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RESEARCH ARTICLE

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Identifying consistent echocardiographic thresholds for risk stratification in pulmonary arterial hypertension

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Abstract

Several indices of right heart remodeling and function have been associated with survival in pulmonary arterial hypertension (PAH). Outcome analysis and physiological relationships between variables may help develop a consistent grading system.

Patients with Group 1 PAH followed at Stanford Hospital who underwent right heart catheterization and echocardiography within 2 weeks were considered for inclusion. Echocardiographic variables included tricuspid annular plane systolic excursion (TAPSE), right ventricular (RV) fractional area change (RVFAC), free wall strain (RVFWS), RV dimensions, and right atrial volumes. The main outcome consisted of death or lung transplantation at 5 years. Mathematical relationships between variables were determined using weighted linear regression and severity thresholds for were calibrated to a 20% 1-year mortality risk.

Abbreviations: eRAP, Echo Right atrial pressure; LVEF, left ventricular ejection fraction; LVID, left ventricle internal diameter; RHC, right heart catheterization; rRAP, right heart catheterization measured right atrial pressure; RVEDA, right ventricular end diastolic area; RVEDD, right ventricular end diastolic diameter; RVEF, right ventricular ejection fraction; RVESA, right ventricular end systolic area; RVESD, right ventricular end systolic diameter; RVFAC, RV fractional area change; RVFWS, myocardial RV free wall strain; RVSP, right ventricular systolic pressure; RVTS, right ventricular transverse shortening; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

PAH patients ($n = 223$) had mean (SD) age of 48.1 (14.1) years, most were female (78%), with a mean pulmonary arterial pressure of 51.6 (13.8) mmHg and pulmonary vascular resistance index of 22.5(6.3) WU/m^2. Measures of right heart size and function were strongly related to each other particularly RVFWS and RVFAC ($R^2 = 0.82$, $p < 0.001$), whereas the relationship between TAPSE and RVFWS was weaker ($R^2 = 0.28$, $p < 0.001$). Death or lung transplantation at 5 years occurred in 78 patients (35%). Guided by outcome analysis, we ascertained a uniform set of parameter thresholds for grading the severity of right heart adaptation in PAH. Using these quantitative thresholds, we, then, validated the recently reported REVEAL-echo score (AUC 0.68, $p < 0.001$).

This study proposes a consistent echocardiographic grading system for right heart adaptation in PAH guided by outcome analysis.

KEYWORDS

echocardiography, heart failure, pulmonary arterial hypertension, right ventricle function and dysfunction, risk stratification and biomarkers

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease associated with pulmonary vascular remodeling.[1-9] In patients with PAH, right heart failure (RHF) is the most important cause of mortality.[10] More than 30 years ago, D'Alonzo et al. observed that survival in PAH was closely associated with cardiac index (CI) and right atrial (RA) pressure.[10] Since then, several imaging biomarkers of RHF have predicted event-free survival in PAH including tricuspid annular plane systolic excursion (TAPSE),[7,8,10-12] right ventricular (RV) free wall longitudinal strain (RVFWS), RV end systolic dimensions and more recently RA size and function.[6,13-16]

With the multiplicity of right heart parameters, ensuring consistency in grading systems becomes even more important. While there is variability in how the right heart adapts to PAH, several right heart metrics are related to each other.[12,17,18] For example, Evaldsson et al. have demonstrated that RVFWS is strongly associated with RV ejection fraction (RVEF) in patients with PH.[19] In patients with precapillary PH, Kind et al. have also, shown that RV mid-transverse function is closely associated with RVEF.[20] These relationships are not surprising as the right heart usually adapts to PAH through heterotopic mechanisms (RV dilatation) to compensate for ventriculo-arterial uncoupling.[21] In addition, RV and RA remodeling and function are often linked to each through diastolic dysfunction, tricuspid regurgitation, and ventriculo-atrial coupling, (Figure 1a). These physiological relationships can help ensure consistency between thresholds for risk stratification; in addition, they can help guide consistency between grading systems in PAH.

To be clinically relevant, thresholds for severity should be first and foremost guided by outcome analysis. For PAH, 20% risk of mortality or lung transplantation at year is often used to define high risk. The 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension (PH), have incorporated several imaging parameters in its risk stratification schema. The cardiac magnetic resonance parameters were mainly guided by the study of Lewis et al.[22] Among the echocardiographic indices also proposed in the ESC/ERS guidelines, RA area size > 26 cm^2, the TAPSE/sPAP (systolic pulmonary arterial pressure) ratio < 0.19 mm/mmHg and the presence of moderate pericardial effusion have been incorporated and considered markers of high risk (>20% 1-year mortality). For other echocardiographic parameters such as RV internal diameters or areas or indexed dimensions, severity thresholds have not been as well established. Deriving these quantitative thresholds would not only be variable for consistency but would provide quantitative criteria for imaging-based risk scores such as the recently described REVEAL-ECHO.[23]

The main objective of this study is to propose a consistent echocardiographic grading system in PAH anchored on physiological relationships and outcome analysis. Our first objective was to better quantify mathematical and physiological relationships between right heart variables in PAH. The second objective was to identify right heart severity thresholds in PAH based on

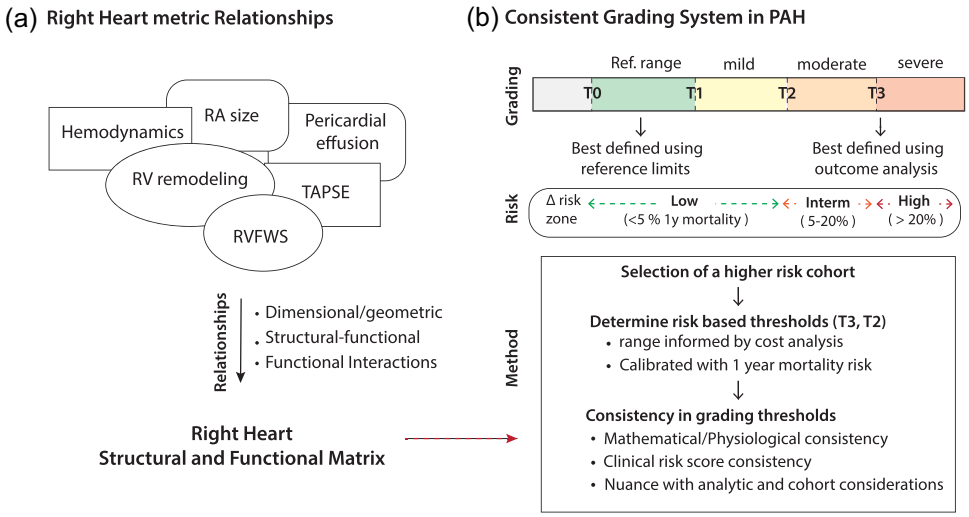

FIGURE 1 (a) Right heart metric relationships (b) Grading system for chamber quantification. Grading systems are guided by reference limits and outcome analysis. In PAH, high risk is defined as a 1-year risk of mortality > 20%. To identify consistent thresholds for right chamber quantification, we first selected a high-risk cohort and then identify thresholds based on outcome analysis with other supporting criteria. PAH, pulmonary arterial hypertension.

outcome analysis. Theoretically, these thresholds should follow their physiological relationship and be consistent with validated clinical risk scores. Finally, we aimed to validate the recently proposed REVEAL-ECHO score using quantitative right heart criteria.

MATERIAL AND METHODS

Study design

The study was a retrospective single center study conducted at the Vera Moulton Wall Center for Pulmonary Vascular Disease. This study was approved by the Stanford University Institutional Review Board and was conducted under the Cardio Share protocol (IRB#25673).

Population

Adult patients (>18 years) with a diagnosis of PAH followed at Stanford Hospital between January 2002 and 2021 were screened for inclusion. The diagnosis of PAH was established clinically and supported by right heart catheterization (RHC) with evidence of mean pulmonary arterial pressure > 25 mmHg and a pulmonary vascular resistance (PVR) > 3 Wood units. In our practice setting, patients who obtain an echocardiogram and a RHC close by are often higher risk patients with a majority having a REVEAL lite score ≥ 8. Therefore, we selected patients who had RHC and echocardiogram within 2 weeks of each other to ensure inclusion of a high-risk cohort. We excluded patients with non-Group 1 PAH and patients with complex congenital heart disease. In addition, for the outcome analysis, we excluded patients with a primary diagnosis of liver cirrhosis as the primary cause of PAH. We also only included who were followed for at least 5 years to allow for sufficient for the combined outcome of death or transplantation to occur.

RHC/hemodynamic assessment

A RHC was performed using when appropriate mild sedation. During the RHC, measures included mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure, RA pressure (RAP), cardiac output (CO), PVR as well as vital signs. CO was measured using the Fick method with the oxygen consumption estimated based on the LaFarge table; both CO and PVR were indexed to body surface area using the Dubois formula.[24]

Echocardiographic assessment

Echocardiographic images were acquired using Hewlett Packard Sonos 5500 or Philips IE33 ultrasound systems according to the American Society of Echocardiography guidelines for chamber quantification.[25] All measurements were performed using the TomTec platform (TomTec Imaging system) by two certified readers (Supporting Information: e-Figure 1). Measures were performed on the RV focused views in the Stanford Cardiovascular Institute Biomarker and Phenotypic Core

Laboratory by a certified sonographer and verified by a trained cardiologist (B. C.). Measures were conducted at end-diastole and end-systole defined by largest and smallest chamber size. Comprehensive measures of the right heart were performed including RV areas, basal and mid-transverse dimensions and RA areas and volumes. We used the method described by Kind et al. to identify the RV transverse axis allowing consistent transverse shortening measures while antero-posterior dimensions were measured.[26] Right heart dimensions were indexed using height for diameters and BSA for areas as well as internally scaled to left ventricular or atrial size as appropriate. Functional indices included RV fractional area change (RVFAC), RVFWS, TAPSE as well as transverse and antero-posterior shortening measures. RVFWS was measured using Lagrangian strain and the lateral wall was measured up to the apico-septal junction. RVFWS and RVFAC were measured using the same frame to ensure maximal consistency. Since M-mode were not available in all patients, TAPSE was measured using anatomical 2D plane (in our laboratory, we observed a strong association between anatomical M-mode and anatomical 2D plane measures $r = 0.81$, $p < 0.001$, $n = 126$). Left ventricular diameters were measured in the parasternal long axis views and LV ejection fraction was quantified using the Simpson's method in the 4-chamber view. Pericardial effusion was measured in the subcostal view during diastole, we used a semi-quantitative method to quantify the severity of the pericardial effusion, <10 mm was considered as mild and ≥10 mm was considered as moderate to severe.

Clinical, laboratory, and outcomes data

Demographic data, anthropometric data, etiology of PAH, treatments, New York Heart Association (NYHA) status, 6-min walk test closest to the RHC and laboratory data (serum creatinine, total bilirubin, sodium, hemoglobin, NT-terminal pronatriuretic peptide (NT-proBNP) were collected. We calculated the REVEAL lite score as well as the recently described REVEAL-echo score for all participants.[23,27] Patients were followed for the primary outcome of time to death or transplantation within 5 years. Mortality and lung transplantation outcome were curated through chart review and national death index.

STATISTICS ANALYSIS

Summary statistics include mean ± standard deviation (SD) and number and percentage. Data with skewed a distribution were presented as median and interquartile range. We compared groups using Student T test with adjustment for unequal variance. To quantify relationships between right heart variables, we performed a weighted linear regression which better adjusts for heteroscedasticity; for selected variables such as NT-proBNP, natural logarithmic transformation was performed before analysis. For variance, we report the average variance terms for the predicted interval. Outcome analysis was based on Cox-proportional hazard model as well as Kaplan Meier survival analysis. Upset plots were used to analyze combinations between variables used in the multivariable survival analysis.

To determine thresholds for grading severity of PH, we used different methods to ensure consistency between the different metrics (Figure 1b). Three thresholds were used to define severity: T0 or the reference limit threshold, T1 or the intermediate risk thresholds and T2 (high risk threshold). To select T2 thresholds, all metrics were calibrated using a 20% 1-year risk of mortality or ung transplantation aligning with the most recent ESC/ERS guidelines;[3] the T0 thresholds were selected using the limits of reference based on the ASE recommendations for chamber quantification, the ESC/ERS guidelines and recent WASE values while T1 was calibrated to a lower than 5% 1-year risk of mortality. The range for T2 was first determined using different classification criterion from cross-over between sensitivity and sensitivity, Youden index or cost-analysis. Cost analysis weighs each category of true positive, true negative, false positive and false negative by their respective prevalence and cost values. The cost matrix for the study was 2 for false negative, 1 for false positive and −1 for true positive and negative; we selected a greater cost for false negative associated with the risk of withholding therapy for a patient. In addition, supporting criteria for the selected threshold included the following: first, mathematical consistency anchored on the value of RVFAC, median value of the REVEAL lite score of 8 and 9 (Figure 1b). For statistical analysis, we used R (version 4.2.1) and MedCalc (version 20.218) software.

RESULTS

Patient characteristics

A total of 424 patients were selected from the RHC database with an initial diagnosis of PAH from 2002 to 2021. Among them, 240 patients had RHC and an echocardiography within 2 weeks and 223 had a final diagnosis of PAH with a median REVEAL lite registry score was 8.0 [IQR 6.0−10.0]. A subgroup of 56 patients had a follow-up echocardiogram and RHC within

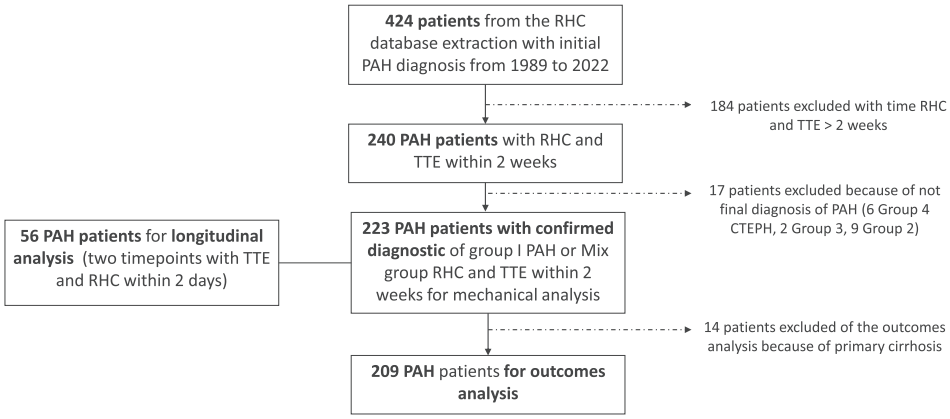

FIGURE 2 Consort diagram. Four hundred twenty-four patients were selected from the Stanford Pulmonary Hypertension Registry Mechanical and mathematical analysis was performed in 223 patients and analysis, for the outcome death or transplant within 5 years, in 198 patients.

TABLE 1 Patient characteristics for the pulmonary arterial hypertension cohort.

	Population ($n = 223$)
Demographics	
Age	48.1 (14.1)
Male	49 (22.0%)
White race	124 (55.6%)
Etiology	
Idiopathic	90 (40.4%)
Connective tissue disease	55 (24.7%)
IV drug abuse	7 (3.2%)
Simple repaired congenital	4 (1.8%)
Comorbidity	
Lung disease	17 (7.6%)
Advanced liver disease	14 (6.3%)
Medications	
Treatment naive	145 (65%)
Biological markers	
NT-proBNP (pg/mL)	
<300	59 (26.5%)
300–1100	55 (24.7%)
≥ 1100	109 (48.9%)
GFR by CKDepi (mL/min/1.73 m^2)	55.0 (22.1)
Sodium (mM)	138 (3.4)
Hemoglobin (g/dL)	13.3 (2.3)
Bilirubin (mg/dL)	0.97 (1.0)
RHC parameters	
mPAP (mmHg)	51.6 (13.8)
RAP (mmHg)	9.3 (5.2)
PAWP (mmHg)	11.1 (4.8)
CI (L/min/m^2)	2.0 (0.6)
PVRi (WU/m^2)	22.5 (6.3)
NYHA status	
1	6 (2.7%)
2	52 (23.3%)
3	80 (35.9%)
4	78 (35.0%)
Reveal lite 2.0 score	
≤5	53 (23.8%)
6–7	42 (18.8%)
≥8	127 (57%)
Outcomes	
Death or transplant within 5 years	78 (35%)

Abbreviations: GFR, glomerular filtration rate; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PAWP, pulmonary capillary wedge pressure; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; RHC, right heart catheterization.

2 weeks and were included for longitudinal analysis. After exclusion of the patients with advanced liver disease ($n = 14$) and patients who did not complete 5 years follow-up ($n = 11$), 198 patients remained for survival analysis (Figure 2).

Most patients were female (78.5%), the mean age was 48.1 (14.1) years and 55.6% (124) were Caucasians (Table 1). The majority had either idiopathic (40.4%) or

TABLE 2 PAH echocardiographic parameters.

Metrics	PAH, $n = 223$ mean (SD)
RV dimensions	
Basal transverse diameter index (mm/m)	
diastole	33.3 (5.9)
systole	29.4 (5.6)
Mid transverse diameter index (mm/m)	
diastole	29.6 (6.3)
systole	27.0 (6.9)
Mid transverse diameter relative (mm/mm)	
Diastole	1.3 (0.4)
RV areas (cm^2/m^2)	
RVEDAi (cm^2/m^2)	20.3 (5.8)
RVESAi (cm^2/m^2)	16.5 (5.6)
RV relative areas	
RVEDAr	1.9 (0.8)
RVESAr	2.9 (1.4)
RA area(cm^2/m^2)	12.6 (4.8)
RA relative area	1.8 (1.1)
RA volume(mL/m^2)	44.9 (28.1)
RV function	
TAPSE (mm)	14.2 (4.9)
TAPSE/RVSP (mm/mmHg)	0.21 (0.14)
RVFAC (%)	19.8 (6.5)
RV free-wall strain (RVFWS) (%)	12.6 (4.5)
Basal transverse shortening fraction (%)	12.0 (8.5)
Mid transverse shortening fraction (%)	9.5 (7.2)
Anteroposterior shortening fraction (%)	15.6 (7.3)
LV metrics dimensional	
LV internal diameter (mm/m)	23.2 (4.0)
LV metrics functional	
LVEF Simpson (%)	64.7 (7.8)

Abbreviations: PAH, pulmonary arterial hypertension; PAWP, pulmonary capillary wedge pressure; RA, right atrial; RAP, RA pressure; RHC, right heart catheterization; RV, right ventricular; RVFAC, RV fractional area change; RVFWS, RV free wall longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

drug and toxin-associated (24.7%) PAH. The cohort had hemodynamically severe disease, with mPAP of 51.6 (13.8) mmHg and pulmonary vascular resistance index of 22.5 (6.3) WU/m^2. Large proportions of the cohort had NYHA functional class IV symptoms (35%) and NT-proBNP > 1100 pg/mL (48.9%). At baseline, 34.5% of PAH patients were treatment naïve.

Relationships between right heart parameters

Right heart metrics in PAH (Table 2) were highly interrelated (Figure 3), with strong linear associations between RVFAC and RVFWS ($R^2 = 0.82$, $p < 0.001$), RV mid-transverse shortening ($R^2 = 0.54$, $p < 0.001$) and RVESA index ($R^2 = 0.54$, $p < 0.001$). In contrast, only a moderate relationship was observed between TAPSE and RVFAC ($R^2 = 0.25$, $p < 0.001$) or RVFWS ($R^2 = 0.28$, $p < 0.001$). In the longitudinal cohort, changes in RVFAC were strongly associated with changes in RVFWS ($R^2 = 0.76$, $p < 0.001$) but only moderately to TAPSE ($R^2 = 0.32$, $p < 0.001$). These relationships and their average variance term are summarized in Table 3 (using RVFAC as the independent variable) and Supporting Information: e-Table 2 (using RVFWS as the independent variable). For reference, Table 3 also includes selected RVFAC or RVFWS-RVEF relationships which have been reported in previous studies.[19,28]

Outcome analysis and guidelines imaging based criteria for risk stratification

Death or transplantation occurred in 78 individuals (35%) at 5 years. Before comprehensive outcome analysis for right heart metrics, we first assessed whether out cohort was representative usinf the REVEAL-lite score and echocardiographic metrics for risk stratification including in the ESC/ERS guidelines for PH.[3] In our cohort, a REVEAL lite score of ≥8 was associated with a 20% risk of death or transplantation at 1 year and a 50% risk at 5 years (Figure 4a). Similarly, the echocardiographic parameters of TAPSE/sPAP, RA area and pericardial effusion were strongly associated with event-free survival with thresholds suggested by the ESC/ERS guidelines consistent with a 20% risk of death or transplantation at 1 year (Figure 4b–d).

Table 4 summarized the high-risk severity thresholds (20% 1 year mortality risk) for significant echocardiographic parameters related to outcome; the table outlines the receiver operating characteristic (ROC) value, the calibrated threshold, the value of the metric derived using the mathematical relationships in Table 3 anchors to the RVFAC values and the median value of the REVEAL score 8–9. (Supporting Information: e-Table 3) presents the criterion obtained using sensitivity/specificity cross-over, Youden index

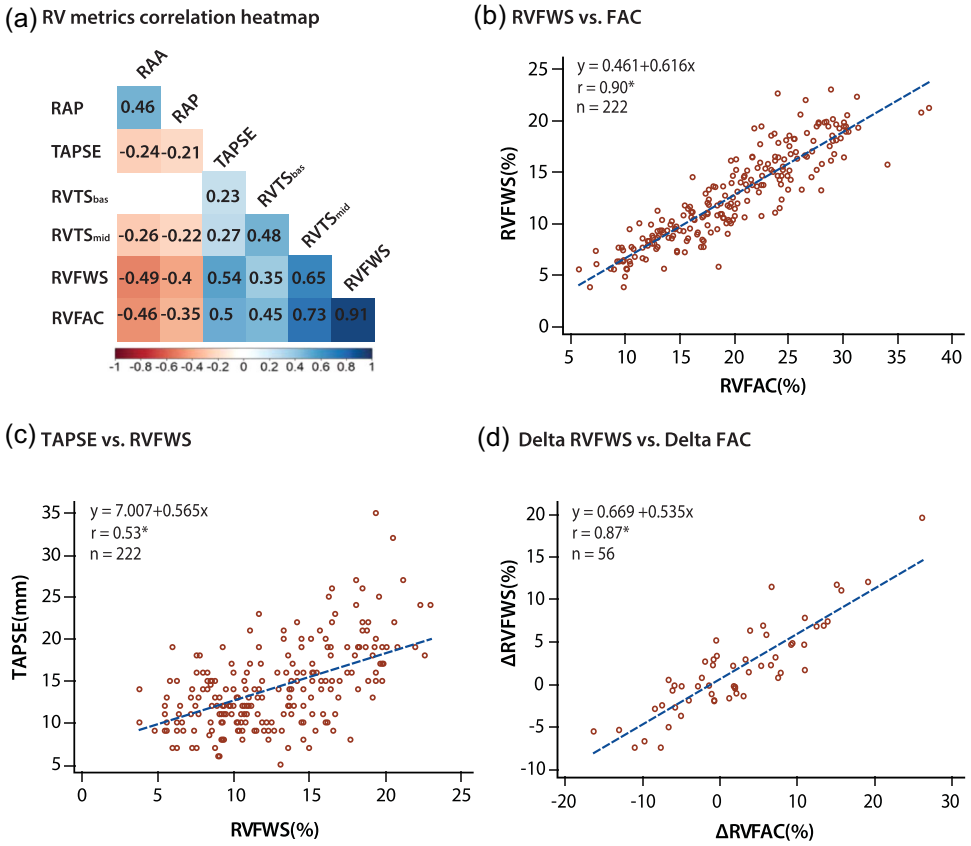

FIGURE 3 Associations and mathematical relationships between measures of right heart remodeling and function. (a) Correlation heatmap showing association between RV and RA metrics. (b) Mathematical relationship between RVFWS and RVFAC ($r = 0.90$, $p < 0.001$). (c) Mathematical relationship between TAPSE and RVFWS ($r = 0.53$, $p < 0.001$). (d) Mathematical relationship between delta RVFWS and delta RVFAC showing consistency ($r = 0.87$, $p < 0.001$). RA, right atrial; RV, right ventricular; RVFAC, RV fractional area change; RVFWS, RV free wall longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

or cost analysis (Supporting Information: e-Figure 2). In general, the classifier thresholds using cost analysis and Youden index were consistent with each other but higher than cross-over values. Example of Youden index and Cost analysis are presented in Supporting Information: Figure 2 while Kaplan–Meier curves are presented in Supporting Information: e-Figure 3. Of note, using classifier criterion won't necessarily yield a calibrated threshold to risk and therefore selection was guided by the nearest unit. Supporting Information: e-Table 4 presents the scaled hazard ratios (per SD) for comprehensive clinical and echocardiographic metrics. Among echocardiographic parameters, TAPSE was borderline significant as were antero-posterior RV dimensions and LVEF while RV antero-posterior shortening was not associated with outcome. Among laboratory data, the strongest predictors were hemoglobin concentration, NT-proBNP and glomerular filtration rate. Table 5 summarizes the thresholds obtained by our analysis with limits of reference informed by ASE and ESC/ERS guidelines, recent WASE initiative studies and selected studies.[29–31]

On multivariable Cox analysis, REVEAL lite score ≥ 8, RVFWS < 10% and the presence of anemia (Hb < 13 g/dL) were independently associated with outcome with a small improvement in AUC of 0.763 ($p < 0.001$) compared to REVEAL lite score with 0.741 ($p < 0.001$) (Supporting Information: e-Figure 4) with the upset plot showing the combination of metrics.

Incorporating parameter thresholds into the REVEAL-ECHO framework

We tested whether the thresholds identified in the current study could be applied to the recently described REVEAL-ECHO score.[23] In our cohort, the median REVEAL-ECHO score was 5 [3–6]. The REVEAL-ECHO was associated with survival and risk categories were associated with survival on Kaplan–Meier analysis (Figure 5).

TABLE 3 Weighted regression between measures of Right heart metrics versus RVFAC.

Variable (y)	Equation	$R2$[a]	Variance term
RV function			
RVFWS (%)	0.54 + 0.61 (FAC)	0.82	SD = 12.1% ŷ
$RVTS_{mid}$ (%)	−5.6 + 0.76 (FAC)	0.54	SD = 33% ŷ
TAPSE (mm)	7.06 + 0.36 (FAC)	0.25	SD = 24.7% ŷ
TAPSE (mm)	7.0 + 0.57 (RVFWS)	0.28	SD = 22% ŷ
RV size			
RVEDAi (cm^2/m^2)	29.3 – 0.46 (FAC)	0.35	SD = 18% ŷ
RVESAi (cm^2/m^2)	26.5 – 0.51 (FAC)	0.54	SD = 18.5% ŷ
RVEDAr	3.4 – 0.076 (FAC)	0.44	SD = 25% ŷ
RVESAr	5.5 – 0.13 (FAC)	0.48	SD = 28.6% ŷ
RVESA (cm2)	−4.7 + 0.94 (RVEDA)	0.97	SD = 5.4% ŷ
RA size			
RAA (cm^2)	34.3 – 0.56 (FAC)	0.19	SD = 27.5% ŷ
RAAi (cm^2/m^2)	18.1 – 0.28 (FAC)	0.16	SD = 26.7% ŷ
RAAr	3.0 −0.063 (FAC)	0.27	SD = 33.9% ŷ
RAVi (mL/m^2)	75− 1.5 (FAC)	0.17	SD = 42.6% ŷ
RAVi (mL/m^2)	−19.1 + 5.05 (RAAi)	0.92	SD = 8.7% ŷ
RVFAC (Echo)[28]	3.9 + 0.7 (RVEF CMR)	0.71	SD = 17% ŷ
RVFAC (Echo)[19]	1.8 + 0.7 (RVEF CMR)	0.46	NA
RVFWS	4.3 + 0.3 (RVEF CMR)	0.61	NA

Abbreviations: RA, right atrial; RV, right ventricular; RVFAC, RV fractional area change; RVFWS, RV free wall longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

[a]All relationships presented are significant $p < 0.001$; variance terms determined after exclusion of outlier values by Tukey method; PP indicates percent predicted value.

DISCUSSION

Our study leveraged physiological relationships and outcome analysis to identify consistent echocardiographic thresholds for risk stratification in PAH. We first quantified the relationships between right heart metrics in PAH highlighting the strong relationship between RVFAC and RVFWS. In contrast, a weaker relationship was found between TAPSE and RVFAC or RVFWS. Second, we validated in an independent cohort, the echocardiographic criteria proposed by the ESC/ESR guidelines for TAPSE/sPAP, RA area and pericardial effusion. We further proposed using calibrated outcome analysis consistent echocardiographic thresholds for risk stratification and grading the severity of right heart maladaptation. The different thresholds were also concordant with their mathematical relationship as well as with median REVEAL lite score of 8. Finally, we validated the recently described REVEAL-ECHO score using quantitative criteria identified in our study. In will be interesting to compare our outcome driven criteria with the upcoming right heart chamber quantification thresholds proposed by the ASE.

Previous studies have analyzed the relationship between right heart variables using echocardiography and CMR. In patients with precapillary PH, Kind et al. showed than mid transverse fractional shortening was more closely related to RVEF and functional status than measures of tricuspid annular displacements.[20] In a recent 3D echocardiography study on 151 consecutive patients with chronic thromboembolic disease, Tao et al.[32] highlighted the strong relationship between RVEF and RVFWS ($r = -0.70$). In multimodality CMR and echocardiographic cohorts, Evaldsson et al.[19] as well as Shiran et al.[28] have also shown the relationships between RVEF and RVFAC or RVFWS. Our study builds on these previous studies by quantifying these relationships (mean function and variance terms) in a larger cohort of patients with PAH. The fact that we observed a stronger relationship between RVFAC, RVFWS and RV

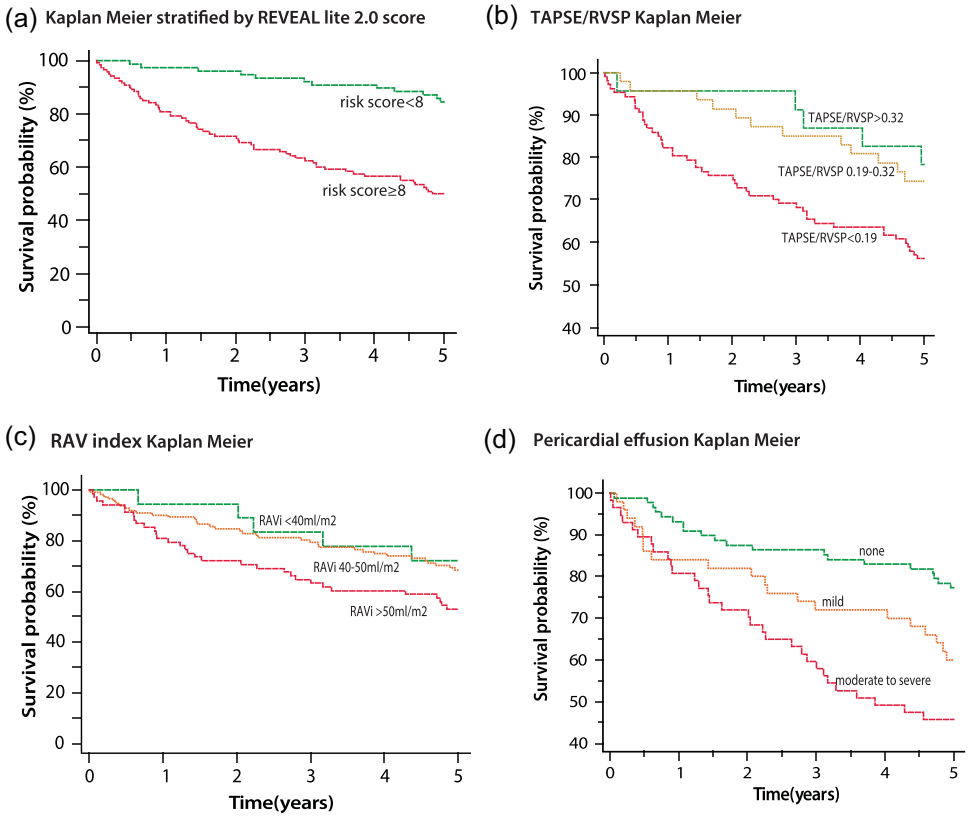

FIGURE 4 Cox regression analysis based on risk score and echocardiographic parameters (a) Kaplan–Meier stratified by Reveal lite score < 8 and ≥ 8. (b) Kaplan–Meier stratified by three groups of TAPSE/RVSP (c) Kaplan Meier stratified by three groups of RAV index. (d) Kaplan–Meir based on the presence of absence of pericardial effusion. RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

areas than with TAPSE is not surprising. In fact, as PAH progress, the right heart often dilates, a process known as heterometric adaptation.[33] The strong association between RVEF, RVFAC, RVFWS, RVTS (all fractional spatial change metrics) can also be explained in part by the dimensional dependency between 3D (volume), 2D (area) and axial (shortening) fractional changes as the right ventricle dilates. In contrast, TAPSE reflects an excursion rather than a relative change and per se will not be as strongly associated with other metrics. Our study also highlights as did the previous work of Kind et al.[26] that both transverse and longitudinal contribute to right heart function in PAH. This is consistent with the architecture of the right heart showing both longitudinal orientated subendocardial myofibers and mid-wall oriented myofibers.[17,34] The observed mathematical relationships have implications for clinical practice. For example, the presence of highly discordant values between RVFAC and RVFWS both cross-sectionally and longitudinally should prompt repeated measures to ensure no error of measurement occurred. In addition, the strong association between many variables will likely simplify the number of features needed for phenomapping and profiling. Finally, these mathematical relationships may further verify consistency in grading between metrics.

Echocardiography and CMR based markers have been recently incorporated to the 2022 ESC/ERS guidelines for the diagnosis and treatment of PH.[3] For CMR variables, the risk stratification three strata model has included for severe thresholds: RVEF (37%), RVES volume index (54 mL/m^2) and stroke volume index (<26 mL/m^2) in large part based on the study of Lewis et al.[22] For echocardiographic variables, the presence of moderate pericardial effusion, TAPSE/RVSP < 0.19 mm/mmHg and RA area (> 26cm^2) were chosen.[3] Different methods have been used in the literature to evaluate thresholds of severity including [1] pre-selection guided by reference limits, or hemodynamically guided thresholds (based on stroke volume or PVR), [2] guided by outcome analysis using a Youden index criteria or [3] based on quantile-risk assessment. In the study of Forfia et al.[11] the threshold of 18 mm for TAPSE was based on ROC analysis of stroke volume index of 29 mL/m^2. The threshold for RV relative area of Goda et al.[35] of 0.93 was based on a ROC analysis for a PVR threshold of

TABLE 4 Identification of thresholds using outcome cost-based analysis and mathematical and risk score consistency.

	Outcome based ROC	Thresholds (calibrated to 1 y survival)	Physiological Consistency (centered on RVFAC relat.)	REVEAL lite (centered on 8/9 score)
REVEAL lite	0.74 (0.04)	≥8	8.0	-
NT-proBNP	0.65 (0.04)	>1100	1031	1626
RV function				
RVFAC (%)	0.63 (0.04)	<19	19†	18
RVFWS (%)	0.64 (0.04)	<10	12	10
TAPSE/RVSP (mm/mmHg)	0.59 (0.04)	<0.19	0.18	0.16
RV base (end-diastolic)				
RVEDD base (mm)	0.62 (0.04)	>55	55	56
RVEDDi (ht) (mm/m)	0.63 (0.04)	>33	34	34
RVEDD/LVID	0.60 (0.04)	>1.5	1.5	1.5
RV mid (end-diastolic)				
RVEDD mid (mm)	0.64 (0.04)	>50	49	51
RVEDDi mid (ht) (mm/m)	0.64 (0.04)	>30	30	31
RVEDD mid/LVID	0.62 (0.04)	>1.4	1.3	1.4
RV areas (end-diastolic)				
RVEDAi (bsa)(cm^2)	0.62 (0.04)	>21	21	21
RVESAi (bsa)	0.63 (0.04)	>17	17	18
RVEDAr	0.59 (0.04)	>2	2	2.0
RVESAr	0.62 (0.04)	>3	3	3.0
RA size (maximal)				
RAA (cm^2)	0.58 (0.04)	>26	24	24
RAAi (cm^2/m^2)	0.60 (0.04)	>14	13	13
RAVi (mL/m^2)	0.60 (0.04)	>50	47	43
RAAr	0.58 (0.04)	>1.9	1.8	1.7
TR severity (grade)	0.57 (0.04)	>2	>2	2
eRAP (mmHg)	0.61 (0.04)	>8	8	15
rRAP (RHC)	0.60 (0.01)	>14	>14	11

Abbreviations: PAWP, pulmonary capillary wedge pressure; RA, right atrial; RAP, RA pressure; RHC, right heart catheterization; ROC, receiver operating characteristic; RV, right ventricular; RVFAC, RV fractional area change; RVFWS, RV free wall longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

3 Wood units. In the study of Fine et al.[6] lower quintiles of RVFWS corresponding to −15% was based on quintile risk association.[6] For RA area indexed values, the study of Raymond et al.[8] and Murata et al.[36] both used median values yielding threshold of 19 cm^2/m^2 and 12 cm^2/m^2, respectively. In the study of Kind et al.[20] an RVEF threshold of 35% was based on ROC analysis (Youden index) for the combined end-point of death or transplantation in a cohort 110 patients with incident PAH. The CMR study of Lewis et al. was comprehensive with a derivation and validation cohort and used quintile-risk associated as well as nonlinear threshold modeling; of note in their study high risk was defined using the previous 10% risk thresholds which now correspond more to the moderate range.[22]

Original to our study, we used multiple criteria to ensure a consistent grading system including calibrated outcome analysis, median REVEAL score values and

TABLE 5 Grading severity of right heart remodeling, dysfunction based on outcome analysis.

	Limits of reference based on ASE, ESC, WASE or other	Mild	Moderate	Severe
RV function				
RVFAC (%)[31]	35	28–34	19–27	<19
RVFWS (%) (absolute)[31]	20	16–19	10–15	<10
TAPSE/RVSP (mm/mmHg)	0.55	0.33–0.55	0.19–0.32	<0.19
RV base diameters				
RVEDD base (mm)[31,32]	45/40	UL-48	49–54	>55
RVEDDI (ht) (mm/m)[31]	25.7/24.5	26–28	29–33	>34
RVEDD/LVID[3]	0.8	0.9–1.1	1.2–1.4	>1.5
RV mid diameters				
RVEDD mid (mm)[31,32]	41/34	UL-43	44–49	>50
RVEDDI mid (ht) (mm/m)	23.7/21.5	UL-25	25–29	>30
RV areas				
RVEDAi (bsa) (cm^2/m^2)[31]	13.6/12.2	UL-17	18–21	>21
RVESAi (bsa) (cm^2/m^2)[31]	7.9/7.1	UL-13	14–17	>17
RVEDAr	0.9	1.0–1.3	1.4–2.0	>2.0
RVESAr	0.9	1.0–2	2.0–3.0	>3.0
RA size				
RA area (cm^2)[3,32]	18	UL-21	22–26	>26
RAVI (BSA) (mL/m^2)[32]	32/28	UL-40	40–50	>50

Abbreviations: PAWP, pulmonary capillary wedge pressure; RA, right atrial; RAP, RA pressure; RHC, right heart catheterization; RV, right ventricular; RVFAC, RV fractional area change; RVFWS, RV free wall longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

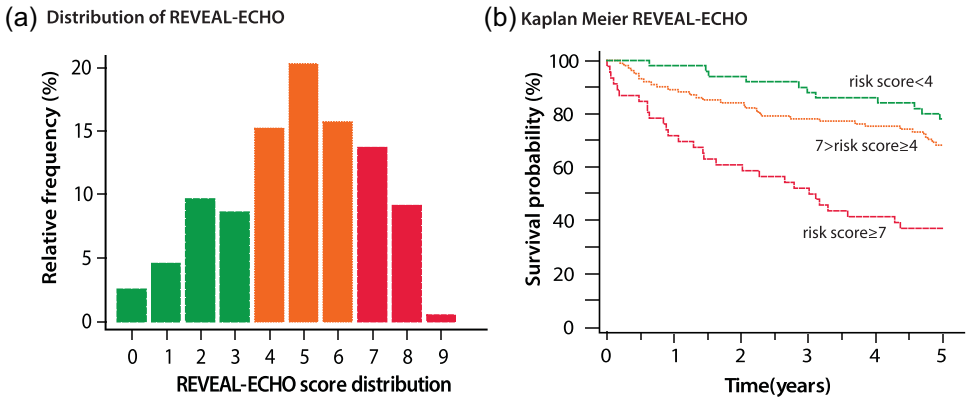

FIGURE 5 REVEAL lite 2.0 and REVEAL-ECHO Score with quantitative echocardiographic criteria. (a) Distribution of the REVEAL-ECHO score in our population. (b) Kaplan–Meier stratified by three groups of REVEAL-ECHO (risk score < 4, risk score between 4 and 7 and risk score ≥ 7.

physiological relationships. The fact that the values for RA area, TAPSE/RVSP and pericardial effusion coincided with the guideline thresholds adds confidence to the representative nature of our cohort (for the high-risk strata). In addition to these variables, other consistent thresholds for other commonly used variables especially right heart enlargement were derived. Right to left chamber indexing also provided internal scaling

measures that emerged valuable in the analysis. Using our quantitative criteria, we were also able to validate the REVEAL-ECHO score in an independent cohort. Finally, our multivariable outcome analysis highlights that right heart imaging parameters and other markers of end-organ dysfunction (anemia) can be complementary to the REVEAL lite score.

Our study also has limitations that should be mentioned. First, the selection of patients with echocardiography and RHC close by favors a higher risk population that may not be representative to a treatment naïve cohort. This has, however, allowed the selection of a cohort that would allow high risk strata analysis. Second, the measures were performed in a core laboratory setting dedicated to right heart measures and may not reflect usual clinical practice. Finally, criterion selection should always be nuanced by methodologic considerations and each laboratory should test its transferability. For example, RVFWS measured in our studies was performed at the mid-myocardial levels and includes the apical region which is likely several percentages lower than speckle tacking based values.

In conclusion, using outcome-based analysis and physiological relationships we propose a consistent grading system for right heart function and remodeling in PAH.

AUTHOR CONTRIBUTIONS

Bettia Celestin and Francois Haddad contributed to the study design. Bettia Celestin and Shadi Bagherzadeh acquired the data. Bettia Celestin, Francois Haddad, Kenzo Ichimura and Everton J. Santana analyzed the data. Bettia Celestin and Francois Haddad conceptualized the study conception, interpreted the data, and participated in drafting the manuscript. Shadi Bagherzadeh, Kenzo Ichimura, Pablo Amador Sanchez, Michael Salerno, Roham T. Zamanian, Andrew J. Sweatt, Anna R. Hemnes, Anton Vonk Noordegraaf, Tobore Tobore and Everton J. Santana revised it critically for important intellectual content. All authors approved the final version for publication and take responsibility for appropriate portions of the content.

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CONFLICTS OF INTEREST STATEMENT

Bettia Celestin, Shadi P. Bagherzadeh, Kenzo Ichimura, Everton J. Santana, Andrew John Sweatt and Pablo Amador Sanchez, have no conflicts to report. Francois Haddad has received funding from Janssen Inc. to conduct the research. Tobore Tobore is a senior director of Medical Affairs at Janssen. Anton Vonk Noordegraaf is supported by the Netherlands CardioVascular Research Initiative (CVON-2012-08 PHAEDRA, CVON-2017-10 DOLPHIN-GENESIS) and the Netherlands Organization for Scientific Research (NWO-VICI: 918.16.610). In addition, his institute received speakers money from Johnson & Johnson, MSD, Actelion, Bayer and Ferrer in the past 3 years. Finally, he served as a member of the scientific advisory board of Morphogen-X, Ferrer, Gosammer Bio Services Inc, Altavant, MSD and Johnson & Johnson. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

Ethical approval for this study was obtained from Stanford University Institutional Review Board and was conducted under the Cardio Share protocol (IRB#25673) and all patients gave written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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