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HEART TRANSPLANT IN INDIA: A SINGLE-CENTRE STUDY

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INTRODUCTION

Despite advances in pharmacological and device treatment of chronic heart failure, long-term morbidity and mortality remain unacceptably high. The 5-year mortality rate for patients with symptomatic heart failure approaches 50% and may be as high as 80% at 1 year for end-stage patients. Since the first successful human heart transplant surgery in 1967 by Christiaan Barnard, the field of heart transplantation has evolved from a novel investigational pursuit to an established therapy for the treatment of end-stage heart failure. Through the work of many innovative surgeons and scientists, heart transplantation has become commonplace.

Pivotal inventions such as cardiopulmonary bypass and the refining of anastomotic techniques made heart transplantation technically possible. The majority of patients with so-called “end-stage” heart failure are characterized by advanced structural heart disease and profound symptoms of heart failure at rest or upon minimal exertion despite maximal guideline-directed medical treatment, and typically fall into stage D of the ABCD classification of the American College of Cardiology (ACC)/American Heart Association(AHA), and class III–IV of the New York Heart Association (NYHA) functional classification.

Selected patients with refractory AHA Stage D or NYHA class III-IV heart failure and poor prognosis are usually referred to a cardiac transplantation center for evaluation and transplant consideration. The most common indications for evaluation for transplantation include refractory cardiogenic shock requiring continuous intravenous inotropic support or mechanical support, refractory

NYHA class III-IV/AHA stage D heart failure, reduced exercise capacity (as defined by peak VO2 below a certain threshold), recurrent arrhythmias with the risk of hemodynamic compromise, and severe untreatable angina and end-stage congenital heart disease.

The heart transplant waiting list is a national computerized list that is managed and maintained by the United Network of Organ Sharing (UNOS).In general, organ donors are diagnosed with brain Death. Any patient with irreversible brain injury and preserved end-organ perfusion and function merits organ donation consideration. All potential donors are rigorously screened for clear contraindications to organ donation, such as active cancer and prohibitive infectious disease.

Standard laboratory values, EKG, and chest x-ray are obtained. All potential cardiac donors require an echocardiogram, with a transthoracic study usually being sufficient. Similarly, right heart

catheterization may be obtained Coronary angiogram is obtained selectively Meticulous preoperative management of the donor is critical for successful organ recovery and post-implant function.

The biatrial method represents the original operative technique for heart transplantation and was widely utilized in the 1980s. This operation has largely been replaced by the bicaval method but it remains useful in certain surgical circumstances.

Most important in determining post-transplant survival is the ability of the newly transplanted heart to generate sufficient cardiac output in the early hours and days following transplantation Developments in immunosuppression in the last 30 years have made heart transplantation a definitive option for end-stage heart failure, with 1-year survival of 90%. While there is no accepted universal protocol for immunosuppression, common standard practice consists of "triple" therapy consisting of a calcineurin inhibitor, an anti-proliferative agent and corticosteroids Future improvements in treatments for heart failure and subsequent heart transplants will rely on improving mechanical circulatory devices, immunosuppression regimens, and ways to increase donor availability. Despite advances in the treatment of heart failure, the prognosis of patients with advanced (stage D) heart failure remains poor, with a 5-year survival of only 20% [1]. In this population, heart transplantation is the most effective therapy for prolonging survival. Other indications for heart transplantation include non revascularizable coronary artery disease with intractable angina, malignant ventricular arrhythmias and primary cardiac tumors [2]. In the current era, the median life expectancy after heart transplantation is around 11 years, and the conditional median survival among transplant recipients surviving the first year is 14 years [3].

While better patient selection, donor heart preservation techniques, immunosuppression and cytomegalovirus prophylaxis have contributed to improvements insurvival over the past three decades, the majority of the gains have been in the first post-transplant year. Cardiac allograft vasculopathy, nonskin malignancies, rejection and infections, continue to limit long-term survival after heart transplantation .Christiaan N. Barnard, MD (Nov. 8, 1922–Sept. 2, 2001), performed the first human-to-human heart transplant on Dec. 3, 1967, at Groote Schuur Hospital in Cape Town, South Africa [4].On 17 February 1968, Bombay surgeon Prafulla Kumar Sen transplanted the heart of a twenty-yearold woman into a twenty-seven-year-old shepherd suffering from chronic, progressive cardiomyopathy.Although the recipient died within three hours(5) His team attempted only two transplants; no one in India tried again for twentyfive years. Cardiac transplantation in India was not possible till June 1994 because the law did not recognize brain death. However, after the passing of the Transplantation of Human Organs Bill, this major hurdle was removed and the first successful cardiac transplant in India became possible. The first successful heart transplant in India was done at the All India Institute of Medical Sciences (AIIMS)(6).Improved coordination between donation, retrieval and transplantation has led to a 10-fold increase in heart transplantations in India since 2016. There have been nearly 300 heart transplantations across India in two years, according to data provided by the National Organ and Tissue Transplantation Organisation (NOTTO) the national coordinating agency for cadaveric organ donation, compared to about 350 between 2015 and 1994 when the first heart transplantation was done in India New Delhi on August 3, 1994 (7). South India is far ahead than north India in heart and other organ donation and transplantation. Today, heart transplantation is performed worldwide and has proven safe and reproducible. By June 2012, the International Society for Heart and Lung Transplantation (ISHLT) registry recorded the total number of heart transplants as 111,068 worldwide with a mean survival of more than 11 years [8].End-stage congestive heart failure patients appear in New York Heart Association (NYHA) class III or class IV heart failure. About 45 % of diagnoses are idiopathic and ischemic cardiomyopathies and the remaining ones are valvular and congenital diseases. When these patients become refractory to maximal medical therapy, they are evaluated for heart transplant therapy. In the United States, solid organ transplantation is regulated, audited and facilitated by the government. The United Network of Organ Sharing (UNOS) is the national organization that maintains organ transplant waiting lists and allocates identified donor organs. The acceptable cold ischemia time (the time from harvest to recipient implantation) for cardiac transplantation is

approximately 4 hours. Prolonged ischemic time has been shown to be significant risk factor for mortality after cardiac transplantation, especially when coupled with other risk factors, such as older donor age. In the first two decades of heart transplant, the upper limit of donor age was 35 years, but older donors are now used frequently, with an age up to 60 years considered safe by most centers [9].

The two most common surgical approaches for the implantation of the donor heart are the biatrial and the bicaval anastomoses. The biatrial anastomosis technique has long enjoyed the reputation of being simple, safe and reproducible. It consists of four suture lines: left atrium, pulmonary artery, aorta, and right atrium. The bicaval anastomosis technique was introduced in the early 1990swith the intention to reduce right the atrial size to minimize distortion of the recipient heart, to preserve the atrial conduction pathways, and to decrease tricuspid regurgitation. In this alternative procedure, there are five anastomoses: left atrium, pulmonary artery, aorta, inferior vena cava, and the superior vena cava. Although there has been no prospective trial to establish the superiority of either technique, the bicaval technique is now being done most often in the United States, primarily because it appears to decrease the need for permanent pacemakers in transplanted recipients(10-12). Some surgeons have become increasingly interested in techniques to minimize subsequent tricuspid regurgitation and have described tricuspid annuloplasty done simultaneously with the transplant surgery(13).

METHODOLOGY

This study is a retrospective-prospective study, approved by the Ethics Committee of AIIMS, which compiled data on Heart Transplant done at AIIMS starting from August 3, 1994, till July 2019. Data available from hospital records and from interviews with the surgeons and cardiologists were collated. Analysis of results of survival, complications, change of protocols over time was analysed.

Study Design: Descriptive

Place of Study: Patients will be recruited in the study at All India Institute of Medical Sciences (AIIMS), New Delhi, Department of Cardiology and cardiothoracic vascular surgery from outpatient and inpatient settings.

Study Population: End-stage heart failure patients who have undergone through heart transplant in AIIMS New Delhi and other new patients during the study period.

Number of patients:

To conduct this study, we included all the patients who had undergone heart transplantation from 1994 to 2019.

Inclusion Criteria:

Subjects: End-stage heart failure patient who has undergone heart transplantation.

Exclusion Criteria:

1) Patients whose data is not available.
2) Patients who refused to participate in the study.

Heart transplant protocol

Preoperative evaluation

This is similar to the protocols followed the world over with evaluation of the functions of all systems, including liver and kidneys, samples for microbiological surveillance and cultures from different sites, serologies to demonstrate Cytomegalovirus (CMV), Hepatitis B and C, and HIV infection. We have also added a non-contrast computerized tomography scan of the brain, chest, and abdomen to rule out any abnormalities, and especially evidence of Tuberculosis. We actively look for reversible causes of respiratory and cardiac causes of dyspnea. Dental evaluation and treatment are done for all patients.

Immunosuppression

In the preoperative period, oral cyclosporine in a dose of 3 mg/kg and mycophenolate mofetil in a dose of 10 mg/kg are given along with other premedication. In some of the recent patients, we have

switched to tacrolimus instead of cyclosporine as standard therapy because the occurrence of rejections had increased with cyclosporine. It is also difficult to maintain therapeutic levels of cyclosporine in most of patients with the available generic preparations of cyclosporine in the market. We have also switched to mycophenolate mofetil from azathioprine, which is used in the initial phases of the program.

We used methylprednisolone 500 mg intravenously at the time of release of the aortic cross clamp and then 8 hourly to complete a total of three doses, then 1 mg/kg/day intravenously divided into two doses till the target cyclosporine/tacrolimus levels were achieved. After the first biopsy (7–10 days), oral prednisolone is given in a 1 mg/kg/day dose. Prednisolone is tapered on a weekly basis in otherwise asymptomatic patients at a rate of 5 mg/week till a dose of 5 mg/day is achieved. This dose of prednisolone is continued. Cyclosporine is started orally on postoperative day 1 in a dose of 2-3 mg/kg/day in two divided doses to achieve a target trough level of 300–350 ng/ml. The following levels are maintained: <6 weeks, 300–350 ng/ml; 6 weeks– 3 months,250–300 ng/ml; 3–6 months, 200–250 ng/ml; and >6 months, 200 ng/ml. Patients who suffered one episode of rejection were switched over to tacrolimus. The following levels were maintained: <2 months, 10–15 ng/ml; 2–6 months, 8–12 ng/ml, and >6 months, 5–10 ng/ml. The dose of mycophenolate mofetil was modified so as to maintain total leukocyte count in the range of 5000–7000/µl. All patients underwent a heart transplant as per the institute's protocol.

Prophylaxis

Bacterial prophylaxis is provided with intravenous (IV)Ceftazidime and Teicoplanin for 48–72 h. Oral valganciclovir 900 mg once daily is used to prevent CMV infection. Oral voriconazole in a dose of 3 mg/kg (200 mg) twice daily is used for fungal prophylaxis. Oral cotrimoxazole (trimethoprim 160 mg and sulfamethoxazole 800 mg) once daily prevents against *Toxoplasma gondii and Pneumocystis jirovecii infection*.

Post-transplantation

Follow-upschedule

After discharge from the hospital, recipients are followed up every week, till 1 month post-transplant, then every 15 days, for 6 months post-transplant; then every month, for 1 year post-transplant; and then every 3 months thereafter.

Biopsyprotocol

First biopsy is done within 7-10 of transplant, then every month for 1 year, and then every year.

Rejectionprotocol

Cell-mediated rejection

Methylprednisolone intravenously 20 mg/kg (up to a maximum of 1 g/day) divided into two equal doses for 3 days, then 1 mg/kg/day. Patients not responding till 1 week after will be given rabbit antithymocyte globulin (ATG) in a dose of1.5 mg/kg/day for duration of 7–10 days.

Antibody-mediated rejection

Methylprednisolone intravenously 20 mg/kg (up to a maximum of 1 g/day) divided into two equal doses for 3 days, then 1 mg/kg/day. If there is no improvement in 1 week or the patient's clinical condition, rituximab is administered intravenously in a dose of 500 mg. The patient is premedicated with IV promethazine (50 mg), hydrocortisone (100 mg), and paracetamol (1 gram) before giving rituximab. Plasmapheresis is done on alternate days with administration of IV immunoglobulin (IVIg) in a dose of 0.5 mg/kg, after every cycle of plasmapheresis. With each plasmapheresis,15 ml/kg of fresh frozen plasma and 4 ml/kg of 20% albumin are exchanged with plasma. Five such cycles will be done, and the patient is reassessed for any further intervention.

Statistical Analysis:

Continuous variables will be described by mean and standard deviation categorical variables will be described using frequency tables with proportions. Quantitative data will be analysed by application of Student t t-test / Mann-Whitney test. The qualitative data will be analyzed by chi-square test / Fisher test, whichever is applicable (p value <0.05 as significant). Other appropriate statistical analysis will be done as indicated**.**

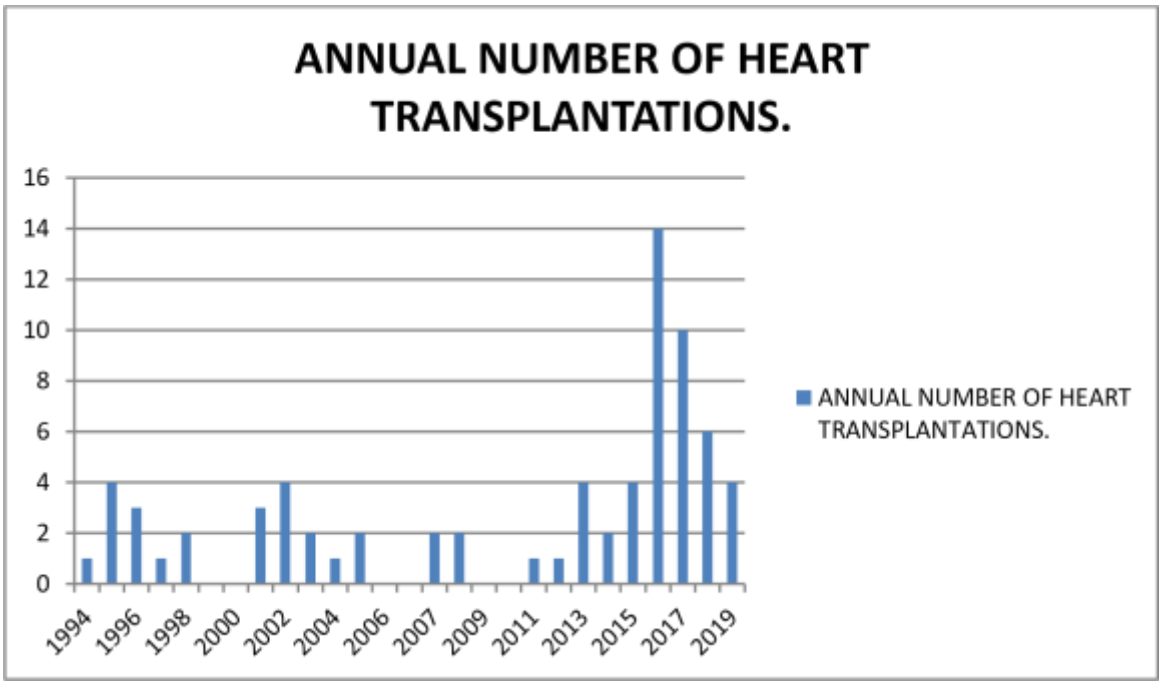
RESULTS

The study population comprised 71 consecutive adult recipients undergoing heart transplantation from the inception of the heart transplant program at the ALL INDIA INSTITUTE OF MEDICAL SCIENCE, NEW DELHI(August 1994) up to the end of June 2019. The annual distribution of heart transplantation is presented in Table 1 and in Figure 1. Our research ethics committee approved this study.

TABLE 1. NUMBERS OF TRANSPLANTS ACCORDING TO YEAR.

YEAR	NUMBER OF TRANSPLANTS
1994	1
1995	4
1996	3
1997	1
1998	2
1999	0
2000	0
2001	3
2002	4
2003	2
2004	1
2005	2
2006	0
2007	0
2008	2
2009	0
2010	0
2011	1
2012	1
2013	4
2014	2
2015	4
2016	14
2017	10
2018	6
2019	4

FIGURE 1. ANNUAL NUMBERS OF HEART TRANSPLANT .



BASELINE CHARACTERISTICS

The indications for transplant were dilated cardiomyopathy in 38 patients (53%), ischemic cardiomyopathy in 19 patients(26%), valvular heart disease in 1 patient(1%), Hypertrophic cardiomyopathy in 1 patient (1%), congenital heart disease in 1patient(1%), myocarditis in 1 patient(1%) and cause could not be found in 7 patients after extensive record searching (10%).

The age range was from 10 years to 55 years, and out of the 71 patients, 61 were male and 10 were female. Distribution is presented in Figure 2 and Table 2.

FIGURE 2. DISTRIBUTION OF TRANSPLANTS ACCORDING TO ETIOLOGY.

TABLE 2. NUMBERS OF TRANSPLANT ACCORDING TO ETIOLOGY

ETIOLOGY	**ETIOLOGY**
DCM	38
ICMP	19
RCMP	3
HOCM	1
CHD	1
RHD/VALVULAR	1
MYOCARDITIS	1
UNKNOWN	7

Early outcome

The Total number of transplant done is 71in the25 year duration of study period.
43 patients survived >1year .
26 patients are alive till now and in active follow up with us presently
25 patients died between o to 3months.
3 patients died between3month to 1 year.
4 patients died between 1year to 3 year.
2 patients died between 3years to 5 years .
2 patients died between 5 years to 10 years .
3 patients survived more than 10 years
At present at the time of writing this study there are 26 patients those are in close follow up and the longest survival is of 19 years.

TABLE 3. DURATION OF SURVIVAL AFTER TRANSPLANT .

MORTALITY DISTRIBUTION	NUMBER OF DEATH
O-3MONTH	25
LESS THAN 1YEAR SURVIVAL (MORTALITY B/W 3MONTH TO 1YR)	3
LESS THAN 3YEAR SURVIVAL (MORTALITY B/W 1YR TO 3YR)	5
LESS THAN 5YEAR SURVIVAL (MORTALITY B/W 3YR TO 5YR)	2
LESS THAN 10YEAR SURVIVAL(MORTALITY B/W 5YR TO 10 YR)	2
MORE THAN 10 YEAR SURVIVAL	3
ALIVE	26
DATA NOT AVAILABLE	5

Mortality dataaccording to cause in the postoperative period are shown in table 4.

TABLE 4. CAUSE OF MORTALITY AFTER TRANSPALNT .

MORTALITY DISTRIBUTION	
ACUTE RV FAILURE	4
SEPSIS /INFECTION /MODS	11
ACUTE LIVER FAILURE	2
ACUTE REJECTION	5
CHRONIC REJECTION	3
ALLOGRAFT VASCULOPATHY	4
MALIGNANCY	1
PNEUMONIA	3
PRIMARY GRAFT DYSFUNCTION /LCOS	4
OTHERS /CORONARY PATHOLOGY	4
UNKNOWN/SCD	4

Between 0to 3month 25 patient died including those who died in the hospital the causes of death were acute RV dysfunction in 4 patients,multiorgan dysfunction syndrome and sepsis in 7 patients, low cardiac output syndrome due to primary graft dysfunction in 1 patient,myocardial infarction /myocardial necrosis (autopsy diagnosis) due to coronary problems in 3 patients, acute liver failure in 1 patient, and 2 patient died SCD one due to intractable arrhythmia and one patient died in train when he was coming to AIIMS for follow up. In 4 patients cause of death could not be ascertainedeven after an extensive search of available records .It is not always possible to certainthe cause of death because it is a outcome of multiple closely related factors .
Those who survived more than 3month but died within 1 year the cause of death was multiorgan dysfunction syndrome in 1 patient MODS was secondary to fungal pneumonia and miliary tuberculosis of pericardium and lung, acute liver failure secondary to MODS in 1 patient and one patient died due to disseminated CMV infection .

Those who survived more than 1 year but died within 3year 1 died due to multi organ dysfunction syndrome due to gastric perforation,1 died due to acute graft rejection complicated in acute left ventricular failure,1 patient died due to chronic graft rejection on retrospective analysis it was found that she was non compliant to drugs 1patient died due to chronic antibody mediated rejection and tuberculosis (Pott's spine)1 patient died due to dog bite complicated in acute rejection he was also non complaint to drugs .

Those who survived more than 3 years but less than 5 years 1 died due to MODS secondary to fungal infectionand 1 died due to chronic allograft vasculopathy with moderate multifocal acute cellular rejection (autopsy finding)

Those who survived between the duration of 5 to 10 years one died due to chronic allograft vasculopathy he was stented also post transplant and 1 died due to acute cellular rejection leading to cardiogenic shock.

Those who survived beyond the period of 10 years 1 died due to malignancy(intra cranial space occupying lesion) and 1 died due to chronic allograft vasculopathy.

There were 45 deaths in the study period during the follow up .Every possible autopsy data is also obtained for clinic pathological correlation between clinical findings and pathological findings .the most common cause of death were multi organ dysfunction syndrome (n=11),early right ventricular dysfunction in (n=4)patients,low cardiac output syndrome (n=3),myocardial infarction (n=4),acute liver failure (n=2),intractable hyperkalemia (n=1),malignancy (n=1),primary and acute graft dysfunction (n=4),chronic allograft vasculopathy (n=4),chronic rejection (n=2),and malignancy in 1 patient .

Chronic allograft vasculopathy –4 patient died due to allograft vasculopathydiagnosis confirmed over autopsy .out of 26 alive patients one patient who is post transplant approximate 3years is living with chronic allograft vasculopathy

INFECTIONS

Infection and latent tuberculosis is more common in our part of world.we found occurrence of all types of infection viral bacterial protozoal and fungal in our study.the first transplant patient developed Plasmodium vivax malaria 6 years after transplant .

The second transplant patient also developed Plasmodium vivax and got infected with Toxoplasmosis in his life span he also completed course of ATT .1 Patient developed Tubercular meningitis and died due to this .one female patient developed pott's spine and Tubercular synovitis of knee which showed response to ATT.1 Patient showed evidence of miliary Tuberculosis of lung and pericardium on autopsy and died of MODS and fungal septicemia .1 another patient developed Tuberculosis 8 years post transplant and completed a course of ATT .10 patients developed lung consolidation and cavitary lesions Aspergilosis as a dominating etiology and bacterial and CMV in other cases .1 patient died of right eye Candidial endopthalmitis .2patients developed dengue and 1 patient developed Chikungunyapost transplant recovered uneventfully .4 patients died of fungal septicemia secondary to lung infection .3 patients developed culture + bacterial UTI and one patient developed left sided epididymoorchitis .7patients developed CMV infections and one of them developed disseminated CMV infection.

1 patient developed harpislabialis 1 developed HSV oral ulcer and 2 persons developed Varicella zoster .1 patient developed Varicella pneumonia.

1 person developed scabies. In the early posttransplant period, the infection we have encountered has been mostly bacterial and has responded to empirical antibiotic therapy and occasionally based on the culture reports.Incidence and etiology of infections are shown in Table 6.

TABLE 6.INCIDENCE AND ETIOLOGY OF INFECTIONS AFTER TRANSPLANT

INFECTION	NUMBER OF PATIENTS
DENGUE	2
MALARIA	2

CMV	7
TUBERCULOSIS(PUL)	2
TUBERCULOSIS(EXT PU)	2
TOXOPLASMOSIS	1
ASPERGILOSIS	8
CHIKUNGUNIYA	1
CANDIDAL OPTHALMITIS	1
BACTERIAL UTI	3
EPIDIDYMOORCHITIS	1
HERPES LABIALIS	1
VARICELLA ZOSTER	2
HSV (ORAL ULCER)	1
VARICELLA PNEUMONIA	1
SCABIES	1

Rejections -Rejection had been relatively uncommon as a problem in the initial years of our experience and easy to handle. Total number of episodes of rejection>1or equal to 1 of ISHLT classification were 51 over a follow up period of 25 years and approximately 250 endomyocardial biopsies performed.
Before 2014 only one patient developed a episode of hyperacute rejection and he was shifted to icu with IABP support and died on same day autopsy record was not available even after extensive search. Rejection data are shown in TABLE 7.

TABLE 7. EPISODES OF REJECTION AFTER TRANSPLANT

REJECTION TIME	REJECTION EPISODE (TOTAL NUMBERS)
0-3MONTH	22
3MONTH-1YR	10
>1YR	19
TOTAL	51

Side effects of drug therapy.
Glucocorticoid induced myopathy3patients developed glucocorticoids induced myopathy they presented with difficulty in standing from sitting position few patients developed new onset insulin dependent diabetes.

Renal dysfunction
Renal dysfunction is very common post heart transplant in our study 11 patients required any form of renal replacement therapy in study period one patient required renal replacement therapy for persistent hyperkalemia and died during an episode of hyperkalemia one patient developed acyclovir induced renal dysfunction 1 patient developed cyclosporine induced nephrotoxicity requiring hemodialysis.

OTHER COMPLICATIONS

Cholelithiasis4 patients developed cholelithiasispost transplant and one patient developed acalculous cholecystitis.

Avascular necrosis of femur 3patient developed avascular necrosis of femur for which they has to gone through surgical treatment .

Neurological complications first transplant patient died after 14years due to bleeding in the intracranial space occupying lesion .1 patient developed tubercular meningitis .1 patient developed disseminated CMV infection including CMV meningitis .7 patents develop seizure disorder post transplant

(due to metabolic, infectious and primary CNS cause)

2 patients developed subdural haemorrage which required surgical drainage. One patient developed autoimmune encephalitis 1 year after transplant which presented as a febrile illness worsening rapidly resulting in respiratory failure and ventilation and tracheostomy. He was treated with pulse steroids and IVIg and responded. One child developed posterior reversible encephalopathy syndrome because of high blood pressure and his transplanted adult heart. His symptoms were relieved with strict blood pressure control.

Complete heart block 3 patient developed complete heart block post transplant requiring permanent pacemaker insertion.

ASSISTED MECHANICAL CIRCULATORY SUPPORT REQUIREMENT

IABP ECMO and ventricular assist device requirement 14 patients REQUIRED IABP/ECMOvad and any other form of mechanical circulatory support

in the immediate and late post operative period .1 patient developed hyperacute rejection in 3 patients mechanical circulatory assist device were put due to right ventricular failure one of them also required RVAD support .1 patient developed primary graft dysfunction and 1 patient develop acute cellular rejection so IABP instituted .in 2 patients IABP instituted due to persistent low cardiac output .in 1 patient heart is acquired from outside Delhi so due to prolonged cold ischemia time (290)minutes he required IABP.IN 1 patient IABP inserted due to non responding intractable arrhythmias. Data are shown in Table

8.

TABLE 8. POST OPERATIVE MECHANICAL CIRCULATORY SUPPORT AFTER TRANSPLANT

POST OPERATIVE DEVICE	NUMBERS
RVAD	1
RVAD+IABP	1
IABP+VAD	1
IABP	7
ECMO	1
IABP+ECMO	3

TABLE 9 .POST OPERATIVE COMPLICATIONS AFTER TRANSPLANT.

POST TRANSPLANT COMPLICATIONS	
RENAL FAILIURE REQUIRING HAEMODIALYSIS	11
SEIZURE	7
DRUG RELATED COMPLICATIONS	2
LIVER FAILIURE	2
BACTERIAL INFECTION	4
POST TRANSPLANT MALIGNANCIES	1

EPISODES OF ACUTE REJECTION (ANTIBODY)	4
ALLOGRAFT VASCULOPATHY	5
EPISODES OF ACUTE REJECTION (CELLULAR)	51
NEW ONSET DIABETES	3
VIRAL INFECTION	13
FUNGAL SEPSIS	8
MODS	11
MALIGNANCY	1
ARRYTHMIA /RHYTHM DISORDER /SCD	3
CHB	2
CEREBRAL HEMORRHAGE /SDH	2
SEIZURES	7
PERIPHERAL NERVE AND MUSCLE DISORDER	3
DEPRESSION	8
CEREBRAL ENCEPHALOPATHY	1
TUBERCULAR MENINGITIS	1
CMV MENINGITIS	1
AVASCULAR NECROSIS OF FEMUR	3
CHOLILITHIASIS	4
PNEUMONIA /ARDS	13
TUBERCULOSIS(INCLUDING ATYPICAL)	4

DISCUSSION

The first successful heart transplant in India was done at the All India Institute of Medical Sciences (AIIMS), New Delhi on August 3, 1994, by a team of doctors and led by Dr P. Venugopal .(14) The patient survived for 14 years. Cardiac transplantation in India was not possible till June1994 because the law did not recognize brain death. However, after the passing of the Transplantation of Human Organs Bill, this major hurdle was removed and the first successful cardiac transplant in India became possible. Out of the civilian government hospitals, to date, only AIIMS at New Delhi runs a successful heart transplant program.

The effects of temporal changes in donor and recipient characteristics on early and late survival after adult heart transplantation were examined in a single center experience over a period of 25 years. Our results show that despite these changes, the early and late survival remain stable and encouraging, presumably due to significant improvements in clinical management, including pretransplant medical therapy, timing, route of hemodynamic support, myocardial protection, steady progress in surgical experiences, perioperative intensive care, and immunosuppression protocol.(15)

There are many factors which are responsible for the lack of an upsurge in the number of heart transplant surgeries in India. Being a developing country, there are only a few hospitals that have the infrastructure to perform a transplant. There is also a lack of infrastructure to promptly identify potential donors and transport the harvested heart to the destined center in the stipulated time. NOTTO has taken this challenge and has improved the rate of donations and streamlined the organ allocation throughout the country, but it is still in its nascent stage no other similar study is done in India as per our knowledge.(15,16)

Donor and recipient demographics and characteristics.

Between August 3, 1994, and June 31, 2019, a total of 71 adult patients underwent heart transplant at the AIIMS NEW DELHI. Patient data were analyzed retrospectively and prospectively from

transplants performed from 1994 to 2019 total duration of 25 years . Data were analyzed with respect to survival, cause of death, incidence of acute rejection, CAV, infection, malignancies,post operative complications,requirement of post operative long term and short term mechanical circulatory assistance, drug induced complications and histopathological analysis following mortality results are compared with few previously available studies (16-24) . The approval of the Institutional Review Board was obtained.The youngest patient who gone through transplant in our study was 1o year old and eldest patient was 55 years old in our study 61 patients were male and 10 patients were female .

At the end of 1year 43 patients survived25 patient died between 0 to 3months, 3 patients died between 3month to 1 year, 4 patients died between 1year to 3 year.2 patients died between 3years to 5 years, 2 patients died between 5 years to 10 years . 2 patients survived more than 2 years at the end of three years 2 patient survived, 2patient survived more than 5 year duration and the longest survivor in our study is of 19 years post transplant and are still alive .At present 26 patients are alive and in close follow up with us . Survival after heart transplantation has improved since the 1980s and 1990s due to advances inimmunosuppression and the prevention and treatment of opportunistic infections. Major gains in survival have been largely limited to the first 6 to 12 months post-transplantation. The median survival after heart transplantation is 11 years, and one-year survival approaches 85 percent in the current era. There is substantial mortality in the first six months, followed by a mortality rate ofapproximately 3.4 percent per year thereafter this is in accordance with our results our 25 patients died between 0-3 months that time transplant programme was emerging the number of transplants were very less and there were no defined protocols for preoperative selections and better post operative management administration was also not very much supportive for running a transplant programme. (16-24)

After 2015 our transplant number picked because of positive involvement of administration and we did 31 transplants from 1994 -2013 and 41 transplants from 2014 -2019 at the time of completion of this study . According to various studies, The primary indications for heart transplantation for adult patients have been nonischemic cardiomyopathy (53%) and ischemic cardiomyopathy (38%). Other indications include: valvular heart disease (3%), retransplantation (3%) andothers (<1%) The commonest causes of transplant were dilated cardiomyopathy in our study (53%)patients,ischemic cardiomyopathy in 26% patients valvular heart disease in 1% patients congenital heart disease in 1% of the patients this is similar to other studies done on this subject .

Cause of death according to The Registry of the International Society for Heart and Lung Transplantation:Thirty-fourth adult Heart Transplantation Report—

2017 The leading cumulative causes of death are graft failure,noncytomegalovirus(CMV)infection,and multiple organ failure ,in our study leading three cause of death were or most common cause of death were multi organ dysfunction syndrome (n=11),early right ventricular dysfunction in

(n=4)patients, and low cardiac output syndrome (n=3)although it is not always possible to get the correct cause of death due to multiple variables involved and difference between clinical judgement and autopsy findings of explanted heart

.

Chronic allograft vasculopathy in our study out of 71 patients 4 patient died due to chronic allograft vasculopathy and 1 patient who is at present alive 3 year post transplant has been developed chroicallograftvasculopathy and he is in our strict follow up.In the 2017 International Society for Heart and Lung Transplantation (ISHLT) registry report on data from more than 135,000 heart transplant recipients, the overall prevalence of CAV in survivors at 1, 5, and 10 years after transplantation was 8%, 29%, and 47 %percent, respectively.(16, 17)

Malignancy is the most frequent cause of death beginning at five years postcardiac transplantationCardiac as opposed to kidney transplantation requires a higher level of immunosuppression because of the risk of death associated with organ rejection,in our study only 1 patient developed ICSOL 14 years post transplant and died due to that although intra cranial space

occupying lesion is not a primary malignancy attribuated due to solid oragan transplantation in literature .

Primary graft failure acute allograft rejection and chronic allograft vasculopathy

Acute rejection is a common problem after heart transplantation particularly early after transplantation and is treated in approximately 13 percent of patients during the first year after transplantation. Acute cellular rejection can cause graft dysfunction and contributes to approximately 11 percent of deaths in the first three years after transplantation. Acute cellular rejection is most likely to occur in the first three to six months, with the incidence declining significantly after this time(18).In our study in the initial 0-3 months out of 25 mortality only 1 patient died due to primary graft dysfunction . Acute antibody-mediated rejection may also occur but its impact on morbidity and mortality is less well defined . Antibody mediated rejection, usually due to development of donor specific anti-HLA antibodies, can occur at any time. It is commonly accompanied by hemodynamic compromise when it occurs in the early posttransplant period. It can be diagnosed on endomyocardial biopsy and confirmed by detection of donor specific antibodies.

Rejection had been relatively uncommon as a problem in the initial years of our experience and easy to handle out of 45 mortality 4 of our patient died due to acute cellular rejection and 3 died due to chonic rejection number of rejections were more in the initial 1 year .out of 71 patients Our 4 patients develop antibody mediated rejections, in the initial period we were not doing tests for AMR later pathologist started doing tests for AMR . There were total 51 episodes of rejection over the 25 years of study duration.We changed our immunosuppression protocol we have switched to tacrolimus instead of cyclosporine as standard therapy because the occurrence of rejections had increased with cyclosporine We have also switched to mycophenolatemofetilfrom azathioprine which was used in the initial phases of the program. We used methylprednisolone 500 mg intravenously at the time of release of aortic cross clamp and then 8 hourly to complete a total of three doses, then 1 mg/kg/day intravenously divided into two doses till the target cyclosporine/tacrolimuslevels were achieved.

Most studies in adult heart transplant recipients conducted years ago reported an incidence of bacterial infections of 20–30% In particular,immunocompromised individuals are at an increased risk of opportunistic viral and bacterial infections. Infections in heart transplant recipients represent a real challenge, as they are responsible for increased morbidity, mortality, length of stay andassociated costs

Most infections involve the respiratory system, urinary tract, and the skin .

Commonly reported infections include Cytomegalovirus, Herpes simplex virus, Epstein-Barr virus, Varicella zoster virus, Tuberculosis, and pneumonia . Invasive fungal infections, such as Aspergillus and Candida, are less common in hearttransplant recipients; (although we got higher incidence of these infections in our study)however, they are associated with significant morbidity and mortality . Infection is one of the leading causes of death in the first year after transplant, being the primary cause of death in 25-32% of patientsThe risk of death due to infection is highest between 1 month and 1 year following transplant and then decreases significantly after the first year post-transplant. Infection is also associated with 17% of hospital readmissions in the first year following a heart transplant.

In our study all types of infection occoured bacterial viral fungal protozoal reactivation of latent tuberculosis and occurrence of newer onset infection in a particular period of time we faced more incidence of aspergillosis infection because of construction work was going on in our centre in the intial early time period of transplant programe.

This study has several limitations. First, it is a retrospective - prospective and non-randomized study with observational data. Therefore, the results might be affected by unmeasured confounders.Second, this study incorporates the outcomes of a limited number of patients with limited amount of retrospective data available .

CONCLUSION

In conclusion, heart transplantation is a life-saving procedure for patients with end-stage heart failure with good early outcomes and relatively low catastrophic complications This is first publish Indian data on this subject showing 60% 1 year survival (43 out of 71) of patients.Results are better in later 3-4 years due to better immunosuppression and recipient evaluation protocols and improved postoperative care due to direct involvement of intensivistsin postoperative patient management . Heart failure patients are actively screened and evaluated in separate heart failure clinic than again actively evaluated before listing in transplant list by the cardiologist and consultations and clearance from other specialities is frequently obtained In our cohort, the main reason of increased complications in the first half of the study is the seemingly low volume of transplant surgeries The association of the annual number of heart transplants and outcomes at a center is well established by many studies.

Most of the early postoperative complications can be adequately managed with surgical or medical treatment and did not result in an extended hospital stay. We hope that this study can be used as a reference and can provide guidance for management after heart transplantation in India but more data from other transplant centers in India is needed for better formulations of guidelines and management protocol.

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