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ORIGINAL RESEARCH

Right Heart Score for Predicting Outcome in Idiopathic, Familial, or Drug- and Toxin-Associated Pulmonary Arterial Hypertension

François Haddad, MD,* Onno A. Spruijt, MD,† Andre Y. Denault, MD, PhD,‡ Olaf Mercier, MD, PhD,§ Nathan Brunner, MD,‖ David Furman, PhD,* Elie Fadel, MD, PhD,§ Harm J. Bogaard, MD, PhD,† Ingela Schnittger, MD,* Bojan Vrtovec, MD, PhD,* Joseph C. Wu, MD, PhD,* Vinicio de Jesus Perez, MD,‖ Anton Vonk-Noordegraaf, MD, PhD,† Roham T. Zamanian, MD‖

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From the *Division of Cardiovascular Medicine, Stanford University and Stanford Cardiovascular Institute, Palo Alto, California; †Division of Pulmonary Medicine, VU University Medical Center, Amsterdam, the Netherlands; ‡Department of Anesthesia and Division of Critical Care, Montreal Heart Institute, Montreal University, Montreal, Quebec, Canada; §Cardiovascular and Thoracic Research Center, Marie-Lannelongue Surgical Center, Université Paris-Sud, Paris, France; and the ‖Division of Pulmonary and Critical Care Medicine, Stanford University and Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford, California. This work was supported by the Vera Moulton Wall Center for Pulmonary Vascular Disease at Stanford University, Stanford Cardiovascular Institute, and the Pai Chan Lee Research Fund. Dr. Denault has received speaker fees from Covidien and CAE Healthcare. Dr. Brunner has been a consultant for Actelion and Bayer. Dr. Zamanian has received research grants from United Therapeutics and Actelion; and has received consulting fees from United Therapeutics and Bayer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Right Heart Score for Predicting Outcome in Idiopathic, Familial, or Drug- and Toxin-Associated Pulmonary Arterial Hypertension

ABSTRACT

OBJECTIVES This study sought to determine whether a simple score combining indexes of right ventricular (RV) function and right atrial (RA) size would offer good discrimination of outcome in patients with pulmonary arterial hypertension (PAH).

BACKGROUND Identifying a simple score of outcome could simplify risk stratification of patients with PAH and potentially lead to improved tailored monitoring or therapy.

METHODS We recruited patients from both Stanford University (derivation cohort) and VU University Medical Center (validation cohort). The composite endpoint for the study was death or lung transplantation. A Cox proportional hazard with bootstrap CI adjustment model was used to determine independent correlates of death or transplantation. A predictive score was developed using the beta coefficients of the multivariable models.

RESULTS For the derivation cohort ($n = 95$), the majority of patients were female (79%), average age was 43 $\pm$ 11 years, mean pulmonary arterial pressure was 54 $\pm$ 14 mm Hg, and pulmonary vascular resistance index was 25 $\pm$ 12 Wood units $\times$ m^2. Over an average follow-up of 5 years, the composite endpoint occurred in 34 patients, including 26 deaths and 8 patients requiring lung transplant. On multivariable analysis, RV systolic dysfunction grade (hazard ratio [HR]: 3.4 per grade; 95% confidence interval [CI]: 2.0 to 7.8; $p < 0.001$), severe RA enlargement (HR: 3.0; 95% CI: 1.3 to 8.1; $p = 0.009$), and systemic blood pressure <110 mm Hg (HR: 3.3; 95% CI: 1.5 to 9.4; $p < 0.001$) were independently associated with outcome. A right heart (RH) score constructed on the basis of these 3 parameters compared favorably with the National Institutes of Health survival equation (0.88; 95% CI: 0.79 to 0.94 vs. 0.60; 95% CI: 0.49 to 0.71; $p < 0.001$) but was not statistically different than the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) score c-statistic of 0.80 (95% CI: 0.69 to 0.88) with $p = 0.097$. In the validation cohort ($n = 87$), the RH score remained the strongest independent correlate of outcome.

CONCLUSIONS In patients with prevalent PAH, a simple RH score may offer good discrimination of long-term outcome. (J Am Coll Cardiol Img 2015;8:627–38) © 2015 by the American College of Cardiology Foundation.

Pulmonary arterial hypertension (PAH) is a rare condition caused by the progressive narrowing of the small pulmonary arteries, leading to increased pulmonary vascular resistance and right-sided heart failure (1). Despite advances in therapy, the mortality remains high, approaching 30% to 50% at 5 years in symptomatic patients (1,2). In recent years, right ventricular (RV) function has emerged as one of the strongest predictors of outcome in PAH (3). Hemodynamic studies have highlighted the prognostic importance of elevated right atrial (RA) pressure and decreased cardiac output, whereas imaging studies have highlighted the importance of RV remodeling and systolic function (2,4-6). Moreover, recent scores, such as the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) score, have integrated several of the clinical and functional parameters (2).

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To date, only a few studies have investigated whether RA size or function has incremental value to RV function in predicting outcome in PAH. The importance of RA size in PAH was first suggested by Bustamente-Labarta et al. (7) in their series of 25 patients. In a larger study in patients with PAH ($n = 81$), Raymond et al. (8) found that there was a trend for an independent association between RA area index ($p = 0.106$) and the composite endpoint of death or transplantation. To our knowledge, no study has of yet also investigated the prognostic value of RA function measured by active and passive emptying fractions (RAEF) in PAH.

For our study, we first hypothesized that measures of RA size or function would be independently associated with event-free survival in PAH. We further hypothesized that a simple score combining quantitative measures of right heart size or function would provide good discrimination of outcome in PAH.

METHODS

STUDY DESIGN. Our study included a derivation cohort at Stanford University, followed by a validation cohort at the VU Medical Center. After ethics committee approval, consecutive adult patients followed at Stanford University between January 11, 1999 and January 12, 2009 with a confirmed diagnosis of idiopathic or drug and toxin PAH were considered for inclusion in the study. The diagnosis of PAH was on the basis of the standard definition of mean pulmonary arterial pressure ≥25 mm Hg and pulmonary artery wedge pressure ≤15 mm Hg (9). We excluded patients for whom an echocardiogram was not available and patients with evidence of atrial fibrillation at baseline, left heart failure, and significant parenchymal lung disease. Patients recruited at the VU Medical Center had a diagnosis of idiopathic or familial PAH and underwent cardiac magnetic resonance (CMR) as part of a prospective study to evaluate the role of CMR in the management of PAH, for which medical ethical consent approval was obtained.

The composite endpoint of the study was death or lung transplantation. Death was verified through the national Social Security Death Index and transplantation through chart review. Data collection included demographics, 6-min walking distance (6MWD), estimated glomerular filtration rate, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, diffusion capacity of carbon monoxide, and hemodynamics. Renal function was estimated using the modified diet and renal equation (10). For purposes of standardization, data were collected on the first outpatient visit after stabilization on disease-modifying medications (prostanoids, endothelin receptor blockers, or phosphodiesterase inhibitors). We chose this time point for 2 reasons. First, this time point corresponded to the same day patients completed echocardiography, 6MWD, and laboratory testing (metabolic panel and NT-proBNP). In addition, the baseline right heart catheterization was often obtained within a 3- to 6-month time frame of this visit.

ECHOCARDIOGRAPHY. Digitized echocardiographic studies were analyzed by the Stanford Cardiovascular Institute biomarker and phenotypic core laboratory in accordance with published guidelines of the American Society of Echocardiography (ASE) (11). All measures were averaged over 3 cycles, and RV or RA size measures were indexed to body surface area. RV end-diastolic and end-systolic areas, as well as RA size, were measured from the apical 4-chamber view (Figure 1). RV function was quantified using right ventricular fractional area change (RVFAC), tricuspid annular systolic excursion (TAPSE), and right ventricular myocardial performance index (RVMPI), as previously described (11–13). RA size was measured at end-systole (RA_{max}), pre-atrial contraction ($RA_{pre\text{-}A}$), and end-diastole (RA_{min}) (Figure 2), and total, passive, and active RAEF were calculated as follows: $RAEF_{total} = (RA_{max} - RA_{min})/RA_{max}$; $RAEF_{passive} = (RA_{max} - RA_{pre\text{-}A})/RA_{max}$; and $RAEF_{active}$ = (RA pre-A size − RA min size)/$RA_{pre\text{-}A}$.

REFERENCE VALUES FOR RIGHT HEART REMODELING AND FUNCTION. RV systolic dysfunction was classified as mild, moderate, or severe if RVFAC was 25% to 35%, 18% to 24%, or ≤17%, respectively (11). For indexed values of RA size and function, because no values are referenced in the ASE guidelines, we used 95% of the upper limit of 95 prospectively recruited age- and sex-matched healthy controls on the basis of a 50-point questionnaire. Dimensions were categorized using similar thresholds as the left atrial volumes: <18% from reference value increase for mild increase and >40% increase for severe increase. For indexed RA area and right ventricular end-diastolic area (RVEDA), the upper limit of normal was 11 cm^2/m^2 and for indexed right ventricular end-systolic area (RVESA), the upper limit was 7.5 cm^2/m^2.

CMR PROTOCOL IN THE VALIDATION COHORT. CMR was performed on a 1.5-T Sonato scanner (Siemens Medical Solutions, Erlangen, Germany), equipped with a 6-element phased-array receiver coil. Short-axis images from base to apex of the ventricles were obtained with a typical slice thickness of 5 mm, and an interslice gap of 5 mm was used for estimation of ventricular volumes using the Simpson method, as previously described (14). The thresholds chosen for the CMR categorical classification were pre-defined at the beginning of the study. We chose the threshold of 35% for moderate RVEF dysfunction similar to the previously established cutoff in the study of van de veerdonk et al. (14). In addition, on the basis of a prior study from our group, we found that RVFAC of 25%

ABBREVIATIONS AND ACRONYMS

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PAH = pulmonary arterial hypertension

PVRI = pulmonary vascular resistance index

RAEF = right atrial emptying fractions

RAP = right atrial pressure

RVEDA = right ventricular end-diastolic area

RVEF = right ventricular ejection fraction

RVESA = right ventricular end-systolic area

RVFAC = right ventricular fractional area change

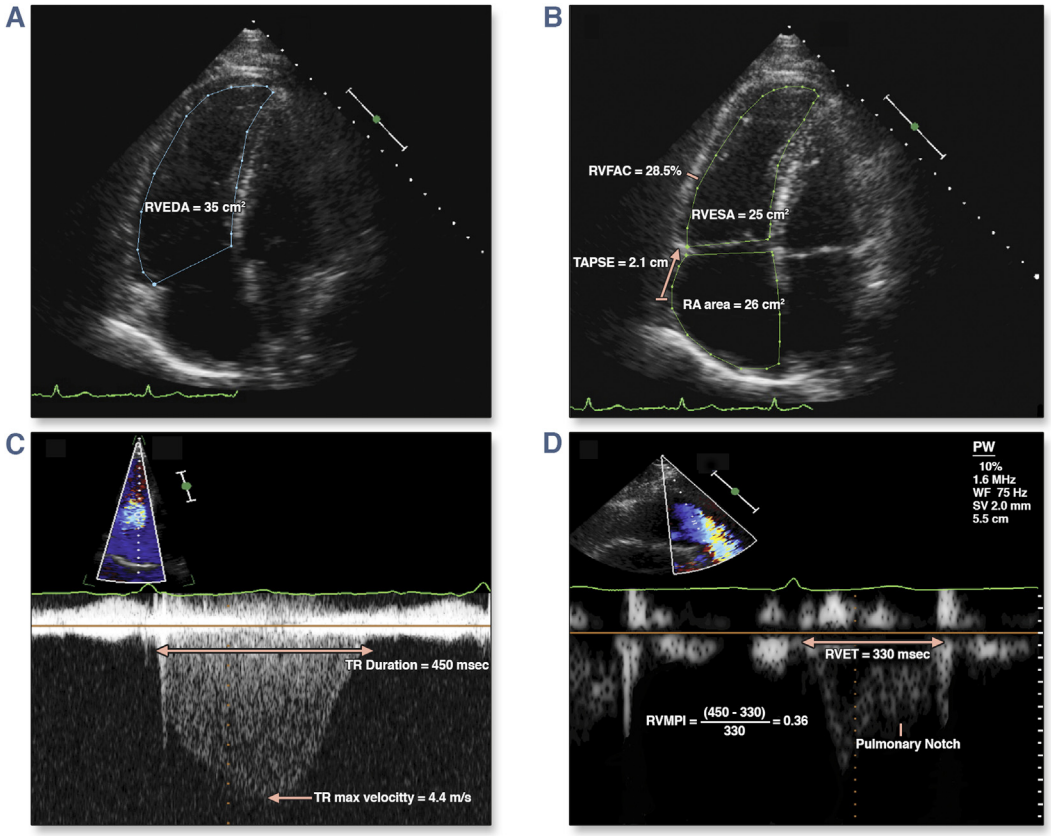
RVGLS = right ventricular global longitudinal strain

RVMPI = right ventricular myocardial performance index

SBP = systolic blood pressure

TAPSE = tricuspid annular systolic excursion

FIGURE 1 Representative Measures of Right Heart Size and Functional Parameters



(A) Measures of right ventricular end-diastolic area (RVEDA). **(B)** Measures of right ventricular end-systolic area (RVESA) and 2-dimensional tricuspid annular systolic excursion (TAPSE). **(C)** Measures of tricuspid regurgitation (TR) duration. **(D)** Measures of RV ejection time. RA = right atrial; RVET = right ventricular ejection time; RVFAC = right ventricular fractional area change; RVMPI = right ventricular myocardial performance index.

corresponded best to an RVEF of 35% (15). We used the same threshold for RA area for the echocardiographic and CMR studies.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD if the Kolmogorov-Smirnov test showed a normal distribution; otherwise, data are presented as median ± interquartile range (IQR). Categorical variables are expressed as frequency and percentage. Comparisons between groups were performed using 2-sided Student *t* tests with adjustment for unequal variance as needed. For non-normally distributed variables such as NT-pro-BNP level, transformation to the common logarithm was performed before analysis. Linear regression analysis was used to determine independent associations between hemodynamic and structural or functional right heart parameters. The association between clinical and echocardiographic parameters and outcome was analyzed using Cox proportional hazards models. The assumption of proportional hazards was assessed by plotting the scaled Schoenfeld residuals for each independent variable against time; these correlations were found to be nonsignificant for all variables included in the multivariable model. We used hierarchical modeling to determine factors independently associated with outcome and chose to include at maximum 1 covariate per 10 events to minimize overfitting of the model. We avoided including in the model variables that were collinearly related to each other. We used bootstrapping with 5,000 iterations to estimate hazard ratios and bias-corrected 95% confidence interval (CI) for the multivariable models. For building the predictive score, the smallest absolute beta coefficient was assigned a value of 0 and values for subsequent variables were assigned on the basis of

multiples of their respective beta coefficients to the nearest 0.5 approximation for categories with significantly different beta coefficients (16). The survival c-statistic was calculated to show the discriminatory ability of the models and was used to compare the predictive score with the validated REVEAL score and National Institutes of Health (NIH) survival equation. Intraobserver variability was assessed using the average difference in absolute measurement and the intraclass correlation coefficient (ICC). Statistical analysis was done using PASW statistical program (version 18.0, SPSS Inc., Chicago, Illinois).

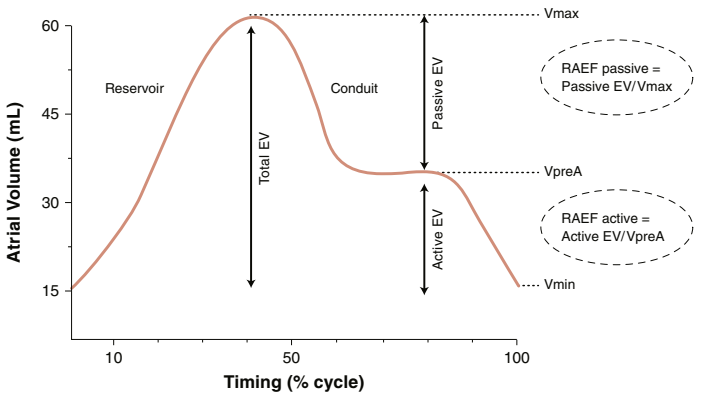
RESULTS

STUDY POPULATION. Of 128 patients with idiopathic and drug- and toxin-associated PAH who were seen during the study period, 106 were enrolled in the prospective registry. Eleven patients were excluded from the study for the following reasons: unavailable echocardiogram (n = 2), atrial fibrillation (n = 1), lost to follow-up (n = 5), left heart failure (n = 2), and restrictive lung disease (n = 1). Table 1 summarizes the characteristics of the study population. The average follow-up time for our study was 5.0 ± 2.4 years. The mean pulmonary arterial pressure was 54 ± 14 mm Hg, and the pulmonary vascular resistance index (PVRI) score was 25 ± 12 Wood units × m^2. Forty-five percent of patients (n = 43) were on prostanoid therapy, and 19% of patients (n = 18) were on combination therapy.

Figure 3 summarizes the relationship between RA size, RAEF, and RV function as assessed by RVFAC. Compared with healthy controls, patients with PAH had a greater degree of RA and RV enlargement and lower RAEF. In general, RA enlargement and impaired active RAEF were more common among patients with severe RV dysfunction (Figures 3B and 3D).

RELATIONSHIP BETWEEN METRICS OF RIGHT HEART FUNCTION AND HEMODYNAMICS. The different parameters of right heart size and function are not independent of each other; their inter-relationship is important to consider before outcome models are built. As expected, there was also strong collinearity between parameters of RV function (R^2 = 0.61 between RVFAC and TAPSE [$p < 0.001$] and R^2 = 0.51 between RVFAC and RVMPI [$p < 0.001$]), as well as between RVEDA and RA area (R^2 = 0.51; $p < 0.001$). Table 2 summarizes factors independently associated with RVFAC, RA area index, active and passive RAEF, and log NT-proBNP levels. We favored including in the model factors that were not only correlates but also potential determinants. As covariates, factors considered included demographic factors (age and sex), load parameters (PVRI and right atrial pressure [RAP]), functional indexes (tricuspid regurgitation and TAPSE), or renal function for NT-proBNP. Among other associations, we found that pericardial effusion, which was present in 17 patients, was strongly related to both RAP and RA size (chi-square = 22; p = 0.01). Systolic blood pressure (SBP) was significantly correlated with cardiac output, as well as the use of intravenous prostanoids (R^2 = 0.28; $p < 0.011$; r = 0.40 with cardiac output and r = −0.28 with prostanoids).

FIGURE 2 Atrial Size and Emptying Fractions



The figure depicts the different concepts related to RA volumes and the related concepts of total, passive, and RA emptying fractions. EV = emptying volume; RAEF = right atrial emptying fractions; V_{max} = maximal volume; V_{min} = minimal volume; V_{preA} = pre-atrial contraction volume.

OUTCOME ANALYSIS IN THE DERIVATION COHORT. The composite endpoint occurred in 34 patients (36%), including 26 deaths and 8 lung transplants. Event-free survival at 1, 3, and 5 years was 95%, 89%, and 81%, respectively. The predicted NIH survival equation 1-, 3-, and 5-year survival estimates were 66%, 44%, and 33%, respectively, and the revised NIH prediction scores were 91%, 71%, and 63% (17).

Several parameters of right heart structure and function were strongly related to outcome on univariate analysis (Table 3). The strongest relationships were found with RVEDA index, RVESA index, RVFAC, TAPSE, RA size, active RAEF, and log NT-proBNP levels. In addition, New York Heart Association (NYHA) functional class, resting SBP, kidney function, low cardiac index on right heart catheterization, and PVRI were associated with outcome. Figure 4 presents the c-statistic of the RV and RA parameters, as well as their Kaplan-Meier survival curves from RVFAC and RA index categories. With the area-length

TABLE 1 Patient Characteristics for the Derivation Cohort (N = 95)

Age, yrs	43 ± 11
Women	75 (79)
White	84 (88)
Etiology of PAH	
Idiopathic or familial	44 (46)
Drugs and toxin (history of use)	51 (55)
Body mass index, kg/m^2	30 ± 6
Right heart catheterization	
HR, beats/min	82 ± 14
SBP, mm Hg	120 ± 17
RAP, mm Hg	10 ± 6
MPAP, mm Hg	54 ± 14
PCWP, mm Hg	10 ± 4
CI, l/min/m^2	2.0 ± 0.6
PVRI, Wood units × m^2	25 ± 12
6-min walking distance, m	432 ± 117
DLCO, %	75 ± 23
Comorbid conditions	
CKD (eGFR <60 ml/min/1.73 m^2)	22 (23)
Hyponatremia (<136 mEq/l)	9 (9.5)
Diabetes mellitus	3 (3)
Systemic hypertension	4 (4)
Medication	
Diuretic	48 (51)
Prostanoid therapy	43 (45)
Phosphodiesterase inhibitor	31 (33)
Endothelin receptor blocker	39 (41)
Warfarin	59 (63)

Values are mean ± SD or n (%).

CI = cardiac index; CKD = chronic kidney disease; DLCO = diffusion of carbon monoxide; eGFR = estimated glomerular filtration rate; HR = heart rate, MPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; SBP = systolic blood pressure.

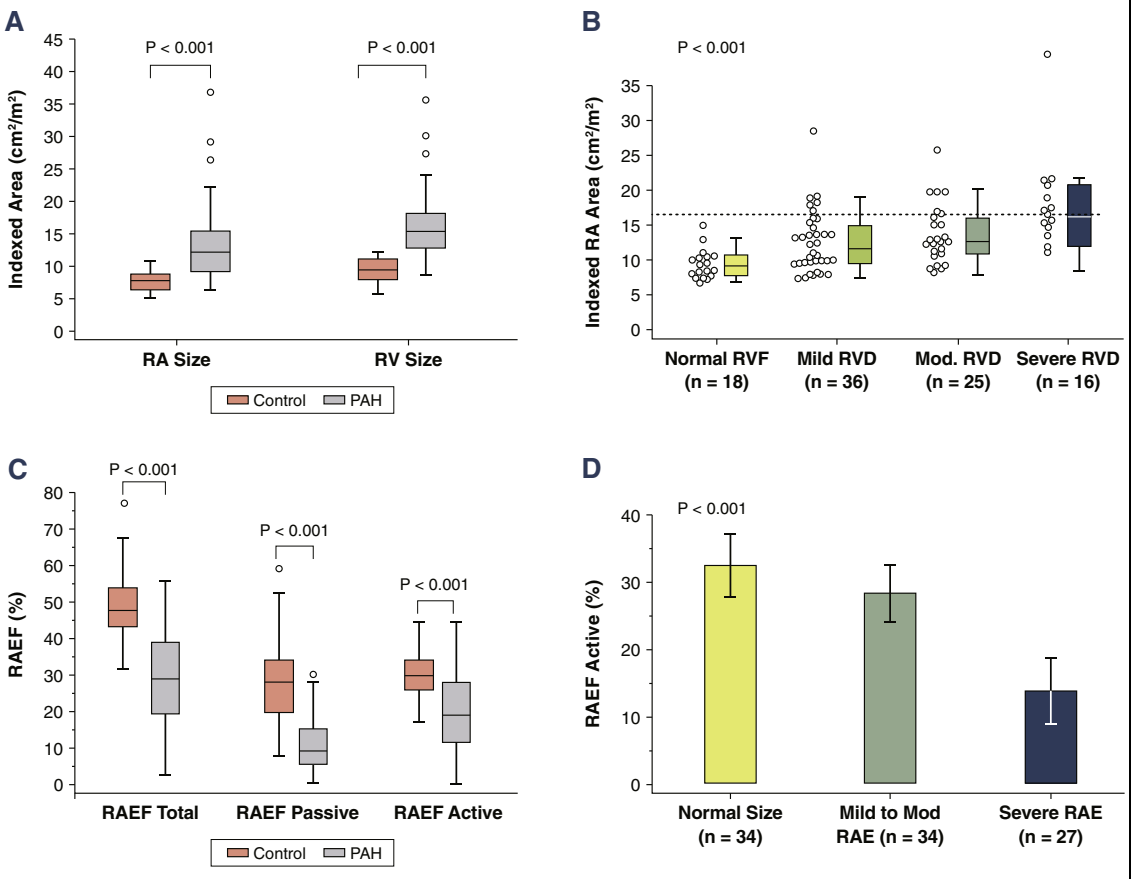
method, volumetric measures of RA size or RAEF were not associated with significantly different c-statistics (p = 0.79 and p = 0.87, respectively).

To minimize overfitting the multivariable Cox proportional hazards model, we only included 4 variables in the initial analysis (i.e., RVFAC, RA index, resting SBP, and NYHA functional class III and IV vs. I and II). The choice of variables was based on the following rationale: 1) RVFAC was more strongly associated with outcome than other RV functional parameters and was not collinearly related to RA size in contrast to RVEDA or RVESA; 2) RA size was more reproducible than active RAEF in our study population; 3) SBP was not collinearly related to RVFAC—in contrast, there was a moderate relationship between RV systolic pressure or relative RV systolic pressure and RVFAC (r = 0.45; p < 0.001 and r = 0.48; p < 0.001); and 4) NYHA functional class was related to outcome in many previous studies. On multivariable analysis, RVFAC, RA size, and SBP were strongly and independently associated with outcome, as shown in Table 4 (both in continuous and categorical analyses). In the subgroup of patients for whom NT-proBNP level was available (n = 79), NT-proBNP level was not retained in the multivariable model.

RIGHT HEART SCORE AND OTHER VALIDATED SCORES. A right heart score was built on the basis of the beta coefficients of the multivariable model, assigning a baseline value of 1 and additional points for each category of risk (Table 5). The right heart score had a c-statistic of 0.88 (95% CI: 0.79 to 0.94), the REVEAL score had a c-statistic of 0.80 (95% CI: 0.69 to 0.88), and the NIH survival equation had a c-statistic of 0.60 (95% CI: 0.49 to 0.71). With the DeLong method, both the right heart score and the REVEAL score had significantly higher c-statistics than the NIH survival equation (p < 0.001 and p = 0.013, respectively). There was no statistical difference between the right heart score and the REVEAL score in the cohort (p = 0.097). Figure 5 illustrates the Kaplan-Meier survival curves associated with the right heart score, as well as its relationship with other scores.

VALIDATION COHORT. The validation cohort included 87 patients with idiopathic or familial PAH followed at VU Medical Center between 2001 and 2012. The average age was 47.8 ± 16.0 years, the majority of patients were female (75%), baseline PVR was 11.2 ± 5 Wood units, and baseline 6MWD was 407 ± 127 m. All patients were on disease-modifying therapy, the average time between CMR and diagnosis was 1.5 ± 1.5 years, and the average follow-up time was 4.2 ± 3.2 years. The composite endpoint occurred in 29 patients, including 23 deaths and 6 lung transplants. On univariate analysis, the strongest correlates of outcome included right ventricular ejection fraction (RVEF) (chi-square = 12; p < 0.001), RA index (chi-square = 11; p < 0.001), RV end-systolic volume index (chi-square = 9; p < 0.001), right heart score (chi-square = 14; p < 0.001), and more weakly 6MWD (chi-square = 5; p = 0.03). On multivariable analysis, right heart score (hazard ratio [HR]: 1.9 per grade; 95% CI: 1.4 to 2.6) and age (HR: 1.3 per grade; 95% CI: 0.98 to 1.69) were the only 2 variables independently associated with outcome, with chi-square = 19 (p < 0.001). The c-statistic for the right heart score in the validation cohort (0.76; IQR: 0.66 to 0.84) was significantly different from the c-statistic for the NIH survival equation (0.59; IQR: 0.48 to 0.70; p = 0.030). Because NT-proBNP levels and the percentage-predicted diffusion capacity of carbon monoxide were not systematically available, the derived REVEAL score could not be calculated in the majority of patients at the time of follow-up.

FIGURE 3 Ventricular and Atrial Remodeling and Function in the Study Population



(A) Box-and-whisker plot of indexed RA and RV areas of patients with pulmonary arterial hypertension (PAH) and healthy controls. **(B)** Box-and-whisker plot of indexed RA area according to the pre-defined categories of right ventricular dysfunction (RVD). **(C)** Box-and-whisker plot of total, active, and passive RAEF of patients with PAH and healthy controls. **(D)** Bar graph with 95% confidence interval for mean value for active RAEF, stratified according to the pre-defined categories of RA size. In the box-and-whisker plots, the central box represents the values from the lower to upper quartile (25th to 75th percentile); the middle line represents the median; and the line extends from the minimum to the maximum value, excluding outlier values. RAE = right atrial enlargement; RVF = right ventricular function; other abbreviations as in Figures 1 and 2.

INTERVARIABILITY OF ECHOCARDIOGRAPHIC MEASURES. For RVFAC, the average difference in absolute measurement was 2.1 ± 1.6%, with an ICC of 0.84; for TAPSE, the average difference in absolute measurement was 0.1 ± 0.1 cm, with an ICC of 0.93; and for RVMPI, the average difference in absolute measurement was 0.09 ± 0.11, with an ICC of 0.85. The ICCs for maximal, minimal, and pre-atrial systole

TABLE 2 Potential Determinants of RV and RA Indexes (Multivariable Regression Models)

	RVFAC	RAI	$RAEF_{active}$	$RAEF_{passive}$	Log NT-proBNP
R^2	0.32	0.61	0.41	0.27	0.59
Correlates	PVRI (r = −0.44) Male (r = −0.30)	RAP (r = 0.44) TR (r = 0.45)	RAP (r = −0.27) TAPSE (r = 0.33) Male (r = −0.27)	Age (r = −0.35) TAPSE (r = 0.47)	RVFAC (r =−0.48) RAI (r = 0.40) eGFR (r = −0.31) Male (r = −0.24)

The multivariate models presented are all $p < 0.001$. PVRI is based on the most recent right heart catheterization. r corresponds to partial correlation coefficients.

NT-proBNP = N-terminal pro-B-type natriuretic peptide; RAEF = right atrial emptying fractions; RAI = right atrial area index; RVFAC = right ventricular fractional area change; TAPSE = tricuspid annular systolic excursion; TR = tricuspid regurgitation; other abbreviations as in Table 1.

TABLE 3 Univariable Analysis of Factors Associated With the Composite Endpoint

	Hazard Ratio	95% CI	p Value
Clinical			
Age, per 10 yrs	0.75	0.54–1.03	0.082
Male	1.90	0.90–4.03	0.094
DT vs. idiopathic	0.94	0.47–1.85	0.84
NYHA functional class, III and IV vs. I and II	2.67	1.34–5.32	0.005*
Walking distance, per 100 m	0.73	0.55–0.96	0.026*
SBP, per 10 mm Hg	0.73	0.58–0.92	0.009*
HR, per 10 beats/min	1.17	0.89–1.54	0.26
DLCO, per 10%	0.97	0.88–1.09	0.61
Comorbidities			
CKD	2.18	1.07–4.46	0.033*
Hyponatremia	1.80	0.69–4.68	0.23
Log NT-proBNP	4.81	2.13–10.86	<0.001*
Echocardiography parameters			
Right ventricular			
RVEDAI, per 3 cm^2/m^2	1.60	1.29–2.04	<0.001*
RVESAI, per 3 cm^2/m^2	1.82	1.49–2.22	<0.001*
RVFAC, per 5%	0.52	0.41–0.67	<0.001*
TAPSE, per 0.3 cm	0.61	0.46–0.82	0.001*
RVMPI, per 0.3 U	2.06	1.16–3.69	0.015*
Right atrial			
RAI, per 5 cm^2/m^2	1.81	1.44–2.28	<0.001*
RAEF active, per 5%	0.69	0.57–0.83	<0.001*
RAEF passive, per 5%	1.27	1.02–1.58	0.029
Septal curvature			
Diastolic EI, per 0.5 U	1.84	1.19–2.87	0.007*
Systolic EI, per 0.5 U	1.33	1.11–1.57	0.001*
Tricuspid regurgitation	1.95	1.30–2.90	0.002*
Hemodynamic			
RAP, per 5 mm Hg	2.12	1.51–3.01	<0.001*
RVSP, per 10 mm Hg	1.14	0.91–1.43	0.25
RVSP/SBP, per 0.25	2.77	1.61–4.75	<0.001*
SVI, per 5 ml/m^2	0.82	0.70–0.97	0.019
Left ventricular			
LVID, per 0.5 cm	0.79	0.54–0.99	0.049*
LVEF, per 5%	0.72	0.60–0.88	0.001*
Right heart catheterization			
Cardiac index <1.8 $l/min/m^2$	2.22	1.09–4.50	0.025
PVRI, per 10 Wood units × m^2	1.41	1.02–1.96	0.039

*Statistically significant.

DT = drug and toxin; EI = eccentricity index; LVID = left ventricular internal dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RVEDAI = right ventricular end-diastolic area index; RVESAI = right ventricular end-systolic area index; RVMPI = right ventricular myocardial performance index; RVSP = right ventricular systolic pressure; SVI = stroke volume index; other abbreviations as in Tables 1 and 2.

RA volumes were 0.95, 0.97, and 0.87, respectively. The ICC was 0.89 for total RAEF, 0.72 for active RAEF, and 0.84 for passive RAEF.

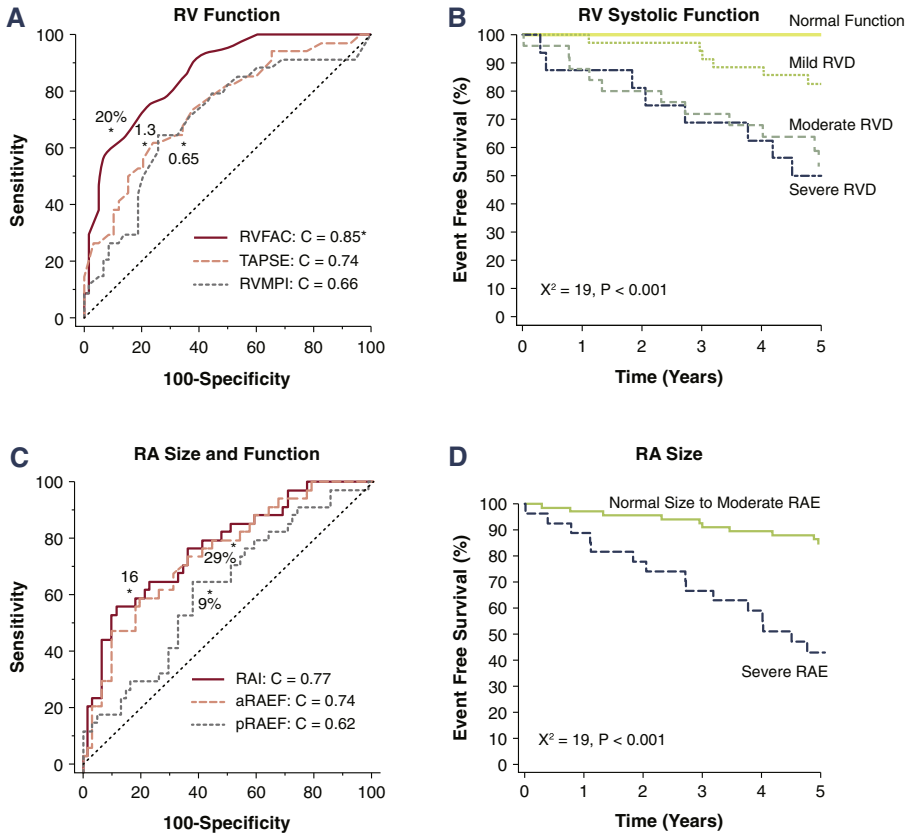
DISCUSSION

Our study is the first to demonstrate that a simple score combining measures of RV systolic function, RA size, and SBP offered a good discrimination of outcome in patients with established PAH. Consistent with other studies, the results of our study highlighted that the quantitative metrics of right heart remodeling or function may simplify the risk stratification of patients with PAH (3,18).

The REVEAL score and the NIH survival equation represent the 2 most validated survival scores in PAH (2,4). The NIH registry score relies on hemodynamic parameters, whereas the REVEAL registry score incorporates clinical, functional, and imaging parameters. Although our sample size was small, confidence in our results is provided by the fact that the right heart score correlated well with established outcome scores, the findings were validated in an independent cohort, and the results were consistent using different imaging modalities. In a recent publication, in a large series of patients with PAH, Fine et al. (18) showed that RV global longitudinal strain (RVGLS), log NT-proBNP levels, and NYHA functional class were independent correlates of clinical deterioration in patients with PAH. Consistent with the study of Fine et al. (18), our study also highlighted the importance of right heart function. In contrast, NYHA functional class and log NT-proBNP levels did not emerge as independent correlates of outcome due to their strong relationship with RV function and RA size; alternatively, our study may have been underpowered to assess their incremental value. In the REVEAL registry score, qualitative assessment of RV function was considered but did not emerge in the multivariate model; one can theorize, although not yet proven, that this may reflect the interlaboratory variability in assessing RV function and the multiple grades of dysfunction considered (5 classes).

With echocardiography, different metrics of RV systolic function have been considered, including RVFAC, TAPSE, RVMPI, and more recently RVGLS (3,12,13,18). In our study, RVFAC emerged as a stronger correlate of outcome than either TAPSE or RVMPI. In a recent study, we showed that RVFAC was more closely related to RVEF than TAPSE (19). Moreover, we showed that an RVFAC of 25% corresponded best to an RVEF of 35%, a commonly chosen threshold for moderate RV dysfunction in CMR imaging studies of patients with PAH (14,15). In comparison to RVFAC, TAPSE has the advantage of reproducibility but does not take into account the radial component of RV contraction (20). Although RVMPI combines information of both systolic and diastolic function, in different studies it has not appeared to carry stronger prognostic value than RVFAC, TAPSE, or RVGLS (18,21). Although not yet proven, this may be in part due to pseudonormalization of RVMPI values, which can occur in patients with severe dysfunction. As shown in the recent study of Fine et al. (18), RVGLS emerged as the best metric of RV

FIGURE 4 C-statistics and Kaplan-Meier Curves for Selected Parameters of RV and RA Function



(A) C-statistic between indexes of RV function. **(B)** Five-year Kaplan-Meier curve of RV systolic dysfunction on the basis of RVFAC. **(C)** C-statistic between RA indexes. **(D)** Five-year Kaplan-Meier curve and severe RA enlargement. *In **A** and **C**, the criterion value noted on the graph is the optimal criterion value corresponding with the Youden index J with equal weight given to sensitivity and specificity. aRAEF = active right atrial emptying fractions; pRAEF = passive right atrial emptying fractions; RAI = right atrial area index; other abbreviations as in Figures 1, 2, and 3.

function compared with RVFAC and TAPSE in PAH; ongoing studies are currently validating the findings in independent cohorts.

One of the most important contributions of our study was to prove the independent contribution to RA size (22). In fact, in contrast to studies on atrial remodeling in left heart failure, there have been a limited number of studies addressing atrial remodeling or atrial function in PAH (7,8,23). Bustamante-Labarta et al. (7) were the first to suggest an association between RA size and outcome in 25 patients with PAH. In the study of Raymond et al. (8), in 81 patients with NYHA functional class III or IV PAH, there was a trend for an independent association between RA area indexed to height and the composite endpoint of death or transplantation (p = 0.106). In the recent study of Kane et al. (23),

TABLE 4 Independent Correlates of the Composite Endpoint in the Derivation Cohort

	Hazard Ratio	95% CI	p Value	Overall Chi-Square
Multivariable model—continuous				
RVFAC per 5%	0.6	0.4-0.7	<0.001	44
RAI, per 5 cm^2/m^2	1.4	1.1-2.8	0.021	–
SBP baseline, per 10 mm Hg	0.7	0.5-0.9	0.007	–
Multivariable model—categorical				
RV systolic dysfunction per grade*	3.4	2.0-7.75	<0.001	47
Severe RAE, >16 cm^2/m^2	3.0	1.3-8.1	0.009	–
SBP <110 mm Hg	3.3	1.5-9.4	0.002	–
RH score (categorical)				
RH score, per grade	3.2	2.3-5.4	<0.001	47

*RV dysfunction was classified into normal (no dysfunction), mild, or moderate to severe according to the American Society of Echocardiography criteria. The 95% CI are reported after 5,000 iterations of the bootstrap procedure. Model was adjusted for age and sex.

RAE = right atrial enlargement; RH = right heart; other abbreviations as in Tables 1 and 2.

TABLE 5 Example of RH Score and Point Allocation

Baseline value	1 +
RV function*	
Normal	0
Mild	1
Moderate to severe	2
Less than severe RAE	0
Severe RAE	1
SBP >110 mm Hg	0
SBP <110 mm Hg	1
RH score	1 to 5

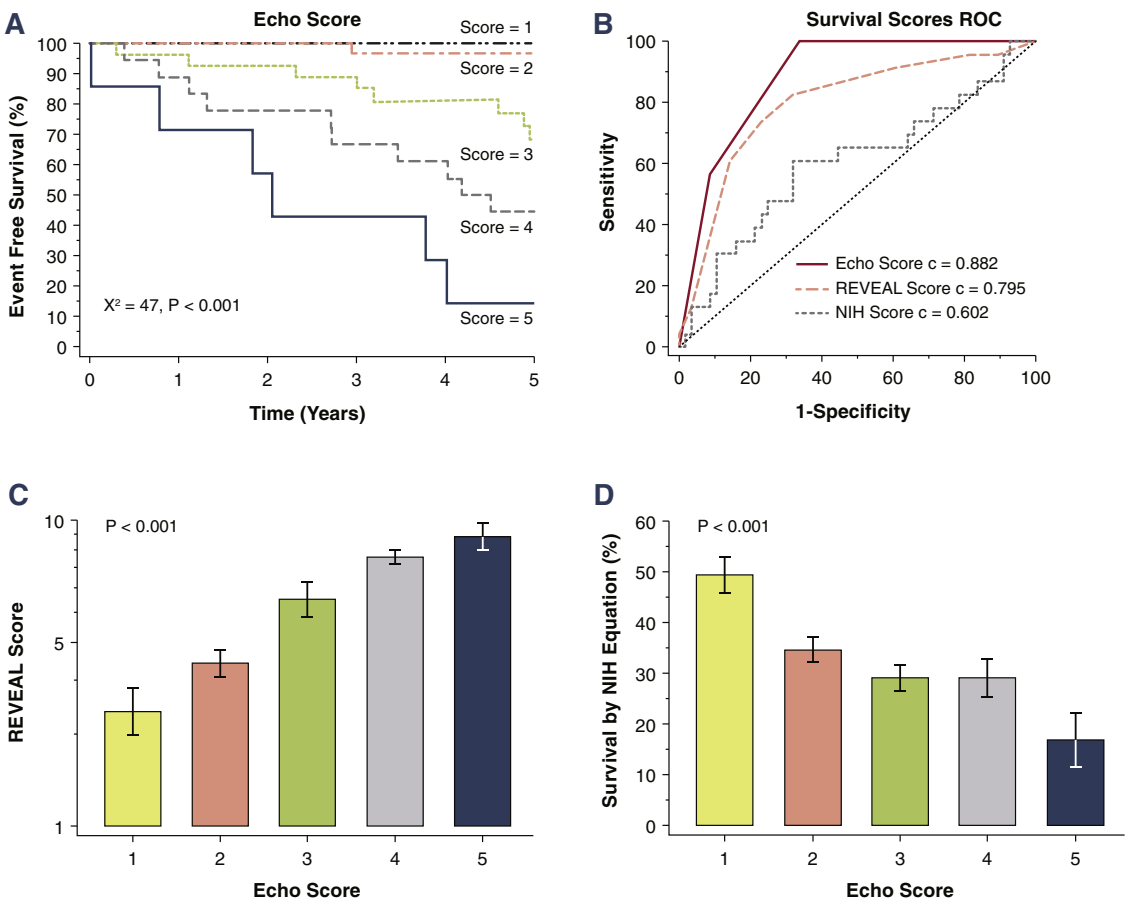
*RV dysfunction was classified into normal (no dysfunction), mild, or moderate to severe according to the American Society of Echocardiography criteria.

Abbreviations as in Tables 1, 2, and 4.

severe RA enlargement assessed qualitatively were also predictive of survival when corrected for age, sex, and functional class. Mechanistically, RA size is strongly associated with RAP, and tricuspid regurgitation severity can therefore provide important information on adverse ventricular remodeling. However, further studies are needed to provide better normative indexed thresholds of RA size.

In addition to changes in RA remodeling, we showed that RA function was significantly impaired in patients with PAH. Although the change affected both passive and atrial components of atrial function, better prognostic information was provided by active atrial emptying. The association between active RAEF and RAP, as well as TAPSE, is not surprising because RAP may be an indirect metric of RA afterload and

FIGURE 5 Right Heart Score in Relation to the REVEAL and NIH Scores



(A) Five-year Kaplan-Meier curve on the basis of the right heart score. **(B)** C-statistic between the right heart score and the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) score and 5-year predicted National Institutes of Health (NIH) survival. **(C)** Strong relationship between the right heart score and the REVEAL score, with 95% CI for the mean value. **(D)** Strong relationship between the right heart score and the NIH score, with 95% confidence interval for the mean value.

TAPSE may limit the extent of active RAEF as the atria cannot contract if the ventricle has a limited annular excursion. As a marker of outcome, active RAEF has the potential disadvantage of lower reproducibility compared with maximal RA size; in addition it is more collinearly related with metrics of RV systolic function, which may limit its incremental value in multivariate models. Conversely, RA size was more related to RV end-systolic dimensions, which may limit their incremental values if considered together as covariates. The sex differences related to active RAEF will require further study and validation. The association that we found between SBP and outcome was consistent with the findings of the REVEAL registry and may reflect lower cardiac output or the use of prostanoid therapy.

Our study has 3 main clinical implications. First, a simple right heart score can be useful for stratified randomization strategies in phase II clinical trials because matching based only on NYHA functional class may not capture the complexity of the disease process and all variables from the REVEAL registry may not be available. Second, a simple right heart score can serve as a "benchmark" against which the incremental value of novel biomarkers can be assessed. Third, empirically patients with higher scores could be monitored more closely clinically because they are at higher risk of clinical deterioration. However, it is important to mention that our study was not designed to provide a comparison with well-validated scores, such as the REVEAL registry score, and should by no means be considered interchangeable. Our study does however suggest, as did the study of Fine et al. (18), that quantitative assessment of right heart function and remodeling may simplify risk assessment in patients with PAH.

STUDY LIMITATIONS. The small sample size limited the number of variables that we could consider in the multivariable model. The strong relationship with the REVEAL registry and NIH survival equation, however, brought indirect external validation to our findings, as did the validation cohort. Second, we did not include more complex imaging modalities, such as strain imaging, in our study. Finally, it is important to emphasize that our study focused on prevalent cases of patients with PAH, rather than incident treatment-naive patients.

CONCLUSIONS

In this study, we showed that in patients with idiopathic, familial, or drug- and toxin-associated PAH, a simple right heart score combining indexes of right heart remodeling and function could predict long-term outcome. If further validated, this simple score may significantly improve the evaluation of novel biomarkers and help guide stratified randomization in clinical trials.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. François Haddad, Division of Cardiovascular Medicine, Stanford University, 300 Pasteur Drive, Palo Alto, California 94305. E-mail: fhaddad@stanford.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Imaging cardiovascular biomarkers have diagnostic and prognostic value and are useful in guiding clinical management in patients with PAH. Finding the best combination of biomarkers is essential to translate into better diagnostic or predictive tools. In this study, we identified right ventricular function by conventional echocardiography, right atrial enlargement, and systemic systolic blood pressure as key factors determining outcome, and a score derived from these simple 3 parameters had prognostic power superior to an established PAH score.

TRANSLATIONAL OUTLOOK: Additional clinical studies are needed to validate the incremental prognostic value of simplified imaging scores in patients with PAH.

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