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HEART TRANSPLANTATION OUTCOMES FOR RHEUMATIC HEART DISEASE: ANALYSIS OF INTERNATIONAL REGISTRY DATA

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Abstract

Background: Rheumatic heart disease (RHD), an autoimmune sequela of Group A streptococcal infection, is a chronic valvular disease affecting 32 million people worldwide, predominantly in developing nations. As the predisposition to autoimmune sequela still remains post transplantation, our primary objective was to assess if there were differences in mortality and rejection rates.

Methods and Results: Using the International Society for Heart and Lung Transplantation (ISHLT) adult heart transplant registry, we identified 42 RHD patients who had undergone heart transplantation between 1988–2014. We matched the 42 RHD recipients by transplant year, age, and gender to 420 dilated cardiomyopathy (DCM) recipients. One year mortality in the RHD group was 17.95% vs. 7.92% in the DCM group (p=0.07). Survival was significantly reduced in the RHD group vs. the DCM group via Kaplan Meier curves (P = 0.04). In a multivariate model, RHD status (OR 3.19, 95% CI 1.15–8.83, p=0.025) and serum creatinine (OR 1.41, 95% CI 1.09–1.82, p=0.009) were associated with an increased odds of one year mortality (p=0.0013).

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Conclusions: At one year post transplantation, RHD recipients had a significantly lower survival than DCM recipients. RHD status was also an independent predictor of mortality at 1 year post transplantation.

Keywords

rheumatic heart disease; transplantation; ISHLT

1 INTRODUCTION

Rheumatic heart disease (RHD) is one of the leading causes of heart disease in the developing world, with an estimated prevalence of 32 million affected persons and 200,000 – 250,000 deaths per year.[1,2] RHD is an autoimmune-mediated disease with a clinical spectrum of pericarditis, myocarditis, and valvulitis.[3] Valvular damage is hypothesized to result from molecular mimicry to prior group A streptococcus pharyngitis, during which the patient's own immune system responds to both Group A streptococcus (GAS) and cardiac proteins.[4] Without penicillin prophylaxis, re-exposure to GAS may boost cross-reactive $CD4^+$ T cells and autoreactive antibody responses, resulting in progressive valvular damage and subsequent heart failure. Operative interventions include valvuloplasty or valve replacement. Heart transplantation remains the only curative intervention after other operative interventions have failed. Post transplantation, GAS re-exposure may elicit similar pre-transplantation pathology. The goal of this study was to assess if there were differences in mortality and graft survival following heart transplantation compared to non-RHD recipients.

2 METHODS

We queried the International Society for Heart and Lung Transplantation (ISHLT) adult heart transplant registry for patients who had undergone heart transplantation for RHD from 1988 to 2014 using the following search terms: "rheumatic", "rheumatic fever", "rheumatic heart disease" or "RHD" under the diagnosis category. We carried out a retrospective cohort study matching RHD patients by transplant year, gender, and age ± 5 years to 10 patients with dilated cardiomyopathy (DCM). Matching to transplant year controlled for confounders such as changes in immunosuppression and medical progress with ventricular assist devices (VADs) as a bridge to transplantation. Age ± 5 years was utilized, as there were not enough age-matched DCM individuals that were also matched to the year of transplant. A 1:10 matching increased the power of the study ($\beta \geq 0.8$ and $\alpha = 0.05$), based on p-values for Kaplan Meier Curves at 10 years in an RHD Taiwanese study.[5] No data was provided for institution or country in the ISHLT Registry. No data for cardiac function was available other than what was provided pre-transplant, as listed in Table 1. The study was approved by the ISHLT Thoracic Transplant Registry Steering Committee. Data was de-identified and thus the country or collective of origin cannot be identified. Consent for the data collection and analysis was obtained from individual centers according to individual center Review Board requirements by the ISHLT registry.

Baseline demographic variables including co-morbidities as well as details regarding immunosuppression were collected. Primary outcome was one-year mortality following heart transplantation. Follow-up of surviving recipients was reported as days post transplantation last reported to be alive. Secondary outcomes included 3-year mortality and prevalence of first episode of acute rejection.

Baseline and immunosuppression characteristics, post-transplant outcomes were compared using Mann-Whitney U test for non-parametric continuous variables and Fisher's exact tests for categorical variables. For survival analyses, out of the 462 patients (420 controls + 42 RHD recipients), there were 43 patients for whom follow-up data was missing (3 RHD and 40 control recipients) and were not included in the survival analyses. Kaplan-Meier (KM) survival curves were compared by log-rank test. We first compared variables with our primary outcome of one year mortality via univariate analysis. Variables with p-value ≤0.2 were used to build the multivariate model using step-wise selection and goodness of fit testing.

3 RESULTS

Between 1988 and 2014, 112,213 adult patients underwent a first heart transplant. We identified 42 RHD patients (0.037% of all patients) and 420 DCM patients, matched by transplant year, age ± 5 years, and gender. The majority of RHD patients were female (n=24, 57%) with a median age of 54 years (IQR 47–60 years). The majority of heart transplantation (81%) occurred between 2001–2014. The mean follow-up was 2271 ± 1693 days (2525 days ± 2090 days for RHD, 2245 days ± 1649 days for DCM).

Baseline characteristics recorded prior to transplantation are detailed in Table 1. In univariate analyses, RHD patients had a higher rate of prior cardiac surgeries (82.6% vs. 46.8%, p< 0.01), mainly prior valvular surgery (94.74% vs. 27.27%, p = 0.001). RHD patients also had higher pulmonary capillary wedge pressures (22 vs. 18 mmHg, p=0.02), lower body mass index (24 vs 25.6 kg/m^2, p=0.02), and lower rate of LVAD usage (3.45% vs. 22.99%, p=0.01) than DCM patients.

Use of induction immunosuppression was comparable between the groups (58.5% for RHD vs 48% for the DCM, Table 2A). Basiliximab was the most common drug used for induction (24.4% for RHD vs 17.6% for DCM, Table 2A). There were no significant differences between types of maintenance immunosuppression between both groups; though there was a trend towards higher cyclosporine use in the RHD group (51.2% vs. 36.8% in the control group). There was no difference in the rate of the 1^{st} episode of rejection within the first year of transplant (RHD 10.26% vs. control 8.42%, p=0.76).

One year mortality in the RHD group was 17.95% vs. 7.92% in the DCM group (p=0.07). Kaplan-Meier survival curves, including acute mortality, demonstrated significantly lower survival in the RHD group compared to the DCM group (p=0.04, Figure 1, Day 0=Day of transplantation). Three year mortality in the RHD group was 38.46% vs. 28.95% in the DCM group (p= 0.27); no difference in survival curves was noted (p=0.15, data not shown).

The multivariate analysis model with 1 year post-transplant mortality as primary outcome found that RHD status (OR 3.19, 95% CI 1.15–8.83, p=0.025, Table 3) and pre-transplant creatinine (OR 1.41, 95% CI 1.09–1.82, p=0.009, Table 3) were independent predictors of death (p=0.0013).

4. DISCUSSION

We present data for the largest cohort of RHD heart transplant recipients to date. As RHD is predominantly found in developing nations,[6,7] few studies have assessed outcomes for heart transplantation performed for RHD.[5,8] A recently published study conducted in Taiwan, an RHD-endemic country, found significantly reduced survival at 15 years post transplantation for RHD patients compared to DCM patients, though both had comparable rejection rates and valve function.[5] At 5 and 10 years post transplantation, both groups had comparable mortality rates. No analysis was done at 1 year post transplantation.

Outcomes with heart transplantation in general are excellent. About 4,500 heart transplants are performed annually in the world with 1-year survival approaching 90% in the current era.[9] In our study, we observed a higher mortality at one year post transplantation among RHD patients compared to DCM patients, matched for age ± 5 years, gender and year of transplantation. RHD was also a significant predictor of one year mortality in our multivariate analysis. More RHD recipients used cyclosporine as part of their maintenance immunosuppression regimen than DCM recipients, though cyclosporine use was not associated with the 1-year mortality in the final multivariate model. Cyclosporine has been associated with reduced survival and more rejection compared to tacrolimus[10,11]. The rate of the 1st episode of rejection within the first year was similar between both groups. The reason(s) underlying this increased mortality rate is unclear form our current retrospective analysis of registry data. At baseline, RHD patients had higher mean PCWP, which may be an indication of the severity of heart failure. They also had a greater percentage of cardiac surgeries (mainly valvular). However, neither factor was significant in the multivariate model. As noted from epidemiologic studies, RHD patients have circulating antibodies against GAS, some of which may be cross-reactive and boosted with recurrent infection.[12,13] Re-exposure to GAS post-transplantation may therefore theoretically increase the likelihood for valve destruction, graft dysfunction, and survival, though we would not expect this process to occur rapidly within the first year.[14,15] Regardless, we believe that RHD recipients may benefit from continued penicillin prophylaxis in the first year following transplantation, tonsillectomy to remove a potential nidus, and minimization of exposures to GAS (e.g. close contact with children). Baseline renal dysfunction has already been described as an independent predictor of mortality in heart transplant studies, as we also found in our analysis.[16,17] Additional cofactors contributing to the mortality difference at 1 year post transplantation would be better addressed in a prospective study.

This study has several limitations. As it is a retrospective study, conclusions about causation may not be drawn. As with all registry studies, our results are dependent on coding techniques and completion of data entry. Systematic biases may be introduced due to differences in data collection. A high proportion of missing data may have affected our reported results such as a few reported recipient CMV and EBV serologies. This study is

limited to the data captured by the ISHLT registry, reported by each institution or network. Our ability to identify patients who have undergone transplantation for RHD was limited to what was recorded in the diagnosis category. It is unlikely that individuals with endocarditis as an etiology of their valvular disease were included in our RHD group, as we had searched the Registry for different permutations of “rheumatic heart disease”. Missing data for this large registry was excluded for survival curves. The influence of each institution’s immunosuppression protocol cannot be excluded. The entirety of the RHD recipient history was not captured including: episodes of streptococcal pharyngitis, family history of RHD, prior tonsillectomy, and RHD involvement of multiple valves. Moreover, details about the prior cardiac surgery including valvuloplasty versus repair versus replacement, affected valves, and prior atrial fibrillation were not included in the registry.

Conclusion:

We conducted a large case-control analysis of RHD patients that underwent heart transplantation using an international registry and demonstrated that RHD was an independent predictor of 1-year mortality following transplantation. We were unable to elucidate the etiologic factors leading to this increased mortality from our retrospective study. We recommend that a future prospective study should include streptolysin O antibody titers (a serodiagnostic marker for prior GAS infection), history of tonsillectomy, penicillin prophylaxis pre- and post- transplantation, and valvular pathology allowing us to interrogate potential RHD immunopathologic components. This may help us address the role of penicillin prophylaxis in RHD transplant recipients.

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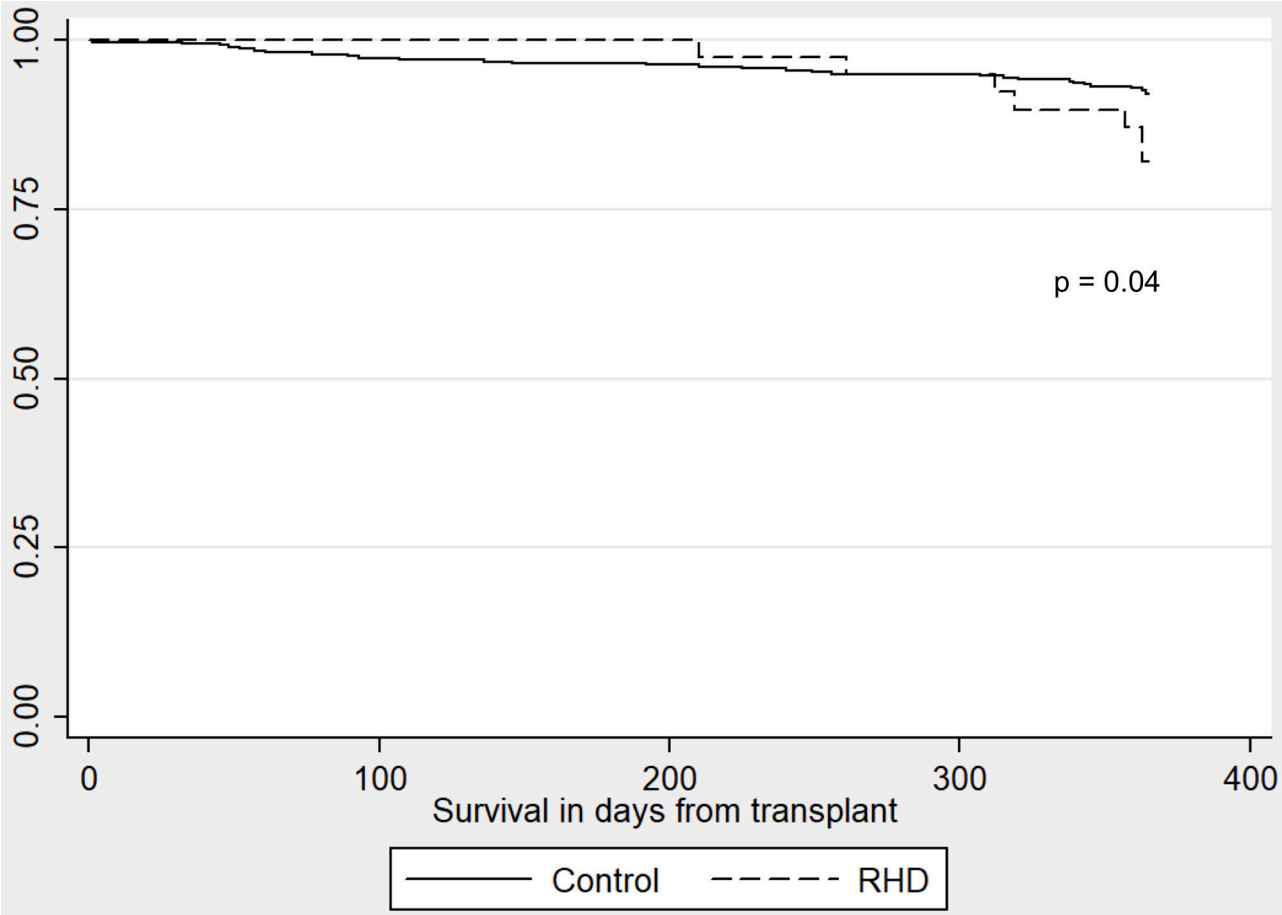

Figure 1.

Survival curve at 1 year post transplantation between RHD and DCM

P-value <0.04 by log-rank test. Day 0 = Day of transplantation

Table 1:

Pre-transplantation characteristics of patients with rheumatic heart disease (RHD) and controls. Controls were matched based on age ± 5 years, gender and year of transplantation.

	RHD (n=42)	Control (n=420)	P-value
Median Age (years) [median, IQR]	54.50 [47–60]	55 [47–60]	
Male (%)	18 (42.86%)	180 (43.59%)	
Transplantation Era 2001-2014 (%)	34 (80.95%)	340 (80.95%)	
Transplantation Era 1988-2000 (%)	8 (19.05%)	80 (19.05%)	
BMI (kg/m^2) [median, IQR]	24.0 [22.5 – 27.3]	25.6 [14.6-29.4]	0.022
Diabetes mellitus (%)	5 (12.5%)	88 (25.23%)	0.080
Serum creatinine (median, IQR)	1.05 [0.85 – 1.50]	1.10 [0.9-1.44]	0.71
Hemodialysis (%)	2 (5.13%)	10 (2.99%)	0.36
COPD (%)	3 (7.89%)	13 (4.14%)	0.40
Cigarette Use (%)	8 (32.0%)	103 (47.25%)	0.20
Hypertension (%)	14 (35.90%)	162 (48.80%)	0.17
Peripheral Vascular Disease (%)	1 (2.63%)	10 (3.09%)	1.00
Prior cardiac surgery (%)	19 (82.60%)	99 (46.7%)	0.0016
Prior valvular surgery (%)	18 (94.74%)	27 (27.27%)	0.001
Prior CABG (%)	0	34 (34.34%)	0.0015
Other surgery (%)	1 (5.26%)	38 (38.38%)	0.0035
Intra-aortic Balloon Pump (%)	1 (2.50%)	29 (8.26%)	0.34
LVAD (%)	1 (3.45%)	60 (22.99%)	0.014
CMV Seropositivity (%)	25 (73.53%)	198 (68.04%)	0.56
EBV Seropositivity (%)	12 (92.31%)	78 (89.66%)	1.00
PCWP (mmHg) [median, IQR]	22 [17-26]	18 [12-25]	0.020
PA (mmHg) [median, IQR]	32 [26-35]	29 [21-35]	0.056
Cardiac Output (L/minute) [median, IQR]	4.0 [3.1-5.0]	4.2 [3.3-5.0]	0.61
Hospitalized Days Post Transplant (mean, IQR)	20 [11.5-24.0]	14 [10-21]	0.026

P-values for Proportions were determined by Fisher-Exact with significant level of <0.05. P-values for Body Mass Index (BMI) and Creatinine were determined by Mann-Whitney U-test. COPD is chronic obstructive pulmonary disease. CABG is coronary artery bypass graft. LVAD is left ventricular assist device. CMV is cytomegalovirus. EBV is Epstein Barr Virus. PCWP is pulmonary capillary wedge pressure. PA is pulmonary artery pressure.

Table 2A:

Induction Immunosuppression.

	RHD (n=41)	Control (n=377)	P-value
Induction	24 (58.5%)	181 (48.0%)	0.25
Daclizumab	6 (14.6%)	34 (9.2%)	0.27
Basiliximab	10 (24.4%)	65 (17.6%)	0.29
OKT3	4 (9.8%)	17 (4.6%)	0.15
Thymoglobulin	5 (12.2%)	37 (10%)	0.59
ATGAM	0	15 (4.1%)	ND

P-values for proportions were determined by Fisher Exact test with significant level of <0.05.

OKT3 is anti-CD3 mAb, ATGAM is anti-thymocyte globulin.

Table 2B:

Maintenance Immunosuppression

	RHD (n=41)	Control (n=377)	P-value
Cyclosporine	21 (51.2%)	136 (36.8%)	0.09
Mycophenolate mofetil	33 (80.5%)	278 (75.1%)	0.57
Steroid	38 (92.7%)	304 (82.2%)	0.12
Azathioprine	9 (22.0%)	69 (18.7%)	0.67
Tacrolimus	20 (48.8%)	217 (58.7%)	0.25
Sirolimus	0	2 (0.5%)	ND
Everolimus	1 (2.4%)	4 (1.1%)	0.41

P-values for proportions were determined Fisher Exact test with significant level of <0.05

Table 3:

Predictors of Mortality at 1 year Post Transplantation in Multivariate Model.

	OR	CI	P-value
RHD	3.19	(1.15, 8.83)	0.025
Creatinine	1.41	(1.09, 1.82)	0.009

P-values determined by logistic regression.