Characteristics of Patients with Pulmonary Venocclusive Disease Awaiting Transplantation

Keith M. Wille¹, Nirmal S. Sharma¹, Tejaswini Kulkarni¹, Matthew R. Lammi², Joseph B. Barney¹, S. Christopher Bellot³, Ryan S. Cantor³, David C. Naftel³, Enrique Diaz-Guzman¹, and David C. McGiffin⁴

¹Department of Medicine, and ³Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama; ²Department of Medicine, Louisiana State University Health Sciences Center, New Orleans, Louisiana; and ⁴Department of Cardiothoracic Surgery, The Alfred Hospital and Monash University, Melbourne, Victoria, Australia

Abstract

Rationale: Pulmonary venocclusive disease (PVOD) is an uncommon cause of pulmonary arterial hypertension (PAH). However, unlike PAH, treatment options for PVOD are usually quite limited. The impact of the lung allocation score on access to transplantation for patients with PVOD and the clinical course of these patients have not been well-described.

Objectives: To examine the association between the diagnosis of PVOD and lung transplantation for patients on the transplant waiting list.

Methods: Patients with a diagnosis of PVOD and PAH registered on the United Network for Organ Sharing wait list for transplantation from May 4, 2005 to May 3, 2013 were included. Lung transplantation was the primary outcome measure. Multivariable analyses were performed to determine the odds of dying or receiving a lung transplant after listing. Survival was compared using Kaplan-Meier and competing risks methods.

Results: Of 12,251 patients listed for lung transplantation, 49 with PVOD and 647 with PAH were identified. There were no significant differences in the lung allocation score between patients with PVOD and PAH at listing, transplant, or wait list removal for death/too sick for transplant. By 6 months, 22.6% of patients with PVOD had been removed from the wait list due to death, compared with 11.0% of patients with PAH (Chi-square $P = 0.03$). Patients with PVOD who died or were considered too sick for transplant were removed from the waiting list sooner after listing (22 vs. 105 d, $P = 0.08$). There was no difference in the proportion of patients with PVOD and PAH transplanted (50.0 vs. 47.6%, $P = 0.60$).

Conclusions: In the lung allocation score era, patients with PVOD may be at higher risk for death while on the transplant waiting list. After wait list registration, close monitoring for disease progression is advised.

Keywords: pulmonary venocclusive disease; venocclusive; pulmonary hypertension; transplant

(Received in original form August 4, 2014; accepted in final form October 4, 2014)

Supported in part by the University of Alabama at Birmingham Comprehensive Transplant Institute.

The Transplant and Waiting List data reported herein have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network. The content of this analysis of the data is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Author Contributions: Study design and concept (K.M.W., E.D.-G., D.C.M.); acquisition (K.M.W., N.S.S., T.K.), analysis (K.M.W., T.K., R.S.C., D.C.N., E.D.-G.) and interpretation of the data (K.M.W., N.S.S., T.K., M.R.L., J.B.B., S.C.B., R.S.C., D.C.M.), and writing or revising the article before submission (K.M.W., N.S.S., T.K., M.R.L., J.B.B., S.C.B., R.S.C., D.C.N., E.D.-G., D.C.M.).

Correspondence and requests for reprints should be addressed to Keith M. Wille, M.D., M.S.P.H., 1900 University Boulevard 422 THT, Birmingham, AL 35294-0006. E-mail: wille@uab.edu

Ann Am Thorac Soc Vol 11, No 9, pp 1411–1418, Nov 2014

Copyright © 2014 by the American Thoracic Society

DOI: 10.1513/AnnalsATS.201408-354OC

Internet address: www.atsjournals.org

Pulmonary venocclusive disease (PVOD) is an uncommon cause of pulmonary arterial hypertension (PAH). Histopathologically, it is characterized largely by occlusion of the pulmonary veins by fibrous tissue, although

lesions affecting the arterial vasculature may also be observed. The pathogenesis of PVOD remains poorly understood, although several risk factors have been reported, including genetic factors (1–3), toxic exposures (4–8),

hypercoagulability (9, 10), infection (11–13), and autoimmune disorders (14–19). Although the true prevalence and incidence of PVOD are unknown, data from the French National PAH registry estimate an annual incidence of

0.1 to 0.2 cases per million in the general population (20, 21). However, this is believed to underestimate the true incidence of PVOD, as many cases are likely diagnosed incorrectly as idiopathic PAH (22). Most PVOD cases are discovered in children or young adults; however, age at diagnosis has varied from 8 weeks to more than 70 years. Unlike idiopathic PAH, where there is a female predominance, the male to female ratio for PVOD is approximately 1:1 (23–25). The diagnosis of PVOD is suggested by the presence of severe PAH, evidence of pulmonary edema by radiography, and a normal pulmonary artery occlusion pressure. The prognosis of PVOD is typically poor; most patients die within 2 years of diagnosis.

In contrast to PAH, treatment options for PVOD are quite limited. Evidence supporting vasodilator therapy for PVOD is restricted to case reports and case series (26, 27). However, vasodilator use is typically discouraged in PVOD, as increased transcapillary hydrostatic pressure and massive pulmonary edema may result from dilating the pulmonary arterioles but not the fixed pulmonary veins (28). Other medications, including immunosuppressants, anticoagulants, and newer experimental agents, have not consistently had a beneficial effect (29–34). Lung transplantation has been the only intervention that may prolong life for patients with PVOD, and as a result, referral for lung transplantation is advised at the time of diagnosis (27, 35).

The lung allocation score, implemented in 2005 as the primary method of lung allocation in the United States, significantly changed how patients are prioritized for transplantation (36). The lung allocation score is a numerical value used by the United Network for Organ Sharing to assign relative priority for distributing lungs donated for transplantation within the United States. It is based on survival models that estimate both wait list and post-transplant survival, and it reflects the net benefit of transplantation. Initial studies evaluating the lung allocation score suggest that waiting time has decreased, the total number of organs transplanted has increased, overall wait list mortality has decreased, and post-transplant survival has not changed (37–41). However, under the new allocation system, wait list mortality for patients with PAH has remained high when compared with other major diagnoses (42). It has also been suggested that

a modification to the lung allocation score, incorporating variables such as the 6-minute-walk distance and mean right atrial

pressure, may better define wait list urgency for patients with PAH (43, 44). The impact of the lung allocation score on access to

Table 1. Characteristics of patients with pulmonary venoocclusive disease and pulmonary arterial hypertension on the United Network for Organ Sharing lung transplantation waiting list, May 2005–May 2013

	PVOD (n = 49)	PAH (n = 647)	P Value
Characteristics			
Age, mean (SD), yr	34.1 (22.8)	36.8 (18.2)	0.33
Male sex	24 (49.0)	196 (30.3)	0.007
Serum albumin, g/dl	3.87 (0.37)	3.89 (0.70)	0.88
BMI	24.1 (4.8)	23.9 (5.4)	0.87
	(n = 49)	(n = 642)	
Diabetes	7 (14.3)	41 (6.4)	0.04
Performance status			
	(n = 49)	(n = 647)	
Mean 6-min-walk distance, ft	760 (394)	729 (525)	0.86
Poor performance status, registration	20 (40.8)	236 (36.5)	0.73
Median FVC, %	72 (50, 98)	79 (65, 88)	0.70
Median FEV ₁ , %	68 (41, 81)	72 (57, 83)	0.69
Median O ₂	(n = 7)	(n = 105)	
Requirement, L	2 (2, 6)	2 (0, 4)	0.55
Hemodynamics			
	(n = 37)	(n = 475)	
CO, mean, L/min	4.7 (1.4)	4.2 (1.6)	0.09
	(n = 42)	(n = 577)	
PA systolic, mm Hg	71.2 (19.8)	87.3 (24.6)	<0.001
	(n = 41)	(n = 572)	
PA diastolic, mm Hg	35.2 (12.1)	39.8 (14.6)	0.053
	(n = 42)	(n = 555)	
PA mean, mm Hg	49.2 (14.7)	57.7 (17.0)	0.002
	(n = 39)	(n = 506)	
PCWP, mm Hg	14.3 (9.0)	13.0 (7.6)	0.34
Allocation score, median (IQR)			
	(n = 49)	(n = 647)	
LAS at listing	33.6 (3.4)	33.7 (4.5)	0.66
LAS at removal			
	(n = 24)	(n = 307)	
Transplant	33.9 (4.9)	34.4 (4.8)	0.68
	(n = 13)	(n = 166)	
Too sick/died	36.5 (8.2)	35.9 (7.6)	0.76
Time on waiting list, median (IQR), d			
	(n = 49)	(n = 647)	
Overall	98 (22, 217)	117 (33, 361)	0.46
	(n = 24)	(n = 308)	
Transplanted patients	89 (22, 207)	75 (21, 148)	0.67
	(n = 13)	(n = 166)	
Patients removed for death/too sick	22 (5, 100)	105 (30, 312)	0.08
Organ received, n (%)			
Heart lung	2 (8.3)	75 (24.6)	
Lung	22 (91.7)	230 (75.4)	0.07
Bilateral	22 (100)	226 (98.3)	0.53
Removal code*			
	(n = 49)	(n = 647)	
Still waiting	5 (10.2)	56 (8.7)	0.60
Transplanted	24 (50.0)	308 (47.6)	
Too sick for lung transplant	1 (2.0)	43 (6.6)	
Died	12 (24.5)	123 (19.0)	
Other	7 (14.3)	117 (18.1)	

Definition of abbreviations: CO = cardiac output; LAS = lung allocation score; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVOD = pulmonary venoocclusive disease; UNOS = United Network for Organ Sharing. N = 696.

*Removal code refers to patients who are removed from the waiting list for reasons such as lung transplantation, too sick for transplantation, death, or other reasons.

transplantation for patients with PVOD, as compared with PAH, has not been well described.

The primary objective of this study was to examine the association between the diagnosis of PVOD and lung transplantation for patients on the transplant waiting list. Secondary objectives included quantifying differences in time to transplantation or wait list removal for death by diagnosis. We hypothesized that patients with PVOD listed for lung transplantation might have a worse prognosis when compared with those listed for PAH, given the fewer treatment options for PVOD.

Methods

The Organ Procurement and Transplant Network database of the United Network for Organ Sharing was used to identify patients registered on the waiting list between May 4, 2005 and May 3, 2013. The study population included all patients with a primary diagnosis of either PVOD or PAH who were listed for lung transplantation. Patients with pulmonary hypertension related to secondary causes, such as COPD and pulmonary fibrosis, were excluded.

We used a research file available as of May 3, 2013. Variables collected from the United Network for Organ Sharing included listing date, diagnosis, age, sex, ABO blood type, race, education level, region, insurance payer, calculated lung allocation score at time of listing and time of removal, waiting time accrued, reason for removal from the waiting list, and comorbid illnesses. Data on diagnosis were typically reported by the transplant center. Waiting list time was determined as the time between the date a patient was first placed on the waiting list and the date of removal from the list. Date of death was determined using data from the Social Security Master Death File that were collected by the United Network for Organ Sharing and provided to the investigators.

The 11 United Network for Organ Sharing regions were aggregated into four categories as previously described (45). Listing diagnoses are grouped as: (1) Group A = obstructive diseases, (2) Group B = pulmonary vascular disease, (3) Group C = cystic fibrosis/immunodeficiency disorders, and (4) Group D = restrictive diseases. Attained education level was grouped as: (1) none/grade school, (2) high

Table 2. Univariate analyses of likelihood of transplant for patients with pulmonary venoocclusive disease compared with patients with pulmonary arterial hypertension

Variable	Estimate (SE)	OR	95% CI	P Value
Female sex	−0.24 (0.10)	0.62	0.41–0.93	0.02
LAS	−0.05 (0.02)	0.95	0.91–0.99	0.01
Mean PA pressure	−0.01 (0.006)	0.98	0.97–0.99	0.03
Thoracic diagnosis (PVOD vs. PAH)	−0.003 (0.18)	0.99	0.49–2.01	0.99

Definition of abbreviations: CI = confidence interval; LAS = lung allocation score; OR = odds ratio; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PVOD = pulmonary venoocclusive disease.

school/attended college without a degree, (3) college degree/higher, and (4) unknown/unavailable. Insurance provider was grouped as: (1) Medicare, (2) Medicaid, (3) private/self-insurance, and (4) other. To evaluate neighborhood level socioeconomic status, 2010 U.S. Census Bureau data were used to obtain median household income in each patient's residential zip code, as previously described (46).

Lung transplant status was grouped as: (1) transplanted = patients with reasons for removal from the waiting list that included transplant, died during transplant, and transplanted at another center; (2) too sick = patients removed from the waiting list with reasons such as too sick or medically unstable for lung transplantation; (3) died = patients who died before lung transplantation; (4) still waiting = patients who were still awaiting transplant; and (5) other = patients whose reasons for removal from the waiting list included refused transplant, transferred to another center, condition improved, living donor, other, and removed in error.

Our primary aim was to test the association of PVOD with receipt of a lung transplant. We also aimed to assess the influence of diagnosis on time to

transplantation or removal from the waiting list during the study period.

Multiple-variable logistic regression was performed to determine whether a diagnosis of PVOD is associated with the likelihood of (1) death or becoming too sick for lung transplantation, and (2) likelihood of lung transplantation. Patients categorized as “still waiting” or “other” were excluded from these analyses. Time to event analyses were performed using Kaplan-Meier methodology. Patients who did not experience the event of interest were censored.

A competing risks analysis was performed to characterize outcomes after patients were listed for lung transplantation (47). The competing risks analysis estimates, at each time point after listing, the likelihood of each competing event occurring against all others, according to a parametric survival model for each event. To create the competing risks, parametric survival models were created for each of the following competing outcomes: (1) lung transplant, (2) death while awaiting transplant, (3) delisting because of clinical deterioration or loss of transplant candidacy (too sick for transplant), (4) still awaiting transplant, and (5) delisting

Table 3. Multivariable analysis of likelihood of transplant for patients with pulmonary venoocclusive disease compared with patients with pulmonary arterial hypertension

Variable	Estimate (SE)	OR	95% CI	P Value
Female sex	−0.32 (0.12)	0.53	0.33–0.84	0.007
LAS	−0.04 (0.02)	0.96	0.91–1.00	0.05
Thoracic diagnosis (PVOD vs. PAH)	−0.08 (0.21)	0.85	0.36–1.99	0.71

Definition of abbreviations: CI = confidence interval; LAS = lung allocation score; OR = odds ratio; PAH = pulmonary arterial hypertension; PVOD = pulmonary venoocclusive disease. Adjusted for age, sex, race, LAS at listing, thoracic diagnosis, and mean pulmonary arterial pressure.

for other reasons (clinical improvement, transfer to another center, etc.).

Cox proportional hazards regression models were used to study the association between diagnosis and time to death on the waiting list, while controlling for confounders. These models covered the entire listing period to account for differences in follow-up times after wait list registration. Patients who did not die were censored. The proportional hazards assumption was assessed using log-log survival functions.

To determine which variables to include in the multivariable models, univariate comparisons by the outcome of interest (lung transplantation, or died/too sick for transplantation) were performed for each potential covariate. Patients with missing data on a specific covariate were excluded from analyses involving that covariate. Variables significant ($P \leq 0.05$) in univariate analysis were retained in the multivariable model for that outcome. Age, race, sex, and diagnosis were retained in all multivariable models.

Differences in continuous variables were tested using two-group t tests or Wilcoxon rank sum tests, depending on their distribution. Pearson Chi-square tests or Fisher exact tests were used to test for associations between categorical variables.

Statistical tests were two-sided. Results with $P \leq 0.05$ were considered significant. Hazard ratios (HRs) and adjusted odds ratios (ORs) were reported for the proportional hazard regression models and logistic regression models, respectively. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, NC).

This study was approved by the Institutional Review Board of the University of Alabama at Birmingham, Birmingham, Alabama.

Results

Of 12,251 patients registered for lung or heart-lung transplant during the study period, 49 (0.40%) with PVOD and 647 (5.28%) with PAH were identified and included in the analyses. Baseline characteristics of the patients listed for transplantation are shown in Table 1, stratified by diagnosis. Patients with PVOD were more often men (49.0 vs. 30.3%, $P = 0.007$), had diabetes (14.3 vs. 6.4%,

$P = 0.04$), and had a lower mean PA pressure at listing (49.2 mm Hg vs. 57.7 mm Hg, $P = 0.002$). There were no significant differences in ethnicity, region, ABO blood group, or insurance status between groups.

In the study period, 24 (50.0%) patients with PVOD and 308 (47.6%) patients with PAH who were listed underwent transplantation. There was no statistical difference in the number of patients who died or became too sick for transplant between groups (PVOD: 26.5% vs. PAH: 25.6%, $P = 0.60$). However, patients with PVOD who were removed from the wait list for becoming too sick or dying had a shorter median waiting time (22 d vs. 105 d, $P = 0.08$). Despite this finding, there were no differences in lung allocation score between PVOD and PAH groups at listing for transplant or at wait list removal for either transplant or becoming too sick/died.

Logistic regression analyses were performed to determine the likelihood of:

(1) becoming too sick or dying before transplant, or (2) receiving a transplant. Univariate analyses demonstrated that female sex, lung allocation score, and mean PA pressure were significantly associated with death while on the waiting list (Table 2). Diagnosis (PVOD vs. PAH) was not significant in univariate analysis (OR, 0.99; 95% confidence interval [CI], 0.49–2.01; $P = 0.99$). These characteristics were included in the multivariable analyses.

After adjusting for relevant covariates, a diagnosis of PVOD, compared with PAH, did not result in a lower likelihood of transplantation (OR, 0.85; 95% CI, 0.36–1.99; $P = 0.71$) (Table 3). Female sex remained associated with a lower likelihood of transplantation (OR, 0.53; 95% CI, 0.33–0.84; $P = 0.007$). No significant interactions were found in the multivariable analyses.

Kaplan-Meier survival estimates of the time to wait list removal due to: (1) death while waiting for transplant (Figure 1A), or (2) lung transplant (Figure 1B) for

Figure 1. Kaplan-Meier estimate of the time to waitlist removal for (A) death while waiting for transplant, and (B) transplant. PAH = pulmonary arterial hypertension; PVOD = pulmonary venoocclusive disease.

patients with PVOD and PAH are presented. Patients with PVOD were statistically more likely to be removed from the waiting list due to death (12/13) or becoming too sick for transplant (1/13). This effect was more pronounced in the early period after listing ($P = 0.007$, Wilcoxon rank sum). Median (interquartile range) time to wait list removal for death or becoming too sick for transplant was 22 (5, 100) days (PVOD) versus 105 (30, 312) days (PAH), $P = 0.08$.

As removal from the wait list due to one cause typically excludes removal for

another cause, competing risks analyses were performed (Figure 2). By 6 months, 22.6% of patients with PVOD had been removed from the wait list due to death, as opposed to 11.0% of patients with PAH (Chi-square, $P = 0.03$). Group differences were less significant when patients removed for becoming too sick were combined with those who died on the wait list (23.7% PVOD vs. 14.3% PAH). By contrast, more comparable percentages of each cohort had undergone transplant (33.7% PVOD vs. 34.4% PAH) and were still awaiting transplant (34.6% PVOD vs. 44.6% PAH).

For patients with PVOD, the most common cause of death was cardiac arrest, followed by respiratory failure and multiple organ failure.

Time to death by diagnosis was assessed over the entire period by proportional hazards modeling with adjustment for other predictor variables (Table 4). Both lung allocation score and mean PA pressure were associated with time to death (HR, 1.10; 95% CI, 1.05–1.15; $P < 0.001$ for lung allocation score, and HR, 1.02; 95% CI, 1.01–1.04; $P = 0.004$ for mean pulmonary arterial [PA] pressure). After controlling for age, race, sex, diabetes, region, allocation score at listing, thoracic diagnosis, and mean PA pressure, patients with PVOD had a higher risk of wait list removal for death compared with patients with PAH (HR, 2.05; 95% CI, 1.01–4.14; $P = 0.046$). Proportional hazards assumptions were satisfied for these analyses.

Discussion

The lung allocation score was implemented in 2005 by the United Network for Organ Sharing as the primary method for donor lung allocation in the United States and has had several measurable effects (48). Studies have reported decreases in wait times for transplantation, a decrease in wait list mortality, a change in the distribution of diagnoses receiving transplantation, and no change in survival after transplant (37–42, 49). However, there has been recent concern that the lung allocation score may inaccurately predict survival for PAH—specifically, it may overestimate predicted wait list survival for PAH and thereby place these patients at a disadvantage, as compared with other wait-listed patients (43, 50). This is suggested by the higher wait list mortality for patients with PAH, as compared with patients listed for other diagnoses, after adoption of the lung allocation score (42). It also stands to reason that patients with PVOD might have an even greater disadvantage while awaiting transplant, given their usual poor response to PAH therapies. To our knowledge, ours is the first study to assess differences in access to lung transplantation between patients with PVOD and patients with PAH using data from a national registry.

We found that patients with PVOD were more likely to be removed from the

Figure 2. Competing risks analysis of outcomes after listing for lung transplantation, for (A) patients with PVOD, and (B) patients with PAH. Dashed vertical line denotes the 6-month time point, where outcomes are presented as percentages. PAH = pulmonary arterial hypertension; PVOD = pulmonary venoocclusive disease.

Table 4. Proportional hazards modeling of the risk of death while on the waiting list for lung transplantation for patients with pulmonary venoocclusive disease compared with patients with pulmonary arterial hypertension

Variable	Estimate (SE)	HR	95% CI	P Value
LAS	0.09 (0.02)	1.10	1.05–1.15	<0.001
Mean PA pressure	0.02 (0.007)	1.02	1.01–1.04	0.004
Diabetes	1.13 (0.49)	3.10	1.19–8.05	0.020
Thoracic diagnosis (PVOD vs. PAH)	0.65 (0.36)	2.05	1.01–4.14	0.046

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; LAS = lung allocation score; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PVOD = pulmonary venoocclusive disease.

Adjusted for age, sex, race, diabetes, region, LAS at listing, thoracic diagnosis, and mean pulmonary arterial pressure.

transplant waiting list because of death, as compared with patients with PAH. This finding was particularly evident in the time to event analyses, where the proportion of patients with PVOD removed for death by 6 months was twice that for patients with PAH in a competing risks analysis, and the risk of death while waiting was increased nearly twofold over patients with PAH. Notably, patients with PVOD more often died while awaiting transplant despite having a lower mean PA pressure and higher cardiac output at listing, no difference in performance status at listing, and comparable allocation scores both at listing and removal. We were unable to observe this finding in the logistic analyses (which predict the probability of an event by a specified time), likely because of the relatively small sample of patients with PVOD and lack of censoring in this type of analysis, which results in loss of information.

Prior studies, most being case reports or series, have largely highlighted the rarity of PVOD, lack of diagnostic methods and poor response to therapy, the importance of early transplant referral, and similar post-transplant outcomes as PAH (51–54). Although an explanation for the higher wait list mortality for patients with PVOD is not entirely clear, their usual poor response to PAH therapies may account for these findings. Alternatively, there may be other disease-specific factors associated with increased mortality that manifest as PVOD advances. Importantly, delays in establishing a correct diagnosis and subsequent late transplant referral may also account for these findings. Nearly all patients with PVOD and PAH receive bilateral lung transplantation; however,

success with single lung transplantation in PVOD has been reported (55). Stewart and colleagues described the histopathology of explanted lungs from patients receiving transplants over a 10-year period; of 183 explants, 3 (1.6%) had PVOD, and all were unsuspected preoperatively (56). Although a PVOD diagnosis has largely been confirmed by surgical biopsy, modern high-resolution chest tomography may help to distinguish PVOD with a diagnostic accuracy up to 90.5% (57). Additionally, measurement differences in centrilobular ground-glass opacities may help to distinguish PVOD from PAH (58). Serologic testing for PVOD is not currently available; however, patients with PVOD, as compared with patients with PAH, were recently found to have fewer granulysin-containing cells and yet higher serum levels of granulysin, an effector protein for cytotoxic T, natural killer, and natural killer T cells (59). This suggests that alterations of circulating cytotoxic cells and dysregulation within the granulysin gene may account for the pathophysiologic findings associated with PVOD and may serve as a target for new diagnostic instruments. Using exome sequencing, Eyries and colleagues detected recessive mutations in the eukaryotic translation initiation factor 2 α kinase 4 gene (EIF2AK4, also called GCN2), which cosegregated with PVOD in all familial cases and 25% of sporadic cases studied (60). Mutations of EIF2AK4 were also recently implicated in the pathogenesis of pulmonary capillary hemangiomatosis, a rare disease of capillary proliferation associated with PAH that also responds poorly to therapy (61).

The strengths of this study include a large number of transplant candidates (including all identifiable patients with a diagnosis of PVOD listed in the lung allocation score era), use of a national database, and the availability of several variables that may influence wait list outcomes. Our study also has several limitations. First, the accuracy of the United Network for Organ Sharing database, on which our results are based, depends on accurate data reporting from individual transplant centers. Although the type of data collected has changed over time and in part resulted in some missing data, our analyses were limited to the lung allocation score era to minimize the effect of missing data and waiting time differences between groups on outcomes. We excluded missing data from analyses rather than perform imputation methods to reduce the potential introduction of bias. Given the difficulty establishing a diagnosis of PVOD pretransplant, it is possible that some misclassification of patients by diagnosis and outcome occurred; however, centers are required to report candidate deaths within 24 hours of notification, and the United Network for Organ Sharing regularly updates their death records from the Social Security Master Death File. Additionally, as transplant centers closely monitor listed candidates for clinical deterioration, we reasoned that delisted or deceased patients should be accurately reported. Assessment of the veracity of the diagnosis (PVOD vs. PAH) as submitted by the transplant center was not possible.

Another limitation pertains to changes in the database during the course of the study period. The lung allocation score often increases as disease progresses; however, because the score at the time of listing correlated closely with values at wait list removal, only the score at listing was used for analyses. There may be significant predictors of outcome that are not captured by the United Network for Organ Sharing database, or other variables like a center's transplant volume, that were not included in our analyses but may affect the results (41). It is possible that we failed to identify some outcome differences between groups based on sample size (type 2 error), particularly given the number of patients with PVOD; however, we report on all identifiable patients with PVOD, and ours is the largest collection of patients with PVOD to date. Finally, we evaluated wait

list outcomes among patients with PVOD and PAH already listed for transplant, but there may be differences in referral practices or timing, or access to medical care, not captured by this analysis.

Our findings suggest that in the lung allocation score era, patients with PVOD may be at higher risk for death while on the lung transplant waiting list, compared with patients with PAH. PVOD should be suspected in the appropriate clinical setting and particularly when the response to PAH therapy is poor. Given the limited treatment options for this disorder, patients with

PVOD should be referred as early as possible for lung transplantation. After wait list registration, close monitoring for disease progression is recommended, and petition for an exception, which increases the lung allocation score to the 90th percentile, can be considered. Whether or not these patients should receive exception scoring above the 90th percentile, due to a greater pretransplant mortality risk, remains debated. Future studies should include a careful evaluation of diagnostic tools and newer therapies for PVOD. Finally, additional modifications to the lung

allocation process that better estimate pretransplant survival and determine appropriate transplant priority for these patients are warranted. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Dr. Ashita Tolwani, Ms. Kela Bean, and Ms. Sofia Bell for their critical review and preparation of the manuscript. They also thank the staff at the United Network for Organ Sharing for collecting and providing the data used in this analysis.

References

- Bjornsson J, Edwards WD. Primary pulmonary hypertension: a histopathologic study of 80 cases. *Mayo Clin Proc* 1985;60:16–25.
- Davies P, Reid L. Pulmonary veno-occlusive disease in siblings: case reports and morphometric study. *Hum Pathol* 1982;13:911–915.
- Runo JR, Vnencak-Jones CL, Prince M, Loyd JE, Wheeler L, Robbins IM, Lane KB, Newman JH, Johnson J, Nichols WC, et al. Pulmonary veno-occlusive disease caused by an inherited mutation in bone morphogenetic protein receptor II. *Am J Respir Crit Care Med* 2003;167:889–894.
- Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;335:609–616.
- Bunte MC, Patnaik MM, Pritzker MR, Burns LJ. Pulmonary veno-occlusive disease following hematopoietic stem cell transplantation: a rare model of endothelial dysfunction. *Bone Marrow Transplant* 2008;41:677–686.
- Doll DC, Yarbrow JW. Vascular toxicity associated with chemotherapy and hormone therapy. *Curr Opin Oncol* 1994;6:345–350.
- Gagnadoux F, Capron F, Lebeau B. Pulmonary veno-occlusive disease after neoadjuvant mitomycin chemotherapy and surgery for lung carcinoma. *Lung Cancer* 2002;36:213–215.
- Williams LM, Fussell S, Veith RW, Nelson S, Mason CM. Pulmonary veno-occlusive disease in an adult following bone marrow transplantation. Case report and review of the literature. *Chest* 1996;109:1388–1391.
- Townend JN, Roberts DH, Jones EL, Davies MK. Fatal pulmonary venoocclusive disease after use of oral contraceptives. *Am Heart J* 1992;124:1643–1644.
- Orisman A, Leard LE, Nathan M, Elicker BM, Hoopes C, Kukreja J, Jones KD. Rapidly progressive pulmonary venoocclusive disease in young women taking oral contraceptives. *J Heart Lung Transplant* 2012;31:1031–1036.
- Escamilla R, Hermant C, Berjaud J, Mazerolles C, Daussy X. Pulmonary veno-occlusive disease in a HIV-infected intravenous drug abuser. *Eur Respir J* 1995;8:1982–1984.
- McDonnell PJ, Summer WR, Hutchins GM. Pulmonary veno-occlusive disease. Morphological changes suggesting a viral cause. *JAMA* 1981;246:667–671.
- Ruchelli ED, Nojadera G, Rutstein RM, Rudy B. Pulmonary veno-occlusive disease. Another vascular disorder associated with human immunodeficiency virus infection? *Arch Pathol Lab Med* 1994;118:664–666.
- Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 14–1983. A 67-year-old woman with pulmonary hypertension. *N Engl J Med* 1983;308:823–834.
- Dwyer N, Smith R, Challis D, Reid D, Kilpatrick D. Granulomatous angitis leading to a pulmonary veno-occlusive disease-like picture. *Eur Respir J* 2009;33:666–669.
- Hamada K, Teramoto S, Narita N, Yamada E, Teramoto K, Kobzik L. Pulmonary veno-occlusive disease in pulmonary Langerhans' cell granulomatosis. *Eur Respir J* 2000;15:421–423.
- Johnson SR, Patsios D, Hwang DM, Granton JT. Pulmonary veno-occlusive disease and scleroderma associated pulmonary hypertension. *J Rheumatol* 2006;33:2347–2350.
- Kishida Y, Kanai Y, Kuramochi S, Hosoda Y. Pulmonary venoocclusive disease in a patient with systemic lupus erythematosus. *J Rheumatol* 1993;20:2161–2162.
- Zhang L, Visscher D, Rihal C, Aubry MC. Pulmonary veno-occlusive disease as a primary cause of pulmonary hypertension in a patient with mixed connective tissue disease. *Rheumatol Int* 2007;27:1163–1165.
- Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023–1030.
- Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997;336:111–117.
- Palazzini M, Manes A. Pulmonary veno-occlusive disease misdiagnosed as idiopathic pulmonary arterial hypertension. *Eur Respir J* 2009;18:177–180.
- Huertas A, Girerd B, Dorfmueller P, O'Callaghan D, Humbert M, Montani D. Pulmonary veno-occlusive disease: advances in clinical management and treatments. *Expert Rev Respir Med* 2011;5:217–229; quiz 230–231.
- Veeraraghavan S, Koss MN, Sharma OP. Pulmonary veno-occlusive disease. *Curr Opin Pulm Med* 1999;5:310–313.
- Wagenvoort CA. Pulmonary veno-occlusive disease. Entity or syndrome? *Chest* 1976;69:82–86.
- De Vries TW, Weening JJ, Roorda RJ. Pulmonary veno-occlusive disease: a case report and a review of therapeutic possibilities. *Eur Respir J* 1991;4:1029–1032.
- Montani D, Jais X, Price LC, Achouh L, Degano B, Mercier O, Mussot S, Fadel E, Dartevelle P, Sitbon O, et al. Cautious epoprostenol therapy is a safe bridge to lung transplantation in pulmonary veno-occlusive disease. *Eur Respir J* 2009;34:1348–1356.
- Palmer SM, Robinson LJ, Wang A, Gossage JR, Bashore T, Tapson VF. Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease. *Chest* 1998;113:237–240.
- Frank H, Milczoch J, Huber K, Schuster E, Gurtner HP, Kneussl M. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. *Chest* 1997;112:714–721.
- Gilroy RJ Jr, Teague MW, Loyd JE. Pulmonary veno-occlusive disease. Fatal progression of pulmonary hypertension despite steroid-induced remission of interstitial pneumonitis. *Am Rev Respir Dis* 1991;143:1130–1133.
- Hackman RC, Madtes DK, Petersen FB, Clark JG. Pulmonary venoocclusive disease following bone marrow transplantation. *Transplantation* 1989;47:989–992.

- 32 Kataoka M, Yanagisawa R, Fukuda K, Yoshino H, Satoh T. Sorafenib is effective in the treatment of pulmonary veno-occlusive disease. *Cardiology* 2012;123:172–174.
- 33 Overbeek MJ, van Nieuw Amerongen GP, Boonstra A, Smit EF, Vonk-Noordegraaf A. Possible role of imatinib in clinical pulmonary veno-occlusive disease. *Eur Respir J* 2008;32:232–235.
- 34 Willems E, Canivet JL, Ghaye B, de Leval L, Radermecker M, Preiser JC, Beguin Y. Pulmonary veno-occlusive disease in myeloproliferative disorder. *Eur Respir J* 2009;33:213–216.
- 35 Izbicki G, Shitrit D, Schechtman I, Bendayan D, Fink G, Sahar G, Saute M, Ben-Gal T, Kramer MR. Recurrence of pulmonary veno-occlusive disease after heart-lung transplantation. *J Heart Lung Transplant* 2005;24:635–637.
- 36 Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, Coke MA, Garrity ER, Sweet SC, Heiney DA, et al. Development of the new lung allocation system in the United States. *Am J Transplant* 2006;6:1212–1227.
- 37 Gries CJ, Mulligan MS, Edelman JD, Raghu G, Curtis JR, Goss CH. Lung allocation score for lung transplantation: impact on disease severity and survival. *Chest* 2007;132:1954–1961.
- 38 Kozower BD, Meyers BF, Smith MA, De Oliveira NC, Cassivi SD, Guthrie TJ, Wang H, Ryan BJ, Shen KR, Daniel TM, et al. The impact of the lung allocation score on short-term transplantation outcomes: a multicenter study. *J Thorac Cardiovasc Surg* 2008;135:166–171.
- 39 Lingaraju R, Blumenthal NP, Kotloff RM, Christie J, Ahya VN, Sager JS, Pochettino A, Hadjiliadis D. Effects of lung allocation score on waiting list rankings and transplant procedures. *J Heart Lung Transplant* 2006;25:1167–1170.
- 40 McCue JD, Mooney J, Quail J, Arrington A, Herrington C, Dahlberg PS. Ninety-day mortality and major complications are not affected by use of the lung allocation score. *J Heart Lung Transplant* 2008;27:192–196.
- 41 Weiss ES, Allen JG, Meguid RA, Patel ND, Merlo CA, Orens JB, Baumgartner WA, Conte JV, Shah AS. The impact of center volume on survival in lung transplantation: an analysis of more than 10,000 cases. *Ann Thorac Surg* 2009;88:1062–1070.
- 42 Chen H, Shiboski SC, Golden JA, Gould MK, Hays SR, Hoopes CW, De Marco T. Impact of the lung allocation score on lung transplantation for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2009;180:468–474.
- 43 Benza RL, Miller DP, Frost A, Barst RJ, Krichman AM, McGoon MD. Analysis of the lung allocation score estimation of risk of death in patients with pulmonary arterial hypertension using data from the REVEAL Registry. *Transplantation* 2010;90:298–305.
- 44 Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010;122:164–172.
- 45 Moylan CA, Brady CW, Johnson JL, Smith AD, Tuttle-Newhall JE, Muir AJ. Disparities in liver transplantation before and after introduction of the MELD score. *JAMA* 2008;300:2371–2378.
- 46 Wille KM, Harrington KF, de Andrade JA, Vishin S, Oster RA, Kaslow RA. Disparities in lung transplantation before and after introduction of the lung allocation score. *J Heart Lung Transplant* 2013;32:684–692.
- 47 McGiffin DC, Naftel DC, Kirklin JK, Morrow WR, Towbin J, Shaddy R, Alejos J, Rossi A. Predicting outcome after listing for heart transplantation in children: comparison of Kaplan-Meier and parametric competing risk analysis. Pediatric Heart Transplant Study Group. *J Heart Lung Transplant* 1997;16:713–722.
- 48 Takahashi SM, Garrity ER. The impact of the lung allocation score. *Semin Respir Crit Care Med* 2010;31:108–114.
- 49 McCurry KR, Shearon TH, Edwards LB, Chan KM, Sweet SC, Valapour M, Yusem R, Murray S. Lung transplantation in the United States, 1998–2007. *Am J Transplant* 2009;9:942–958.
- 50 Gomberg-Maitland M, Glassner-Kolmin C, Watson S, Frantz R, Park M, Frost A, Benza RL, Torres F. Survival in pulmonary arterial hypertension patients awaiting lung transplantation. *J Heart Lung Transplant*. 2013;32:1179–1186.
- 51 Kano G, Nakamura K, Sakamoto I. Pulmonary veno-occlusive disease in an 11-year-old girl: diagnostic pitfalls. *Pediatr Int* 2014;56:119–122.
- 52 Rodriguez Rodriguez P, Pedraza Serrano F, Moran Caicedo LP, Rodriguez de Guzman MC, Cebollero Presmanes M, de Miguel Diez J. Pulmonary veno-occlusive disease in a female gardener. *Arch Bronconeumol* 2014;50:40–41.
- 53 Sourla E, Paspala A, Boutou A, Kontou P, Stanopoulos I, Pitsiou G. A case of pulmonary veno-occlusive disease: diagnostic dilemmas and therapeutic challenges. *Ther Adv Respir Dis* 2013;7:119–123.
- 54 Woerner C, Cutz E, Yoo SJ, Grasemann H, Humpl T. Pulmonary veno-occlusive disease in childhood. *Chest* 2014;146:167–174.
- 55 Cassart M, Gevenois PA, Kramer M, Jacobovitz D, de Francquen P, Yernault JC, Estenne M. Pulmonary venoocclusive disease: CT findings before and after single-lung transplantation. *AJR Am J Roentgenol* 1993;160:759–760.
- 56 Stewart S, McNeil K, Nashef SA, Wells FC, Higenbottam TW, Wallwork J. Audit of referral and explant diagnoses in lung transplantation: a pathologic study of lungs removed for parenchymal disease. *The J Heart Lung Transplant* 1995;14:1173–1186.
- 57 Mineo G, Attina D, Mughetti M, Balacchi C, De Luca F, Niro F, Ciccarese F, Lovato L, Russo V, Buia F, et al. Pulmonary veno-occlusive disease: the role of CT. *Radiol Med* 2014;119:667–673.
- 58 Miura A, Akagi S, Nakamura K, Ohta-Ogo K, Hashimoto K, Nagase S, Kohno K, Kusano K, Ogawa A, Matsubara H, et al. Different sizes of centrilobular ground-glass opacities in chest high-resolution computed tomography of patients with pulmonary veno-occlusive disease and patients with pulmonary capillary hemangiomatosis. *Cardiovasc Pathol* 2013;22:287–293.
- 59 Perros F, Cohen-Kaminsky S, Gambaryan N, Girerd B, Raymond N, Klingelschmitt I, Huertas A, Mercier O, Fadel E, Simonneau G, et al. Cytotoxic cells and granulysin in pulmonary arterial hypertension and pulmonary veno-occlusive disease. *Am J Respir Crit Care Med* 2013;187:189–196.
- 60 Eyries M, Montani D, Girerd B, Perret C, Leroy A, Lonjou C, Chelghoum N, Coulet F, Bonnet D, Dorfmueller P, et al. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet* 2014;46:65–69.
- 61 Best DH, Sumner KL, Austin ED, Chung WK, Brown LM, Borczuk AC, Rosenzweig EB, Bayrak-Toydemir P, Mao R, Cahill BC, et al. EIF2AK4 mutations in pulmonary capillary hemangiomatosis. *Chest* 2014;145:231–236.