



Heart Transplantation in Iran, a Single Center 15 Years Registry Report, Early and Mid-term Outcomes and Survival Rate

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Abstract

Introduction: Heart transplantation was first performed in Iran in July 1993 in Shariati Hospital affiliated with Tehran University of Medical Sciences. Cardiac transplants in Iran are described as being among the most successful of the routine surgeries performed within major Iranian medical centers. This study was conducted to evaluate the outcomes of patients who underwent a heart transplant at Imam Khomeini Medical Center affiliated with Tehran University of Medical Sciences via examination of 1-month, 1-year, 3-year, and 5-year survival rates.

Methods: We analyzed data of 276 patients who underwent heart transplantation in two different periods, (000-2005 and 2006-2016). The 1,3 and 5 years survival rate was analyzed to show the outcome and survival rate.

Results: Overall 1, 3 and 5-years survival rate in our center was $46.6 \pm 28.1\%$, $37.8 \pm 28.8\%$, and $28.5 \pm 25.8\%$ respectively. Overall 1-year survival excluding 30 days hospital mortality was $96.7 \pm 3.3\%$. The 1,3 and 5 years survival in the first period were $14.5 \pm 2\%$, $14.5 \pm 2\%$, and $10.4 \pm 2\%$ respectively however in the second period it raised to $64.9 \pm 10.6\%$, $57.8 \pm 18\%$, and $50.4 \pm 8.6\%$ respectively. In first period overall 30 days mortality was 76.6%, although it declined to 29.6% in the second term. RV dysfunction and multiple organ failure in 38 (14.5%) patients were the most common cause of early death in our patients. CMV infection was detected in 76 (29%) patients which was the most common infection in our cases.

Conclusion: This study shows that overall 1, 3, and 5 years survival rates in our recipients are going to raise which is noteworthy despite vast variety of impediment in our course of progress.

Keywords: Iran; Heart transplant; Treatment outcome; Survival rate; Graft rejection; Registries

Introduction

Heart Failure (HF) affects over 5.7 million patients in the U.S., with 915,000 new cases occurring annually and a resultant 1,000,000 hospitalizations, which translates into an annual estimated cost of over \$30 billion dollars. Mortality with this condition is high, approximately 50% at 5 years. Heart transplantation is a lifesaving procedure for patients with end-stage heart diseases [1]. More than 29 countries have a membership of the Middle East Society for Organ Transplantation (MESOT), and collectively these countries have a population > 600 million. These include all Arab countries, Iran, Turkey, Pakistan, and countries of Central Asia [2]. The current state of heart transplantation in Middle East countries (MESOT) isn't as clear as the United States and European countries; therefore this study was conducted to demonstrate updated results of heart transplantation in our center as an active member of MESOT.

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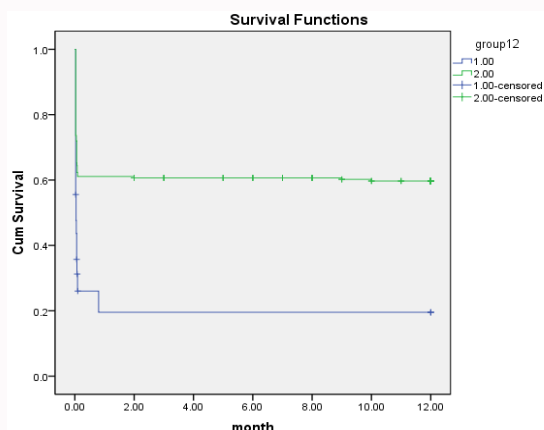


Figure 1: 1 year survival comparison including 30 days mortality (Kaplan-Meier curve).

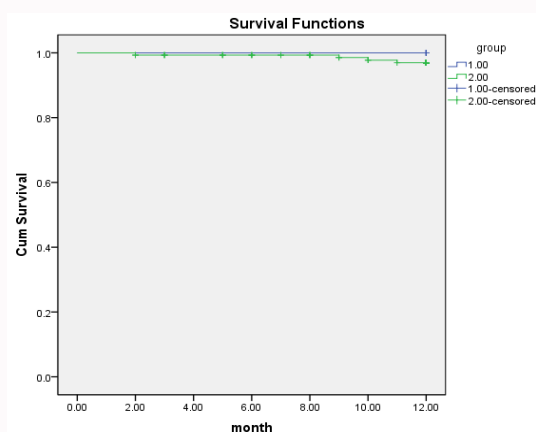


Figure 2: 1 year survival comparison excluding 30 days mortality (Kaplan-Meier curve).

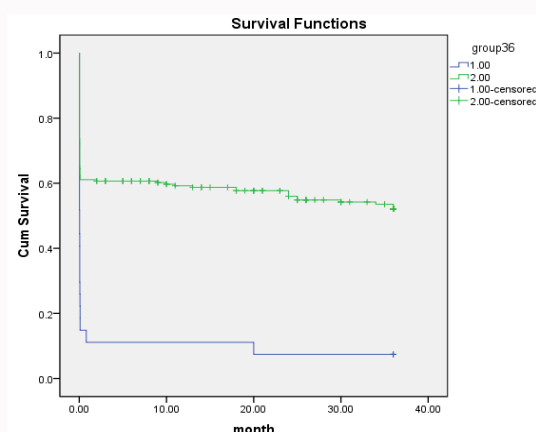


Figure 3: 3 years survival comparison (Kaplan-Meier curve).

Methods

This study was conducted between January 2000 and December 2016 on 276 heart recipients in Department of Cardiovascular Surgery, Imam Khomeini Medical Center, Tehran University of Medical Sciences to present the results of early and midterm outcomes and survival rates. Our technique of choice for heart transplantation was ortho topic biatrial between 2000 to 2005 which changed to ortho topic bicaval after that. Our strategy for long-term immuno

Number of Heart Transplantat in IKHC 2000-2015

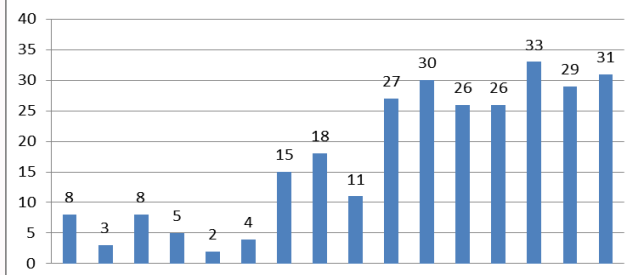


Figure 4: Number of heart transplant in IKHC 2000-2015.

Comparative 1,3 & 5 years survival in Group 1 & 2

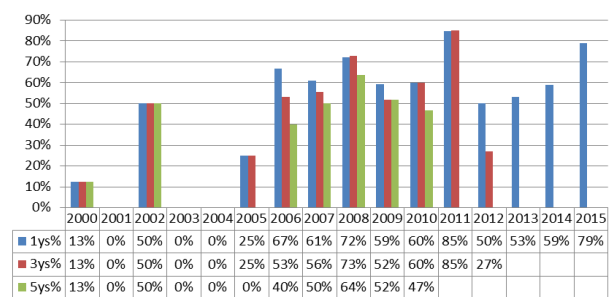


Figure 5: Comparative 1,3 & 5 years survival in Group 1 & 2.

suppression was triple therapy including steroid, a calcineurin inhibitor (Prograf or Neoral) and Mycophenolate Mofetil (Cellcept). Also, we used Antithymocyte globulin (ATG) for induction of immuno suppression. We have weekly heart transplant program, monthly selection committee meeting, weekly postoperative clinic for observation, and annual patient education symposium by speakers from transplant social work, pharmacy, rehabilitation and other transplant specialties. We also coordinate with the Ronald Reagan Hospital Heart Transplant Program at UCLA. All data were collected retrospectively on standard forms and entered into a computerized database. SPSS version 18 (SPSS, Inc., Chicago IL, USA) was used for statistical analysis. All descriptive data were expressed as a mean \pm standard deviation. A p-value < 0.05 was considered to be statistically significant. Cumulative survival was analyzed with the Kaplan-Meier actuarial method. Excluded were 13 transplants performed between January 2000 and November 2002, due to incomplete data.

Results

The mean ages of recipients and donors were 31.3 ± 14.1 and 24.6 ± 9.2 years, respectively. Recipients were female in 64 (24.4%) and male in 198 (75.6%) patients. Donors were female in 78 (29.7%) and male in 184 (70.3%) patients. Head trauma and intracranial hemorrhage were the most common cause of brain death in our donors.

According to UNOS classification, 25 (9.5%) patients were in status IA, 53 (20.2%) patients were in status IB and 184 (70.2%) patients were in status II. The most common cause of heart failure and need to transplant was dilated cardio myopathy in 168 (64.1%) patients. In 65 (24.8%) patients, they had at least one or more previous operation.

Table 1: Recipients characteristics.

Age	31.3±14.1
Sex	
Female	64 (23.1%)
Male	212 (76.8%)
Ethnicity	Asian
NYHA class	
II	104 (37.6%)
III	152 (55%)
IV	11 (3.9%)
UNOS status	
IA	25 (9%)
IB	53 (19.2%)
II	198 (71.7%)
Diabetic	73 (26.4%)
Hypertensive	89 (33.3%)
Dislipidemia	102 (38.2%)
History of cerebrovascular accident	23 (8.6%)
Preoperative mechanical ventilation	25 (9%)
Preoperative mechanical circulatory support	4(1.4%)
Chronic kidney disease	15 (5.6%)
History of cardiac surgery	65 (24.3%)
Cardiomyopathy	
Dilated	168 (62.9%)
Ischemic	98 (36.7%)
Hypertrophic	3 (1.1%)
Restrictive	2 (0.7%)
Postpartum	5 (1.8%)
Sex of donor/recipient	
Male to Male	105 (39.3%)
Male to Female	33 (12.3%)
Female to Female	31 (11.6%)
Female to Male	93 (34.8%)
Heart transplant	257 (96.2%)
Heart-Kidney	7 (2.6%)
Redo heart transplant	3 (1.1%)
Mean follow-up duration (month)	21.3±24.6

Table 2: Operative room data.

Donor ischemic time (min)	60±15
Recipient cross clamp time (min)	50±10
Recipient cardiopulmonary time (min)	95±15
Circulatory support (IABP)	15 (5.6%)

Our preferred technique of heart transplant was orthotopicbiatrial during the first six years, but we changed our procedure to orthotopicbicaval after that. Re-transplant occurred in two patients and heart-kidney in 7 (2.6%) patients. Mean ICU stay was 3.5±1 days and mean hospital stay was 13.4±4.8 days. Mean number of inotropes which was needed in ICU and operation room was 1.8±0.56; epinephrine and milrinone were the most common inotropes which

Table 3: Postoperative morbidity.

Acute renal failure	13 (4.8%)
Prolonged mechanical ventilation	24 (8.9%)
Adult respiratory distress syndrome	13 (4.8%)
Septicemia	3 (1.1%)
Stroke	3 (1.1%)
Seizure	6 (2.2%)
Posterior reversible encephalopathy syndrome	5 (1.8%)
Primary graft failure	32 (11.9%)
Isolated right ventricular failure	65 (24.3%)
Mediastinal bleeding	27 (10.1%)
Mediastinitis	3 (1.1%)
Superficial wound infection	6 (2.2%)
Leg ischemia	1 (0.3%)
Atrioventricular block	6 (2.2%)
Need to permanent pacemaker	3 (1.1%)

Table 4: Causes of readmission.

CMV infection	76 (27.5%)
Varicella Zoster infection	8 (2.8%)
Pneumonia	8(2.9%)
Urinary tract unfection	33 (12.3%)
Toxoplasmosis brain abscess	1 (0.3%)
LVEF drop (5-10%)	65 (24.3%)
LVEF drop > 10%	8 (2.9%)
Seizure	2(0.7%)
Post-transplant lymphoproliferative disease	2 (0.7%)
Calcineurin inhibitor induced renal dysfunction	11 (4.1%)
Elephantiasis NostrasVerrucosa	2 (0.7%)
Skin cancer	5 (1.8%)
Leukopenia	10 (3.7%)
Elective laparoscopic cholecystectomy	3 (1.1%)
Elective hysterectomy	2 (0.7%)
Elective pedicectomy	2 (0.7%)
Deep vein thrombosis	1 (0.3%)
Pericardial effusion	2 (0.7%)
Chronic allograft vasculopathy	7 (2.6%)

were used. IABP was required in 15 (5.7%) patients. Primary graft failure was seen in 32 (12.2%) patients, and isolated RV failure was an issue in 65 (24.8%) patients. RV dysfunction and multiple organ failure in 38 (14.5%) patients were the most common cause of early death in our patients. Atrioventricular block developed in 6 (2.2%) patients and a permanent pacemaker was needed in 3 patients. The average time of early death in our patients was 1.8±1 days. In 8 (3%) patients with stage 3 chronic kidney disease (glomerular filtration rate 30–59 ml/min) before the operation, hemodialysis was needed after the operation. Calcineurin inhibitor-associated neuropathy (posterior reversible encephalopathy syndrome) was seen in 6 (2.2%) patients. Acute calcineurin inhibitor-induced renal dysfunction was detected in 11 (4.19%) patients whom reversed with dose reduction and in 3 of them, temporary hemodialysis was needed. Skin cancer was seen in 5 (1.9%) patients. Post-transplant lympho proliferative

disease (PTLD) was observed in 2 (0.7%) patients, and chronic allograft vasculopathy eligible for re-transplantation was detected in 7 (2.6%) patients.

CMV infection was recognized in 76 (29%) patients which was the most common infection in our cases. Pneumonia in 8 (3%) and urinary tract infections in 53 (19.2%) patients were among less frequent after CMV infection. Varicella zoster infection was seen in 8 (3%) patients, with one infection being complicated by Ramsay Hunt syndrome. Increased donor age had a significant negative impact on survival ($p=0.005$); the lowest mortality rate was detected in recipients of donors less than 25 years old. Among the patients who died, 28% had the same sex as the donor, whereas 72% of survivors had the same sex as the donor ($p\text{-value} < 0.05$). Recipients UNOS status was significantly related to 1-month and 1-year survival rate ($p=0.005$). Overall mean 1, 3 and 5-years survival rate in our center was $46.6\pm28.1\%$, $37.8\pm28.8\%$, and $28.5\pm25.8\%$ respectively, although overall 1-year survival excluding 30 days hospital mortality was $96.7\pm3.3\%$. The 1,3 and 5 years survival in the first period (2000-2005) was $14.5\pm2\%$, $14.5\pm2\%$, and $10.4\pm2\%$ respectively however in the second period (2006-2016) it raised to $64.9\pm10.6\%$, $57.8\pm18\%$, and $50.4\pm8.6\%$ respectively (Figure 1-3). In first period overall 30 days mortality was 76.6%, although it declined to 29.6% in the second period.

Discussion

Cardiac transplants are performed sporadically or not at all in the majority of countries in the Middle East. While the North American continent and Europe account for only 17% of the world population, they donate and receive over 95% of the heart transplants performed worldwide [3]. In this study, we sought to report and evaluate the immediate and mid-term outcomes of our 15 years experience in adult heart transplant (Figure 4).

Examination of early mortality after heart transplant documented in the Registry reveals that 66% of the deaths that occur in the first 30 days after transplant are due to graft failure and multi-organ dysfunction [4]. In our study, primary graft failure was seen in 32 (12.2%) patients, and isolated RV failure was an issue in 65 (24.8%) patients. Primary graft failure is fairly common early after a heart transplant, and agreed risk factors for this entity include donor, recipient, and surgical procedural factors. We believe that quality of donor management is the most determinative factor in early outcome after a heart transplant. Lacks of experienced medical staff and facility in the aerial transfer of donor from small towns have marked negative impact on donor management and outcome.

Right ventricular dysfunction and pulmonary hypertension have long been considered problematic complications in heart transplantation. Registry data from the International Society of Heart and Lung Transplantation show that despite advances in perioperative management, right ventricular dysfunction accounts for 50% of all cardiac complications and 19% of all early deaths in patients after heart transplantation [5]. RV dysfunction and multiple organ failure in 38 (14.5%) patients were the most common cause of premature death in our patients. Clinical experience and the literature certainly suggest that a significant factor in the successful management of RV failure is recipient selection. In our patients, most commonly it was the result of right ventricle after load mismatch.

The risk of early mortality after heart transplantation from donors older than 40 years is increased nearly threefold and is multi

factorial in nature. There is evidence in the literature to suggest that this increase may be due to native CAD in the donor [6]. In our study, increased donor age had a significant negative impact on 1-years survival ($p=0.005$); the lowest mortality rate was detected in recipients of donors less than 25 years old ($p < 0.05$). Several early studies identified female donor sex as an independent predictor of recipient mortality after orthopedic heart transplant [7-10]. Further investigations, however, highlighted the importance of donor: recipient sex mismatch, with a demonstration of reduced short- and long-term survival in male recipients of female allografts [11-14].

Among our recipients who died, 28% had the same sex as the donor, whereas 72% of survivors had the same sex as the donor ($p\text{-value} < 0.05$). In particular, male recipients of female allografts had reduced overall survival while female recipients of male allografts had the best early and mid-term outcomes.

Overall mean 1, 3 and 5-years survival rate in our center was $46.6\pm28.1\%$, $37.8\pm28.8\%$, and $28.5\pm25.8\%$ respectively, although overall 1-year survival excluding 30 days hospital mortality was $96.7\pm3.3\%$. The 1,3 and 5 years survival in the first period (2000-2005) was $14.5\pm2\%$, $14.5\pm2\%$, and $10.4\pm2\%$ respectively however in the second period (2006-2016) it raised to $64.9\pm10.6\%$, $57.8\pm18\%$, and $50.4\pm8.6\%$ respectively (Figure 1-3). In the first period overall 30 days mortality was 76.6%, although it declined to 29.6% in the second period. Maximum and mean follow-up time was 13 and 3.9 ± 2.9 years respectively.

We think that improvement of early and mid-term outcomes in our center since 2006 is the result of a more coordinated multidisciplinary team management before and after transplant. We have weekly heart transplant program, monthly selection committee meeting, weekly postoperative clinic and observation and annual patient education symposium by speakers from transplant social work, pharmacy, rehabilitation and other transplant specialties. Our heart transplant program has the support of the UCLA Ronald Reagan Hospital Heart Transplant Program.

We believe that our more standardized pre/postoperative management and follow-up care, earlier detection of rejection, infection and better management of chronic allograft vasculopathy and continuous communication with well-known heart transplant centers around the world are leading factors in the dramatic improvement of our results. However we have still many limitations in our way; very limited access to assist devices, unavailable new tools in detection of rejection such as Cylex (Immuknow test), Allomap test and intermittent fluctuation in the availability of immunosuppressive drugs are noticeable. As illustrated in (Figure 5), the progressive improvement in early post-transplant survival after 2005 has benefited heart transplant recipients; a finding described as the "era effect" in heart transplantation. This outstanding progress in early and mid-term outcome is the result of better recipient selection and preparation, a better technique of transplantation, shorter cross clamp and ischemic time, more organized postoperative care and fastidious follow-up after discharge from the hospital. We attest that the early and mid-term results in our center are below the worldwide standard but both are improving, and among Middle East countries, we have attained an impressive level of care. The results, showing 10 or more years survival in our patients, although not optimal, are improving and we plan to report on subsequent follow-up in the near future.

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