

The Impact of First Year Clinical Variables of Heart Transplant Recipients on Ten-Year Survival

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ABSTRACT

Objective: Heart transplantation (HTx) is the treatment of choice for patients with end-stage heart failure. It is important to determine the factors related to long-term mortality at HTx. We aim to evaluate the effect of the first year clinical variables on 10-year survival at HTx.

Methods: The data of 76 consecutive adult HTx recipients who survived more than 1 year after transplantation between April 1998 and July 2007 in a tertiary medical center were retrospectively evaluated. The survival status was checked for each patient at December 2018. We analyzed the effect of renal function through creatinine levels, average resting heart rate, acute rejection episodes, infections, and left ventricular ejection fraction (LVEF) within the first year after HTx on survival.

Results: The mean age was 41 ± 12 years. Percentage of male was 84%. Median survival was 145 ± 32 months (95% CI, 80.72-209.27), and 36 out of 76 (47.3%) patients died during follow-up. LVEF was found lowered in nonsurvived group compared to survived ones [$57.2 \pm 5.8\%$ vs $59.3 \pm 2.1\%$ ($P = .043$)]. Cox regression analyses revealed that only LVEF and creatinine at the end of the first year after HTx were found to be significantly associated with mortality [(HR = 0.91, 95% CI, 0.85-0.98, $P = .012$) and (HR = 1.09, 95% CI, 1.68-5.67, $P < .001$), respectively].

Conclusion: Decrease in LVEF and high serum creatinine level at the end of the first year after HTx were found to be associated with poor 10-year survival in HTx recipients.

Keywords: Heart transplantation, renal insufficiency, mortality

INTRODUCTION

Heart transplantation (HTx) is the gold standard treatment method that improves quality of life and survival of the patients with refractory heart failure since it was performed in 1967 by Christian Bernard in South Africa. Although the number of new adults on the waiting list shows an increase by almost 20%, the number of adult transplant (approximately 4,000 per year worldwide) has not increased over the last decade due to scarcity of donors.^{1,2} Beside this, exceptional advances that have been achieved in immunosuppression, rejection control, and infection control have resulted in improvement in outcomes of HTx. However, it is important to determine the factors related to mid and long-term survival of HTx recipients despite the continuous improvements of survival particularly in the short-term over time. The mortality rate due to operation remains at 5-10%; on the other hand, first year survival rate reaches up to 85%, which decreases linearly by 3.4% per year. Infection, graft failure, and acute rejection are the most common causes of mortality within first year of transplantation. In the following years, cardiac allograft vasculopathy (CAV) and malignancy

become the most common causes of death.³ It is crucial to determine the factors related to mortality in terms of improving the mid- and long-term survival of adult HTx recipients especially in countries like ours, which have relatively limited number of HTx. In this regard, investigating some factors possibly related to mortality within the first year after HTx may provide an alerting data for long-term survival, so that necessary interventions can be made timely. Therefore, we aimed to evaluate the effect of some variables including renal function, resting heart rate, acute rejection episodes, infections, and left ventricular ejection fraction (LVEF) within the first year after HTx on mortality over a period more than 10 years in a cohort of HTx patients at our center.

METHODS

Patients at ages ranging from 18 to 70 who underwent HTx between April 1998 and July 2007 in Ege University Medical Faculty Hospital were retrospectively analysed, and each patient's survival status at least 10 years from transplantation was evaluated. Pediatric transplants, patients who died in the

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first year after transplantation, and who had pace maker were excluded from the study.

The study was conducted in accordance with the principles of the Declaration of Helsinki.

The data regarding patient's gender, age at transplantation, baseline heart rhythm and baseline medication after transplantation, preoperative diabetes mellitus, hypertension, hyperlipidemia history of recipients, donor age-gender, and etiology for transplantation were taken from patients' records. The reason for transplantation was classified into two groups as ischemic and nonischemic. Patients who had coronary artery disease were regarded as ischemic group. Nonischemic group composed of idiopathic cardiomyopathy, heart valve disease, congenital heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and other etiologies. Similarly, according to patients' records, the cause of death was evaluated in five categories as cardiac, acute rejection, infection, malignancy, and unknown. Cardiac death was defined as sudden cardiac death (SCD) and fatal myocardial infarction.

The event was described as end of life due to one of the reasons mentioned earlier. The survival status of each patient who survived at least 1 year after HTx was checked in December 2018. The period of time from transplantation to the event was recorded as time to event in months. For patients who were alive at December 2018, time from transplant to December 2018 was calculated and recorded in months as well. None of the patients was dropped out as all follow-up data were available.

The heart rate was determined by analyzing the electrocardiograms or rhythm strip and recorded as beat per minute. The average values of heart rate at 1st, 6th, and 12th months were recorded as continuous variable. Renal function was estimated by serum creatinine levels, and ventricular dysfunction was defined as LVEF <50% with echocardiography; measurements of both serum creatinine and LVEF at the end of the first year after HTx were used in the study. Rejection episodes (ACR) were defined according to the standardized nomenclature of the International Society of Heart and Lung Transplantation (ISHLT).⁴ Rejection episode was considered when a rejection was at a grade $\geq 2R$ with a significant need of increase in immunosuppressive or steroid treatment. CAV was considered when an intimal proliferation was ≥ 5 mm with the intravascular ultrasound in one or more epicardial coronary vessels. All variables and survival status were obtained from patient's archive files.

Main Points

- Mild decrease of left ventricular ejection fraction even within normal ranges in the first year post-heart transplantation might be associated with 10-year mortality.
- Increase in creatinine levels of heart transplant recipients in the first year after transplantation could be related with 10-year mortality.
- Median survival rate of heart transplant recipients was found at 12.0 years.

Variables were compared between patients who nonsurvived and survived during follow-up.

Statistical Analyses

Statistical Package for the Social Sciences (SPSS) version 20 (IBM SPSS Corp.; Armonk, NY, USA) software was used for statistical analysis. Recipient age, donor age, ischemic time, creatinine levels, LVEF, and mean HR were compared between survived and nonsurvived patient groups by using Student t test. Chi-square was the choice of method to compare recipient gender, donor and recipient gender, the presence of ACR episodes, the presence of CMV and non-CMV infections, and the presence of CAV in the first year after transplantation, and the Fisher's exact test was used where Chi-square was not applicable. A value of $P < .05$ was assumed to be statistically significant. Additionally, Kaplan–Meier survival analysis was used to determine median survival time. Also, all factors possibly associated with survival were initially analyzed with Cox regression with enter method. A second Cox regression analysis with enter method was performed with variables that were found to be significant on survival in the first analysis.

RESULTS

Seventy-six patients were included in the analysis. All patients went through biatrial orthotopic HTx. The study population had a mean age of 41 ± 12 years. Percentage of male and female was accounted for 84 and 16, respectively. The most common reason for HTx was nonischemic etiology (76%). The median survival was 145 ± 32 months (95% CI, 80.72–209.27), and 36 out of 76 (47.3%) patients died during follow-up. The percentage of death causes was ordered from highest to lowest as follows: cardiac ($n = 12$, 33.3%), infection ($n = 9$, 25%), others ($n = 6$, 16.7%), malignancy ($n = 5$, 13.9%), and acute rejection ($n = 4$, 11.1%). The other characteristics of patients and their medications were given in [Table 1](#).

We investigated the factors that may possibly affect mortality. Therefore, some variables, such as ACR episodes, mean heart rate, CMV infection, non-CMV infections within the first year following transplantation, CAV, recipient age–gender, donor age, donor–recipient gender mismatch, graft cold ischemic time, and also LVEF and creatinine levels at the end of the first year after HTx, were compared between patients who survived and nonsurvived during follow-up. Among these variables, LVEF was found mildly lowered in nonsurvived group compared to survived ones [$57.2 \pm 5.8\%$ vs $59.3 \pm 2.1\%$ ($P = .043$)]. Although creatinine levels of patients who died were higher than those of patients who survived, the difference was not statistically significant, but P value was close to significance [1.42 ± 0.95 mg dL⁻¹ vs 1.11 ± 0.30 mg dL⁻¹ ($P = .074$)] ([Table 2](#)). Additionally, only three patients in the nonsurvived group have required hemodialysis at the end of the first year. None of the patients in the survived group required hemodialysis. Furthermore, we used a multivariable Cox regression analysis to determine the effects of possible factors considered to be related to mortality in heart transplant patients. In the first analysis, all factors were assessed, and a negative association of LVEF and a positive association of creatinine level with mortality were found [(HR 0.90, 95% CI, 0.83–0.97, $P = .012$) and (HR 2.54, 95% CI, 1.05–6.16, $P = .038$), respectively]. In the second

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population

Variable	Survived (n = 40)	Nonsurvived (n = 36)
Age at HTx (years)	40.02 ± 12.82	42.94 ± 11.20
Men [n (%)]	35 (87.5)	29 (80.5)
Mean survival time (months)	163.82 ± 31.90	71.13 ± 52.41
BMI (kg m ⁻²)	22.92 ± 3.65	23.22 ± 3.02
DM [n (%)]	1 (2.5)	3 (8.3)
Hypertension [n (%)]	2 (5.0)	0 (0)
Hyperlipidemia [n (%)]	5 (12.5)	2 (5.6)
Preop LVAD [n (%)]	4 (10.0)	0 (0)
Reason for HTx [n (%)]		
Ischemic [n (%)]	11 (27.5)	7 (19.4)
Nonischemic [n (%)]	29 (72.5)	29 (80.5)
Baseline Medications [n (%)]		
Steroids [n (%)]	40 (100)	36 (100)
Induction therapy [n (%)]	2 (5.0)	3 (8.3)
Cyclosporine [n (%)]	33 (82.5)	26 (72.2)
Azathioprine [n (%)]	9 (22.5)	10 (27.8)
Tacrolimus [n (%)]	12 (30.0)	12 (33.3)
Sirolimus [n (%)]	1 (2.5)	2 (5.6)
Everolimus [n (%)]	4 (10.0)	0 (0)
Mycophenolate mofetil [n (%)]	31 (77.5)	26 (72.2)
β blockers [n (%)]	0 (0)	1 (2.8)
Verapamil [n (%)]	5 (12.5)	1 (2.8)
Diltiazem [n (%)]	11 (27.5)	7 (19.4)
ACEI/ARB [n (%)]	17 (42.5)	14 (38.9)
Diuretic [n (%)]	20 (50.0)	13 (36.1)
Donor Characteristics		
Donor age (years)	28.02 ± 8.96	30.94 ± 11.31
Donor gender [(male) %]	35 (87.5)	32 (88.9)
Female donor/male recipient [(n %)]	2 (5.0)	2 (5.5)
Male donor/female recipient [(n %)]	2 (5.0)	5 (13.8)
Cold ischemic time (minutes)	178.61 ± 54.14	158.30 ± 52.87
Cause of Death		
Cardiac [n (%)]	N/A	12 (33.3%)
Acute rejection [n (%)]	N/A	4 (11.1%)

Table 1. (Continued)

Variable	Survived (n = 40)	Nonsurvived (n = 36)
Infection [n (%)]	N/A	9 (25%)
Malignancy [n (%)]	N/A	5 (13.9%)
Other [n (%)]	N/A	6 (16.7%)

Abbreviations: BMI, body mass index; DM, diabetes mellitus; LVAD, left ventricular assist device; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; N/A, not applicable.

Table 2. Comparison of Assessed Possible Risk Factors Related to Mortality Between Survived and Nonsurvived Groups in Study Population

Variables	Survived (n = 40)	Nonsurvived (n = 36)	P
Recipient age (years)	40.02 ± 12.82	42.94 ± 11.20	.293
Recipient gender (male, %)	87.5	80.6	.303
Donor age (years)	28.26 ± 8.96	30.94 ± 11.31	.228
Male donor/male recipient [n (%)]	33 (55.0)	27 (45.0)	.246
Male donor/female recipient [n (%)]	2 (28.6)	5 (71.4)	
Female donor/male recipient [n (%)]	2 (50.0)	2 (50.0)	1.000
Female donor/female recipient [n (%)]	3 (60.0)	2 (40.0)	
Ischemic time (minutes)	178.61 ± 54.14	158.30 ± 52.87	.105
ACR episode in first year (%)	20.0	22.2	.517
Creatinine in first year (mg dL ⁻¹)	1.11 ± 0.30	1.42 ± 0.95	.074
LVEF in first year (%)	59.38 ± 2.14	57.23 ± 5.85	.043
Mean heart rate in first year (bpm)	98.98 ± 9.81	97.30 ± 15.25	.565
CMV infection (%)	52.5	36.1	.114
Non-CMV infections (%)	22.5	36.1	.146
CAV in first year (%)	2.5	9.4	.228

Abbreviations: ACR, acute cellular rejection; LVEF, left ventricular ejection fraction; CMV, cytomegalo virus; CAV, cardiac allograft vasculopathy.

analysis, only these two variables were analyzed using Cox regression with enter method, and their significance was remained for mortality [(HR 0.91, 95% CI, 0.85-0.98, $P = .012$) and (HR 1.09, 95% CI, 1.68-5.67, $P < .001$), respectively] (Tables 3 and 4).

DISCUSSION

HTx is the treatment of choice for patients with end-stage heart failure. According to ISHLT 2017, median survival is 10.7 years for adult HTx patients. In our study, median survival was slightly higher at 12.0 years.

Looking at the factors related to mortality, LVEF and serum creatinine level at the end of the first year after HTx showed an association with long-term survival in this study. LVEF was found mildly lowered in nonsurvived group compared with survived ones [$57.2 \pm 5.8\%$ vs $59.3 \pm 2.1\%$, $P = .043$], and also it was detected significantly associated with mortality in final regression analysis (HR 0.91, 95% CI, 0.85-0.98, $P = .012$). Left ventricular systolic function that is commonly assessed by echocardiographic LVEF usually shows lower values in clinically stable HTx patients compared with healthy subjects.⁵ It is a well-established method of short- and long-time evaluation of

Table 3. Initial Multivariate Analysis of Possible Risk Factors Related to Mortality

Variable	B	HR	P	95% CI
Recipient age	0.00	1.00	.779	0.96-1.04
Recipient gender	-0.57	0.56	.247	0.21-1.48
Donor age	0.02	1.02	.367	0.97-1.06
Ischemic time	0.00	1.00	.922	0.99-1.00
ACR episode	0.11	1.12	.821	0.40-3.13
Creatinine level	0.93	2.54	.038	1.05-6.16
LVEF	-0.10	0.90	.012	0.83-0.97
Mean heart rate	0.00	1.00	.985	0.96-1.04
CMV infection	-0.22	0.79	.618	0.33-1.93
Non-CMV infections	0.60	1.82	.202	0.72-4.61
CAV in rst year	0.80	2.23	.267	0.54-9.20

Abbreviations: ACR, acute cellular rejection; LVEF, left ventricular ejection fraction; CMV, cytomegalo virus; CAV, cardiac allograft vasculopathy; HR, hazard ratio.

Table 4. Second Multivariate Analysis of Possible Risk Factors Related to Mortality

Variable	B	HR	P	95% CI
Creatinine level	1.12	3.09	<.001	1.68-5.67
LVEF	-0.08	0.91	.012	0.85-0.98

Abbreviation: LVEF, left ventricular ejection fraction; HR, hazard ratio.

graft condition and an important predictor of outcomes in heart transplant.⁶ Barbir et al.⁷ showed that LVEF >60% was significantly able to predict survival without myocardial infarction and/or heart failure and/or and also was able to predict cardiac death in HTx patients. Additionally, the study of Vakil et al.⁸ revealed that the percentage of SCD accounted for approximately 10% among all deaths after HTx, and LVEF ≤40% was the important predictor of SCD in adult HTx patients. However, some limitations regarding LVEF should be noted. LVEF is a volume-based echocardiographic parameter providing an indirect assessment of myocardial function. Although it is an important predictor of outcomes in various cardiac disease including heart transplant patients, it could be in normal ranges even in patients with early systolic dysfunction detected by global longitudinal strain measurements.⁹⁻¹¹ On the other hand, LVEF measurements have an interobserver variability relating to LV cavity border tracing and geometric assumptions.¹² Therefore, these factors should be considered when interpreting our results, which showed LVEF was in normal ranges and there was a small difference between groups.

ISHLT registry has revealed that renal failure is one of the leading causes of death among HTx patients, especially in long term. Approximately 25% of HTx patients showed elevated serum creatinine levels at the end of the first year post-HTx, 51% at 5-year post-HTx, and 68.4% at 10-year.¹³ Post-transplant renal failure has been mostly attributed to calcineurin inhibitors that are used for immunosuppression. On the other hand, several other non-immunosuppression-related factors such as recipient age, female gender, diabetes, hypertension, hepatitis C infection, and impaired renal and postoperative acute renal failures have been found to contribute to impaired kidney function during the first year after HTx.^{14,15} We found that creatinine levels of patients who died were higher than those of patients who survived. Although the difference was not statistically significant in univariate analysis, P value was close to significance [$1.42 \pm 0.95 \text{ mg dL}^{-1}$ vs $1.11 \pm 0.30 \text{ mg dL}^{-1}$, $P = .074$]. However, Cox regression analysis revealed that creatinine level at first year after HTx was associated with increased risk of mortality (HR 1.09, 95% CI, 1.68-5.67, $P < .001$). The significant association between renal failure after HTx and mortality and morbidity has been previously reported.¹⁶⁻¹⁹ Arora et al.²⁰ have shown that the significant number of HTx recipients demonstrated a decrease by 25 mL/min/1.73 m² at glomerular filtration rate (GFR) within the first year after HTx, and this decline of GFR was associated with a higher risk of both all cause and cardiac mortality. Also, GFR at first year ($<60 \text{ mL/min/1.73 m}^2$) post-HTx was found to be capable of predicting 5, 10, and 15-year all-cause and cardiac mortality. Additionally, Navarro-Manchon et al.²¹ concluded that although GFR shows rapid reduction in the first few months, it might be a reliable indicator of renal reserve as it stabilizes at the end of first year after HTx and shows slow, continuous deterioration. Furthermore, only severe renal dysfunction at first year was found to be an independent predictor of all-cause mortality among various

factors in HTx patients. GFR is usually a preferred method for the assessment of renal function in HTx patients because of fluctuations can be seen in creatinine levels due to a number of factors. On the other hand, it has been shown that GFR calculated by the abbreviated MDRD (Modification of Diet in Renal Disease) equation is no superior to serum creatinine at first year after HTx in terms of predicting long-term mortality.²² Therefore, we thought that creatinine level at the end of first year after HTx could be a reliable marker to define renal reserve. In this regard, as it was reported that renal protective approaches probably could be effective at early phases of renal damage.²³

We found that mean first year heart rate was similar between groups and did not affect survival in HTx patients. Denervation of the donor heart during HTx, which causes loss of parasympathetic and sympathetic regulation, results in increased resting heart rate and also loss of expected rapid heart rate response to exercise.²⁴ The studies regarding heart rate and survival after HTx reported that higher heart rates within the first year after HTx could be related to cardiovascular and all-cause mortality.^{25–28} Nonetheless, the relation between increased heart rate and poor prognosis has not been fully understood yet. It is not clear whether tachycardia is simply an outcome of clinical status or it is a cause of worsening prognosis on its own. From another point of view, increased heart rate could be a compensatory response to underlying conditions such as hypovolemia, anemia, graft dysfunction, bronchopulmonary disease, or infection.^{29,30}

Regarding the other factors that were investigated in our study, ACR episodes, infections, and CAV seen within first year after HTx were not found to be related to long-term mortality. Infection and acute rejection are among the most commonly reported causes of mortality particularly within first year of transplantation¹³; therefore, our findings could be expected as patients who died within first year after HTx were not included in this study. With respect to CAV which is one of the common causes of death after transplantation, it is usually seen in the following years rather than in the first year after transplantation.¹³ Therefore, the reason why we could not find a relation between CAV and mortality could be related to the design of our study investigating variables including CAV only in the first year after transplantation.

There are some worth mentioning limitations of our study. This study reflects the data of a single center. The retrospective design and relatively small number of patients are other limitations of this study. As it is known, the retrospective collection of data may cause data inaccuracy, lack of information, and patient selection bias in comparison to prospectively acquired data. Also, including large number of variables in the logistic regression model with a relatively small number of patients in the study cohort may have a potential risk for statistical anomaly. Nevertheless, we managed to gather a comprehensive database, and our analysis has revealed several important findings related to post-HTx mortality within 10 years.

CONCLUSION

This study demonstrated that even small decrease in LVEF and increase in serum creatinine level at the end of the first year

after HTx might be associated with poor long-term survival in heart transplant recipients. Therefore, these parameters need to be checked carefully and monitored particularly within the first year after transplantation as they can potentially affect the long-term outcome of HTx.

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