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Echocardiography and PESI have independent prognostic role in pulmonary embolism

Running head: Risk stratification in pulmonary embolism

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Abstract

We analyzed a cohort of patients with normotensive pulmonary embolism (PE) in order to assess whether combining echocardiography and biomarkers with the pulmonary embolism severity index (PESI) improves the risk-stratification in comparison to the PESI alone.

The PESI was calculated in normotensive patients with PE who also underwent echocardiography and assays of troponin and brain natriuretic peptide. Thirty-day adverse outcome was defined as death, recurrent PE or shock.

529 patients were included, 25 (4.7%; 95% confidence interval (CI), 3.2% to 6.9%) had at least one outcome event. The proportion of patients with adverse events increased from 2.1% in PESI class I-II to 8.4% in PESI class III-IV, and to 14.3% in PESI class V ($P < 0.001$). In PESI class I-II, the rate of outcome events was significantly higher in patients with abnormal values of biomarkers or right ventricular (RV) dilatation. In multivariate analysis, the PESI (Odds Ratio (OR) III-IV versus I-II: 3.1; 95%CI, 1.2-8.3; OR V versus I-II: 5.5; 95%CI, 1.5-25.5) and echocardiography (RV/left ventricular ratio, OR for an increase of 0.1: 1.3; 95%CI, 1.1-1.5) were independent predictors of an adverse outcome.

In patients with normotensive PE, biomarkers and echocardiography provided additional prognostic information to the PESI.

Keywords: pulmonary embolism; prognosis; BNP; troponin; echocardiography; score

Introduction

Early mortality from pulmonary embolism (PE) depends on the clinical consequences of PE and on the underlying disease (1). Risk stratification of patients with PE may enable a low risk-group to be defined that may be treated on an outpatient basis, and a high-risk group that should be admitted for hospitalization under close medical supervision (2). The Pulmonary Embolism Severity Index (PESI), a clinical rule based on 11 clinical variables, defines five classes of patients with PE with different mortality rates at 90 days (3). The PESI has been validated in several large cohorts and is now available as a simplified version based on 7 variables (4-6). Right ventricular dysfunction assessed by either echocardiography or spiral CT and high levels of biomarkers including troponin, brain natriuretic peptide (BNP), have been linked to an increased risk of death or adverse outcome in patients with PE (7-9). Little is known about the respective roles of clinical findings summarized in the PESI, echocardiography and biomarkers for the risk assessment of patients with PE. We analyzed the results of a large prospective multicenter cohort of consecutive patients with PE in order to determine whether the combination of echocardiography and biomarkers with the PESI improves the risk-stratification of patients with PE compared to the PESI alone (8). Because cardiogenic shock at admission represents one of the most important prognostic factor in patients with PE and according to the current guidelines of the European Society of Cardiology, it is widely admitted that further risk stratification by biomarkers, echocardiography or the PESI is not needed in these patients (2). Therefore, we focused our study on patients with normotensive PE.

Material and methods

Patients

Consecutive adult patients with symptomatic normotensive PE admitted in the 11 participating sites in France, Belgium and Switzerland were recruited for the study. Patients were eligible if their PE was objectively confirmed according to current guidelines, as previously reported (2, 8). Patients were ineligible for the study if they had received therapeutic doses of anticoagulant treatment for more than 24 hours or had cardiogenic shock at admission defined by at least one of the following criteria: systolic blood pressure (SBP) < 90 mm Hg, signs of end-organ hypoperfusion or a need for catecholamine administration to maintain SBP > 90 mm Hg. Because the role of thrombolytic therapy remains unclear in clinically stable patients, we excluded patients with normotensive PE who received fibrinolytic treatment. Demographic data, symptoms and risk factors for venous thromboembolism, including all variables of the PESI were obtained at the time of admission. Patients were managed according to the usual practices of each participating site by physicians blinded to the results of cardiac biomarkers.

The study protocol strongly recommended a transthoracic echocardiography within 24 hours of PE diagnosis by an experienced physician unaware of the results of cardiac biomarker determinations. The end-diastolic diameters of the right and left ventricles (RV and LV) were measured along the long axis of the parasternal view and the RV/LV ratio was calculated (8).

On admission, blood samples were collected in heparinized tubes for cardiac troponin I (cTnI) assay and in EDTA tubes for BNP determination, were centrifuged and the resulting plasma was frozen and stored at -80°C. At the end of the study, circulating levels of cTnI, and BNP were determined in a central laboratory by investigators blind to the patients' baseline characteristics and clinical outcome. cTnI were determined with quantitative photometric immunoassays using a Dimension-RxL Max analyzer (Dade-Behring, Siemens Healthcare Diagnostics), according to the manufacturer's instructions. The lower limits of detection of cTnI and was 0.04 µg/L. BNP levels were determined with an electrochemiluminescence

immunoassay (BNP-Triage Biosite assay) on a DxI analyzer (Beckman Coulter Inc., USA). The lower limit of detection in the BNP assay was 10 ng/L.

Outcomes

Thirty-day clinical follow-up data were obtained for all patients. Adverse clinical events were defined as all-cause death, secondary cardiogenic shock as previously defined, or objectively confirmed symptomatic recurrent venous thromboembolism. All adverse events and the cause of death (*i.e*. related or unrelated to PE) were adjudicated by an independent committee of two physicians unaware of the results of the initial clinical examination, echocardiography and biomarker determinations.

The study was an academic trial sponsored by the "Délégation à la Recherche Clinique d'Ile de France". The funding body had no role in the design of the study, data analysis, or drafting the manuscript. The study was approved by local ethics committees (Ile de France II, Saint-Luc University Hospital, and Geneva University Hospital committees for the French, Belgian and Swiss centers, respectively). All patients signed a written informed consent form.

Statistical methods

Categorical variables were summarized using numbers and percentages, and continuous variables using medians [25% percentile - 75% percentile]. PESI score was categorized into low risk (PESI class I or II), intermediate risk (PESI class III or IV) and high risk (PESI class V) categories. Proportions of deaths and adverse events according to the PESI risk class were compared using chi-square tests; median values of markers according to PESI risk class were compared using Kruskall-Wallis tests.

Univariate analyses, based on chi-squared tests or Student's t-tests, were performed. Independent associations with the outcome were assessed by including variables with a significance level of $p < 0.20$ on univariate analysis in a multivariate logistic regression

model. Variables associated with the outcome at a significance level of $p < 0.05$ in backward stepwise regression analysis were retained. For the multivariate analysis, we conducted multiple imputation analysis to ensure that the results were robust for missing data. For each variable, we further estimated the proportion of explained variation (PEV) and partial PEV. The PEV measures the proportion of variation of the outcome variable that can be attributed to the variable, relative to the total variation of the outcome variable. Partial PEV measures the decline in explained variation when removing the prognostic factor from the model containing the other four factors.

In order to determine if echocardiography and biomarkers improved the risk stratification, we first constructed box plots showing the distributions of biomarkers and echocardiography values within each PESI risk class and among patients who did or did not experience an adverse event. In subsequent analyses, echocardiography and biomarkers were dichotomized according to threshold validated in previous studies. We defined BNP concentration > 100 ng/L as positive BNP (10, 11), cTnI concentration > 0.1 µg/L as positive cTnI (10, 12) and RV/LV ratio > 0.9 as positive RV/LV ratio (10, 12). We then cross-classified patients according to their PESI risk category, and then according to their RV/LV ratio or biomarker risk category, each in turn. Within each sub-stratum, we estimated the risk of an adverse event. Finally, logistic regression analyses were conducted to determine possible links between prognostic factors (PESI risk category, BNP, troponin and RV/LV EDD ratio) and the risk of an adverse event.

Results

Patients

A total of 592 consecutive patients were included in the study between January 2006 and May 2007. Forty-one patients were excluded because of cardiogenic shock at inclusion. Twenty-

two haemodynamically stable patients were excluded because they were receiving fibrinolytic treatment. None of these normotensive patients experienced a 30-day adverse event. The final study population therefore comprised 529 patients with normotensive PE (table 1). At inclusion, 528 patients (99%) were receiving an anticoagulant treatment. Fibrinolytic therapy was administered to 8 patients (1.5%) because of secondary cardiogenic shock. A vena cava filter was inserted in 22 patients (4%).

Outcome

The 30-day prospective follow-up was complete for all patients. During follow-up, 25 patients (4.7%; 95% confidence interval (CI), 3.2% to 6.9%) suffered adverse events: death in 15 cases (2.8%; 95% CI, 1.7% to 4.6%), secondary cardiogenic shock in 15 (2.8%) and recurrent venous thromboembolism in 8 patients (1.5%). One patient may have had several events qualifying for complicated outcome.

PESI

The PESI was calculated for all 529 patients; among them, 329 (62%) were at low risk (PESI class I or II), 179 patients (34%) were at intermediate risk (PESI class III or IV) and 21 patients (4%) were at high risk (PESI class V). The mortality rate and the rate of adverse outcome including mortality, secondary cardiogenic shock and recurrent PE increased significantly from 0.6% and 2.1% in the low-risk category to 9.5% and 14.3% in the high-risk category, respectively (table 2).

Biomarkers and echocardiography

Plasma concentrations of BNP and troponin, and the RV/LV ratio increased significantly with the PESI (table 2).

Predictors of adverse outcome

Figure 1 shows the number and proportion of patients with an adverse outcome at 30 days in the six categories defined by cross-tabulation of the PESI risk class (low, intermediate or high risk) and the RV dysfunction marker category (normal or elevated biomarkers; normal or abnormal RV/LV ratio). All biomarkers and echocardiography results enabled patients belonging to the low-risk category (PESI class I or II), to be further stratified into two subgroups, one with a very low risk ($\leq$1%) of an adverse outcome and one with a 6% risk of 30-day adverse outcome, with significant differences in the event rate between the subgroups with normal and abnormal biomarker and RV/LV ratio values ($P = 0.03$ for BNP; $P < 0.001$ for troponin and $P < 0.001$ for RV/LV ratio) (figure 1a). In the intermediate risk group of patients (PESI class III-IV), elevated biomarkers and right ventricular dilatation on echocardiography were associated with higher rates of adverse outcomes, but difference with patients having normal values was significant for troponin only ($P = 0.02$ for troponin; $P = 0.42$ for BNP and $P = 0.9$ for echocardiography) (figure 1b). In the high-risk group, differences in the event rates between patients with normal and abnormal biomarker value and echocardiography were less pronounced and not significant, but the patient population was small (figure 1c).

Results of univariate logistic regression analyses showed that the PESI, BNP and RV/LV ratio were significantly associated with the occurrence of an adverse outcome (table 3). Multivariate analysis showed that, in addition to the PESI risk class, echocardiography but not biomarkers remained independent predictors of adverse outcome at day 30 in the study population (table 4). The variables included in the model accounted for about 10% of the variation in individual 30-day outcomes; the proportions of variance explained by each RV dysfunction marker (as well as partial PEV) were similar to those explained by the PESI risk class. Finally, multiple imputation analysis provided estimates consistent with the complete case analysis (table 4). The PESI was associated with a moderate prognostic sensitivity (72%)

and high negative predictive value (NPV) (98%) (table 5). Interestingly, the combination of PESI with RV/LV had a higher sensitivity and NPV for predicting 30-day complicated outcome (table 5).

Discussion

This study shows that in patients with normotensive PE, right ventricular dysfunction on echocardiography provides prognostic information that is independent of clinical findings summarized by the PESI. In patients considered at low-risk according to the PESI, echocardiography and biomarkers identified two subgroups with different risks of adverse events. Among patients belonging to PESI class I or II, those with normal echocardiography results and normal levels of biomarkers had a very low risk of adverse events which was significantly lower than the rate observed in patients with an abnormal echocardiography or elevated levels of biomarkers.

Five groups of patients with different risk of death were described in the original report describing the PESI. Subsequently, class I and II patients were combined in a low-risk group and were selected as possible candidates for outpatient treatment (13) and patients in class III to V were considered as "high-risk" patients (5, 6). In the present study, three groups were considered, one "low-risk" group corresponding to the usual low-risk group (defined as PESI class I or II), an "intermediate-risk" group defined as PESI class III or IV patients, and a "high-risk" group defined as PESI class V patients. This was done to comply with the recommendations of the European Society of Cardiology where three groups are considered (2). Clustering the high-risk and intermediate groups or using the simplified PESI (sPESI) did not change the results (data not shown). Previous studies have compared the clinical approach based on the PESI and biomarkers or echocardiography for the risk stratification of PE with varying results. The respective values of troponin I and the original PESI for the prediction of

mortality at 30 days were evaluated in a monocentric cohort of 567 patients with clinically stable PE (14). In this study, the combination of troponin I with the clinical variables did not improve the negative predictive value of the PESI for the risk of 30-day mortality but the other major adverse events, such as recurrent PE or cardiogenic shock, were not evaluated (14). The prognostic value of the new high sensitivity troponin T (hsTnT) assay and of the simplified PESI (sPESI) was evaluated in a multicenter study including 526 normotensive patients with PE (15). The hsTnT was associated with a high prognostic sensitivity and negative predictive value comparable to those of sPESI. High sensitivity troponin T and sPESI were identified as independent predictors of 30-day complicated outcome defined by all-cause death or secondary shock or cardiopulmonary resuscitation (15). Interestingly, the combination of elevated hsTnT with high risk sPESI had a sensitivity and negative predictive value of 100% (15). On the other hand, none of the patients with low risk sPESI and low level of hsTnT experienced an adverse outcome but the authors didn't report whether patients with low risk sPESI and elevated hsTnT have higher rate of adverse outcome (15). Recently, the simplified PESI (sPESI) has been compared to a risk-stratification method based on echocardiography and biomarkers proposed by recent ESC recommendations (12). The combined end-point of all-cause mortality, objectively confirmed non-fatal symptomatic recurrent venous thromboembolism, or non-fatal major bleeding was lower in the low-risk group identified by the sPESI than in the low-risk group identified by normal echocardiography findings and biomarker assays (12). An approach combining clinical findings, echocardiography and biomarkers was not tested in this study. In another monocentric study, it was shown that right ventricular dysfunction and/or a high troponin level increased the risk of death in patients classified as intermediate-risk according to the PESI, whereas this was not observed in low-risk patients (16). The additional role of

echocardiography and biomarkers in predicting other major complications was not tested in this study.

Recently, Aujesky et al. demonstrated in an open-label multicenter randomized trial that outpatient treatment is not inferior to inpatient care in terms of efficacy and safety in selected low-risk patients (PESI class I or II) (13). In this study, neither echocardiography nor biomarkers were used for the risk stratification but more than two thirds of the patients included were in very low class risk PESI class I (13). Our results suggest that among patients belonging PESI class I or II, those with elevated levels of biomarkers or abnormal echocardiography results could require hospitalization instead of outpatient care. However, our results must be confirmed in large independent cohort studies before use to make a therapeutic decision.

The present study has several strengths; it was multicentric, enabling greater generalization of the results, and patients were consecutively and prospectively recruited, limiting the possibility of major biases. All outcomes were assessed by an independent central committee whose members were unaware of the initial clinical data and results of echocardiography and biomarkers. The biomarkers were measured at the end of the study and the responsible physicians were also unaware of the results of biomarker assays and these results did not influence initial treatment. Conversely, participating physicians were aware of echocardiography results and their initial treatment option, i.e. anticoagulation alone or anticoagulation and thrombolysis may have been influenced by the results of echocardiography; this is why normotensive patients who received thrombolytic treatment were excluded from the analysis. The study was also limited by the low number of events and by the small number of patients in the intermediate and high-risk categories. This may explain why, despite the doubling the proportion of patients with outcomes in intermediate-risk patients having abnormal echocardiography results or elevated levels of biomarkers compared

to patients with normal echocardiography and biomarkers, the difference was not statistically significant.

In conclusion, if confirmed in independent cohort studies, the present findings suggest that cardiac biomarkers and/or echocardiography enable patients with a PESI I-II to be further stratified into two sub-groups, one with a very low level of adverse outcome that can be safely treated as outpatients, and one with a slightly higher risk requiring hospitalization. The role of biomarkers and echocardiography in patients at intermediate or high-risk according to the PESI is more questionable and should be evaluated in larger cohorts.

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Legends

Figure 1: Number and proportion of patients with an adverse 30-day outcome in categories defined by cross-tabulation of PESI risk classes and right ventricular dysfunction defined by elevated cardiac biomarker levels or RV/LV ratio according to previously validated threshold.

Complete cases were presented. PESI: Pulmonary Embolism Severity Index; BNP: brain natriuretic peptide; RV: right ventricle; LV: left ventricle; *: p = 0.03; **: p < 0.001; †: p = 0.02

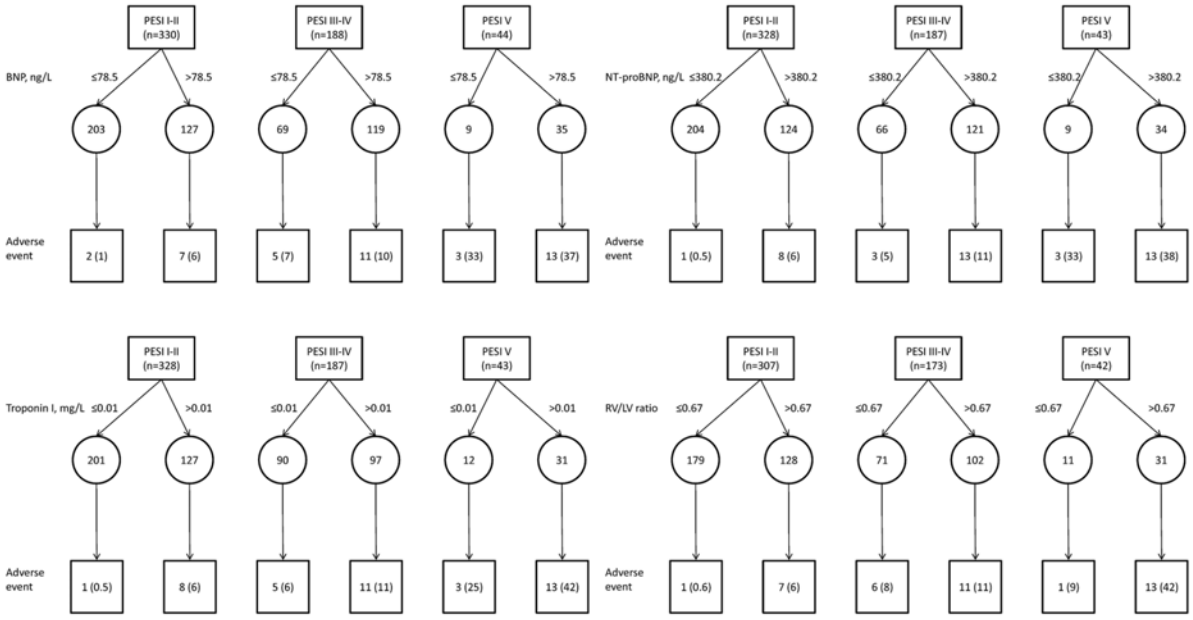

Table 1 Characteristics of the 529 patients with pulmonary embolism

Characteristics	Available data, n	All (n=529)	*30-day adverse event* Yes (n=25)	No (n=504)
Age, years, median (25^{th}-75^{th} percentiles)	529	67 (52-77)	70 (60-81)	67 (51-77)
Male	529	247(47)	12 (48)	235(47)
Cancer	529	77(15)	7(28)	70(14)
Altered mental state	529	7(1)	1 (4)	6 (1)
Syncope	529	24 (5)	2 (8)	22 (4)
Heart rate, bpm, median (25^{th} -75^{th} percentiles)	526	88 (75-100)	90 (80-103)	88 (74-100)
Systolic BP, mm Hg, median (25^{th}-75^{th} percentiles)	529	134 (120-150)	130 (124-140)	135 (120-150)
Cardiogenic shock on admission	529	0(0)	0(0)	0(0
PESI class	529			
I (≤65 points)		131(25)	1 (4)	130 (26)
II (66-85 points)		198 (37)	6 (24)	192 (83)
III (86-105 points)		109 (21)	10 (40)	99 (20)
IV (106-125 points)		70 (13)	5 (20)	65 (13)
V (>125 points)		21 (4)	3 (12)	18 (4)
Echocardiography and cardiac biomarkers, median (25^{th} -75^{th} percentiles)				
BNP, ng/L	521	71.0 (27.0-210.0)	275.0 (69.0-431.0)	67.0 (27.0-190.0)
Troponin I, mg/L	517	0.01 (0.00-0.06)	0.11 (0.01-0.34)	0.01 (0.00-0.05)
RV/LV EDD	484	0.65 (0.53-0.79)	0.76 (0.63-1.11)	0.65 (0.53-0.79)

PESI: Pulmonary Embolism Severity Index; SBP: systolic blood pressure; BNP: brain natriuretic peptide; RV: right ventricle; LV: left ventricle; EDD: end-diastolic diameter

Table 2. Rate of adverse outcomes and value of biomarkers and echocardiography according to the PESI classes

	PESI class I-II (very low to low risk) (n=329)	PESI class III-IV (intermediate to high risk) (n=179)	PESI class V (very high risk) (n=21)	P value
Endpoints, n (%)				
30-day mortality	2 (0.6)	11 (6.1)	2 (9.5)	< 0.001
30-day adverse event	7 (2.1)	15 (8.4)	3 (14.3)	< 0.001
Echocardiography and cardiac biomarkers, median (25^{th}-75^{th} percentiles)				
BNP, ng/L	44.5 (21.5-146.0)	126.5 (46.0-299.0)	221.0 (130.0-385.0)	< 0.001
Troponin I, µg/L	0.01 (0.00-0.04)	0.01 (0.00-0.10)	0.03 (0.00-0.19)	< 0.01
RV/LV EDD	0.63 (0.51-0.76)	0.71 (0.56-0.86)	0.59 (0.51-0.88)	0.02

Distributions of deaths and adverse events according to PESI risk class were compared using chi-square tests; distributions of markers according to PESI risk class were compared using Kruskall-Wallis tests.

PESI: Pulmonary Embolism Severity Index; BNP: brain natriuretic peptide; RV: right ventricle; LV: left ventricle; EDD: end-diastolic diameter

Table 3. Univariate analysis

Variable	Complete case, n	OR [95% CI]	P
PESI class	529		<0.01
III-IV vs. I-II		4.2 [1.7;10.5]	
V vs. I-II		7.7 [1.8;32.1]	
BNP (for an increase of 250 ng/L)	521	1.3 [1.1;1.6]	<0.01
Troponin (for an increase of 0.7 µg/L)	517	1.2 [0.9;1.5]	0.20
RV/LV EDD (for an increase of 0.1)	484	1.3 [1.2;1.5]	<.0001

OR: odds ratio; 95% CI: 95% confident interval; PESI: Pulmonary Embolism Severity Index; BNP: brain natriuretic peptide; RV: right ventricle; LV: left ventricle; EDD: end-diastolic diameter

Table 4. Multivariate analysis

	Complete case (n=473)				Multiple imputation (n=529)	
Variable	OR [95% CI]	P	PEV (%)	Partial PEV (%)	OR [95% CI]	P
PESI class		0.03				0.02
III-IV vs. I-II	3.1 [1.2;8.3]		1.5	0.0	3.4 [1.3; 8.8]	
V vs. I-II	5.5 [1.2;25.5]		0.9	1.0	6.2 [1.3; 28.2]	
BNP (for an increase of 250 ng/L)	1.1 [0.8;1.4]	0.58	0.8	0.0	1.1 [0.8; 1.5]	0.49
Troponin (for an increase of 0.7 µg/L)	1.3 [0.9;2.0]	0.23	0.2	0.3	1.1 [0.8; 1.6]	0.45
RV/LV EDD (for an increase of 0.1)	1.3 [1.1;1.5]	<0.01	6.7	3.1	1.3 [1.1; 1.5]	<0.01
Model			10.1			

OR: odds ratio; 95% CI: 95% confident interval; PEV = proportion of explained variation, i.e. the amount of variation of the outcome variable that is attributable to the variable, relative to the total variation of the outcome variable. Partial PEV measures the decline in explained variation when removing the prognostic factor from the model containing all other four factors. PESI: Pulmonary Embolism Severity Index; BNP: brain natriuretic peptide; RV: right ventricle; LV: left ventricle; EDD: end-diastolic diameter.

Missing values for any prognostic variable (heart rate n=3, respiratory rate n=71, temperature n=4, arterial oxyhemoglobin saturation n=4) were assumed to be normal, a strategy used in the original determination of the PESI (3).

Table 5: Value of PESI alone and RV/LV ratio alone and in combination for predicting a 30-day complicated outcome

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive value
PESI class III-IV-V	72% (18/25)	64% (294/459)	10%	98%
RV/LV > 0.9	36% (9/25)	85% (389/459)	11%	96%
PESI class III-IV-V *AND* RV/LV > 0.9	88% (22/25)	57% (261/459)	10%	99%