Interactive CardioVascular and Thoracic Surgery 25 (2017) 384–390
doi:10.1093/icvts/ivx151 Advance Access publication 24 May 2017

ORIGINAL ARTICLE

Cite this article as: Schmidhauser M, Regamey J, Pilon N, Pascual M, Rotman S, Banfi C *et al*. The impact of multidisciplinary care on early morbidity and mortality after heart transplantation. Interact CardioVasc Thorac Surg 2017;25:384–90.

The impact of multidisciplinary care on early morbidity and mortality after heart transplantation

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Received 22 November 2016; received in revised form 31 March 2017; accepted 14 April 2017

Abstract

OBJECTIVES: The impact of multidisciplinary care on outcome after heart transplantation (HTx) remains unclear.

METHODS: This retrospective study investigates the impact of multidisciplinary care on the primary end point 1-year all-cause mortality (ACM) and the secondary end point mean acute cellular rejection (ACR) grade within the first postoperative year.

RESULTS: This study includes a total 140 HTx recipients (median age: 53.5 years; males: 80%; donor/recipient gender mismatch: 38.3%; mean length of in-hospital stay: 34 days; mean donor age: 41 years). Multidisciplinary care was implemented in 2008, 66 HTx recipients had operation in 2000–07 and 74 patients had HTx thereafter (2008–14). Non-ischaemic dilated cardiomyopathy was more prevalent in HTx recipients of 2000–07 (63.6 vs 43.2%; $P = 0.024$). Pre-transplant mechanical circulatory support was more frequent in 2008–14 (9.1 vs 24.3%; $P = 0.030$). Groups were not different for pre-transplant cardiovascular risk factors or other comorbidity, invasive haemodynamics or echocardiographic parameters. In-hospital and 1-year ACM were numerically lower in 2008–14 (16.2 vs 22.2%; 18.9% vs 25.8%; $P = 0.47/0.47$, respectively). In 2000–07, pre-transplant weight and diabetes mellitus predicted in-hospital ACM (odds ratio -0.14, $P = 0.02$; OR 5.24, $P = 0.01$, respectively) while post-transplant length of in-hospital stay was related with in-hospital ACM (odds ratio -0.10; $P = 0.016$) and 1-year ACM (odds ratio -0.07; $P = 0.007$). In 2000-07, the mean grade of ACR within the first postoperative year was higher (0.65 vs 0.20; $P < 0.0001$) and ≥moderate ACR was associated with in-hospital mortality ($\chi^2 = 3.92$; $P = 0.048$).

CONCLUSIONS: Multidisciplinary care in HTx compensates post-transplant risk associated with pre-transplant disease and has beneficial impact on the incidence of ACR and ACR-associated early mortality.

Keywords: Heart transplantation • Multidisciplinary care • Early mortality

INTRODUCTION

The care of heart transplant (HTx) patients is complex, requiring a finely orchestrated effort of different disciplines in order to improve outcome. Recognizing the complexity of pre- and post-transplant care, the University Hospitals of Lausanne and Geneva implemented in 2008 the multidisciplinary care procedures for the pre-transplant listing process and post-transplant in-hospital and ambulatory follow-up.

The clinical impact of multidisciplinary care was investigated using the primary end point 1-year all-cause mortality (ACM) and the secondary end point mean acute cellular rejection (ACR) grade during the first post-transplant year. These outcome parameters were chosen because 1-year ACM after HTx still remains high [1], and ACM is an unambiguous end point in particular for a retrospective study. The secondary end point ACR is likewise unambiguous, however, interpretation of this end point in the context of multidisciplinary care is a challenge because immunosuppression and patient's adherence are both relevant. The two end points were compared between HTx recipients with operation in 2000–07 and 2008–14 since selection criteria for HTx candidates have remained largely unchanged between 2000 and 2014 at the local and the international level [2, 3]. Furthermore, local protocols of pre-transplant care [4–6] and post-transplant guidance of immunosuppressive drug treatment have remained largely unmodified [7], suggesting that this

background should permit a retrospective study on the impact of multidisciplinary care.

METHODS

Multidisciplinary team approach

The multidisciplinary team approach in HTx was based on the quality initiative of the University Hospitals of Lausanne and Geneva, which collaborate for solid organ transplantation within a common structure, the Centre Universitaire Romand de Transplantation. HTx operation and immediate postoperative care are performed at the University Hospital of Lausanne, whereas pre- and post-transplant follow-up of local patients is established at both sites. Teams at both sites consist of nurses, cardiologists and cardiac surgeons trained in pre- and post-transplant care for solid organ transplant recipients; furthermore, experts from anaesthesiology, intensive care, pathology, infectious disease, psychiatry, immunology, nutrition and physical therapy join the local teams.

Implementation of common multidisciplinary care in HTx (*italics* mark interventions established with implementation) included the introduction of *biweekly conferences* between both teams using a common video-based platform for presentation of HTx candidates and patients in pre- and post-transplant follow-up. In addition, *structured interaction of the HTx teams with other solid organ transplant teams* was established for monthly discussion of complex cases after transplantation. Furthermore, common pre- and post-transplant procedures were facilitated using *common protocols for pre- and post-transplant care*. In detail, workup of a potential HTx candidate uses a *scripted clinical presentation format* for workup and presentation of potential HTx candidates. A *protocol of the session is written* and *HTx candidates enter into a regular follow-up by the local transplant cardiologist* and the transplant coordinator. The *list of HTx recipients is revisited on a biweekly basis* by the transplant cardiologists and the transplant coordination. After listing for HTx, every HTx candidate obtains a *brochure on post-transplant rules of conduct. Regular visits of the transplanting center team of the University Hospital of Lausanne* (transplant cardiologist, transplant cardiac surgeon and transplant coordinator) *at the University Hospital of Geneva* (every 3 months) assure the contact between HTx candidates of the University Hospital Geneva with the team of the HTx centre.

The script for intra- and postoperative immunosuppression and antibiotic treatment is filled out preoperatively and accompanies the patient in the operating room and on the intensive care unit. There, *daily morning rounds assemble transplant cardiologist, cardiac surgeons and the intensive care takers* until patient transferal to the wards. On the wards, *twice a week the daily visit assembles the assistant physician, nurses, physiotherapist, the transplant cardiologist* and other specialists, if necessary.

Patients' drug adherence and rules of conduct post-transplant are trained in 3 modules, the first during post-transplant in-hospital stay, the second when patients are in the rehabilitation clinics and the third during ambulatory follow-up. The transplant nurse assures unfractured follow-up of each HTx recipient on the basis of an *immunosuppression protocol, which is common to both University Hospitals* and is described below.

Furthermore, *postgraduate education of* transplant team members is provided on a weekly basis, *rounds with pathologist on a monthly basis*. Procedures for care of HTx candidates and recipients are revisited on an annual basis.

Study population

This study includes all adult patients with HTx at the University Hospital of Lausanne and Hospital of Geneva from 1 January 2000 to 31 August 2014. Of note, the University Hospital of Geneva stopped HTx operation in 2003. The study was approved by the local ethics and research committee and complies with the Declaration of Helsinki.

Demographic, clinical, and laboratory data derive from the day of admission for HTx and were obtained retrospectively from electronic chart records archived at the University Hospital of Lausanne and University of Geneva. Donor data were retrieved from the Swiss Organ Allocation System data bank. Regular endomyocardial biopsies (EMBs) were scheduled at Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 and 52. All biopsies were graded using the International Society of Heart and Lung Transplantation (ISHLT) working formulation 2004 [8]. The histological result of EMB always guided immunosuppressive treatment in agreement with the ISHLT guidelines for the care of HTx recipients [6]. The common immunosuppression protocol, which was established in 2008, aims at corticosteroid withdrawal after 12–18 months. The average ACR grade of the individual patient was derived from the sum of histological grades of all EMBs obtained during the first year after HTx divided by the number of EMBs. Pre-transplant echocardiographic data derive from standard transthoracic studies signed by board-certified cardiologists at both University Hospitals. Physicians' diagnosis of comorbidity followed the respective guidelines [9–11]. A random sample of 20 patients was chosen for control of data quality.

Statistical analysis

Continuous variables are presented as mean (±SD) or median (±interquartile range). Categorical variables are presented as numbers and percentages. Analysis of variance compared continuous variables; and χ^2 statistic compared categorical variables.

Association of explanatory variables with either outcome parameter was analysed for the whole study population and separately for the 2 groups. Variables predicting in-hospital and 1-year ACM were identified from parameters associated with the respective outcome in univariate analysis. Parameters associated with a threshold of 10% were tested for their significance using the 'stepwise backward-forward' analysis applying the Akaike information criteria to increase the likelihood of the model. The final model was adjusted for age of the donor and the recipient. Survival curves were calculated using the Kaplan–Meier method; comparison of survival curves used the log-rank test. All tests were 2-sided and used a significance level of $P < 0.05$. Analyses were performed using the R statistical software (version R 3.1.0; R Development Core Team).

RESULTS

Altogether, all 140 consecutive adult HTx recipients were included into this retrospective analysis (Table 1). Patients had a median age of 53.5 years, were predominantly male (80%), length of in-hospital stay (LoS) post-transplant was 34 days; these

Table 1: Recipients and donor characteristics

	All ($n = 140$)	2000–07 ($n = 66$)	2008–14 ($n = 74$)	P-value
Recipient demographics				
Age (years)	53.52 [47–60]	53.52 [47, 60]	53.2 [48, 60]	0.66
Female	28 (20%)	15 (22.7%)	13 (17.6%)	0.58
Time on waiting list (days)	152 [63, 387]	109.5 [50, 314]	177 [88, 426]	0.040
Mean rejection grade	0.4 [-0.3, 1.2]	0.65 [-0.1, 1.4]	0.20 [-0.3, 0.7]	<0.0001
≥Moderate acute cellular rejection	67	55	12	<0.0001
LoS (days)	34 [26, 61]	32 [25, 53]	36 [27, 62]	0.22
Donor demographics				
Age (years)	41 [26, 51]	40.5 [26, 51]	43 [29, 51.9]	0.89
Aetiology of CMP				
Ischaemic CMP	49 (35.0%)	20 (30.3%)	29 (39.2%)	0.36
Dilated CMP	74 (52.9%)	42 (63.6%)	32 (43.2%)	0.025
Congenital CMP	18 (12.9%)	9 (13.6%)	9 (12.2%)	0.99
ARVD	5 (3.6%)	1 (1.5%)	4 (5.4%)	0.43
HCM	14 (10.0%)	7 (10.6%)	7 (9.5%)	0.99
Doxocyclin-induced CMP	2 (1.4%)	0 (0%)	2 (2.7%)	0.53
Myocarditis	2 (1.4%)	0 (0%)	2 (2.7%)	0.53
Device treatment				
PM	71 (50.7%)	22 (33.3%)	49 (66.2%)	0.0002
AICD	59 (42.1%)	14 (21.2%)	45 (60.8%)	<0.0001
VAD	24 (17.1%)	6 (9.1%)	18 (24.3%)	0.031
Clinical parameters				
LVEF (%)	20 [15, 25]	20 [15, 25]	22 (15, 30]	0.39
PVR (WU)	2.3 [1.4, 3.2]	2.63 [1.46, 3.63]	2.15 [1.4, 3.1]	0.39
BSA (m^2)	1.86 [1.7, 2]	1.86 [1.7, 2]	1.88 [1.7, 2]	0.90
Size (m)	1.72 [1.7, 1.8]	1.72 [1.6, 1.8]	1.71 [1.7, 1.8]	0.75
Weight (kg)	73.8 [62, 83]	71.8 [61.3, 83]	74 [63, 84]	0.66
BMI	24.27 [22, 28]	23.62 [22, 28]	24.73 [22, 28]	0.60
Risk factors/comorbidities				
Previous thoracic surgery	53 (37.9%)	20 (30.3%)	33 (44.6%)	0.12
HTA	44 (31.4%)	17 (25.8%)	27 (36.5%)	0.24
Diabetes	22 (15.7%)	10 (15.2%)	12 (16.2%)	0.99
History of tobacco abuse	63 (45.3%)	25 (38.5%)	38 (51.4%)	0.18
Dyslipidaemia	60 (43.8%)	28 (43.8%)	32 (43.8%)	0.99
Thyroid disease	18 (12.9%)	5 (7.6%)	13 (17.6%)	0.13
COPD	12 (8.6%)	4 (6.1%)	8 (10.8%)	0.48

[IQR]: interquartile range; LoS: length of stay; CMP: cardiomyopathy; ARVD: arrythmogenic right ventricular dysfunction; HCM: hypertrophic cardiomyopathy; LVEF: left ventricular ejection fraction; PVR: pulmonary vascular resistance; PM: pacemaker; AICD: automated internal cardio-defibrillator; VAD: ventricular assistant device; BSA: body surface area; BMI: body mass index; HTA: arterial hypertension; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; TSH: thyroid-stimulating hormone.

characteristics were not different between HTx recipients of 2000–07 and 2008–14. Time on the waiting list was significantly longer in patients with HTx between 2008 and 2014 (177 vs 109 days; $P = 0.04$). Mean ACR grade of biopsies obtained within the first year post-transplant was 0.4 in the entire cohort and lower in HTx recipients of 2008–14 (0.65 vs 0.20; $P < 0.0001$). Median donor age was 41 years in the entire cohort and not different between groups (Table 1).

The prevalence of dilated cardiomyopathy of non-ischaemic origin was higher in HTx recipients of 2000–07 (63.6 vs 43.2%; $P = 0.024$); more patients in 2008–14 were treated with resynchronization (66.2 vs 33.3%; $P = 0.0002$), implantable cardioverter-defibrillator (60.8 vs 21.2%; $P < 0.0001$) or ventricular assist devices (24.3 vs 9.1%; $P = 0.031$) (Table 1).

Mean left ventricular ejection fraction before HTx was 20%, mean pulmonary vascular resistance was 2.3 Woods units, mean body mass index was 24.3; these parameters were not different between groups. The prevalence of the pre-transplant cardiovascular risk factors was similar in both periods (arterial hypertension: 31.4%, diabetes mellitus: 15.7%, history of tobacco abuse: 45.3%, dyslipidaemia: 43.8%; respectively, for the entire cohort); chronic obstructive pulmonary disease and thyroid disease were prevalent in equal measure (Table 1).

Pre-transplant drug treatment was not significantly different between the 2 periods, except for the use of eplerenone, which was administered more often in patients of the second period (25.7 vs 1.5%; $P = 0.0001$)—without surprise because of its arrival on the market in 2005 (Table 2).

Laboratory values at the day of HTx were not different between groups except for the serum iron, which was higher in the second period (12.5 vs 10.2 μmol/l; $P = 0.048$). The prevalence of positive serology for cytomegaly virus, Ebstein–Barr virus and toxoplasma gondii was not different between recipients and donors of the 2 groups (Table 3). Likewise, the incidence of mismatch for donor and recipient serology was not different between groups (Table 4).

In-hospital mortality/1-year ACM was 21.2/22.7% in 2000–07 and 15.1/16.4% in 2008–August 2014 (always $P > 0.05$) (Fig. 1). For the earlier period but not for the second period, univariate analysis showed an association between in-hospital/1-year ACM and left ventricular ejection fraction [odds ratio (OR) 1.04 95% confidence interval (CI) (1.01–1.08), $P = 0.026$; OR 1.04 (1.0–1.08);

$P = 0.034$], diabetes mellitus [OR 9 (2.1–39.1), $P = 0.0034$; OR 7.8 (1.8–33.5), $P = 0.0055$], leucocyte count [OR 0.63 (0.46–0.88), $P = 0.0065$; OR 0.62 (0.45–0.86), $P = 0.0046$] and length of stay [OR 0.91 (0.86–0.96), $P = 0.0012$; 0.92 (0.87–0.97), $P = 0.0013$]. The second period noted an association between pre-transplant spironolactone treatment and in-hospital mortality [OR 10 (1.2–82.9), $P = 0.033$] but not for 1-year ACM (Table 5).

For the first period, the predictive model of in-hospital mortality retained the pre-transplant parameters diabetes [OR 5.24 (1.2–9.3), $P = 0.011$], weight [OR -0.14 (-0.27 to -0.015), $P = 0.028$] and LoS [OR -0.10 (-0.18 to -0.02), $P = 0.016$], while logistic regression for 1-year ACM retained LoS [OR -0.07 (-0.13 to -0.021), $P = 0.0069$]. In patients with HTx between 2008 and 2014, the 1-year ACM mortality end point was not associated with any pre-transplant parameter (Table 5).

Table 2: Pre-transplant drug treatment

Drugs	All	2000–07	2008–14	*P*-value
Metoprolol	31 (22.1%)	10 (15.2%)	21 (28.4%)	0.093
Bisoprolol	7 (5.0%)	4 (6.1%)	3 (4.1%)	0.87
Carvedilol	37 (26.4%)	20 (30.3%)	17 (23.0%)	0.43
Nebivolol	8 (5.7%)	1 (1.5%)	7 (9.5%)	0.10
ACE inhibitors	68 (48.6%)	37 (56.1%)	31 (41.9%)	0.13
AT_1-receptors blockers	37 (26.4%)	16(24.2%)	21 (28.4%)	0.72
Spironolactone	80 (57.1%)	38 (57.6%)	42 (56.8%)	0.99
Eplerenone	20 (14.3%)	1 (1.5%)	19 (25.7%)	0.0001
Torasemide	111 (79.3%)	49 (74.2%)	62 (83.8%)	0.24
Hydrochlorthiazid	22 (15.7%)	12 (18.2%)	10 (13.5%)	0.60

ACE: angiotensin-converting enzyme; AT_1: angiotensin II receptor type 1.

The number of biopsies procured during the first and second period did not differ (587 vs 575 biopsies). However, the mean ACR grade of patient biopsies collected within the first year post-transplant was higher in 2000–07 when compared with 2008–14 (0.65 vs 0.20; $P < 0.0001$; Table 1), and ≥moderate ACR was more frequent (9.4% vs 1.9%, $P < 0.0001$). Histological grading with ≥moderate ACR [8] was related to increased in-hospital ACM in 2000–07 ($P = 0.048$).

DISCUSSION

Implementation of preoperative and postoperative multidisciplinary care decreased numerically but not significantly 1-year ACM in patients with HTx in 2008–14. The mean ACR grade in endomyocardial biopsies obtained during the first postoperative year was significantly lower in HTx recipients operated in 2008–14. And ≥moderate ACR, which had been associated with in-hospital ACM in 2000–07, was no longer associated with mortality in 2008–14.

Table 4: Donor/recipient match

	All	2000–07	2008–14	*P*-value
Gender mismatch	49 (38.3%)	29 (43.9%)	20 (32.2%)	0.24
Age mismatch (>20%)	53 (43.4%)	34 (51.51%)	20 (35.7%)	0.12
CMV mismatch	29 (22.3%)	18 (26.9%)	11 (17.5%)	0.24
EBV mismatch	9 (6.71%)	5 (7.8%)	4 (5.71%)	0.85
Toxoplasmose mismatch	29 (21.32%)	15 (22.4%)	14 (20.3%)	0.86

CMV: cytomegaly virus serology; EBV: Ebstein–Barr virus serology.

Table 3: Pre-transplant recipient laboratory findings

	All	2000–07	2008–14	*P*-value
Bicarbonate (mmol/l)	22.3 [20, 23]	22.45 [21, 25]	21.4 [20, 23]	0.049
Creatinine (mmol/l)	111.5 [91, 135]	112.5 [91, 137]	109 [93, 135]	0.63
Blood urea nitrogen (mmol/l)	8.95 [7, 12]	9.05 [7, 14]	8.65 [7, 11]	0.40
Bilirubin (mg/l)	<6.5 [<10, 15]	11 [<10, 17]	<10 [<10, 14]	0.14
ASAT (U/l)	31 [23, 42]	31 [23, 38]	31 [23, 43]	0.71
ALAT (U/l)	27 [19, 45]	27.5 [20, 46]	27 [19, 42]	0.73
CRP (mg/l)	6 [2,14]	13 [0.5, 27]	6 [2, 13]	0.34
Iron (μmol/l)	11.95 [8, 17]	10.2 [8, 14]	12.5 [9, 18]	0.048
Albumin (mg/l)	28 [25, 34]	28 [26,32]	28 [25, 34]	0.94
Hemoglobin (g/l)	130 [115, 142]	129 [113, 142]	131 [116, 141]	0.50
Leucocytes (G/l)	8.1 [6, 10]	8.5 [6, 10]	7.6 [6, 10]	0.41
Thromocytes (G/l)	212 [170, 258]	213.5 [172, 239]	209 [168, 266]	0.89
TSH (U/l)	1.64 [1, 3]	3.01 [2, 3]	1.42 [1, 2]	0.42
Free T4 (μg/l)	13 [12, 16]	13 [13, 18]	13 [11, 16]	0.79
Serological data				
Anti-CMV antibodies	81 (58.7%)	34 (53.1%)	47 (63.5%)	0.29
Anti-EBV antibodies	123 (90.4%)	56 (90.3%)	67 (90.5%)	0.99
Anti-Toxoplasmosis antibodies	87 (63%)	39 (60.9%)	48 (64.9%)	0.76
Donors serological data				
Anti-CMV antibodies	69 (56.6%)	33 (59%)	36 (64.3%)	0.16
Anti-EBV antibodies	111 (91%)	60 (90.9%)	51 (91.1%)	0.99
Anti-Toxoplasmosis antibodies	87 (63%)	39 (60.9%)	48 (64.9%)	0.76

ASAT: alanine–serine transferase; ALAT: alanine–aspartate transferase; CMV: cytomegaly virus; EBV: Ebstein–Barr virus; CRP: C-reactive protein; TSH: thyroid-stimulating hormone.

Furthermore, preoperative weight, diabetes and LoS, which had been associated with in-hospital ACM in 2000–07, did not remain related to in-hospital ACM in 2008–14. Altogether, implementation of multidisciplinary care compensated in our regional cohort of HTx recipients the hazard associated with previously established risk factors for post-transplant mortality.

Since 2008, implementation of multidisciplinary care at the University Hospital of Lausanne and the University Hospital of Geneva has established changes in the review process of the potential HTx candidate. Furthermore, we implemented multidisciplinary in-hospital rounds on a daily basis in the intensive care unit and twice a week basis on the normal wards as well as structured protocols for prevention of ACR and repeated modules training patients' adherence. In the literature, implementation of multidisciplinary care has been shown to decrease the time to listing of HTx candidates and the readmission rate after HTx [14]. And the guidelines for the care of HTx recipients recommend multidisciplinary care in analogy to positive experience with multidisciplinary care in non-transplant specialties [6, 12, 13, 17]. However, impact of the multidisciplinary team care on ACM after HTx has not been investigated so far. The present study tested therefore the impact of multidisciplinary care on the primary end point 1-year ACM; in addition, the secondary end point mean ACR grade in endomyocardial biopsies obtained during the first postoperative year was investigated since this typical post-transplant morbidity may benefit from implementation of structured multidisciplinary care.

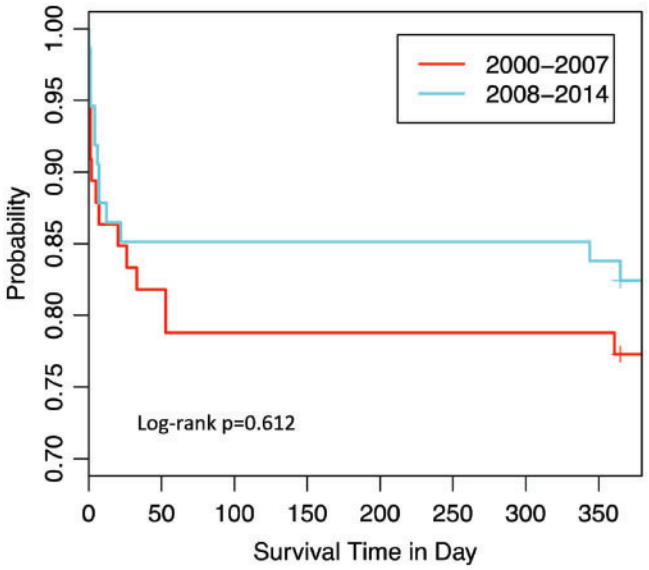

Figure 1: Kaplan–Meier survival curves for all patients, and HTx recipients from period 2000–07 to 2008–August 2014.

The impact of multidisciplinary care was investigated in HTx recipients of our regional cohort with transplantation in the years 2000–14. Throughout this period, immunosuppression had always been guided by histological grading of endomyocardial biopsies within the first post-transplant year; in addition, immunosuppression had always been applied in accordance with the guidelines [6]. The change associated with implementation of multidisciplinary care was the introduction of a structured protocol on the basis of the existing practice in order to assure common guidance of immunosuppression at both University Hospitals. Everolimus was introduced for prevention from ACR in HTx recipients in 2004 [15], which could introduce bias in this retrospective comparison. However, everolimus in combination with cyclosporine was shown to be non-inferior to standard treatment for the end point ACM and ACR [16], suggesting that a relevant impact of everolimus treatment on the primary or secondary end point of the present study is unlikely.

One-year ACM was not significantly different for HTx recipients with operation in the period 2000–07 and 2008–14, although a numerically lower number of HTx recipients reached the mortality end point in 2008–14. Likewise, in-hospital mortality was not different between groups, suggesting that multidisciplinary care did not impact on early post-transplant mortality in

Table 5: Predictors of in-hospital and 1-year ACM

	All	*P*-value	2000–07	*P*-value	2008–14	*P*-value
Univariable analysis of parameters associated with in-hospital ACM						
Spironolactone	1.44 (0.6, 3.5)	0.43	0.47 (0.2, 1.6)	0.22	10 (1.2, 83)	0.033
HTx of DM	2.78 (1, 7.8)	0.053	9 (2, 39)	0.0034	0.52 (0.06, 4.3)	0.55
Leucocyte	0.79 (0.6, 1.0)	0.019	0.63 (0.5, 0.9)	0.0065	0.94 (0.7, 1.2)	0.58
LVEF	1.02 (1.0, 10.5)	0.11	1.04 (1.01, 1.08)	0.026	0.99 (0.93, 1.04)	0.67
LoS	0.99 (0.97, 1)	0.093	0.91 (0.86, 0.96)	0.0012	1 (0.99, 1.01)	0.81
Weight	0.99 (0.96, 1.01)	0.34	0.96 (0.92, 1)	0.079	1 (0.97, 1.04)	0.83
Univariable analysis of parameters associated with 1-year ACM						
LVEF	1.02 (0.99, 1.05)	0.13	1.04 (1.01, 1.08)	0.026	1.04 (1.01, 1.08)	0.034
HTx of DM	2.45 (0.88, 6.84)	0.087	7.83 (1.83, 33.5)	0.0055	0.46 (0.05, 4)	0.49
Leucocytes	0.78 (0.65, 0.95)	0.015	0.62 (0.45, 0.86)	0.0046	0.94 (0.75, 1.17)	0.57
LoS	0.99 (0.98, 1)	0.17	0.92 (0.87, 0.97)	0.11	1 (0.99, 1.01)	0.99
Multivariable analysis of parameters associated with in-hospital ACM						
HTx of DM			5.24 (1.22, 9.3)	0.011		
Weight			-0.14 (-0.27, -0.15)	0.029		
LoS			-0.10 (-0.18, -0.02)	0.016		
Multivariable analysis of parameters associated with 1-year ACM						
LoS			-0.07 (-0.13, -0.021)	0.0069		

Numbers are odds ratio with 95% confidence interval in parenthesis.
ACM: all-cause mortality; LVEF: left ventricular ejection fraction; HTx: heart transplantation; LoS: length of stay.

our patient cohort. In-hospital and 1-year ACM are known for their association with various pre- and post-transplant clinical parameters [7]. Therefore, we investigated the profile of established risk factors for post-transplant ACM in both groups, which, in theory, could bias the primary end point. Recipient age, gender, donor age, biological variables, pulmonary vascular resistance, body mass index, cardiovascular risk factors and comorbidities were not different between groups [20]. Likewise, the prevalence of transplant-associated risk factors such as donor/recipient mismatch for gender; age, cytomegaly virus or Ebstein–Barr virus serology status did not differ between the earlier and the later period. However, end-stage heart failure of non-ischaemic origin was more prevalent in 2000–07, which has been shown to impact on the primary end point since it has been associated with lower post-transplant mortality [20, 21]. In the present cohort, 1-year ACM was numerically lower in patients with transplantation in 2008–14, suggesting that multidisciplinary care more than compensated for the increased mortality risk of patients with HTx in 2008–14.

Multidisciplinary care has been shown to decrease in-hospital and early post-discharge mortality in patients hospitalized with heart failure [18, 19]. Furthermore, favourable effects of multidisciplinary care are reported for patients with diabetes [20]. We therefore investigated which pre-transplant parameters were associated with post-transplant 1-year ACM in HTx recipients of 2000–07 and 2008–14. In the period 2000–07, pre-transplant weight, pre-transplant diabetes and postoperative LoS predicted in-hospital ACM, while only postoperative LoS was associated with 1-year ACM. However, no pre-transplant parameter was related with in-hospital or 1-year ACM in patients with HTx in 2008–14, suggesting that multidisciplinary care in the hospital compensated the hazard associated with previously established risk factors diabetes, body weight and LoS.

The secondary end point investigated whether multidisciplinary care had an impact on the mean grade of ACR within the first postoperative year. In 2000–07, the mean grade of ACR had been higher and ACR of ≥moderate grade was associated with ACM immediately after HTx. In addition, the number of EMB procurements was similar in both groups, despite of a lower number of HTx recipients in 2000–07. Studies in renal transplant recipients have shown that subclinical non-adherence with immunosuppressive therapy directly influences the incidence of ACR and kidney transplant dysfunction [21]. In accordance, the ISHLT registry and another cohort report worsened long-term outcome for HTx recipients with treated ACR [22, 23]. Aiming at the optimal patients' adherence to immunosuppressive therapy, we had implemented in 2008 training modules broaching drug treatment after HTx. These modules were provided while the HTx recipients was hospitalized after transplantation, and repeated during rehabilitation and when patients entered ambulatory follow-up. We hypothesize that the favourable results obtained for the period 2008–14 are related with improved patients' adherence to immunosuppressive drug treatment. However, we cannot entirely exclude that immunosuppression of HTx recipients in interim follow-up by primary care physicians may have had occasionally increased strength of immunosuppressive drug treatment. Likewise, we cannot exclude an effect of steroid treatment since the structured immunosuppression protocol implemented in 2008 advises complete steroid withdrawal within 12–18 months, while there was no respective recommendation before 2008. However, everolimus should not have an impact on ACR, since the incidence of ACR was not different in a randomized multicentre trial comparing the combinations cyclosporine with mycophenolate mofetile and cyclosporine with everolimus [16].

Limitations

This study investigated in a retrospective manner the impact of multidisciplinary care in a regional cohort of 140 HTx recipients using post-transplant 1-year ACM as primary and ACR as a secondary end point. Our results suggest an impact of multidisciplinary care because risk factors relevant for in-hospital and 1-year ACM before the implementation of multidisciplinary care did not remain related thereafter. However, this evidence is indirect and derives from a retrospective study, therefore, should be confirmed in larger cohorts using a prospective study design. Furthermore, a limitation as to the interpretation of in-hospital mortality is possible since this analysis did not include operating room parameters, which have been related with primary graft dysfunction [24]. However, operating room parameters and cold ischaemic time are not predictors of 1-year ACM [1], therefore, and because of incomplete documentation of operating room parameters, we decided not to analyse this data.

CONCLUSION

The results of this study indicate that multidisciplinary care in HTx is able to compensate post-transplant risk associated with pre-transplant disease. In addition, this study shows that multidisciplinary care impacts on ACR-associated morbidity and early post-transplant mortality. It remains to be shown whether this benefit transforms into decreased intermediate term and late mortality after HTx.

Funding

This work was accomplished with support by the Master Thesis Program of the Faculty of Biology and Medicine of the University of Lausanne.

Conflict of interest: none declared.

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