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Journal: Interactive cardiovascular and thoracic surgery

Year: 2017 May 24

DOI: 10.1093/icvts/ivx151

The Impact of Multidisciplinary Care on Early Morbidity and Mortality after Heart Transplantation

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Word count (text + references) : 4589

Key words : Heart transplantation - multidisciplinary care - early mortality

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Disclosure

The corresponding author receives support from Swiss National Science Foundation (320030_147121/1), the SWISSHEART Foundation, and the Foundation Muschamp. No other disclosures.

SUMMARY

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 endpoint 1-year all-cause mortality (ACM) and the secondary endpoint 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 (LoS): 34 days; mean donor age: 41 years). Multidisciplinary care was implemented in 2008, 66 HTx recipients had operation in 2000-2007 and 74 patients had HTx thereafter (2008-2014). Non-ischemic dilated cardiomyopathy was more prevalent in HTx recipients of 2000-2007 (63.6 vs. 43.2 %; p=0.024). Pre-transplant mechanical circulatory support was more frequent in 2008-2014 (9.1 vs. 24.3%; p=0.030). Groups were not different for pretransplant cardiovascular risk factors or other comorbidity, invasive hemodynamics, or echocardiographic parameters. In-hospital and 1-year ACM were numerically lower in 2008-2014 (16.2 vs. 22.2%; 18.9% vs. 25.8%; p=0.47/0.47, respectively). In 2000-2007, pretransplant weight and diabetes mellitus predicted in-hospital ACM (OR -0.14, p=0.02; OR 5.24, p=0.01; respectively) while posttransplant LoS was related with in-hospital ACM (OR -0.10; p=0.016) and 1-year ACM (OR -0.07; p=0.007). In 2000-2007, 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 (χ^2=3.92; p=0.048).

Conclusion:

Multidisciplinary care in HTx compensates posttransplant risk associated with pretransplant disease and has beneficial impact on the incidence of ACR and ACR associated 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 posttransplant care, the University Hospitals of Lausanne and Geneva implemented in 2008 multidisciplinary care procedures for the pretransplant listing process and posttransplant in-hospital and ambulatory follow-up.

The clinical impact of multidisciplinary care was investigated using the primary endpoint 1-year all cause mortality (ACM) and the secondary endpoint mean acute cellular rejection (ACR) grade during the first posttransplant year. These outcome parameters were chosen because 1-year ACM after HTx still remains high (1), and, ACM is an unambiguous endpoint in particular for a retrospective study. The secondary endpoint ACR is likewise unambiguous, however, interpretation of this endpoint in the context of multidisciplinary care is a challenge because immunosuppression and patient's adherence are both relevant. The two endpoints were compared between HTx recipients with operation in 2000-2007 and 2008-2014 since selection criteria for HTx candidates have remained largely unchanged between 2000-2014 at the local and the international level (2,3). Furthermore, local protocols of pretransplant care (4-6) and posttransplant 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 posttransplant 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 posttransplant care for solid organ transplant recipients; furthermore, experts from anesthesiology, 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

posttransplant 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 posttransplant procedures were facilitated using *common protocols for pre- and posttransplant care*. In detail, work-up of a potential HTx candidate uses a *scripted clinical presentation format* for work-up 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 posttransplant rules of conduct*. *Regular visits of the transplanting center team of the University Hospital of Lausanne* (transplant cardiologist, transplant cardiac surgeon, 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 center. *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 posttransplant are trained in three modules the first during posttransplant 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 the 1.1.2000 to the 31.8.2014. 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 (EMB) were scheduled at week 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, 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 co-morbidity 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; IQR). Categorical variables are presented as numbers and percentages. Analysis of variance compared continuous variables; and chi^2-statistic compared categorical variables.

Association of explanatory variables with either outcome parameter was analyzed for the whole study population and separately for the two 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 (AIC) 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 two-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:

Table 1 Altogether, all 140 consecutive adult HTx recipients were included into this retrospective analysis. Patients had a median age of 53.5 years, were predominantly male (80%), LoS post-transplant was 34 days; these characteristics were not different between HTx recipients of 2000-2007 and 2008-2014. Time on the waiting list was significantly longer in patients with HTx between

2008-2014 (177 vs. 109 d; 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 2008-2014 (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-ischemic origin was higher in HTx recipients of 2000-2007 (63.6 vs. 43.2%; p=0.024); more patients in 2008-2014 were treated with resynchronization (66.2 vs. 33.3%; p=0.0002), ICD (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 BMI 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%, dyslipidemia: 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 two 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 umol/l; p=0.048). The prevalence of positive serology for CMV, EBV, and toxoplasma gondii was not different between recipients and donors of the two 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 2000-2007 and 15.1/16.4 % in 2008-8/2014 (always p>0.05) (figure 1). For the earlier period but not for the second period, univariate analysis showed an association between in-hospital/1-year ACM and LVEF (OR 1.04 (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 CI95% 0.46-0.88, p=0.0065; OR 0.62 CI95% 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, 95%CI 1.2-9.3; p=0.011), weight (OR -0.14, 95%CI -0.27- -0.015;

p=0.028), and LoS (OR -0.10, 95%CI -0.18- -0.02; p=0.016) while logistic regression for 1-year ACM retained LoS (OR -0.07, 95%CI -0.13 - -0.021; p=0.0069). In patients with HTx between 2008-2014 the 1-year ACM mortality endpoint was not associated with any pretransplant parameter (Table 5). 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 2000-2007 when compared to 2008-2014 (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 2000-2007 (p=0.048).

DISCUSSION

Implementation of preoperative and postoperative multidisciplinary care decreased numerically but not significantly 1-year ACM in patients with HTx in 2008-2014. The mean ACR grade in endomyocardial biopsies obtained during the first postoperative year was significantly lower in HTx recipients operated in 2008-2014. And, ≥moderate ACR, which had been associated with in-hospital ACM in 2000-2007, was no longer associated with mortality in 2008-2014. Furthermore, pre-operative weight, diabetes and LoS, which had been associated with in-hospital ACM in 2000-2007, did not remain related to in-hospital ACM in 2008-2014. Altogether, implementation of multidisciplinary care compensated in our regional cohort of HTx recipients the hazard associated with previously established risk factors for posttransplant 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). 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 endpoint 1-year ACM; in addition, the secondary endpoint mean ACR grade in endomyocardial biopsies obtained during the first post-operative year was

investigated since this typical posttransplant morbidity may benefit from implementation of structured multidisciplinary care.

The impact of multidisciplinary care was investigated in HTx recipients of our regional cohort with transplantation in the years 2000-2014. Throughout this period, immunosuppression had always been guided by histological grading of endomyocardial biopsies within the first posttransplant 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 endpoint ACM and ACR (16) suggesting that a relevant impact of everolimus treatment on the primary or secondary endpoint of the present study is unlikely.

One-year ACM was not significantly different for HTx recipients with operation in the period 2000-2007 and 2008-2014, although a numerically lower number of HTx recipients reached the mortality endpoint in 2008-2014. Likewise, in-hospital mortality was not different between groups suggesting that multidisciplinary care did not impact on early posttransplant mortality in our patient cohort. In-hospital and 1-year ACM are known for their association with various pre- and posttransplant clinical parameters (7). Therefore, we investigated the profile of established risk factors for postransplant ACM in both groups, which, in theory, could bias the primary endpoint. Recipient age, gender, donor age, biological variables, pulmonary vascular resistance, BMI, cardiovascular risk factors, and co-morbidities were not different between groups (19). Likewise, the prevalence of transplant associated risk factors such as donor/recipient mismatch for gender; age, CMV or EBV serology status did not differ between the earlier and the later period. However, end-stage heart failure of non-ischemic origin was more prevalent in 2000-2007, which has been shown to impact on the primary endpoint since it has been associated with lower post-transplant mortality (19,20). In the present cohort, 1-year ACM was numerically lower in patients with transplantation in 2008-2014 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 (17,18). Furthermore, favorable effects of multidisciplinary care are reported for patients with diabetes (19). We therefore investigated which pre-transplant parameters were associated with posttransplant 1-year ACM in HTx recipients of 2000-2007 and 2008-2014. In the period 2000-2007, pretransplant weight, pretransplant diabetes and post-operative 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 2008-2014 suggesting that multidisciplinary care in the hospital compensated the hazard associated with previously established risk factors diabetes, body weight and LoS.

The secondary endpoint investigated whether multidisciplinary care had an impact on the mean grade of ACR within the first postoperative year. In 2000-2007, 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 2000-2007. Studies in renal transplant recipients have shown that subclinical non-adherence with immunosuppressive therapy directly influences the incidence of ACR and kidney transplant dysfunction (20). In accordance, the ISHLT registry and another cohort report worsened long-term outcome for HTx recipients with treated ACR (21,22). 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 favorable results obtained for the period 2008-2014 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 multicenter trial comparing the combinations cyclosporine with mycophenolate mofetile and cyclosporine with everolimus (23).

Limitations of the study

This study investigated in a retrospective manner the impact of multidisciplinary care in a regional

cohort of 140 HTx recipients using posttransplant 1-year ACM as primary and ACR as a secondary endpoint. 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 ischemic time are not predictors of 1-year ACM (1), therefore, and because of incomplete documentation of operating room parameters, we decided not analyze this data.

Conclusion

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

297 *Disclosure:*

298 Roger Hullin receives grant support from NOVARTIS, the SWISSHEART foundation, and the Swiss
299 National Science Foundation (320030_147121/1), and the Emma Muschamp Foundation.

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LEGENDS :

TABLE 1

[IQR]= Inter quartile 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.

TABLE 2

ACE=angiotensin converting enzyme; AT_1=angiotensin II receptor type 1.

TABLE 3

ASAT= alanine-serine transferase; ALAT=alanine-aspartate transferase ; CMV= cytomegaly virus; EBV=Ebstein-Barr virus.

TABLE 4

CMV= cytomegaly virus serology; EBV=Ebstein-Barr virus serology.

TABLE 5

Numbers are OR with 95% confidence interval in parenthesis. For other abbreviations see legend table 1.

TABLE 1 RECIPIENTS AND DONOR CHARACTERISTICS :

	all (n=140)	2000-2007 (n=66)	2008-2014 (n=74)	p-value
RECIPIENT DEMOGRAPHICS :				
Age (y)	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 (d)	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 (d)	34 [26, 61]	32 [25, 53]	36 [27, 62]	0.22
DONOR DEMOGRAPHICS				
Age (y)	41 [26, 51]	40.5 [26, 51]	43 [29, 51.9]	0.89
ETIOLOGY of CMP				
Ischemic 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
Dyslipidemia	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

Table 2 PRE-TRANSPLANT DRUG TREATMENT

	all	2000-2007	2008-2014	p-value
DRUGS				
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

TABLE 3 PRE-TRANSPLANT RECIPIENT LABORATORY FINDINGS

	all	2000-2007	2008-2014	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 (umol/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 (ug/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

TABLE 4 DONOR / RECIPIENT MATCH

	all	2000-2007	2008-2014	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

Table 5 PREDICTORS OF IN-HOSPITAL AND 1-YEAR ACM

Univariable analysis of parameters associated with in-hospital ACM

	all	p-value	2000-2007	p-value	2008-2014	p-value
spironolactone	1.44 (0.6, 3.5)	0.43	0.47 (0.2, 1.6)	0.22	10 (1.2, 83)	0.033
Hx 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

	all	p-value	2000-2007	p-value	2008-2014	p-value
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
Hx 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

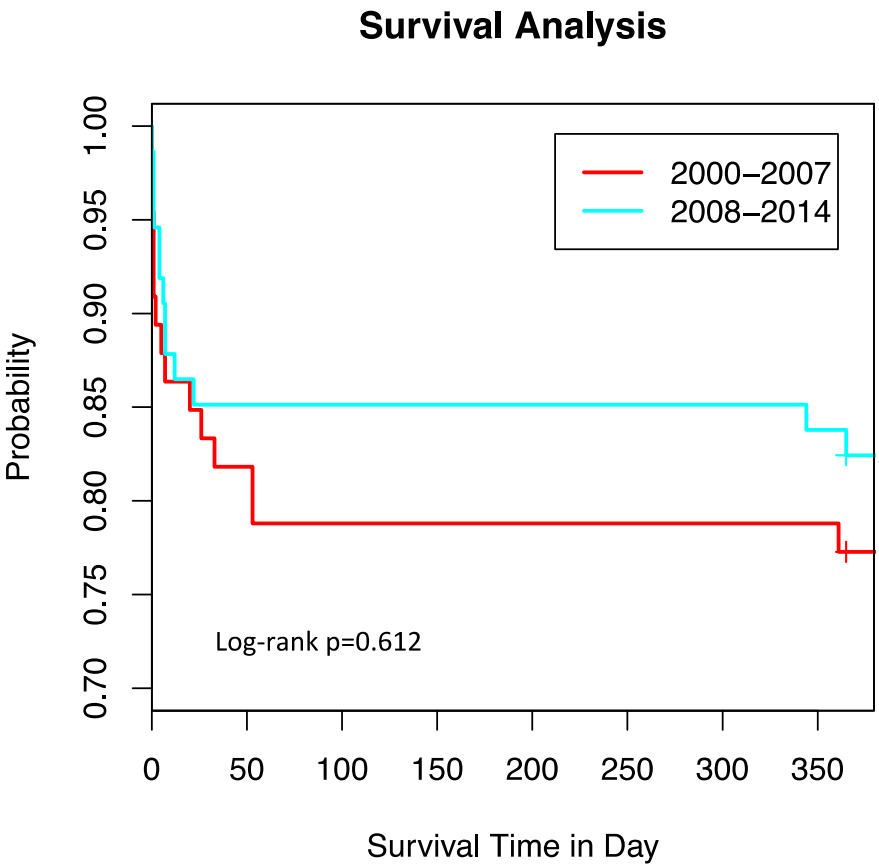
Multivariable analysis of parameters associated with in-hospital ACM

	2000-2007	p-value	2008-2014	p-value
Hx 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

	2000-2007	p-value	2008-2014	p-value
LoS	-0.07 (-0.13, -0.021)	0.0069		

Figure 1
Kaplan Meier Survival curves for all patients, and HTx recipients from period 2000-2007 and 2008-8/2014



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