1; 1)	0.026
Pacemaker[1]	1.02	(0.80; 1.36)	0.888
Dialysis[1]	1.64	(1.09; 2.30)	0.020
Mod-sev TR (value)	1.07	(1.01; 1.15)	0.010
Mod-sev TR (slope)	0.97	(0.35; 1.95)	0.978
Mod-sev TR (area)	1.00	(1.00; 1.00)	0.046

Supplementary table 2: Estimates of the relative hazard model (cox) in the joint-model using the ridge global-local shrinkage prior and value, slope and area under the curve association structures. 1: exogenous time-dependent covariate

Variable	HR	95% CI	P value
Receiver age	1.01	(1.00; 1.03)	0.060
Receiver female sex	1.41	(0.97; 1.97)	0.066
Donor female sex	1.04	(0.76; 1.42)	0.802
Ischemia time	1.00	(1; 1.01)	0.064
Cardiac reoperation	1.22	(0.90; 1.62)	0.188
Urgency1 vs 0	0.93	(0.63; 1.38)	0.722
Urgency2 vs 0	0.76	(0.47; 1.21)	0.232
Urgency3 vs 0	7.57	(1.42; 32.30)	0.022
No mechanical assistance prior HTx	0.63	(0.24; 1.68)	0.308
Donor Age	0.99	(0.98; 1.01)	0.302
Non-ischemic CMP vs ischemic	1.14	(0.84; 1.61)	0.402
Other diagnosis vs ischemic	1.15	(0.59; 2.07)	0.618
Pre HTx diabetes	2.45	(1.53; 3.96)	0.002
Creatinine	1.00	(1; 1)	0.040
Pacemaker[1]	1.03	(0.66; 1.56)	0.902
Dialysis[1]	1.78	(1.21; 2.49)	0.006
Mod-sev TR (value)	1.09	(1.02; 1.15)	0.006
Mod-sev TR (slope)	0.95	(0.53; 1.42)	0.770
Mod-sev TR (area)	1.00	(1.00; 1.00)	0.050

Supplementary table 3: Estimates of the relative hazard model (cox) in the joint-model using value, slope and area under the curve association structures but with no shrinkage. 1: exogenous time-dependent covariate

Variable	HR	95% CI	P value
Receiver age	1.01	(1.00; 1.03)	0.158
Receiver female sex	1.44	(0.96; 2.12)	0.074
Donor female sex	1.03	(0.76; 1.43)	0.904
Ischemia time	1.00	(1; 1.01)	0.112
Cardiac reoperation	1.24	(0.91; 1.70)	0.218
Urgency1 vs 0	0.92	(0.62; 1.37)	0.720
Urgency2 vs 0	0.77	(0.44; 1.22)	0.308
Urgency3 vs 0	8.74	(1.39; 48.33)	0.028
No mechanical assistance prior HTx	0.67	(0.23; 2.15)	0.474
Donor Age	0.99	(0.98; 1.01)	0.348
Non-ischemic CMP vs ischemic	1.15	(0.81; 1.67)	0.442
Other diagnosis vs ischemic	1.12	(0.56; 2.15)	0.752
Pre HTx diabetes	2.52	(1.46; 4.22)	<0.001
Creatinine	1.00	(0.99; 1)	0.070
Pacemaker[1]	1.01	(0.65; 1.50)	0.918

Supplementary table 3: Estimates of the relative hazard model (cox) in the joint-model using value, slope and area under the curve association structures but with no shrinkage. 1: exogenous time-dependent covariate (continued)

Variable	HR	95% CI	P value
Dialysis[1]	1.83	(1.26; 2.64)	0.002
Mod-sev TR (value)	1.12	(1.03; 1.22)	0.010
Mod-sev TR (slope)	0.53	(0.07; 3.27)	0.546
Mod-sev TR (area)	1.00	(1.00; 1.00)	0.046

Supplementary table 4: Estimates of the relative hazard model (cox) in the joint-model with left vertical function as time-varying covariate predicting mortality. 1: exogenous time-dependent covariate

Variable	HR	95% CI	P value
Receiver age	1.04	(1.03; 1.06)	<0.001
Receiver female sex	1.16	(0.84; 1.64)	0.344
Donor female sex	1.37	(1.03; 1.82)	0.04
Ischemia time	1.00	(1; 1)	0.534
Cardiac reoperation	1.49	(1.08; 2.03)	0.012
Urgency1 vs 0	1.16	(0.78; 1.78)	0.436
Urgency2 vs 0	0.80	(0.49; 1.3)	0.356
Urgency3 vs 0	11.69	(2.08; 45.83)	0.018
No mechanical assistance prior HTx	1.66	(0.63; 4.58)	0.296
Donor Age	0.98	(0.97; 0.99)	<0.001
Non-ischemic CMP vs ischemic	1.19	(0.85; 1.62)	0.272
Other diagnosis vs ischemic	0.92	(0.48; 1.75)	0.764
Pre HTx diabetes	1.43	(0.85; 2.27)	0.136
Creatinine	1.00	(1; 1)	0.658
Pacemaker[1]	0.99	(0.66; 1.45)	0.932
Dialysis[1]	1.37	(0.94; 2.03)	0.102
Moderately/severe LV function vs normal[1]	110.23	(53.51; 252.98)	<0.001
Mod-sev TR	1.07	(1.02; 1.12)	0.008

1: Time-varying covariate

Supplementary table 5: Random correlation matrix of the multivariate longitudinal model with creatinine and tricuspid regurgitation. Random effect were: intercept for patients and slope over time in both models. No splines were added in the random effects for time in order to enhance interpretability.

	Intercept TR	Random slope TR	Random slope creatinine	Intercept creatinine
Intercept TR	1	X	X	X
Random slope TR	0.1791	1	X	X
Random slope creatinine	-0.6112	0.4540	1	X
Intercept creatinine	0.0464	0.0775	-0.5634	1

Supplementary table 6: Estimates for the relative hazard model (cox) a in the joint model predicting dialysis.

Variable	OR	95% CI	P value
Reciever Age	0.99	(0.97; 1.02)	0.546
Baseline creatinine	1.00	(0.99; 1.01)	0.784
Receiver female sex	0.58	(0.26; 1.21)	0.150
Moderate-to-severe TR	1.21	(1.04; 1.44)	0.012

Supplementary table 7: Estimates for the relative hazard model (cox) a in the joint model predicting mortality, with both longitudinal evolution of right ventricular function and moderate-to-severe TR as predictor. The current value parametrization was used in both predictors. 1: exogenous time-dependent covariate

Variable	HR	95% CI	P value
Receiver age	1,04	(1; 1,07)	0.028
Receiver female sex	1,64	(0,87; 3,27)	0.12
Donor female sex	0,92	(0,45; 1,81)	0.82
Ischemia time	1,01	(1; 1,01)	0.026
Cardiac reoperation	1,08	(0,57; 1,97)	0.82
Urgency1 vs 0	0,34	(0,12; 0,86)	0.020
Urgency2 vs 0	0,37	(0,14; 0,94)	0.036
Urgency3 vs 0	3,50	(0,22; 34,2)	0.32
No mechanical assistance prior HTx	0,40	(0,08; 2,53)	0.33
Donor Age	1,00	(0,97; 1,03)	0.84
Non-ischemic CMP vs ischemic	1,06	(0,57; 1,95)	0.85
Other diagnosis vs ischemic	1,17	(0,15; 7,83)	0.88
Pre HTx diabetes	3,16	(1,32; 7,08)	0.012
Creatinine	1,00	(0,99; 1,01)	0.93
Pacemaker[1]	1,03	(0,46; 2,22)	0.95
Dialysis[1]	2,44	(1,16; 4,95)	0.014
Right ventricle dyfunction	1,02	(0,93; 1,13)	0.63
Mod-sev TR	1,06	(1,02; 1,12)	0.002

Supplementary table 8: Estimates for the logistic mixed-effects model part from the joint model predicting mortality with year as predictor. 1: exogenous time-dependent covariate

Variable	Log(OR)	Log(95% CI)	P value
Intercept	-3,24	(-15,24; 23.964)	0.736
Spline 1 of time[1]	-2,24	(-4,613; -0.245)	0.026
Spline 2 of time[1]	-9,60	(-13,239; -6.197)	<0.001
Spline 3 of time[1]	-8,45	(-13,605; -4.063)	<0.001
Receiver age	-0,05	(-0,095; -0.004)	0.028
Donor age	0,04	(-0,004; 0)	0.064
Receiver female sex	-1,23	(-2,502; -)	0.042

Supplementary table 8: Estimates for the logistic mixed-effects model part from the joint model predicting mortality with year as predictor. 1: exogenous time-dependent covariate (continued)

Variable	Log(OR)	Log(95% CI)	P value
Donor female sex	1,01	(-0,08; 2.156)	0.064
Ischemia time	-0,01	(-0,025; 0)	0.096
Cardiac reoperation	0,10	(-0,796; 1.004)	0.84
Urgency 1 vs 0	0,96	(-0,39; 2.371)	0.18
Urgency 2/3 vs 0	0,03	(-1,286; 1.441)	0.96
No mechanical assistance prior HTx	5,43	(1,779; 9.868)	0.006
Pre HTx diabetes	-0,37	(-2,194; 1.495)	0.69
Number rejection first year	0,08	(-0,2; 0.342)	0.50
Mildly impaired LV function vs normal[2]	0,27	(-0,194; 0.714)	0.26
Moderately impaired LV function vs normal[2]	1,54	(0,676; 2.359)	0.002
Severely impaired LV function vs normal[2]	4,31	(2,26; 6.859)	<0.001
Pacemaker[2]	-0,56	(-2,257; 1.264)	0.50
Creatinine	0,01	(0,001; 0.024)	0.044
Year of surgery	-0,01	(-0,016; 0.004)	0.32

Supplementary table 9: Estimates for relative hazard model (cox) part from the joint model predicting mortality with year as predictor. 1: exogenous time-dependent covariate

Variable	OR	95% CI	P value
Receiver age	1,04	(1,02; 1,06)	<0.001
Receiver female sex	1,49	(1; 2,19)	0.046
Donor female sex	1,09	(0,78; 1,49)	0.60
Ischemia time	1,00	(1; 1,01)	0.098
Cardiac reoperation	1,24	(0,91; 1,67)	0.18
Urgency1 vs 0	0,83	(0,53; 1,27)	0.39
Urgency2 vs 0	0,80	(0,45; 1,35)	0.38
Urgency3 vs 0	10,67	(1,26; 56,75)	0.034
No mechanical assistance prior HTx	0,59	(0,21; 1,91)	0.36
Donor Age	0,99	(0,98; 1,01)	0.33
Non-ischemic CMP vs ischemic	1,18	(0,8; 1,67)	0.36
Other diagnosis vs ischemic	1,05	(0,52; 2,13)	0.90
Pre HTx diabetes	2,27	(1,3; 4)	0.004
Creatinine	1,00	(0,99; 1)	0.096
Pacemaker[1]	0,99	(0,61; 1,58)	0.94
Dialysis[1]	1,75	(1,19; 2,53)	0.004
Year of surgery	1,00	(1.00; 1.00)	0.14
Mod-sev TR	1,06	(1,02; 1,12)	0.006