ISHLT Primary Graft Dysfunction incidence, risk factors and outcome: a UK National Study

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Abbreviations

BiVAD – Bilateral Ventricular Assist Device

ECMO – Extracorporeal Membranous Oxygenation

IABP – Intra-Aortic Balloon Pump

LVAD- Left Ventricular Assist Device

NHSBT – National Health Service Blood and Transplant

OCS– Organ Care System (OCS™ Heart) by Transmedics Inc., Andover, MA, USA

RVAD- Right Ventricular Assist Device

VAD- Ventricular Assist Device

Terminology

Cold Ischemic Time – Duration of cold storage packed with ice after cold cardioplegia

Warm Ischaemic Time – Time from application of cross clamp on donor aorta until heart is placed on ice plus implant time

Implant time –time between removal from cold storage or OCS until the heart is re-perfused in the recipient

Extracorporeal Time: Time spent on transferring the heart onto the OCS machine + Time the heart is perfused on the OCS machine + time from when heart is removed from the machine to the moment when the aortic cross clamp is removed following implantation into the recipient

Inotrope Score - dopamine(X1) + dobutamine(X1) amrinone (X1) + milrinone (X15) +adrenaline(X100) + noradrenaline(X100) with each drug dosed in μg/kg/min.

Donor/recipient mismatch measurements were calculated as follows:

$[(\text{Measure}_{(\text{recipient})} - \text{Measure}_{(\text{donor})}/\text{Measure}_{(\text{recipient})}] \times 100$

Abstract

Background: Heart transplantation (HTx) remains the most effective long-term treatment for advanced heart failure. Primary graft dysfunction (PGD) continues to be a potentially life-threatening early complication. In 2014, a consensus statement released by ISHLT established diagnostic criteria for PGD. We studied the incidence of PGD across the UK.

Methods: We analysed the medical records of all adult patients who underwent heart transplantation between October 2012-October 2015 in the 6 UK heart transplant centers Preoperative donor and recipient characteristics, intraoperative details and posttransplant complications were compared between the PGD and non PGD groups using the ISHLT definition. Multivariable analysis was performed using logistic regression.

Results: The incidence of ISHLT PGD was 36%. Thirty-day all-cause mortality in those with and without PGD was 31(19%) vs 13(4.5%) (p=0.0001). Donor, recipient and operative factors associated with PGD were: recipient diabetes mellitus (p=0.031), recipient preoperative BIVAD(p<0.001) and preoperative ECMO (p=0.023), female donor to male recipient gender mismatch(p=0.007) older donor age (p=0.010) and intracerebral haemorrhage/thrombosis in donor (p=0.023). Intra-operatively, implant time (p=0.017) and bypass time(p<0.001) were significantly longer in the PGD cohort. Perioperatively, patients with PGD received more blood products (p<0.001). Risk factors identified by multivariable logistic regression were donor age (p=0.014), implant time (p=0.038), female: male mismatch (p=0.033), recipient diabetes (p=0.051) and preoperative VAD/ECMO support (p=0.012),

Conclusion: This is the first national study to examine the incidence and significance of PGD after heart transplantation using the ISHLT definition. PGD remains a frequent early complication of heart transplantation and is associated with increased mortality.

Introduction

Heart transplantation remains the most successful long-term treatment for advanced chronic heart failure. Survival after cardiac transplantation has improved but primary allograft dysfunction (PGD) remains a significant problem and the predominant cause of early mortality during the first month(1). In a previous UK study, the incidence of PGD was 32% using a study-specific definition comprising of severely impaired systolic function affecting 1 or both ventricles accompanied by hypotension, low cardiac output, and high filling pressures occurring in the first 72 hours (in the absence of hyper acute rejection and technical surgical factors, such as cardiac tamponade)(2).

However, comparative studies of the incidence and outcome of PGD have been hampered by the lack of an agreed definition until, in 2014, an international consensus statement was developed under the auspices of ISHLT.

The consensus classified graft dysfunction as primary graft dysfunction (PGD) or secondary graft dysfunction which had a discernible cause such as hyper-acute rejection, pulmonary hypertension, or surgical complications. PGD must be diagnosed within 24 hours of completion of surgery. PGD is divided into PGD-left ventricle and PGD-right ventricle. PGD-left ventricle is categorized into mild, moderate, or severe grades depending on the level of cardiac function and the extent of inotrope and mechanical support required. Risk factors for PGD include donor, recipient, and surgical procedural factors(3).

In this study, we aimed to ascertain the incidence of PGD using the ISHLT criteria and examine preoperative donor and recipient characteristics as well as procedural risk factors for PGD in a study of an unselected national population of adult heart transplants.

Methods

Inclusion Criteria

All first time orthotopic heart transplants in adults from donors after brainstem death (DBD).

From October 2012-October 2015, 450 adult heart transplants which met our inclusion criteria were performed in the United Kingdom. Data were collected prospectively at the time of the heart transplant and incorporated into the UK Transplant database hosted by NHSBT. Data were retrospectively validated from case records for each of these patients and additional information necessary for the study was extracted from the clinical records by SS. Patients with combined organ transplants were excluded from this study. Donor procurement was performed by the National Organ Retrieval Service(NORS) with all but 1 center using 1 litre of cold St Thomas's solution (supplied by Martindale Pharmaceuticals, Romford, Essex, UK) followed by cold stage packed with surrounding ice during transportation. One center utilized the OCS (TransMedics Inc) and used Custodiol solution cardioplegia (supplied by Pharmapal Ltd, Elstree, Borehamwood, UK) at the beginning and end of the OCS run. A Pulmonary Artery Catheter was inserted after the transplantation. If this was not possible, primary graft dysfunction was diagnosed using echocardiographic parameters as per Kobashigawa et al(3). Induction and maintenance immunosuppression was as per local hospital protocols.

Primary Graft Dysfunction was defined using the 2014 ISHLT Consensus(3).

The use of postoperative mechanical support was determined by individual surgeons

Statistical Analysis

Continuous variables were described by mean and standard deviation or by median and interquartile range as appropriate. Categorical variables were expressed as number and

proportion. Baseline characteristics were compared between PGD and non-PGD groups using Student's t-test and Mann Whitney U test as appropriate and chi-square test or Fisher's exact test for categorical variables. Variables with significance of $p<0.1$ in the unadjusted analysis were initially introduced as candidate variables in a multivariable logistic regression model for the probability of PGD and removed by stepwise backward elimination. Variables were retained in the model if they reduced the model deviance significantly ($p<0.05$). This was done using a complete case dataset to ensure appropriate comparison of nested models (however missing data were minimal due to interrogation of data at source). A further subgroup analysis was performed on just those with PGD using the same methodology to compare variables that predict the different severities of PGD as defined. Analysis was conducted in Minitab 17 Statistical Software (2010). Minitab, Inc.

Results

450 adults received heart transplants between 1 October 2012- 1 October 2015. The mean age was 46.3±13.5 years. 348 (77.3%) of the recipients were males. During this period there were 10 Donation after Circulatory Death (DCD) transplants and these were excluded from the study. There were also 3 patients who were re-transplanted. Their second transplants were excluded from this study. 98.2% of patients had PA catheters inserted postoperatively. Preoperative, operative and postoperative details of the PGD and non-PGD cohorts are shown in Table 1. The overall incidence of Primary Graft Dysfunction was 36.2% (163 patients). There were 7 (16%) cases of Secondary Graft Dysfunction. These were graft failure secondary to bleeding, hyperacute rejection and elevated pulmonary pressures as defined by Kobashigawa et al(3).The phenotype and severity of PGD is shown in Figure 1.

We identified donor, recipient and operative risk factors for PGD. Preoperative factors that were significantly associated with PGD in the unadjusted analysis were recipient diabetes mellitus, and female donor to male recipient gender mismatch (Table 1). There was no significant difference between the donor-recipient height and weight mismatch but the estimated LV mass showed more downsizing of donor to recipient in the PGD cohort. Intra-operatively, implant time and bypass time were significantly longer in the PGD cohort (Table 2)). Patients with PGD had increased transfusion of blood products (Table 3). 30-day mortality for patients with primary graft dysfunction was 31(19%) vs 13(4.5%) ($p<0.001$). The 6-month mortality for patients with PGD was 52 (31.9%) vs 18 (6.3%) ($p<0.001$). Comparing the PGD groups, there was a significantly higher 30-day mortality in the severe PGD-LV group vs moderate PGD-LV group 27(30%) vs 4(5%) respectively, $p<0.001$).

The total extracorporeal time for the OCS subset was significantly longer than after cold storage (309.4±88.4 minutes vs 100.3±45.8 minutes; $p<0.001$. However, the incidence of PGD was similar to the non-OCS cases (30.3% vs 37.2%, respectively) ($p=0.279$). In a subgroup analysis of the OCS cases, extracorporeal time was significantly longer in the PGD group (344.9±95 minutes vs 294.8±81 minutes; $p=0.048$)

The following variables were considered for a multivariable analysis of the probability of PGD in which 21 (5%) patients were excluded due to missing data.

Continuous Variables: Recipient age, donor age, explant time, implant time

Categorical Variables: Recipient diabetes, recipient preoperative inotropes, recipient preoperative VAD/ECMO support, female donor: male recipient mismatch, donor smoking history, OCS usage, recipient aetiology, donor cause of death and recipient preoperative IABP usage.

Bypass time and total blood were excluded from this analysis because these results may have arisen from Primary Graft Dysfunction rather than being causative of it. OCS use was not included because it occurred in a small surgeon-selected subset. The final model is shown in Table 4.

In donors, the likelihood of PGD increased by 20% for each decade increment in donor age. A female donor: male recipient combination was 1.7 times more likely to develop PGD.

Recipients requiring preoperative mechanical circulatory support also conferred almost a 2-fold increase in likelihood of PGD. Diabetic recipients were more than twice likelier to develop PGD. There was also 1% increase for each minute increment during implantation of the heart.

As an illustrative example, the absolute risk of developing PGD in an average donor (40-year old) to an average recipient (nondiabetic, no preoperative MCS, implant time = 54 minutes, without female donor to male recipient gender mismatch) was 28.7%. This absolute risk increased to 45.1% if there was recipient diabetes or 41.9% if there was preoperative MCS. A female donor to male recipient increased the absolute risk to 41.2%.

The absolute PGD risk of advancing donor age in an average recipient is computed in the Figure 2a. Figure 2b shows the effect of advancing implant time (mins) in a 40-year old donor to an average recipient, who wasn't on any MCS support.

A further subgroup logistic regression analysis was performed to identify risk factors for severe PGD vs mild/moderate PGD on the 163 patients who experienced some degree of PGD. The variables included for analysis were

Continuous Variables: Recipient age, donor age, explant time, implant time

Categorical Variables: Recipient diabetes, recipient preoperative inotropes, recipient preoperative VAD/ECMO support, female donor: male recipient mismatch, donor smoking

history, OCS usage, recipient aetiology, recipient re-sternotomy donor cause of death and recipient preoperative IABP usage

This subgroup analysis revealed implant time, female donor: male recipient gender mismatch and recipient re-sternotomy to be independent risk factors for severe PGD as opposed to mild or moderate PGD as seen in Table 5.

Discussion

This study is the first national study of PGD in an unselected population of adult heart transplants using the ISHLT consensus definition. The main findings were, first, a high overall incidence of PGD and, second, a significant increase in perioperative mortality in the PGD group. Third, the risk factor analysis identifies not only donor and recipient factors but potentially modifiable procedural risk factors such as surgical implant time and use of blood products. Finally, the use of the OCS allowed an extension of the extracorporeal time for the donor heart with a similar incidence of PGD. Nevertheless, increasing extracorporeal time in the OCS group was associated with an increase in PGD indicating that any protection afforded by OCS was relative, not absolute.

Incidence of PGD

There was a relatively high incidence of PGD (36.2%) in this cohort. This finding is similar to that reported by Dronavalli et al which reported an incidence of about 32%(2). The changing patient demographics with increasing use of pretransplant mechanical circulatory support and increased utilization of marginal donors could be a contributory factors as donor age and preoperative MCS usage were independent risk factors for PGD(4). Dronavalli et al also

mentioned the lack of echocardiographic criteria which reduced the sensitivity of diagnosing PGD in the previous study. There were more severe PGD-LV patients (18%) and moderate PGD-LV (16%) than mild PGD-LV (1%) and PGD-RV (1%). These findings were similar findings noted in a single center series by Sabatino et al(5). Majority of their patients were classified as severe PGD (65%) followed by moderate (12%) and mild (0%; $p < 0.01$). The low rates of mild PGD-LV could be as a result of earlier intervention by physicians and surgeons by increasing the inotropic treatment in response to a low cardiac output state to the point where the inotrope score will meet the ISHLT definition of moderate PGD_LV. The clinical significance of the mild PGD-LV group is uncertain as there was no 30-day mortality in this group.

PGD-related Mortality

The 30-day mortality in our cohort was lower than the previous study (19% vs 37%) and in other studies(6-8).The lack of a standardized definition previously also potentially resulted in more conservative definitions of PGD which was the need for instituting MCS. This could also explain the improved mortality figures due to the inclusion of inotrope dependence as part of the definition. The improved 30-day survival could also be a result of improvements in recognition and treatment of PGD. Short term PGD related mortality rates in our cohort was also similar to that described by Squiers et al from a high volume center in the United States(9). They had a 30-day mortality rate of 25% in the moderate/ severe PGD group. Sabatino et al also reported similar mortality rates in their cohort (37% in-hospital mortality)(5). However, the mortality rate at 6-months remains high in the PGD cohort (31.9% vs 6.3%). There is a paucity of data regarding longer term outcomes following PGD. Kim et al retrospectively reviewed a single center cohort of patients and noted that moderate and severe PGD-LV patients had worse long-

term outcomes(10). Given the large proportion of moderate and severe PGD-LV patients in our cohort, further studies may be needed to evaluate longer term outcomes of PGD survivors vs non-PGD patients.

Risk Factors

The increased incidence of PGD reported is multifactorial. It highlights several vascular risk factors that may shed light on the aetiology of PGD. Increasing donor age and recipient diabetes were both independent risk factors in our cohort and have identified in previous studies prior to the ISHLT definition(8).

Donor age was a significant risk factor for both PGD and severe PGD in the subgroup analysis. This finding was also noted by Russo et al during interrogation of the UNOS database(11). They concluded that the effect of ischemic time on survival after heart transplantation is dependent on donor age, with greater tolerance for prolonged ischemic times among grafts from younger donors.

Ischemic time was subdivided into warm and cold ischemic time in our cohort(12). Warm ischemic time was defined as the explant time + the implant time. The implant time was found to be a strong predictor of primary graft dysfunction. Marasco et al(13) retrospectively reviewed 206 patients over a period of around 10 years (June 2001-November 2010). Their definition of warm ischemic time included the implant time. They found that poorer survival with a warm ischemia time(WIT) of >80 minutes having a compared to WIT group of <60 minutes. Donor age was once again an independent predictor of outcome in this cohort.

The role of recipient diabetes as a predictor of primary graft dysfunction was evident in our study as it was in the RADIAL study. The UK prospective Diabetes Study trial established a link

between microvascular complications and glycemic control(14). In recipients with diabetes, there may be a combination of direct glucose-mediated endothelial damage, oxidative stress from superoxide overproduction and production of advanced glycation end-products, which may result in changes in endothelial permeability, excessive vascular protein deposition and altered blood flow(15). A recent metanalysis, diabetes mellitus was an independent predictor of 1-year mortality postheart transplant(16). They attributed this to the summative increased hazard for comorbidities of diabetes at time of transplant which was also noted by Russo et al(17). In a subgroup analysis, diabetic recipients with well controlled diabetes had similar survivals to nondiabetic patients. Interrogation of the UNOS database by Taghavi et al(18) revealed that of 20,348 patients undergoing orthotopic heart transplantation, 496 (2.4%) received hearts from diabetic donors. The diabetic donors were likelier to be females and older. The recipients of diabetic hearts were also older. However, on multivariable analysis of subgroups, neither insulin-dependent diabetes (1.173; 95% CI, 0.884-1.444; P = .268) nor duration of diabetes for more than 5 years (HR, 1.239; 95% CI, 0.914-1.016; P = .167) were risk factors once the groups had been matched. A similar finding was noted by Smits et al (2012) in a European cohort(19).

The odds ratio for severe PGD was double that of mild/moderate PGD in female donor – Male recipient gender mismatched patients in our study. It has also been identified as a risk in several previous studies. Jalowiec et al conducted a study on early outcomes after heart transplantation in gender mismatched patients(20). 74/347 patients received a heart from an opposite gender. They concluded that gender-mismatched heart transplant recipients had more complications due to rejection and higher resource utilization due to more re-hospitalization during the first postoperative year as compared to gender-matched recipients. Stehlik et al published similar findings with female donor: male recipients having a higher risk of posttransplant death(21).

Some have postulated the relative differences between the size (body surface area) or weight mismatch between female donor and male recipient, citing a smaller female donor heart being unable to sustain the demands of a larger male patient although there was no significant size mismatch (>20%) noted in our cohort(22, 23).

Recipient re-sternotomy was identified as a risk factor for developing severe PGD in our subgroup analysis. Patients with previous sternotomies develop adhesions which complicate the surgical dissection thereby prolonging the explantation period and bypass time. They are also at an increased risk of infections(24).This may further exaggerate the inflammatory response explaining the need for increased support postoperatively. Analysis of the UNOS database revealed an increased risk of all cause mortality in patients with re-sternotomies.(24)

OCS

It is widely believed that an important factor in the pathogenesis of PGD is acute ischemia-reperfusion injury. The donor heart is exposed to variable blood pressures, hypothermic storage, warm ischemia and finally reperfusion. The role of the OCS in reducing the impact of this has not been studied. A multivariable analysis has not been done here owing to the relatively small number of OCS transplants during the study period (n=66). However, in the unadjusted analysis, length of time on the OCS machine was a strong predictor of PGD. One hypothesis for this phenomenon is the lack of metabolic and excretory functions within the OCS circuit to sustain the metabolically active heart within the machine. The mean extracorporeal time of hearts on the OCS was significantly longer than cold storage with similar PGD rates. Garcia-Saez et al reported improved short-term outcomes from the use of the OCS in extended criteria donors(25). The OCS may have a role in improving logistical limitations of organ procurement. The ex-vivo

perfusion of the heart allows evaluation of extended criteria allografts prior to implantation. It also reduces functional ischemia by means of continuous oxygenation and perfusion which may be importance in higher risk recipients who are on MCS. Nevertheless, a randomized study of a larger cohort of donors is needed to establish any benefit of the OCS in reducing PGD.

Size mismatch

The height and weight profiles of donors and recipients in our cohort were not significantly different in both groups. This could be due to careful donor selection and matching process to ensure accurate sizing of the cardiac allograft for the recipient. Height mismatch and weight mismatch were negligible in our cohort. However, a composite of the 2 measurements to calculate the estimated LV mass showed a higher proportion of downsizing in the PGD cohort. We used the following equation which has been published and validated in the literature(26).

Predicted left ventricular mass(g) = α X Height$^{0.54}$ (m) X Weight$^{0.61}$ (kg),

where α = 6.82 for women and 8.25 for men

However, this was not a significant finding on multivariable analysis. This could be due to the co-efficient weightage which may reflect the potential downsizing in a female donor to male recipient gender mismatch using this equation. The equation is also limited as there is no correlation with other confounders of LV mass such as ethnicity, history of cardiovascular disease and valvular heart disease. Size mismatching has been noted in other studies(5, 9, 27, 28). Transplanted hearts are denervated and thus rely on increased stroke volume to augment workload(29). Consistent increments of stroke volume results in increasing filling pressure. Smaller hearts are also prone to tachycardia to meet the demands of the previously larger sized heart which is mediated by catecholamine release(30, 31). Tachycardia may worsen episodes of

myocardial ischaemia and significantly increases the production of oxygen free radicals by increased metabolic demand(32). These results in immune infiltration and activation, potentially causing acute or chronic rejection.

Consequently, undersized hearts are shown to undergo pathological cardiac hypertrophy, which may cause fibrosis(33, 34). Fibrosis of myocardium and conduction fibres are likely to increase the risk of arrhythmias which may be misconstrued as rejection(35).

Bypass time and blood transfusion

Patients with PGD in our cohort had a significantly longer bypass time. We considered that this may have been due to the need to institute further treatment by means of insertion of IABP or institution of mechanical circulatory support. However, prolonged bypass time in itself is an independent predictor of morbidity and mortality in general cardiac surgery(36, 37).

The mechanism of injury from CPB and ischaemic-reperfusion of the myocardium is similar; both producing a systemic inflammatory response syndrome (SIRS). They result in a hyperdynamic circulatory state due to the vasoplegia reducing vascular resistance, platelet and coagulation factor dysfunction, inflammatory pathway activation triggered by leucocytes and endothelial cells and finally cytokine release and formation of oxygen free radicals(38). Prolonged cardiopulmonary bypass also increases transfusion requirement(39). Our PGD cohort had higher blood transfusion requirements compared to the non-PGD cohort. This could once again be a response to the vasoplegic state caused by the SIRS effect from either prolonged bypass time or PGD itself. Blood transfusion in general cardiac surgery is associated with both infection and ischaemic postoperative morbidity, increased hospital stay, increased early and late mortality, and increased hospital costs(40, 41). In animal models, stored red blood cells have

implicated in causing organ hypoxia(42). Blood transfusion also increases pulmonary vascular resistance thereby affecting right ventricular ejection, without improving systemic or regional oxygen utilization(43).

Given these findings, blood transfusion and cardiopulmonary bypass time may both contribute to the worsening of the ischaemic injury caused by PGD.

Treatment of PGD

Treatment of PGD is primarily supportive. As the definition of PGD is based on the treatment modality, mild and moderate PGD-LV is primarily inotropic support. Moderate PGD-LV is also treated with implantation of IABP. Escalation from this usually requires ECMO. Most cases of severe PGD-LV involve failure to wean from bypass, necessitating the institution of ECMO or short term VAD support. PGD-RV is initially treated with inotropic support including agents such as milrinone to promote pulmonary vasodilation. A RVAD is cited if right heart failure persists(3). Due to the shortage of organs and the increasing waiting list, re-transplantation is rarely done (3 in this study period).

Limitations

This was a retrospective analysis of prospectively collated national data. This study design is advantageous because the risk factors were recorded before the occurrence of the outcome(PGD). This is important because it allows the temporal sequence of risk factors and outcomes to be assessed. Selection bias was also minimized by including all adults with heart-only transplants during the study period. However, as an observational study, only association

and not causation can be inferred from the results. Other unrecorded factors may have affected the outcome(44).

As the data collected were from different hospitals, variations in practice was unaccounted for. This included postoperative immunosuppression regimes, choice of inotropes, myocardial preservation methods and MCS experience with some centers having a greater proportion of patients on LVADs. We relied on both PAC measurements and Echocardiography for defining PGD in patients without devices where possible. Some patients did not have PCWP readings and then we were reliant on echocardiographic criteria and vice versa.

The ISHLT consensus definition relies on the use of mechanical circulatory support to define the more severe forms of PGD. The use of MCS was decided by individual surgeons and this is a potential weakness of the consensus definition. However, the national multicenter nature of this study is likely to have mitigated this problem.

We performed an exploratory analysis of transplants performed on the OCS device but were unable to perform a multivariable analysis because of the limited number of cases and events.

Conclusion

PGD remains a significant risk factor for early mortality in heart transplant recipients. The standardized definition allows early diagnosis and recognition of this condition. There are several donor, recipient and procedural risk factors that may be contributory to the pathogenesis of PGD that should be considered for predicting outcomes. Further studies are warranted to establish the long-term outcomes of PGD using the current definition.

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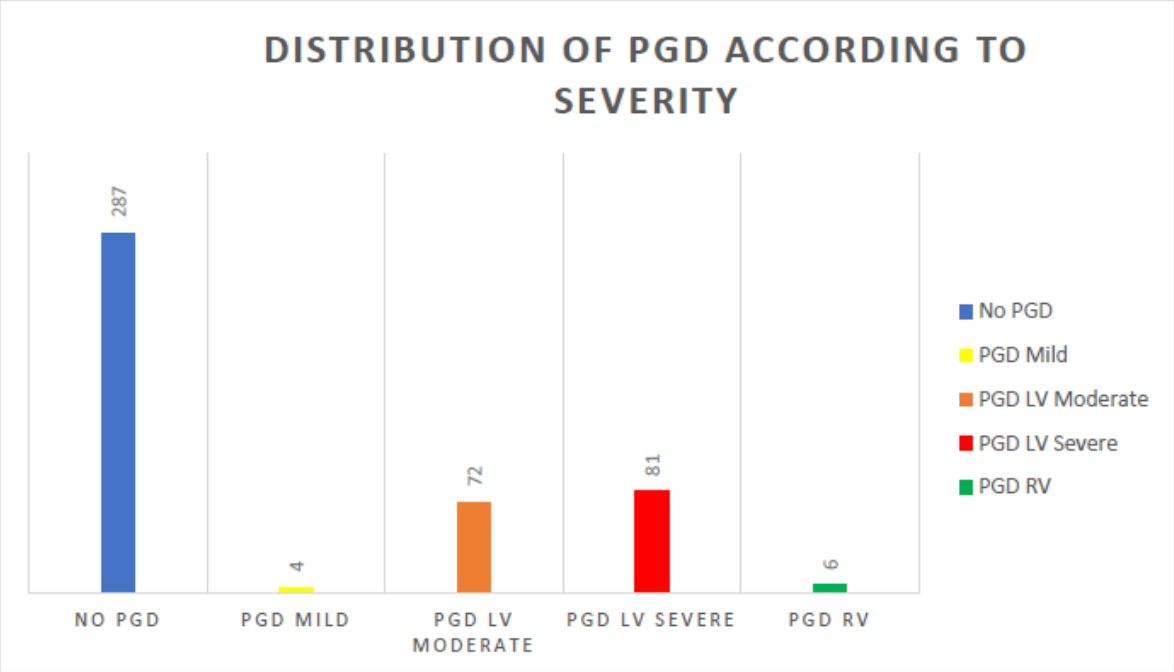

Figure 1

Figure 1: Distribution of PGD according to Severity

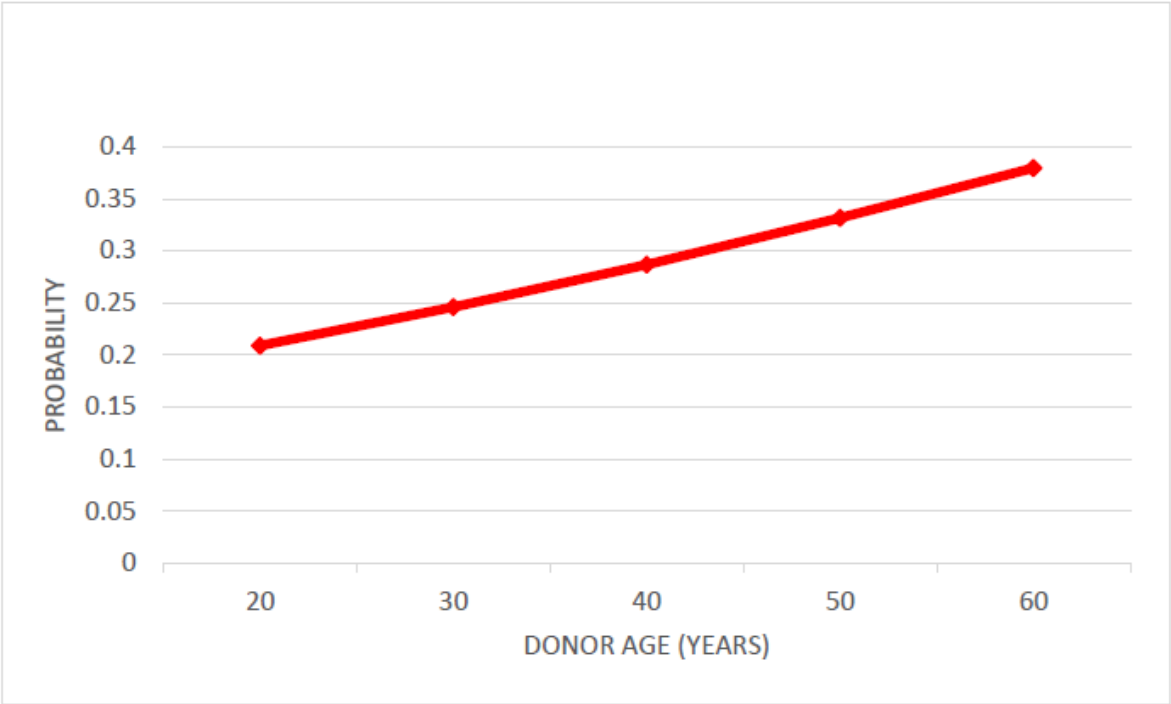

Figure 2a. Probability of PGD with advancing donor age

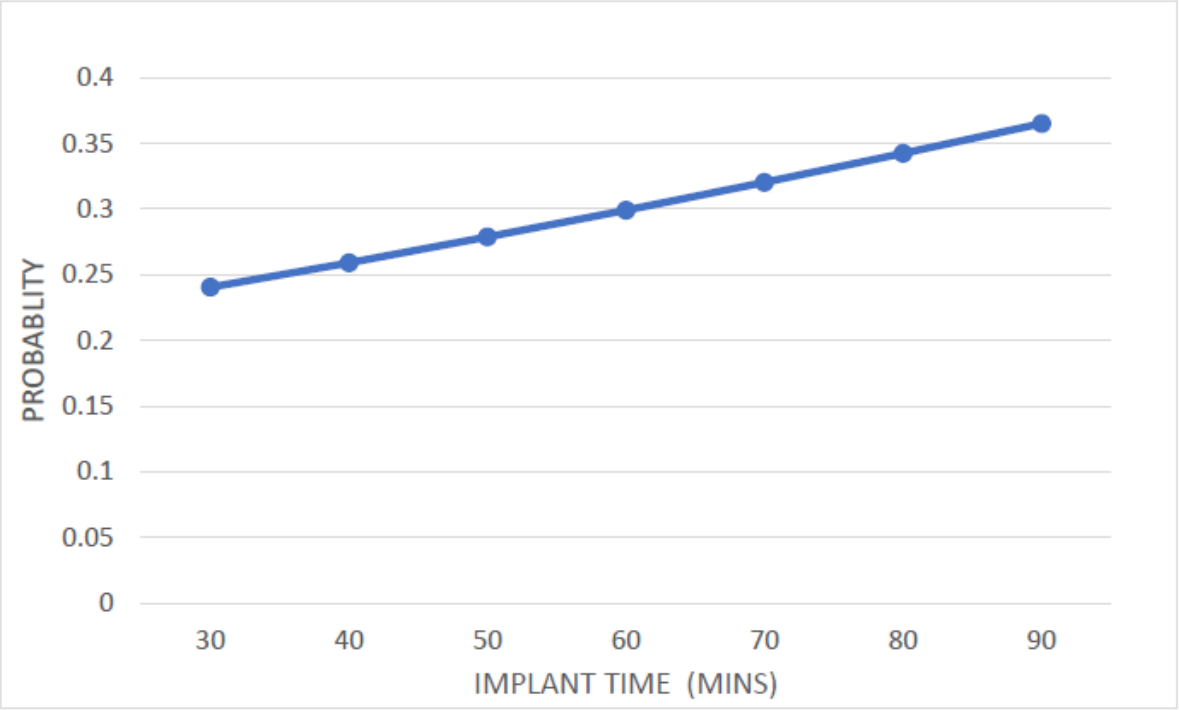

Figure 2b. Probability of PGD with increasing Implant Time

Recipient Factors	PGD (n=163)	Non-PGD (n=287)	P- value
Male:Female ratio	127:36	221:66	0.824
Age (years)	47.1±14.1	46.1±13.8	0.449
BMI (Kg/m^2)	25.68±3.96	25.34±3.98	0.388
Recipient Creatinine (μmol/L)	98.00 (48)	99.00 (46)	0.217
Recipient Diabetes Mellitus	19 (11.7%)	17 (5.9%)	**0.031**
Recipient Re-sternotomy	33 (20.2%)	47 (16.4%)	0.302
Preoperative Inotropes	82 (50.3%)	171(59.6%)	0.056
Preoperative ECMO	5 (3.1%)	1 (0.3%)	**0.023**
Preoperative IABP	15 (9.2%)	17 (5.9%)	0.193
Preoperative LVAD	25(15.4%)	35(12.2%)	0.345
Preoperative BiVAD	20(12.3%)	9(3.1%)	**<0.001**
Preoperative RVAD	3(1.8%)	20(7.0%)	**0.018**
Preoperative antiarrythmics	58 (35.6%)	111(38.7%)	0.514
Recipient Aetiology			
Ischaemic Cardiomyopathy	38 (23.3%)	62 (21.6%)	
Dilated Cardiomyopathy	87 (53.3%)	160 (55.7%)	
Congenital Heart Disease	13 (8.0%)	26 (9.1%)	
HOCM	9 (5.5%)	15 (5.2%)	
Restrictive Cardiomyopathy	5 (3.1%)	8 (2.8%)	
Other	11 (6.7%)	7 (2.7%)	0.464

Table 1. Preoperative characteristics of recipients

Donor Factors	PGD (n=163)	Non-PGD (n=287)	p- value
Donor Cause of death			
Intracerebral haemorrhage/Thrombosis	107 (65.6%)	157 (54.7%)	**0.023**
Hypoxic brain injury	21(12.9%)	48 (16.7%)	0.277
Road Traffic Accident(RTA)	23 (14.1%)	51(17.8%)	0.314
Meningitis	4 (2.5%)	11 (3.8%)	0.434
Brain Tumour	3 (1.8%)	8 (2.8%)	0.216
Other	5 (3.1%)	10 (3.5%)	(0.967
Gender Mismatch	52 (31.9%)	59 (20.6%)	**0.007**
Height Mismatch (%)	-0.55 (6.8)	-1.16 (6.8)	0.166
Weight mismatch (%)	-0.44 (27.8)	-3.90 (33.8)	0.464
Estimated LV mass mismatch (%)	2.76 (25.5)	-1.90 (25.3)	**0.020**
Donor Age	41.6±12.2	38.5±12.4	**0.010**
Donor LVEF (%)	57.77±9.36	58.88±7.41	0.279
Donor Smoker	74	140	0.489

Table 2. Preoperative characteristics of donors

Mismatch calculated as [(Measure ($_{recipient}$) − Measure($_{donor}$)/Measure($_{recipient}$)] X 100

Operative Details	PGD (n=163)	Non-PGD (n=287)	P- value
Perfusion Solution			
St Thomas	139 (85.3%)	233 (81.2%)	
Custodiol	24 (14.7%)	51 (17.8%)	0.378
*Cold Ischaemic Time (mins)	103(66)	99(62)	0.392
Explant Time (mins)	17 (9)	18 (10)	0.513
Implant Time (mins)	56(24)	52(24)	**0.017**
Warm Ischaemic Time (mins)	72 (28)	70 (27)	**0.045**
Total Ischaemic Time (mins)	179 (86)	171(71)	0.426
Bypass Time (mins)	206(113)	162 (68)	**<0.001**
Postoperative details			
Right Atrial Pressure (mmHg) ϒ	13.01±4.37	11.98±3.97	**0.016**
PA Mean(mmHg) ϒ	22.39±6.02	22.43±5.95	0.958
PA Systolic(mmHg) ϒ	31.75±9.52	32.08±9.23	0.789
PCWP(mmHg) ϒ	12.83±4.92	13.53±5.76	0.355
Transpulmonary Gradient (mmHg)	8.000 (9)	9.000 (8)	0.593
Cardiac Index ϒ	2.5654 (2.4)	3.1074 (1.59)	**0.005**
MAP (mmHg) ϒ	73.1±15.2	80.9± 16.9	**<0.001**
Inotrope Score ϒ	14.533(14.56)	9.985(10.43)	**<0.001**
Blood Products Transfused (units)	9 (11)	5 (6)	**<0.001**
RBCs(units)	4(7)	2(3)	**<0.001**
FFP(units	2.000 (2.8)	2.000 (4)	**0.032**
Platelets(units)	2.0000 (2)	1.0000 (2)	**<0.001**

Table 3: Postoperative details

*Excluding patients on OCS
ϒPart of ISHLT 2014 severity definition

Factors	Odds Ratio	95% Confidence Intervals	P- value
Donor age	1.02	(1.0043, 1.0383)	**0.014**
Implant time	1.01	(1.0005, 1.0195)	**0.038**
Female: male mismatch	1.74	(1.0464, 2.9086)	**0.033**
Recipient diabetes	2.04	(0.9993, 4.1720)	**0.051**
Preoperative VAD/ECMO support	1.79	(1.1371, 2.8295)	**0.012**

Table 4: Results of multivariable analysis for risk factors for PGD

Factors	Odds Ratio	95% Confidence Intervals	P- value
Implant time	1.02	(1.0003, 1.0342)	**0.037**
Female: male mismatch	2.43	(1.0966, 5.3722)	**0.026**
Recipient Resternotomy	3.21	(1.3215, 7.8084	**0.008**

Table 5: Results of multivariable analysis for risk factors for severe PGD