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RESEARCH ARTICLE

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E-REVEAL Lite 2.0 scoring for early prediction of disease progression in pulmonary arterial hypertension

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Abstract

Risk stratification is an essential tool in the management of pulmonary arterial hypertension (PAH). These tools lack detailed echocardiographic assessment which plays a central role in clinical risk assessment in PAH. Thus, we aimed at assessing whether adding echocardiography-driven data to REVEAL Lite 2.0 (Registry to Evaluate Early and Long-Term PAH Disease Management) improves the assessment of risk stratification in PAH. A retrospective analysis of 134 consecutive patients between January 2016 and December 2019 was done. We identified patients who experienced a disease progression "event" defined by the initiation of intravenous (IV) or parenteral prostacyclin, transplant referral, or death due to PAH. All other PAH patients who did not experience an "event" during this period were included in the analysis as controls. Echocardiography and REVEAL Lite 2.0 were collected from 4 to 8 months before the event and compared with the control group to predict the risk of a disease progression event. One hundred and ten patients were included in the final analysis with 22 experiencing a disease progression event and 88 remaining stable during the study period. Different echocardiographic parameters were combined with REVEAL Lite 2.0 scores in both groups. The combination of REVEAL Lite 2.0 and the left ventricular end-diastolic (LVED) eccentricity index (as a continuous variable) had the highest area under the curve (AUC) of 0.87, which approached a significant difference with that of the REVEAL Lite 2.0 alone ($p = 0.052$). An additional multivariable regression model that included REVEAL Lite 2.0, LVED eccentricity index as a continuous variable, and RAP achieved the best AUC at 0.88 (0.80, 0.96), which was significantly different from that of the REVEAL Lite 2.0 alone (AUC 0.77 [0.66, 0.88]; $p = 0.049$). These results suggest that combining different echocardiographic parameters to REVEAL Lite 2.0 provides more statistically accurate risk predictions compared to REVEAL Lite 2.0 alone. A combination of

Sandeep Sahay and Jiken Bhatt contributed equally to this study.

LVED eccentricity index with REVEAL Lite 2.0 achieved the best AUC in predicting the event in our cohort.

KEYWORDS
echocardiography, pulmonary arterial hypertension, REVEAL, risk score, survival

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronically progressive disease that leads to right heart failure and premature death.[1] Despite advances in PAH treatment options, survival has remained suboptimal.[2] The 2015 ESC/ERS (European Society of Cardiology/European Respiratory Society) guidelines recommended a flexible approach to PAH patient risk assessment with multidimensional stratification using modifiable clinical, functional, exercise, biochemical, echocardiographic, and hemodynamic variables with known prognostic significance.[1] Several PAH risk assessment tools have been developed and validated from large registry populations to facilitate a more formal evaluation of risk. The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk calculator was developed in 2010 to estimate PAH mortality risk based on up to 12 variables.[3] This calculator was recently updated (REVEAL 2.0) to include an additional variable and to revise cutoffs for seven variables.[4] REVEAL Lite 2.0, an abridged version of REVEAL 2.0, was recently published using a smaller number of only noninvasively derived variables.[5] Three additional PAH risk assessment methods, the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) method,[6] the French Pulmonary Hypertension Registry (FPHR) method,[7] and the Swedish PAH registry (SPAHR)[8] are also available and incorporate data from up to six variables, using thresholds suggested by the ESC/ERS pulmonary hypertension guidelines.[1] Most of these risk scoring methods have shown that achieving PAH low-risk status is associated with better survival.[9]

REVEAL Lite 2.0 includes six noninvasive variables: functional class (FC), vital signs (systolic BP [SBP] and heart rate), 6-min walk distance (6MWD), brain natriuretic peptide (BNP)/N-terminal prohormone of BNP (NT-proBNP), and renal insufficiency (by estimated glomerular filtration rate [eGFR]).[5] REVEAL Lite 2.0 offers some advantages by including only noninvasive parameters but has a limitation that the score is only predictive for 1-year mortality risk. In chronic progressive diseases like PAH, regular monitoring is paramount to identifying early signs of clinical worsening. Thus, it is imperative to identify disease progression or clinical worsening early during regular clinic evaluations. However, current PAH risk assessment tools utilize limited information from conventional transthoracic echocardiography (TTE) for a formal risk assessment[10] and are limited to the presence of pericardial effusion.[1,3] Echocardiography is a noninvasive tool that can provide valuable information about right ventricular (RV) structure and function which may be an early predictor of disease progression. In this study, we analyzed several echocardiographic parameters in conjunction with the REVEAL Lite 2.0 assessment tool. Our objective was to see if a combination of detailed cardiac imaging parameters using echocardiography with a traditional risk assessment tool (REVEAL Lite 2.0) would have additive prognostic value in predicting an early decline in PAH.

METHODS

We retrospectively analyzed data from our comprehensive PAH center at our tertiary level accredited pulmonary hypertension comprehensive care center between January 2016 and December 2019 for consecutive Group 1 PAH patients seen in our clinic. The study was approved by the hospital's Institutional Review Board (IRB). PAH patients who were already getting worse clinically or undergoing transplant evaluation at the beginning of this period were excluded. During this period, we identified patients who experienced a disease progression event ("event") defined by the initiation of intravenous (IV) or parenteral prostacyclin, transplant referral, or death due to PAH. All other PAH patients who did not experience an "event" during this period were included in the analysis as the "no event" group (Figure 1). Patients being treated with parenteral prostacyclins at the beginning of the study period whose treatment doses were not changed during the study period were included in the "no event" group. All patients had a hemodynamically confirmed diagnosis of PAH as defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg with a mean wedge pressure or left ventricular (LV) EDP of $\leq$ 15 mmHg with a pulmonary vascular resistance (PVR) $\geq$ 3 Wood units.[11] Data collection for this study was performed on patients

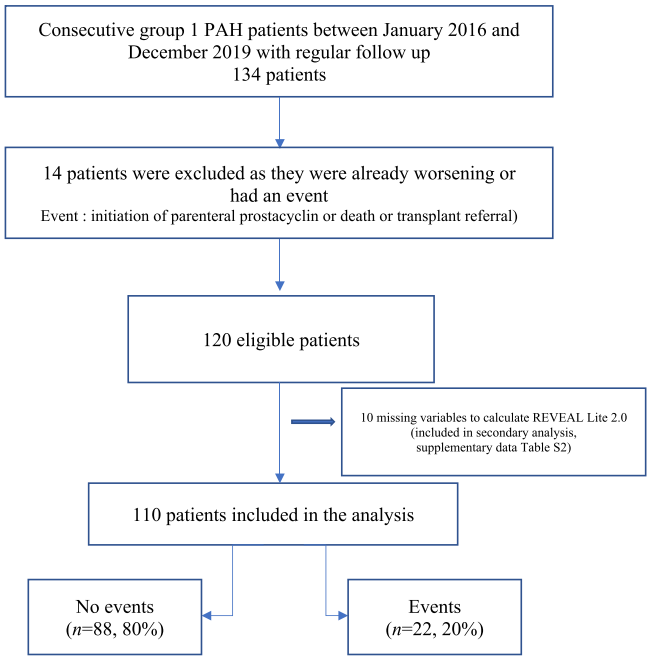

FIGURE 1 Flowchart of the study cohort

treated before the new hemodynamic definition by the Sixth World Symposium on Pulmonary Hypertension (WSPH).[12] The clinical data collected included variables needed for the REVEAL Lite 2.0 score calculation along with other relevant demographic, treatment-related, and laboratory data.

Definition of the "event"

We selected three major considerations to define the "event" for this analysis. At our center, initiation of parenteral prostacyclin is done as an in-patient, as a result, hospitalization due to worsening PAH resulting in the initiation of parenteral prostacyclin was considered as a worsening event for this analysis. If hospitalization did not result in the initiation of parenteral prostacyclin, we did not include it as an event regardless of the cause of hospitalization. We considered transplant referral as opposed to transplantation or transplant listing, as transplant referral is the earliest opportunity to identify poor responses to maximal medical therapy. Last, death due to PAH was the additional endpoint included to define an event. At our institution, it is very unlikely that a patient would need inpatient admission due to worsening PAH needing intravenous diuresis or inotropic support without initiation of parenteral prostacyclin. Thus, we considered transplant referral or the initiation of parenteral prostacyclin as one of the endpoints for this analysis.

Echocardiograms

In the event group, the echocardiogram from four to eight months before the event was reviewed (when these patients were clinically stable) to observe if any early changes in echocardiography could predict decline four to eight months later. If no echocardiogram was found between four to eight months before the "event", the patient was excluded from the analysis. In the "no event" group, we identified the most recent clinic visit at the same time, we then selected the echocardiogram 4–8 months before the clinic visit for this analysis.

Standard resting echocardiographic views were obtained including Doppler and tissue Doppler imaging. All measurements were performed according to the American Society of Echocardiography recommendations[13] using the Digisonics Cardiovascular Information System. Tricuspid annular plane systolic excursion (TAPSE) was obtained using M-Mode imaging of the RV free wall in systole and diastole and RV fractional area change was made using apical views in end-systole and end-diastole. RV peak systolic velocity (S') was made using Tissue Doppler Imaging. LV eccentricity index was obtained using short-axis views of the mid-LV cavity in both systole and diastole. All echocardiograms were reviewed by two board-certified cardiologists who were blinded to the clinical status of the patient. If there was a disagreement, then a third cardiologist reviewed the images. We collected all relevant structural and functional, atrial, and ventricular information along with estimated hemodynamic information available by echocardiography.

Statistical methods

Patient characteristics, right heart catheterization (RHC), and echocardiographic parameters were reported as frequencies and proportions for categorical variables and as median and interquartile range (IQR) for continuous variables. Differences between groups were determined by χ^2 or Fisher's exact tests for categorical variables and Kruskal–Wallis test for continuous variables as appropriate. The optimal thresholds of continuous covariates such as end-systolic eccentricity index and TAPSE in discriminating the composite event were determined by the receiver operating characteristic (ROC) curve analysis with a Youden index.[14] Logistic regression analysis was used to determine the characteristics associated with the composite outcomes (of death, transplant referral, and parenteral medication initiation). Discrimination power of the different variables including the REVEAL Lite 2.0 score was evaluated using the area under the

ROC curve (AUC). The improvement in the diagnostic performance between the REVEAL Lite 2.0 score alone and the combination of REVEAL Lite 2.0 score plus one of the select echocardiography parameters was determined using the difference in the AUCs, Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI) indexes. Taking into account the small number of events, additional multivariable models were explored with variable selection based on the clinical importance and also by the least absolute shrinkage and selection operator (Lasso) method with the cross-validation (CV) selection option.[15,16] Briefly, the Lasso program was run to evaluate possible model sets from all variables evaluated in the univariate analysis. The program suggested good initial models which included the variables with a high probability of being a risk factor for having the outcome events. The Likelihood Ratio (LR) test was used to further reduce the model subsets. The selected covariates were reviewed by experienced clinicians on the research team to ensure biological plausibility. Missing data were assessed for missing completely at random (MCAR) and covariate-dependent missingness (CDM) using Little's χ^2 test.[17] Additional analysis was performed in the entire cohort of patients that also included 10 patients whose REVEAL Lite 2.0 information was missing ($N = 120$, 95 in the no event group, and 25 in the event group). Differences between groups in the demographic, echocardiographic, and RHC parameters were reported. To evaluate the reliability of the echocardiography readings, echocardiography data of a subset of patients ($n = 10$), were randomly selected from the studied cohort and were read by a second blinded physician who was board certified by the American Society of Echocardiography. Interobserver reliability was assessed using the intraclass correlation coefficient (95% CI) and F-statistic p values.[18] All the analyses were performed on Stata version 17.0 (StataCorp LLC). A $p < .05$ was considered statistically significant.

RESULTS

There were 134 patients identified who were regularly followed in the Houston Methodist Hospital PAH clinic during the study period. Fourteen patients were excluded as they were already deteriorating clinically at the beginning of the study period. Of the remaining 120 patients, 10 were missing one or more of the parameters needed to calculate the REVEAL Lite 2.0 score and were excluded (Figure 1). Of the 110 patients included in the analysis, no "events" occurred in 88 (80%) patients, and "events" were observed in 22 (20%). The median age of the whole cohort was 51 years (IQR 40, 61) with 96 (87.3%) females. The baseline demographic and clinical characteristics are shown in Table 1. Most of the patients were on dual or triple combination treatment regimens. Based on the patients' REVEAL Lite 2.0 score, in the "no event" group, 63 (71.6%) were low risk (Score 1–5), 18 (20.5%) were intermediate risk (Score 6–7) and 7 (8.0%) were high risk (Score ≥ 8). In the "event" group, 7 (31.8%) were low risk, 6 (27.3%) were intermediate risk, and 9 (40.9%) were high risk. Echocardiograms were reviewed for the 110 included patients. The univariate analysis of the echocardiographic parameters for the composite endpoints of death, transplant referral, or parenteral prostacyclin is shown in Table 2. A variety of echocardiographic parameters as highlighted in Table 2 had prognostic value in predicting disease progression events in PAH. Qualitatively measured moderate to severely depressed RV function and severely enlarged RV size was significantly predictive of a disease progression event. Echocardiographic parameters like RV function severity, LV end-systolic volume (LVESV), LVESV index, end-systolic/diastolic eccentricity index (both as continuous and categorical variables) were significantly associated with predict events. Many of the well-established parameters like estimated right atrial pressure (RAP) and TAPSE were also significantly associated with the occurrence of events and are shown in Table 2. Pericardial effusion, however, was not significantly associated with a predictive event (Table 2). Median REVEAL Lite 2.0 score was significantly higher in the event group (6.5 [5.0, 8.0]) compared to the no event group (4.0 [3.0, 6.0]) ($p < 0.001$).

Pulmonary function testing data in the entire studied cohort ($N = 110$) were presented in Table S1. The sensitivity analysis in the entire cohort that included 10 patients whose REVEAL Lite 2.0 information was missing found that several echocardiographic parameters were associated with the occurrence of an event in this group as well (Table S2).

Multivariable analysis: REVEAL Lite 2.0 and echocardiographic parameters in predicting the disease progression event

Table 3 shows the area under the curve (AUC) with a combination of the REVEAL Lite 2.0 score and specific echocardiographic parameters. REVEAL Lite 2.0 with LV end-diastolic (LVED) eccentricity index (as a continuous variable) had the highest AUC of 0.87, which had a trend toward statistically significant compared with REVEAL Lite 2.0 alone ($p = 0.052$). The combination of the LVED eccentricity index as a categorical variable with the cut-off value of ≥ 1.2 and

TABLE 1 Demographic and clinical characteristics of the final cohort of patients

	Total ($N = 110$)	No event ($n = 88$)	Event ($n = 22$)	Unadjusted OR (95% CI)	p values
Demographic and clinical characteristics					
Age at time of echo, median (IQR)	51 (40, 61)	52 (41, 61)	44.5 (37, 55)	0.98 (0.95, 1.01)	0.18
Gender					
Female	96 (87.3)	78 (88.6)	18 (81.8)	(reference)	
Male	14 (12.7)	10 (11.4)	4 (18.2)	1.73 (0.49, 6.16)	0.4
Race/ethnicity					
White	47 (42.7)	38 (43.2)	9 (40.9)	(reference)	
Black	25 (22.7)	20 (22.7)	5 (22.7)	1.06 (0.31, 3.58)	0.93
Hispanic	31 (28.2)	24 (27.3)	7 (31.8)	1.23 (0.40, 3.74)	0.71
Asian	7 (6.4)	6 (6.8)	1 (4.5)	0.70 (0.08, 6.60)	0.76
Hispanic					
No	79 (71.8)	64 (72.7)	15 (68.2)	(reference)	
Yes	31 (28.2)	24 (27.3)	7 (31.8)	1.24 (0.45, 3.42)	0.67
Pulse (b/min), median (IQR)	76.0 (70.0, 85.0)	75.0 (69.5, 85.0)	80.5 (71.0, 97.0)	1.02 (0.99, 1.06)	0.18
Systolic blood pressure (mmHg), median (IQR)	114.5 (105.0, 127.0)	115.0 (105.5, 127.5)	112.5 (102.0, 124.0)	1.00 (0.98, 1.03)	0.86
Diastolic blood pressure (mmHg), median (IQR)	65.0 (57.0, 73.0)	65.0 (57.0, 73.5)	64.0 (57.0, 73.0)	1.00 (0.98, 1.02)	0.69
WHO classification					
I	5 (4.5)	5 (5.7)	0 (0.0)	-	-
II	57 (51.8)	47 (53.4)	10 (45.5)	(reference)	
III	46 (41.8)	35 (39.8)	11 (50.0)	1.48 (0.56, 3.86)	0.43
IV	2 (1.8)	1 (1.1)	1 (4.5)	4.70 (0.27, 81.63)	0.29
WHO classification					
I–II	62 (56.4)	52 (59.1)	10 (45.5)	(reference)	
III–IV	48 (43.6)	36 (40.9)	12 (54.5)	1.73 (0.68, 4.44)	0.25
WHO Group 1 details					
Idiopathic	38 (34.5)	32 (36.4)	6 (27.3)	(reference)	
Drug induced	6 (5.5)	6 (6.8)	0 (0.0)	-	-
Connective tissue disease	47 (42.7)	38 (43.2)	9 (40.9)	1.26 (0.41, 3.93)	0.69
Pulmonary veno-occlusive disease	1 (0.9)	0 (0.0)	1 (4.5)	-	-
Congenital	8 (7.3)	5 (5.7)	3 (13.6)	3.20 (0.60, 17.10)	0.17
Portopulmoanry hypertension	2 (1.8)	1 (1.1)	1 (4.5)	5.33 (0.29, 97.48)	0.26
Familial/heritable	8 (7.3)	6 (6.8)	2 (9.1)	1.78 (0.29, 11.00)	0.54
WHO Group 1 details					
Idiopathic	38 (34.5)	32 (36.4)	6 (27.3)	(reference)	
Connective tissue disease	47 (42.7)	38 (43.2)	9 (40.9)	1.26 (0.41, 3.93)	0.69

(Continues)

TABLE 1 (Continued)

	Total ($N = 110$)	No event ($n = 88$)	Event ($n = 22$)	Unadjusted OR (95% CI)	p values
Other	25 (22.7)	18 (20.5)	7 (31.8)	2.07 (0.60, 7.12)	0.25
Six-min walk distance (m), median (IQR)	400.0 (337.0, 460.0)	407.5 (341.5, 472.5)	383.0 (280.0, 419.0)	1.00 (0.99, 1.00)	0.09
B-type natriuretic peptide (BNP, pg/ml), median (IQR)	42.5 (20.0, 124.0)	33.0 (17.5, 68.5)	136.0 (87.0, 250.0)	1.01 (1.00, 1.01)	<0.001
Creatinine (mg/dl), median (IQR)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.9 (0.7, 1.0)	0.99 (0.61, 1.62)	0.98
MDRD eGFR (ml/min/1.73 m^2), median (IQR)	85.0 (68.0, 90.0)	85.0 (68.5, 90.0)	78.5 (67.0, 90.0)	0.99 (0.97, 1.01)	0.41
Time from echo to event (days), median (IQR)	-	-	190.5 (146.0, 235.0)	-	-
REVEAL Lite 2.0 score, median (IQR)	5.0 (3.0, 6.0)	4.0 (3.0, 6.0)	6.5 (5.0, 8.0)	1.63 (1.27, 2.10)	<0.001
REVEAL Lite 2.0 score					
1–5	70 (63.6)	63 (71.6)	7 (31.8)	(reference)	
6–7	24 (21.8)	18 (20.5)	6 (27.3)	3.00 (0.89, 10.06)	0.08
≥8	16 (14.5)	7 (8.0)	9 (40.9)	11.57 (3.29, 40.76)	<0.001
Treatment					
Monotherapy	5 (4.5)	4 (4.5)	1 (4.5)	1.00 (0.11, 9.42)	1.00
Dual therapy	55 (50.0)	44 (50.0)	11 (50.0)	1.00 (0.39, 2.55)	1.00
Triple therapy	47 (42.7)	39 (44.3)	8 (36.4)	0.72 (0.27, 1.88)	0.50
Treatment specified					
PDE5i only	4 (3.7)	3 (3.4)	1 (5.0)	0.42 (0.16, 1.11)	0.08
ERA only	1 (0.9)	1 (1.1)	0 (0.0)	0.42 (0.14, 1.29)	0.13
PDE5i + ERA	27 (25.2)	24 (27.6)	3 (15.0)	0.42 (0.11, 1.55)	0.19
PDE5i + PCA	9 (8.4)	7 (8.0)	2 (10.0)	1.16 (0.22, 6.00)	0.86
ERA + PCA	9 (8.4)	5 (5.7)	4 (20.0)	3.69 (0.90, 15.11)	0.07
ERA + cGC	8 (7.5)	7 (8.0)	1 (5.0)	0.55 (0.06, 4.73)	0.59
PCA + cGC	2 (1.9)	1 (1.1)	1 (5.0)	4.14 (0.25, 68.98)	0.32
PDE5i + ERA + PCA	37 (34.6)	31 (35.6)	6 (30.0)	0.69 (0.24, 1.94)	0.48
ERA + PCA + sGC	10 (9.3)	8 (9.2)	2 (10.0)	1.00 (0.20, 5.08)	1.00

Note: Values are in number and % unless otherwise indicated.

Abbreviations: ERA, endothelin receptor antagonists; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; PCA, prostacyclin analog; PDE5i, phosphodiesterase-5 inhibitors; sGC, soluble guanylate cyclase; WHO, World Health Organization.

REVEAL Lite 2.0 had an AUC of 0.85 (0.77, 0.94), which was a significantly better model ($p = 0.042$) compared with REVEAL Lite 2.0 alone. LV end-systolic (LVES) eccentricity index and REVEAL Lite 2.0 as a continuous variable showed an AUC of 0.83 (0.74, 0.92) but the p value was not statistically significant ($p = 0.08$) when compared to REVEAL Lite 2.0 alone.

Exploratory analyses were performed to assess the AUC of additional models, which combined the REVEAL Lite 2.0, LVED eccentricity index/LVES eccentricity index, and other well-established echocardiographic parameters like TAPSE and RAP. Pairwise comparisons of the AUCs of those additional models and that of the REVEAL Lite 2.0 alone are presented in Table 4 (A–D). The REVEAL Lite 2.0 alone (Model 1) was significantly

TABLE 2 Univariate analysis of the echocardiographic parameters for the composite end point of death or transplant referral or parenteral prostacyclin use among the event group and no event group

Echocardiographic parameters	Total ($N = 110$)	No event ($n = 88$)	Event ($n = 22$)	Unadjusted OR (95% CI)	p values
LVEF biplane, median (IQR)	64.5 (61.0, 68.0)	64.0 (61.0, 67.0)	66.0 (62.0, 71.0)	1.04 (0.97, 1.12)	0.24
LVEF visual, median (IQR)	60.0 (60.0, 65.0)	60.0 (60.0, 65.0)	65.0 (60.0, 70.0)	1.08 (0.98, 1.20)	0.12
RV function					
Normal/lower normal	31 (28.2)	28 (31.8)	3 (13.6)	(reference)	
RV dysfunction					
Mild/mild-moderate	32 (29.1)	30 (34.1)	2 (9.1)	0.62 (0.10, 4.00)	0.62
Moderate/moderate-severe	28 (25.5)	20 (22.7)	8 (36.4)	3.73 (0.88, 15.85)	0.07
Severe	19 (17.3)	10 (11.4)	9 (40.9)	8.40 (1.89, 37.38)	0.01
RV size					
Normal/lower normal	24 (21.8)	22 (25.0)	2 (9.1)	(reference)	
Mild/mild-moderate	17 (15.5)	16 (18.2)	1 (4.5)	0.69 (0.06, 8.25)	0.77
Moderate/moderate-severe	32 (29.1)	27 (30.7)	5 (22.7)	2.04 (0.36, 11.53)	0.42
Severe	37 (33.6)	23 (26.1)	14 (63.6)	6.70 (1.36, 32.92)	0.02
LA volume index (ml/m^2), median (IQR)	28.0 (23.0, 33.0)	29.0 (23.0, 33.0)	23.0 (17.0, 32.0)	0.95 (0.89, 1.01)	0.07
RA volume index (ml/m^2), median (IQR)	37.0 (28.0, 47.0)	34.0 (27.5, 43.0)	54.0 (39.0, 66.0)	1.04 (1.01, 1.06)	0.002
LVSV by LVOT (ml), median (IQR)	64.0 (55.0, 75.0)	65.0 (57.0, 76.0)	55.5 (42.0, 73.0)	0.95 (0.92, 0.99)	0.01
LVSV index (ml/m^2), median (IQR)	35.9 (30.5, 40.0)	36.9 (32.2, 41.3)	30.6 (25.0, 38.5)	0.91 (0.85, 0.97)	0.004
End diastolic eccentricity index, median (IQR)	1.1 (1.0, 1.2)	1.0 (0.9, 1.1)	1.3 (1.2, 1.7)	108.94 (12.82, 925.89)	<0.001
End diastolic eccentricity index ≥ 1.2	30 (27.8)	14 (16.3)	16 (72.7)	13.71 (4.57, 41.16)	<0.001
End systolic eccentricity index, median (IQR)	1.2 (1.0, 1.4)	1.1 (1.0, 1.4)	1.4 (1.2, 2.6)	4.75 (2.02, 11.18)	<0.001
End systolic eccentricity index ≥ 1.2	52 (47.7)	34 (39.1)	18 (81.8)	7.01 (2.19, 22.51)	0.001
MV inflow E (cm/s), median (IQR)	70.5 (57.5, 85.5)	71.0 (59.0, 85.5)	67.5 (54.0, 84.5)	0.99 (0.96, 1.02)	0.48
W sign					
No	74 (67.9)	62 (71.3)	12 (54.5)	(reference)	
Yes	35 (32.1)	25 (28.7)	10 (45.5)	2.07 (0.79, 5.39)	0.14
MV lateral e', median (IQR)	10.5 (8.0, 12.0)	10.5 (7.8, 12.0)	11.0 (9.9, 13.1)	1.16 (0.97, 1.37)	0.10
MV septal e', median (IQR)	6.0 (4.6, 7.5)	6.0 (4.7, 7.5)	5.9 (4.5, 6.7)	0.90 (0.71, 1.14)	0.39
RV S', median (IQR)	10.5 (8.9, 12.0)	10.9 (9.4, 12.4)	8.9 (8.1, 10.5)	0.68 (0.53, 0.88)	0.003
TAPSE (mm), median (IQR)	19.0 (16.0, 22.0)	20.0 (17.0, 23.0)	16.0 (15.0, 18.0)	0.78 (0.67, 0.90)	0.001
TAPSE < 18 mm	40 (39.6)	26 (32.5)	14 (66.7)	4.15 (1.50, 11.53)	0.01
TR velocity (m/s), median (IQR)	3.8 (3.4, 4.2)	3.7 (3.4, 4.0)	4.0 (3.7, 4.5)	2.84 (1.17, 6.91)	0.02
RAP (mmHg), median (IQR)	5.0 (5.0, 10.0)	5.0 (5.0, 10.0)	10.0 (10.0, 15.0)	1.25 (1.11, 1.41)	<0.001
PASP (mmHg), median (IQR)	67.8 (54.0, 79.0)	65.8 (53.6, 74.0)	77.8 (61.8, 91.0)	1.04 (1.01, 1.07)	0.01
RV FAC (%), median (IQR)	29.0 (22.0, 34.0)	30.0 (24.0, 35.0)	24.0 (15.0, 30.0)	0.93 (0.88, 0.98)	0.01

(Continues)

TABLE 2 (Continued)

Echocardiographic parameters	Total ($N = 110$)	No event ($n = 88$)	Event ($n = 22$)	Unadjusted OR (95% CI)	p values
RV basal dimension (mm), median (IQR)	4.4 (4.1, 5.1)	4.4 (4.1, 4.8)	5.3 (4.7, 6.2)	2.93 (1.65, 5.21)	<0.001
LV basal dimension (mm), median (IQR)	4.2 (3.9, 4.4)	4.2 (3.9, 4.5)	4.2 (3.8, 4.4)	0.50 (0.22, 1.14)	0.10
RV:LV dimension, median (IQR)	1.1 (0.9, 1.3)	1.1 (0.9, 1.2)	1.3 (1.1, 1.6)	16.00 (2.87, 89.02)	0.002
Pericardial effusion					
None	80 (72.7)	65 (73.9)	15 (68.2)	(reference)	
Trace/small	28 (25.5)	22 (25.0)	6 (27.3)	1.18 (0.41, 3.42)	0.76
Moderate	2 (1.8)	1 (1.1)	1 (4.5)	4.33 (0.26, 73.29)	0.31
PCWP (mmHg) Nagueh formula, median (IQR)	10.4 (8.6, 13.0)	10.6 (8.7, 13.1)	9.7 (8.2, 10.9)	0.83 (0.69, 1.02)	0.07

Note: Values are in number and % unless otherwise indicated.

Abbreviations: 95% CI, 95% confidence interval; AUC, area under the ROC curve; FAC, fractional area change; IQR, interquartile range; LV, left ventricular; LVEF, ventricular ejection fraction; LVOT, left ventricular outflow tract; LVSV, left ventricular stroke volume; MV, mitral valve; OR, odds ratio; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid valve.

associated with the having an event (odds ratio [OR] 1.63; 95% confidence interval [CI] 1.27, 2.10; $p < 0.001$) and had an AUC of 0.77 (0.66, 0.88). The combination of LVES eccentricity index and TAPSE as continuous and categorical variables along with RAP (model 2) achieved an AUC of 0.81 (0.69, 0.92) and 0.81 (0.70, 0.91), respectively (Table 4 (A and C)). Similarly, AUC obtained using LVED eccentricity index and TAPSE as continuous and categorical variables with RAP were 0.85 (0.75, 0.96) and 0.82 (0.70, 0.93), respectively (Table 4 (B and D)). Model 3 used a combination of echocardiographic parameters with REVEAL Lite 2.0. LVED eccentricity index as a continuous variable with REVEAL Lite 2.0 achieved the best AUC 0.88 (0.80, 0.96) (Table 4 (B)) against other echocardiographic parameters. Compared with the REVEAL Lite 2.0 alone, only Model 3 which included the continuous LVED eccentricity index had a significant increase in the AUC ($p = 0.049$). Notably, only this model 3 had a significant increase in the NRI 0.717 (95% CI 0.102, 1.348) and IDI 0.155 (95% CI 0.007, 0.387) (Table 3).

The missing data proportion found for covariates included in the models were 0.9% (LV stroke volume index), 0.9% (LVES eccentricity index), and 1.8% (LVED eccentricity index). Little's χ^2 test for MCAR and CDM had nonsignificant p-values (0.44 and 0.97, respectively), which suggests that the missing values could be completely at random and had no influence on the outcome.

ROC curves

ROC curves were obtained for each of the models (Figures 2a–d) to show the discriminatory ability in predicting composite endpoints of disease progression. LVED as a continuous variable in combination with REVEAL Lite 2.0 achieved the best and most parsimonious AUC of 0.88.

Interobserver variability analysis

Interobserver variability analysis on 10 randomly selected patients from our cohort (five from each event and control group) was performed. Two board-certified cardiologists blinded to the patient's clinical status interpreted the echocardiograms. We found excellent agreement in interpretation of LVED eccentricity index and LVES eccentricity index of 0.95 (0.52, 0.99, $p < 0.001$) and 0.88 (0.50, 0.97), respectively, as well as other echocardiographic parameters (Table S3).

DISCUSSION

Multiparametric risk assessment in PAH is now strongly recommended by most guidelines.[1,19] Current risk assessment tools recommend adjusting for treatment strategy to achieve a low-risk profile to minimize the risk

TABLE 3 Multivariable analysis using echocardiographic parameters and REVEAL Lite 2.0 in predicting the disease progression event

Model #	Models' covariates	Adjusted OR* (95% CI)	*p* value	AUC (95% CI)	AUC Improvement**		Reclassification improvement (NRI) index**	Discrimination improvement (IDI) index**
					AUC delta***	*p* value		
1	REVEAL Lite 2.0 score alone	1.63 (1.27, 2.10)	<0.001	0.77 (0.66, 0.88)	–	–	–	–
2	REVEAL Lite 2.0 score + LV stroke volume index			0.81 (0.73, 0.91)	0.04	0.25	0.423 (−0.201, 1.028)	0.040 (−0.010, 0.181)
	REVEAL	1.58 (1.22, 2.05)	0.001					
	LV stroke volume index	0.93 (0.87, 0.99)	0.03					
3	REVEAL Lite 2.0 score + LV ES eccentricity index (continuous)			0.83 (0.74, 0.92)	0.06	0.08	0.220 (−0.281, 0.809)	0.051 (−0.014, 0.224)
	REVEAL	1.49 (1.14, 1.94)	0.003					
	LV ES eccentricity index	3.44 (1.31, 9.02)	0.01					
4	REVEAL Lite 2.0 score + LV ES eccentricity index ≥1.2			0.83 (0.74, 0.92)	0.06	0.09	0.855 (0.371, 1.212)	0.041 (−0.011, 0.165)
	REVEAL	1.53 (1.18, 1.98)	0.001					
	LV ES eccentricity index ≥1.2	4.92 (1.44, 16.77)	0.01					
5	REVEAL Lite 2.0 score + LV ED eccentricity index (continuous)			0.87 (0.79, 0.95)	0.10	0.052	0.717 (0.102, 1.348)	0.155 (0.007, 0.387)
	REVEAL	1.37 (1.04, 1.82)	0.03					
	LV ED eccentricity index	49.51 (5.81, 422.16)	<0.001					
6	REVEAL Lite 2.0 score + LV ED eccentricity index ≥1.2			0.85 (0.77, 0.94)	0.08	0.049	1.129 (0.454, 1.500)	0.106 (−0.007, 0.315)
	REVEAL	1.35 (1.02, 1.80)	0.04					
	LV ED eccentricity index ≥1.2	8.05 (2.46, 26.34)	0.001					
7	REVEAL Lite 2.0 score + RV basal diameter			0.80 (0.70, 0.90)	0.03	0.35	0.903 (−0.072, 1.215)	0.043 (−0.019, 0.182)
	REVEAL	1.47 (1.12, 1.93)	0.01					
	RV basal diameter	2.09 (1.12, 3.91)	0.02					
8	REVEAL Lite 2.0 score + RV/LV dimension			0.79 (0.70, 0.89)	0.02	0.38	0.295 (−0.390, 0.914)	0.033 (−0.023, 0.177)
	REVEAL	1.44 (1.10, 1.89)	0.01					
	RV/LV dimension index	6.06 (1.01, 36.46)	0.049					

(Continues)

TABLE 3 (Continued)

Model #	Models' covariates	Adjusted OR* (95% CI)	*p* value	AUC (95% CI)	AUC Improvement**		Reclassification improvement (NRI) index**	Discrimination improvement (IDI) index**
					AUC delta***	*p* value		
9	REVEAL Lite 2.0 score + estimated RA pressure			0.81 (0.70, 0.91)	0.04	0.37	0.347 (−0.427, 0.905)	0.008 (−0.018, 0.121)
	REVEAL	1.70 (1.30, 2.21)	<0.001					
	Estimated RA pressure	1.10 (0.98, 1.23)	0.11					
10	REVEAL Lite 2.0 score + RA volume index			0.81 (0.72, 0.91)	0.04	0.10	0.568 (−0.474, 1.128)	0.013 (−0.021, 0.148)
	REVEAL	1.53 (1.17, 1.99)	0.002					
	RA volume index	1.02 (1.00, 1.05)	0.10					
11	REVEAL Lite 2.0 score + TAPSE (per mm)			0.82 (0.74, 0.92)	0.05	0.14	0.583 (0.038, 1.194)	0.053 (−0.006, 0.209)
	REVEAL	1.54 (1.16, 2.03)	0.002					
	TAPSE	0.82 (0.70, 0.96)	0.01					
12	REVEAL Lite 2.0 score + TAPSE < 18 mm			0.81 (0.70, 0.91)	0.04	0.26	0.683 (−0.448, 1.135)	0.020 (−0.017, 0.153)
	REVEAL	1.58 (1.21, 2.08)	0.001					
	TAPSE	3.20 (1.06, 9.65)	0.04					
13	REVEAL Lite 2.0 score + RV S'			0.82 (0.73, 0.92)	0.05	0.06	0.554 (0.024, 0.967)	0.043 (−0.012, 0.176)
	REVEAL	1.55 (1.19, 2.01)	0.001					
	RV S'	0.75 (0.58, 0.96)	0.03					

Abbreviations: AUC, area under the receiver operating characteristic (ROC) curve; "–", not applicable.

*Except for REVEAL Lite 2.0 score alone, which is unadjusted OR.

**Compared with REVEAL Lite 2.0 score alone.

***AUC delta = AUC of the evaluated model − AUC of model 1 (REVEAL Lite 2.0 score alone).

TABLE 4 A pairwise comparison of the area under the curve (AUC) of REVEAL Lite 2.0 alone and with other well established echocardiographic parameters like TAPSE and RAP against systolic and diastolic LV eccentricity indices (both as continuous and categorical variables)

	Model 1 (REVEAL Lite 2.0) ($N = 110$)		**Model 2 (Echo only) ($N = 100$)**		**Model 3 (Echo + REVEAL Lite 2.0) ($N = 100$)**		
	Unadjusted OR (95% CI)	***p* value**	**Adjusted OR (95% CI)**	***p* value**	**Adjusted OR (95% CI)**	***p* value**	**Pairwise comparisons for the AUC, *p* value**
A. Using the continuous end systolic eccentricity index							
End systolic eccentricity index (continuous)	-	-	2.57 (1.11, 5.96)	0.03	2.34 (0.87, 6.32)	0.09	Model 1 versus Model 2: $p = .58$ Model 1 versus Model 3: $p = .13$ Model 2 versus Model 3: $p = .14$
TAPSE (mm)	-	-	0.85 (0.72, 1.00)	0.045	0.86 (0.74, 1.01)	0.08	
RAP (mmHg)	-	-	1.20 (1.05, 1.37)	0.01	1.14 (0.97, 1.34)	0.10	
REVEAL Lite 2.0 score	1.63 (1.27, 2.10)	<0.001	–	–	1.37 (1.01, 1.85)	0.04	
AUC (95% CI)	0.77 (0.66, 0.88)		0.81 (0.69, 0.92)		0.85 (0.75, 0.94)		
B. Using the continuous end diastolic eccentricity index							
End diastolic eccentricity index (continuous)	-	-	24.68 (2.14, 284.22)	0.01	18.12 (1.42, 230.94)	0.03	Model 1 versus Model 2: $p = .18$ Model 1 versus Model 3: $p = .049$ Model 2 versus Model 3: $p = .36$
TAPSE (mm)	-	-	0.89 (0.77, 1.04)	0.14	0.90 (0.76, 1.05)	0.19	
RAP (mmHg)	-	-	1.16 (0.99, 1.35)	0.06	1.12 (0.94, 1.34)	0.21	
REVEAL Lite 2.0 score	1.63 (1.27, 2.10)	<0.001	–	–	1.29 (0.93, 1.78)	0.13	
AUC (95% CI)	0.77 (0.66, 0.88)		0.85 (0.75, 0.96)		0.88 (0.80, 0.96)		
C. Using the bivariate end systolic eccentricity index							
End systolic eccentricity index ≥1.2	-	-	3.57 (0.98, 13.04)	0.06	3.28 (0.84, 12.75)	0.09	Model 1 versus Model 2: $p = .56$ Model 1 versus Model 3: $p = .07$ Model 2 versus Model 3: $p = .16$
TAPSE < 18 mm	-	-	2.41 (0.75, 7.70)	0.14	2.21 (0.64, 7.62)	0.21	
RAP (mmHg)	-	-	1.19 (1.03, 1.39)	0.02	1.13 (0.94, 1.36)	0.18	
REVEAL Lite 2.0 score	1.63 (1.27, 2.10)	<0.001	-	-	1.42 (1.03, 1.95)	0.03	
AUC (95% CI)	0.77 (0.66, 0.88)		0.81 (0.70, 0.91)		0.85 (0.77, 0.93)		

(Continues)

TABLE 4 (Continued)

	Model 1 (REVEAL Lite 2.0) ($N = 110$)		Model 2 (Echo only) ($N = 100$)		Model 3 (Echo + REVEAL Lite 2.0) ($N = 100$)		
	Unadjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value	Pairwise comparisons for the AUC, *p* value
D. Using the bivariate end diastolic eccentricity index							
End diastolic eccentricity index ≥1.2	-	-	6.41 (1.79, 22.90)	0.004	4.73 (1.27, 17.64)	0.02	Model 1 versus Model 2: $p = .46$
TAPSE < 18 mm	-	-	1.59 (0.45, 5.60)	0.47	1.63 (0.43, 6.19)	0.47	Model 1 versus Model 3: $p = .07$
RAP (mmHg)	-	-	1.15 (0.99, 1.34)	0.07	1.12 (0.95, 1.31)	0.19	Model 2 versus Model 3: $p = .18$
REVEAL Lite 2.0 score	1.63 (1.27, 2.10)	<0.001	–	–	1.32 (0.95, 1.83)	0.09	
AUC (95% CI)	0.77 (0.66, 0.88)		0.82 (0.70, 0.93)		0.85 (0.76, 0.95)		

Abbreviations: AUC, area under the curve; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; TAPSE, tricuspid annular plane systolic excursion.

for 1-year mortality.[5] Most of these tools rely heavily on clinical symptoms, biomarkers, and FC assessment, along with invasive hemodynamic measurements. The current risk stratification tools are limited in their use of cardiac imaging parameters despite the 2015 ESC/ERS guidelines which recommend echocardiography as a central component of monitoring.[1] REVEAL 1.0, REVEAL 2.0 and REVEAL Lite 2.0 all include pericardial effusion as the only echocardiographic parameter in defining risk stratification.[3–5] Pericardial effusion is a well-established poor prognostic sign in PAH and is reflective of an already poorer hemodynamic system.[20,21] In PAH management, early detection, and treatment are pivotal. Current risk stratification tools prognosticate one-year mortality, but these current tools lack the ability to identify early decline or disease progression. A recent cluster analysis of idiopathic PAH patients showed that most patients were at intermediate risk and were characterized as a heterogeneous population.[22] The addition of echocardiography may play a significant role in detecting early disease progression in such patients. In PAH, survival is dependent on the RV's ability to adapt to the ever-increasing afterload while maintaining function and preserving cardiac output.[23,24] Echocardiography is a cost-effective, easily available, and noninvasive imaging tool for the detailed assessment of both RV structure and function as well as other indices which are sensitive to changes in RV afterload.[25]

Univariate analysis in our cohort (Table 2) showed a variety of echocardiographic parameters which were early predictors of disease progression. Most of these parameters are surrogates of RV structure and function and are used in daily clinical practice and may help in clinical decision-making. Many studies have shown different echocardiographic parameters that prognosticate poor outcomes in PAH.[26–28] Commonly, echocardiographic presence of pericardial effusion and right atrial size are considered poor prognostic markers for survival in PAH.[27,28] Mazurek et al. showed TAPSE of ≥2 cm at follow-up strongly predicted survival in PAH.[29] In our analysis, however, we did not find these markers to be significant on multivariable analysis. This is likely due to the timing of the echocardiograms in this study, as they were four to eight months before a disease progression event when the patient was deemed clinically stable by their treating physician.

The patients in our analysis were relatively low risk as indicated by their REVEAL Lite 2.0 scores. The "event" and "no event" groups had a median REVEAL Lite 2.0 score of 6.5 (5.0, 8.0) and 4.0 (3.0, 6.0) respectively. This further validates the prognostic value of REVEAL Lite 2.0 scoring even in a low- to intermediate-risk patient population. Of the 22 patients who experienced an event, 13 (59%) patients were in the low to intermediate-risk group.

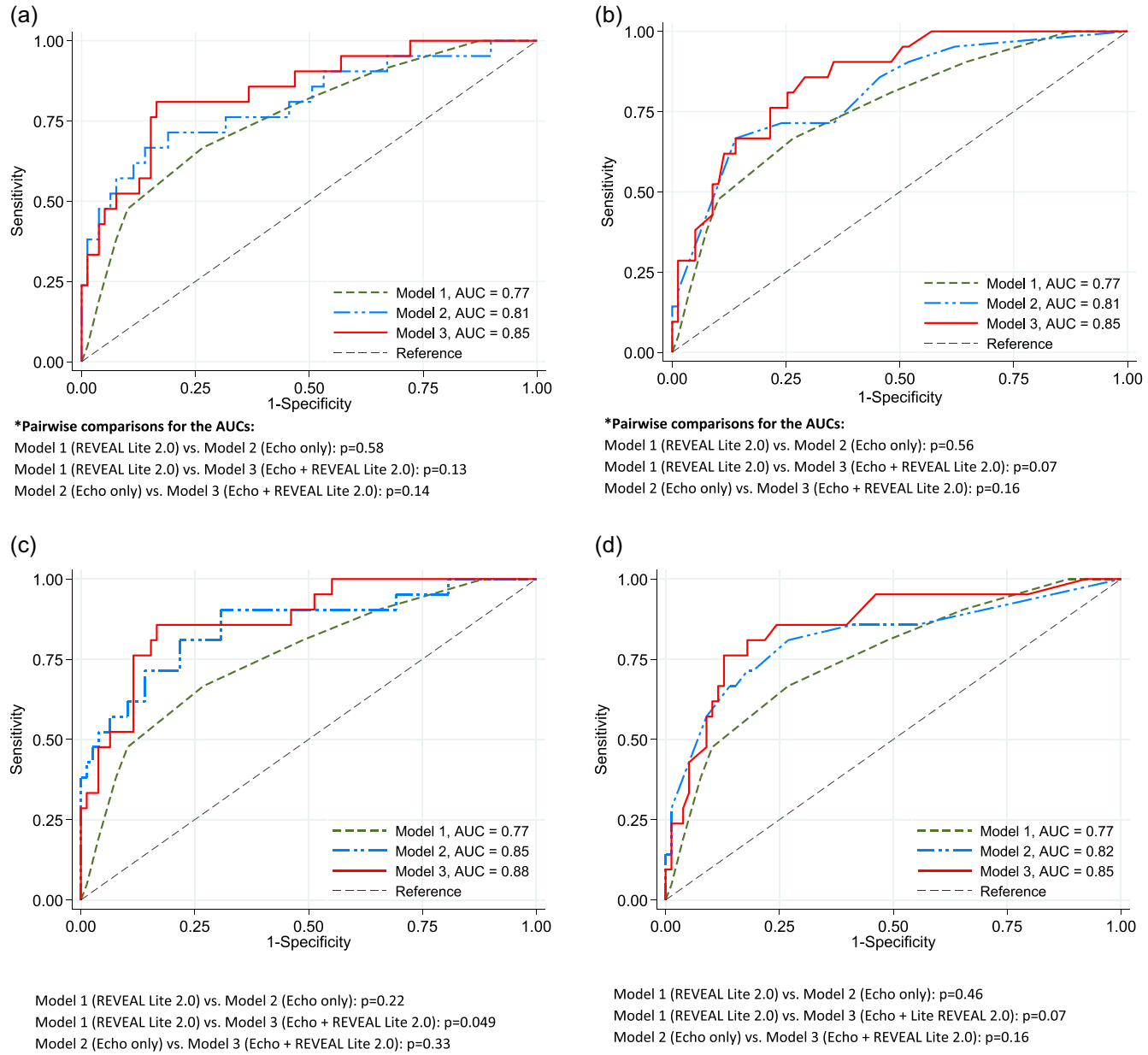

FIGURE 2 (a) ROC curve using end-systolic eccentricity index and TAPSE as a continuous variable in combination with REVEAL Lite 2.0. (b) ROC curve using end-systolic eccentricity index and TAPSE as a categorical variable in combination with REVEAL Lite 2.0. (c) ROC curve using end-diastolic eccentricity index and TAPSE as a continuous variable in combination with REVEAL Lite 2.0. (d) ROC curve using end-diastolic eccentricity index and TAPSE as a categorical variable in combination with REVEAL Lite 2.0. ROC, receiver operating characteristic; TAPSE, tricuspid annular plane systolic excursion

Thus, achieving a low to intermediate risk status with REVEAL Lite 2.0 alone may not be sufficient to predict disease progression and additional refinement of the scoring method may be needed. In our multivariate analysis, REVEAL Lite 2.0 was discriminatory in predicting a PAH event with an AUC of 0.77. However, when echocardiographic parameters were added to REVEAL Lite 2.0, the AUC improved significantly as shown in Table 3. Different echocardiographic parameters were evaluated in the models in Table 4. The best models were chosen based on the largest C-statistic. The LVED eccentricity index in combination with REVEAL Lite 2.0 achieved the best AUC in predicting poorer PAH outcomes. The increase in the AUC from 0.77 with REVEAL Lite 2.0 alone to 0.85 with the combination of REVEAL Lite 2.0 and LV end-diastolic eccentricity index ($p = 0.049$) is significant, both statistically and clinically. We also compared the LVED eccentricity index as a categorical variable and TAPSE along with REVEAL Lite 2.0. Different combinations of ROC analyses are shown in Figure 2. Although our

analysis found LVED eccentricity index as the most sensitive echocardiographic parameter to be used with REVEAL Lite 2.0 in predicting a disease progression event, we believe that other parameters, TAPSE (as previously shown by Mazurek et al.[29]), RA volume index, estimated RAP, and LVES eccentricity index can also achieve an excellent AUC of more than 0.80. Clearly, adding echocardiographic parameters to the REVEAL Lite 2.0 covariate improved the sensitivity to predict disease progression compared to each prognostic factor used alone (Tables 3 and 4 (A–D)).

Our study had limitations. Its retrospective nature led to missing data points. Although we used consecutive patients from our clinic, we did exclude those who were already declining at the beginning of the study duration, and this may have contributed to possible selection bias and a smaller event cohort. Although the model using the LVED eccentricity index had the highest C-statistic, the wide CI indicates inconsistent validity and small sample size. Therefore, the model using the LVES eccentricity index may be more practical. In addition, this project involved a single-center study, and these findings need to be validated. Considering PAH is a rare disease we had a cohort of over one hundred patients, but our event cohort was rather small which limits the validity of these findings. We believe that these findings are hypothesis-generating and larger studies will be beneficial to confirm this relationship.

In conclusion, our study is the first study that we know of, to systematically analyze the additive effect of routine echocardiographic parameters to the REVEAL Lite 2.0 scoring method used for the early detection of PAH disease progression. These findings clearly show the advantage of adding echocardiography to a routine risk assessment scoring system and comprehensive echocardiography must be performed routinely with the risk assessment. Larger, prospective studies are needed to validate the observations seen in our current study.

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CONFLICTS OF INTEREST

Sandeep Sahay: Speaker and advisor for Actelion, Bayer, and United Therapeutics. Advisor for Boehringer Ingelheim, Liquidia Technologies, Gossamer Bio and Altavant Sciences. Clinical trial endpoint adjudication committee member for a GSK sponsored RCT, Research grant from ACCP CHEST Foundation, Research grant from United Therapeutics, Consultant for Acceleron Pharmaceuticals. **Ashrith Guha**: Speaker for Actelion (Jansen), Speaker, and advisor to Bayer. The remaining authors declare that there are no conflict of interests.

ETHICS STATEMENT

None.

AUTHOR CONTRIBUTION

Sandeep Sahay: Participated in the design of the study, data collection, statistical analysis, interpretation of the results, writing, and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted. Dr. Sahay is the guarantor of the paper, taking responsibility for the integrity of the work, from inception to published article. Jiken Bhatt: Participated in the data collection, interpretation of the results, and final approval of the manuscript submitted. Sarah Beshay: Participated in the data collection and critical revision of the manuscript for important intellectual content. Ashrith Guha: Participated in the interpretation of the results and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted. Duc T. Nguyen: Participated in the statistical analysis of the data and critical statistical input and revision of the manuscript for important intellectual content. Edward A. Graviss: Participated in the statistical analysis of the data and critical statistical input and revision of the manuscript for important intellectual content. Sherif Nagueh: Participated in the interpretation of the results and critical revision of the manuscript for important intellectual content.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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