Original Article

Medium term results following heart transplantation for end stage heart failure: A single center experience of 257 patients☆

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A B S T R A C T

Objective: End stage heart failure is a lethal disease with a dismal 5 year survival. Heart transplantation has proven to be a highly effective modality of treatment in appropriately selected group of such patients. This is a retrospective analysis of medium term outcomes of heart transplantation in the setting of a private health facility in India. The objective of this study was two fold.

1. To document the short term and medium term survival of patients undergoing a heart transplant procedure
2. To identify the risk factors for unfavorable outcomes with subgroup analysis.

Methods: The outcome of 257 heart transplants done at a single centre from October 2012 to October 2019 was analyzed. Patients with combined Heart and lung transplants and those whose complete medical records were unavailable were excluded from the study. Survival was tracked at 60 days, 90 days, one year and beyond for a maximum of 7 years. Preoperative patient risk profiles were characterized on the basis of INTERMACS category.

Results: There were 176 male and 81 female patients. The age range was from 8 months to 78 years with a mean of 32.9 years. Survival at 2 months was 87%, at 90 days was 83%, at one year was 81%, 2 years was 75%, at 3 years was 72% and at 5 years and beyond was 62% for the whole series. Strong predictors of 90 day mortality included INTERMACS category (odd's ratio 0.289, $p = 0.000$) and creatinine more than 1.5 mg/dl (odd's ratio 2.48, $p = 0.056$). Recipient pulmonary vascular resistance and donor organ ischemic times were not found to be statistically significant factors affecting outcome. Medium term survival was influenced by INTERMACS category (Hazard ratio > 3 for INTERMACS category 1 compared to INTERMACS 4 or 5, $p < 0.0001$) and creatinine > 1.5 mg/dl (Hazard ratio 2.15, $p = 0.003$). This effect of creatinine was related to the age of the recipient. Hazard ratio 1.4, $p = 0.524$ if age <30 and Hazard ratio 4.78, $p = 0.006$, if age was >50.

Conclusion: Satisfactory medium term outcome is possible after heart transplantation even in resource constrained environment of a developing country.

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1. Introduction

End stage heart failure is a lethal disease and carries a very significant long term mortality with a 5 year survival of only 25% if all categories and ages are included.[1] Despite impressive advances in the field of implantable ventricular assist devices, Heart transplantation continues to be the gold standard for patients with end stage heart failure failing medical therapy.[2] It provides better survival than medical therapy alone for ACC Grades C, D Heart failure and INTERMACS grades 4 and below.[3,4] The International Society for Heart and Lung Transplantation (ISHLT) registry currently reports survival rates of 79% at 1 year, 65% at 5 years and 45% at 10 years.[5] Even though heart transplantation in India started more than a quarter century ago, only limited data is available about survival after the procedure in India or indeed the entire subcontinent.[6]

This primary aim of this study was to analyze the survival of isolated heart transplant procedures performed at a single hospital in India. The secondary objective was to study the factors affecting survival during a follow up of over 7 years.

1.1. Materials and Methods

After obtaining ethical clearance from the hospital ethics committee this retrospective study included 257 patients who underwent heart transplantation at our hospital from October 2012 to October 2019. The patients whose medical records were incomplete, those who had a combined heart and Lung Transplant or those who were operated in other hospitals by the same team were excluded from this study. Patient consent was waived off by the hospital ethics committee.

1.1.1. Recipient evaluation

All potential recipients were evaluated following a well-defined protocol. If the patients were ambulatory, a 6-min walk test and peak oxygen consumption with VO2 max was done and a value of less than 12 ml/kg/mt was considered significant for recommending a transplant. The function of various organ subsystems like liver and kidney was evaluated, as was infectious disease screening and blood grouping.

1.1.2. Hemodynamic evaluation

All patients had a hemodynamic evaluation for estimating the pulmonary vascular resistance. This test was mostly done in the intensive care unit with a Swan Ganz catheter over a period of several hours, if needed. Cath labs in our hospital tend to be very busy and important decisions regarding the reversibility of a high PVR in a potential heart transplant recipient cannot be based on a rushed hemodynamic study. If the PVR was high, several attempts were made to assess reversibility using intravenous Milrinone starting from 0.375 μg/kg/min to 0.75 μg/kg/min for up to 48 h. If the results were inconclusive, Sildenafil (0.2–0.5 mg/kg intravenously over 5 min) and inhaled Nitric oxide (2 parts/million by mask for 5 min) were tried. In rare instances, a trial of endothelin receptor blocker ambrisentan was tried for a few weeks at a dose of 5 mg twice a day. In patients with high baseline PVR, the decision to accept for transplant was taken on the basis of reversibility with pulmonary vasodilators. There were instances when a good pulmonary artery wedge tracing could not be obtained, despite repeated attempts, making estimations of pulmonary vascular resistance difficult. Under these circumstances mean pulmonary artery pressure estimations were used to guide decision making aided by echocardiographic estimations of left atrial pressure.[7,8] We validated the relationship between PVR and Mean PA pressure. There was a linear relationship between mPAP and PVR ($r^2 = 0.079$,

$p = 0.000$), and mPAP and trans-pulmonary gradient (TPG) in our patients.

The PVR tended to be higher in children compared to adults and did not seem to have a significant bearing on the outcome (Fig. 1). Decisions regarding operability were taken after considering the values for pulmonary and systemic resistance, trans pulmonary gradient, weight of the patient and the right ventricular function. In patients who were not very obese, an attempt was made to select a donor heart from a higher body weight individual. In appropriate patients, if economically feasible, an LVAD was offered if the PVR was considered prohibitively high, over 6 wood units. One of the challenges of PVR estimations is the fact that very often the PVR at initial estimation can be quite different from the PVR at the time of transplant which may be several months later with a significant change in the value during the interim period. The cath study was repeated if more than three months had elapsed awaiting a transplant.

Cardiac cath test was not done in emergency situations on patients on ECMO and in small children especially with restrictive cardiomyopathy where it can be a high-risk procedure.

1.1.3. Preformed panel reactive antibodies (PRA)

All patients were evaluated for pre-existing HLA class I and II antibodies in the blood. Patients with PRA levels of more than 50% were not denied transplant but had a direct Complement Dependent cytotoxicity (CDC) cross match with the donor blood at the time of donor evaluation and if it was negative, transplant was offered. If CDC cross match was positive, one cycle of plasmapheresis was done during cardiopulmonary bypass. Rituximab was used, if donor specific antibody was positive in the postoperative period. In 3 patients, preoperative Rituximab (375 mg/m2 over 4 h, 3 doses at weekly intervals) and immunoglobulin treatment (0.5 gm/kg at induction) was carried out prior to transplant. We consider the cross match to be particularly important in patients with a high PRA with previous cardiac operations, especially the Fontan procedure, where typically several operative interventions are common prior to referral for a transplant.

Following work up and after the suitability of a transplant was ascertained, the patients were listed for a transplant in the State Transplant waiting list. The typical period of waiting in our state is less than 3 months for most adult recipients. Pediatric donors are scarce and the waiting times for small children can be considerably longer.

The commonest modality of hemodynamic support for sick preoperative patients was ambulatory milrinone, followed by Intra-aortic balloon pump, veno arterial extracorporeal membrane oxygenation (VA ECMO) and CENTRIMAG LVAD (Abbot park, Illinois, USA). Unfortunately, implantable modern LVADS are not of much use as a bridge to transplant in the Indian context in view of the cost.

1.1.4. Donor evaluation

Donor assessment was done by a well-trained cardiac anesthesiologist with a transesophageal echo except in very small donors, where only transthoracic imaging was used. An assessment was made of the cause of brain death, history of cardiac arrests in the donor, inotrope usage and expected ischemic times taking into account the modality of organ transport. In pediatric patients, an assessment of size matching of the heart between the donor and recipient chest cavity was done on the basis of echocardiogram, CT scan and in a few instances 3D printing of the recipient heart. In donors with significant ventricular dysfunction, optimization of the organ by titrating the inotropes was done before a final decision regarding organ usage. In select instances, hearts with very significant dysfunction were utilized taking into consideration the
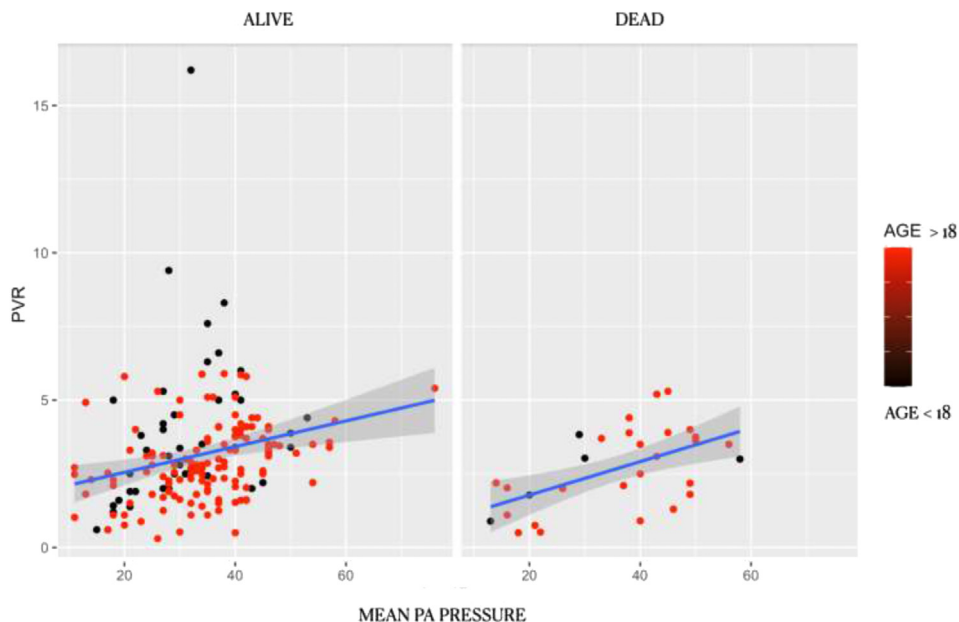
Fig. 1. A scatter plot of PVR and PA mean pressure with a regression line The red colored dots are patients older than 18 and the black colour represents patients younger than 18. The panel on the left is patients who survived and on the right is those who died. PVR values in pediatric patients are higher but do not seem to affect mortality. The graph was generated using a graphics package (gg plot 2) in R.

recipient's condition and the donor recipient weight ratio. Donor coronary angiograms are seldom possible and were done only in a few instances. Organs were turned down if significant coronary plaques were present.

1.1.5. Technique of transplantation

Standard techniques were used for the harvesting of the heart and protection was by custodial cardioplegia. For recipients with bilateral vena cava and those with malposed great vessels, a long segment of the innominate vein attached to the SVC and pulmonary artery with branches and long segment of the aorta with the arch were harvested. All the transplants were done using bicaval anastomosis except in one child with previously repaired partial anomalous pulmonary venous return where a Shumway technique was used.

1.1.6. Immunosuppression

Since many of our patients had cardiorenal syndrome with deranged renal function, induction therapy became a standard procedure. Advantage of induction therapy is that it allows delayed initiation of nephrotoxic immunosuppressive drugs and early weaning of steroids.[9] Patients who are allosensitized with preformed antibodies also benefit from induction therapy.[10] Our induction protocol is with Inj. Basiliximab an IL-2 receptor antagonist given at a dose of 12 mg/m^2 up to 20 mg over 30 min before initiation of cardiopulmonary bypass (CPB) along with Inj. Methylprednisolone given at a dose of 20 mg/kg up to 1 gm in divided doses and given at the time of initiation of CPB and during aortic cross clamp release.

1.1.7. Maintenance therapy

Mycophenolate mofetil is started on 1st postoperative day in a dose of 10—20 mg/kg/dose up to a dose of 600 mg/m^2 twice daily and has to be continued lifelong. Azathioprine is given in a dose of 2 mg/kg/day in patients who cannot tolerate Mycophenolate due to diarrhoea. Myelosuppression caused by both the drugs is generally reversible on discontinuation. Therefore, doses of antimetabolites

are adjusted according to the white cell count, especially if it starts to drop less than 4000/dl.

Tacrolimus is usually started on 2nd postoperative day at a dose of 0.5—1 mg, considering numerous factors like renal profile, gut absorption, drug interaction and genetic polymorphisms of cytochrome enzymes. The dose is adjusted according to the tacrolimus genotype sensitivity test, with low dose for poor metabolizers and high dose up to 0.3 mg/kg/day in two divided doses for extensive metabolizers. Blood tacrolimus trough level is monitored and maintained between 8 and 12 ng/ml. In an occasional patient with tacrolimus intolerance, Cyclosporine was started, at an initial dose of 25—50 mg/dose twice daily, and blood trough level was maintained between 200 and 300 ng/ml. If tacrolimus could not be started by postoperative day 4 because of inadequate urine output or high creatinine, Basiliximab was repeated. Unlike what is recommended in the literature, we do not routinely repeat another 20 mg on day 4. Instead a CD 25 profile is done. If the CD25 level is less than 2%, immunosuppression is considered adequate and Basiliximab is not repeated. With this strategy, we have postponed Tacrolimus for up to 3 weeks without repeating Basiliximab.

Parenteral Methylprednisolone is initiated at one-fourth the induction dose in the postoperative period. It is then tapered by 50% daily till 10 mg/day it is then changed to oral prednisolone, usually 5 mg/day, which is usually at the end of one week posttransplant. A flow chart of the immunosuppression protocol is shown in the table (a).

1.1.8. mTOR inhibitors

Everolimus in low doses of 0.5—0.75 mg twice a day to maintain a trough level of 3—8 ng/ml was used to prevent intimal proliferation and reduce chronic allograft vasculopathy[11] and to permit a renal sparing dose of tacrolimus. This was usually done after three months had elapsed after the transplant to avoid poor wound healing and pedal edema.

1.1.9. Treatment of rejection

Although immunosuppressive agents significantly reduce acute and long-term rejection after heart transplant, rejection still

Table 1
Diagnosis of patients in this series.

Dilated cardiomyopathy	56%
Ischemic cardiomyopathy	17%
Restrictive cardiomyopathy	12%
Congenital heart disease	10%
Others	5%

happen in about 10—25% of patients.[12] Rejection can be cell mediated rejection or antibody mediated rejection. Steroids play major role in both types of rejection, pulse steroids given at a dose of 250—1000 mg/day in two divided doses for three days and tapered off slowly.

1.1.9.1. Cell mediated rejection. Patients not responding to pulse steroid regimen are given ATG at a dose of 1.5 mg/kg/day for 7—10 days. ATG is associated severe anaphylaxis, serum sickness as its protein is xenogenic in origin.

1.1.9.2. Antibody mediated rejection. Pulse steroid is the primary treatment regimen, if no significant improvement with steroids, Inj. Rituximab which is an anti-CD20 monoclonal antibody eliminates the B cell. Rituximab was also given in allosensitized patients for desensitization at a dose of 375 mg/m^2 up to 500 mg i.e. weekly for 4 weeks. This drug needs to be given as a slow infusion and may cause fever or allergic reactions. In severe antibody mediated rejection IV Immunoglobulin and plasmapheresis are done.[13] A flow chart of our rejection protocol is shown in Table (b).

Immunosuppressive drug therapy increases not only the risk and severity of nosocomial infections but also the risk of opportunistic infections. Typical signs of infection like fever and chills may be mitigated by the reduced immune response and the course of infections can develop rapidly into serious life-threatening symptoms. Empirical broad-spectrum antibiotics are started before surgery and continued in the early postoperative period to prevent bacterial infection.[14]

Prophylaxis against Pneumocystis jiroveci and Toxoplasma gondii are initiated in the early postoperative period and continued lifelong. Patients without history of sulfa allergy are started on oral Co-trimoxazole. Antiviral prophylaxis against cytomegalovirus (CMV) also started in early postoperative period and continued for 3 months.[15] Oral valganciclovir is given depending on CMV serologic status of donor and recipient Both cotrimoxazole and ganciclovir should be cautiously used in neutropenic patients and in renal dysfunction. Antifungal prophylaxis against Aspergillus is not routinely used in heart transplant recipients. Voriconazole or Itraconazole is used in selective patients who are at higher risk of fungal infection. Drug interaction with tacrolimus should be considered before administering this prophylaxis.

1.1.10. Endomyocardial biopsies

Following the western protocol of endomyocardial biopsies in the first post-transplant year was not practically feasible in our country. Apart from the significant costs involved, patients and their care givers had to be available in the city for up to one year which was impossible given the Indian realities. We limited the number of biopsies to one by the end of the second week and then every year unless otherwise indicated with strict monitoring of the blood levels of tacrolimus. Any drop in ventricular function was aggressively investigated with biopsy and Donor specific antibody level testing and Luminex single bead antigen and high sensitive troponin levels, where possible. Donor derived cell free DNA testing is currently not widely available in this country. The one year survival has been satisfactory with this strategy.[16]

1.2. Statistical analysis

The outcomes were tracked with a dedicated data collection team. This was done by recording patient visits to the hospital and where ever this was not possible, by follow up telephonic contacts for the purpose of this study. The follow up data is complete. The data was analyzed in STATA (Statacorps, Texas) and R. The results of logistic regression are reported as odd's ratio and cox regression analysis as Hazard ratio. Continuous variables were compared with Pearson's correlation coefficient and for categorical variables Pearson's chi2 test was used. Scatter plot was generated in a graphics package in R (gg plot 2).

2. Results

2.1. Age and sex distribution

There were 176 male and 81 female patients. The age range was from 8 months to 78 years with a mean of 32.9 years.

Table 2
The diagnosis of patients with congenital heart disease in this series.

Diagnosis of congenital heart defects undergoing heart transplant
Mitral Atresia, Hypoplastic LV, DORV, Severe PS, Dilated RA and IVC, Supracardiac TAPVC
Severe ventricular dysfunction, Severe AV valve regurgitation, DORV, Non routable VSD, Single ventricle, S/P BT Shunt, S/P BDG + AV valve repair
DORV, Large remote VSD non-routable to aorta, PS, RPA replaced by a leash of collaterals, Mild Kyphoscoliosis, S/P Birth BT Shunt followed by Left BT shunt, S/P BDG with MPA interruption
S/P Sinus Venosus ASD Closure, RV Dysfunction, Early Cirrhotic changes in liver, Massive ascites, TIA
DORV, Severe PS, Perimem branous VSD with outlet extension- Non Routable, Side by side great arteries, S/P BT shunt, S/P BDG + MPA interruption, S/P LV aneurysm repair
Single Ventricle, PS, S/P Fontan with Norwood modification, S/P fenestration creation, S/P device closure of fenestration
CC-TGA, VSD, PS, Severe biventricular dysfunction with aneurysmal dilatation of vena caval side of Glenn anastomosis, S/P Bidirectional Glenn
Tricuspid Atresia, Single ventricle, Severe PS, TGA
Mitral Atresia, Hypoplastic LV, DORV, Severe PS, ASD, AV Valve regurgitation, S/P left BT shunt
Single ventricle, DIRV, DORV, PS, Hypoplastic LV, Dilated common atrium, common AV valve, Moderate AV valve regurgitation, Atrial Arrhythmias, Interrupted IVC with hemiazygous continuation, two hepatic veins, entering separately into common atrium, moderate ascites, S/P Left BT shunt, S/P Left Kawashima operation + LPA plasty
S/P Fontan with LPA stenting, Stent thrombosis, Failed Fontan, Gross Ascitis, Hypoalbuminemia
Unbalanced AV canal with Severe AV valve regurgitation, Common AV valve, Single ventricle with RV morphology, OP ASD, Bil SVC, Common Atrium, Bilateral SVC, Hepatic veins opening separately into RA, Situs Ambibuous, Malposed great arteries, Severe PS
Unbalanced AV canal deect with Severe AV valve regurgitation, DORV, VSD, PS, S/P Right BT shunt, S/P Glenn with Left PA Central shunt, S/P Left sided stent placement
Tricuspid Atresia, Single ventricle, S/P BT shunt, S/P BDG, S/P Fontan
S/P Senning's procedure, Severe systemic ventricular dysfunction
S/P Fontan procedure, Tricuspid atresia, severe ventricular dysfunction
C-TGA, DILV, Restricted ASD, Hypoplastic RV, S/P PA Band + Atrial septectomy, S/P Fontan completion Ebsteins disease of the tricuspid valve
Post Subaortic obstruction muscle resection
Congenital aortic stenosis with multiple previous surgeries with severe LV dysfunction

Table 3
Clinical profile of patients with the various INTERMACS categories.

INTERMACS		N	MINIMUM	MEAN	MAXIMUM	25THPERCENTILE	MEDIAN	75 TH PERCENTILE	STANDARD DEVIATION
1 (24)	AGE	24	3	30	73	12	20	55	24
	CREATININE	20	1	1.5	4.8	0.7	1.0	2.0	1.2
	PA MEAN	15	17	36.1	58.0	22.0	37.0	49.0	13.5
	PVR	12	1	3.1	5.3	2.1	3.4	4.0	1.4
	PCWP	12	12	27.2	40.0	20.5	27.5	34.5	9.1
	CARDIAC INDEX	8	1	1.8	2.6	1.3	1.9	2.3	0.5
2 (46)	AGE	46	3	30	66	11	24	50	20
	CREATININE	38	0	1.1	3.3	0.7	1.1	1.5	0.7
	PA MEAN	41	13	35.0	56.0	30.0	35.0	43.0	9.6
	PVR	39	1	3.1	8.3	2.0	2.7	4.1	1.7
	PCWP	38	7	25.8	40.0	20.0	25.0	31.0	8.4
	CARDIAC INDEX	30	1	1.8	3.0	1.4	1.7	2.3	0.6
3 (131)	AGE	131	1	35	78	17	37	53	20
	CREATININE	113	0	1.2	5.9	0.8	1.0	1.4	0.8
	PA MEAN	118	11	34.6	76.0	27.0	35.0	41.0	11.3
	PVR	111	0	3.2	16.2	2.3	3.0	4.0	1.8
	PCWP	106	7	25.6	52.0	18.0	26.0	32.0	9.5
	CARDIAC INDEX	82	1	2.0	4.4	1.5	1.9	2.3	0.6
4 (55)	AGE	55	2	30	67	14	26	45	19
	CREATININE	54	0	1.0	2.2	0.6	0.9	1.1	0.5
	PA MEAN	50	11	29.5	50.0	21.0	28.0	36.0	9.9
	PVR	46	1	2.7	9.4	1.6	2.5	3.5	1.6
	PCWP	47	2	22.2	36.0	16.0	23.0	28.0	8.7
	CARDIAC INDEX	41	1	2.1	4.4	1.7	2.0	2.4	0.7
5 (1)	AGE	1	44	44	44	44	44	44	–
	CREATININE	1	1	0.8	0.8	0.8	0.8	0.8	–
	PA MEAN	1	18	18.0	18.0	18.0	18.0	18.0	–
	PVR	1	2	2.1	2.1	2.1	2.1	2.1	–
	PCWP	1	11	11.0	11.0	11.0	11.0	11.0	–
	CARDIAC INDEX	1	2	1.9	1.9	1.9	1.9	1.9	–

2.2. Diagnosis

The most common diagnosis was dilated cardiomyopathy (56%), followed by ischemic cardiomyopathy (17%), restrictive cardiomyopathy (12%), congenital heart disease (10%) and others (5%) including post-partum cardiomyopathy, post chemotherapy and post viral myocarditis. The etiology of patients is shown in Tables 1 and 2.

2.3. INTERMACS category

INTERMACS is a convenient way of capturing the degree of cardiac disability in patients with end stage heart failure and is widely used as a prognostic criterion in patients undergoing heart transplants and LVAD implantations[17] The hemodynamic parameters and creatinine values with different INTERMACS profile of our patients is given in Tables 3 and 4. The patient characteristics for the entire series are shown in Table 5 and the details of prior cardiac interventions in Table 6.

2.4. 90 Day MORTALITY

84% of the patients were alive 90 days after the transplant

A logistic regression analysis of 90 day mortality revealed INTERMACS category (odd's ratio 0.289, $p = 0.000.$) and creatinine more than 1.5 mg/dl (odd's ratio 2.48, $p = 0.056$) as strong predictors of death after transplant. Recipient pulmonary vascular resistance and donor organ ischemic times were not found to be statistically significant factors affecting outcome.

The hospital mortality for INTERMACS 1 and 2 was 34% vs 9% for INTERMACS 3,4 and 5 $p = 0.000$ (Table 7). The outcome results stratified by creatinine levels <1.2 (12.6%), 1.2–1.5 (18.7%) and >1.5 mg/dl (31.8%) $p = 0.012$ are shown in Table 8. The sex of the patient had no bearing on mortality.

2.5. Medium term survival

The Kaplan Meier survival curve shows the survival at one year was 81%, 2 years was 75%, at 3 years was 72% and 62% at 5 years and more for a maximum duration of follow up of 7 years (Fig. 2). Out of the 31 patients operated before 2015 March and thus completed 5 years after surgery, 21 are alive. The five year survival was 68% in this cohort.

The outcomes were better for patients under 18 years of age as compared to more than 18 but was not statistically significant ($p = 0.356$) (Fig. 3).

Medium term survival was significantly affected by INTERMACS category (Hazard ratio > 3 for INTERMACS 1 category compared to INTERMACS 4 or 5, $p < 0.0001$).Table 9 (Fig. 4). and creatinine >1.5 mg/dl (Hazard ratio 2.15, $p = 0.003$) (Fig. 5). This effect of creatinine was related to the age of the recipient (Hazard ratio 1.4, $p = 0.524$) if age < 30 and (Hazard ratio 4.78, $p = 0.006$) if age was >50. Figs. 6–8.

2.6. Analysis of mortality

The causes of death in the first 90 days are shown in Table 10. The causes are not mutually exclusive. Sepsis was the commonest

Table 4
Creatinine values at different INTERMACS categories.

INTERMACS	STRATIFIED BY CREATININE LEVELS			Total
	1	2	3	
1	11	1	8	20
2	22	8	8	38
3	73	18	22	113
4	43	5	6	54
5	1	0	0	1
Total	150	32	44	226

Pearson chi2(8) = 12.7338 Pr = 0.121.

Table 5
Details of investigation for the entire series.

stats	INTERMACS	AGE	ISCHEMIC TIME	PVR	PCWP	PAMEAN	CREATININE	BILIRUBIN	ALBUMIN	CARDIAC INDEX
N	257	257	257.0	209.0	204.0	225.0	226.0	182.0	183.0	162.0
MINIMUM	1	1	41.0	0.3	2.0	11.0	0.2	0.2	0.2	0.7
MAXIMUM	5	78	420.0	16.2	52.0	76.0	5.9	19.8	5.4	4.4
MEAN	2.9	33	171.5	3.1	24.9	33.6	1.2	2.0	3.5	2.0
25th PERCENTILE	2	15	95.0	2.0	18.0	26.0	0.7	0.7	3.1	1.5
MEDIAN	3	31	178.0	2.8	25.0	34.0	1.0	1.2	3.5	1.9
75th PERCENTILE	3	49	238.0	3.8	31.5	41.0	1.4	2.1	3.9	2.3
STANDARD DEVIATION		20	81.5	1.7	9.2	11.1	0.8	2.7	0.7	0.6

Table 6
Prior cardiac interventions.

Ischeamic etiology	113
Non Ischeamic etiology	144
Previous Cardiac Procedures	98
Previous CABG//PCI	34
Mitral Valve repair/Replacement	8
Congenital Heart Repair	15
LVAD	8
CRT/ICD	33
PRA> 50%	8

mode of death in patients with high creatinine and in INTERMACS 1.and 2.The diagnosis of primary graft dysfunction was made if there was ventricular dysfunction. whether right or left. Isolated right ventricular dysfunction with preserved left ventricular function was seen more often in patients with significant ascites. The PVR was not always very high in these patients and may have been underestimated at the time of hemodynamic study due to the profound RV failure. Big heart syndrome was an entity we saw early on in our experience when very sick children who received hearts from bigger donors and had a clinical picture of excessive cardiac output, high blood pressure with headache followed by convulsions and neurologic sequelae in some cases, with death in 2 patients. Late mortality was again multifactorial. Rejection was the cause in some patients followed by deteriorating renal function, graft coronary vasculopathy and sudden unexplained sudden death. There were two instances of CMV infection causing death.

2.7. Quality of life after transplantation

No formal exercise testing with VO2 max has been done for all the survivors. The quality of life is excellent with normal exercise capacity. A few patients have competed in transplant Olympic games and have won marathons in an open field.

3. Discussion

We have attempted to document medium term outcomes of a large series of heart transplant recipients in the Indian subcontinent. When we first embarked on this programme, we were mostly concerned with operative survival, with all its challenges. Heart

Table 7
Hospital mortality stratified by INTERMACS. 1 is for mortality, 0 for survivors.

Survival at 90 days	INTERMACS					Total
	1	2	3	4	5	
0 (ALIVE)	12	34	119	49	1	215
1 (DEAD)	12	12	12	6	0	42
Total	24	46	131	55	1	257

Pearson chi2(4) = 29.4068 Pr = 0.800.

transplant was the first solid organ transplant programme in India to rely completely on cadaveric brain dead organ donation, unlike kidney and liver. Several of the challenges were unique to a developing country like transporting organs over long distances by commercial flights and limiting endomyocardial biopsies, with no precedence elsewhere to seek guidance from. The risk of infection especially tuberculosis and water borne illnesses in an immuno-compromised patient was an unknown entity. It was, therefore, very gratifying to see a one year survival in excess of 80% and a 5 year survival greater than 60%. It must be acknowledged that the overall improvement in the country in terms of communication, availability of internet and smart phones and better laboratory facilities with a capacity to do blood levels of Tacrolimus even in remote locations contributed very significantly to these results.

The message from these outcome data is very clear. If patients are referred early, in good clinical condition, excellent long term outcomes are possible, especially if renal function is well preserved. Our results compare favorably with other groups.[18] The correlation between worse outcomes in lower INTERMACS categories after heart transplant are well documented in other reports as well.[19]

Table 8
Hospital mortality stratified by creatinine levels.1 is for mortality,0 is for survivors. CREATININE LEVEL 1 (< 1.2 mg /dl) 2 (1.2-1.5 mg/dl) 3 (>1.5 mg/dl) Higher mortality with higher creatinine levels is evident.

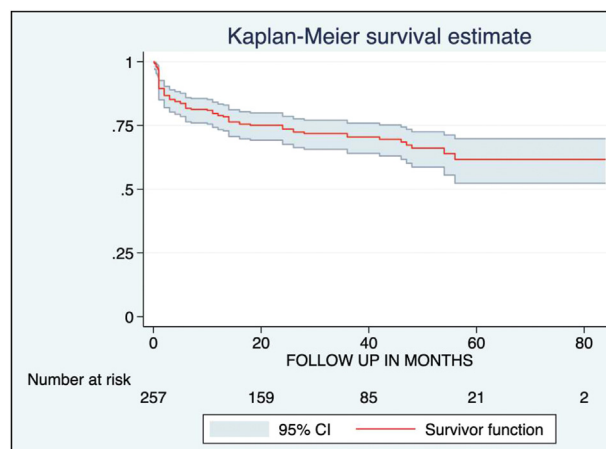| Survival at 90 days	STRATIFIED BY CREATININE LEVELS			Total
	1	2	3	
0	131	26	30	187
1	19	6	14	39
Total	150	32	44	226

Pearson chi2(2) = 8.7972 Pr = 0.012.

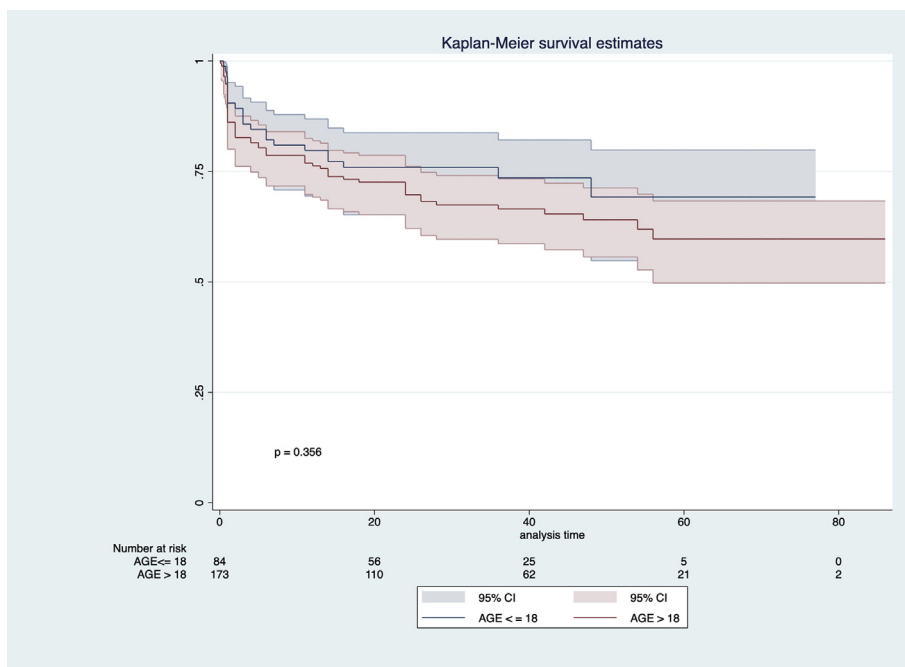**Fig. 2.** Kaplan meier survival estimate for the entire series.

Fig. 3. Effect of age on survival. Patients less than 18 tended to have better survival but the difference is statistically not significant.

The absence of impact of PVR and ischemic times on outcomes is probably reflective of our donor selection criteria. Choosing a young donor heart with excellent ventricular function when longer ischemic times are expected and choosing a LVAD if the PVR was felt to be very high. There was no absolute upper limit to PVR values beyond which patients were denied a transplant but PVR values beyond 5 wood units in big built recipients need careful evaluation. In general, children tended to have a higher PVR. Using an oversized donor heart often overcomes this problem. The most unfavorable situation is a recipient weighing in excess of 90 kg with a high PVR. If the right ventricular function is satisfactory, they are best treated with an LVAD.

The underlying diagnosis of the heart disease did not significantly affect outcomes. Restrictive cardiomyopathy had similar outcomes to dilated cardiomyopathy. Congenital heart disease had excellent results, except for a subset of patients with univentricular heart with a previous Fontan operation. This is a difficult category of patients because of several risk factors including multiple previous operations, blood transfusions and multiple pulmonary artery interventions including stents. They are often sensitized due to higher PRA values increasing the risk of rejection.

Rejection is an important and potentially preventable cause of mortality both early and late. Cell mediated rejection is easier to diagnose and treat than antibody mediated rejection. Donor

specific antibody testing is not available easily across the country, is expensive and often the result is available only a few days later. Immunohistochemistry of biopsy specimens need expertise, not always found. The protocol of limiting biopsies was based on our infrastructural realities and is not a virtue in the absence of blood based immune monitoring strategies like donor derived cell free DNA estimations and Immune Cell Function Assay (Cylex, Inc., Columbia, MD, USA) developed to measure the activity of CD4+ T cells as a marker of global immune-competence and allogene map testing. None of these tests are currently commercially available in this country. The results presented here may be encouraging but clearly there is a great scope for improvement.

An analysis of our early mortality is very revealing. Patients resuscitated on ECMO are high risk recipients. Clearly earlier referral can improve the situation.

As is evident from this study, the impact of renal dysfunction on outcomes after transplantation is profound. Creatinine had a significant effect on both early and medium term survival. The effect of higher creatinine values was strongly influenced by increasing age of the recipient. The incidence of chronic kidney disease (CKD) increases progressively with time after transplantation especially in those with pre-existing medical renal disease. Therefore, this problem is becoming more apparent as long-term survival improves. A number of factors contribute to CKD after a transplant. Calcineurin inhibitors have been recognized as an important nephrotoxic factor. Other predictors of CKD include post-operative acute renal failure, DM and increasing recipient age. Although CKD was mostly asymptomatic, some patients went on to end-stage disease requiring long-term dialysis. Lubitz et al reported a cumulative probability of end-stage renal disease (ESRD) of 4.5% at 5 years, 19.6% at 10 years and 44.6% at 15 years following HTx, while ISHLT reported a 27% cumulative probability of developing severe renal dysfunction dialysis or renal transplant] by 5 years, 34% by 7 years and 42% by 10 years.[20] There is no clear policy in India for organ allocation for combined heart and kidney transplant. In our state, the kidney draws the heart and not the other way around, as it should be. That needs to change as the kidney wait list time is in

Table 9
Cox regression based equality of survival curves. INTERMACS 1 and 2 have a significantly higher relative hazard for death as compared to higher categories.

INTERMACS	Events	Events	Relative
	observed	expected	Hazard
1	14	5.710	3.242
2	20	12.570	2.093
3	34	45.060	0.985
4	13	17.310	0.982
5	0	0.350	0.000
Total	81	81.000	1.000

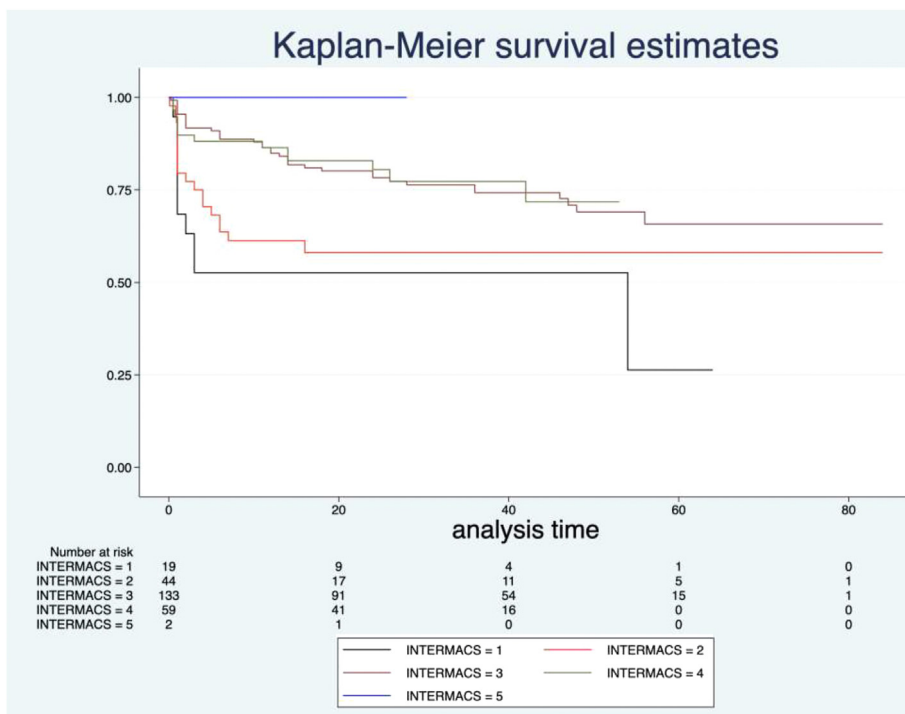LR chi2(3) = 17.25 Pr > chi2 = 0.0006.

Fig. 4. Kaplan meier survival estimate stratified by INTRERMACS. Categories 1 and 2 have significantly inferior survival.

years. Lot of these patients with profound renal dysfunction would be better candidates for a combined organ transplant. Also more affordable VADs would allow us to offer transplants to patients best suited to receiving them, improving long term outcomes. Malignancy is a serious complication following transplantation that appears to be mainly caused by pharmacological immunosuppression. Surprisingly there was only one documented case of non Hodgkins lymphoma in our series and that patient recovered completely with treatment. In three other patients there was new onset malignancy including one recurrence of a breast carcinoma. All of them are alive after appropriate therapy.
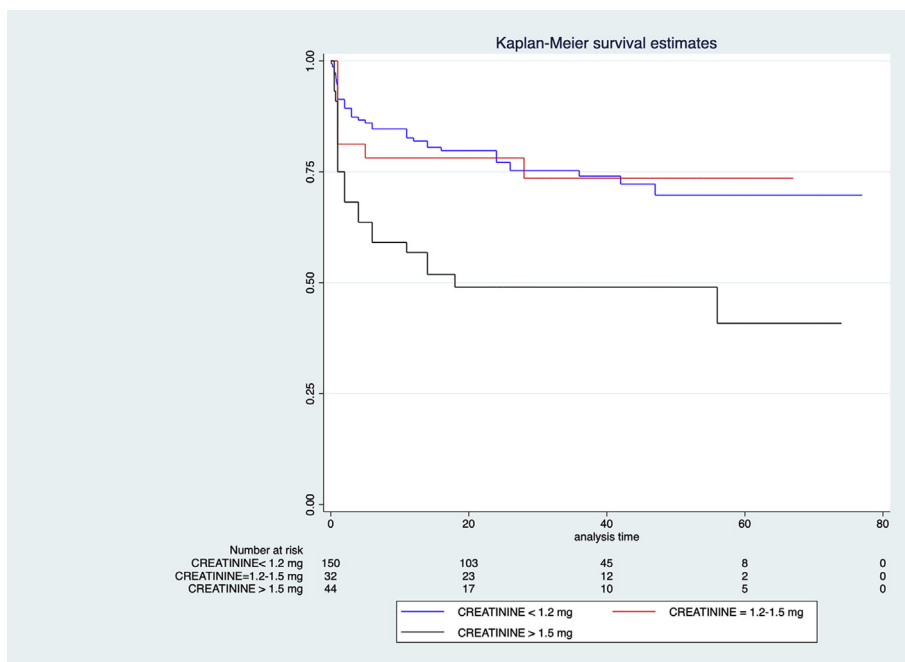

Fig. 5. Kaplan meier Survival curve stratified by 3 different creatinine values. Survival is worse if Creatinine is > 1.5 mg/dl has.
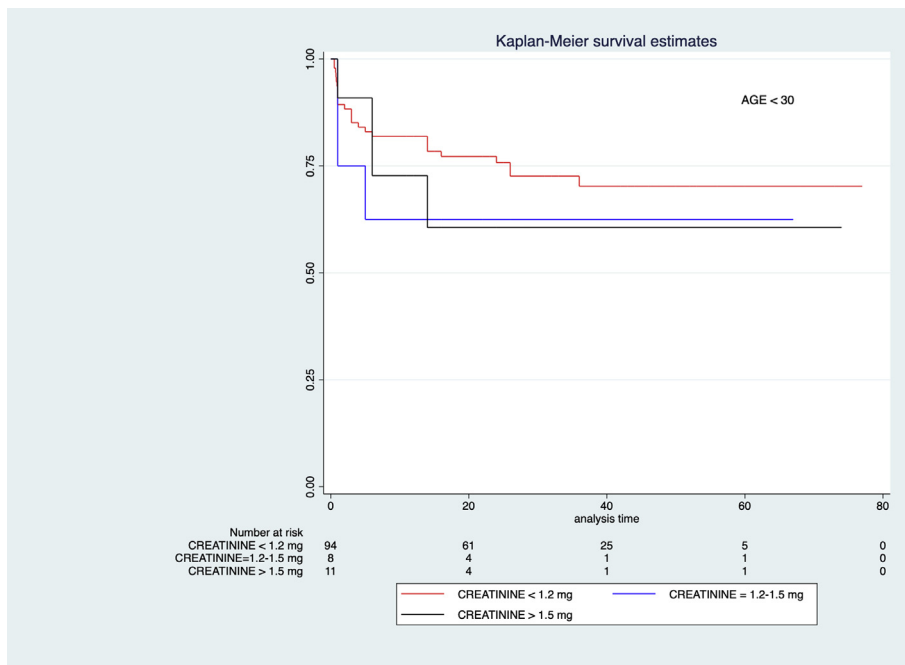
Fig. 6. Kaplan meier curve stratified by creatinine. Influence of age <30. All the three survival curves are better. Age has a significant bearing on the effect of creatinine on survival.

CMV infection is the most common opportunistic infection following transplantation. 4 patients developed CMV infection necessitating treatment with 2 deaths. This probably reflects effective prophylaxis with valganciclovir.[21] There were 5 deaths related to other opportunistic infections including tuberculosis in 1. In striking contrast to LVAD therapy, only one patient in the entire series developed a stroke after surgery.

3.1. Study limitations

This was an observational cohort study giving an overall survival data. The exact cause of death occurring several years after surgery, in many instances, was not easy to ascertain with great certainty, in the absence of records or autopsy. The exact incidence of Cardiac allograft function remains conjectural as patient evaluation was by echocardiography, coronary angiography and endomyocardial
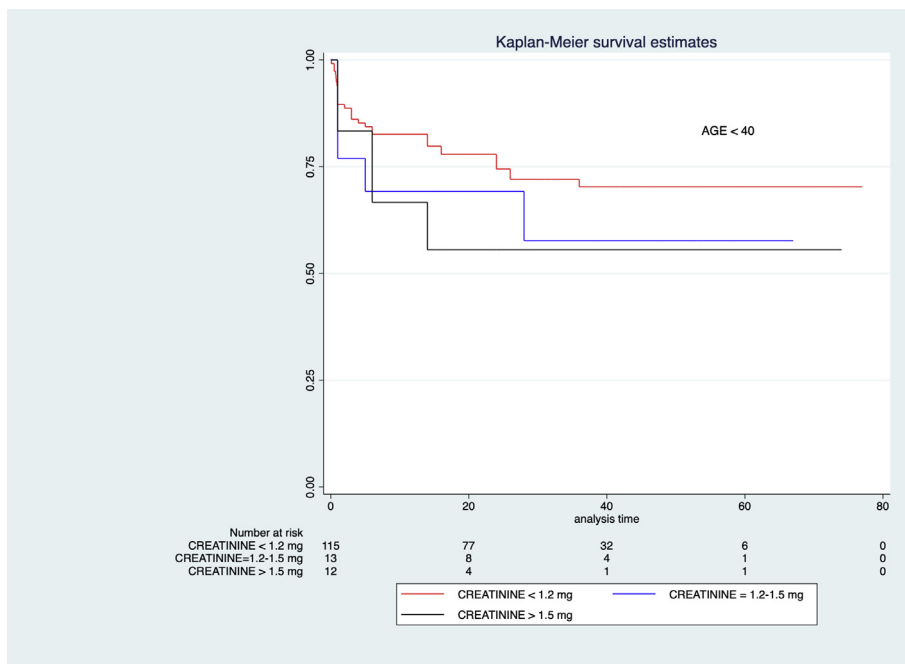

Fig. 7. Kaplan meier survival curve stratified by creatinine levels. If the age <40. As age increases, the influence of creatinine on survival is more.
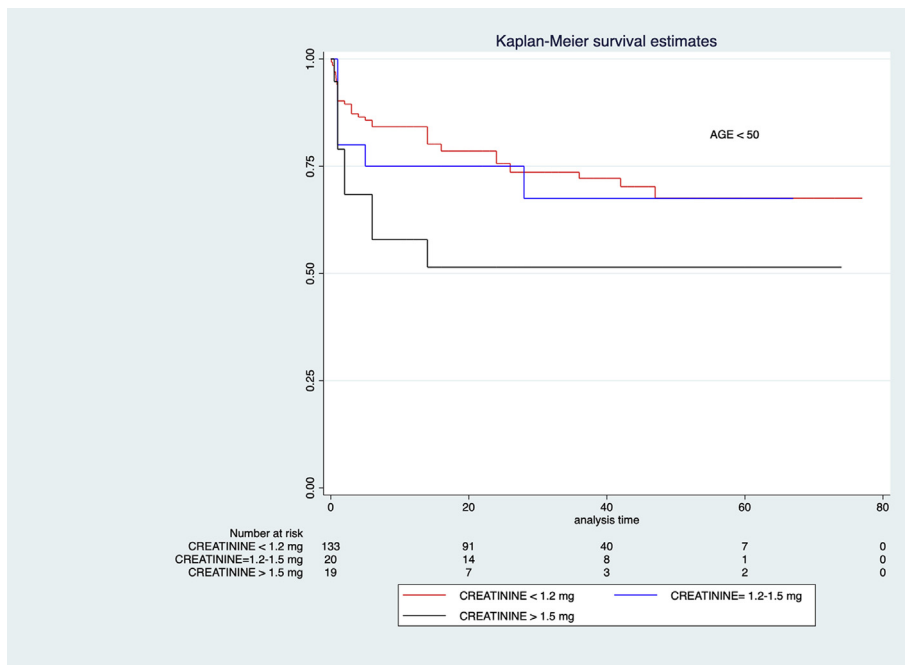
Fig. 8. Kaplan meier survival curve influence of creatinine levels. Age <50. Effect of age is obvious.

Table 10
Causes of 90 day mortality.

Sepsis	16
Ventricular dysfunction	17
Rejection	7
Stroke	1
Big heart syndrome	2

biopsy and only few patients were tested by intra-vascular ultra-sound or optical coherence tomography.

4. Conclusions

The medium term outcomes after heart transplantation are satisfactory in India with results comparable to outcome data from ISHLT. The risk factors for both early and late mortality are INTER-MACS categories 1 and 2 and creatinine values greater than 1.5 mg/dl especially in older patients. Patients need to be referred early in good functional class for optimal outcomes.

Our sincere thanks to Aishwarya trust for help in data collection.

Conflicts of interest

All authors have nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2020.09.010.

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