# Clinical profiles and risk factors for early and medium-term mortality following heart transplantation in a pediatric population: A single-center experience

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## ABSTRACT

**Aims and Objectives** : **There is a paucity of data regarding the outcomes of Heart transplantation in children from the Indian subcontinent. The data of patients under the age of 18 undergoing an isolated heart transplantation was analyzed for patient clinical profiles and risk factors for early and medium-term mortality. Hospital mortality was defined as death within 90 days of transplantation and medium-term survival as follow up of up to 6 years.**

**Materials and Methods** : **A total of 97 patients operated between March 2014 and October 2019 were included in this study .Data was collected about their INTERMACS status, pulmonary vascular resistance, donor heart ischemic times, donor age, donor to recipient weight ratio and creatinine levels.**

**Results** : **The age range was from 1 to 18 with a mean of 10.6 ± 4.6 years. 67 % patients were in INTERMACS category 3 or less.12 children were on mechanical circulatory support at the time of transplant. The 90 day survival was 89 %.The risk factors for hospital mortality was lower INTERMACS category (odd's ratio 0.2143, *P* = 0.026), elevated creatinine (odd's ratio 5.42, *P* = 0.076) and elevated right atrial pressure ( odd's ratio 1.19, *P* = 0.015).Ischemic time, pulmonary vascular resistance (PVR) and PVR index (PVRI) had no effect on 90 day survival. Kaplan Meier estimates for 5 year survival was 73 %.The medium term survival was affected by INTERMACS category (Hazard ratio 0.7, *P* = .078) , donor age > 25 ( Hazard ratio 1.6, *P* = 0.26) and raised serum creatinine values.(Hazard ratio 2.7, *P* = 0.012). All the survivors are in good functional class.**

**Conclusions** : **Excellent outcomes are possible after heart transplantation in a pediatric population even in a resource constrained environment of a developing economy. More efforts are needed to promote pediatric organ donation and patients need to be referred in better INTERMACS category for optimal outcomes.**

**Keywords** : **Pediatric Heart transplant, Pediatric heart transplant India, pediatric heart transplant Outcomes**



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## INTRODUCTION

There is a paucity of data regarding the outcomes of heart transplantation in children from the Indian subcontinent despite the fact that the first successful heart transplant was reported more than a quarter of a century ago.[1] This study was undertaken to analyze the clinical profiles and the risk factors for early and medium-term mortality in a pediatric population undergoing heart transplantation in a single center in a private health care setting in India.

## MATERIALS AND METHODS

The data of patients under the age of 18 years undergoing isolated heart transplantation were analyzed for patient clinical profiles and risk factors for early and medium-term mortality. Hospital mortality was defined as death within 90 days of transplantation, and medium-term survival involved follow-up of up to 6 years.

A total of 97 patients operated between March 2014 and October 2019 were included in this study. Patients undergoing a combined Heart and lung transplant and those whose complete medical records could not be accessed were excluded ($n$ = 7). The age of the patients ranged from 1 to 18 (mean 11 ± 4.5, median 12) years. The youngest was 1 year old at the time of transplant and 40 patients were 10 years or younger. There were 52 males and 45 females. The age distribution is shown in Figure 1.

### Diagnosis

The most common indication for a transplant was dilated cardiomyopathy as a clinical diagnosis, followed by restrictive cardiomyopathy and congenital heart disease [Tables 1 and 2].

### Functional status

The functional class of these patients was captured by the Interagency registry of Mechanically Assisted Circulatory Support (INTERMACS) score, which is currently widely used to categorize the degree of the sickness of adult patients in end-stage heart failure awaiting transplantation or mechanical assist devices.[2,3] The INTERMACS profile of the patients in this series is given in Figure 2 and the United Network for Organ Sharing (UNOS) category[4] in Figure 3. Thirty-five percent of patients were in INTERMACS 1 or 2 category.

### Patient characteristics

These details are given in Tables 3 and 4. Ten percent of these patients had a history of stroke though, by the time of the surgery, no patient had a significant neurologic deficit. Clinically obvious ascites was seen in 12 patients and in 14 more patients, there was ultrasound evidence of free fluid in the abdomen. A modified MELDS score without INR was calculated in these children [Table 5].[5]

A total of 12 children were on mechanical circulatory support before transplant, 11 on Extra corporeal membrane oxygenator (ECMO) and one on Heart ware HVAD (Medtronic, Minneapolis, USA) pump. Out of the 11 patients on ECMO, 3 were converted to CENTRIMAG (Abbot, Chicago, Illinois, USA) and one to an axillary IMPELLA pump (Abiomed, Danvers, Massachusetts) before transplant.

### Hemodynamic evaluation

Whenever possible, a hemodynamic evaluation for estimating the pulmonary vascular resistance (PVR)

**Table 1: Diagnosis of pediatric patients undergoing cardiac transplantation**

| Diagnosis | Numbers |
|---|---|
| Dilated cardiomyopathy | 61 |
| Restrictive cardiomyopathy | 16 |
| Hypertrophic cardiomyopathy | 6 |
| Congenital heart defect | 11 |
| Viral myocarditis | 3 |

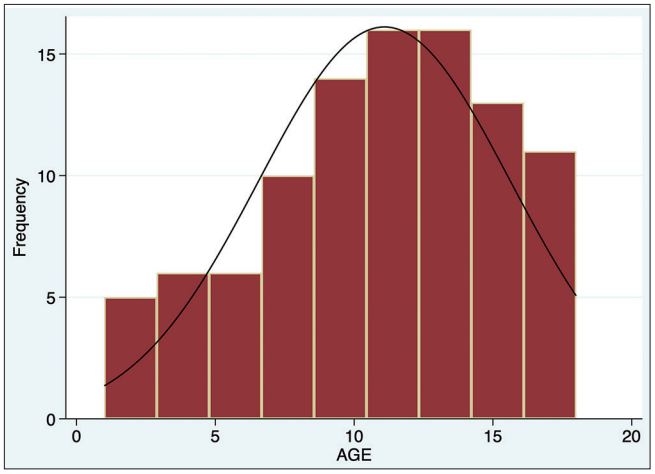


**Figure 1: Age distribution**

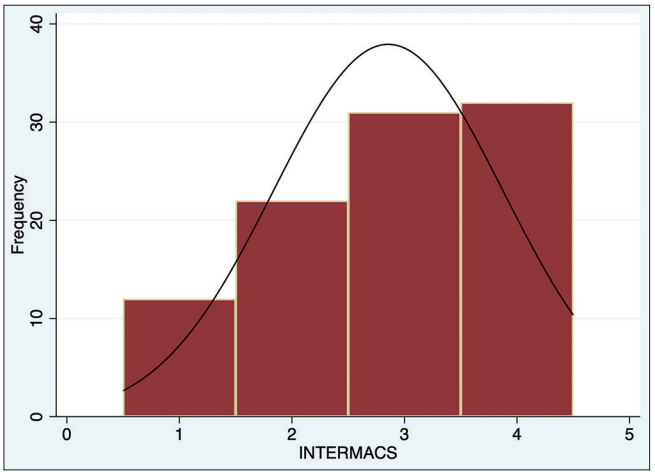


**Figure 2: Intermacs category**

**Table 2: Diagnosis in patients with congenital heart disease**

| Diagnosis |
|---|
| 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 |
| S/P Sinus Venosus ASD Closure, RV Dysfunction, Early Cirrhotic changes in liver, Massive ascites, TIA |
| DORV, Severe PS, Perimembranous VSD with outlet extension- NonRoutable, Side by side great arteries, S/P BT shunt, S/P BDG + MPA interruption, S/P LV aneurysm repair |
| Tricuspid Atresia, Single ventricle, Severe PS, TGA |
| Mitral Atresia, Hypoplastic LV, DORV, Severe PS, ASD, AV Valve regurgitation, S/P left BT shunt |
| 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 |
| Tricuspid Atresia, Single ventricle, S/P BT shunt, S/P BDG, S/P Fontan |
| 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 |

LV: Left ventricle, DORV: Double outlet right ventricle, PS: Pulmonary stenosis, RA: Right atrium, IVC: Inferior venacava, TAPVC: Total anomalous Pulmonary venous connection, AV: Atrioventricular, VSD: Ventricular septal defect, S/P: Status post, BT: Blalock taussig, BDG: Bidirectional glenn, MPA: Main pulmonary artery, TGA: Transposition of great arteries, ASD: Atrial septal defect, LPA: Left pulmonary artery, OP: Ostium primum, SVC: Superior vena cava, DILV: Double inlet left ventricle

**Table 3: Patient details**

| | Age | Weight | Bsa | Intermacs | Ischemic time | Right atrial pressure | PVR | PVRI | Creatinine | Bilirubin | Albumin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Minimum | 1.0 | 7.0 | 0.4 | 1.0 | 41.0 | 2.0 | 0.6 | 0.7 | 0.2 | 0.2 | 0.2 |
| Maximum | 18.0 | 81.0 | 2.0 | 4.0 | 395.0 | 35.0 | 16.2 | 11.3 | 2.3 | 16.2 | 5.4 |
| 25$^{th}$ Percentile | 8.0 | 20.0 | 0.8 | 2.0 | 113.0 | 8.0 | 2.0 | 2.2 | 0.5 | 0.5 | 3.1 |
| Median | 12.0 | 28.0 | 1.0 | 3.0 | 200.0 | 13.0 | 3.0 | 3.6 | 0.6 | 1.1 | 3.6 |
| 75$^{th}$ Percentile | 14.0 | 42.0 | 1.3 | 3.0 | 247.0 | 20.0 | 4.2 | 4.8 | 0.9 | 2.0 | 4.1 |
| Mean | 10.9 | 31.3 | 1.1 | 2.8 | 185.6 | 14.0 | 3.5 | 3.8 | 0.7 | 1.9 | 3.5 |
| Standard Deviation | 4.6 | 15.6 | 0.4 | 0.9 | 76.4 | 7.1 | 2.5 | 2.1 | 0.4 | 2.6 | 0.8 |

Age in years, weight in kilograms, BSA in m2, ischemic time in minutes, right atrial pressure in mmHg, PVR in Woods Units, PVRI in Woods Units m2, Creatinine in mg/dl, bilirubin in mg/dl, albumin in g/dl. INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support, BSA: Body surface area, PVR: Pulmonary vascular resistance, PVRI: PVR indexed

was carried out. This was often done in the intensive care unit. This was avoided in children with restrictive cardiomyopathy because of the risks involved in the procedure. Hemodynamic studies were also not performed on patients presenting for the first time on ECMO. If the PVR was high, 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. The range of PVR and pulmonary resistance indexed (PVRI) to the body surface area (PVR × BSA) encountered is shown in Table 3. The mean PVR was 3.5 ± 2.5 wood units. There were instances when a good pulmonary artery (PA) wedge tracing could not be obtained, despite repeated attempts, making estimations of pulmonary vascular resistance difficult. Under these circumstances, mean PA pressure estimations were used to guide decision-making aided by echocardiographic estimations of left atrial pressure knowing fully well the possible errors this entails in a pediatric population.[6,7] We validated the relationship between PVR and Mean PA pressure [Figures 4 and 5]. The correlation coefficient between mean pulmonary pressure and PVR or PVRI in children was lower than the value in adults in our series. Decisions regarding operability were taken after considering the values for pulmonary and systemic resistance, transpulmonary gradient, weight of the patient, and the right ventricular function. In patients with a high PVR, an attempt was made to select a donor heart with higher body weight.

### Preformed panel reactive antibodies

All patients were evaluated for preexisting HLA class I and II antibodies in the blood. Patients with PRA levels of >50% ($n$ = 7) 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 crossmatch was positive, plasmapheresis was done on cardiopulmonary bypass (CPB) and rituximab was added If donor-specific antibody was positive postoperatively. In 3 patients, preoperative Rituximab and immunoglobulin treatment was carried out prior to transplant. This was particularly seen in patients with previous cardiac operations, especially the FONTAN procedure, where typically several operative interventions are common prior to referral for a transplant.

### Preoperative recipient and donor evaluation

Patients with congenital heart disease had a computed tomography (CT) scan to evaluate the anatomy and plan for the technical aspects of the transplant. 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. 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 3 instances 3D printing of the recipient's 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 recipient's condition and the donor-recipient weight ratio.

**Table 4: Patient details - Preoperative characteristics**

| | |
|---|---|
| Previous stroke | 9 |
| History of cardiac arrest | 10 |
| Significant ascites | 12 |
| Cirrhotic changes in the liver | 6 |
| Prior cardiac surgery | 14 |
| Malignancy | 2 |
| Crtd/ pacemaker/ RF ablation | 3 |
| Popliteal embolectomy | 1 |

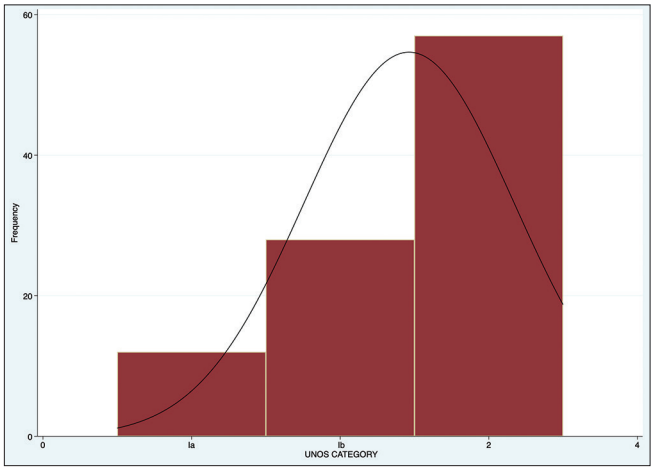


**Figure 3: United Network for Organ Sharing category of the patients**

### Ischemic time

The details are given in Figure 6. The median ischemic time was 200 min.

### Technique of transplantation

Standard techniques were used for the harvesting of the heart, and protection was by Custodial-HTK (Histidine- Tryptophan- Ketoglutarate Sandor, Hyderabad, Telangana) cardioplegia. For recipients with bilatéral vena cava and those with malposed great vessels, a long segment of the innominate vein attached to the superior vena cava (SVC) and PA with branches and a 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 (Biatrial anastomosis) was used.[8]

Congenital heart disease was the indication in 11 patients and the detailed diagnosis is shown in Table 2. A variety of techniques were used in these patients to do the transplant and that is the subject of a separate manuscript.

Three patients had significant pulmonary branch abnormalities. Two had a left PA stent with significant stenosis, one had an absent Right PA. One patient had an aneurysmal SVC to PA anastomosis.

Five patients had a previous Fontan procedure or its variants.

### Hearts from older and bigger donors

Pediatric donors are scarce in India, and we have used hearts from older and bigger donors to overcome the problem of organ shortage. This is especially so

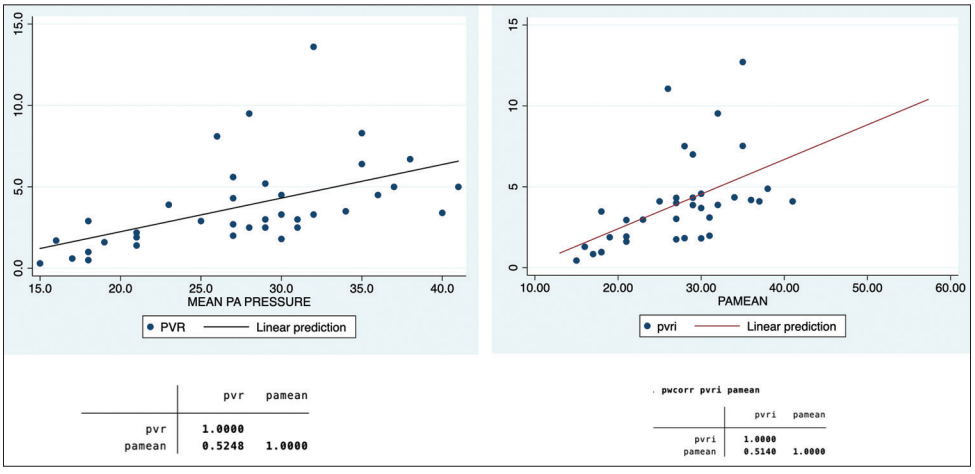


**Figure 4: Scatter plot between PVR (L) and PVRI (R) and mean pulmonary pressure with a regression line and a Pearson's coefficient in the inset**

**Table 5: Meld score of the children in this series**

| | Minimum | 25th Percentile | Median | 75th Percentile | Maximum | Mean | Standard deviation |
|---|---|---|---|---|---|---|---|
| Meld Score | 6 | 10 | 14 | 19 | 33 | 15 | 6 |

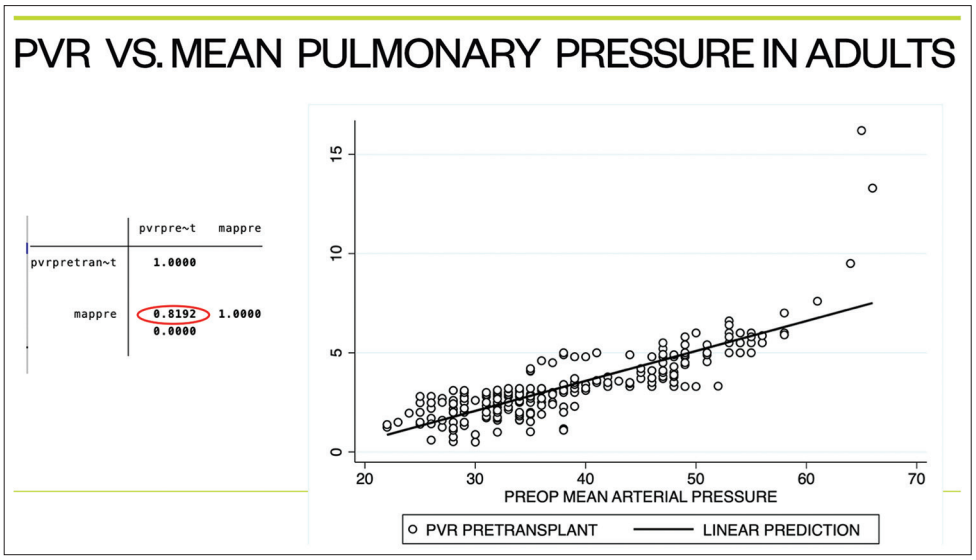


**Figure 5: Correlation between pulmonary vascular resistance and mean pulmonary pressure in adults in our series. The correlation is better**

because mechanical circulatory support is often difficult in children, given our realities. The disease is often biventricular, restrictive cardiomyopathy imposes significant challenges in terms of the ventricular cavity size, and longer-term devices are expensive. We have used a heart ware HVAD (Medtronic, Minneapolis) in 3 children successfully. The mainstay of mechanical support is Veno arterial ECMO and CENTRIMAG (Abbot, Illinois, USA).

### Donor to recipient weight ratio

Data was available for 91 patients. There were 61 patients with donor: Recipient weight <2.5:1 and 30 with donor weight more than 2.5:1 [Figure 7].

### Donor age

The details were available for 91 patients. In 51 patients the donor was ≤25 and in 40 patients, the donor age was more than 25 years.

### Immunosuppression

Since cardiorenal syndrome with deranged renal function was seen in over 10% of the patients, induction therapy became a standard procedure. 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 CPB along with injction methylprednisolone given at a dose of 20 mg/kg up to 1 g in divided doses and given at the time of initiation of CPB and during aortic cross-clamp release.

### Maintenance therapy

Mycophenolate mofetil is started on the 1st postoperative day in a dose of 10–20 mg/kg/dose up to a dose of 600 mg/$m^2$ twice daily and is continued lifelong. Tacrolimus is usually started on the 2nd postoperative day at a dose of 0.5–1 mg, considering numerous factors such as renal profile, gut absorption, drug interaction, and genetic polymorphisms of cytochrome enzymes. The dose is adjusted more recently (after 2018) according to the tacrolimus genotype sensitivity test, with low dose for poor metabolizers and a 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. Steroids are rapidly tapered by the end of the week to 5 mg/day and usually stopped by 6 months.

### Endomyocardial biopsies

Following the Western protocol of endomyocardial biopsies in the 1st posttransplant year was not practically feasible in our country.[9,10] Apart from the significant costs involved, patients and their caregivers had to be available in the city for up to 1 year, which was impossible given the Indian realities. We limited the number of biopsies to one by the end of the 2nd 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.

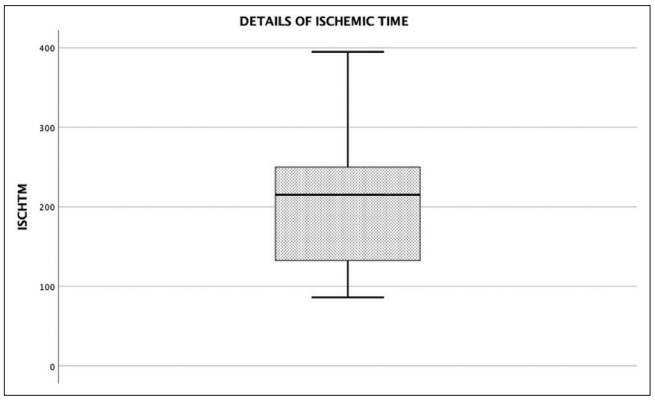


**Figure 6 : A box plot of the ischemic time.The line in the middle is the median value.The edges of the box are the 25th and 75th percentile and the edges of the whiskers represent the lowest and highest values**

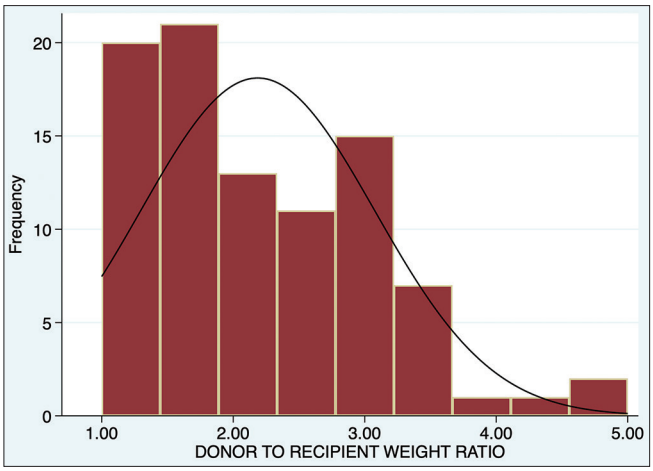


**Figure 7: Histogram of the donor to recipient weight ratio. The line represents the distribution curve**

### Statistical analysis

The outcome data were tracked by dedicated staff who tracked all the patients in this series, either during direct visits to the hospital or telephonically. The widespread availability of smartphones in recent times has been a great boon for follow-up studies. Statistical analysis was done using STATA 16 (Stata Corps, LLC, Texas, USA) and SPSS (IBM) (version 25). In relevant situations, we have provided "*P*" values, out of consideration for established traditions. We are fully aware of the recent position statement regarding *P* values by the American statistical association.[11,12] While using logistic regression, we have chosen to use odd's ratios rather than log coefficients. Cox regression results are reported with hazard ratios and not coefficients.

## RESULTS

### Hospital mortality

The survival was 89% at 90 days with 11 deaths of 97 patients within 90 days of transplant. The risk factors for hospital mortality was lower INTERMACS category (odds ratio 0.2143, $P = 0.026$), elevated creatinine (odds ratio 5.42, $P = 0.076$) and elevated right atrial pressure more than 15 (odds ratio 5.2, $P = 0.054$), donor to recipient weight ratio >2.5 (odds ratio 2.8, $P = 0.1$), presence of ascites (odds ratio 4.07, $P = 0.020$) and MELD score (odd's ratio 1.17, $P = 0.074$). A margins plot using logistic regression shows the increasing risk of hospital death with higher MELDS scores [Figure 8]. Ischemic time, PVR and PVRI had no significant effect on 90-day survival. The mortality for INTERMACS 1 and 2 was 23. 5% versus 4.7% for INTERMACS 3 and more ($P = 0.047$).

### Medium-term survival

At the conclusion of the study period, 73 of the 97 patients were alive. The Kaplan–Meir estimate for survival at 5 years and beyond was 73% [Figure 9]. The longest follow-up was 6 years. A cox proportional hazard analysis showed the medium-term survival to be significantly impacted by the preoperative INTERMACS category (hazard ratio 0.701, $P = 0.078$) [Figure 10], donor age more than 25 (hazard ratio 1.6, $P = 0.26$) [Figure 11], creatinine more than 1.2 mg/dl (hazard ratio 2.53, $P = 0.130$), presence of ascites (hazard ratio 1.84, $P = 0.16$) [Figure 12] and MELD score more than 20 (hazard ratio 2.36, $P = 0.161$) [Figure 13]. Results similar to INTERMACS were obtained by UNOS categorization,[4] [Figure 14]. Preoperative PVR and PVRI had no effect on early or late survival (PVR cutoff 4 woods units). The duration of cold ischemia of the donor's heart had no effect on short-term or long-term survival.

### Donor weight on survival

The Kaplan–Meir curve stratified by donor-recipient weight ratio is shown Figure 15. There was no incremental risk noted on late survival stratified by donor to recipient weight ratio of less than or more than 2.5:1. Early on in our experience, excessive donor weight posed problems. "Big heart syndrome" was an entity when very sick children who received hearts from bigger donors had a clinical picture of excessive cardiac output, high blood pressure with headache followed by convulsions and neurologic sequalae in some cases, with death in 2 patients. Five other children had convulsions needing anti convulsive treatment. We now avoid inotropes, decrease the cardiac output, reduce the dp/dt with aggressive vasodilatation and it is no longer a problem. In 3 instances, the chest had to be kept open for a few days to accommodate the bigger donor heart.

### Effect of donor age on survival

The medium-term outcomes are significantly decreased if the donor age is >25 [Figure 11]. The event-free survival rates in terms of need for angioplasty or

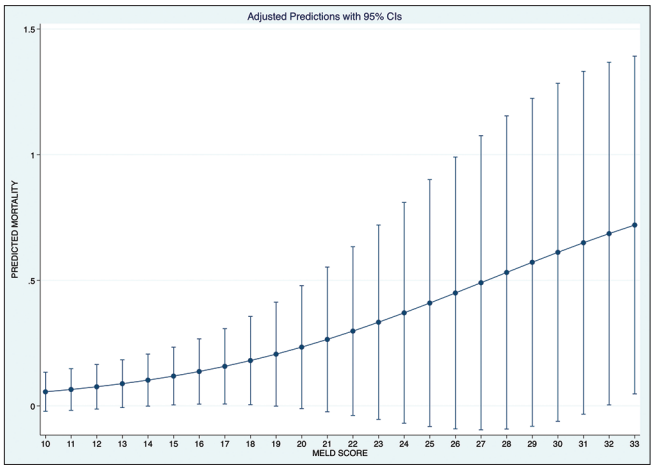


**Figure 8: A "margins" plot derived from logistic regression analysis of the predicted hospital mortality with increasing MELD score. The bars represent the confidence intervals of each value**

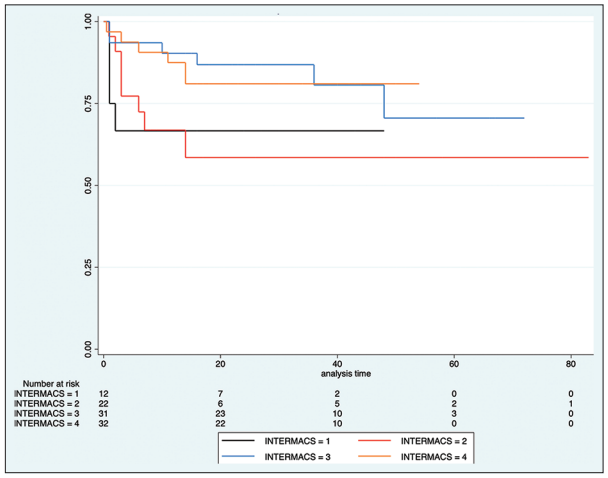


**Figure 10: Kaplan–Meier curve stratified by Interagency registry of Mechanically Assisted Circulatory Support**

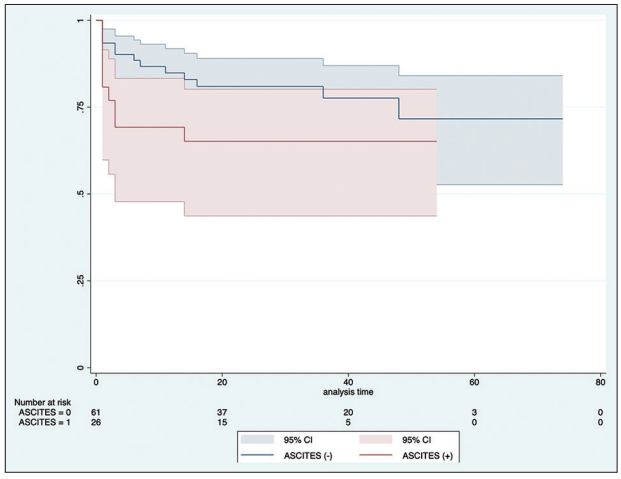


**Figure 12: Kaplan–Meier survival curve of patients with and without ascites**

coronary bypass grafting was also worse if the donor age was >25 years [Figure 16].

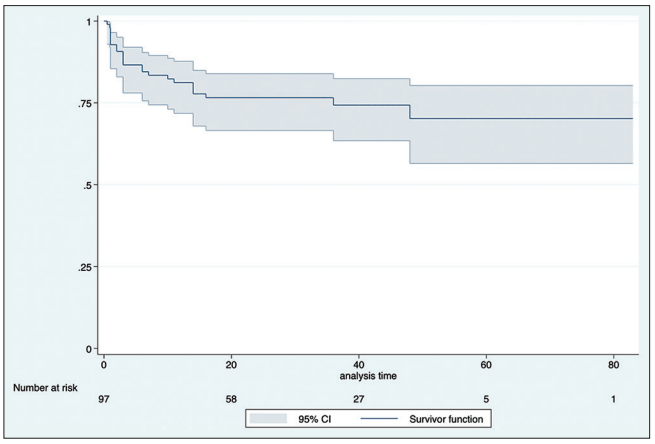


**Figure 9: Kaplan–Meier survival curve for the series. The numbers in the inset represent the number of patients at risk**

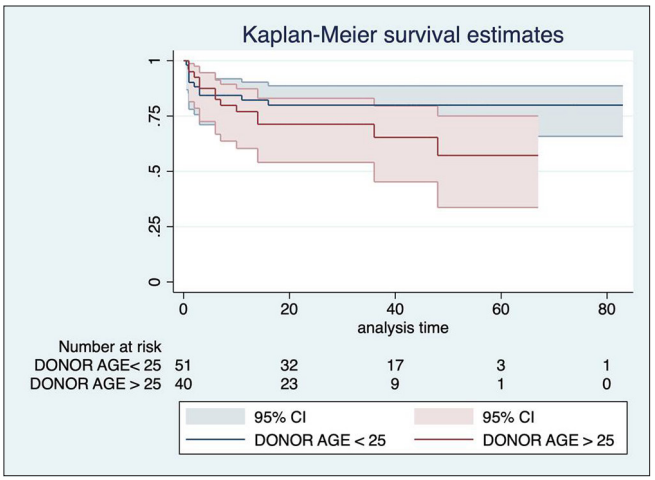


**Figure 11: Kaplan–Meier curve stratified by donor age more or <25**

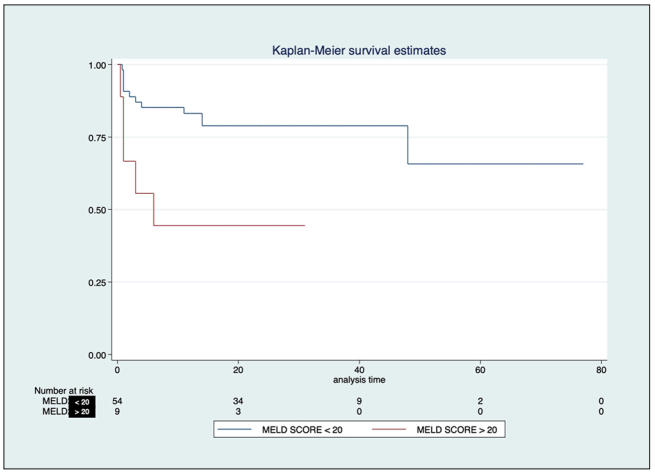


**Figure 13: Kaplan–Meier curve stratified by MELD score more than and <20**

## Mechanical circulatory support on survival

Out of the 12 children who were on mechanical circulatory support in this series, 8 are long-term survivors, including the child on a Medtronic HVAD who

was on VAD support for 9 months. One of the patients on ECMO followed by CENTRIMAG support developed severe mixed antibody and cell-mediated rejection after 4 years with severe ventricular dysfunction and recovered completely with pulse steroids. Out of the 4 children who died, 3 had bacterial sepsis and died within 3 weeks of transplant and one patient died 80 days after the heart transplant of viral meningitis. The longest duration of ECMO support was 6 weeks followed by a successful transplant. Another child needed ECMO support 3 times during the hospital stay, one for pre-transplant cardiac arrest, one on the night of transplant for severe primary graft dysfunction and one three weeks later for severe right ventricular dysfunction due to donor coronary artery disease. This child is a long-term survivor.[13]

### Incidence of rejection

Sixteen patients had at least one episode of clinical rejection by 6 years. If detected in time, usually by a drop in ventricular function, they responded very well to pulse steroid therapy and increasing immunosuppression. The true incidence of rejection is impossible to estimate because we do only one biopsy before discharge and then one every year. We had 4 asymptomatic children where biopsy showed cell-mediated rejection. Biopsies are expensive, cost INR 85,000 in our hospital. If antibody-mediated rejection is seen, then a Donor-specific antibody test is done, which is another INR 45,000. Unexplained sudden death or rapid deterioration in ventricular function was presumed to be rejection. Since no autopsies were done, it is not easy to be certain about the cause of death.

### Causes of hospital mortality

Out of the 11 patients who died within the first 90 days after surgery, 3 died of acute rejection, 2 died of neurological consequences due to a bigger donor heart, 2 had primary graft dysfunction, and 4 died of sepsis. Causes of death were not mutually exclusive, and often the final common pathway of death was sepsis.

### Quality of life

We have not done formal exercise testing studies in transplant survivors. The quality of life, as reported by the patient or caregivers is excellent, and all the survivors are in functional Class I, able to take part in strenuous physical activity and competitive sports.

### Coronary reinterventions

Three patients have needed coronary reinterventions, 2 of them multiple. One 14-year-old girl received a 41-year-old donor heart, which showed premature coronary artery disease at 6 months. She needed three percutaneous interventions and finally needed a Left internal mammary artery to LAD through a small thoracotomy. Another 7-year-old boy needed an LAD and RCA stent 3 weeks after surgery. He was on ECMO with torrential gastrointestinal bleed and we had to use a heart from a donor in his fifties. At the end of 1 year, he needed left main stenting and at 3 years follow up, a percutaneous intervention to the circumflex, which was

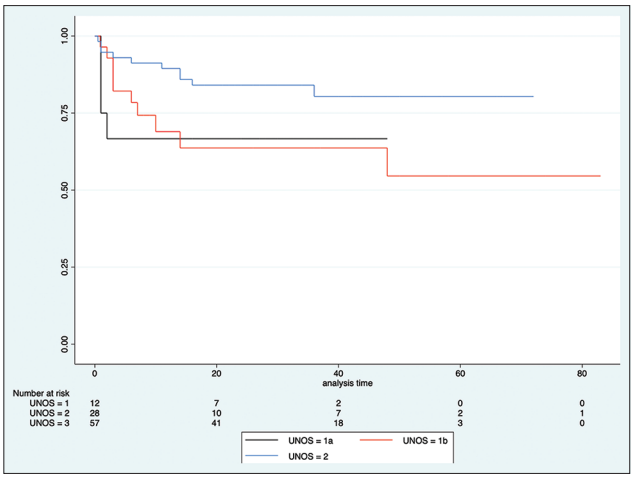


**Figure 14: Kaplan–Meier survival curve stratified by United Network for Organ Sharing category**

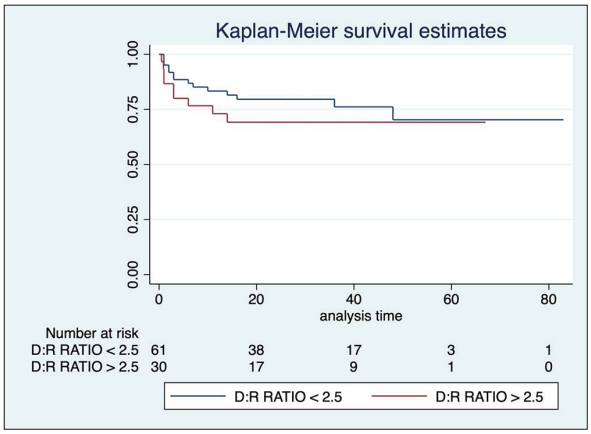


**Figure 15: Kaplan–Meier curve stratified by Donor to recipient weight ratio of more than and <2.5:1**

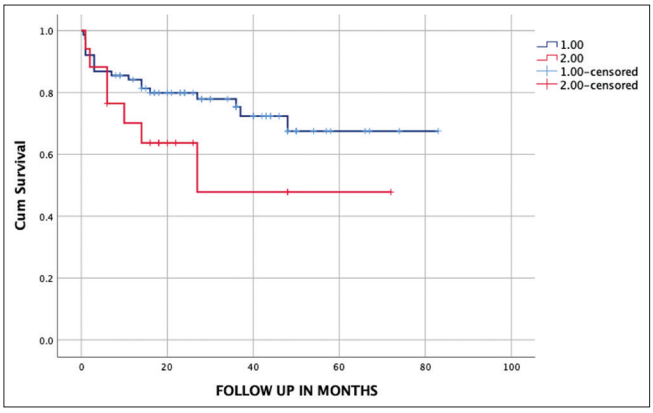


**Figure 16: Effect of older donor age on event free survival. Blue is donor age less than 25 and red is more than 25**

not tackled in the earlier sitting.[13] Both these patients have excellent ventricular function and are normal.

## DISCUSSION

This study is an attempt at a detailed analysis of mortality, both short and medium term, of heart transplants in a pediatric population in the Indian subcontinent. When we embarked on this project, organ donation in India was in its infancy, organ transport was a logistic nightmare and pediatric donors were scarce. There were huge challenges in preventing waiting list mortality, managing mechanical circulatory support in children and of course the cost. Our attempt at solving these problems has been published[14] including transport of donor organs across this vast country[15] In a country with significant levels of water and air pollution and chronic communicable diseases like tuberculosis, we did not know what to anticipate at long term follow up. A 73% 5-year survival with several children approaching 7 years is much better than we expected when we first started the program and compares well with other published results.[16-18]

As expected, INTERMACS category had the most significant impact on early survival and beyond the first 6 months, the effect of INTERMACS was not very pronounced. INTERMACS is not commonly used in transplant literature and is used more in the domain of continuous flow left ventricular assist devices (CFLVADS).[19] We found that INTERMACS gives greater granularity than the UNOS category[4] in stratifying patient functional class, especially when a significant number of patients are very sick, as was true in our series. We feel It is also particularly relevant considering the increasingly improved survival with CFLVADS comparable to transplant outcomes,[20] to have a common categorization of patient risk profiles.

The fact that PVRI and Ischemic time did not have a significant impact on survival might seem surprising at first but perhaps is explained by the fact that these are well-known risk factors and the selection of donor organs was based on recipient PVRI and expected ischemic times. For example, when ischemic times are expected to be long, only a young donor with excellent cardiac function is chosen. Other groups have also found PVR to be not a risk factor for heart transplantation.[21]

The donors in our series were older with much higher donor to recipient weight ratios from what is published where the most common D:R weight ratio is 1.5:1.[22,13] This is because pediatric donors are rare in India, with no organ donation programs in any of the pediatric hospitals in the country as of date, despite our constant efforts. As a consequence, we are forced to use the available older and bigger hearts for pediatric recipients. In dilated cardiomyopathy, there is enough space in the chest to accommodate bigger hearts. The technique of transplant needs to be tailored according to the situation. Managing disparities in great vessel sizes is common in congenital heart surgery and the same techniques are applicable here. The problem is in restrictive cardiomyopathy and failing Fontans with normal sized hearts where sometimes, the chest needs to be kept open for a few days before it can be safely closed. While some groups have found increased donor to recipient weight ratio to be a risk factor,[22] there is an increasing trend towards accepting bigger donors with acceptable results.[23] There have been attempts at virtual implantation of the donor heart to ensure a size fit.[24] We have used 3D printing on three occasions. We have not tried a virtual heart transplant though we use a virtual implant for sizing in pediatric LVAD implants.

Late survival was significantly impacted by higher baseline creatinine and older donor hearts. Both these have been documented by other researchers as well.[25,26] The practice of using older donor hearts needs an explanation. Long term mechanical support with Berlin Heart or CFLVADS are expensive. Even though we have a robust LVAD program and have recently started using Berlin heart, for the majority of children, mechanical support is restricted to a few weeks of ECMO or CENTRIMAG support. Under these circumstances, we are forced to use any heart which is available. We clearly need an affordable mechanical circulatory support option. It is clear that, a more efficient system of patient referral, when the children are not in extremis, will yield better outcomes, both early and late as we will have time to wait for an ideal younger donor.

The impact of MELDS score on hospital and late mortality is significant and perhaps should logically lead to a rational basis for patient selection. Patients with high MELDS score are probably better managed with a combined heart and liver transplant. As of date, only one combined heart and liver transplant has been done in our country.

The problem of rejection is an important one and its solution is not easy. Biopsies are expensive and these patients are in geographically distant locations making frequent biopsies in the 1st year a difficult proposition. Blood-based tests, including IMMUKNOW (CylexInc., Columbia, MD, USA) and donor-derived cell-free DNA are not available in India. In a few instances, the rejection was clearly because of noncompliance in taking immunosuppressive medication either because of financial reasons or ignorance, despite repeated patient education programs. Donor Specific Antibodies and Luminex single bead antigen tests are not widely available yet. All that we have is tacrolimus levels and echocardiogram. Interestingly, the incidence of postoperative rejection had no correlation with preoperative PRA levels What we really need in this country is a CPRA calculator with every state transplant

authority with a list of unacceptable antigens.[27] We are currently involved in such an initiative.

Where do we go from here? More awareness needs to be created about organ donation in pediatric hospitals. Patients need to be referred reasonably early to give them the best chance for survival. Pediatric heart failure and its comprehensive management, including in patients with previously operated congenital heart disease needs a fully dedicated specialized team and India has the talent and skill to provide it.

### Limitations

We are fully aware of the significant limitations of our study.

Despite having a dedicated staff for data collection, not all the data is available for all patients. Not all patients send their lab results, including tacrolimus levels back to us on a regular basis during follow-up. The cause of late mortality is mostly a matter of conjecture in the absence of autopsy studies. Similarly, in case of suspected rejection, biopsy results are only available if it was done in our hospital. Despite these limitations, we believe we have made a very sincere effort to gather as much data as possible for us to have meaningful inferences about the outcomes of heart transplantation in this country, which can serve as a reference point for future outcome studies.

## CONCLUSIONS

Good medium-term survival is possible after pediatric transplants in India with excellent quality of life. The most important factors related to survival are pretransplant functional class, donor age more than 25, and higher MELDS score. Patients need to be referred early for optimal outcomes. More awareness needs to be created regarding organ donation in pediatric hospitals if these precious lives are to be saved.

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### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Venugopal P. The first successful heart transplant in India. Natl Med J India 1994;7:213-5.
2. Stewart GC, Kittleson MM, Patel PC, Cowger JA, Patel CB, Mountis MM, *et al.* INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) Profiling identifies ambulatory patients at high risk on medical therapy after hospitalizations for heart failure. Circ Heart Fail 2016;9:e003032.
3. Barge-Caballero E, Paniagua-Martín MJ, Marzoa-Rivas R, Campo-Pérez R, Rodríguez-Fernández JÁ, Pérez-Pérez A, *et al.* Usefulness of the INTERMACS Scale for Predicting outcomes after urgent heart transplantation. Rev Española de Cardiol (English Edition) 2011;64:193-200.
4. Rules A, Donor D, Procurement O, Registrations C, Offers O, Donation L, *et al.* Policy 1 : Administrative rules and definitions active candidate. [https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf].
5. Deo SV, Al-Kindi SG, Altarabsheh SE, Hang D, Kumar S, Ginwalla MB, *et al.* Model for end-stage liver disease excluding international normalized ratio (MELD-XI) score predicts heart transplant outcomes: Evidence from the registry of the United Network for Organ Sharing. J Heart Lung Transplant 2016;35:222-7.
6. Gorcsan J, Snow FR, Paulsen W, Nixon JV. Noninvasive estimation of left atrial pressure in patients with congestive heart failure and mitral regurgitation by Doppler echocardiography. Am Heart J 1991;121:858-63.
7. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: A noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527-33.
8. Aziz TM, Burgess MI, El-Gamel A, Campbell CS, Rahman AN, Deiraniya AK, *et al.* Orthotopic cardiac transplantation technique: A survey of current practice. Ann Thorac Surg 1999;68:1242-6.
9. Daly KP, Marshall AC, Vincent JA, Zuckerman WA, Hoffman TM, Canter CE, *et al.* Endomyocardial biopsy and selective coronary angiography are low-risk procedures in pediatric heart transplant recipients: Results of a multicenter experience. J Heart Lung Transplantat 2012;31:398-409.
10. Daly KP, Marshall AC, Vincent JA, Zuckerman WA, Hoffman TM, Canter CE, *et al.* Endomyocardial biopsy and selective coronary angiography are low-risk procedures in pediatric heart transplant recipients: Results of a multicenter experience. Journal of Heart and Lung Transplantation. 2012. p. 398–409.
11. Buchinsky FJ, Chadha NK. To P or Not to P: Backing Bayesian Statistics. Otolaryngology Head and Neck Surgery. United States: SAGE Publications Inc.; 2017. p. 915-8.
12. Wasserstein RL, Lazar NA. The ASA statement on *P* values: Context, process, and purpose. Am Stat 2016;70:129-33.

13. Ezhumalai B, Rao S, Balakrishnan KR. Triple ECMO therapy and emergency PCI performed perioperatively during pediatric heart transplantation. IHJ Cardiovasc Case Rep (CVCR) 2019;3:4-6.
14. Balakrishnan K. Heart transplantation in India – Are we there yet? Indian J Thorac Cardiovasc Surg 2020;36 Suppl 2:159-65.
15. Krishnan KB, Rao KS, Tanguturu MK, Rajam M, Aravind A, Dushyanthan J, *et al*. Commercial airlines as a viable, safe and cost effective way for transporting the donor hearts across the country: Single center experience. J Heart Lung Transplant 2019;38 (Supplement):S133-4.
16. Kirk R, Dipchand AI, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, *et al*. The registry of the international society for heart and lung transplantation: Fifteenth pediatric heart transplantation report – 2012. J Heart Lung Transplantat 2012;31:1065-72.
17. Colvin M, Smith JM, Hadley N, Skeans MA, Uccellini K, Lehman R, *et al*. OPTN/SRTR 2017 annual data report: Heart. Am J Transplant 2019;19 Suppl 2:323-403.
18. Dipchand AI, Laks JA. Pediatric heart transplantation: Long-term outcomes. Indian J Thorac Cardiovasc Surg 2020;36:175-89.
19. Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, *et al*. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplantat 2017;36:1080-6.
20. Shaw SM, Callan P, Kore S, Venkateswaran R. Improved survival trend following the introduction of heartmate 3. A single centre experience. J Heart Lung Transplantat 2019;38 (Supplement):S352-3.
21. Chiu P, Schaffer JM, Sheikh AY, Ha R, Reinhartz O, Mainwaring R, *et al*. Elevated pretransplant pulmonary vascular resistance index does not predict mortality after isolated orthotopic heart transplantation in children: A retrospective analysis of the UNOS database. Pediatr Transplant 2015;19:623-33.
22. Bayoumi AS, Liu H, Fynn-Thompson F. Donor-recipient size matching in pediatric heart transplantation: Is weight the most appropriate parameter to predict outcomes in all age groups? J Heart Lung Transplant 2013;32:S128-9.
23. Kanani M, Hoskote A, Carter C, Burch M, Tsang V, Kostolny M. Increasing donor-recipient weight mismatch in pediatric orthotopic heart transplantation does not adversely affect outcome. Eur J Cardiothorac Surg 2012;41:427-34.
24. Singh N, Raees MA, Zafar F. Donor considerations in pediatric heart transplantation. Transl Pediatr 2019;8:284-9.
25. Tang L, Du W, L'Ecuyer TJ. Perioperative renal failure in pediatric heart transplant recipients: Outcome and risk factors. Pediatr Transplant 2011;15:430-6.
26. Westbrook TC, Morales DL, Khan MS, Bryant R, Castleberry C, Chin C, *et al*. Interaction of older donor age and survival after weight-matched pediatric heart transplantation. J Heart Lung Transplant 2017;36:554-8.
27. Organ Procurement and Transplantation Network. CPRA Calculator OPTN. Available from: https://optn.transplant.hrsa.gov/resources/allocation-calculators/cpra-calculator/.