



Validation of the International Society for Heart and Lung Transplantation primary graft dysfunction instrument in heart transplantation

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BACKGROUND: In 2014, the International Society for Heart and Lung Transplantation (ISHLT) developed a classification instrument for left ventricular (LV) and isolated right ventricular (RV) primary graft dysfunction post-heart transplant. The instrument classifies LV-PGD as mild, moderate, or severe. In this study, we evaluated the predictive validity of this instrument.

METHODS: We conducted a cohort study of 412 consecutive patients transplanted between 2004 and 2015 at the Toronto General Hospital and Ottawa Heart Institute (Canada). We classified LV-PGD as mild, moderate, or severe, using the ISHLT instrument. To assess predictive validity, we evaluated the association between LV-PGD severity and 1-year post-transplant mortality using a Cox regression model adjusted for recipient age.

RESULTS: The cohort was predominantly male (71%), mean age 50 ± 13 years, mean donor age 38 ± 14 years, with 25% female donors. Mean ischemic time was 3.7 ± 1.1 hours. LV-PGD was mild in 3.6% of patients, moderate in 9.5%, and severe in 3.9%. All levels of LV-PGD were associated with increased 1-year mortality, with a gradient in the association between mild, moderate, and severe. We only observed a statistically significant association for moderate and severe forms of LV-PGD (mild: hazard ratio [HR] 2.4, 95% confidence interval [CI] 0.6 to 10.2; moderate: HR 7.0, 95% CI 3.4 to 14.6; severe: HR 15.9, 95% CI 7.2 to 35.0).

CONCLUSIONS: The ISHLT LV-PGD classification convincingly identifies a substantial increase in the risk of death at 1 year, and an increased gradient of risk, in those with moderate or severe LV-PGD.

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The 2017 International Society for Heart and Lung Transplantation (ISHLT) registry report described

outcomes on 80,000 heart transplants performed from 1994 to 2015. The risk of 1-year mortality in this cohort

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was 16.5%. Of these, 5,400 (41%) deaths occurred within the first year post-transplant due to, or related to, graft dysfunction.¹

Early graft dysfunction without a clear precipitating cause, termed primary graft dysfunction (PGD), is infrequent, but it is associated with significant morbidity and mortality. Studies published before 2014 utilized various definitions of PGD (ranging from the need for mechanical circulatory support within the first 30 days to use of low-dose inotropes) and reported variable incidence rates (2.8% to 23%).² Variability in the definition of PGD created difficulty in comparing the risk of mortality over time and across centers, limiting the potential for development of management strategies for such patients.

To address these challenges, in 2014, the ISHLT developed a consensus-based definition and classification instrument for PGD.³ The Society now defines PGD as graft dysfunction, not due to rejection, volume overload, or pulmonary hypertension, that occurs within the first 24 hours post-transplant. The consensus panel classified PGD as left ventricular (LV), biventricular (BV)-PGD, or isolated right ventricular (RV)-PGD. For LV and BV-PGD, the instrument further sub-classified dysfunction as mild, moderate, or severe (distinguished by the level of support required). Since the ISHLT publication, 4 studies that used the consensus definition observed 30-day mortality incidence of 30% to 51% in patients with severe PGD.⁴

For an instrument such as the ISHLT PGD classification, association with subsequent outcomes represents a potentially powerful demonstration of validity. To date, no study has formally assessed the performance of the severity classification of the PGD instrument when applied within the first 24 hours post-transplant in relation to 1-year mortality. Therefore, we evaluated the association between the ISHLT classification of graft dysfunction and mortality during the first post-transplant year in heart transplant recipients.

Methods

Population

We collected a cohort of 412 consecutive adult heart transplant recipients (January 1, 2004, to January 1, 2015), followed at the Toronto General Hospital or Ottawa Heart Institute. We excluded patients <18 years of age, patients undergoing re-transplantation, and recipients of more than 1 organ.

Recipient data

We abstracted age, sex, comorbidities, heart failure etiology, pre-transplant laboratory values, and pre-transplant support of transplant recipients, as well as inotropic support and mechanical circulatory support (intra-aortic balloon pump, extracorporeal membrane oxygenation, ventricular assist devices) post-transplant.

Donor data

We abstracted donor age, sex, total ischemic time (clamp of the aorta in the donor, the release of the clamp in recipient), inotropic support (only available post-2013), echocardiographic assessment, cause of brain death, troponin (only available post-2013), and angiography (only available post-2013).

Primary graft dysfunction

We identified PGD using data from the first 24 hours post-transplant. We excluded other potential causes for graft dysfunction on the basis of the clinician team’s consensus assessment and the results of specific test results (including, e.g., acute cellular rejection by endomyocardial biopsy). We recorded diastolic pulmonary artery pressure in the post-operative period as an alternative when pulmonary capillary wedge pressure measures were unavailable.⁵ We classified patients according to the ISHLT PGD instrument described by Kobashigawa et al³ (Table 1). As per the instrument definition, we classified individuals with both LV and RV dysfunction as LV-PGD. One individual blinded to the outcomes of recipients considered all hemodynamic measures and supports recorded in the medical records of patients within the first

Table 1 Primary Graft Dysfunction Classification

Ventricle	Severity	Criteria
LV or BV PGD	Mild	LVEF ≤40% or RAP >15 mm Hg and PCWP >20 mm Hg and CI <2.0 liters/min/m ² (>1 hour) and requiring low-dose inotropes
	Moderate	(i) LVEF ≤40%, or RAP >15 mm Hg and PCWP >20 mm Hg and CI <2.0 liters/min/m ² and MAP <70 mm Hg (>1 hour) (ii) High-dose inotropes, or newly placed IABP
	Severe	Dependence on LV or biventricular MCS (excluding IABP)
RV-PGD		(i) RAP >15 mm Hg and PCWP <15 mm Hg and CI <2.0 liters/min/m ² (ii) TPG < 15 mm Hg, and/or PA systolic >50 mm Hg (iii) Need for RVAD

Inotrope score = dopamine (X1) + dobutamine (X1) + amrinone (X1) + milrinone (X15) + epinephrine (X100) + norepinephrine (X100), with each drug dosed in micrograms per kilogram per minute. BV, biventricular; CI, cardiac index; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; MCS, mechanical circulatory support; LV, left ventricular; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PGD, primary graft dysfunction; RAP, right atrial pressure; RV, right ventricular; RVAD, right ventricular assist device; TPG, transpulmonary gradient.

24 hours. We classified patients with PGD at the first instance it was observed based on criteria proposed by the ISHLT. We extracted all data necessary for classification of PGD from intensive care unit flowsheets and charts and echocardiographic reports.

Outcome

The primary outcome of our study was all-cause 1-year mortality. All patients were followed for 1-year without any loss to follow-up.

Statistical analysis

We summarized continuous variables as mean and standard deviation (for normally distributed data) or median and interquartile range (IQR) (for skewed data) and categorical data using absolute counts and proportions. For comparison of continuous data across different PGD severity groups, we utilized the one-way analysis of variance (ANOVA). In cases of skewed continuous data, we utilized the non-parametric Dunn's test. To compare continuous data between patients with RV-PGD and no PGD, we utilized the two-way *t*-test. We used the chi-square test (or Fisher's exact test if the number of patients was <5) to compare categorical data across no-PGD, LV-PGD severity groups, and RV-PGD.

We depicted the observed survival with Kaplan–Meier analysis, using the log-rank test to assess whether chance could explain differences in observed survival across PGD severity classes. For prognostication and generalizability for future transplant recipients, we modeled the association between severity levels of LV-PGD and all-cause 1-year mortality using Cox proportional hazard regression analysis. Each severity level of PGD was entered as a dummy variable with the no-PGD group as the reference group. Because of the small number of events, to avoid overfitting we restricted adjustment of the model to recipient age. We could not conduct a similar analysis for RV-PGD due to the low number of deaths. We tested the proportional hazard assumption graphically using a log–log plot of survival, and statistically using Schoenfeld residuals. All statistical analyses were conducted with Stata version 15.1 (StataCorp, College Station, TX). $p < 0.05$ was considered statistically significant.

The research ethics boards of both the University Health Network and Ottawa Heart Institute approved the study.

Results

Table 2 presents the characteristics of the 412 eligible heart transplant recipients, of whom 249 received their transplant at the Toronto General Hospital and 163 at the Ottawa Heart Institute. The majority of recipients were male (71%), with a mean age of 50 ± 13 years. Bridging to transplant with a left ventricular assist device occurred in 127 (32%) patients. Of the donors, 67% were male, with an average donor age of 38 ± 14 years; 25% of transplants were donor/recipient sex-mismatched. The mean ischemic time was 3.7 ± 1.1 hours. **Table 3** summarizes the hemodynamic findings used for classification of PGD within the first 24 hours.

LV-PGD

The ISHLT system classified 15 (3.6%) patients as mild, 39 (9.5%) as moderate, and 16 (3.9%) as severe PGD (**Figure 1**).

Patients with severe PGD had longer ischemic times (4.4 ± 1.3 hours vs 3.5 ± 1.1 in patients without PGD, $p < 0.001$) and a higher proportion of patients bridged to transplant with an LVAD (67% vs 31% in patients without PGD, $p = 0.03$). The recipient, donor, and transplant characteristics proved comparable across different LV-PGD severity levels (**Table 2**). Of the 44 deaths in the first year post-transplant, retrospective chart review showed cause of death as graft failure in 35%, multiple-organ failure in 28%, stroke in 11%, sepsis in 11%, infection in 7%, and pulmonary bleeding in 2%. Almost all deaths occurred within the first 30 days post-transplant: 30-day survival of 97.6% (95% confidence interval [CI] 95.2% to 98.8%) in those without LV-PGD; 86.7% (95% CI 56.4% to 96.5%) in those with mild LV-PGD; 71.8% (95% CI 54.9% to 83.3%) in those with moderate LV-PGD; and 47.4% (95% CI 21.8% to 69.4%) in those with severe LV-PGD (log-rank test, $p < 0.001$; **Figure 2**).

In a Cox regression model adjusted for recipient age, only moderate and severe levels of LV-PGD were significantly associated with 1-year mortality (**Table 4**). We observed a graded increase in the strength of association between mild, moderate, and severe LV-PGD, with wide CIs. We excluded an association by chance ($p < 0.05$) for moderate and severe LV-PGD. Our Cox regression model met the proportional hazard assumption. In the baseline group of no LV-PGD, there was an absolute mortality risk of 6%. This risk increased to 16% (95% CI 3% to 52%) for mild, 40% (95% CI 22% to 65%) for moderate, and 68% (95% CI 41% to 92%) for severe PGD. In a separate Cox regression model (data not shown), we adjusted for the transplant center to ensure center-specific differences in treatment are not influencing our primary outcome of 1-year mortality. Adjustment for this made no significant difference in the association between each LV-PGD severity and 1-year mortality.

RV-PGD

Isolated RV-PGD defined by hemodynamic criteria ($N = 11$) or RVAD ($N = 1$) occurred in 12 (3.5%) recipients. Patients with RV-PGD were predominantly male (58.3%), with a mean age of 52 ± 16 years (**Table 1**). Of the donors, 50% were men and their mean age was 35 ± 16 years. Patients with RV-PGD were more frequently female (58%) compared with the no-PGD patients (27%). Two patients with RV-PGD died during a mean follow-up of 11.6 ± 2.4 months. The observed 30-day survival in patients with RV-PGD was 92% (95% CI 54% to 99%) ($p = 0.16$ vs patients without PGD).

Discussion

Principal findings

Our findings demonstrate a strong association between the ISHLT PGD classification of LV dysfunction and 1-year mortality, particularly for those recipients with moderate or severe dysfunction (**Figure 1**), thus providing strong

Table 2 Baseline Recipient, Donor, and Transplant Characteristics

	All (n = 412)	None (n = 330)	Mild (n = 15)	Moderate (n = 39)	Severe (n = 16)	p-value	RV-PGD (n = 12)	p-value
Recipient characteristics								
Age	50 ± 13	50 ± 13	49 ± 13	53 ± 11	49 ± 15	0.439	51 ± 12	0.667
Male sex	294 (71%)	240 (73%)	12 (80%)	27 (69%)	10 (62%)	0.706	5 (42%)	0.043
BMI	25 ± 5	25 ± 5	25 ± 5	26 ± 4	26 ± 5	0.638	24 ± 5	0.362
Pre-transplant diabetes	81 (21%)	64 (20%)	6 (43%)	9 (25%)	2 (12%)	0.173	2 (17%)	1.000
Ischemic HF etiology	115 (28%)	93 (28%)	2 (13%)	9 (23%)	7 (44%)	0.280	4 (33%)	0.747
Previous sternotomy	202 (50%)	162 (50%)	7 (47%)	20 (56%)	11 (73%)	0.326	2 (17%)	0.036
LVAD	127 (32%)	103 (31%)	3 (20%)	11 (30%)	10 (67%)	0.032	3 (25%)	0.762
ECMO	7 (2%)	6 (2%)	0 (0%)	0 (%)	1 (6%)	0.337	0 (0%)	1.000
IABP	3 (1%)	0 (0%)	0 (0%)	3 (8%)	0 (0%)	0.002	0 (0%)	1.000
Inotropes	142 (34%)	117 (35%)	4 (27%)	14 (36%)	3 (19%)	0.592	4 (33%)	1.000
Donor characteristics								
Donor age	38 ± 14	38 ± 14	44 ± 15	35 ± 15	44 ± 15	0.062	35 ± 16	0.418
Male donor	274 (67%)	224 (68%)	8 (53%)	27 (71%)	9 (56%)	0.463	6 (50%)	0.211
Donor sodium	144 ± 6	144 ± 6	145 ± 7	146 ± 4	143 ± 6	0.814	149 ± 7	0.060
Donor troponin I	0.46 (0.19 to 0.88)	0.50 (0.20 to 0.90)	0.16 (0.12 to 0.20)	0.40 (0.17 to 1.47)	0.40 (0.34 to 0.44)	0.525	0.59 (0.22 to 1.00)	0.926
Dobutamine	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0.073	0 (0%)	0.070
Dopamine	1 (2%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)		0 (0%)	
Epinephrine	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)	
Levophed	3 (6%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)		2 (50%)	
Levothyroxine	41 (76%)	35 (82%)	1 (50%)	0 (0%)	3 (100%)		2 (50%)	
Vasopressin	7 (13%)	5 (12%)	0 (0%)	2 (100%)	0 (0%)		0 (0%)	
Donor EF	60 ± 7	60 ± 7	62 ± 8	57 ± 9	61 ± 4	0.060	61 ± 6	0.599
LV hypertrophy	21 (8%)	16 (8%)	1 (12%)	3 (12%)	1 (12%)	0.491	0 (0%)	1.000
Transplant characteristics								
Sex mismatch	104 (25%)	81 (24%)	6 (40%)	9 (23%)	5 (31%)	0.493	3 (25%)	1.000
Ischemic time	3.7 ± 1.1	3.6 ± 1.1	3.5 ± 1.0	4.2 ± 1.1	4.4 ± 1.3	0.00005	3.8 ± 1.3	0.532
RADIAL score	2 (2 to 3)	2 (2 to 3)	3 (2 to 3)	3 (2 to 3)	3 (1 to 3)	0.2320	1 (2 to 3)	0.8331

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; HF, heart failure; IABP, intra-aortic balloon pump; LV, left ventricle; LVAD, left ventricular assist device.

Table 3 Hemodynamic Assessment From First 24 Hours Post-transplant

	All (n = 412)	None (n = 330)	Mild (n = 15)	Moderate (n = 39)	Severe (n = 16)	RV-PGD (n = 12)
LVEF $\leq 40\%$	43 (11%)	0 (0%)	9 (60%)	27 (75%)	7 (47%)	0 (0%)
RAP (mm Hg)	13 \pm 6	13 \pm 6	17 \pm 8	16 \pm 7	17 \pm 5	19 \pm 3
Systolic PAP (mm Hg)	33 \pm 8	32 \pm 8	39 \pm 11	34 \pm 9	29 \pm 7	35 \pm 6
Diastolic PAP (mm Hg)	14 \pm 7	14 \pm 6	20 \pm 6	16 \pm 7	29 \pm 9	5 \pm 5
Mean PAP (mm Hg)	20 \pm 6	20 \pm 6	26 \pm 7	22 \pm 7	23 \pm 8	16 \pm 3
TPG (mm Hg)	6 \pm 3	6 \pm 2	6 \pm 2	6 \pm 3	3 \pm 2	10 \pm 3
MAP (mm Hg)	66 \pm 17	66 \pm 16	72 \pm 5	62 \pm 18	71 \pm 13	52 \pm 31
Cardiac index (ml/min/m ²)	2.2 \pm 0.6	2.3 \pm 0.6	1.8 \pm 0.5	1.9 \pm 0.4	1.4 \pm 0.4	1.7 \pm 0.1
Inotrope score	17 (8 to 28)	16 (8 to 28)	8 (4 to 13)	27 (18 to 38)	26 (8 to 53)	24 (9 to 27)

Inotrope score = dopamine (X1) + dobutamine (X1) + amrinone (X1) + milrinone (X15) + epinephrine (X100) + norepinephrine (X100) with each drug dosed in micrograms per kilogram per minute. LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PAP, pulmonary artery pressure; RAP, right atrial pressure; RV-PGD, right ventricular pulmonary graft dysfunction; TPG, transpulmonary gradient

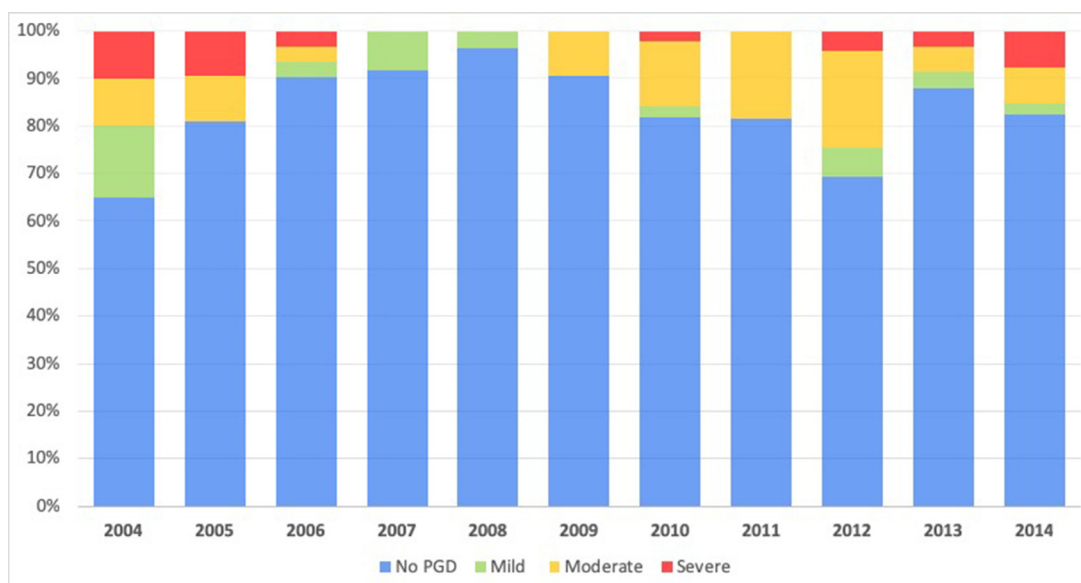
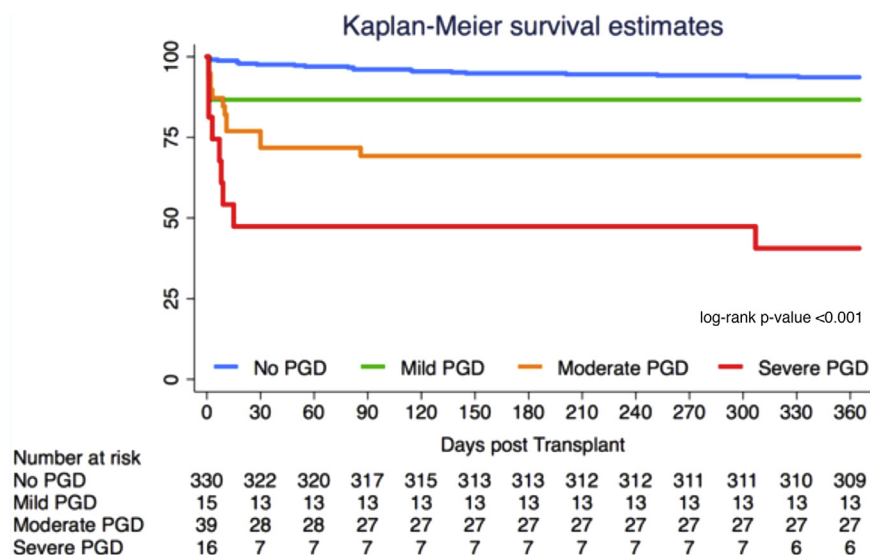
**Figure 1** Rates of PGD over the years.**Figure 2** Survival stratified by PGD severity.

Table 4 Cox Proportional Hazard Model for Impact of PGD on 1-Year Mortality, Adjusted for Age

Predictor	Study results and measurements	Absolute effect estimates		Plain text summary
		Baseline	With predictor	
Mild LV-PGD	HR 2.40 (95% CI 0.56 to 10.23), $p = 0.238$	6 per 1,000	14 per 1,000	Mild LV-PGD makes little or no difference in 1-year all-cause mortality
		Difference: 8 more per 1,000 (95% CI, 2 less, 34 more)		
Moderate LV-PGD	HR 7.03 (95% CI 3.39 to 14.59), $p < 0.001$	6 per 1,000	35 per 1,000	Moderate LV-PGD increases risk for 1-year all-cause mortality
		Difference: 29 more per 1,000 (95% CI, 19 more, 59 more)		
Severe LV-PGD	HR 15.87 (95% CI 7.20 to 34.98), $p < 0.001$	6 per 1,000	62 per 1,000	Severe LV-PGD strongly increases risk for 1-year all-cause mortality
		Difference: 56 more per 1,000 (95% CI, 36 more, 88 more)		
Recipient Age (per 10-year increase)	HR 0.75 (95% CI 0.60 to 0.93), $p < 0.010$	6 per 1,000	5 per 1,000	Increasing recipient age decreases risk for 1-year all-cause mortality
		Difference: 1 less per 1,000 (95% CI, 2 less, 2 more)		

Associations between each severity level of primary graft dysfunction and mortality are adjusted for recipient age. CI, confidence interval; HR, hazard ratio; LV-PGD, left ventricular primary graft dysfunction.

support for the validity of the LV component of the ISHLT system. Most deaths occurred in the first 30 days, with a gradient in deaths between the 4 categories (Figure 1). Isolated RV dysfunction was not associated with mortality, with very few deaths; thus, our results do not support the validity of this aspect of the ISHLT system.

Relation to earlier studies

Previous studies addressing the validity of the ISHLT PGD classification system modified the definition of PGD and its severity levels or aggregated the different severity levels.⁶⁻⁹

Our study is the first to validate the severity classifications of PGD without modifying the originally published criteria. The age-adjusted predicted risks of 1-year mortality in our study are similar to the unadjusted observed 1-year mortality reported by Dronavalli et al⁹ (15%, 41%, and 67% in mild, moderate, and severe, respectively). These authors reported validity of the ISHLT PGD instrument based on classification from the first 72 hours as opposed to the first 24 hours post-transplant, lowering confidence in applicability and performance of the instrument when assessments are made within the first 24 hours. Dronavalli et al observed no difference in the survival of mild PGD patients when compared to those without PGD. In our cohort, we observed a 2-fold increase in the risk of mortality in these patients, although this was not statistically significant.

In this investigation, we observed a statistically significant association between increasing recipient age and decreasing risk of 1-year mortality. Two previous studies also observed a protective association between increasing recipient age and mortality.^{10,11} One possible explanation for the protective association may be due to the confounding effect of

congenital heart disease, as these patients are significantly younger compared with all other heart failure etiologies, and have the highest risk of 1-year mortality.¹ In addition, older heart transplant candidates are less likely to have comorbidities due to the careful candidate selection process, which could minimize their post-operative risk. The increased prevalence of comorbidities necessitates the careful selection of candidates, relative to the higher risk tolerance for younger recipients.¹²

Implications

The ISHLT classification for moderate and severe LV-PGD has major prognostic information for the first year post-transplant. If a prediction model with adequate discrimination and calibration that identifies patients at high risk of developing moderate or severe cases of PGD were available, it could be useful for recipient selection and organ allocation.

To date, the most utilized risk prediction tool for early graft dysfunction is the RADIAL risk score. Authors of the RADIAL score defined early graft dysfunction by the presence of at least 1 of the following criteria: (1) significant impairment of systolic function affecting both left, right, or both ventricles; (2) severe hemodynamic compromise lasting >1 hour: systolic blood pressure <90 mm Hg and/or cardiac index <2.2 liters/min/m² and requiring 2 or more intravenous inotropes/pressor drugs, or mechanical circulatory support (MCS) support; (3) occurrence within the first 24 hours; and (4) absence of any other obvious cause. The RADIAL score's classification of early graft dysfunction does not categorize patients based on severity. Our study showed a major difference across severity levels of PGD. Therefore, there is a need for future studies to develop

novel risk models to predict not only PGD but also its severity as defined by the ISHLT instrument.

Strengths and limitations

We designed our study to assess the predictive validity of the PGD severity classification, as originally proposed by the ISHLT, ensuring that our classification of PGD severity was blinded to recipient outcomes. We enrolled a consecutive sample of patients, ensuring proper representation of the population, and achieved 100% follow-up at 1 year. We assessed predictive validity using the Cox proportional hazard model, which met the proportional hazards assumption and provided hazard ratios for mild, moderate, and severe LV-PGD.

Limited information required 1 minor modification to the instrument. Pulmonary capillary wedge pressure (PCWP) was measured in only 65 patients from the Ottawa Heart Institute and 3 from the Toronto General Hospital. To meet the PCWP criteria for the classification of PGD, we, therefore, relied on diastolic pulmonary artery (PA) pressure. Although diastolic PA is a good surrogate for PCWP in healthy individuals with normal pulmonary vasculature,⁵ its validity in the heart transplant (HT) population remains unknown. Given that irreversible pulmonary hypertension is a relative contraindication to HT,¹² diastolic PA may serve as an adequate surrogate in this population as well. Our results apply directly to all centers that do not use the routine measurement of PCWP in the post-operative setting and indirectly to those that do.

Only 1 individual, on the basis of chart review, made the decision that there was no other cause of cardiac dysfunction, and classified the PGD severity of patients using hemodynamic data from the first 24 hours post-transplant. Ideally, to assess replicability, these judgments should have been made by 2 independent individuals.

Only 70 patients met the classification criteria for LV-PGD. Hence, our study lacked the power to provide precise 95% confidence intervals when modeling the impact of each severity level on 1-year mortality. Although our model validates the use of the ISHLT instrument for classifying the severity of PGD, the observed imprecision decreases our confidence in the impact of each PGD severity level on 1-year mortality.¹³

The ISHLT PGD instrument is a valid tool for classifying the severity of graft dysfunction observed in the post-operative period. The instrument, however, utilizes both functional thresholds and medical therapy (in the form of inotropic agents) for classification of patients. The threshold for timing, type, and titer of inotropic support may vary considerably across physicians and programs. Such variability in practice may influence the associations between LV-PGD severity and mortality. Therefore, there is a potential limitation in applying our results across centers with different approaches to use of inotropes in patients with compromised cardiac function.

In our study, we did not capture information on the proportion of patients transplanted from extracorporeal membrane

oxygenation (ECMO), intra-aortic balloon pump (IABP), or inotropic support. This lack of information limits attempts to compare and contrast our cohort to those at other centers.

In conclusion, the ISHLT PGD instrument defines and classifies the severity of a well-recognized post-transplant occurrence. Before publication of the ISHLT's PGD instrument, variation in the classification of PGD created difficulty in understanding the possible underlying causes. With a valid consensus instrument, we can better study the risk factors, histology, and biologic manifestations of PGD (all of which help in definitively understanding the underlying etiologies). Our results provide support for the validity of the ISHLT's LV-PGD system as well as its use in future studies of PGD.

Disclosure statement

The authors have no conflicts of interest to disclose. We acknowledge the Trillium Gift of Life Network for providing data on the donors.

References

1. Lund LH, Khush KK, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult heart transplantation report—2017; Focus theme: Allograft ischemic time. *J Heart Lung Transplant* 2017;36:1037-46.
2. Segovia J, Cosio MD, Barcelo JM, et al. RADIAL: a novel primary graft failure risk score in heart transplantation. *J Heart Lung Transplant* 2011;30:644-51.
3. Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant* 2014;33:327-40.
4. Foroutan F, Ross HJ. Primary graft dysfunction: the devil is in the details. *Transplantation*.
5. Wright SP, Esfandiari S, Gray T, et al. The pulmonary artery wedge pressure response to sustained exercise is time-variant in healthy adults. *Heart* 2016;102:438-43.
6. Lima EB, Cunha CR, Barzilai VS, et al. Experience of ECMO in primary graft dysfunction after orthotopic heart transplantation. *Arq Bras Cardiol* 2015;105:285-91.
7. Sabatino M, Vitale G, Manfredini V, et al. Clinical relevance of the International Society for Heart and Lung Transplantation consensus classification of primary graft dysfunction after heart transplantation: epidemiology, risk factors, and outcomes. *J Heart Lung Transplant* 2017;36:1217-25.
8. Squiers JJ, Saracino G, Chamogeorgakis T, et al. Application of the International Society for Heart and Lung Transplantation (ISHLT) criteria for primary graft dysfunction after cardiac transplantation: outcomes from a high-volume centre. *Eur J Cardiothorac Surg* 2017; 51:263-70.
9. Dronavalli VB, Rogers CA, Banner NR. Primary cardiac allograft dysfunction—validation of a clinical definition. *Transplantation* 2015;99:1919-25.
10. Custódio IL, Lima FET, Lopes MV, et al. Results of medium-term survival in patients undergoing cardiac transplantation: institutional experience. *Rev Bras Cir Cardiovasc* 2013;28:470-6.
11. Vakil K, Taimeh Z, Sharma A, et al. Incidence, predictors, and temporal trends of sudden cardiac death after heart transplantation. *Heart Rhythm* 2014;11:1684-90.
12. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart and Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016;35:1-23.
13. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol* 2011;64:1283-93.