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ORIGINAL ARTICLE

Haemodynamically Derived Pulmonary Artery Pulsatility Index Predicts Mortality in Pulmonary Arterial Hypertension

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Background Pulmonary artery (PA) pulsitility index (PAPi) is a novel haemodynamic index shown to predict right ventricular failure in acute inferior myocardial infarction and post left ventricular assist device surgery. We hypothesised that PAPi calculated as [PA systolic pressure – PA diastolic pressure]/right atrial pressure (RAP) would be associated with mortality in the National Institutes of Health Registry for Primary Pulmonary Hypertension (NIH-RPPH).

Methods The impact of PAPi, the Pulmonary Hypertension Connection (PHC) risk score, right ventricular stroke work, pulmonary artery capacitance (PAC), other haemodynamic indices, and demographic characteristics was evaluated in 272 NIH-RPPH patients using multivariable Cox proportional hazards (CPH) regression and receiver operating characteristic (ROC) analysis.

Results In the 272 patients (median age 37.7 +/− 15.9 years, 63% female), the median PAPi was 5.8 (IQR 3.7–9.2). During 5 years of follow-up, 51.8% of the patients died. Survival was markedly lower (32.8% during the first 3 years) in PAPi quartile 1 compared with the remaining patients (58.5% over 3 years in quartiles 2–4; $p < 0.0001$). The best multivariable CPH survival model included PAPi, the PHC-Risk score, PAC, and body mass index (BMI). In this model, the adjusted hazard ratio for death with increasing PAPi was 0.946 (95% CI 0.905–0.989). The independent ROC areas for 5-year survival based on bivariable logistic regression for PAPi, BMI, PHC Risk, and PAC were 0.63, 0.62, 0.64, and 0.65, respectively ($p < 0.01$). The ROC area for 5-year survival for the multivariable logistic model with all four covariates was 0.77 ($p < 0.0001$).

Abbreviations: BMI, Body Mass Index; CI, Cardiac Index; IQR, Interquartile range; LVAD, Left ventricular assist device; NIH-RPPH, National Institutes of Health Registry for Primary Pulmonary Hypertension; PA, Pulmonary artery; PAC, Pulmonary arterial capacitance; PADP, Pulmonary arterial diastolic pressure; PASP, Pulmonary arterial systolic pressure; PAH, Pulmonary arterial hypertension; PAPi, Pulmonary artery pulsatility index; PCWP, Pulmonary capillary wedge pressure; PHC, Pulmonary hypertension connection; PPP, Pulmonary artery pulse pressure; RAP, Right atrial pressure; ROC, Receiver operating characteristic; RV, Right ventricle; RVSWI, Right ventricular stroke work index; VA, Ventriculo-arterial; WHO, World Health Organization

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Conclusions Pulmonary artery pulsatility index was independently associated with survival in PAH, highlighting the utility of PAPi in combination with other key measures for risk stratification in this population.

Keywords Pulmonary hypertension • Heart failure • PAPi

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterised by pathological pulmonary vascular remodelling that invariably leads to severe elevation in the right ventricle (RV) afterload leading to RV failure and ultimately death [1,2]. In the early phase of the disease, the RV may be able to compensate, remodel and accommodate the increased afterload imposed on it. Anatomically, the RV is a thin walled structure and, by extension, subjected to a greater wall stress for any given unit increase in pressure. Furthermore, the RV is constitutively adapted to function more as a high volume–low pressure chamber making it extremely vulnerable to conditions of increased pressure overload. Although the locus of the initial insult in PAH lies within the pulmonary vasculature, the towering determinants of survival and overall prognosis are intricately correlated with the integrity of the RV function [3–5]. Thus, there is a growing interest in the physiological interactions between the RV and the pulmonary artery (PA) in patients with PAH [6]. Ventriculo-arterial (VA) haemodynamics in PAH have been demonstrated to parallel clinical outcomes [6]. A novel haemodynamic index that represents VA interaction has been recently described, PA pulsatility index (PAPi) calculated as [PA systolic pressure − PA diastolic pressure]/right atrial pressure (RAP), is associated with RV failure in patients with acute inferior myocardial infarction requiring temporary mechanical support as well in the postoperative patients with continuous flow left ventricular assist devices (LVADs) [7–9]. To our knowledge, the utility of PAPi in predicting mortality in patients with PAH has never been tested. Accordingly, we sought to test the hypothesis that low PAPi among patients with PAH would be associated with an increased probability of death in the National Institutes of Health Registry for Primary PH (NIH-RPPH) database.

Methods

The NIH-RPPH database was one of the first PAH registries established (patients included idiopathic, familial, and anorexigen-associated PAH; now called WHO Group 1) with the specific purpose of defining the natural history of the disease, determinants of severity and how the disease trajectory was modified with therapy. The methodology and enrolment including the determinants of 5-year survival have previously been published [3]. Briefly, PAH patients were enrolled from 32 medical centres across the United States. Pulmonary hypertension was haemodynamically defined as mean pulmonary artery pressure (mPAP) of greater than 25 mmHg at rest with a pulmonary artery wedge pressure (PAWP) of less than 15 mmHg. Other secondary causes of pulmonary hypertension were excluded. For example, pulmonary hypertension related to congenital abnormalities of the heart, lung and diaphragm, chronic pulmonary thromboembolic disease (now WHO group 4), sickle cell anaemia (WHO group 5), prior use of intravenous recreational drugs, chronic obstructive lung disease, interstitial lung disease, arterial hypoxaemia (WHO group 3), collagen vascular disease, parasitic disease with lung involvement, and pulmonary hypertension secondary to left heart disease (WHO group 2). The current analysis was conducted with a de-identified public release of the NIH primary PH database.

Study Design and Outcomes

In order to investigate the association between PAPi and survival probability in the NIH-RPPH database, we analysed all patients in the database with complete invasive haemodynamic variables for the calculation of PAPi and the pulmonary hypertension connection (PHC) risk equation. The PHC is a contemporary PAH risk equation that was derived in the current era of pulmonary vasodilator therapy [10].

We calculated PAPi and the PHC risk equation from invasively derived haemodynamic data. The 5-year probability of survival using the PHC risk equation was calculated as an integer between 0 and 1 based on the mPAP, right atrial pressure (RAP), and cardiac index (CI). Patients were then stratified based on PAPi quartiles with their representative haemodynamic profiles. The 5-year survival probabilities and group comparisons for the four PAPi quartiles characteristics were then evaluated using a multivariable Cox proportional hazards model. Kaplan-Meier survival curves were generated, and the log-rank statistic was used to determine differences between groups. Multivariable logistic regression and receiver operating characteristic (ROC) analysis were used to analyse the impact of PAPi and other key covariates on 5-year survival.

Statistics Analysis

Statistical analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). Analyses of categorical variables were conducted using the Chi-square test. The Fisher's exact test was used for categorical variables with low frequencies. The Wilcoxon rank sum test was used to test for differences in continuous variables. Categorical variables are presented as frequencies with percentages, whereas continuous variables are described using medians and interquartile ranges (IQR). Survival analysis and Kaplan-Meier plots are used to show differences in adverse events between groups with stratification based on key predictor variables. The log rank test was used to compare differences between groups. Multivariable Cox proportional hazards regression and multivariable logistic regression were used to model associations of multiple independent variables of interest with the endpoints of interest during follow-up. Receiver operating characteristic curves

were constructed based on logistic regression results. An alpha value of 0.05 was used for statistical significance.

Results

Baseline Characteristics

The database for the NIH-RPPH contains records for 310 patients. Of these, 272 had complete invasive haemodynamics for determination of the PHC risk equation and the PAPi, and these patients (n = 272) were used in the present analysis. The mean age of patients was 37.7 ± 15.9 years old, 63% were female, and 72% had race reported as ''white''. 141 of the 272 patients (51.8%) died during 5 years of follow-up. The distribution of baseline demographic characteristics, by quartile of PAPi is shown in Table 1, while the distribution of baseline haemodynamic characteristics by quartile of PAPi is shown in Table 2. Of note, there were no significant differences in age, gender, or race in PAPi quartiles. With respect to haemodynamic measurements, Table 2 demonstrates that the following variables were significantly different among PAPi quartiles: PAWP, PA diastolic pressure (PADP), mean RA pressure, PA pulse pressure (PPP), RV stroke work index (RVSWI), and cardiac index (CI).

Distribution of PAPi

As shown in Figure 1, the distribution of PAPi was skewed to the right in this cohort with a median value of 5.8 (IQR 3.7–9.2). Higher values above 10–56 were present and driven by either low right atrial pressure or high pulmonary pulse pressures.

Survival Analysis

As shown in Figure 2, survival was different among PAPi quartiles (log-rank p = 0.0001) and was lowest in the PAPi quartile 1. The separation between the quartile 1 survival curve

Table 1 Demographics of the population cohort by quartiles (Q1–Q4).

Variables	PAPi Q1 (<3.7) n = 67	PAPi Q2 (3.7–5.8) n = 69	PAPi Q3 (5.9–9.2) n = 68	PAPi Q4 (>9.2) n = 68	P-value
Age	38 (28-48)	40 (33-50)	35 (26-46)	36 (23-48)	0.13
Female gender (n, %)	42 (63%)	40 (58%)	39 (57%)	49 (72%)	0.26
Race (%)					
''White''	54 (78%)	50 (74%)	49 (72%)	43 (63%)	0.21
AA	9 (13%)	6 (9%)	9 (13%)	13 (19%)	
Other	6 (9%)	11 (17%)	10 (15%)	12 (18%)	
BMI	23 (19-28)	24 (20-26)	22 (19-27)	23 (19-25)	0.62

Abbreviations: AA, African American; BMI, body mass index; PAPi, pulmonary artery pulsatility index.

Table 2 Haemodynamic measurements and calculation by quartiles (Q1–Q4).

Variables	PAPi Q1 (<3.7)	PAPi Q2 (3.7-5.8)	PAPi Q3 (5.9-9.2)	PAPi Q4 (>9.2)	P-value
Directly measured haemodynamics					
Mean PAP (mmHg)	58 (48-67)	56 (48-64)	54 (44-65)	55 (48-65)	0.75
PCWP (mmHg)	10 (7-13)	9 (6-11)	8 (6-10)	5 (4-8)	<0.0001
PASP (mmHg)	84 (70-95)	85 (72-100)	85 (70-103)	90 (76-104)	0.40
PADP (mmHg)	43 (33-50)	40 (34-46)	36 (30-45)	35 (30-43)	0.01
Mean RAP (mmHg)	17 (13-21)	10 (38-12)	7 (5-8)	3 (2-5)	<0.0001
Calculated haemodynamics					
TPG (mmHg)	46 (38-55)	46 (36-57)	45 (36-57)	50 (42-59)	0.38
PVR (Wood units)	15 (10-19)	12 (8-19)	12 (9-17)	12 (9-19)	0.28
PA pulse pressure (mmHg)	40 (30-53)	45 (37-55)	50 (38-58)	53 (44-60)	<0.0001
PA capacitance (ml/mmHg)	0.8 (0.6-1.2)	1.0 (0.7-1.7)	0.9 (0.5-1.5)	0.9 (0.6-1.3)	0.62
RVSWI (g/m^2)	10 (8-14)	16 (12-20)	20 (13-25)	24 (15-28)	<0.0001
PA elastance (mmHg/ml)	2.6 (2-3)	1.9 (1-3)	1.8 (1-3)	2.0 (1-3)	0.10
CI ($L/min/m^2$)	1.8 (1-2)	2.1 (2-3)	2.2 (2-3)	2.5 (2-3)	<0.0001

Abbreviations: CI, cardiac index; PA, pulmonary artery; PAP, pulmonary artery pressure; PADP, pulmonary artery diastolic pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricle stroke work index; TGP, transpulmonary gradient.

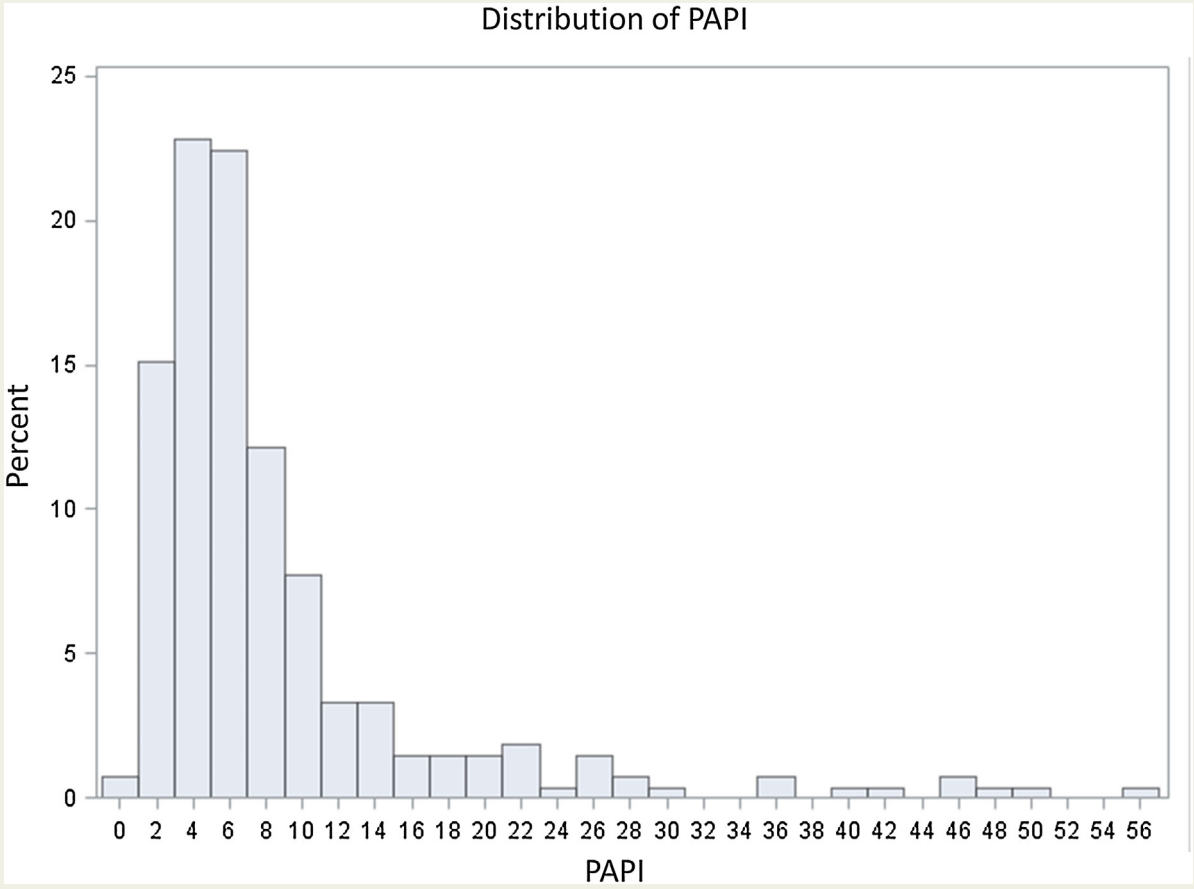

Figure 1 Histograms of (A) PAPi Distribution. The histogram shows the distribution of the pulmonary artery pulsatility index (PAPi).

and the survival curves for quartiles 2–4 is evident within the first few months of follow-up. Survival in the middle PAPi quartiles was similar, while separation between the quartile 4 survival curve and the quartile 2–3 survival curves became more prominent after the first year of follow-up.

Because the survival curve for quartile 1 was distinctly worse compared with the survival curves for quartiles 2–4, we constructed survival curves dichotomised for these two groups in Figure 3. The distinct prognosis for patients in PAPi quartile 1 at baseline compared with the other groups is evident graphically and is statistically significant ($p < 0.0001$). One-year survival was 50.7% in PAPi quartile 1 versus 74.6% in the remaining patients, and 3-year survival was 32.8% in PAPi quartile 1 versus 58.5% in the remaining patients ($p < 0.0001$).

Bivariable Associations for Haemodynamic Parameters With Respect to Survival With Cox Proportional Hazards Regression

Bivariable Cox proportional hazards regression was performed to evaluate associations for demographic and haemodynamic variables with survival (Table 3). Significant bivariable hazard ratios were obtained for PAPi, the PHC risk equation, body mass index (BMI), RVSWI, PA capacitance (PAC), PA elastance, and right atrial pressure. The bivariable hazard ratio for PAPi was 0.955 (95% CI 0.927–0.983) per unit increase. Right atrial pressure, however, had an even stronger association with adverse events than PAPi 1.064 (95% CI 1.037–1.092) per unit increase, $p < 0.0001$.

Multivariable Associations for Haemodynamic Parameters With Respect to Survival With Cox Proportional Hazards Regression

Variable selection for the multivariable Cox proportional hazards regression model was performed iteratively with only variables that had an adjusted p-value less than 0.05 accepted for the final model. As shown in Table 4, the best four-variable model included PAPi, the PHC-Risk score (range 0–1), BMI, and PAC. When right atrial pressure was added as a fifth covariate in this model, it was not statistically significant ($p = 0.99$), and all four other covariates remained significant ($p < 0.05$) The adjusted hazard ratio for PAPi in this model was 0.946 (95% CI 0.905–0.989) per unit increase in PAPi, indicating that increasing PAPi was associated with better outcomes. As hypothesised, a PHC score closer to 1 was associated with better

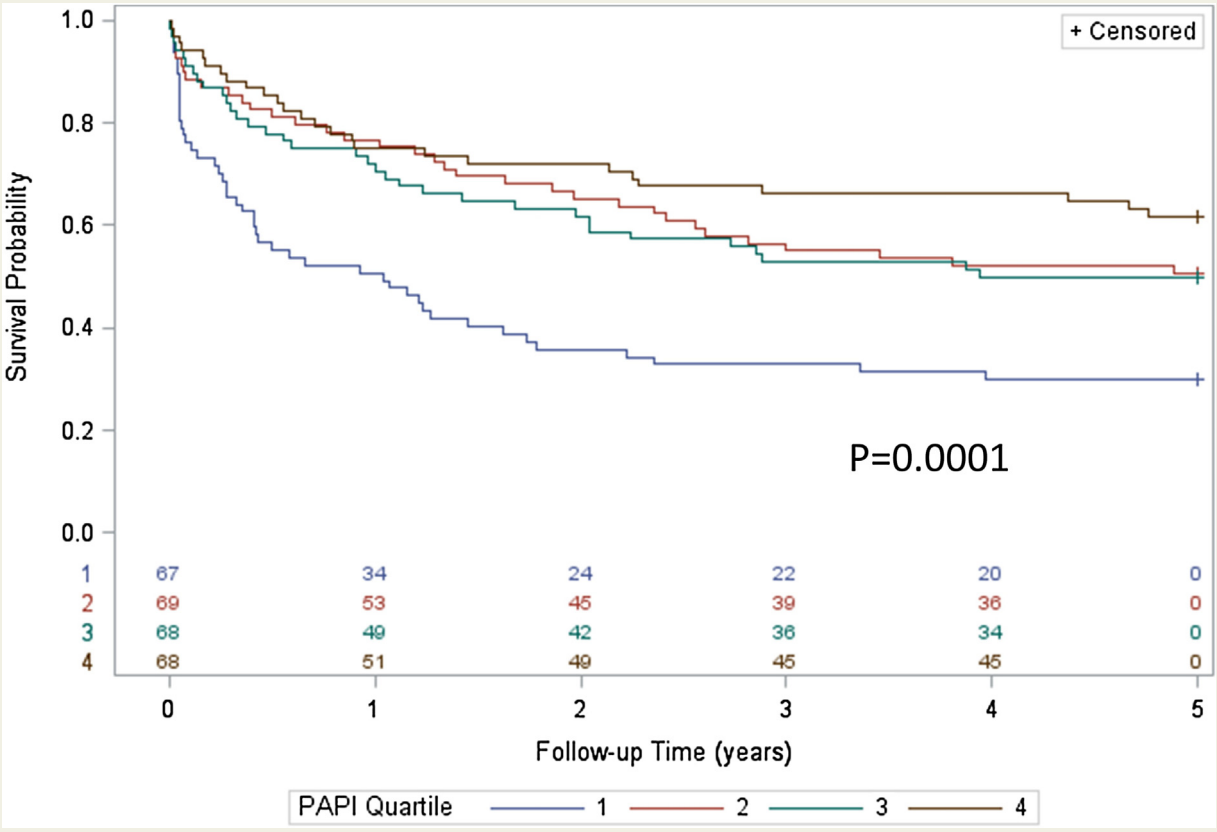

Figure 2 Kaplan Meier Survival Curves for the Quartiles of PAPi. Kaplan Meier survival curves are shown by quartiles of the pulmonary artery pulsatility index (PAPi).

outcomes, as was increasing BMI and increasing PAC. None of the other haemodynamic or demographic variables (including age and gender) were significant when adjusted for these four covariates.

Receiver Operating Characteristic Analysis and Multivariable Logistic Regression Model

The corresponding multivariable logistic regression analysis for these covariates for the outcome of 5-year survival is shown in Table 5. Pulmonary artery pulsatility index had an odds ratio (OR) of 0.930 (95% CI 0.877–0.986) and the second-highest chi-square statistic in the model. The corresponding receiver operating characteristic (ROC) analysis is shown in Figure 4. The ROC areas for 5-year survival for bivariable models with PAPi, BMI, PHC Risk, and PAC were 0.63, 0.62, 0.64, and 0.65, respectively ($p < 0.01$ for all). The ROC area for all four covariates was 0.77 ($p < 0.0001$).

Discussion

The present analysis investigated the relationship between a novel haemodynamic marker, PAPi and the probability of 5-year survival in patients with pulmonary arterial hypertension in the NIH-RPPH database. Our results demonstrate that PAPi is strongly associated with mortality among patients with PAH. The first key finding was that decreased PAPi was independently associated with mortality during the 5 years of follow-up even after adjustment for the PHC risk equation and key haemodynamic indices. Second, patients in the lowest PAPi quartile had a profile of haemodynamic indices associated with severe RV failure. Notably, these patients had significantly elevated RAP, lower CI, and RSVWI. Third, the range of distribution of PAPi in PAH was wider than that reported in prior PAPi studies involving acute RV failure (in the clinical context of inferior acute myocardial infarction (AMI) and postoperative cLVAD placement) [7–9]. This broader range of PAPi distribution may very well be a reflection of the sustained adaptive RV remodelling in the face of persistently elevated PA pressures, in marked contrast to the RV failure in relation to acute inferior MI and postoperative LVAD.

In PAH, increased afterload impairs RV contractility leading to RV failure and death. The degree to which the RV adapts to the chronically elevated pulmonary artery pressures is a key determinant of survival and prognosis [11,12]. Pulmonary artery pulsatility index is an integrated haemodynamic index of VA coupling, and more specifically, a marker of RV adaptive response to afterload. The component variables used in the calculation of PAPi are pulmonary artery pulse pressure (PPP) as the numerator and RAP as

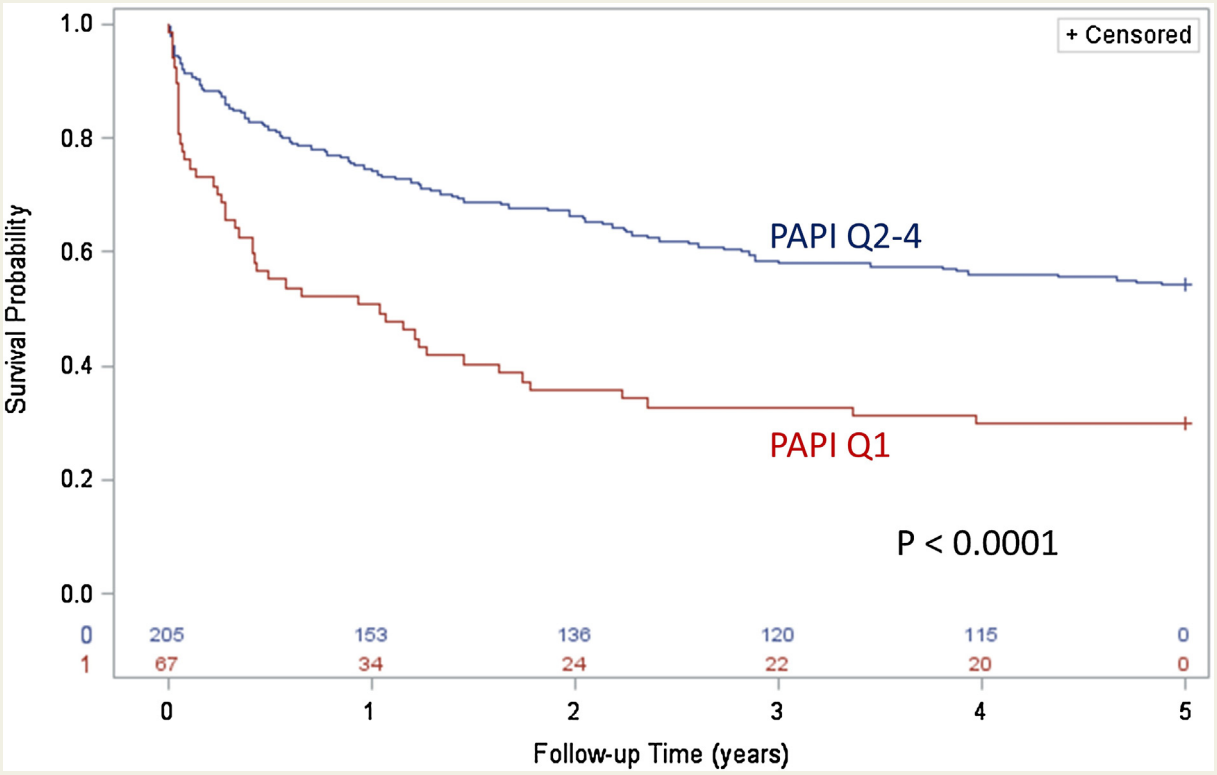

Figure 3 Kaplan Meier Survival Curves for PAPi. Kaplan Meier survival curves comparing the pulmonary artery pulsatility index (PAPi) in the lowest quartile versus remaining patients are shown.

Table 3 Bivariable (Univariable) Cox Regression Analysis for Survival.

	HR (95% CI)	Chi Square χ^2	P-value
PAPi (per 1 unit)	0.955 (0.927-0.983)	9.6	0.002
PHC-RISK (per 0.01)	0.954 (0.934-0.974)	19.2	<0.0001
BMI (per kg/m^2)	0.959 (0.935-0.984)	10.1	0.002
RVSWI (g/m^2)	0.965 (0.941-0.990)	7.6	0.006
PAC (per ml/mmHg)	0.529 (0.378-0.740)	13.8	0.002
PCWP (per mmHg)	1.005 (0.970-1.041)	0.08	0.78
RAP (per mmHg)	1.064 (1.037-1.092)	22.6	<0.0001

Abbreviations: BMI, body mass index; PAC, pulmonary artery capacitance; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricle stroke work index.

the denominator. Pulmonary artery pulse pressure reflects the combined effects of RV contractility and pulmonary vascular distensibility (pulmonary arterial capacitance) [13,14]. Taken in isolation, PPP in prior studies has not been shown to linearly correlate with mortality [15]. However, PPP invariably rises with the progression of PAH and parallels a worsening of pulmonary vascular bed stiffness. Distal pulmonary vascular bed stiffness mirrors elevations in pulmonary vascular resistance (PVR), a pernicious marker of mean resistive load and pulmonary arterial stiffness. Importantly this has profound haemodynamic implications on the RV. For example, decreased pulmonary arterial compliance enhances premature reflection of arterial wave from the distal vascular bed, further increasing the pulmonary artery systolic pressure (PASP). Taken together, this has a net effect of augmenting the pulsatile load on the right ventricle [16]. Importantly, however, the magnitude of PASP and the amplitude of PPP can both be attenuated by the development of severe RV dysfunction. When the RV contractile reserve is exhausted and the RV is unable to generate sufficient pulsatility to offset the increased afterload, then the PA pressures and PPP concurrently decrease [17]. We observed statistically significant lower PPP among patients in the lowest PAPi quartile compared to the rest of the quartiles, although the

Table 4 **Best Multivariable Cox Regression Model for Survival.**

	HR (95% CI)	Chi Square χ^2	p value
PAPi (per 1 unit)	0.946 (0.905-0.989)	6.0	0.01
PHC-RISK (per 0.01)	0.969 (0.944-0.996)	5.2	0.02
BMI (per kg/m^2)	0.943 (0.912-0.974)	12.2	0.0005
PAC (per ml/mmHg)	0.613 (0.434-0.864)	7.8	0.005

Abbreviations: BMI, body mass index; PAC, pulmonary artery capacitance; PAPi, pulmonary artery pulsatility index; PHC, pulmonary hypertension connection risk equation.

Table 5 **Best Multivariable Logistic Regression Model for 5-Year Survival (ROC = 0.774).**

	OR (95% CI)	Chi Square χ^2	p value
PAPi (per 1 unit)	0.930 (0.877-0.986)	5.9	0.02
PHC-RISK (per 0.01)	0.944 (0.899-0.991)	5.5	0.02
BMI (per kg/m^2)	0.899 (0.849-0.951)	13.6	0.0002
PAC (per ml/mmHg)	0.614 (0.388-0.971)	4.4	0.04

Abbreviations: BMI, body mass index; PAC, pulmonary artery capacitance; PAPi, pulmonary artery pulsatility index; PHC, pulmonary hypertension connection risk equation; ROC, receiver operating characteristic.

mean pulmonary artery pressure was not statistically different between these groups. As we anticipated, the lowest PAPi quartile had significantly higher RAP signalling the important role of right-sided filling pressures in predicting RV failure. In fact, RAP in isolation on bivariable analysis (Table 3) had a higher odds ratio than PAPi (22.1 vs 9.6), implying that the strength of PAPi in predicting outcomes was driven by the increase in RAP.

There is overwhelming evidence from multiple studies validating the prognostic role of elevated RAP in PAH [3,10,18,19]. The fact that the lowest PAPi quartile had a constellation of unfavourable haemodynamic variables associated with poor RV function (low CI and RVSWI) [3,18], was perhaps a reflection of the maladaptive heterometric remodelling of the RV in the face of chronically elevated RV afterload. It has been previously shown, within normal physiological limits, that the RV adapts to increased afterload by increasing contractility (without chamber dilatation), through a homeometric response referred to as the Anrep effect [20,21]. In addition to the aforementioned autoregulatory mechanism, right ventricular performance is further maintained, in conditions of chronically elevated RV afterload, by yet another adaptive mechanism that involves RV chamber dilatation (heterometric autoregulation) in line with the Frank-Starling law. However, these adaptive mechanisms come at a price of greater increase in right ventricular end-diastolic filling pressures and central venous congestion as evidenced by the haemodynamic profiles in this cohort [22,23]. Additionally, we noted a higher PAWP in the lower PAPi quartile compared to the rest of the quartiles (albeit below the threshold 15 mmHg). One could speculate that the higher left-sided filling pressures in the lowest quartile group were related to abnormalities in left ventricular relaxation owing to interventricular interactions. In severe PAH, decreased RV output results in decreased left ventricle end-diastolic volume (LVEDV) through mechanical impingement of the left chamber by a dilated RV (reverse Bernheim effect) [24,25]; however, we did not have echocardiographic data to correlate these haemodynamic parameters of severe RV failure and the effect on the left ventricle.

To our knowledge, this is the first study to employ PAPi in the risk stratification of patients with PAH. These findings support the use of PAPi in the risk stratification of patients with PAH. From a clinical utility standpoint, PAPi is easy to calculate and relies on only three invasively measured parameters (PASP, PADP and RAP) and may be better applied in combination with other variables (Figure E) rather than in isolation. The sparse availability of clinical risk stratification tools in PAH dictates the adoption of multiple risk models. Accordingly, there have been clarion calls for the adoption of more robust markers and endpoints that mirror disease severity and track with treatment response [26–29].

Limitations

In this retrospective analysis of a well-conducted NIH-RPPH, we note some limitations worthy of mention; first, the phenotype of PAH patients has considerably changed over the years with respect to age and gender. The NIH-RPPH had relatively younger, predominantly female patients compared to the more contemporary PAH registries [30]. Second,

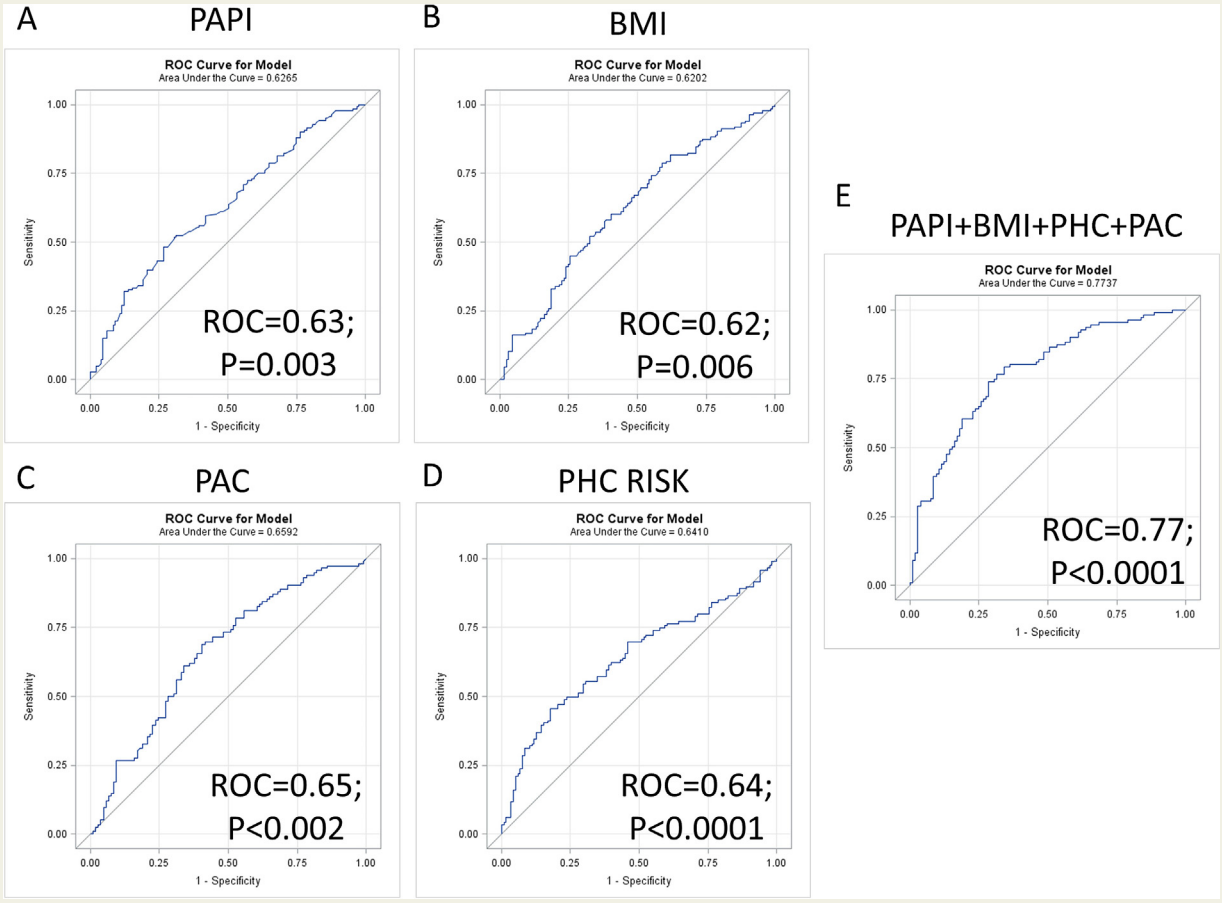

Figure 4 ROC Analysis. Receiver Operating Characteristic (ROC) curves are shown for the multivariable logistic regression model for 5-year survival with the pulmonary artery pulsatility index (A), BMI (B), PAC (C), the PHC risk equation (D), and all four variables together (E).
Abbreviations: BMI, body mass index; PAC, pulmonary artery capacitance; PHC, pulmonary hypertension connection

survival of patients with PAH in the current era of pulmonary vasodilator therapies has modestly improved by about 10%, in contrast to the era when this study was conducted [18,31]. Third, there have been multiple PH guideline updates since the conclusion of the Registry, including several schematic modifications in the classification system [32]. Fourth, we did not have echocardiographic images to correlate with the haemodynamic data. These are offset by the many strengths of this analysis, including a primary focus on objective haemodynamic measurements, the use of the contemporaneous PHC equation for risk adjustment and the multicentre enrolment nature of the study.

Conclusions

The PAPi was independently associated with survival in PAH patients even after adjustment for the PHC risk equation. Right atrial pressure in isolation, however, had higher odds of adverse events than PAPi. These findings support further investigation into the use of PAPi in multivariable models in guiding PAH risk stratification.

Disclosure Statement

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.

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