Original Article

Heart Transplantation in Singapore

Cumaraswamy Sivathasan,[1] *FRCS (Eng), FRCS (Edin), FAMS*

Abstract

Introduction: The status of heart transplantation in Singapore is reviewed in this article. Materials and Methods: The database of 40 consecutive heart transplantations from July 1990 through December 2007 is reviewed retrospectively. The data is compared with the 2008 registry data of the International Society for Heart and Lung Transplantation (ISHLT). Results: The average age of recipients was 45.3 years. Ages ranged from 14 to 64 years. Ischaemic cardiomyopathy (52.5%) and dilated cardiomyopathy (42.5%) were the major indications. From 1990 to 1999, 50% of the donors sustained brain death from road traffic accident, 25% from cerebrovascular accident and 25% from falling from height, whereas the cause of brain death in the donors from 2000 to 2007 was 33%, 47% and 9.5%, respectively. The average donor age increased from 28.3 to 38.1 years. The significant morbidities in the recipients were hypertension, cytomegalovirus (CMV) infection, cardiac allograft vasculopathy and renal dysfunction. Thirty-two required treatment for hypertension. 67.5% developed CMV disease requiring treatment. Cardiac allograft vasculopathy was diagnosed in 10. Rising creatinine levels reaching over 2.5 mg/dL was seen in 7. Three required renal dialysis. Epstein-Barr virus related lympho proliferative disorder occurred in 2 patients. One patient developed adenocarcinoma of stomach. The 30-day mortality was 10% and half life was 10 years. Cardiac allograft vasculopathy and sepsis caused 41.7% of mortality each. 11.7% of the mortality was due to cerebrovascular accident. Conclusion: The status of heart transplantation in Singapore is comparable to the ISHLT registry data. Transplant provides excellent early survival of 80%; however, the expected half life is around 10 years after cardiac transplantation. The late mortality is mainly caused by cardiac allograft vasculopathy (CAV) and renal failure. More effort and research needs to be directed towards these issues to improve the long-term results.

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Status of Heart Transplantation in Singapore

The introduction of cyclosporine as an immunosuppressant in the early 1980s revolutionised the results of organ transplantation and made heart transplantation an accepted therapeutic modality for end-stage heart failure. The 2008 Registry Report of The International Society for Heart and Lung Transplantation (ISHLT) received 80,106 reports of heart transplants between 1982 and 30 June 2007.[1] However, heart transplants remain a challenge in Asia. Although 60% of the world's population lives in Asia, only about 4% of heart transplantations are performed in Asia.[2] North America which has 5% of the world's population performs 71% of transplantations and Europe with 12% of the world's population contributed to 25% of the heart transplants performed.[3] The number of cardiac donors in the United States (US) in year 2000 was 8 per million population (pmp), whereas in Asia it was 0.03 pmp.[4]

The distribution of heart transplantations done in South East Asia from 1987 to 2004 is illustrated in Table 1.[3] The paucity of heart transplantation in Asia can be attributed to various factors such as the lack of infrastructure, lack of funding, lack of trained personnel, facilities, low priority compared to other health problems, diverse cultural barriers and beliefs, etc.

The following is a review of heart transplantations performed in Singapore. The programme was established in 1990. Between July 1990 and December 2007, 40 heart

[1] Heart and Lung Transplantation Programme, National Heart Centre, Singapore
Address for Correspondence: Dr C Sivathasan, National Heart Centre, Department of Cardiothoracic Surgery, Mistri Wing, 17 Third Hospital Avenue Singapore 168752.
Email: c_sivathasan@nhc.com.sg

Table 1. The Distribution of Heart Transplantation Done in South East Asia from 1987 to 2004

Country	%
Taiwan	51
Korea	22
Thailand	11
China	11
Japan	2
Singapore	2
Malaysia	1

Table 3. The Comparison of cause of Brain Death in Cardiac Donors During 1990-2000 and 2000-2007

	1999-1999	2000-2007
Number of donors	20	21
Road traffic accident	10 (50%)	7 (33.3%)
Cerebrovascular accident	5 (25%)	10 (47.1%)
Fall from heights	5 (25%)	2 (9.5%)
Status asthmaticus	0	2 (9.5%)

transplantations were performed. The demographic data is given in Table 2.

Aetiology of End-stage Heart Failure

The cause of end-stage heart failure in 21 (52.5%) recipients was ischaemic cardiomyopathy. In 17 (42.5%), the aetiology was dilated cardiomyopathy. One had adriamycin-induced cardiomyopathy following treatment of osteosarcoma. Another patient underwent heart transplantation due to recurrent aorto mitral annular dehiscence following repeated prosthetic valve replacements, due to aortitis.

Donor Statistics

Forty-one donor hearts were utilised during the period of study. One recipient received a second heart transplant 8 days after the first heart transplant due to graft failure.

Seventeen (41.4%) cardiac donors sustained cerebrovascular accidents. Fifteen (36.5%) suffered brain death from head injuries due to road traffic accidents. Seven (17%) from falling from heights while 2 (4.8%) sustained hypoxic brain death from status asthmaticus.

During the years between 1990 and 1999, there were 17 male donors and 3 female donors giving a ratio of 5.6:1. The average age of these donors was 28.3 years. During the second time period between 2000 and 2007, there were 13 males and 8 females giving a ratio of 1.6:1. The average age of these donors was 38.1 years (Table 3).

Table 2. Demography of Heart Transplant Recipients in Singapore (July 1990-December 2007)

Number of recipients	40
Males	34
Females	6
Male-to-female ratio	5.6:1
Age range (y)	14 to 64
Average age (y)	45.3

Table 4 illustrates the annual statistics of donors for heart transplantation between 2000 and 2007. Table 5 illustrates the statistics of patients referred for transplant.

Immunosuppression

Our current protocol consists of cyclosporine, prednisolone and mycophenolate mofetil along with basiliximab as induction therapy. The steroid is withdrawn in the majority of patients from 6 months onwards after transplant. In patients who develop renal dysfunction, an attempt is made to reduce the dose of cyclosporine and increase the dose of mycophenolate. In selected patients, proliferation signal inhibitor (mTOR inhibitor) is substituted for cyclosporine.

Morbidity

The significant morbidities in our experience were hypertension, cytomegalovirus infection, cardiac allograft vasculopathy and renal dysfunction. Thirty-two of the 40 patients required treatment for hypertension. The absolute number of patients who developed hyperlipidaemia is not available as currently all the patients are prescribed statin as prophylaxis.

Cytomegalovirus (CMV) Infection

All the transplant recipients had positive CMV serology prior to the transplant except for a 14-year-old recipient. All the donors too had positive serology for CMV, except for 2 donors. Twenty-seven recipients (67.5%) developed CMV disease that required treatment. We have used various forms of prophylaxis as well as pre-emptive treatment for CMV in this series.

Cardiac Allograft Vasculopathy (CAV)

CAV was diagnosed in 10 patients. In 2 patients who died within 1 year after heart transplantation, the diagnosis was made at autopsy. CAV was diagnosed in 8 patients during regular surveillance follow-up. We have been using sestamibi (MIBI) scanning annually along with protocol based coronary angiogram in order to detect vasculopathy. In our experience, radionuclear perfusion (MIBI) scan has not proven to be sensitive to identify myocardial ischaemia

Table 4. Annual Statistics of Donors for Heart Transplantation for Year 2000-2007

	Total Calls	Unsuitable	No suitable recipients	Suitable but no consent (MTERA)	Suitable with consent (MTERA)	Suitable - HOTA	Transplanted
2007	25	18	4	0	0	7	3
2006	30	16	4	1	1	5	6
2005	21	13	3	0	0	3	3
2004	17	6	5	0	2	2	4
2003	10	0	1	1	0	N.A.	0
2002	15	3	1	3	2	N.A.	2* (re-transplanted)
2001	25	6	2	6	2	N.A.	2
2000	22	10	1	2	1	N.A.	1

HOTA: Human Organ Transplant Act; MTERA: Medical (Therapy, Education and Research) Act; N.A.: Heart donation was not included under HOTA prior to 2004

* Recipient received second heart after graft failure of the first donor heart

Table 5. Status of Transplant Referral

Status of heart transplant referal	2001	2002	2003	2004	2005	2006	2007
No. of referrals	25	36	21	27	17	23	33
No. with no contraindications	22	35	21	20	13	17	31
No. rejected	3	1	0	1	4	6	2
No. refused transplant	4	0	2	0	2	3	2
No. placed on waiting list	6	6	5	0	1	4	9
No. transplanted	2	1	0	4	3	6	4
No. died while on waiting list	1	3	3	3	0	0	0
No. removed from waiting list in view of clinical improvement	5	0	3	0	1	2	0
No. removed from list for other reasons	0	0	0	0	0	3	1

Table 6. The Diagnosis of Cardiac Allograft Vasculopathy (CAV) in Relation to Time after Transplantation

Time period after transplantation	No. of recipients diagnosed with CAV
<1 year	2
3 years	2
4 years	1
9 years	2
10 years	1
11 years	2

in recipients. Two patients had false positive scans and the coronary angiogram did not show CAV. Four other patients who had angiographic evidence of CAV had negative MIBI scans. CAV was detected in 8 patients with coronary angiography. The diagnosis of CAV in relation to the time after transplantation is shown in Table 6. Three of these patients underwent percutaneous intervention with stent placements. Altogether 7 of them died due to CAV.

Renal Impairment

Seven patients showed progressive rising creatinine levels reaching over 2.5 mg/dL. The Kaplan-Meier curve for freedom from severe renal impairment as defined as creatinine level over 2.5 mg/dL is shown in Figure 1. Three patients progressed to renal failure requiring dialysis.

Malignancy

Three patients presented with neoplasm. Two developed Epstein-Barr virus related lympho proliferative disorder (LPD). One of them presented with LPD involving the stomach, infiltrating into the small intestine, 5 years after his transplantation. He underwent surgical resection and reduction in immunosuppression resulting in a complete recovery. He remains well 17 years after his transplantation. The second patient developed cervical, mediastinal and

Table 7. Cause of Mortality

Cause	Mortality
Cardiac allograft vasculopathy	7 (41.7%)
Sepsis	7 (41.7%)
Cerebrovascular accident	2 (11.7%)
Pulmonary embolism	1 (5.8%)

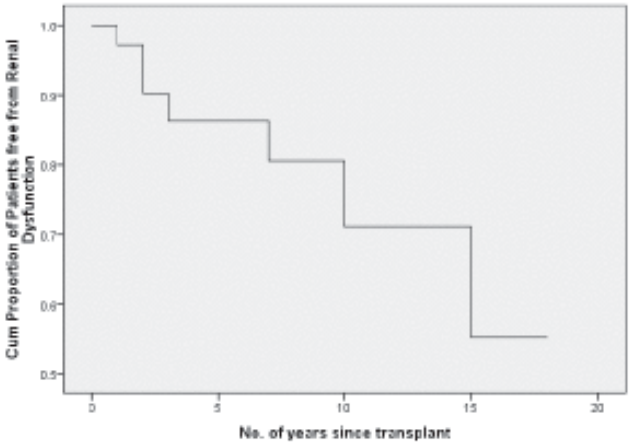

Fig. 1. Kaplan-Meier curve for freedom from renal dysfunction.
Based on the 40 patients with heart transplant, the above graph shows the cumulative proportion of patients free from renal dysfunction at the respective stage (year) of their heart transplant using survival analysis.
*Cumulative proportion indicates the proportion of patients free from renal dysfunction given that he/she has survived the previous years without onset.
Renal dysfunction defined as serum creatinine >2.5 mg/dL.

abdominal lymphadenopathy due to LPD, 13 years after his transplantation. He was treated with various combinations of immunosuppression and chemotherapy. He died a year later from CAV. The third patient developed adenocarcinoma of the stomach, 5 years after receiving his heart. He underwent gastrectomy and remained tumour free. Two years later he died of CAV.

Mortality

The 30-day mortality was 4 (10%). Two died due to sepsis, 1 due to graft failure and the fourth patient died due to cerebrovascular accident. Seventeen deaths occurred in this series. The survival curve is illustrated in Figure 2. The cause of mortality is given in Table 7. The effect of severe renal dysfunction on mortality is shown in Figure 3.

Discussion

The Registry of the ISHLT has been collecting data on heart transplantations since 1982.[5] The registry is construed on data submitted to the society. Hence, it may not reflect the true status of numbers reported; but the registry provides valuable data on the current practice and status of heart transplantation in the international scene. Hence in this

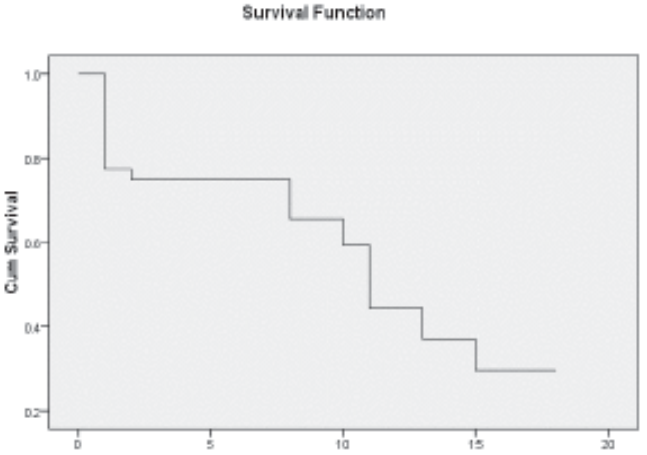

Fig. 2. Kaplan-Meier survival for 40 heart transplant patients performed between 1990 and 2007.

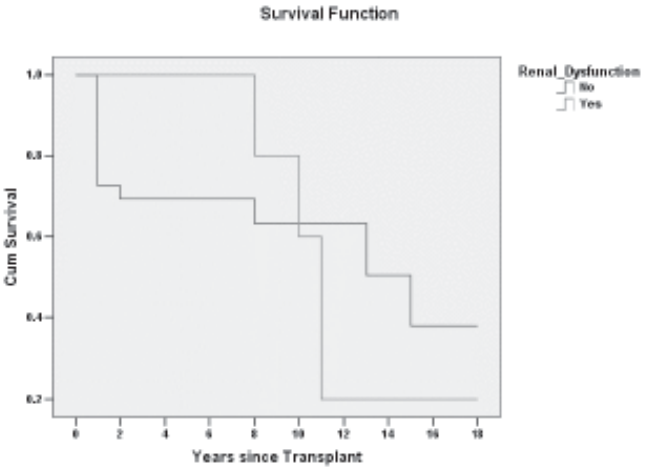

Fig. 3. Kaplan-Meier survival for 40 heart transplant patients performed between 1990 and 2007, with and without severe renal dysfunction (creatinine >2.5 mg/dL). $P = 0.9192$ [Log Rank (Mantel-Cox)].

discussion, Singapore's experience will be discussed in relation to the 2008 Report of the Registry.

According to the registry, 42% of the reporting centres averaged less than 10 procedures per year and these centres accounted for approximately 13% of all heart transplantations performed. Furthermore, 18% of active centres averaged only 4 or less procedures per year. Since the inclusion of heart under the HOTA in 2004, an average of 4 transplants per year has been done in Singapore between 2004 and 2007, similar to 18% of the international transplant centres.[6]

The average age of current donors in the International Registry is 30 years old compared to 38.1 years old since year 2000 in Singapore. It is also relevant to note that the cause of brain death in donors in Singapore has changed during the 2 decades of heart transplantation. During the period between 1990 and 1999, the cause of brain death due

to road traffic accidents (RTAs) was 50% (Table 3) compared to 33.3% between 2000 and 2007. Brain death due to cerebrovascular accident increased from 25% to 47.1%. The average age of donors increased from 28.3 to 38.1 years old. The male-to-female ratio of 5.6:1 changed to 1.6:1, with more female donors. This seems to be keeping in with the fall in RTA fatality rate from 5.63 per 100,000 population in 1998 to 4.68 in 2007.[7]

With the drop in RTA-related donor brain deaths, more CVA-related donors were utilised in the second group between 2000 and 2007. As the CVA other than sub-arachnoid haemorrhage occurs more in the older age group, the average donor age in the period from year 2000 was higher.

After the inclusion of the heart in the HOTA Act of 2004 as shown in Table 4, 4 suitable donor hearts were not utilised due to unavailability of suitable recipients at the point of donor availability.[5] This was due to either ABO incompatibility or due to significant mismatch in weight between the donor and the available recipient. From Table 5, it is apparent that the number of new suitable heart transplant candidates added to the waiting list is small at any time. The majority of the patients referred for transplant were managed adequately by optimising medical therapy. Greater utilisation of available donor hearts can only be achieved by increasing the number of patients on the waiting list.

Ischaemic cardiomyopathy was the cause in 35% of heart transplants, dilated cardiomyopathy in 44% and others formed 21%, in the international registry between 2004 and 2007. Ischaemic cardiomyopathy and dilated cardio-myopathy were the indications in 52.5% and 42.5% of cardiac transplants, respectively, in Singapore's experience.

CAV is the leading cause of death after heart transplantation.[8] It is thought to be due to chronic rejection which occurs within months to years after transplantation. In our series, CAV was detected within a year after transplantation to 11 years. Immunologic and non-immunologic endothelial damage initiates pathologic remodelling, resulting in diffuse myointimal proliferation and the narrowing of distal coronary arteries leading to ischaemia, infarction and allograft failure. Non-immunologic risk factors include diabetes smoking, hyperlipidaemia, hypertension, allograft ischaemia during transplantation and CMV infection.[9,10]

There is no proven treatment for CAV, although mTOR inhibitors and mycophenolate have been shown to reduce intimal proliferation.[10-12] Although angioplasty may be performed when focal ischaemia is demonstrable, angioplasty and coronary artery bypass grafting are not effective in many patients because of the diffuse nature of the disease. As many as 50% of heart transplant recipients have been reported to have angiographically confirmed CAV by 5 years after transplantation.[5] In our series, 5 out of 30 who survived over 5 years after transplantation were diagnosed with CAV.

Progressive renal dysfunction is a major morbidity after transplantation mainly due to calcinurin inhibitors. In the ISHLT registry, the cumulative incidence of creatinine over 2.5 mg/dL, within 10 years of transplant is 8.2% while 4.9% underwent renal transplantation. In our series (Fig. 1), 70% of patients were free from severe renal dysfunction at 10 years. Three (7.5%) required dialysis. Freedom from severe renal dysfunction appears to have resulted in superior survival after transplantation. The median survival time for patients who did not suffer renal dysfunction was 14.04 years versus 10.25 years for those with renal dysfunction (Fig. 3). However, the difference in survival did not reach statistical significance. The *P* value by Log Rank (Mantel-Cox) was 0.9192. This could be due to the relatively small number of patients with renal dysfunction.

The survival rate in this series is comparable to the ISHLT data. The half life – the time at which 50% of those transplanted remain alive – was 10 years and is similar to the ISHLT registry. Acute rejection was not a cause of mortality in our series. In the ISHLT registry from 31 to 365 days, non CMV infection was the cause in about 33% of the mortality, 12% was due to acute rejection. After 5 years, CAV accounted for 33% of deaths. Malignancy caused 23% of deaths. Malignancy was not a direct cause of mortality in our series. CAV accounted for 41.7% of the total mortality in our series.

Conclusion

Cardiac transplantation is the accepted therapy for patients with end-stage heart failure. It improves survival and the quality of life. Current regimes of immunosuppression provide excellent 1-year rates of patient survival of 80%; however, the expected half life is around 10 years. The late mortality is caused by CAV, renal failure and increased occurrence of tumours.[5] More effort and research needs to be directed towards these issues to improve the long-term results of heart transplantation.

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