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Orginal Article

Factors associated with survival of patients with cardiac transplantation

Kalp nakil olan hastaların hayatta kalması ile ilgili faktörler

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Abstract

Aim: Heart transplantation is currently considered the optimal surgical approach for the treatment of refractory heart failure, as it offers a higher likelihood of survival as well as significant improvements to quality of life. We aim to identify factors that relate to post-transplantation survival among patients who received a cardiac transplantation.

Material and Methods: We retrospectively included all cardiac transplant recipients who underwent cardiac transplant operations at the Başkent University Faculty of Medicine between February 1, 2003 and December 1, 2019. We examined various demographic and clinical factors. This study was approved by the Başkent University Medical and Health Sciences Research Board (Project no KA20 / 326) and supported by the Başkent University Research Fund. The principles of the Declaration of Helsinki were complied with during the study.

Results: A total of 99 patients were involved in the study. The mean age was 41.65 ± 14.89 years. The underlying cardiac condition for cardiac transplantation was ischemic dilated cardiomyopathy in 20 patients (20.2%),non-ischemic dilated cardiomyopathy in 66 patients (66.7%),restrictive cardiomyopathy in five patients (5.1%),myocarditis in one patient (1.0%),and another cause in seven patients (7.1%). Binary logistic regression analysis indicates that transplant rejection was the sole independent predictor of mortality.

Conclusion: The survival of cardiac transplant recipients is significantly correlated to transplant rejection and patient age. However, we observed a significant correlation between survival status and hyperlipoproteinemia. Furthermore, the mortality rates among patients with cellular, humoral, and cellular-humoral diseases were found to be lower than the mortality rate of patients without rejection.

Keywords: Heart transplantation; transplantation; graft rejection; survival; heart failure; mortality

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Öz

Amaç: Kalp transplantasyonu, daha yüksek hayatta kalma olasılığının yanı sıra yaşam kalitesinde önemli iyileşmeler sunduğundan, refrakter kalp yetmezliğinin tedavisi için şu anda en uygun cerrahi yaklaşım olarak kabul edilmektedir. Bu çalışmada, kurumumuzda kalp nakli yapılan hastalarda nakil sonrası sağkalım ile ilgili faktörleri belirlemeyi amaçladık.

Gereç ve Yöntemler: 1 Şubat 2003-1 Aralık 2019 tarihleri arasında Başkent Üniversitesi Tıp Fakültesi'nde kalp nakli operasyonu geçiren tüm kalp nakli alıcılarını retrospektif olarak dahil ettik. Çeşitli demografik ve klinik faktörleri inceledik. Bu çalışma Başkent Üniversitesi Tıp ve Sağlık Bilimleri Araştırma Kurulu (KA20/326 no'lu proje) tarafından onaylanmış ve Başkent Üniversitesi Araştırma Fonu tarafından desteklenmiştir. Çalışma sırasında Helsinki Bildirgesi ilkelerine uyuldu.

Bulgular: Çalışmaya toplam 99 hasta dahil edildi. Ortalama yaş 41,65 ± 14,89 yıl idi. Kalp nakli için altta yatan kalp rahatsızlığı 20 hastada (%20,2) iskemik dilate kardiyomiyopati, 66 hastada (%66,7) iskemik olmayan dilate kardiyomiyopati, beş hastada (%5,1) restriktif kardiyomiyopati, bir hastada (%1,0) miyokardit idi ve yedi hastada (%7,1) başka bir neden. İkili lojistik regresyon analizi, transplant reddinin mortalitenin tek bağımsız belirleyicisi olduğunu gösterir.

Sonuçlar: Kalp nakli alıcılarının sağkalımı, nakil reddi ve hasta yaşı ile önemli ölçüde ilişkilidir. Bununla birlikte, hayatta kalma durumu ile hiperlipoproteinemi arasında anlamlı bir ilişki gözlemledik. Ayrıca hücresel, hümoral ve hücresel hümoral hastalığı olan hastalarda ölüm oranları, reddedilmeyen hastaların ölüm oranından daha düşük bulundu.

Anahtar kelimeler: Kalp transplantasyonu; transplantasyon; greft reddi; sağkalım; kalp yetmezliği; mortalite

Introduction

Heart transplantation is a life-saving procedure among patients with end-stage heart failure.

The number of newly diagnosed patients with heart failure has increased exponentially, but the survival of these patients has been prolonged by sophisticated treatment modalities and the widespread use of mechanical circulatory support in many settings [1]. Due to the scarcity of donors and the high need for heart transplants, appropriate patient selection is crucial. Such selection is decisive for not only the subsequent transplant process and surgery but also the success in the follow-up period. Thus, selection criteria and indications for patients who require a heart transplant have been established [2].

Heart transplantation is used in cases where "end-stage heart disease is not remediable by more conservative measures." Indications include the following: a restricted left ventricular ejection fraction (LVEF) of less than 25% persists despite adequate medical therapy in accordance with the guidelines for existing New York Heart Association (NYHA functionality III or IV; traditional or alternative surgical techniques cannot be performed or have already been employed; recurring ventricular arrhythmias with persistent symptoms are present; intravenous inotropic or mechanical circulatory support cannot be discontinued; and recurring hospitalizations have occurred for acute heart failure, which is one of the most important indications (Table I) [3].

Table I. The ACC/AHA guidlines include the following indications for cardiac transplantation

1. Refractory cardiogenic shock requiring intra-aortic balloon pump counterpulsation of left ventricular assist device (LVAD)
2. Cardiogenic shock requiring continuous intravenous inotropic therapy (i.e., dobutamine, milrinone, etc.)
3. Peak VO2 (VO2 max) less than10 mL/kg perm in
4. NYHA class of III or IV despite maximized medical and resynchonization therapy
5. Recurrent life-threatening left ventricular arrhythmias despite an implantable cardiac defibrillator, antiarrhytmic therapy, or catheter-based ablation
6. End-stage congenital HF with no evidence of pulmonary-hypertension
7. Refractory angına without potential medical or surgical therapeutic options

Further indications are as follows: refractory cardiogenic shock requiring intra-aortic counterpulsation of the balloon pump via a left ventricular assist device (LVAD); a cardiogenic shock necessitating continuous intravenous inotropic therapy (e.g. dobutamine, milrinone); a peak oxygen uptake (VO2 max) of less than 10 ml / kg perm in NYHA class III or IV despite maximized medical and resynchronization therapy; recurrent life-threatening left ventricular arrhythmias despite an implanted heart defibrillator, antiarrhythmic therapy, or catheter-based ablation; end-stage congenital heart failure with no evidence of pulmonary hypertension; and refractory angina with no potential medical or surgical treatment options [4].

Cardiac transplantation substantially improves patient survival and well-being [5]. However, post-transplant mortality continues to be a significant problem [6]. Various factors have been associated with post-transplant mortality [7–9]. For example, rejection is a predominant source of mortality in this population, and factors such as cancer [10], infection [11], acute coronary syndromes [12], and pulmonary and renal problems [13,14] may also contribute to mortality. In this study, we aim to identify factors that relate to the survival of cardiac transplant recipients who received a cardiac transplantation at our institution.

Material and Methods

We retrospectively included all cardiac transplant recipients who underwent cardiac transplant operations at the Başkent University Faculty of Medicine between February 1, 2003 and December 1, 2019. We examined various demographic and clinical factors, including age, sex, rejection status, progressive coronary vasculopathy, hyperlipidemia, diabetes, hypertension, cancer, and infection. Table II presents the demographic and clinical properties of the study population.

Table II. Demographic and Clinical Properties of the study population

Characteristic	Result
Sex (Male,%)	71.7%
Age at the time of transplant (years, mean + SD)	41.65 + 14.89
Indication of cardiac transplant	
Ischemic dilated cardiomyopathy (n,%)	20 (20.2%)
Non-ischemic dilated cardiomyopathy (n%)	66 (66.7%)
Restrictive cardiomyopathy (n,%)	5 (5.1%)
Myocarditis (n,%)	1 (1.0%)
Other causes (n,%)	7 (7.1%)
HT (n,%)	38 (38.4%)
HL (n,%)	49 (49.5%)
DM (n,%)	25 (25.3%)
Smoker (n,%)	13 (13.1%)
Time to death (month, mean + SD)	58.38 + 54.12

The types of rejection are defined as Acute Cellular Rejection (ACR) and antibody-mediated rejection (AMR) based in the International Society and Heart Lung Transplant (ISHLT) scale in Table III. Antibody-mediated rejection is a type of chronic or late rejection that represents a series of humoral reactions to the cardiac allograft. It is detected by cardiac biopsy and the detection of donor-specific antibodies in the blood. We applied univariate logistic regression analysis to determine the individual predictors of mortality. Subsequently, we performed a binary logistic regression analysis to identify the independent predictors of mortality. This study was approved by the Başkent University Medical and Health Sciences Research Board (Project no KA20 / 326) and supported by the Başkent University Research Fund. The principles of the Declaration of Helsinki were complied with during the study.

Table III. Types of rejection, the İnternational Society and Heart Lung Transplant (ISHLT) scale.

Acute Cellular Rejection (ACR)
0= No evidence of rejection (NER)
1R= Mild rejection
2R= Moderate rejection
3R= Severe rejection
Antibody-mediated rejection (AMR)

Results

A total of 99 patients were involved in the study. The mean age was 41.65 ± 14.89 years, and the gender distribution was 28 females (28.3 %) versus 71 males (71.7%). The underlying cardiac condition for cardiac transplantation was ischemic dilated cardiomyopathy in 20 patients (20.2%), non-ischemic dilated cardiomyopathy in 66 patients (66.7%), restrictive cardiomyopathy in five patients (5.1%), myocarditis in one patient (1.0%), and other causes in seven patients (7.1%) (coronary artery disease, ventricular arrhytmias, heart valve disease, congenital heart defect and failure of a previous heart transplant).

A total of 52 patients (52.5%) died within the mean follow-up duration of 58.38 + 54.12 (range 0–191) months. Forty-three patients (82.7%) died within the first five years, six (11.5%) died between the 6th to 10th years, and three (5.8%) died between the 10th and 15th years (5.8%). Causes of death were progressive end-stage heart failure (n=81, 81.8%), cancer (n=2, 2.0%), infection-sepsis (n=1, 1.0%), and other causes (n=15, 15.2%). In univariate analysis, hyperlipidemia, transplant rejection, and age were significant predictors of mortality ($p<0.05$ for all).

A difference was observed between the ages of the individuals in relation to survival status. Specifically, the average age of the deceased individuals was approximately 10 years above that of the surviving individuals. This difference was found to be significant ($p<0.05$; see Table IV).

Table IV. Difference between the age measurements of the individuals according to the Survival status was tested with the Mann Whitney U test

	N	Mean	Sandard deviation	Mann Whitney U	P
alive	47	36.04	13.65	717.500	.000*
dead	52	46.73	14.24		

While the rate of individuals living without DM (diabetes mellitus) is 46.6%, the rate of individuals living with DM is 52.0%.

However, there was no significant relationship found between survival status and DM (p>0.05) shown on Table V.

Table V. Relationship between survival status and DM was tested with the chi-square test

			Survival		total
			alive	dead	
DM	none	N	34	39	73
		%	46.6%	53.4%	100.0%
	available	N	13	12	25
		%	52.0%	48.0%	100.0%
Total		N	47	51	98
		%	48.0%	52.0%	100.0%

↓ 2 = 0.220 p=0.639

Also there was no significant relationship found between survival status and HT (hypertension) (p>0.05). Althogh the rate of individuals living without HT is 48.3%, the rate of individuals living with HT is 47.4% shown on Table VI.

Table VI. Relationship between survival status and HT was tested with the chi-square test

			Survival		Total
			alive	dead	
HT	None	n	29	31	60
		%	48.3%	51.7%	100.0%
	Available	n	18	20	38
		%	47.4%	52.6%	100.0%
Total		n	47	51	98
		%	48.0%	52.0%	100.0%

↓ 2 = 0.009 p=0.926

However, a significant correlation between survival status and HL (hyperlipidami) was found according to the chi-square test (p <0.05). The rate of people living without HL is 34.7%, the rate of people living with HL is 61.2% as shown on Table VII.

Table VII. Relationship between survival status and HL was tested with the chi-square test

			Survival		total
			alive	dead	
HL	None	n	17	32	49
		%	34.7%	65.3%	100.0%
	Available	n	30	19	49
		%	61.2%	38.8%	100.0%
Total		n	47	51	98
		%	48.0%	52.0%	100.0%

↓ 2 = 6.909 p=.009

While the rate of individuals living without cancer is 51.2%, the rate of individuals living with cancer is 26.7%. However, according to the chi-square test, no significant relationship was found between survival and cancer (p>0.05) shown on Table VIII.

Table VIII. Relationship between survival status and cancer was tested with the chi-square test

			Survival		total
			alive	dead	
Cancer	None	n	43	41	84
		%	51.2%	48.8%	100.0%
	Available	n	4	11	15
		%	26.7%	73.3%	100.0%
Total		n	47	52	99
		%	47.5%	52.5%	100.0%

↓ 2 = 3.070 p= 0.080

Mortality rates in patients with cellular, humoral and cellular + humoral were found to be lower than in individuals without rejection. A statistically significant correlation was found between survival status and rejection (p<0.05) shown on Table IX.

Table IX. Relationship between survival status and rejection was tested with the chi-square test

			Survival		total
			alive	Dead	
Rejection	none	N	29	37	66
		%	43.9%	56.1%	100.0%
	cellular	N	11	6	17
		%	64.7%	35.3%	100.0%
	humoral	N	1	1	2
		%	50.0%	50.0%	100.0%
	cellular+ humoral	N	6	0	6
		%	100.0%	0.0%	100.0%
Total		N	47	44	91
		%	51.6%	48.4%	100.0%

↓ 2 = 8.350 p=0.039

Discussion

Cardiac transplantation is considered the optimal surgical approach for the treatment of patients with end-stage heart failure. The number of patients diagnosed with heart failure has increased annually, but their life expectancy has been prolonged by progress in medical treatments. However, there is still excess mortality among cardiac transplant recipients compared to the general population. Rejection, and particularly ACR, is a common problem after orthotopic heart transplantation [15] and one of the mechanisms associated with poor transplant survival [11]. Since a transplanted heart originates from another organism, the recipient's immune system typically attempts to reject it. Therefore, treatment with immunosuppressant therapy, which can include steroids and antiproliferative agents such as cyclosporine, sirolimus/tacrolimus, and antimetabolites (e.g. azathioprine, mycophenolate mofetil, and rapamycin), has been introduced into clinical

practice, which has significantly reduced the rate of rejection and, in turn, of post-transplant mortality [16–19]. However, in previous studies, certain factors other than rejection have also been operational in increasing mortality rates in this population. These factors include cancer [10], infection [11], transplant vasculopathy [20,4], acute coronary syndromes [12], and pulmonary and renal problems [13,14]. In accordance with previous reports, the present study illustrates that transplant rejection is an important predictor of mortality [21].

Early detection of a rejection and the provision of care and therapy for that rejection are crucial for the success of a transplantation. A frequent complication following orthotopic heart transplantation is ACR [15], which is associated with poor transplant survival [11]. In our study, rejection occurred in 25 patients; of these cases, 17 were cellular (18.7%), two were humoral (2.2%), and six were both cellular and humoral (6.6%). The data reflect a significantly lower mortality rate among patients with cellular, humoral, and cellular-humoral disease than among patients who did not experience rejection. In research by Aziz et al. [11], graft failure (34.0%), infection (21.0%), and acute rejection (22.0%) were causes of death associated with poor transplant survival. In-Cheol Kim et al. [22] have also identified infection as a main cause of death that usually occurs in the first postoperative year but can remain a threat throughout the life of a chronically immunosuppressed patient.

Subherwal et al. [23] have revealed that cellular rejection may occur despite the use of immunosuppressive therapy, which reflects a need for new immunosuppressive agents.

Malignancy is one of the most prevalent causes of late mortality in heart transplant recipients. In our study, 15 patients (15.2%) developed cancer, which resulted in death for two of them (13.3%). However, the data do not evidence a significant association between cancer and mortality. Kittleson et al. [24] and Dantal et al. [25] have reported that malignancies are about two to four times more common after heart transplants than after kidney transplants. The heightened risk of cancer in heart transplant recipients is believed to derive from the higher level of immunosuppression in heart transplant recipients.

Age has also been significantly associated with increased mortality. Age causes a progressive decline in both organ functions and overall body condition [26]. As such, some researchers have considered an age above 65 years to be a contraindication of cardiac transplant, although that view has recently been challenged by the increasingly higher ages of transplant recipients [27,28]. The literature on this issue presents contradictory data. Several clinical studies have observed a lower survival rate following cardiac transplantation in elderly patients than in younger patients. Meanwhile, Bull et al. [29] have noted significantly poorer short-term and long-term survival and a higher risk of death from infection and malignancy in transplant recipients over 60 years of age.

Conclusion

Heart transplantation is the life-saving procedure for patients with end-stage heart failure. As well as the developments and improvements in immunosuppressive therapy, donor procurement, improved surgical techniques and better aftercare after heart transplantation have led to a significant reduction in the acute rejection of allografts. In order to provide patients with a long, healthy life after heart transplantation, we have to pay attention to rejection, infection, coronary vasculopathy, and malignancy. With a careful balance between immunosuppressive therapy and vigilant monitoring for complications, we can expect a bright future for these patients. In summary, our study showed no significant correlation between survival status and diabetes mellitus or between survival status and arterial hypertension. In addition, there was no significance between survival and the presence of cancer, but there was a significant correlation between survival status and hiperlipoproteinami. Furthermore, the mortality rates in patients with cellular, humoral and cell-humoral diseases were found to be lower than in patients without rejection. A statistically significant correlation between survival status and rejection was found.

In addition, there was a significant difference between the age measurements of the individuals by survival status.

In order to be able to lead a long, healthy life, hiperliporoteinemia should be prevented. To keep mortality as low as possible, the likelihood of rejection should also be avoided as much as possible.

Heart transplantation is a life-saving procedure for patients with end-stage heart failure. Advancements in immunosuppressive therapy, donor procurement, surgical techniques, and heart transplantation aftercare have substantially reduced the acute rejection of allografts. To enable patients to live long, healthy lives after a heart transplantation, we must be attentive to rejection, infection, coronary vasculopathy, and malignancy. A careful balance between immunosuppressive therapy and vigilant monitoring for complications can yield a bright future for these patients.

Study limitations

The limitations of our study are its retrospective design and a relatively number of our patients.

The causes of death after heart transplantation were complex, so the assignment of a single cause was difficult. In most cases underlying disease was considered to be the cause of death.

Declaration of conflict of interest

The authores declare that there is no conflict of interests regarding the publication of this paper.

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