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Prognostic value of the pre-transplant diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension

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BACKGROUND: Although the transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR) are commonly used to differentiate heart failure patients with pulmonary vascular disease from those with passive pulmonary hypertension (PH), elevations in TPG and PVR may not always reflect pre-capillary PH. Recently, it has been suggested an elevated diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient (DPG) may be a better indicator of pulmonary vascular remodeling, and therefore, may be of added prognostic value in patients with PH being considered for cardiac transplantation.

METHODS: Using the United Network for Organ Sharing (UNOS) database, we retrospectively reviewed all primary adult (age $>$ 17 years) orthotropic heart transplant recipients between 1998 and 2011. All patients with available pre-transplant hemodynamic data and PH (mean pulmonary artery pressure $\geq$ 25 mm Hg) were included (n = 16,811). We assessed the prognostic value of DPG on post-transplant survival in patients with PH and an elevated TPG and PVR.

RESULTS: In patients with PH and a TPG $>$ 12 mm Hg (n = 5,827), there was no difference in survival at up to 5 years post-transplant between high DPG (defined as $\geq$3, $\geq$5, $\geq$7, or $\geq$10 mm Hg) and low DPG ($<$3, $<$5, $<$7, or $<$10 mm Hg) groups. Similarly, there was no difference in survival between high and low DPG groups in those with a PVR $>$ 3 Wood units (n = 6,270). Defining an elevated TPG as $>$ 15 mm Hg (n = 3,065) or an elevated PVR $>$ 5 (n = 1,783) yielded similar results.

CONCLUSIONS: This large analysis investigating the prognostic value of DPG found an elevated DPG had no effect on post-transplant survival in patients with PH and an elevated TPG and PVR. J Heart Lung Transplant 2014;33:289–297

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Significant pre-capillary pulmonary hypertension (PH) is a relative contraindication to cardiac transplantation due to the risk of post-operative right heart failure.[1] Clinicians commonly use the transpulmonary gradient (TPG) and

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pulmonary vascular resistance (PVR) to determine the degree of pre-capillary PH and suitability of potential heart recipients.[1] However, these metrics are not perfect surrogates for pulmonary vascular remodeling. In particular, the TPG varies with differences in cardiac output and left atrial pressure, and neither measure clearly differentiates fixed pulmonary vascular remodeling from reversible changes in pulmonary vascular smooth muscle tone.[2–4]

For this reason, acute and chronic vasodilator response is often tested to determine the reversibility of the pre-capillary PH; yet, even when reversibility is demonstrated, post-transplant mortality remains higher than that seen in patients without PH.[5] Because of these limitations, a metric to better differentiate high and low risk among patients with PH is needed. Interest has been growing in using the diastolic pulmonary gradient (DPG), defined as the diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient, as a means to identify those left heart failure patients with clinically significant pre-capillary PH.[4,6] A recent analysis of patients with left heart disease and PH suggested that a TPG $>$ 12 mm Hg and a DPG $\geq$ 7 mm Hg were associated with worse survival compared with a TPG $>$ 12 mm Hg and a DPG $<$ 7 mm Hg .[6] Our purpose was to use the United Network of Organ Sharing (UNOS) database to explore whether differences in DPG define high-risk and low-risk sub-populations among patients with PH being considered for orthotopic heart transplant (OHT).

Methods

Data source

UNOS provided Standard Transplant Analysis and Research (STAR) files with donor-specific data from December 1988 to June 2011. The data set included prospectively collected metrics from all patients who underwent thoracic transplantation in the United States. The current study was granted an exemption by the Johns Hopkins Institutional Review Board because none of the investigators had access to data sets containing protected health information.

Study design

We retrospectively examined all primary, adult (aged $>$ 17 years) OHT patients (1988 to 2011) with a complete set of pre-transplant hemodynamic data, which at minimum included systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output. Only patients with PH (defined as mPAP $\geq$ 25 mm Hg) were included in the analysis. Patients with multiorgan transplants and redo transplants were excluded. Outcomes of interest included survival at 30 days, 1 year, and 5 years.

Statistical analysis

Continuous variables were compared by Student's *t*-test (parametric) or Wilcoxon rank sum test (non-parametric) as appropriate. Categoric variables were compared with chi-square or Fisher's exact test. Receiver operator characteristic (ROC) curves were constructed for DPG, TPG, and PVR to assess their utility in discriminating survivors from non-survivors after transplant. Total area under the curve (AUC) was considered to assess the value of these measures. ROC cut points were defined using the Youden's index. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. A 2-tailed *p*-value of $<$ 0.05 was considered significant. Means are presented with standard deviations. Because the cause of death was not available, a sensitivity analysis was performed to ascertain the effect of cause of death on our findings. All statistical analyses were performed using Stata 12.1 software (StataCorp LP, College Station, TX).

Results

Cohort statistics

From December 1988 to June 2011, 43,494 patients aged $>$ 17 years underwent primary OHT. After excluding 18,041 patients without complete hemodynamic data and 8,642 patients without PH (mPAP $<$ 25 mm Hg), the final study cohort consisted of 16,811 patients.

ROC curve analyses

When considering all patients with PH (mPAP $\geq$ 25 mm Hg), DPG, TPG, and PVR all had poor ability to discriminate survivors from non-survivors, as evidenced by the AUC values near 0.5 (Table 1). The optimal cut points for DPG in those patients with PH and an elevated TPG, PVR, or both, were determined (Table 2). DPG did not discriminate survivors from non-survivors significantly better than chance in any of these groups at any of the 3 time points ($p > 0.05$ for all).

PH with an elevated TPG

Demographic, acuity, and hemodynamic data for patients with PH and a TPG $>$ 12 mm Hg in strata of DPG ($n = 5{,}827$) are presented in Table 3. Given the variable ROC cut points for

Table 1 Survival in Patients With a Mean Pulmonary Artery Pressure $\geq$ 25 mm Hg

Variable	AUC
DPG	
30-day survival	0.52
1-year survival	0.51
5-year survival	0.52
Transpulmonary gradient	
30-day survival	0.54
1-year survival	0.52
5-year survival	0.52
Peripheral vascular resistance	
30-day survival	0.53
1-year survival	0.52
5-year survival	0.51

AUC, area under the curve; DPG, diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient.

Table 2 Survival in Patients With Mean Pulmonary Artery Pressure ≥ 25 mm Hg

Pre-capillary PH parameter	DPG cut point	AUC	*p*-value
TPG > 12 mm Hg			
30-day survival	11.5	0.50	0.89
1-year survival	1.2	0.51	0.77
5-year survival	8.5	0.50	0.90
TPG > 15 mm Hg			
30-day survival	5.9	0.50	0.98
1-year survival	10.1	0.50	0.91
5-year survival	8.5	0.51	0.70
PVR > 3 WU			
30-day survival	2.9	0.52	0.25
1-year survival	6	0.51	0.54
5-year survival	2.9	0.51	0.64
PVR > 5 WU			
30-day survival	8.5	0.52	0.69
1-year survival	4	0.52	0.52
5-year survival	8.5	0.52	0.57
TPG > 12 mm Hg and PVR > 3 WU			
30-day survival	11.5	0.50	0.94
1-year survival	1.70	0.50	0.97
5-year survival	8.5	0.50	0.73
TPG > 15 mm Hg and PVR > 5 WU			
30-day survival	8.5	0.51	0.77
1-year survival	14	0.50	0.94
5-year survival	8.5	0.51	0.67

AUC, area under the curve; DPG, diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient; WU, Woods units.

DPG in our analyses as well as various cut points proposed in the literature, we explored 4 cut points for DPG chosen a priori: 3, 5, 7, and 10 mm Hg. Compared with the lower DPG groups (defined as < 3, <5, <7, or <10 mm Hg), higher DPG groups (as ≥3, ≥5, ≥7, or ≥10 mm Hg) were younger and more likely to be of black race, have a diagnosis of idiopathic cardiomyopathy, and have a ventricular assist device. The lower DPG groups were more likely to have an ischemic cardiomyopathy and carry a diagnosis of diabetes. There were no differences in gender, creatinine, bilirubin, ventilator support, or cardiac output. PCWP and pulmonary pulse pressure were higher in the lower DPG groups than in the higher DPG groups. TPG and PVR were higher in the high DPG groups. Post-OHT survival at 30 days, 1 year, and 5 years was similar between low DPG and high DPG groups ($p > 0.05$ for all; Table 4, Figure 1). Defining an elevated TPG as > 15 mm Hg ($n = 3,065$) had no affect on the ability of the DPG cutoffs to predict survival at any time point (Table 4).

PH with an elevated PVR

Demographic, acuity, and hemodynamic data for patients with a PVR > 3 Woods units (WU) and PH ($n = 6,270$) are presented in (Table 5). Compared with the lower DPG groups, higher DPG groups were on average younger, male predominant, and more likely to be of black race. PCWP, pulmonary pulse pressure, TPG, PVR, and cardiac output were lower in the low DPG groups than in the high DPG groups. Similar to the TPG analysis, there was no difference in survival at up to 5 years post-OHT in the low vs high DPG groups ($p > 0.05$ for all; Table 4, Figure 2). Defining an elevated PVR as > 5 WU ($n = 1,783$) had no effect on the ability of DPG to predict post-OHT survival (Table 4).

PH with an elevated TPG and elevated PVR

In 4,419 patients with a TPG > 12 mm Hg and PVR > 3 WU and in 1,290 with a TPG > 15 mm Hg and PVR > 5 WU, there was no difference in survival between low and high DPG groups at up to 5 years post-OHT (Table 4).

Discussion

In OHT candidates with PH, determining the non-reversible component is vital for proper patient selection and good outcomes. Recent studies have suggested the dPAP-to-PCWP gradient may be useful in this regard,[4,6] but this has not been confirmed by large, multicenter studies. Using the UNOS database, we show that the DPG does not meaningfully delineate risk among patients with elevated TPG and PVR undergoing OHT.

An elevated TPG or PVR does not always reflect irreversible pulmonary vascular disease. In left heart failure, the TPG can be elevated not only as a result of pulmonary vascular remodeling but also due to the effects of elevated left-sided filling pressures. As pressures in the left atrium increase, this pressure is passively transmitted back to the pulmonary vasculature, resulting in elevation of the dPAP. This increased venous pressure also leads to more vascular stiffness (or lower vascular compliance) than one would predict based on the PVR alone.[3] The lower compliance leads to enhanced pulmonary arterial wave reflections that result in an increased sPAP, and therefore, mPAP. This occurs without an increase in dPAP, thereby raising the TPG. PVR is subject to the same effects because TPG is in the numerator of its calculation. Both parameters may also be affected by cardiac output, as elegantly described by Naeije et al.[4]

Given known limitations of TPG and PVR measurements, the DPG would appear an attractive alternative because dPAP is presumably not affected by the above mechanisms. However, other factors must be considered. From a technical measurement standpoint, the dPAP is particularly prone to the effects of catheter whip and catheter "ringing" when fluid-filled catheters are used.[7] Even a small error in the measured dPAP may lead to a significant change in the DPG. The use of high-fidelity catheters could eliminate or reduce this error, yet these are not commonly used in clinical practice. Using computer-generated mean values for hemodynamic measurements (averaged over the entire respiratory cycle) rather than manually determined end-expiration values may lead to inaccuracies, especially

Table 3 Variables in Outcomes in Patients With Transpulmonary Gradient > 12 mm Hg

Variable[a]	DPG < 3 mm Hg (n = 1,605)	DPG ≥ 3 mm Hg (n = 4,222)	p-value	DPG < 5 mm Hg (n = 2,506)	DPG ≥ 5 mm Hg (n = 3,321)	p-value	DPG < 7 mm Hg (n = 3,542)	DPG ≥ 7 mm Hg (n = 2,285)	p-value	DPG < 10 mm Hg (n = 4,679)	DPG ≥ 10 mm Hg (n = 1,148)	p-value
Demographics												
Age, years	53.9 ± 10.7	52.6 ± 11.0	<0.001	53.8 ± 10.7	52.3 ± 11.0	<0.001	53.6 ± 10.7	52.0 ± 11.2	<0.001	53.3 ± 10.8	51.7 ± 11.2	<0.001
Female	23.2	22.7	0.68	23.4	22.5	0.39	23.6	21.8	0.11	23.0	22.3	0.60
White	73.6	69.9	0.006	72.0	70.1	0.10	72.6	68.2	<0.001	71.7	67.8	0.009
Black	16.1	20.9	<0.001	17.7	21.0	0.001	17.7	22.5	<0.001	18.9	22.3	0.01
BMI, kg/m^2	26.7 ± 5.0	26.5 ± 5.5	0.33	26.5 ± 5.9	26.5 ± 5.0	0.88	26.6 ± 5.6	26.5 ± 5.0	0.50	26.6 ± 5.5	26.2 ± 5.2	0.022
Diagnosis												
Idiopathic	35.1	44.4		38.0	44.8		39.7	45.2		41.1	45.2	
Ischemic	54.1	46.3		52.0	45.8		50.4	45.5		49.4	45.0	
Congenital	1.6	1.3		1.4	1.4		1.4	1.4		1.4	1.5	
Other	9.1	8.0	<0.001	8.6	8.0	<0.001	8.5	7.9	0.001	8.3	8.4	0.06
Acuity												
Diabetes, No.	426/1,502	991/3,954	0.01	650/2,342	767/3,114	0.009	903/3,318	514/2,138	0.009	1,169/4,382	248/1,074	0.02
Ischemic time, hours	3.1 ± 1.0	3.0 ± 1.0	0.03	3.1 ± 1.0	3.0 ± 1.1	0.047	3.1 ± 1.0	3.0 ± 1.0	0.02	3.1 ± 1.0	3.0 ± 1.0	0.12
Creatinine, mg/dl	1.5 ± 1.7	1.4 ± 1.5	0.55	1.5 ± 1.6	1.5 ± 1.5	0.94	1.5 ± 1.5	1.5 ± 1.6	0.94	1.5 ± 1.6	1.5 ± 1.2	0.98
Bilirubin, mg/dl	1.5 ± 3.8	1.3 ± 2.7	0.06	1.5 ± 3.8	1.3 ± 2.3	0.06	1.4 ± 3.5	1.3 ± 2.2	0.25	1.4 ± 3.2	1.3 ± 2.7	0.71
IABP	5.7	6.1	0.55	5.4	6.4	0.08	5.4	6.9	0.20	5.6	7.6	0.01
VAD	11.7	14.0	0.02	11.7	14.5	0.002	12.3	14.8	0.006	13.1	14.2	0.33
Ventilation	2.5	2.3	0.74	2.6	2.3	0.46	2.4	2.4	0.93	2.4	2.3	0.77
Hemodynamics												
sPAP, mm Hg	60.9 ± 12.6	55.4 ± 12.8	<0.001	59.1 ± 12.2	55.2 ± 13.3	<0.001	57.8 ± 12.2	55.4 ± 14.0	<0.001	56.9 ± 12.4	56.9 ± 15.2	0.85
dPAP, mm Hg	25.1 ± 7.5	28.7 ± 8.1	<0.001	25.4 ± 7.3	29.4 ± 8.3	<0.001	26.0 ± 7.3	30.3 ± 8.6	<0.001	26.5 ± 7.4	32.5 ± 9.3	<0.001
mPAP, mm Hg	40.9 ± 8.1	38.6 ± 9.0	<0.001	39.8 ± 8.1	38.8 ± 9.2	<0.001	39.3 ± 8.1	39.2 ± 9.7	0.64	38.9 ± 8.3	40.8 ± 10.4	<0.001
PCWP, mm Hg	25.7 ± 7.4	20.7 ± 7.7	<0.001	24.6 ± 7.4	20.1 ± 7.8	<0.001	23.8 ± 7.4	19.3 ± 7.9	<0.001	22.9 ± 7.5	18.4 ± 8.4	<0.001
CO, liters/min	4.38 ± 1.5	4.35 ± 1.5	0.54	4.3 ± 1.6	4.4 ± 1.5	0.47	4.4 ± 1.5	4.4 ± 1.5	0.94	4.4 ± 1.5	4.3 ± 1.5	0.11
PVR, WU	3.91 ± 1.9	4.73 ± 2.9	<0.001	4.0 ± 2.2	4.9 ± 2.9	<0.001	4.0 ± 2.1	5.2 ± 3.2	<0.001	4.1 ± 2.2	6.0 ± 3.6	<0.001
TPG, mm Hg	15.2 ± 3.0	17.9 ± 5.5	<0.001	15.3 ± 2.9	18.6 ± 5.9	<0.001	15.5 ± 2.9	19.8 ± 6.5	<0.001	15.9 ± 3.3	22.3 ± 7.4	<0.001

BMI, body mass index; CO, cardiac output; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient; IABP, intra-aortic balloon pump; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; sPAP, systolic pulmonary artery pressure; TPG, transpulmonary gradient; VAD, ventricular assist device; WU, Woods unit

[a]Continuous data are shown as the mean ± standard deviation and categoric data as percentage, or as indicated.

Table 4 Survival by Kaplan-Meier Analysis in All Patients With Mean Pulmonary Artery Pressure ≥ 25 mm Hg

	Survival			Survival			Survival			Survival		
Variable	DPG < 3 mm Hg (%)	DPG ≥ 3 mm Hg (%)	*p*-value	DPG < 5 mm Hg (%)	DPG ≥ 5 mm Hg (%)	*p*-value	DPG < 7 mm Hg (%)	DPG ≥ 7 mm Hg (%)	*p*-value	DPG < 10 mm Hg (%)	DPG ≥ 10 mm Hg (%)	*p*-value
TPG > 12 mm Hg												
30 days	93.4	93.2	0.89	93.4	93.2	0.95	93.3	93.1	0.89	93.3	93.0	0.70
1 year	84.3	85.7	0.21	84.9	85.6	0.41	85.2	85.4	0.76	85.4	85.0	0.65
5 years	71.2	70.8	0.94	71.2	70.8	0.95	71.2	70.5	0.82	70.5	72.5	0.31
TPG > 15 mm Hg												
30 days	93.1	93.0	0.66	93.7	92.8	0.29	93.1	93.0	0.64	93.0	93.0	0.84
1 year	85.3	85.4	0.90	85.2	85.5	0.87	85.5	85.4	0.81	85.4	85.4	0.83
5 years	72.3	71.4	0.66	71.4	71.6	0.83	71.8	71.4	0.82	70.7	73.3	0.27
PVR > 3 WU												
30 days	94.5	93.1	0.09	94.1	93.1	0.20	93.9	93.1	0.39	93.8	92.7	0.22
1 year	86.4	85.6	0.44	86.1	85.6	0.66	86.2	85.2	0.44	86.1	84.9	0.31
5 years	73.6	70.9	0.054	72.9	70.9	0.17	72.4	70.9	0.30	71.7	73.2	0.57
PVR > 5 WU												
30 days	93.1	93.0	0.58	92.7	93.2	0.50	92.6	93.4	0.31	92.9	93.2	0.65
1 year	82.7	85.6	0.15	83.3	85.9	0.15	83.6	86.3	0.10	84.4	86.1	0.34
5 years	71.0	72.9	0.36	71.9	72.7	0.56	71.0	73.8	0.15	70.7	75.9	0.04
TPG > 12 mm Hg and PVR > 3 WU												
30 days	93.4	92.9	0.97	93.2	92.9	0.97	93.1	93.0	0.88	93.1	92.7	0.73
1 year	84.9	85.4	0.63	85.0	85.4	0.59	85.3	85.2	0.92	85.3	85.1	0.81
5 years	72.0	71.2	0.80	71.6	71.3	0.95	71.6	71.1	0.90	70.8	73.2	0.24
TPG > 15 mm Hg and PVR > 5 WU												
30 days	91.3	93.1	0.49	92.7	92.9	0.93	92.7	92.9	0.94	92.6	93.1	0.81
1 year	82.9	85.9	0.34	84.1	85.9	0.54	85.1	85.7	0.84	85.1	85.9	0.75
5 years	69.3	74.0	0.25	70.7	74.1	0.30	71.9	74.1	0.47	71.4	75.7	0.15

DPG, diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient; WU, Wood units.

in situations of marked respiratory excursion.[8] Incomplete catheter wedging may lead to an overestimation of PCWP and, therefore, a falsely low DPG. Although these types of error may also affect the TPG and PVR, the relative effects on DPG may be more profound.

In addition, and most importantly, the DPG can change acutely in situations such as sepsis,[9,10] after bypass surgery,[11] acute respiratory distress syndrome,[12,13] acidosis,[2] and hypoxia.[2,14] The mechanism behind an elevated DPG in sepsis remains uncertain, but theories include microthrombi,[15] effects of endogenous prostaglandins,[16] acidosis,[2] and/or serotonin release.[12] Using intracardiac pacing, Enson et al[17] demonstrated that increases in heart rate alone lead to an increase in DPG. This later phenomenon may be particularly relevant to the heart failure population where tachycardia is common, compensating for a low cardiac output or as a result of inotropic medications.

Gerges et al[6] recently reported that a DPG ≥ 7 mm Hg in heart failure patients with an elevated TPG was associated with worse long-term prognosis compared with those with a DPG < 7 mm Hg.[6] These findings may simply suggest that elevated DPG identifies a sicker patient population, as evidenced by their faster heart rates, higher pulmonary pressures, and overall worse hemodynamic profiles compared with the lower DPG group. Once patients have resolution of their left heart failure (i.e., through OHT), many of these "reversible" factors that may elevate the DPG are no longer present.

This retrospective study has several limitations that merit discussion. First, data on vasodilator testing before OHT was not available in the UNOS database, and thus, the reversibility of PH in patients with significant PH is not known. Some patients who did not demonstrate reversibility were likely excluded as OHT candidates and are therefore not included in this database. These excluded patients may have had an elevated DPG. However, the large numbers of patients with an elevated DPG in this database help to lessen this potential impact. Similarly, post-OHT hemodynamic data were not available, preventing us from determining if the DPG normalized after OHT or if those with persistently elevated DPG had worse outcomes. Goland et al[18] showed that failure to normalize PVR to < 3 WU after OHT (i.e., those with truly fixed PH) is a risk factor for long-term survival. In our analysis, pre-OHT DPG did not discriminate long-term (5-year) survival.

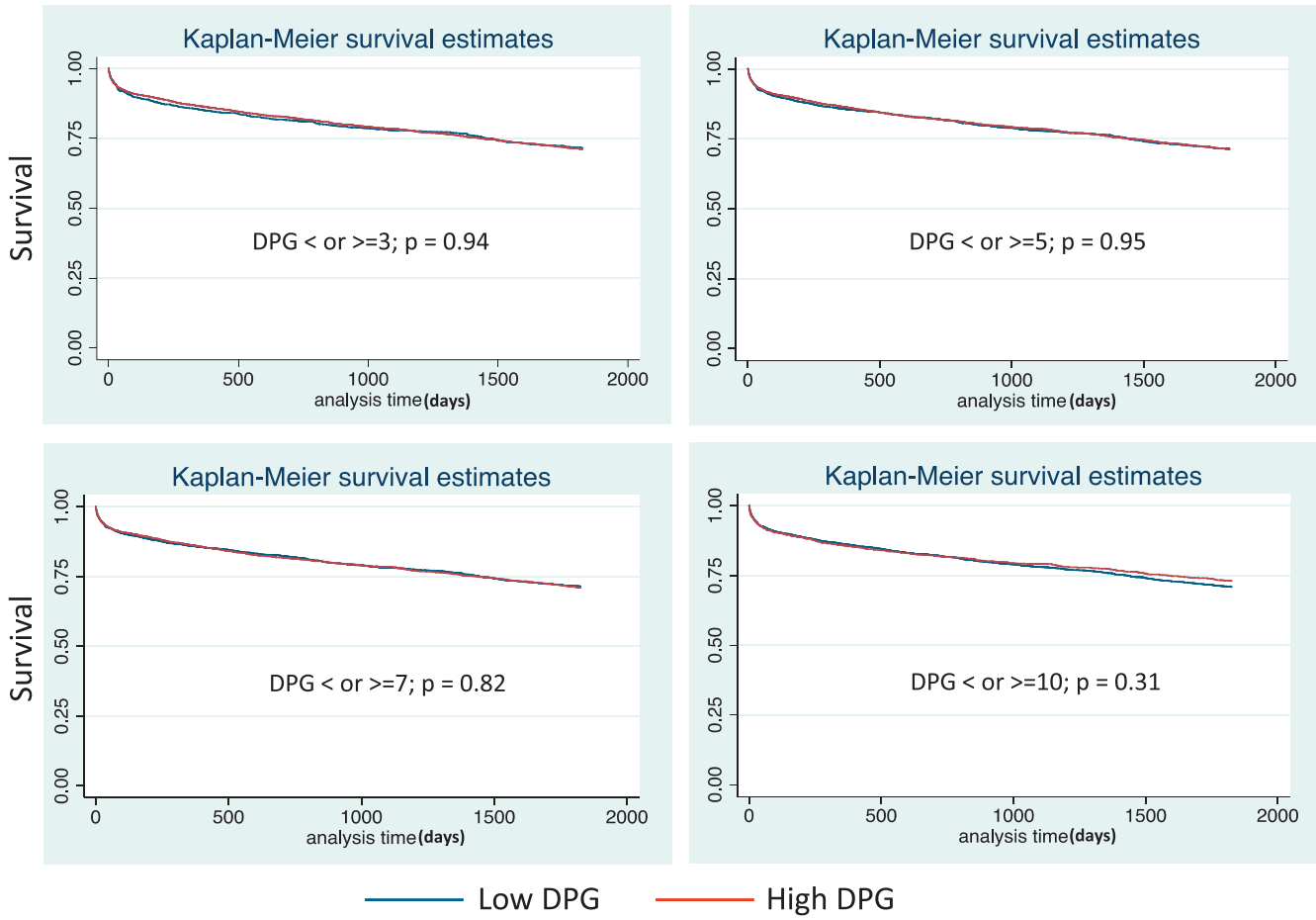

Figure 1 Kaplan-Meier plots for the diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient (DPG) in patients with pulmonary hypertension and an elevated transpulmonary gradient > 12 mm Hg: (A) 3 mm Hg, (B) 5 mm Hg, (C) 7 mm Hg, and (D) 10 mm Hg.

The cause of death was not available in post-OHT patients, and not all patients died as a consequence of PH and right heart failure. Therefore, it remains possible that the low DPG groups died of different causes (i.e., rejection or infection) than the high DPG group (i.e., right heart failure), diluting the true ability of DPG to discriminate right heart failure death in our mixed population. However, by selectively analyzing groups of patients at the highest risk of right heart failure (i.e., PVR > 3, PVR > 5, TPG > 12, TPG > 15) we should have enriched the proportion of deaths from right heart failure. Furthermore, given the large number of patients within each group, we should have had ample power to detect even small differences introduced through dilution of a hypothesized narrow relationship between right heart failure and DPG (illustrated in sensitivity analysis in Supplementary Table S1, available online on the jhltonline.org Web site). That we still did not detect any such significant difference in mortality along a gradient of DPG minimizes the effect of this limitation on our results.

It is also possible that factors that affect the DPG (i.e., heart rate, sepsis, hypoxia, etc) could have a confounding influence on the DPG to discriminate survivors from non-survivors. Importantly, these factors that may alter DPG are not routinely considered (in part because their relative effect on DPG is not known) by clinicians when reporting pre-OHT hemodynamics. Therefore, the analysis is similar to the real world practice in which the measured DPG is taken as "true DPG." In addition, acuity data was relatively similar in low and high DPG groups.

Finally, to address the many cut points already described in the literature, we performed many analyses. The multiple significance tests performed in our work increased the chance that we would see a "significant" association by chance alone. The fact that we saw no such association despite this propensity may further support the poor ability of DPG to discriminate survivors from non-survivors when applied broadly to a pre-transplant population.

In conclusion, in this large population of heart failure patients with evidence of pre-capillary PH (elevated TPG and PVR) undergoing OHT, the DPG did not predict survival after OHT. Coupled with our previous knowledge that factors other than pulmonary vascular remodeling may contribute to an elevated DPG, the findings of this study urge caution before DPG is routinely incorporated into pre-OHT or PH-related clinical decision making.

Table 5 Pulmonary Vascular Resistance > 3 Wood units

Variables[a]	DPG < 3 mm Hg (n = 2,439)	DPG ≥ 3 mm Hg (n = 3,831)	p-value	DPG < 5 mm Hg (n = 3,391)	DPG ≥ 5 mm Hg (n = 2,879)	p-value	DPG < 7 mm Hg (n = 4,287)	DPG ≥ 7 mm Hg (n = 1,983)	p-value	DPG < 10 mm Hg (n =5,227)	DPG ≥ 10 mm Hg (n = 1,043)	p-value
Demographics												
Age, years	52.9 ± 11.5	52.2 ± 11.4	0.02	52.8 ± 11.5	52.1 ± 11.3	0.01	52.8 ± 11.5	51.9 ± 11.3	0.01	52.6 ± 11.5	51.9 ± 11.2	0.05
Female	29.2	26.5	0.02	29.3	25.4	0.001	29.0	24.4	<0.001	28.2	24.2	0.008
White	70.6	68.1	0.03	69.5	68.7	0.51	70.0	67.2	0.03	69.5	66.9	0.10
Black	18.6	21.5	0.005	19.2	21.7	0.015	19.2	22.8	0.001	19.9	22.5	0.06
BMI, kg/m^2	25.4 ± 5.6	25.8 ± 5.5	0.001	25.4 ± 6.1	25.9 ± 4.8	<0.001	25.5 ± 5.8	26.0 ± 4.9	<0.001	25.6 ± 5.7	25.8 ± 4.9	0.26
Diagnosis												
Idiopathic	42.4	46.3		43.7	46.1		44.3	45.8		44.8	44.9	
Ischemic	45.4	43.7		44.8	43.9		44.4	44.4		44.4	44.6	
Congenital	1.2	1.5		1.2	1.5		1.2	1.6		1.3	1.7	
Other	11.0	8.6	0.001	10.3	8.5	0.03	10.1	8.1	0.048	9.6	8.8	0.60
Acuity												
Diabetes, No.	495/2,287	810/3,588	0.40	683/3,179	622/2,696	0.15	881/4,022	424/1,853	0.40	1,082/4,899	223/976	0.60
Ischemic time, hours	3.1 ± 1.0	3.0 ± 1.0	0.36	3.1 ± 1.0	3.0 ± 1.0	0.08	3.1 ± 1.0	3.0 ± 1.0	0.03	3.1 ± 1.0	3.0 ± 1.0	0.19
Creatinine, mg/dl	1.4 ± 1.0	1.4 ± 1.5	0.09	1.36 ± 1.2	1.44 ± 1.5	0.04	1.4 ± 1.2	1.4 ± 1.6	0.08	1.4 ± 1.4	1.5 ± 1.2	0.15
Bilirubin, mg/dl	1.5 ± 3.6	1.4 ± 2.5	0.02	1.5 ± 3.3	1.4 ± 2.5	0.06	1.5 ± 3.2	1.3 ± 2.4	0.11	1.4 ± 3.0	1.3 ± 2.8	0.30
IABP	5.0	6.5	0.02	5.1	6.8	0.004	5.3	7.2	0.004	5.5	7.9	0.003
VAD	10.9	12.5	0.06	10.9	13.0	0.009	11.3	13.0	0.06	11.7	12.9	0.28
Ventilation	1.9	2.7	0.06	2.2	2.5	0.45	2.3	2.6	0.39	2.4	2.4	0.96
Hemodynamics												
sPAP, mm Hg	58.0 ± 12.2	56.0 ± 12.9	<0.001	57.1 ± 12.0	56.4 ± 13.4	0.03	56.7 ± 12.0	56.9 ± 14.1	0.59	56.5 ± 12.1	58.2 ± 15.2	<0.001
dPAP, mm Hg	26.3 ± 7.0	29.7 ± 8.0	<0.001	26.6 ± 6.9	30.5 ± 8.3	<0.001	27.0 ± 6.9	31.3 ± 8.7	<0.001	27.4 ± 7.1	33.1 ± 9.5	<0.001
mPAP, mm Hg	39.8 ± 7.8	39.4 ± 8.8	0.05	39.3 ± 7.8	39.8 ± 9.2	0.01	39.2 ± 7.8	40.3 ± 9.7	<0.001	39.1 ± 8.0	41.6 ± 10.3	<0.001
PCWP, mm Hg	27.2 ± 7.1	21.7 ± 7.7	<0.001	26.3 ± 7.1	21.0 ± 7.9	<0.001	25.6 ± 7.2	20.1 ± 8.1	<0.001	24.9 ± 7.4	18.8 ± 8.6	<0.001
CO, liters/min	3.1 ± 0.9	3.7 ± 1.1	<0.001	3.2 ± 0.9	3.8 ± 1.1	<0.001	3.3 ± 0.9	3.9 ± 1.1	<0.001	3.4 ± 1.0	4.0 ± 1.2	<0.001
PVR, WU	4.2 ± 1.5	5.2 ± 2.9	<0.001	4.3 ± 1.9	5.4 ± 3.0	<0.001	4.3 ± 1.8	5.7 ± 3.3	<0.001	4.5 ± 2.0	6.4 ± 3.8	<0.001
TPG, mm Hg	12.6 ± 3.8	17.7 ± 6.1	<0.001	13.0 ± 3.8	18.8 ± 6.4	<0.001	13.6 ± 3.9	20.3 ± 6.8	<0.001	14.3 ± 4.3	22.8 ± 7.6	<0.001

BMI, body mass index; CO, cardiac output; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient; IABP, intra-aortic balloon pump; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; sPAP, systolic pulmonary artery pressure; TPG, transpulmonary gradient; WU, Woods units.

[a]Continuous data are shown as the mean ± standard deviation and categoric data as percentage, or as indicated.

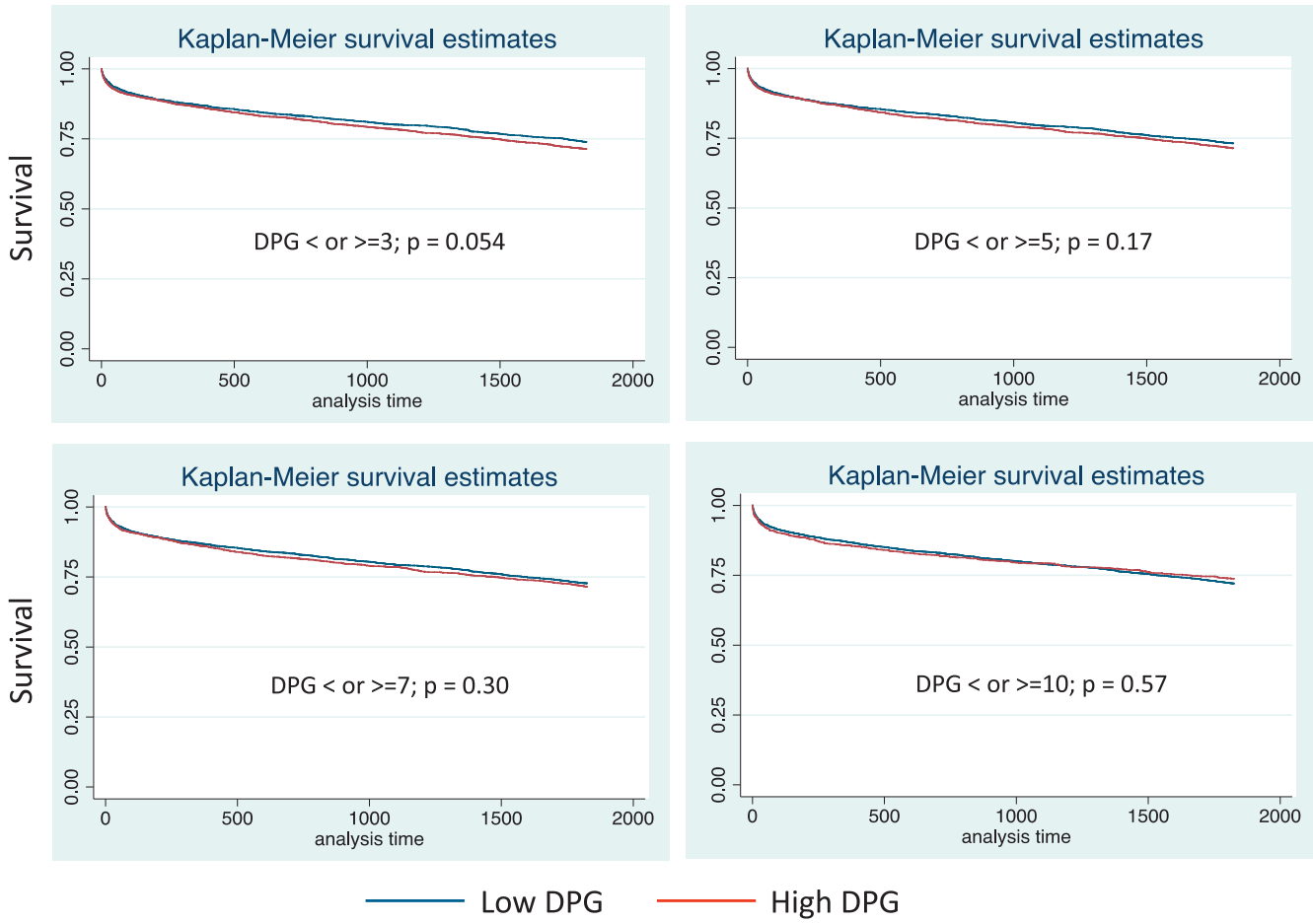

Figure 2 Kaplan-Meier plots for the diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient (DPG) in patients with pulmonary hypertension and an elevated pulmonary vascular resistance > 3 Wood units: (A) 3 mm Hg, (B) 5 mm Hg, (C) 7 mm Hg, and (D) 10 mm Hg.

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Supplementary data

Supplementary data are available in the online version of this article at jhltonline.org.

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