PREDICTA: A Model to Predict Primary Graft Dysfunction After Adult Heart Transplantation in the United Kingdom

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ABSTRACT

Background: Primary graft dysfunction (PGD) is a major cause of morbidity and mortality post-heart transplantation. The rates of PGD across Europe are higher than North America possibly because of the increasing use of extended criteria donors because of organ shortage. Our aim was to derive a novel scoring system based on data collected nationally in the UK over a 3-year period. We compared this scoring system to a previously validated (RADIAL) score in a contemporary cohort of patients.

Methods: Medical records of all adult patients who underwent heart transplantation between October 1, 2012 and September 30, 2016 in the 6 UK heart transplant centers were analyzed. Preoperative donor and recipient characteristics, intraoperative details and post-transplant complications were compared between the PGD and non-PGD groups using the International Society of Heart and Lung Transplant definition. Multivariable logistic regression was used to build the predictive model. An area under receiver operating characteristics curve was used to test the novel scoring system (PREDICTA) versus the RADIAL score.

Results: Six hundred and thirteen heart transplants were included in the study. There were 233 patients who had PGD. The variables included in the model were recipient diabetes mellitus, preoperative mechanical circulatory support (short-term ventricular assist devices/extracorporeal membrane oxygenation), implant time, donor age, and bypass time >180 minutes. The C statistic of the PREDICTA score was 0.704 versus 0.547 for the RADIAL score indicating an acceptable discriminatory value.

Conclusion: The PREDICTA score is a novel scoring tool with improved ability to predict the development of PGD compared with the RADIAL score. Its application in the prevention and early management of PGD needs further evaluation. (*J Cardiac Fail 2019;25:971–977*)

Key Words: Primary graft dysfunction, scoring systems, heart transplantation, mechanical circulatory support.

The incidence of primary graft dysfunction (PGD) in Western Europe is ~30%.[1] This is because of several factors such as increasing donor and recipient age, increased pulmonary vascular resistance in recipients, donor and recipient comorbidities, and prolonged ischemic time.[2,3] PGD remains an important cause of morbidity and mortality following heart transplantation. Improvements in immunosuppression and surgical techniques have resulted in good long-term survival post-transplant; however, the rate of PGD has remained unchanged in the past decade.[3] Although PGD has been recognized as the primary cause of death within 30-days of transplantation, a uniform definition was only established by the International Society of Heart and Lung Transplant (ISHLT) in a consensus statement in 2014.[2,4] To date there has been no predictive models for PGD in using the current definition. A previous center-specific definition was used to create a 6-point RADIAL score by Segovia et al[5] which considers donor and recipient factors, namely Right atrial pressure ≥ 10 mm Hg, recipient Age ≥ 60 years, Diabetes mellitus, Inotrope dependence, donor Age ≥ 30 years, Length of ischemic time ≥240 minutes.[4,5]

Given the relatively high incidence of PGD across Western Europe, it is imperative that a new predictive model is sought to assist in decision-making and resource allocation for heart transplantation. This is an area of increasing significance with increasing patients on the waiting list with a

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Manuscript received February 1, 2019; revised manuscript received June 26, 2019; revised manuscript accepted July 15, 2019.

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See page 976 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.07.009

finite donor pool primarily consisting of donors after brainstem death (DBD). Recently, ex vivo normothermic perfusion (EVNP) and hearts from donors after circulatory death (DCD) have been use to expand the donor pool. Advancements in mechanical circulatory support, especially implantable left ventricular assist devices (LVADs) have also changed recipient demographics. However, the association between these procedures and PGD has not been clearly established. Most studies in the literature are single-center studies with the inherent weakness of applicability to wider practice. We therefore conducted a multicenter, national study to established trends and independent risk factors for PGD after heart transplantation. Our aim was to derive a multivariable model to identify and predict PGD.

We then explored the performance of a previously validated PGD scoring system, the RADIAL score as a comparison using our validation cohort. Our aim was to develop a predictive risk score for ISHLT-defined PGD that would be applicable at present with the abovementioned developments.

Methods

Patient Population

All consecutive adult patients who underwent first time orthotopic heart transplants from October 1, 2012 to September 30, 2016 from 6 heart transplant centers in the United Kingdom (UK) were included in our study(n = 613). Data were collected 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. Patients with combined organ transplants (n = 23) were excluded.

Donor Organ Procurement

DBD Donation. Donor procurement was performed by the National Organ Retrieval Service (NORS) with all but one center using cold St. Thomas' solution followed by static cold storage packing during transportation. One center utilized the Organ Care System (OCS; TransMedics Inc.), an EVNP device, and used Custodiol (PHARMAPAL Limited) solution cardioplegia at the beginning and end of the OCS run.

DCD Donation. DCD donations were done by direct procurement or normothermic regional perfusion. During the duration of the study, only 2 centers performed DCD heart transplants. All DCD hearts were placed on the OCS with one center using Custodiol solution cardioplegia and the other using St. Thomas' solution.

Postoperative Hemodynamic Measurements

PGD was diagnosed using echocardiographic parameters or invasive cardiac monitoring parameters as per ISHLT definition.[2] Induction and maintenance immunosuppression were as per local hospital protocols. The use of postoperative mechanical support was determined by individual surgeons.

Primary Graft Dysfunction

Primary Graft Dysfunction was defined by the 2014 ISHLT Consensus.[2] PGD was diagnosed within 24 hours after completion of transplantation. The severity of left-sided PGD (PGD-LV) was determined by the inotrope score, placement of a new intra-aortic balloon pump or institution of mechanical circulatory support as detailed by the consensus statement. Echocardiographic findings of left ventricular ejection fraction (LVEF) of <40% could also be used for determination of mild/moderate PGD in the absence of pulmonary pressure and cardiac monitoring measurements. Right-sided PGD (PGD-RV) was determined by a right VAD implantation or elevated right atrial pressure in the absence of elevated pulmonary pressures.

Statistical Analysis

Continuous variables were described by mean and standard deviation. Categorical variables were expressed as the actual 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. Survival data were analyzed using the Kaplan−Meier method and survival curves were compared using the log rank test. Surviving patients were censored at their last known follow-up. $P < .05$ was considered statistically significant.

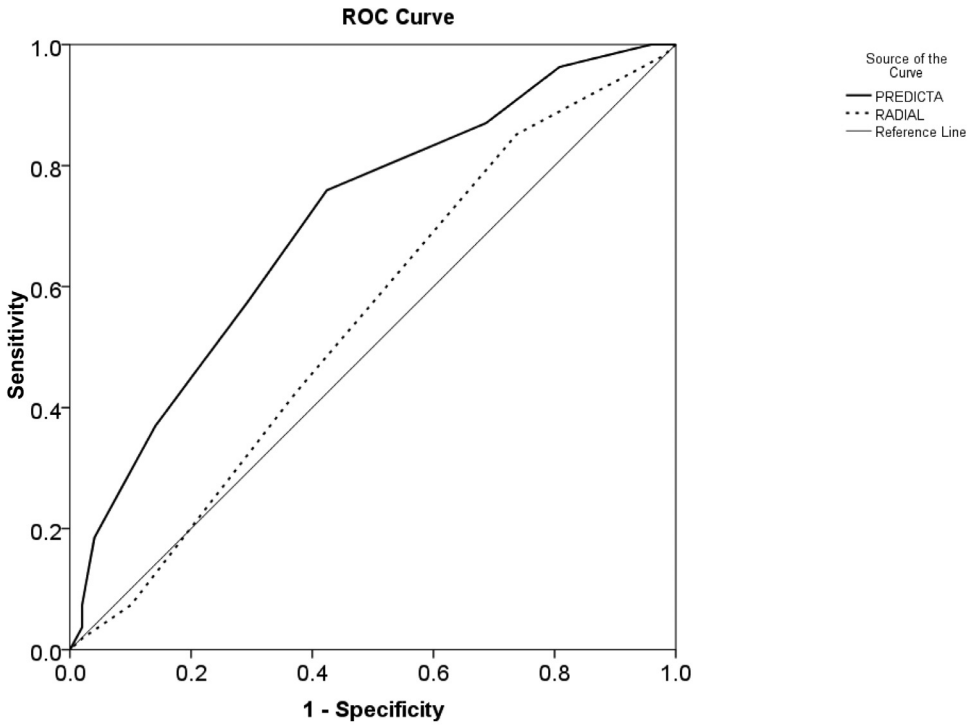
Derivation Cohort. A number generator was used to randomly select 75% of the cohort for the purpose of model derivation (n = 460). Variables with significance of $P < .1$ in the unadjusted analysis above were initially introduced as candidate variables in a multivariable logistic regression model for the probability of PGD and removed by stepwise backward elimination. The goodness of fit of the model to the observed event rates (PGD) was evaluated by calculating the Hosmer−Lemeshow statistic. All statistical analysis was undertaken using SPSS v18.0 (IBM Corp., Armonk, NY).

Validation Cohort. The remainder of patients (n=153) were used as for validation of the model. The ability of the model to identify patients with PGD was evaluated using the C statistic, equivalent to the area under a receiver-operating characteristic (AUROC) curve for dichotomous outcomes. AUROC values of 0.7 to 0.8 were considered acceptable as defined by Hosmer and Lemeshow.[6]

Results

Demographic Data

The demographic details of these patients are listed below in Supplementary Table 1. The incidence of PGD was 38%. Patients with PGD had a poorer survival post-transplant with higher 30-day (18.9% vs 3.9%, $P < .001$) and 1-year mortality rates (32.6% vs 6.6%, $P < .001$). Supplementary Fig. 1 depicts the 5-year survival of both cohorts.



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Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
PREDICTA	0.704	0.619	0.790
RADIAL	0.547	0.453	0.640

Fig. 1. AUROC curves depicting the discriminatory value of the PREDICTA score versus RADIAL score in the validation cohort.

The *P* value for the log rank test for the Kaplan−Meier curve depicting survivals of the two groups of patients was <0.001

Cohort Comparisons

To ensure applicability of data, demographic data of both cohorts were compared. The demographic data of both cohorts are shown in Supplementary Table 2, depicting no statistically significant differences between the derivation and validation cohort of patients.

The incidence of PGD in the derivation cohort was 38.3% (n = 176) and 37.5% (n = 57) in the validation cohort.

There was no statistically significant difference between the total ischemic time (for hearts procured using cold storage) for the derivation cohort (n=374) and the validation cohort (n = 133; 163.7±63.7 vs 163.0±57.3 min, *P* = .93). No differences were noted between the time on OCS (for hearts procured using EVNP) for the derivation cohort (n=86) and the validation cohort (n = 20; 262.3±122.1 vs 246.9±97.2 min, *P* = .66).

Derivation Cohort

The demographic details of the derivation cohort are listed below.

Table 1: Recipient variables between PGD and non-PGD patients in the derivation cohort.

Table 2: Donor variables between PGD and non-PGD patients in the derivative derivation cohort.

Table 3: Perioperative and postoperative variables between PGD and non-PGD patients in the derivative derivation cohort.

From the unadjusted analysis, variables with $P < .1$ were included in the multivariable analysis. Continuous data were stratified into categorical variables with reference categories. Five variables were identified as significant predictors of PGD on multivariable analysis. These include 1 donor variable (donor age), 2 recipient variables (recipient diabetes mellitus and preoperative recipient mechanical circulatory support [MCS]), and 2 procedural variables (implant time and bypass time).

Table 4: Multivariable analysis of risk factors for PGD from the derivation cohort. Binary variables in grey, non-binary variables in white. Odds ratios depicted with 95% confidence intervals.

An additive score was formulated using the odds ratios (rounded) of binary variables with an ordinal scoring system for the non-binary variables with respect to the odds

Table 1. Recipient Variables Between PGD and non-PGD Patients in the Derivation Cohort

Recipient Variables	PGD (n=176)	No PGD (n=284)	*P* value
Male−female ratio	125:51	211:73	.44
Age (years)	47.1 ± 13.5	46.3 ± 13.3	.54
Recipient height (cm)	172.0 ± 8.8	173.0 ± 9.5	.27
Recipient weight (kg)	76.8 ± 14.0	76.6 ± 14.7	.93
Recipient BMI (kg/m^2)	25.9 ± 3.9	25.5 ± 3.9	.33
Recipient creatinine (μmol/L)	105.7 ± 45.7	106.7 ± 38.1	.38
Recipient Re-sternotomy (%)	42 (23.9)	57 (20.1)	.34
Recipient diabetes (%)	27 (15.3)	19 (6.7)	**.003**
Recipient preoperative inotropes (%)	90 (51.1)	171 (60.2)	.056
Preoperative ECMO (%)	5 (2.8)	1 (0.4)	**.033**
Preoperative IABP (%)	15 (8.5)	17 (6.0)	.25
Preoperative LVAD (%)	26 (14.8)	32 (11.3)	.27
Preoperative BiVAD (%)	21 (11.9)	16 (5.6)	**.016**
Preoperative RVAD (%)	3 (1.7)	8 (2.8)	.45
Preoperative amiodarone usage	63 (35.8)	116 (40.8)	.28
Recipient Etiology			
Ischemic cardiomyopathy (%)	40 (22.7)	54 (19.0)	.34
Dilated cardiomyopathy (%)	95 (53.9)	147 (51.8)	
Congenital heart disease (%)	18 (10.2)	28 (9.9)	
Other (%)	23 (13.1)	55 (19.4)	

BiVAD: biventricular ventricular assist device; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; RVAD: right ventricular assist device.

Recipient variables between PGD and non-PGD patients in the derivation cohort. Continuous data shown as mean ± SD with categorical data shown as absolute number and (percentage). Recipient etiology shown in grey.

Table 2. Donor Variables Between PGD and non-PGD Patients In The Derivation Cohort

Donor Factors	PGD (n=176)	No PGD (n=284)	*P* value
Donor height (cm)	174.9±9.1	174.4±9.2	.59
Donor weight (kg)	80.1±15.4	79.0±13.6	.45
Estimated donor LV mass (g)	148.6±26.9	149.9±28.1	.64
Gender mismatch (%)	26.1	23.9	.60
Height mismatch (%)	2.0±7.6	1.5±8.0	.54
Weight mismatch (%)	8.0±30.9	5.6±28.2	.41
Estimated LV mass mismatch (%)	3.81±22.9	4.13±22.8	.81
Donor age	41.6±12.6	38.4±12.6	**.007**
Donor LVEF (%)	57.7±10.3	58.9±7.8	.3
Donor smoker (%)	88(50.0)	147(51.7)	.722
Donor cause of death			
Intracerebral hemorrhage/ thrombosis (%)	106(60.4)	164(57.8)	.31
Hypoxic brain injury (%)	12(6.7)	27(9.5)	
RTA (%)	22(12.7)	47(16.6	
Meningitis (%)	4(2.2)	12(4.3)	
Other (%)	32(17.9)	34(11.8)	
*DCD (%)	6(30)	14(70)	.44
*DBD (%)	170(38.6)	270(61.4)	

DCD, donation after circulatory death, DBD, donation after brainstem death; RTA, road traffic accident.

Donor variables between PGD and non-PGD patients in the derivation cohort. Continuous data shown as mean ± SD with categorical data shown as absolute number and (percentage). Donor cause of death shown in grey.

ratio. The scoring system was entitled the PREDICTA (**Pre**operative mechanical circulatory support in recipient (short-term ventricular assist device/extracorporeal membranous oxygenation), **DI**abetes mellitus in recipient, **C**ardiopulmonary bypass time>180 minutes, implant **T**ime, donor **A**ge) score with the breakdown listed in Table 5.

Table 5: The PREDICTA score points allocation.

Table 3. Perioperative and Postoperative Variables Between PGD and non-PGD Patients in the Derivation Cohort

Operative Details	PGD (n=176)	Non-PGD (n=284)	*P* value
Perfusion solution			
St Thomas (%)	146(83.0)	242(85.2)	.52
Custodiol (%)	30(17.0)	42(14.8)	
EVNP (%)	33(18.7)	54(19.0)	.94
Cold storage (%)	143(81.3)	230(81.0)	
Cold ischemic time (mins)*	102.5±44.1	99.6±48.6	.33
Time on OCS†	221.8±155.8	232.2±136.9	.72
Explant time (mins)	20.0±10.7	20.5±10.5	.60
Implant time (mins)	59.6±21.1	53.0±20.7	**.001**
Total ischemic time (mins)	166.9±63.7	160.5±62.9	.11
Bypass time (mins)	196.3±77.3	187.9±76.2	.095
Postoperative details			
Right atrial pressure (mmHg)‡	13.8±4.4	11.7±4.1	<**.001**
PA mean (mmHg)‡	22.0±6.0	22.2±5.3	.93
Cardiac index‡	2.2±1.3	3.1±1.1	<**.001**
MAP (mmHg)‡	71.5±13.0	78.7±15.8	<**.001**
Inotrope score‡	18.9±12.4	12.3±8.8	<**.001**
Blood products transfused (units)	8.6±11.3	9.0±34.7	.078

MAP, mean arterial pressure; PA, pulmonary artery.

Perioperative and postoperative variables between PGD and non-PGD patients in the derivation cohort. Continuous data shown as mean ± SD with categorical data shown as absolute number and (percentage).

*Non-OCS donors.

†OCS donors.

‡Denotes measures used in the current ISHLT PGD definition.

Table 4. Multivariable Analysis of Risk Factors for PGD From the Derivation Cohort

Variable	Odds Ratio	95% Confidence Intervals	*P* value
Recipient diabetes mellitus	3.04	(1.49, 6.21)	.002
Preoperative MCS (ST-VADs and ECMO)	2.73	(1.35, 5.55)	.009
Implant time			.021
≤45 min	Reference category		
46-60 min	1.80	(1.11, 2.93)	
61-90 min	1.96	(1.22, 3.15)	
>90 min	2.15	(1.01, 4.60)	
Donor age			.025
<21 years	Reference category		
21-40 years	1.44	(0.72, 2.85)	
41-50 years	1.81	(0.89, 3.67)	
>50 years	2.60	(1.26, 5.37)	
Bypass time >180 min	2.53	(1.75, 3.66)	.000

ECMO, extracorporeal membrane oxygenation; ST-VADs, short-term ventricular assist devices.

Multivariable analysis of risk factors for PGD from the derivation cohort. Binary variables in grey, non-binary variables in white. Odds ratios depicted with 95% Confidence intervals.

Validation Cohort

We used the validation cohort to compare the predictive value of the PREDICTA score versus the RADIAL score, a validated published PGD predictive score. AUROC curves

Table 5. PREDICTA Score Points Allocation

Variable	Points
Preoperative MCS (ST-VADs and ECMO)	3
Recipient diabetes mellitus	3
Cardiopulmonary bypass time >180 min	2
Implant time	
≤45 min	0
46-60 min	1
61-90 min	2
>90 min	3
Donor age	
<21 years	0
21-40 years	1
41-50 years	2
>50 years	3
Total	__/14

ECMO, extracorporeal membrane oxygenation; ST-VADs, short-term ventricular assist devices.

The PREDICTA score points allocation. For binary variables, points are allocated as 0 or values depicted in the following boxes. For continuous variables, points are allocated based on the values they lie in.

were used to compare the observed and expected rate of moderate/severe PGD in this cohort. The AUROC curves are depicted in Fig. 1.

The C statistic of the PREDICTA score was 0.704 versus 0.547 for the RADIAL score indicating an acceptable discriminatory value.

Discussion

The incidence of PGD in the UK from October 2012 to October 2016 was 38% as defined by the ISHLT consensus statement. The risk factors identified from the derivation cohort included recipient diabetes mellitus, prolonged cardiopulmonary bypass time, increasing donor age, preoperative mechanical circulatory support usage and prolonged implant time. The 30-day and 1-year mortality was significantly higher in the PGD cohort as shown in Supplementary Fig. 1. The rate of PGD in our study was also higher when compared with recent single-center studies reported in the literature ranging from 10% to 31%.[3,7–11] Older studies prior to the consensus statement have shown a PGD range of between 2.5% and 24% with varying center-specific definitions of PGD.[2] Our previous multicenter study showed an incidence of 36% with little variation over the 3 years.[12] We strictly adhered to the ISHLT guidelines thereby preventing underestimation of the true PGD rate by using both LVEF and/or inotrope score definitions with corresponding cardiac monitoring studies in all of our patients, which may have led to the significantly higher number.

A variety of donor, recipient, and procedural factors have been identified in the literature to be associated with PGD. However, given the variability in definitions and the different periods analyzed, there was significant heterogeneity noted in risk factors. Some of the risk factors that have been suggested include donor age,[10] preoperative mechanical support, length of ischemic time,[10] and recipient diabetes mellitus[10]; all of which were noted in our study. Other risk factors such as recipient age,[13] preoperative recipient amiodarone therapy,[14] recipient inotropic support,[5] donor inotropic support,[13] donor-to-recipient size mismatching,[15] and donor etiology of death,[13] did not possess predictive value in our study.

Recipient age was not noted to be significant in more recent studies, potentially because of improving medical and device therapy. Recipient amiodarone therapy was not noted to be an increased risk factor for PGD in our study and other previous studies.[16–19] Amiodarone therapy may reflect the pro-arrhythmogenic state of unwell patients and therefore be a surrogate for the critical state of these patients. Analysis of ISHLT registry highlighted an increased mortality in recipients with previous amiodarone therapy; however, recipient age was a major confounder with more older patients receiving amiodarone.[19] Preoperative inotropic support in both the donor and recipient were not risk factors for PGD in our study. This could possibly reflect the increasing use of VADs in recipients with escalating inotropic requirement in the current era and better donor management strategies including the use of vasopressin as an inotropic sparing agent.[20] The universal improvement in donor management could also explain the lack of difference in donor etiology of death as a risk factor for PGD.

We emulated the methodology for LV mass prediction to study the effect of donor−recipient mass mismatch as a potential cause for PGD as suggested by Gong et al.[15] However, there was no significant difference in the predicted mass mismatch between the two groups, with no donor under-sizing >30%.

Prolonged bypass time was noted to be a risk factor for PGD post-transplant. Although the etiology of PGD is multifactorial, the unifying pathophysiology is the occurrence of ischemic reperfusion injury (IRI).[21] There are a variety of neutrophil-mediated post-ischemic inflammatory responses that propagate this condition, alongside formation of free radicals that result in a cascading series of insults resulting in the inability of the implanted graft to meet the circulatory requirements of the recipient. Efforts to minimize the effects of IRI include minimizing ischemic time and bypass time have been used to good effect in general cardiac surgery.[22] Although reperfusion occurs while the heart is on the cardiopulmonary bypass circuit, the adequacy of reperfusion especially to the ventricles is uncertain.[23] Prolonged bypass time also causes vasoplegia with a reduced vascular resistance with platelet and coagulation factor dysfunction, further contributing to IRI.[24]

The RADIAL score was the only validated scoring system for prediction of PGD. Segovia and colleagues validated it in a Spanish cohort of heart transplant patients using a center-specific definition of PGD.[5] It consists of 6 risk factors derived from a multivariable analysis of 621 heart transplants between 1984 and 2006 with a PGD incidence of 9%. From this study, they noted that an increased right atrial pressure ≥10 mm Hg, recipient age ≥ 60 years, recipient diabetes mellitus, recipient inotrope dependence, donor age ≥30 years, and length of ischemic time ≥240 minutes to be significant risk factors. We did not find the

RADIAL score to be predictive of PGD in our cohort as demonstrated by Fig. 1. This similar finding was noted by Alina et al.[3] They attributed this to the different periods in which the heart transplantations had occurred. Certainly, there were increasing numbers of re-sternotomies with an increasing number of patients on both short-term and long-term mechanical assist devices compared with those in the studies by both Carmena[25] and Segovia.[5] The donors in our cohort of patients were older as well, in keeping with the general trend noted worldwide and especially in Europe with an increased number of donors, which would be considered extended criteria in previous eras forming a substantial proportion of donors today.[26] Total ischemic time has been described as a predictor of mortality by Banner et al.[27] However, when looking at it in greater detail, inclusion of total ischemic time (summation of warm ischemic time/implant time and cold ischemic time) resulted in a reduced odds ratio compared to warm ischemic time alone. Similar findings were noted by Marasco's group.[28] Warm ischemic time also proved detrimental in kidney transplantation.[29] In addition, the introduction of DCD and EVNP has also reduced total ischemic times and negated the use of static cold storage.

We used a random number generator to ensure there were equal numbers of patients in the validation and derivation cohort with DCD and EVNP, which were more prevalent in the latter years of the study. This is the first scoring system derived from multiple centers to include patients who have undergone transplants using DCD and EVNP hearts. It is therefore a more accurate representation of the cohort of patients undergoing heart transplantations in the current era.

We report a 30-day mortality of 18.9% (n = 44) in the PGD cohort, majority (88.7%) of whom required MCS and therefore were classed as severe PGD. The in-hospital mortality however was 22.7%. A recent study by Sabatino[10] reported a higher in-hospital mortality of 12% for moderate PGD and 68% for severe PGD. Nicoara et al[3] reported an in-hospital mortality of 23% in the PGD cohort, whereas Squiers et al.[11] reported an in-hospital mortality of ~25%. These figures are indicative of the nature of the condition which has a high postoperative mortality and morbidity. Identification of risk factors using scoring systems like the PREDICTA or RADIAL may therefore assist in resource allocation and planning.

Limitations

There are several limitations to our study. The multicenter nature of the study introduces several different peri-transplant protocols especially in postoperative management. The choice of inotropes and escalation of therapy is determined by center-specific experience and clinician familiarity. The retrospective nature of the study may also introduce uncontrolled biases that may have influenced decision-making at the time of transplantation. The score was tested in a UK cohort of patients and may require external validation to ascertain feasibility and suitability in other centers.

We were unable to collect accurate cumulative dosages of amiodarone therapy. We were however able to ascertain if a recipient had previously received amiodarone. The relatively small sample size is also a limiting factor in this study. However, to date, this is the largest multicenter PGD study in the literature.

The PREDICTA is a novel scoring tool with superior predictive function compared with the RADIAL score in our multicenter cohort. However larger sample sizes and external validation in other heart transplant populations are needed. Given the retrospective nature of this study, the model is exploratory and requires cross validation in a prospective cohort.

Conclusion

This is the first comprehensive national model for PGD after heart transplantation using the ISHLT definition. It identifies the donor, recipient and procedural risk factors for PGD. The PREDICTA score is able to accurately predict PGD with better predictive function compared with the RADIAL score in our multicenter cohort of patients. It may help identify patients who are at risk of PGD and therefore allow risk stratification and resource planning for management and therapeutic interventions. Further multicenter studies are needed to determine the applicability and validity of the PREDICTA score in other centers.

Declaration of Competing Interest

All authors have no conflicts of interest to disclose.

Acknowledgements

The authors thank Dr Nicholas Banner for his significant contribution in overlooking the procurement of data for this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.07.009.

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