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Right ventricular systolic to diastolic duration ratio: A novel predictor of outcome in adult idiopathic pulmonary arterial hypertension

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ABSTRACT

Background: The systolic to diastolic (SD) duration ratio reflects global RV performance in pulmonary arterial hypertension (PAH) yet limited data exists on its application to adult non-congenital PAH. We measured SD ratios on echocardiogram in idiopathic PAH (IPAH) to establish its response to pulmonary vasodilator therapy and prognostic value at diagnosis and follow up.
Methods: Incident patients with IPAH undergoing echocardiogram, haemodynamic and exercise assessments were identified within our centre between 2005 and 2018. SD ratios were adjusted for heart rate at diagnosis and follow up.
Results: In 98 patients at diagnosis, the mean SD ratio was 1.03 ± 0.37 decreasing to 0.85 ± 0.25, $p < 0.001$ at follow-up echocardiogram performed at a median interval of 9.0 months. The SD ratio at diagnosis correlated weakly with RV basal diameter ($r = 0.24$, $p = 0.04$) and 6MWD ($r = 0.23$, $p = 0.04$). At follow up, the mean SD ratio was lower in those receiving combination vs monotherapy pulmonary vasodilator treatment (71 ± 25 vs 92 ± 22% baseline respectively, $p < 0.001$). After a median follow-up of 4.8 years, 3 patients were transplanted and 23 patients died. The SD ratio at diagnosis and follow up predicted an increased risk of death/transplantation (HR 2.41 (1.09–5.29), $p = 0.03$; HR 5.02 (1.27–19.77), $p = 0.02$ respectively), retaining its predictive value at diagnosis in bivariate models with 6MWD (HR 2.18 (1.06–4.08)), WHO Functional Class (HR 2.33 (1.04–5.21)) and TAPSE (HR 2.36 (1.07–5.19)), all $p < 0.05$.
Conclusions: The SD ratio carries prognostic value at diagnosis and follow up in IPAH. Its further evaluation alongside current PAH risk stratification parameters should be considered.

1. Introduction

Right ventricular (RV) function remains a principle determinant of prognosis in pulmonary arterial hypertension (PAH) the assessment of which relies heavily on transthoracic echocardiography at diagnosis and follow up. Echocardiographic variables with prognostic value in PAH include the tricuspid annular plane systolic excursion (TAPSE), TAPSE/pulmonary artery systolic pressure (TAPSE/PASP) and right atrial area, however all rely on RV geometric assumptions and do not consistently differentiate optimal RV performance [1–5]. The ratio between the duration of RV systole and diastole (SD ratio) may be calculated using the tricuspid regurgitation (TR) Doppler envelope which may be considered a surrogate for systolic duration. A higher SD ratio reflects worsening global RV performance and has demonstrated a negative impact on prognosis in congenital heart disease-associated PAH [6–8].

Given the different treatment approaches between congenital and non-congenital PAH, we evaluated the relationship between the SD ratio and traditional echocardiographic and haemodynamic risk stratification parameters in our cohort of patients with idiopathic PAH (IPAH). Secondly, we assessed the effect of pulmonary vasodilator therapies on the SD ratio and its prognostic value on mortality.

2. Methods

We interrogated our centre's database containing patients diagnosed with IPAH between 1st July 2005 and 31st January 2018, selecting only incident patients undergoing their initial diagnostic evaluation and follow up echocardiogram at our institution. All patients were aged between 18 and 80 years and had undergone echocardiogram, right heart catheterization and six minute walk distance (6MWD) within a 30 day period of initial treatment. Pulmonary vasodilator monotherapy was defined as prescription of a single pulmonary vasodilator exclusively between diagnosis and follow up echocardiogram. Combination therapy was defined as receipt of two or more concomitant pulmonary

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vasodilator drug classes for at least three months between diagnosis and follow up echocardiogram. Where combination therapy lasted <3 months between diagnostic and follow up echocardiogram, patients were classified in the monotherapy arm. Further exclusion criteria included the administration of pulmonary vasodilators at study entry as well as the presence of cardiac arrhythmia at the time of diagnostic or follow up echocardiogram.

2.1. SD ratio measurement

SD ratios were measured in triplicate as previously described (Fig. 1) [8]. Briefly, the SD ratio was taken as the TR duration on continuous wave Doppler divided by the time from the end of TR to the onset of the subsequent TR signal. Measurements were made by two independent echocardiographers to obtain mean systolic and diastolic durations including standard deviation values for each patient. To account for the effect of differing heart rates on systolic/diastolic duration [9], all SD ratios were standardized at 60 beats/min as follows:

$$\text{SD ratio}^{\text{adj}} = \text{SD ratio}^{\text{abs}} \times (((60/\text{HR}) - \text{ST})/(1 - \text{ST}))$$

where HR = heart rate, adj = adjusted, abs = absolute, ST = Systolic Time measured in milliseconds. An analysis of absolute SD ratio values was also undertaken. Absolute values for the SD ratio were also recorded.

2.2. Statistical design

Baseline information at study entry was summarised as mean ± SD or frequencies and proportions. Study enrolment lasted from the date of first echocardiography to the time of death, transplantation or censoring. The association between mortality and longitudinal information from 6MWD and pulmonary haemodynamics were measured both from the date of study entry and the date of follow up echocardiogram to determine variables with predictive value. Univariate and multivariate Cox regression were used to assess relationships between the SD ratio and clinical parameters to mortality. The optimal cut-off in SD ratio that predicted death/transplantation was evaluated using survival ROC analysis (Youden method). Hazard ratios and 95% CIs were calculated to a 5% significance level. Covariate values were not missing in >15% in any parameter therefore, missing data was imputed using mean values for pulmonary haemodynamics or 6MWD.

3. Results

One hundred two patients had echocardiograms at diagnosis and follow-up. 96 were included in the final cohort (Fig. 2). Two patients demonstrating vasoreactivity to nitric oxide and four with atrial arrhythmia at diagnosis were excluded. 76 were alive at censoring and 26 had died or undergone transplantation. Patient demographics and clinical characteristics are displayed in Table 1. Following diagnosis, 63 patients received pulmonary vasodilator monotherapy and 31 received combination therapy. Four patients receiving monotherapy switched between phosphodiesterase V inhibitor and endothelin receptor antagonist. One patient discontinued therapy before three months and one patient was excluded who had developed atrial flutter at follow-up echocardiogram.

The mean age of our IPAH cohort was 60 ± 18 years. Patients were predominantly female and in WHO FC III/IV (Table 1). Between diagnostic and follow up echocardiogram performed at a median interval of 9.0 months, improvements were noted in 6MWD and WHO Functional Class. Heart rate did not differ between diagnostic and follow up echocardiogram, although RV systolic duration had reduced at follow up. SD ratios reduced in response to pulmonary vasodilator treatment expressed as both adjusted ($p < 0.001$) and absolute values ($p < 0.026$) (Table 1). The mean adjusted SD ratio reduced further in those receiving combination pulmonary vasodilator treatment compared to those treated with monotherapy (71 ± 25 vs 92 ± 22% of baseline respectively, $p < 0.001$) (Fig. 3A). Adjusted SD ratios at diagnosis correlated weakly with RV basal diameter ($r = 0.24$, $p = 0.04$) and 6MWD ($r = 0.23$, $p = 0.04$). SD ratios did not relate to age ($r = 0.04$) or WHO functional class ($r = 0.07$).

After a median follow-up of 4.9 years, 3 patients were transplanted and 23 patients had died. Univariate and multivariate predictors of death/transplantation at the time of diagnostic and follow up echocardiogram are shown in Table 2. Only the adjusted SD ratio was associated with an increased risk of death/transplantation at diagnosis and follow up (Table 2). The absolute SD ratio at diagnosis carried weaker prognostic value which disappeared at follow up. After inclusion of 6MWD, WHO Functional Class and TAPSE in separate bivariate models with the SD ratio at diagnosis, it predictive value at diagnosis and at follow

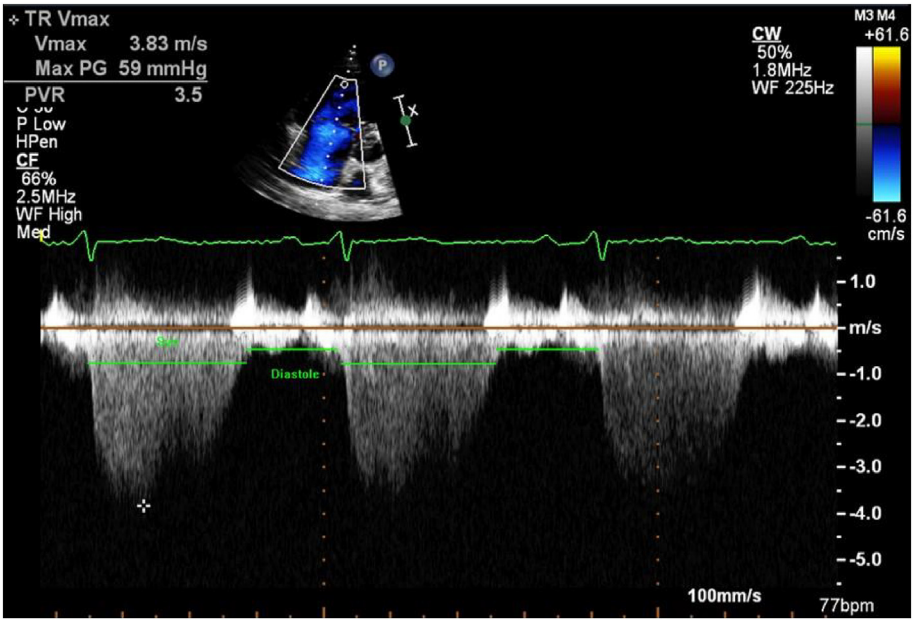


Fig. 1. Measurement of the SD ratio using the tricuspid regurgitant Doppler signal.

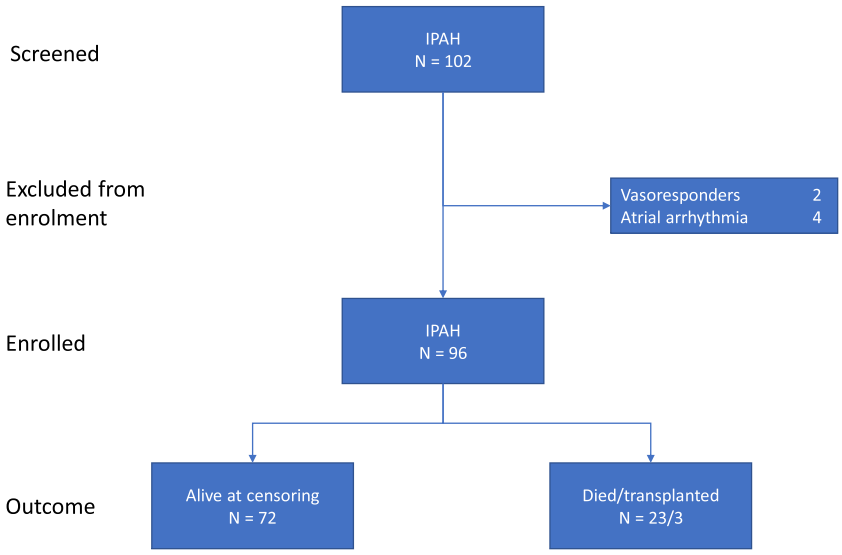


Fig. 2. Flowchart of study participants including excluded patients and outcome measures.

up adjusted for WHO Functional Class (Table 2). In the whole population, IPAH patients receiving combination pulmonary vasodilator therapy had a trend toward improved survival over those who received monotherapy (Fig. 3B). An adjusted SD ratio of ≤1.1 at diagnosis best discriminated patients at increased risk of death/transplantation compared to long-term survivors (Fig. 3C) with an area under the curve of 0.622.

4. Discussion

Our study demonstrates the absolute and heart rate adjusted SD ratio assessed at diagnosis to be a novel outcome predictor in adult IPAH. The predictive value of the adjusted SD ratio was also enhanced at follow up assessment. Reduction in the SD ratio following pulmonary vasodilator treatment was greater in those receiving combination pulmonary vasodilator therapy compared to those receiving monotherapy, which derived from a reduced systolic duration rather than a prolongation in diastole. This implies a predominant influence of lower RV afterload in those patients receiving combination therapy. Weak correlation was found between the SD ratio at diagnosis and RV basal diameter, supporting an association between longer systolic duration and abnormal RV geometry. This contrasts with more established parameters of RV function in PAH such as TAPSE and fractional area change (FAC) which are more volume dependent and rely on RV geometric assumptions. Our study highlights an important interplay between the SD ratio in response to pulmonary vasodilator therapies and prognosis in IPAH broadening its potential application beyond congenital PAH.

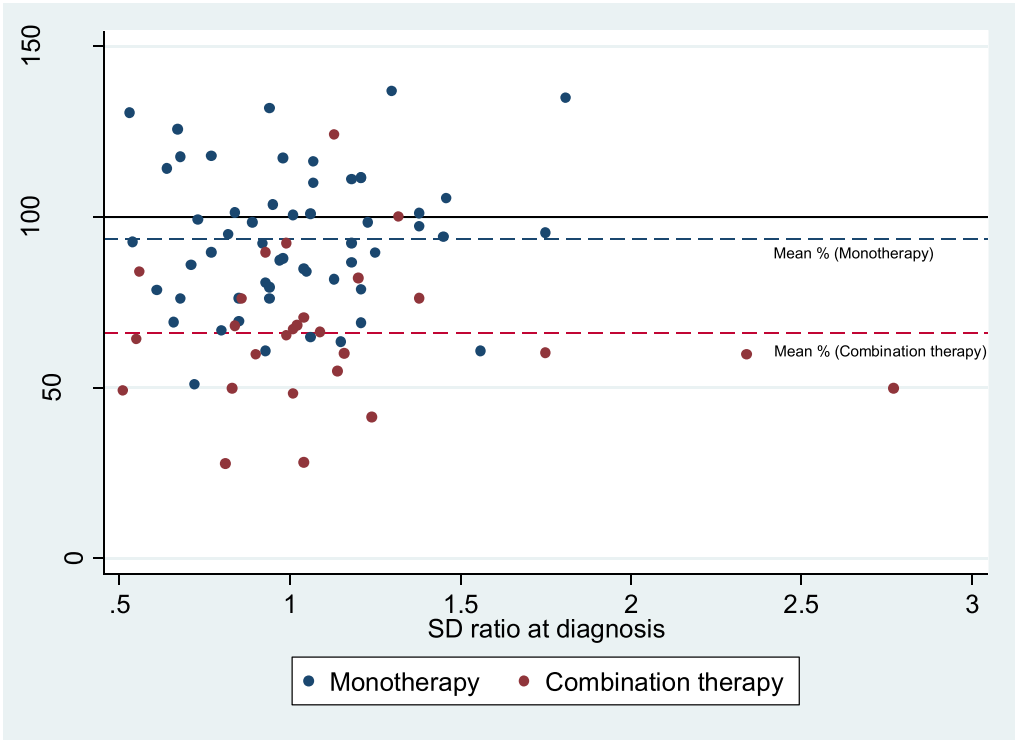
Elevated heart rates predict adverse outcomes in PAH reflecting both the physiological response to a fixed, impaired RV stroke volume and increased burden of disease [10,11]. Despite the prognostic importance of an elevated heart rate, little attention has been paid to the relevance of its systolic and diastolic components. We noted an increased RV systolic duration at diagnosis which reduced at follow up in response to pulmonary vasodilator therapy. Using the RV outflow tract Doppler, Tei et al. showed that prolonged RV systole in IPAH derives from a longer isovolumetric contraction phase and that prolonged RV isovolumetric contraction (and relaxation) is counterbalanced by shorter RV ejection times [12]. The SD ratio represents a simplification of the Tei index in that TR duration includes the isovolumetric phase of RV contraction and may be more readily calculated in the presence of an incomplete TR jet. Following afterload reduction with pulmonary vasodilator treatment, the SD ratio shortened in our cohort due to shortened RV ejection times for a given stroke volume. *Prolonged* RV systolic contraction has been suggested to contribute toward RV remodeling in advanced PAH, a process which ultimately leads to higher wall tension and increased myocardial oxygen demand [13]. Prolonged SD ratios may therefore reflect RV myocardium working at suboptimal efficiency. Furthermore, a failure of the SD ratio to shorten in response to afterload reduction during follow up may signify impaired ability of the RV to reverse remodel giving rise to a higher risk of worse outcome.

A further modifier of RV systolic duration is the presence of RV dyssynchrony, indicative of severe RV dysfunction [14]. Dyssynchrony is defined by a time delay between septal and RV free wall contractile activation which creates a non-uniform distribution of wall stress within RV myocardium. Its presence has been associated with greater RV dilatation and poorer prognosis [15,16]. Within our cohort, increased

Table 1
Demographics, clinical characteristics and pulmonary vasodilator treatments at diagnosis and follow up in IPAH.

Variable	Diagnosis (n = 96)	Follow up (n = 96)	P value
Age (years)	60 ± 18	–	–
Female sex n (%)	59 (61)	–	–
WHO FC III or IV n (%)	62 (65)	47 (49)	**<0.001**
6MWD (m)	293 ± 130	314 ± 135	**0.028**
HR (beats/min)	77 ± 13	79 ± 13	0.079
mPAP (mmHg)	48 ± 16	–	–
CO (L/min)	3.8 ± 1.3	–	–
PVR (Wood units)	11.6 ± 6.0	–	–
Systolic duration (ms)	475 ± 70	458 ± 50	**0.014**
Diastolic duration (ms)	315 ± 101	337 ± 117	0.061
SD ratio (absolute)	1.70 ± 0.70	1.51 ± 0.56	**0.026**
SD ratio (adjusted)	1.01 ± 0.37	0.85 ± 0.25	**<0.001**
Tricuspid regurgitation (mild/mod/severe %)	42/43/15	50/40/10	
RV basal diameter (mm)	50 ± 10	48 ± 8	0.18
RV S′ (cm/s)	10.3 ± 3.0	11.1 ± 2.9	0.11
TAPSE (mm)	17 ± 4	18 ± 5	0.11
Estimated sPAP (mmHg)	81 ± 22	82 ± 24	0.80
LV ejection fraction (%)	63 ± 7	61 ± 5	0.12
Pulmonary vasodilator treatments n, (%)[a]			
PDE V only	–	42 (45)	
ERA only	–	17 (18)	
PDE V/ERA interchanged	–	4 (4)	
PDE V + ERA combined	–	25 (27)	
PDE V + ERA + prostacyclin	–	3 (3)	
PDE V + prostacyclin	–	2 (2)	
ERA + prostacyclin	–	1 (1)	

[a] 94 patients treated at time of follow up echocardiogram.



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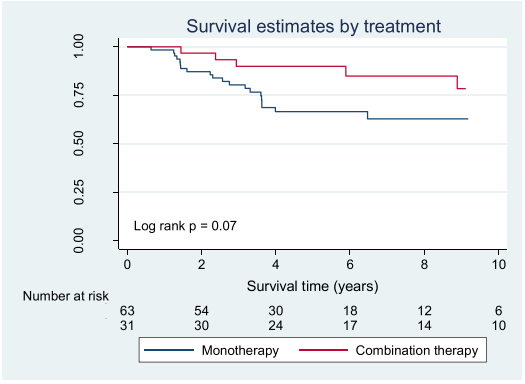

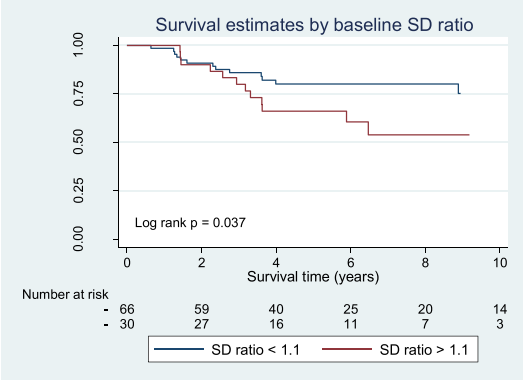

B C

Fig. 3. A - Change in adjusted SD ratio following introduction of pulmonary vasodilator therapy expressed as % of baseline SD ratio (at diagnosis), B – Kaplan Meier survival estimates for IPAH cohort treated with mono and combination pulmonary vasodilator treatments, C – survival estimates according to baseline SD ratio </>1.1.

RV basal diameter in patients with prolonged SD ratio may predispose to dyssynchronous contraction contributing to worse outcomes. We also found the adjusted SD ratio at follow up to predict mortality in our cohort. This suggests that despite patients being assessed at different stages of pathological adaptation, serial measurement of the SD ratio potentially reflect persistent segmental mechanical delay resulting in contractile inefficiency and reduced forward flow. As data on long-term effects of dyssynchrony in PAH remains sparse, the SD ratio may offer potential insight as to what extent pulmonary vasodilators ameliorate dyssynchrony and contribute to restoration of RV function.

Lower SD ratios in patients treated with combination therapy compared to those on monotherapy suggests a dose-response effect between pulmonary vasodilator treatment and reduction in RV systolic duration. In support of this effect, patients receiving dual combination pulmonary vasodilators in connective tissue disease associated-PAH have demonstrated a greater reduction in RV mass in comparison to those on monotherapy [17]. The corollary of shortened systolic duration is prolongation in diastole, a chronotropic property typically associated with beta blockade. Despite promising initial animal studies however, clinical PAH studies of beta blockade have yielded inconsistent findings, perhaps in part driven by inadequate heart rate reduction in the latter [18–20]. Currently, it is still unclear as to whether elevated heart rates in PAH represent a risk factor for disease progression or merely an epiphenomenon of severe disease. Given our observation of reduced systolic duration in response to pulmonary vasodilator treatment, the selection of patients with an unchanged or elevated SD ratio at follow up may conceivably better identify patients more likely to benefit from a heart rate lowering strategy. Future studies evaluating heart rate modulation in IPAH, achieved through either pharmacological or non-pharmacological methods, should consider incorporation of SD ratio measurements to fully elucidate the effects of heart rate on RV systolic and diastolic function.

Limitations in our dataset include its single-centre origin and the small number of outcome measures which restricts power to conduct

Table 2
Univariable and multivariable Cox Proportional Hazard Models for mortality/transplantation with baseline measurements as covariates.

Univariable Cox regression	Diagnosis		Follow up	
	Hazard ratio (CI)	P value	Hazard ratio (CI)	P value
Absolute SD ratio, unit increase	1.69 (1.06–2.71)	**0.028**	1.28 (0.63–2.59)	0.490
Adjusted SD ratio, unit increase	2.41 (1.09–5.29)	**0.029**	5.02 (1.27–19.77)	**0.021**
6MWD, 10 m increase	0.95 (0.91–0.98)	**0.002**	0.90 (0.61–1.20)	0.255
mPAP, 5 mmHg increase	1.04 (0.90–1.21)	0.571	–	–
PVR, unit increase	1.10 (1.01–1.19)	**0.029**	–	–
WHO FC, unit increase	3.13 (1.57–6.24)	**0.001**	1.90 (0.92–3.91)	0.083
TAPSE, 10 mm increase	0.29 (0.10–0.80)	**0.017**	0.47 (0.17–1.27)	0.140
TAPSE/PASP, unit increase	0.002 (0.0001–0.90)	**0.046**	4.18 (0.16–107.65)	0.310
Multivariable Cox regression				
Adjusted SD ratio, unit increase	2.18 (1.06–4.08)	**0.033**[a]	–	–
Adjusted SD ratio, unit increase	2.33 (1.04–5.21)	**0.040**[b]	4.29 (1.00–18.29)	**0.049**[d]
Adjusted SD ratio, unit increase	2.36 (1.07–5.19)	**0.032**[c]	–	–

[a] Adjusted for 6MWD at diagnosis.
[b] Adjusted for WHO FC at diagnosis.
[c] Adjusted for TAPSE at diagnosis.
[d] Adjusted for WHO FC at follow up.

more robust multivariable analyses. An unequal time duration between diagnostic and follow up echocardiogram could also have potentially influenced the extent of RV reverse adaptation and thus SD ratio measured in response to treatment with pulmonary vasodilators. However, during the period of our study the prescription of pulmonary vasodilators was predominantly goal-directed meaning patients were not escalated quickly on to combination therapy prior to clinical reassessment. The timing of follow up echocardiograms was also not standardized. In part, this accounts for the relatively high proportion of patients receiving monotherapy (60%) at the time of follow up assessment. Our results therefore do not reflect effects of contemporary PAH treatment strategies on RV function in which patients in WHO Functional Class II/III receive upfront combination therapy as standard of care. Finally, as patients receiving combination pulmonary vasodilator therapy were grouped together, no conclusions can be drawn about effects of specific pulmonary vasodilator agents, nor the influence of treatment decisions made following patients second echocardiographic evaluation which were not accounted for in our analysis.

Our study demonstrates a prolonged SD ratio to be a readily identifiable echocardiographic parameter of RV dysfunction that carries prognostic value at diagnosis and follow up in adult IPAH. Future studies in PAH should consider its evaluation alongside traditional risk stratification parameters.

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Declaration of Competing Interest

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No authors have any conflicts of interest relevant to this manuscript.

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