Increased Pulmonary-Systemic Pulse Pressure Ratio Is Associated With Increased Mortality in Group 1 Pulmonary Hypertension

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Background Pulmonary arterial hypertension (PAH) is characterised by remodelling of the pulmonary vasculature leading to right ventricular (RV) failure. The failing RV, through interventricular uncoupling, deleteriously impacts the left ventricle and overall cardiac efficiency. We hypothesised that the ratio of the pulmonary artery pulse pressure to the systemic pulse pressure (''pulmonary-systemic pulse pressure ratio'', or PS-PPR) would be associated with mortality in PAH.

Methods We conducted a retrospective analysis of 262 patients in the National Institute of Health Primary Pulmonary Hypertension Registry (NIH-PPH). We evaluated the association between the PS-PPR and mortality after adjustment for the Pulmonary Hypertension Connection (PHC) risk equation.

Results Among 262 patients (mean age 37.5 ± 15.8 years, 62.2% female), median PS-PPR was 1.04 (IQR 0.79–1.30). In the Cox proportional hazards regression model, each one unit increase in the PS-PPR was associated with more than a two-fold increase in mortality during follow-up (HR 2.06, 95% CI 1.40–3.02, p = 0.0002), and this association of PS-PPR with mortality remained significant in the multivariable Cox model adjusted for the PHC risk equation, mean pulmonary artery pressure, and body mass index (BMI) (adjusted HR 1.81, 95% CI 1.13–2.88, p = 0.01). Furthermore, PS-PPR in the upper quartile (>1.30) versus quartiles 1–3 was associated with a 68% increase in mortality after adjustment for these same covariates (adjusted HR 1.68, 95% CI 1.13–2.50, p = 0.01).

Conclusions Pulmonary-systemic pulse pressure ratio, a marker of biventricular efficiency, is associated with survival in PAH even after adjustment for the PHC risk equation. Further studies are needed on the wider applications of PS-PPR in PAH patients.

Keywords Pulmonary hypertension • Right ventricular failure • Ventricular-arterial coupling

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Background

Pulmonary arterial hypertension (PAH) is a disease that is characterised by diffuse remodelling and stiffening of the pulmonary vasculature, thereby imposing excessive afterload on the right ventricle (RV). This sustained load on the RV results in chamber dilation, failure and death [1–3]. The functional integrity of the RV is a strong determinant of outcomes in PAH. A functionally compromised RV imposes unfavourable haemodynamic effects on the left ventricle (LV) that occur in tandem with the spiralling decline in RV function. For example, a dilated RV chamber due to a combination of pressure and volume overload significantly alters the septal and LV contractile dynamics and impairs both diastolic filling and cardiac output. In patients with advanced PAH, these interventricular interactions are often conspicuous on cardiac imaging and have been reported to correlate with adverse outcomes [4–7]. The integration of haemodynamic indices that account for ventricular interactions in the risk stratification of PAH patients is, however, not well studied. We, therefore, tested the hypothesis that the ratio of pulmonary artery (PA) pulse pressure and systemic pulse pressure, PS-PPR, would be associated with mortality in patients with WHO group 1 PH even after adjustment for the contemporary pulmonary hypertension connection (PHC) risk model, which has been derived in the modern era of vasodilator therapy and validated for prediction of outcomes in PAH patients [8,9]. We tested our hypothesis in patients with primary pulmonary hypertension from the National Institute of Health Primary Pulmonary Hypertension (NIH-PPH) database.

Methods

Patient Selection and Data

The NIH-PPH database was established with the purpose of studying the natural history of primary pulmonary hypertension (now group 1 PH) and has provided key data that have advanced our understanding of the clinical determinants of PAH. The methodology has been previously published [2,10]. Briefly, patients in this registry were enrolled from 32 medical centres across the US. Pulmonary hypertension was defined as mean PAP (mPAP) greater than 25 mmHg at rest or 30 mmHg with exercise at cardiac catheterisation; however, nearly all patients (260/262) also met more recent diagnostic criteria of a pulmonary vascular resistance (PVR) greater than 3 Woods units [11]. Systemic blood pressures were acquired using a brachial sphygmomanometer. Secondary causes of PH were excluded, including patients with PH within first year of life or congenital abnormalities of myocardium/valves, lungs, thorax and diaphragm, pulmonary thromboembolic disease as evidenced by lung perfusion scan or pulmonary angiogram, known sickle cell anaemia, history of intravenous (IV) drug abuse, obstructive or interstitial lung disease, collagen vascular disease, parasitic lung disease, pulmonary artery or valve

stenosis, and pulmonary venous hypertension with pulmonary capillary wedge pressures greater than 12 mmHg [2,10]. We used a de-identified public release of the NIH-PPH dataset that was accessed at https://biolincc.nhlbi.nih.gov/studies/pphreg.

Study Design

We analysed all patients in the NIH-PPH database with complete haemodynamic variables for the calculation of both the PS-PPR and the PHC risk model. The PHC risk model

$$[P(t) = e^{(-A(x, y, z)t)}, A(x, y, z)$$
$$= e^{(-1.270 - 0.0148x + 0.0402y - 0.361z)}]$$

is a contemporary predictive equation for survival in PAH in which P(t) is the probability of survival, t the time interval in years, x the mean pulmonary artery pressure, y the mean right atrial pressure, and z the cardiac index [8,9]. We used the haemodynamic data in the registry to calculate the PS-PPR for each available patient, using the formula of pulmonary pulse pressure (pulmonary artery systolic pressure − pulmonary artery diastolic pressure) divided by the systemic pulse pressure (systolic blood pressure − diastolic blood pressure). The patients were then stratified by quartiles based on the calculated PS-PPR values. Baseline clinical characteristics including age, sex, race, and body mass index (BMI) were analysed and compared by quartiles. Haemodynamic variables were also compared by quartiles. Haemodynamic variables included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulmonary artery systolic pressure (PASP), pulmonary artery diastolic pressure (PADP), pulmonary artery wedge pressure (PAWP), and mean right atrial pressure (RAP), as well as calculated parameters including systemic pulse pressure, mean PAP, pulmonary artery pulse pressure, cardiac index (CI), right ventricular stroke work index (RVSWI), transpulmonary gradient (TPG), and pulmonary vascular resistance (PVR). Associations with both short-term survival at 1-year and long-term survival at 5 years were subsequently assessed.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequency and percentages. Differences in categorical variables by PS-PPR groups were assessed using the chi-square test, while the Wilcoxon rank sum test or the Kruskal-Wallis test was used to test for differences in continuous variables. Kaplan-Meier plots were used to compare survival among the four quartiles of PS-PPR, and the log-rank test was used to compare differences in survival in PS-PPR groups. Bivariable Cox proportional hazards regression was used to assess associations of PS-PPR and other covariates with survival. Multivariable Cox hazard regression was used to evaluate the association of PS-PPR with survival with adjustment for other covariates demonstrating significant associations with survival in bivariable Cox regression models. Receiver operating

characteristic (ROC) curves were developed based on logistic regression analysis to assess the relative associations of the PS-PPR with short-term and long-term survival. ROC curves were also constructed for both PS-PPR and PHC risk. Mann-Whitney 95% confidence limits were determined for the ROC area values. An alpha value of less than 0.05 was used for statistical significance. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics

Of the 310 patient records available in the NIH-PPH database, 262 patients had complete haemodynamic data available for the calculation of both PS-PPR and PHC risk equation. The baseline characteristics of these 262 patients stratified by quartiles of PS-PPR are shown in Table 1. The mean age was 37.5 ± 15.8 years, and 62% of patients were female. There were no significant differences in these demographic characteristics among quartiles of PS-PPR. The distribution of PS-PPR in the cohort is shown in Figure 1.

Haemodynamics

Haemodynamic profiles by quartiles of PS-PPR are shown in Table 2. Significant differences among PS-PPR quartiles were observed in the SBP, systemic pulse pressure, PASP, PADP, mean PAP, mean RAP, CI, TPG, and PVR.

Kaplan–Meier Analysis

As seen in Figure 2, short-term survival rates during the first year of follow-up were significantly different in patients among the different PS-PPR quartiles (p = 0.008). Survival was best in quartile 1, lower in quartiles 2–3, and the lowest in quartile 4. Based on the goal of identifying patients with the lowest survival rates, the long-term survival in patients in quartiles 1–3 versus quartile 4 over 5 years is shown in Figure 3. Five-year survival was significantly lower for patients in quartile 4 of PS-PPR (p = 0.006).

Cox Proportional Hazards Analysis

Results of the bivariable Cox proportional hazards regression models are shown in Table 3 for variables with significant associations with survival during 5 years of follow-up. These variables included the PS-PPR, the PHC calculated risk, the mean PAP, the CI, RAP, and BMI. As shown in Table 3, each one-unit increase in the PS-PPR was associated with more than a two-fold increase in mortality during follow-up (HR 2.06, 95% CI 1.40–3.02, p = 0.0002). Evaluation of these covariates in a multivariable model based on stepwise selection showed that PS-PPR, the PHC risk equation, the mean PAP, and the BMI remained significant in the multivariable model (Table 4). As shown in Table 4, this association of PS-PPR with mortality remained significant in this multivariable Cox model with an adjusted HR of 1.81 (95% CI 1.13–2.88, p = 0.01). Furthermore, the hazard ratio for mortality after adjustment for the same variables in Table 4 (PHC risk score, mean PAP, and BMI) for PS-PPR in the upper quartile (>1.30) versus quartiles 1–3 was 1.68 (95% CI 1.13–250, p = 0.01).

ROC Analysis

Based on the hypothesis that the PS-PPR would improve the ROC area for 5-year survival relative to the PHC risk equation alone, we used bivariable and multivariable logistic regression to determine the ROC areas for 1-year and 5-year survival with PHC calculated risk alone and PHC risk combined with the PS-PPR. As shown in Figure 4A, the ROC area for 1-year survival increased from 0.60 (95% CI 0.52–0.68) for the model with the PHC risk equation alone (model p = 0.009) to 0.67 (95% CI 0.60–0.75) for the model with both the PHC risk equation and PS-PPR (model p < 0.0001). Likewise, the ROC increased from 0.63 (95% CI 0.56–0.71) to 0.69 (95% CI 0.62–0.76) for survival at 5 years (p < 0.0001 for both models) with the addition of the PS-PPR (Figure 4B), with significant difference between the two ROC curves (p = 0.038).

Table 1   Baseline Demographic Characteristics by PS-PPR Quartile.

Demographic variable	PS-PPR Q1 (<0.78) N=66	PS-PPR Q2 (0.79–1.04) N=65	PS-PPR Q3 (1.05–1.30) N=62	PS-PPR Q4 (>1.30) N=69	P-value
Age	40 ± 16	37 ± 17	38 ± 15	34 ± 14	0.19
Female gender (n, %)	43 (65%)	36 (55%)	41 (66%)	43 (62%)	0.59
Race (n, %)					
Caucasian	39 (59%)	53 (82%)	45 (73%)	53 (77%)	0.20
AA	16 (24%)	4 (6%)	8 (13%)	9 (13%)	
Other	11 (17%)	8(12%)	9 (14%)	7 (10%)	
BMI, kg/m^2	23 ± 6	22 ± 7	24 ± 8	22 ± 7	0.40

Values are presented as mean $\pm$ SD or n (%).

Abbreviations: AA, African American; BMI, body mass index; PS-PPR, pulmonary-systemic pulse pressure ratio.
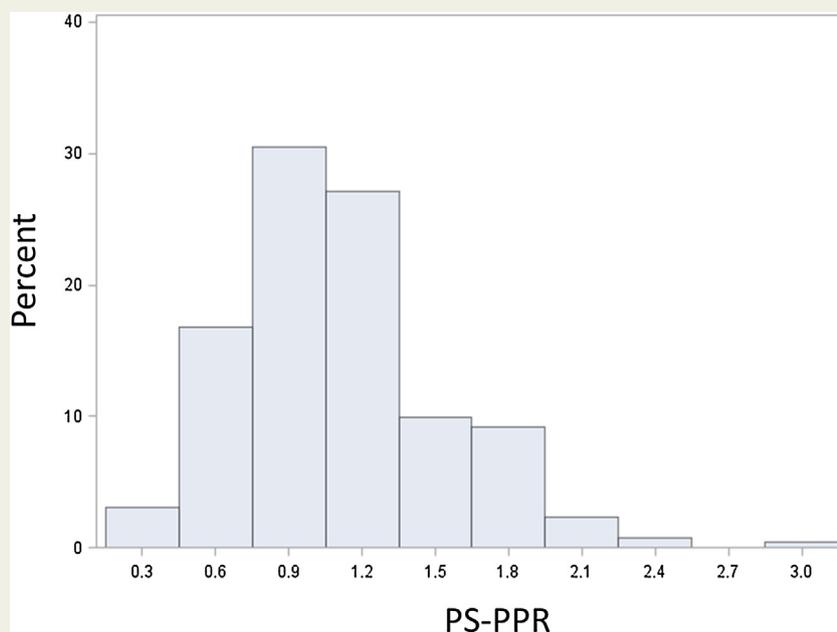
Figure 1 Distribution of Pulmonary Systemic Pulse Pressure Ratio (PS-PPR). The histogram demonstrates the distribution of PS-PPR in the entire cohort.

Discussion

The present study investigated the prognostic role of the novel haemodynamic index PS-PPR with short- and long-term survival among patients enrolled in the NIH-PPH Registry. Foremost, we found that PS-PPR was a strong and independent predictor of short-term and long-term mortality even after adjustment for the contemporary PHC risk model and other significant covariates. Second, patients in the highest quartile of PS-PPR had significantly worse survival compared with the lower quartiles. The highest quartile cohort also had haemodynamic indices that were associated with indices of severe RV failure (elevated RAP, higher PVR, and lower CI.) Third, as one would expect, there was a clinically manifest inverse

Table 2   Haemodynamic Parameters by PS-PPR Quartile.

Haemodynamic variables	PS-PPR Q1 (<0.78) N=66	PS-PPR Q2 (0.79–1.04) N=65	PS-PPR Q3 (1.05–1.30) N=62	PS-PPR Q4 (>1.30) N=69	P-value
SBP (mmHg)	133 ± 21	124 ± 22	122 ± 20	106 ± 22	<0.0001
DBP (mmHg)	76 ± 12	75 ± 15	77 ± 14	73 ± 12	0.48
Systemic pulse pressure (mmHg)	56 ± 17	48 ± 13	45 ± 10	36 ± 10	<0.0001
PASP (mmHg)	68 ± 17	84 ± 21	96 ± 21	106 ± 22	<0.0001
PADP (mmHg)	35 ± 12	40 ± 14	44 ± 15	47 ± 15	<0.0001
Mean PA Pressure (mmHg)	46 ± 12	56 ± 16	63 ± 16	69 ± 16	<0.0001
PA pulse pressure (mmHg)	33 ± 11	44 ± 12	51 ± 11	59 ± 14	<0.0001
PAWP (mmHg)	8 ± 4	9 ± 5	9 ± 5	9 ± 5	0.48
Mean RAP (mmHg)	8 ± 6	9 ± 6	10 ± 6	10 ± 6	0.03
CI (L/min/m^2)	2.77 ± 1.43	2.28 ± 0.92	2.10 ± 0.64	2.32 ± 1.32	0.003
RVSWI (g•m/m^2)	17 ± 10	17 ± 7	18 ± 8	21 ± 10	0.08
TPG (mmHg)	37 ± 11	46 ± 15	54 ± 15	60 ± 15	<0.0001
PVR (Woods units)	10 ± 6	16 ± 14	17 ± 9	20 ± 11	<0.0001

Values are presented as mean ± SD.

Abbreviations: PS-PPR, pulmonary-systemic pulse pressure ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; mean PA pressure, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; mean RAP, mean right atrial pressure; CI, cardiac index; RVSWI, right ventricular stroke work index; TPG, transpulmonary gradient; PVR, pulmonary vascular resistance.
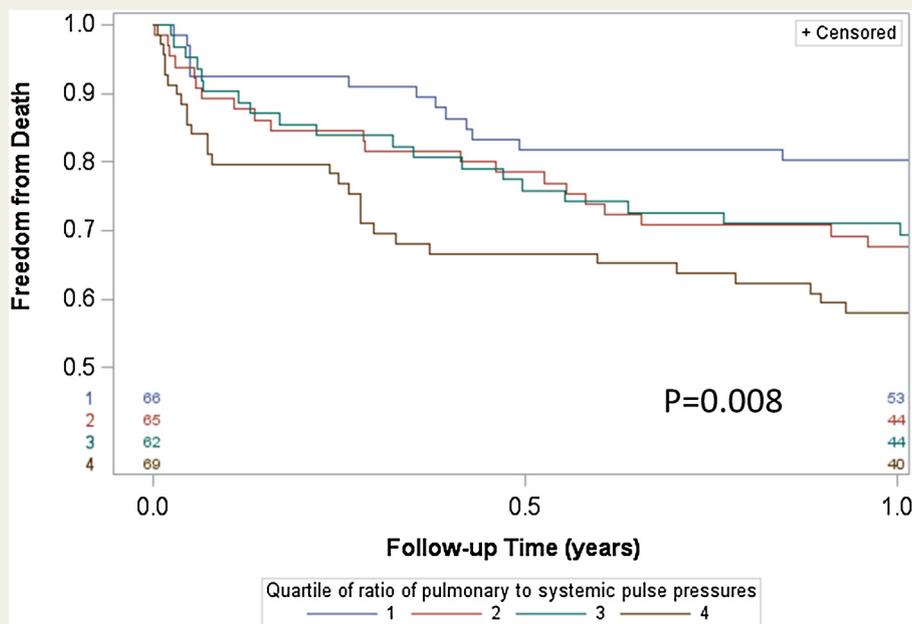
Figure 2 Short-Term Survival Based on Pulmonary Systemic Pulse Pressure Ratio (PS-PPR). The survival for patients by quartile of PS-PPR during the first year of follow-up is shown. Survival was significantly different among the groups (p = 0.008).

relationship between a rising PASP and a decrease in the systemic systolic blood pressure.

It is accepted that the prognosis of PAH is significantly influenced by the functional status of the RV. The anatomic relationship of the RV with the left ventricle (LV) through interlacing muscle fibres and a shared septum and pericardium facilitates coupling between the two chambers in a way that enhances optimal cardiac performance. Bernheim [12] was the first to postulate that haemodynamic perturbation of one chamber leads to the alteration in function of the contralateral chamber. More specifically for PAH, the ''reverse Bernheim'' effect describes the relationship in which LV function deteriorates in the face of a failing RV. Dexter [13] described this ''reverse Bernheim'' phenomenon when he demonstrated the
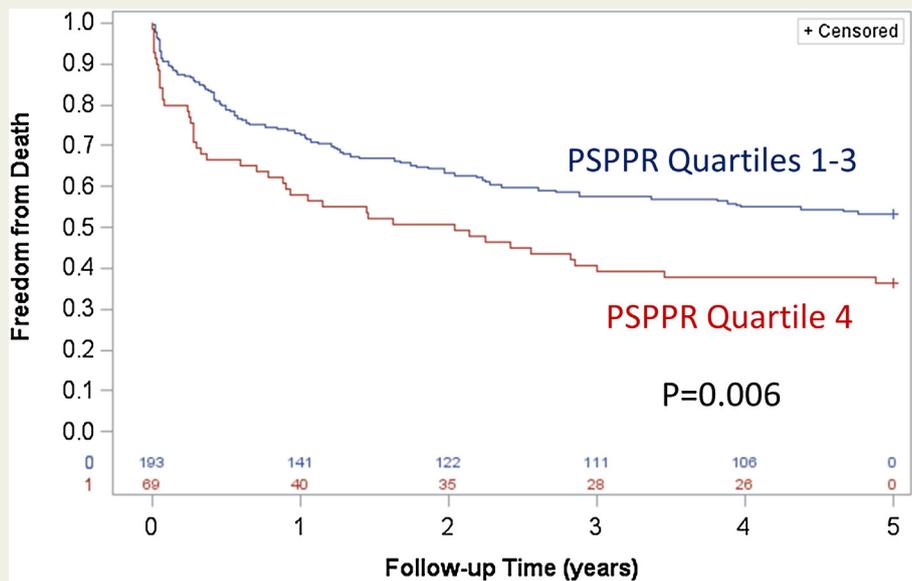

Figure 3 Long-Term Survival Based on Pulmonary Systemic Pulse Pressure Ratio (PS-PPR). The survival for patients in the highest quartile of PS-PPR versus the rest of the cohort is shown during 5 years of follow-up. Survival was significantly different among groups (p = 0.006).

Table 3 Bivariable Cox Regression Analysis for Mortality.

	HR (95% CI)	Chi square χ^2	P-value
PS-PPR (per 1 unit)	2.06 (1.40–3.02)	13.6	0.0002
PHC-risk (per 0.01)	0.96 (0.93–0.98)	18.0	<0.0001
BMI (per kg/m^2)	0.96 (0.93–0.98)	11.0	0.0009
RAP (per mmHg)	1.07 (1.04–1.09)	22.1	<0.0001
mPAP (per mmHg)	1.02 (1.01–1.03)	15.5	<0.0001
CI (L/min/m^2)	0.68 (0.53–0.87)	9.7	0.002

Abbreviations: PS-PPR, pulmonary systemic pulse pressure ratio; PHC-Risk, pulmonary hypertension connection risk equation; BMI, body mass index; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; CI, cardiac index.

deterioration of LV function in patients with atrial septal defects who had developed RV pressure and volume overload. PS-PPR is an integrated haemodynamic index that accounts for this close haemodynamic biventricular coupling. The component variables of PS-PPR are pulmonary artery pulse pressure as the numerator and systemic pulse pressure as the denominator. Pulmonary arterial pulse pressure reflects both right ventricular contractility and the pulmonary artery capacitance, and it is influenced by both pulsatile and resistive load conditions [14–17]. Taken in isolation, PA pulse pressure has not been shown to linearly correlate with mortality [14]; however, there are associations with vascular injury and remodelling [18]. Systemic pulse pressure, on the other hand, is largely reflective of LV function and arterial capacitance and has a complex relationship with mortality. For instance, in a

Table 4 Multivariable Cox Regression Model for Survival.

	HR (95% CI)	Chi square χ^2	P-value
PS-PPR (per 1 unit)	1.81 (1.13–2.88)	6.1	0.01
PHC-risk (per 0.01)	0.94 (0.92–0.96)	38.1	<0.0001
Mean PAP (per mm Hg)	1.02 (1.01–1.03)	11.3	0.008
BMI (per kg/m2)	0.93 (0.90–0.96)	21.4	<0.0001

Abbreviations: PS-PPR, pulmonary systemic pulse pressure ratio; PHC-Risk, pulmonary hypertension connection risk equation; BMI, body mass index.

general population, a high systemic pulse pressure predicts cardiovascular mortality [19–23], while in patients with advanced disease a low systemic pulse pressure has consistently been shown to correlate with a decreased CI and survival [19,24–27]. Similarly, in our current study, we found a significant inverse relationship between systemic pulse pressure (driven by a low systemic systolic pressure) and disease severity based on the PS-PPR quartile stratification, further supporting the importance of ventricular interactions in PAH disease progression [4–7,28].

Our findings are physiologically consistent with other reports highlighting the prognostic implications of systemic systolic blood pressure on mortality in PAH [28,29]; however, this novel measure demonstrates the critical impact of pulmonary and systemic pulse pressures on outcomes in PAH based on RV-LV coupling. Taken together, PS-PPR is an index that incorporates the cardiovascular circulatory efficiency accounting for the central role of ventricular interactions in PAH. The failing RV has deleterious effects on the LV, either directly (through altered septal mechanics and direct impingement) or indirectly through LV maladaptative changes accounting for systolic dysfunction resulting from ventricular muscle fibre atrophy [7]. It is evident from our findings that PS-PPR changes with disease progression. As we have demonstrated in this study, the directionality of this change tended towards higher values of PS-PPR. Conceptually, there may be a threshold at which the PS-PPR would conceivably decrease in the terminal phases of PAH when PA systolic pressure decreases due to a failing RV. Even so, this end stage state may also be balanced by low systemic pressures due to impaired left ventricular filling from a failing RV ventricle. This was, however, not demonstrated in our study. Further studies are needed to examine changes in PS-PPR with pulmonary vasodilator therapy.

In summary, we found that PS-PPR, an integrative index of interventricular interaction, is associated with disease severity and mortality among patients with group 1 PH in the NIH-PPH database. To our knowledge this is the first study to use PS-PPR in the risk stratification for group 1 PH patients. The strong predictive value and relative computational ease support further research and use of this index in expanded settings.

Limitations

While we believe this present study provides strong evidence to support further use of PS-PPR, we do recognise several limitations to our study. Although the NIH-PPH Registry offers high-quality data for a large cohort of PAH patients, therapeutic options have evolved since this time with more widespread availability of pulmonary vasodilator therapies [30–34], and reports from more recent registries have demonstrated a demographic shift toward an older patient population and a modest increase in the percentage of patients surviving the initial diagnosis. Guidelines for the diagnosis and treatment of pulmonary hypertension have also evolved [35]; however, as previously noted, greater than 99% of the
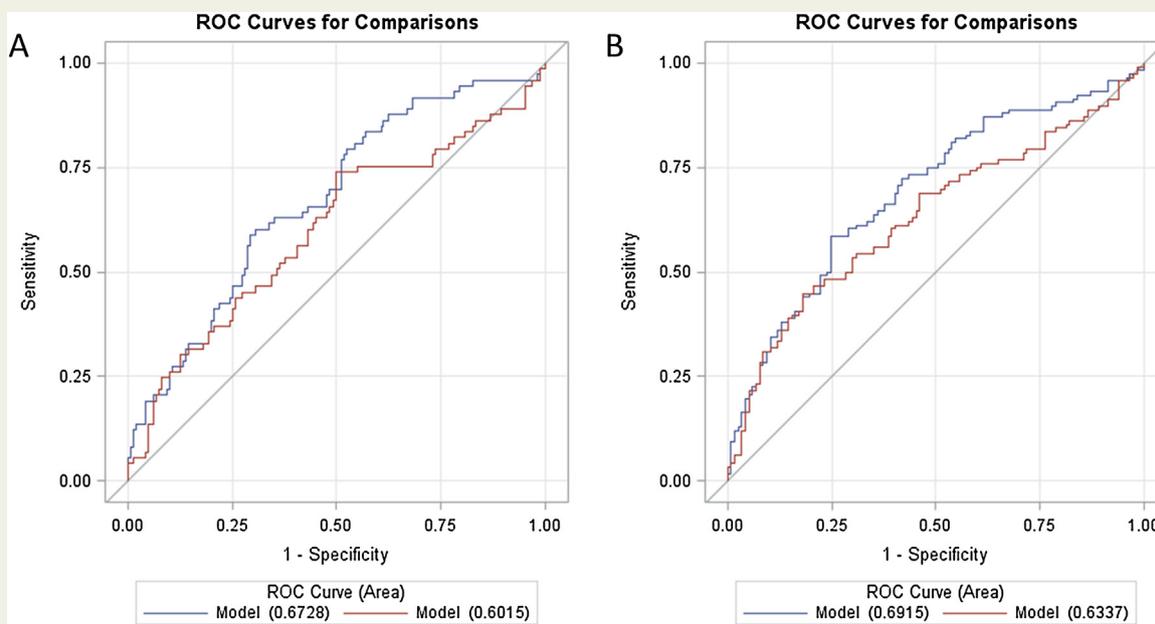
Figure 4 Receiver Operating Characteristic (ROC) Analysis. ROC curves are shown for the model with PHC risk equation (red) and the model with pulmonary systemic pulse pressure ratio (PS-PPR) added to pulmonary hypertension (PHC) risk equation (blue) for survival over 1 year (A) and survival over 5 years (B).

NIH-PPH cohort meet current criteria for the diagnosis of PAH based on the PVR [11].

In addition, we also recognise that there may be some subtypes of group 1 PH in which PS-PPR may need to be further evaluated. For example, in the setting of conditions with significant shunting such as Eisenmenger syndrome, ventricular interactions may be further altered. It is conceivable that the presence of right to left shunting characteristic of Eisenmenger syndrome may modify the PS-PPR to some extent. We speculate that the shunting effect would not only alter the systemic and pulmonary pressures but also the ventricular interactions as a result of increased left ventricular volume. Further studies are needed to examine the relationship of PS-PPR in this patient population.

Conclusions

Pulmonary to systemic pulse pressure ratio is an independent predictor of survival in patients with PAH in the NIH-PPH Registry even after adjustment for currently used risk stratification tools, such as the PHC risk model. This highlights the critical role of RV-LV coupling in these patients and the utility of the PS-PPR as a parameter to characterise RV-LV coupling. These findings support further study of this novel index for guiding treatment and prognosis in PAH patients.

Disclosures

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose. The work performed on this project by one of the authors (KB) was supported by NIH grant R03 HL135463.

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