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ORIGINAL ARTICLE
Vascular medicine

Pulmonary artery capacitance and pulmonary vascular resistance as prognostic indicators in acute pulmonary embolism

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Aims The non-invasive calculation of right ventricular (RV) haemodynamics as pulmonary artery (PA) capacitance (PAC) and pulmonary vascular resistance (PVR) have proved to be feasible, easy to perform, and of high prognostic value. We, therefore, evaluated whether baseline PAC and PVR could predict clinical outcomes for patients with acute pulmonary embolism (PE).

Methods and results We prospectively followed 373 patients [mean (standard deviation) age, 64.1 (14.9) years; 58.4% were men, and 27.9% had cancer] who had acute PE and transthoracic echocardiography within 1 day of diagnosis from 1 March 2013 through 30 June 2020. Pulmonary artery capacitance was calculated as left ventricular stroke volume/(PA systolic pressure - PA diastolic pressure). Pulmonary vascular resistance was calculated as (tricuspid regurgitant velocity/RV outflow tract velocity time integral) $\times$ 10 + 0.16. These two variables were calculated retrospectively from the values obtained with transthoracic echocardiography. Pulmonary artery capacitance was acquired in 99 (27%) patients and PVR in 65 (17%) patients. Univariable and bivariable logistic regression analyses, and receiver operating characteristic curves were used to evaluate the ability of these haemodynamic measurements to predict mortality up to 6 months. After using bivariable models to adjust individually for age, cancer, and pulmonary hypertension. Pulmonary vascular resistance was associated with all-cause mortality at 3 months [area under the curve (AUC) 0.75, 95% confidence interval (CI) 0.61–0.86; $P = 0.01$], and 6 months (AUC 0.81; 95% CI 0.69–0.91; $P \leq 0.03$). Pulmonary artery capacitance was associated with all-cause mortality at 30 days (AUC 0.95; 95% CI 0.82–0.99; $P < 0.001$) and 3 months (AUC 0.84; 95% CI 0.65–0.99; $P = 0.003$).

Conclusion Non-invasive measurement of RV haemodynamics could provide prognostic information of patients with acute PE. Pulmonary artery capacitance and PVR are potentially important predictors of all-cause mortality in these patients and should be explored in future studies.

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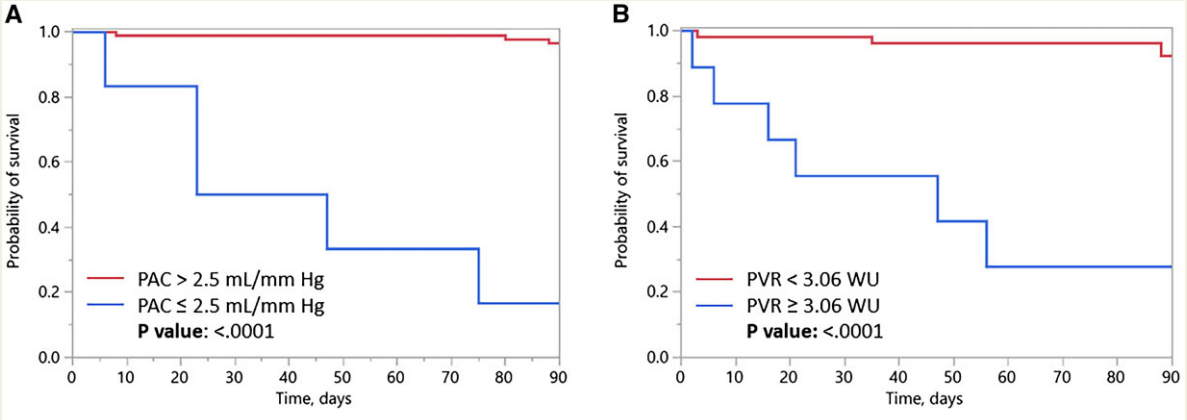
Graphical Abstract



Kaplan-Meier Survival Curves According to Pulmonary Artery Capacitance (PAC) and Pulmonary Vascular Resistance (PVR). A, All-cause mortality 90-day survival for PAC with optimal cutoff point, 2.5 mL/mm Hg. B, All-cause mortality 90-day survival for PVR with optimal cutoff point, 3.06 Woods Units (WU).

Keywords Echocardiography • Pulmonary embolism • Right ventricle

Introduction

The annual incidence of pulmonary embolism (PE) in the USA is 39–115 cases per 100 000 persons.[1] Haemodynamic status and the presence of myocardial dysfunction have been studied as prognostic indicators in this population.[2] Accordingly, PE is classified into three categories that reflect the patient's haemodynamic status and right ventricular (RV) function: (i) *massive PE* (also called *high-risk PE*) in patients who have signs of both haemodynamic instability (e.g. hypotension or cardiogenic shock) and RV dysfunction; (ii) *submassive PE* (also called *intermediate-risk PE*) in patients whose condition is haemodynamically stable, but they have signs of RV dysfunction; and (iii) *low-risk PE* in patients who do not have signs of haemodynamic instability or RV dysfunction.[1] Mortality among patients with massive PE is 25–65%[3]; with submassive PE, 3–14%[4]; and with low-risk PE, 1%.[5] The simplified pulmonary embolism severity index (sPESI) is another risk stratification tool that has been widely validated and used. It incorporates clinical bedside parameters and stratifies 30-day all-cause mortality risk into two groups: *low* (1% mortality) and *high* (11% mortality).[6]

Patients with acute PE commonly present with RV dysfunction due to a sudden increase in pulmonary vascular resistance (PVR) through thrombus obstruction, hypoxaemia, and pulmonary vasoconstrictors.[7] Pulmonary vascular resistance is directly related to the RV afterload, which implies that higher pulmonary resistance is associated with greater afterload. The acutely increased workload for the right heart leads to the development of RV dysfunction and adverse events.[8] In a study that evaluated PVR from echocardiographic measurements in 54 patients who had acute PE, PVR was found to be an independent predictor of all-cause mortality.[9] Non-invasive measurement of PVR has also proved useful for predicting all-cause mortality or other adverse events among patients with heart failure and pulmonary hypertension.[10,11] Pulmonary artery (PA) capacitance (PAC) is another potentially useful haemodynamic measurement that has proved to be a good predictor of mortality among patients with heart failure[12,13] and pulmonary hypertension,[14,15] but it has not been studied in acute PE.

Transthoracic echocardiography (TTE) is a quick, safe, non-invasive bedside diagnostic tool that is available in all hospital settings. With these qualities, TTE is a convenient method to assess haemodynamics in patients with acute PE. Furthermore, the non-invasive measurement of PVR and PAC with TTE has shown a strong correlation when compared with invasive measurements.[16,17]

The aim of this study was to evaluate whether PVR and PAC derived from TTE are useful parameters for risk stratification of patients with acute PE and prediction of all-cause mortality at 30 days, 3 months, and 6 months.

Methods

The study prospectively followed 373 consecutive patients who received a diagnosis of PE from 1 March 2013 through 31 July 2020, which was confirmed with contrast computed tomography (CT) or a ventilation-perfusion scan. All patients were diagnosed and treated at Mayo Clinic in Rochester, MN,[18] and they had been evaluated with echocardiography within 1 day after receiving the PE diagnosis. This study represents every patient with an acute PE in our institution. Patients younger than 18 years and those without Minnesota research authorization were excluded (*Figure 1*). Clinical data collected from the medical records included demographics, clinical characteristics, and comorbidities. The Mayo Clinic Institutional Review Board approved this study and waived the informed consent requirement if patients had provided research authorization.

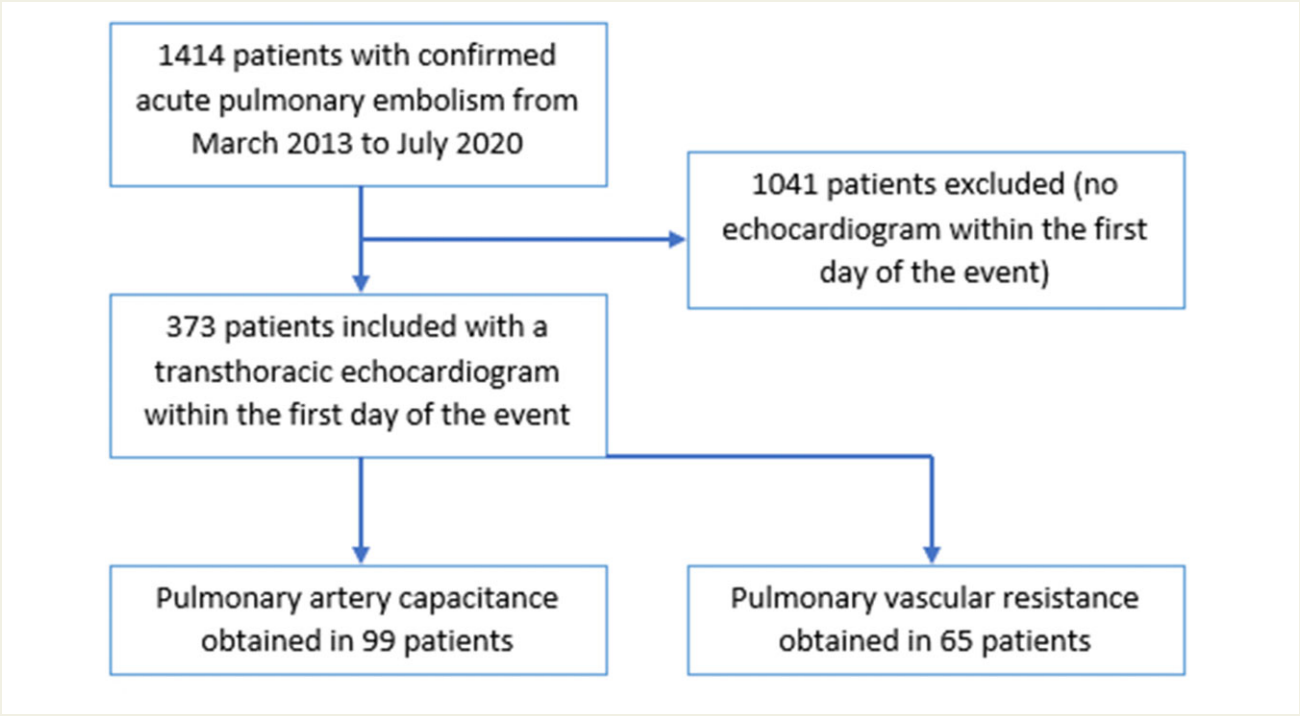


Figure 1 A flowchart of patients with confirmed acute pulmonary embolism.

Categorization of pulmonary embolism

Patients were categorized into one of three groups according to haemodynamic status and RV function as described above: massive PE (high-risk PE), submassive PE (intermediate-risk PE), and low-risk PE.[1] *Haemodynamic instability* was defined as the presence of cardiac arrest, obstructive shock, or persistent hypotension. *Right ventricular dysfunction* was defined according to the European Society of Cardiology guidelines by the presence of (i) a ratio of RV diameter to left ventricular (LV) diameter of 0.9 or more as measured with CT in a four-chamber view, (ii) positive results for cardiac troponins or natriuretic peptides, or (iii) echocardiographic findings of RV pressure overload, which include enlarged RV in the parasternal long-axis view, the McConnell sign, flattened interventricular septum, distended inferior vena cava, mobile thrombus in the right heart, decreased tricuspid annular plane systolic excursion (TAPSE), and decreased peak systolic velocity of the tricuspid annulus.[1]

The sPESI score variables[6] were used to estimate prognosis by classifying patients into low-risk and high-risk categories. Each of the six variables was worth 1 point; patients with a score of 0 points were classified as having a low risk of mortality, and those with a score of 1 or more points were considered to have a high risk of mortality.

Echocardiographic evaluation

Echocardiography was conducted by a registered diagnostic cardiac sonographer following the American Society of Echocardiography guidelines.[19,20] Data were extracted from the echocardiography reports for all eligible patients. Missing data were measured offline with the Echo Information Management System (Kardia Health Systems, Inc).

Pulmonary artery capacitance was calculated as described originally[14]: LV stroke volume/(PA systolic pressure - PA diastolic pressure). Pulsed wave Doppler was used to measure the velocity-time integral (VTI) of the LV outflow tract (LVOT) in either the apical long-axis view or the five-chamber view. Left ventricular outflow tract diameter was measured in the parasternal long-axis view in systole. Stroke volume was derived as follows: (cross-sectional area of the LVOT) $\times$ (VTI of the LVOT).[21]

Continuous-wave Doppler was performed across the tricuspid valve and the pulmonary valve to measure the peak systolic tricuspid regurgitant velocity (TRV) and the late diastolic pulmonary regurgitant velocity (PRV).[22] Right atrial pressure (RAP) was estimated from the inferior vena cava diameter and the inspiratory collapse as described elsewhere.[20] The systolic pulmonary arterial pressure was estimated with the modified Bernoulli equation [(4$\times$ TRV^2) + RAP]. The diastolic pulmonary arterial pressure was estimated from the end-diastolic PRV [(4$\times$ PRV^2) + RAP]. The PVR was estimated with the following formula: [TRV/RV outflow tract (RVOT) VTI] $\times$ 10 + 0.16].[16]

Pulsed wave Doppler sample volume was placed at the RVOT, and the VTI was measured.[22] Tricuspid annular plane systolic excursion was calculated by using M-mode through the lateral tricuspid annulus and measuring its longitudinal motion during peak systole.[23] Fractional area change (FAC) was calculated as [(RV end-diastolic area - RV end-systolic area)/RV end-diastolic area] $\times$ 100 as described elsewhere.[20] Tissue Doppler in an apical four-chamber view was used to measure systolic velocity at the tricuspid valve lateral annulus.[20]

Statistical analysis

Continuous variables were summarized as mean (SDs), and categorical variables were summarized as absolute values and percentages. The Shapiro–Wilk test was used to test the normality of the data. Between-group comparisons among variables were performed with the *t* test or Mann–Whitney test for continuous variables and with the χ^2 test or Fisher's exact test for categorical variables, as appropriate. One-way analysis of variance and the Tukey–Kramer test were used to compare continuous variables among three or more groups. The Kaplan–Meier

method was used to determine the all-cause mortality event-free survival rate, and differences between groups were assessed with the Wilcoxon signed rank test.

Nominal logistic regression analysis was used to evaluate PAC, PVR, and RAP for the prediction of massive PE, submassive PE, and low-risk PE categories. Analyses were also performed to determine PAC, PVR, the studied echocardiographic variables, and sPESI association with 30-day, 3-month, and 6-month mortality. Bivariable or multivariable analyses were performed based on the number of events per variable to adjust for clinical characteristics and comorbidities. Receiver operating characteristic (ROC) curve analysis was performed for only the statistically significant variables to assess the diagnostic value for PE categories and their association with mortality. The Youden index was used to determine the cut-off point with the highest sensitivity and specificity. A *P*-value <0.05 was considered statistically significant. JMP statistical software, version 14.1.0 (SAS Institute Inc), was used for the analyses of all data.

Results

The study included 373 patients [58.4% were men; mean age, 64.1 (14.9) years]. Massive PE was present in 32 patients (8.6%); submassive PE, in 189 (50.7%); and low-risk PE, in 152 (40.8%) (*Table 1*). The most common comorbidities were coronary artery disease (137 patients; 36.7%), heart failure (115; 30.8%), and cancer (104; 27.9%). Other clinical parameters and comorbidities are summarized in *Table 1*. Mild or moderate regurgitation was present in the tricuspid (185 patients; 49.6%), mitral (71; 19.0%), and pulmonary (51; 13.7%) valves. Supplementary material online, *Table S1* includes all collected echocardiographic parameters.

All-cause mortality

The cumulative incidence of all-cause mortality was 3% ($n = 12$) at 30 days, 5% ($n = 18$) at 3 months, and 9% ($n = 35$) at 6 months. Pulmonary embolism categories were not associated with all-cause mortality at 30 days, 3 months, or 6 months. Pulmonary artery capacitance was associated with all-cause mortality at 30 days ($P < 0.001$), 3 months ($P = 0.003$), and 6 months ($P = 0.01$) (*Tables 2* and *3*). Pulmonary vascular resistance was associated with all-cause mortality at 30 days ($P = 0.045$), 3 months ($P = 0.01$), and 6 months ($P = 0.03$). Age, cancer, and pulmonary hypertension were associated with mortality at 30 days, 3 months, and 6 months (Supplementary material online, *Tables S2–S4*).

Logistic regression and ROC analyses were performed for PAC, PVR, and sPESI and their association with all-cause mortality; results are summarized in *Table 4*. Pulmonary artery capacitance was a good predictor of all-cause mortality at 30 days [area under the curve (AUC) 0.95; 95% confidence interval (CI) 0.82–0.99]; 3 months (AUC 0.84; 95% CI 0.65–0.99); and 6 months (AUC 0.77; 95% CI 0.57–0.96). Pulmonary vascular resistance was a good predictor for 30-day mortality (AUC 0.75; 95% CI 0.48–0.95); 3-month mortality (AUC 0.79; 95% CI 0.58–0.94); and 6-month mortality (AUC 0.72; 95% CI 0.50–0.90). Simplified pulmonary embolism severity index predicted 30-day all-cause mortality with an AUC of 0.60 (95% CI 0.51–0.66), 3-month mortality with an AUC of 0.62 (95% CI 0.54–0.66), and 6-month mortality with an AUC of 0.64 (95% CI 0.59–0.67).

Table 1 Clinical characteristics and comorbidities of patients with acute PE

Variables	Patients ($N = 373$)
Age, mean (SD), years	64.1 (14.9)
Sex, *N* (%)	
Male	218 (58.4)
Female	155 (41.6)
Ethnicity not Hispanic or Latino, *N* (%)	362 (97.0)
Clinical parameter, mean (SD)	
SBP, mmHg	127.9 (23.3)
DBP, mmHg	78.1 (15.8)
HR, b.p.m.	92.0 (19.7)
Respiratory rate, rpm	19.9 (4.2)
SPO_2, %	94.9 (3.8)
Temperature, °C	36.7 (0.4)
Height, cm	172.1 (10.3)
Weight, kg	95.2 (25.5)
BSA, m^2	2.07 (0.28)
BMI	32.1 (8.3)
Massive PE, *N* (%)	32 (8.6)
Submassive PE, *N* (%)	189 (50.7)
Low-risk PE, *N* (%)	152 (40.8)
sPESI score ≥1, *N* (%)	269 (72.1)
Comorbidities, *N* (%)	
Coronary artery disease	137 (36.7)
Heart failure	115 (30.8)
Cancer	104 (27.9)
Diabetes	92 (24.7)
CKD	77 (20.6)
Atrial fibrillation	62 (16.7)
COPD	44 (11.8)
Ischaemic stroke	31 (8.3)
Peripheral vascular disease	26 (7.0)
Pulmonary hypertension	18 (4.8)

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); b.p.m., beats per minute; BSA, body surface area; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HR, heart rate; PE, pulmonary embolism; rpm, respirations per minute; SPO_2, oxygen saturation as measured by pulse oximetry; SBP, systolic blood pressure; sPESI, simplified Pulmonary Embolism Severity Index.

Due to our low number of events for PAC and PVR, we could not perform a multivariable model to adjust for clinical characteristics and comorbidities, instead, we performed bivariable models adjusting individually for age, cancer, and pulmonary hypertension (Supplementary material online, *Table S5*). All other results remained significant except for PVR with 30-day mortality after adjusting for pulmonary hypertension ($P = 0.05$) and PAC with 6-month mortality after adjusting for age ($P = 0.06$). Kaplan–Meier survival curves for PAC, PVR, and 3-month all-cause mortality are presented in *Figure 2*.

Right ventricular haemodynamics and pulmonary embolism categories

Mean (SD) PAC in patients with low-risk PE [4.04 (1.58)] was significantly higher ($P < 0.001$) than that in patients with massive PE

Table 2 Echocardiographic measurements, PE categories, and sPESI association with 30-day all-cause mortality

Predictor[a]	All patients (*N* = 373)	Alive at 30 days (*N* = 361)	Dead at 30 days (*N* = 12)	*P*-value[b]
PAC	3.04 (1.50)	3.10 (1.49)	1.13 (0.52)	<0.001
N	99	96	3	
PVR	2.98 (1.20)	2.89 (1.11)	4.15 (1.87)	0.045
N	65	60	5	
FAC	31.1 (11.9)	30.8 (11.2)	41.0 (27.1)	0.09
N	137	133	4	
TAPSE	19.7 (5.1)	19.8 (5.1)	17.8 (3.7)	0.25
N	268	260	8	
S′	0.13 (0.03)	0.013 (0.03)	0.11 (0.03)	0.15
N	337	326	11	
RAP	8.4 (4.8)	8.4 (4.8)	9.5 (4.0)	0.47
N	339	328	11	
sPESI score ≥1, *N* (%)	269 (72.1)	258 (71.5)	11 (91.7)	0.09
Massive PE, *N* (%)	32 (8.6)	31 (8.6)	1 (8.3)	0.98
Submassive PE, *N* (%)	189 (50.7)	181 (50.1)	8 (66.7)	0.26
Low-risk PE, *N* (%)	152 (40.8)	149 (41.3)	3 (25.0)	0.24

FAC, fractional area change; PAC, pulmonary artery capacitance; PE, pulmonary embolism; PVR, pulmonary vascular resistance; RAP, right atrial pressure; S′, systolic velocity of the tricuspid valve lateral annulus; sPESI, simplified Pulmonary Embolism Severity Index; TAPSE, tricuspid annular peak systolic excursion.
[a]Values are mean (SD) unless indicated otherwise.
[b]*P*-values result from univariable logistic regression analyses.

Table 3 Echocardiographic measurements, PE categories, and sPESI association with 3- and 6-month all-cause mortality

Predictor[a]	Alive at 3 months (*N* = 355)	Death at 3 months (*N* = 18)	*P*-value[b]	Alive at 6 months (*N* = 338)	Death at 6 months (*N* = 35)	*P*-value[b]
PAC	3.12 (1.50)	1.58 (0.74)	0.003	3.12 (1.51)	1.82 (0.87)	0.01
N	94	5		93	6	
PVR	2.84 (1.09)	4.18 (1.61)	0.01	2.85 (1.09)	3.85 (1.62)	0.03
N	58	7		56	9	
FAC	30.9 (11.2)	34.9 (21.9)	0.39	31.2 (11.0)	30.6 (18.4)	0.86
N	130	7		123	14	
TAPSE	19.7 (5.1)	19.4 (3.5)	0.78	19.7 (5.2)	19.7 (3.5)	0.99
N	254	14		245	23	
S′	0.13 (0.03)	0.12 (0.03)	0.65	0.13 (0.03)	0.13 (0.03)	0.22
N	320	17		305	32	
RAP	8.4 (4.8)	9.0 (4.0)	0.62	8.4 (4.8)	8.6 (4.1)	0.84
N	323	16		310	29	
sPESI score ≥1, *N* (%)	252 (71.0)	17 (94.4)	0.01	235 (69.5)	34 (97.1)	<0.001
Massive PE, *N* (%)	30 (8.5)	2 (11.1)	0.71	29 (8.6)	3 (8.6)	0.99
Submassive PE, *N* (%)	179 (50.4)	10 (55.6)	0.67	171 (50.6)	18 (51.4)	0.92
Low-risk PE, *N* (%)	146 (41.1)	6 (33.3)	0.51	138 (40.8)	14 (40.0)	0.92

FAC, fractional area change; PAC, pulmonary artery capacitance; PE, pulmonary embolism; PVR, pulmonary vascular resistance; RAP, right atrial pressure; S′, systolic velocity of the tricuspid valve lateral annulus; sPESI, simplified Pulmonary Embolism Severity Index; TAPSE, tricuspid annular peak systolic excursion.
[a]Values are mean (SD) unless indicated otherwise.
[b]*P*-values result from univariable logistic regression analyses.

[2.15 (1.14)] or submassive PE [2.33 (0.90)] (*Table 5*). Mean (SD) PVR in patients with submassive PE [3.45 (1.32)] was significantly higher ($P < 0.001$) than that in patients with low-risk PE [2.28 (0.66)]. Mean (SD) RAP was significantly different ($P < 0.001$) between all three PE categories [massive PE, 13.2 (4.9); submassive PE, 9.1 (4.9); low-risk PE, 6.6 (3.5)]. Mean (SD) TAPSE and systolic velocity of the tricuspid valve lateral annulus (S′) were significantly different ($P < 0.001$) between patients with low-risk PE and the other two PE categories. Mean (SD) RV FAC was significantly different ($P = 0.045$) between patients with low-risk PE and patients with massive PE. The association of clinical characteristics and comorbidities with PE categories is described in Supplementary material online, *Table S6*. Heart failure was associated with all the PE categories ($P = 0.001$).

When univariate analysis was used to evaluate the studied echocardiographic measurements and PE categories, the most significant predictors were PAC, PVR, and RAP; logistic regression models with ROC analyses were performed for these measures to predict massive, submassive, and low-risk PE (*Figure 3*). Predictors for PAC, PVR, and RAP are presented in *Table 6*. When PAC, PVR, and RAP were combined for prediction of PE categories, the best AUCs for massive, submassive, and low-risk PE were obtained (*Figure 3D*). Area under the curves were 0.93 for massive, 0.81 for submassive, and 0.89 for low-risk PE. Results remained significant after adjusting for heart failure.

Table 4 Predictors of all-cause mortality for patients with acute pulmonary embolism

Predictor	Mortality		
	30 days	3 months	6 months
Pulmonary artery capacitance			
AUC (95% CI)	0.95 (0.82–0.99)	0.84 (0.65–0.99)	0.77 (0.57–0.96)
Cut-off point	1.65	2.50	2.98
Sensitivity, %	100	100	100
Specificity, %	85	60	44
P-value	<0.001	0.003	0.01
Pulmonary vascular resistance			
AUC (95% CI)	0.75 (0.48–0.95)	0.79 (0.58–0.94)	0.72 (0.50–0.90)
Cut-off point	3.06	3.06	3.38
Sensitivity, %	80	86	67
Specificity, %	63	65	79
P-value	0.045	0.01	0.03
sPESI score ≥1			
AUC (95% CI)	0.60 (0.51–0.66)	0.62 (0.54–0.66)	0.64 (0.59–0.67)
Cut-off point	1	1	1
Sensitivity, %	92	95	97
Specificity, %	28	29	30
P-value	0.09	0.01	<0.001

AUC, area under the curve; sPESI, simplified pulmonary embolism severity index.

Discussion

To our knowledge, this is the largest single-centre study that has assessed the prognostic value of non-invasive RV haemodynamics (PAC and PVR) in patients with acute PE and the first study that has evaluated echocardiographic PAC in this population. Our main findings were the following: (i) PAC was associated with mortality at 30 days and 3 months. (ii) PVR was associated with mortality at 3 months and 6 months. (iii) The combination of PAC, PVR, and RAP can be used to discriminate massive, submassive, and low-risk PE.

In this study, PAC was associated with all-cause mortality at 30 days and 3 months. This can be explained by the influence that PAC has on RV workload. The energy the RV needs to eject blood to the pulmonary circulation is inversely proportional to the PAC.[24] High capacitance decreases the resistance in the pulmonary vessels, which will consequently decrease the workload of the heart.[25] Contrarily, low capacitance requires more work from the heart to drive the blood downstream[26]; this correlates with our results, which showed that patients with a low PAC had the worst outcomes. The association between load and capacitance in the right heart has been

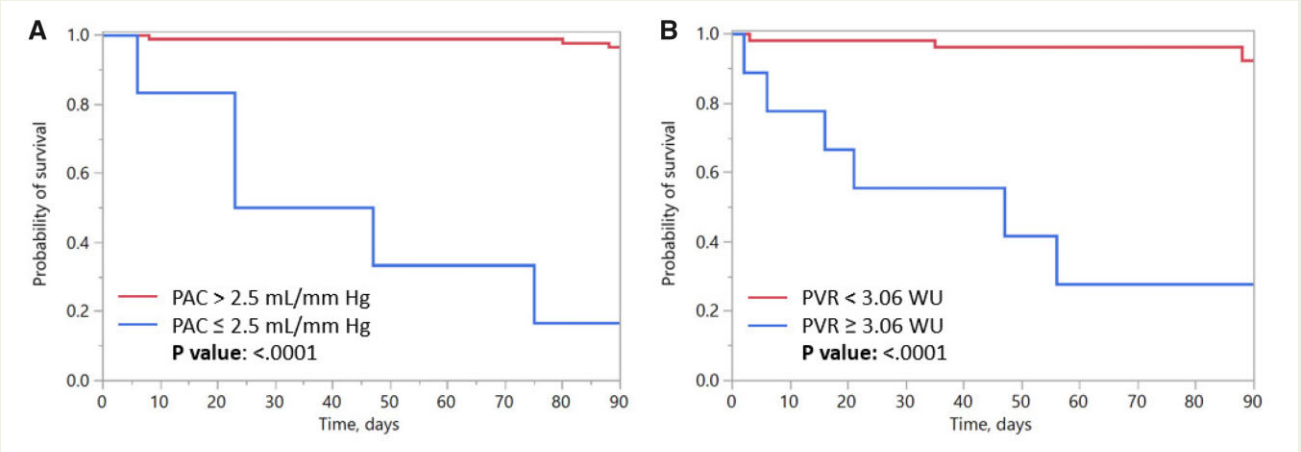


Figure 2 Kaplan–Meier survival curves according to pulmonary artery capacitance and pulmonary vascular resistance. (*A*) All-cause mortality 90-day survival for pulmonary artery capacitance with optimal cut-off point, 2.5 mL/mmHg. (*B*) All-cause mortality 90-day survival for pulmonary vascular resistance with optimal cut-off point, 3.06 woods units.

Table 5 **RV haemodynamic values among patients in three PE categories**

Variables	All patients (*N* = 373)	Massive PE (*n* = 32)	Submassive PE (*n* = 189)	Low-risk PE (*n* = 152)	*P*-value[a]
PAC, mean (SD), *N*	3.04 (1.50), 99	2.15 (1.14), 7	2.33 (0.90), 50	4.04 (1.58), 42	<0.001[b]
PVR, mean (SD), *N*	3.01 (1.27), 65	3.47 (1.07), 5	3.45 (1.32), 34	2.28 (0.66), 26	<0.001[c]
RAP, mean (SD), *N*	8.4 (4.8), 339	13.2 (4.9), 26	9.1 (4.9), 175	6.6 (3.5), 138	<0.001[d]
RV FAC, mean (SD), *N*	31.1 (11.9), 137	24.6 (10.5), 14	31.0 (12.3), 81	33.6 (10.8), 42	0.045[e]
TAPSE, mean (SD), *N*	19.7 (5.1), 268	17.2 (5.0), 24	18.8 (4.7), 147	21.7 (5.0), 97	<0.001[b]
S′, mean (SD), *N*	0.13 (0.03), 337	0.11 (0.04), 29	0.12 (0.03), 172	0.14 (0.03), 136	<0.001[b]

FAC, fractional area change; PAC, pulmonary artery capacitance; PE, pulmonary embolism; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; S′, systolic velocity of the tricuspid valve lateral annulus; TAPSE, tricuspid annular plane systolic excursion.
[a]*P*-values from one-way analysis of variance and the Tukey–Kramer test. $P < 0.05$ was considered statistically significant.
[b]Comparison of low-risk PE vs. massive and submassive PE.
[c]Comparison of low-risk PE vs. submassive PE.
[d]Comparison of low-risk PE vs. submassive PE vs. massive PE.
[e]Comparison of low-risk PE vs. massive PE.

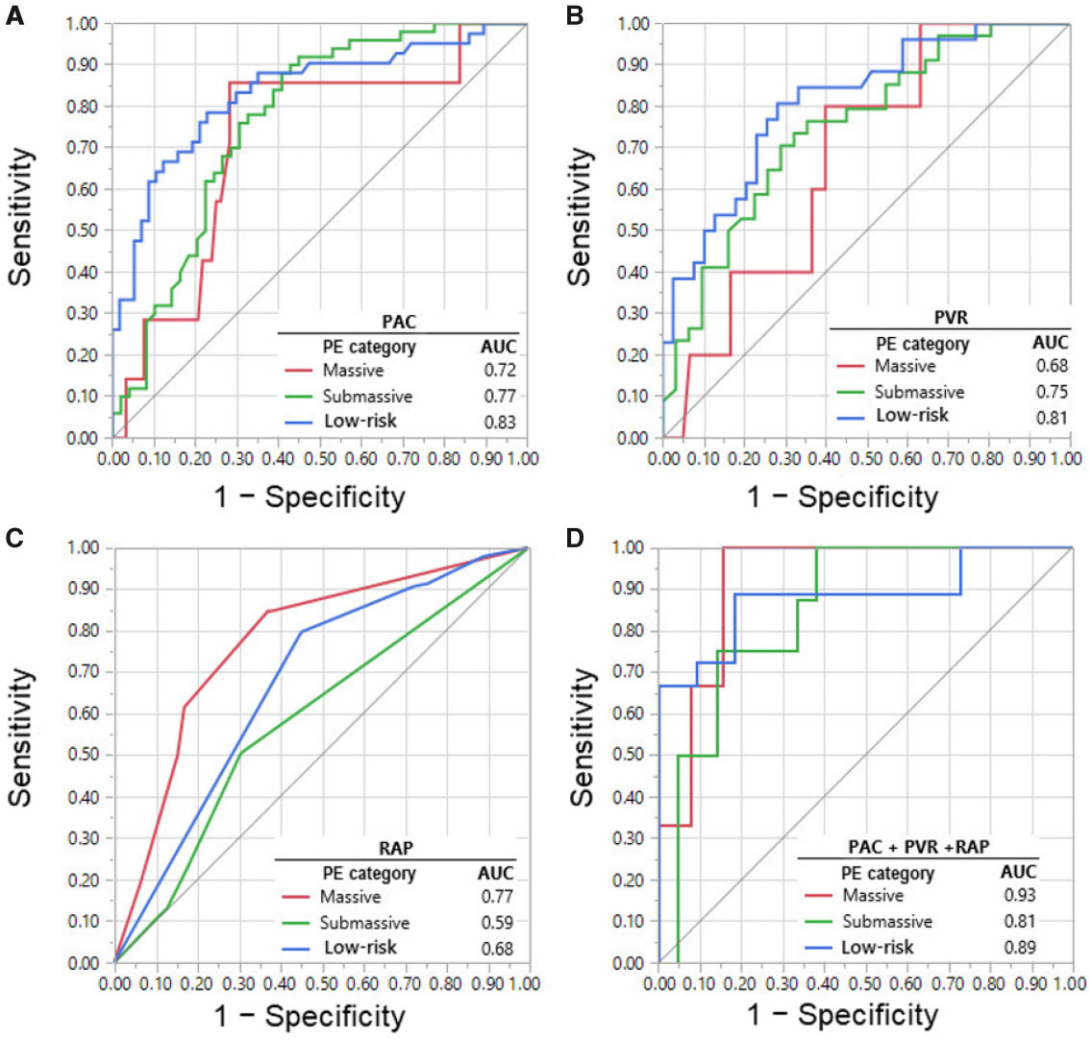


Figure 3 Receiver operating characteristic curves for predicting pulmonary embolism categories. (*A*) Pulmonary artery capacitance. (*B*) Pulmonary vascular resistance. (*C*) Right atrial pressure. (*D*) Combined pulmonary artery capacitance, pulmonary vascular resistance, and right atrial pressure. AUC, area under the curve.

Table 6 Predictors of PE categories

Predictor	Massive PE	Submassive PE	Low-risk PE
PAC			
AUC (95% CI)	0.72 (0.52–0.88)	0.77 (0.67–0.86)	0.83 (0.73–0.91)
Cut-off point	2.13	3.20	3.20
Sensitivity, %	86	90	64
Specificity, %	72	57	87
P-value	0.07	<0.001	<0.001
PVR			
AUC (95% CI)	0.68 (0.42–0.87)	0.75 (0.61–0.86)	0.81 (0.69–0.91)
Cut-off point	2.98	2.06	2.06
Sensitivity, %	80	91	42
Specificity, %	60	36	90
P-value	0.38	<0.001	<0.001
RAP			
AUC (95% CI)	0.77 (0.67–0.86)	0.59 (0.53–0.65)	0.68 (0.62–0.72)
Cut-off point	10	10	5
Sensitivity, %	85	50	79
Specificity, %	62	70	55
P-value	<0.001	<0.001	0.004
PAC, PVR, and RAP			
AUC (95% CI)	0.93 (0.72–0.98)	0.81 (0.56–0.91)	0.89 (0.67–0.97)
P-value	0.04	0.02	<0.001

AUC, area under the curve; PAC, pulmonary artery capacitance; PE, pulmonary embolism; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

described before. One prior study, which used echocardiography to measure the PAC of 104 patients with PA hypertension, showed that the patients with a low PAC had higher mortality.[15] Similarly, another study measured non-invasive PAC in 306 patients with chronic heart failure and found that patients with low PAC had higher mortality.[13]

Non-invasive measurement of PVR is a good prognostic indicator among patients with acute PE[9] because PVR is a good estimate of the RV afterload; thus, higher PVR is associated with the development of RV dysfunction and adverse events. Concordantly, this study showed that increased PVR was associated with all-cause mortality at 3 months and 6 months.

Pulmonary artery capacitance and PVR are not only surrogates of acute haemodynamic changes but can also be influenced by patients with multiple comorbidities and with previously compromised cardiac or respiratory function. This could also explain their association with worst outcomes. We found that comorbidities such as age, cancer, and pulmonary hypertension, were associated with all-cause mortality at 30 days, 3 months, and 6 months. Age and cancer have shown to be independent predictors of worst outcomes including death in patients with acute PE,[27] and along with pulmonary hypertension, they are frequently assessed in scores as PESI or sPESI to predict mortality and adverse events in this population.[6,28]

Pulmonary artery capacitance was significantly associated with 30-day all-cause mortality after using Bivariable models to adjust for age, cancer, and pulmonary hypertension. This suggests that PAC is potentially a stronger predictor of short-term all-cause mortality than PVR among patients with acute PE. Patients in this study who died after an episode of PE could still have normal PVR, but PAC was always low. An explanation may be that although PVR reflects the arterial load under a steady flow, PAC represents the arterial load under a pulsatile flow, which is a better early marker of functional changes in the pulmonary vasculature of these patients.[29,30]

Pulmonary artery capacitance was a good predictor of massive, submassive, and low-risk PE. Our findings agreed with those of previous studies, which have shown that lower levels of PAC are associated with RV dysfunction.[12] The strongest predictor of all three PE categories was the combination of PAC, PVR, and RAP. These findings could point to another advantage of using non-invasive RV haemodynamics for predicting patient outcomes based on RV dysfunction. It is worth noting that we did not find an association of PE categorization or echocardiographic measurements as FAC, TAPSE, and S' with all-cause mortality; this could potentially be explained by our low mortality incidence and the small sample size of the massive PE group.

The estimation of PVR and PAC can be challenging, especially in the acute clinical setting of an PE event when there is time constrain. This limited our sample size for these echocardiographic parameters. Nevertheless, our findings may provide support for future prospective studies designed to evaluate the prognostic value of these variables in larger cohorts of PE patients.

The main finding of this study was that a reduced PAC and increased PVR are associated with a worst prognosis for patients with acute PE independently of other risk factors, such as age, cancer, and pulmonary hypertension. This implies that early echocardiographic measurement of the PAC and PVR in patients with acute PE may be important for stratification and the possible application of different treatment options for these patients.

Limitations

This study had some limitations. First, it was performed in a single centre and findings may not be applicable in other populations with different clinical and demographic characteristics. Also, measuring PAC and PVR using echocardiography is subject to a certain lack of precision when compared with right cardiac catheterization, especially in the acute setting. Nevertheless, non-invasive measurement of PVR and PAC have been shown to have a good correlation with invasive measurements,[16,17] and echocardiography offers an ideal bedside evaluation in this clinical scenario. Another limitation was that only 26.4% of the patients with a confirmed acute PE underwent an echocardiogram within 24 h which could have influenced our patient selection. Moreover, stroke volume was calculated using LVOT velocity, which may not be equal to right side stroke volume. However, measuring volumetric flow from the LVOT is more accurate than measuring it from the RVOT. Additionally, PAC calculation was limited to 99 (27%) patients, this occurred because good quality TRV measurements were only obtained in 87% of them while PRV in 30%. Our acquisition for TRV was high since previous studies have shown TRV to be feasible in only 60% of the patients.[30] Feasibility of PRV is limited. Similarly, good measurements of the RVOT TVI were only obtained in 70 (18.8%) patients limiting PVR calculation to 65 (17.4%) patients. In addition to the small number of patients in this study, multiple comparisons may increase the risk of mistakenly considering a statistically significant difference with a *P*-value of 0.05. Therefore, these findings must be validated in future larger prospective studies. Finally, the small sample size of the massive PE group produced a disproportion between PE categories, which could affect the comparison. This might explain the similar outcomes between PE categories.

Conclusion

Non-invasive PAC and PVR are potentially important predictor variables of all-cause mortality in patients with acute PE, and further prospective multicentre studies are needed to clarify the clinical impact of these findings.

Lead author biography

Dr Hector R. Villarraga is a cardiologist at Mayo Clinic in Rochester, MN, and an Associate Professor of Medicine at the College of Medicine. His research interests include evaluation of myocardial mechanical function by speckle tracking echocardiography (strain) in cardiomyopathies with normal ejection fraction and in cardio-oncology, as well as applicability of echocardiography in day-to-day patient care.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Conflict of interest: none declared.

Data availability

The data underlying this article cannot be shared publicly because the privacy of the individuals that participated in the study must be maintained and because the data underlying this article were provided by the Mayo Thrombophilia Clinic under license and by permission. The data will be shared on reasonable request to the corresponding author with the permission of Mayo Clinic.

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