ORIGINAL ARTICLE

Risk stratification in submassive pulmonary embolism via alveolar-arterial oxygen gradient

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Abstract

Aim: This study investigated the utility of the alveolar–arterial ($AaDO_2$) gradient in predicting the short-term prognosis of submassive pulmonary embolism (PE).

Material and Methods: This study retrospectively enrolled 124 patients with acute submassive PE. During the first 24 h of admission, all patients had initial artery blood gas collected under room air. Cardiac troponin T (cTn-T) was measured and on spiral computed tomography pulmonary angiography (CTPA) and echocardiography both right ventricle diameter and left ventricle diameter was calculated (RV/LV ratio). Patients who did not have objectively confirmed submassive PE and who had curative anticoagulant treatment for more than 24 hours and had a life expectancy less than 3 months were excluded from the study.

Results: The best cut-off value for $AaDO_2$ was 42.38 mmHg and using this, fourteen of 15 patients who died had $AaO_2 \geq 42.38$ and 71 of 109 patients who survived had a AaO_2 lower than 42.38 with a sensitivity, specificity and negative predictive value (NPV) for overall deaths were 93.3%, 65.1% and 98.6% respectively. In addition, $AaDO_2 < 42.38$ showed significant survival benefit for overall mortality rates.

In this study, having high cTn-T and $PaO_2 / PaCO_2 < 1.83$ and pulmonary artery pressure > 47.5 were also an indicator of poor prognosis for patients with submasssive PE.

Conclusion: The AaDO2 measurement is a highly useful and simple measurement for predicting short-term prognosis in patients with submassive PE. It may be used in risk stratification of patients with submassive PE. Aggressive thrombolytic treatment strategies may be considered for patients who have $AaO_2 \geq 42.38$. Hippokratia 2014; 18 (4): 333-339.

Keywords: Submassive pulmonary embolism, alveolar–arterial oxygen gradient, blood arterial gases

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Introduction

Acute pulmonary embolism (PE) is one of the most frequent cardiovascular conditions. The incidence in Europe is about 50 cases/100,000 inhabitants according to data from the European Society of Cardiology[1,2]. The mortality rate of acute pulmonary embolism is about 30% in non-treated patients and about 8% in treated patients. Approximately 11% of patients die of sudden death[1,3].

Acute PE represents a spectrum of clinical syndromes with a variety of prognostic implications. Patients with acute PE who have normal systemic arterial pressure and preserved right ventricular (RV) function have an excellent prognosis with therapeutic anticoagulation alone. In contrast, patients with massive PE present with syncope, systemic arterial hypotension, cardiogenic shock, or cardiac arrest have an increased risk of adverse outcomes, including death[1,4]. Submassive PE is defined as normotensive PE with signs of right ventricular dysfunction (RVD) and/or myocardial damage. The short-term mortality rate of submassive PE ranges from 3 to 15%[1,5,6]. For non-massive PE, the use of anticoagulant therapy is routine. However, the appropriate therapy for submassive PE remains controversial[1,2].

It has been debated that there may be a subgroup of patients with submassive pulmonary embolism whose members may get benefit from thrombolytic agents[7,8]. At this point risk stratification tools may help to the selection of patients with a low risk of complications who could potentially be managed as outpatients and the selection of normotensive patients with a high risk of complication not suggested by the usual clinical predictors and who may be considered candidates for thrombolytic treatment according to some authorities[2,9,10]. Clinical variables have been used to construct a prognostic score that has been validated in different settings[11-13]. It has been reported that right ventricular dysfunction, detected by echocardiography, myocardial injury, detected by high levels of cardiac troponins, and increased alveolar-arterial gradi-

ent ($AaDO_2$) are associated with a higher risk of short-term death[14-16].

Most patients with acute PE have a low partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in the arterial blood and elevated alveolar-arterial oxygen pressure difference[17]. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, a linear correlation existed between $AaDO_2$ and PE severity, as determined by pulmonary artery mean pressure, and with the number of mismatched perfusion defects[18].

There is continued interest in the possibility that different gradients of $AaDO_2$ or other arterial blood gas analyses can be used to predict the prognosis of acute PE. Therefore we performed this study to investigate $AaDO_2$ as a possible predictor of prognosis in submassive PE.

Patients and Methods

We retrospectively identified consecutive patients between January 2006 and August 2011 who were diagnosed as having acute submassive PE in our clinic. In order to diagnose submassive PE, the patients were required to have acute PE with stable hemodynamic functions and evidence of RV dysfunction. The patients who had hemodynamic instability (systolic blood pressure < 90 mm Hg, syncope, and/or shock) which was not otherwise explained by hypovolemia, sepsis, or a new arrhythmia, plus the presence of partial or complete filling defects within the pulmonary arteries on computerized tomography pulmonary angiography (CTPA), were accepted as massive PE and excluded from the study. Other exclusion criteria: if patients did not have objectively confirmed PE according to current guidelines[2] and patients who had curative anticoagulant treatment for more than 24 hours; had a life-expectancy less than 3 months and if they were under age of 18 years. Finally patients who have other conditions that could result in a) ventilation-perfussion mismatch; pneumonia, acute pulmonary edema, acute exacerbation of chronic obstructive pulmonary disease (COPD) b) right to left shunt; patent foramen ovale and c) impaired diffusion capacity; interstial lung disease were excluded from the study.

The study was conducted at 19 Mayis University Hospital and approved by medical ethics committee (Ethical committee number: 201047). This same institutional review board waived informed consent as this was a retrospective study and all data collected was preexisting.

Arterial Blood Gases

Arterial blood samples were obtained in all patients while they were breathing room air in order to avoid any interference caused by the administration of supplemental oxygen. $AaDO_2$ was calculated as follows:

$AaDO_2 = [150 - (1.25 \times PaCO_2)] - PaO_2$[19]

where $PaCO_2$ is the partial pressure of carbon dioxide in arterial blood (mmHg), PaO_2 is the partial pressure of oxygen in arterial blood (mmHg), and PAO_2 is the partial pressure of oxygen in the alveoli.

CT Pulmonary Angiography

CTPA was performed with a spiral CT scanner (GE Healthcare, Milwaukee, WI, USA or Siemens Healthcare, Erlangen, Germany) with 4 and 16-channel multi-slice scanner. CTPAs were obtained using 100-150 ml of non-ionic intravenous contrast agent (Omnipaque®, iohexol, GE Healthcare, Milwaukee, WI, USA) administered at a rate of 4 ml/s with a delay of 15-20 seconds before scanning. Scans were obtained during suspended inspiration or shallow breathing, depending on the patient's respiratory status, and were taken from the level of the aortic arch to 2 cm below the level of the diaphragm. The technical parameters employed were detector section collimation 4 x 1 mm, section thickness 1.25 mm, collimation 4 x 1, table speed 56 mm/rotation and a rotation time of 0.5 sec, kw 80 120 kVp. The diagnosis of acute PE on the CTPA scan was based on the presence of partial or complete filling defects within the pulmonary arteries[20]. RVD was assessed as follows: on the CTPA the minor axes of the right and left ventricles of the heart were measured in the transverse plane at their widest points between the inner surface of the free wall and the surface of the interventricular septum. These maximum dimensions may be found at different levels. The RV/LV ratio was calculated. CTPA scans were considered to show no RVD if the ratio was ≤1.0, modest RVD if the ratio was >1.0 but ≤1.5, and severe RVD if the ratio was >1.5[21].

Deviation of the interventricular septum was evaluated on a three-point scale as follows: 1: normal septum (i.e., convex to- ward the right ventricle); 2: flattened septum, and 3: septum deviation convex toward the left ventricle[21].

The following ancillary findings of PE in the thorax were also assessed: wedge-shaped pleural-based consolidation, non-emphysematous focal decreased attenuation, atelectasis, parenchymal bands, and pleural effusions. The locations and extents of these findings were classified according to the anatomic segment. Wedge-shaped pleural-based consolidation was defined as a wedge-shaped region of homogenous attenuation with the base against the pleural surface and the apex toward the parahilar area[1]. Decreased attenuation was defined as a region of diminished lung attenuation with no evidence of emphysema[1]. Atelectasis was defined as a region of increased attenuation 13 mm thick with evidence of associated volume loss. Linear bands were defined as regions of increased attenuation <3 mm thick oriented approximately perpendicular to the pleural surface. Pleural effusions were classified according to maximal thickness: small (<1 cm); moderate (1-5 cm), and large (15 cm)[1].

Echocardiography

Patients were required to undergo transthoracic echocardiography within 24 hours after PE diagnosis. RV dysfunction was confirmed based on dilatation of the RV (end-diastolic diameter >30 mm from the parasternal view or the RV/left ventricle ratio >1), hypokinesis of the RV-free wall (any view), or the peak systolic pulmonary artery pressure (sPAP) >35 mm-Hg[22].

Biochemical analyses

Venous blood samples were collected on admission. Troponin-T was measured with the use of a quantitative electrochemiluminescence assay method (Elecsys 2010; Roche, Mannheim, Germany; normal value <0.010 ng/mL) on admission. During the first 24 hours after admission, all the patients had initial arterial blood gas collected under room air.

Outcome

Number of deaths due to submassive PE during a 90-day clinical follow-up was our outcome.

Statistical Methods

Categorical variables are presented as numbers and percentages, and continuous variables are presented as means ± standard deviation (SD) or medians (25-75% percentile). Univariate analysis, 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 less than 0.20 on univariate analysis in a multivariate cox regression model. Variables associated with the outcome at a significance level of p less than 0.05 in backward stepwise regression analysis were retained. In the final model, we estimated, for each variable, the proportion of explained variation. As 90-day endpoint data were complete for all study patients. The Cox proportional hazard model was used to calculate the hazard ratios of clinical variables and $AaDO_2$. We used the area under the receiver operating characteristic (ROC) curve to distinguish high-risk subjects from low-risk subjects. Data were analyzed using Statistical Package for the Social Sciences (SPSS) mac version 20.00 (SPSS Inc., Chicago, IL, USA).

Results

We retrospectively identified 141 consecutive patients who were diagnosed as having submassive PE. Ten patients who received thrombolytic therapy prior to CTPA and seven patients in whom complete visualization of the pulmonary vascular system was not achieved on CTPA were excluded; so finally 124 patients were eligible for inclusion in the study. The patients included were 64 women (51.6%) and 60 men aged 18-85 [median (25^{th}-75^{th} percentiles) 56 (46-68)] years (Table 1). Baseline characteristics of the patients are given in Table 1.

Symptoms

The most frequent presenting symptoms were dyspnea (78%), chest/pleuritic pain (66%), back pain (32%), hemoptysis (27%) and syncope (2%). Risk factors for PE included immobility (45%), surgery (31%), cancer (12%) and idiopathic (9%). One or more of the following comorbidities were identified in 61 (62%) of the patients: chronic obstructive pulmonary disease (COPD), cancer, heart failure, and coronary artery disease.

Outcome

PE-related death at day 90 was found to be 12%.

Arterial blood gases analysis

The mean PaO_2 value was 67.9 ± 13.3mmHg. The area under curve (AUC) of the ROC analysis for 90 days mortality was 0.90 (% CI: 0.84-0.96, p<0.0001). Sensitivity, specificity and negative predictive value (NPV) for overall deaths for cut-off value of $PaO_2 \leq 54.5$ mmHg were 67%, 91% and 95.2% respectively. The mean $PaCO_2$ was 33.7 ± 5.7 mmHg. AUC of the ROC analysis for all mortality at 90 days was 0.59 (CI: 0.43-0.76, p<0.25).

Table 1: Demographics and clinical characteristics of the patients with submassive pulmonary embolism.

Variable (n: number)	Total (n: 124)	Alive (n: 109)	Deaths (n: 15)	p value †
Age, years, median (25th–75th percentiles)	56 (46-68)	56 (45-69)	63 (55-68)	0.37
Sex (female/Male)	64/60	54/55	10/5	0.21
Clinical findings, n (%)				
Acute dyspnea	97 (78)	84 (77)	13(86)	0.39
Chest pain	82 (66)	74 (68)	8(53)	0.26
Back pain	40 (32)	36 (33)	4(27)	0.62
Hemoptysis	33 (27)	31(28)	2(13)	0.21
Syncope	3 (2)	2 (2)	1(7)	0.25
Heart rate	97 (78)	85 (78)	12(80)	0.85
EKG right heart block	14 (11)	10 (9)	4(27)	0.04
S_1	31 (25)	28 (26)	3(20)	0.63
Q_3	41 (33)	37 (34)	4(27)	0.57
T_3	79 (64)	69 (63)	10(67)	0.79
Interventricular septal shift	6 (5)	4 (4)	2(13)	0.10
PAP, mean ± SD	46.4 ± 13.5	56.3 ± 16.9	45.0 ± 12.4	**0.002**
Positive spiral CT, n (%)				
Main pulmonary artery	7 (6)	4 (4)	3 (20)	**0.01**
Lobar artery	37 (30)	28 (26)	9 (69)	**0.006**
Segmental artery	36 (29)	34 (31)	2 (13)	0.15
Multi segmental arteries	44 (36)	43 (39)	1 (7)	**0.013**

PAP: pulmonary artery pressure, SD: standard deviation, †: p value, was calculated between in the analysis alive and all death.

Sensitivity, specificity and NPV for overall deaths for cut-off value of $PaCO_2$ > 32.5mmHg were 27%, 48% and 91.3% respectively.

$PaO_2/PaCO_2$ ratio

The mean $PaO_2/PaCO_2$ ratio was 2.05 ± 0.5. AUC of the ROC analysis for 90-day mortality was 0.84 (CI: 0.74– 0.93, p<0.0001) (Figure 1). $PaO_2/PaCO_2$ cutoff value was ≤1.83 by ROC analysis. Ten out of 15 patients who died had a $PaO_2/PaCO_2 \leq 1.83$, and 99 of 109 patients who survived had a $PaO_2/PaCO_2$ >1.83 (p<0.0001). Therefore $PaO_2/PaCO_2 \leq 1.83$ showed sensitivity, specificity and NPV for overall mortality to be 67%, 74% and 94.2%. Accuracy of test for overall deaths was found to be 73.4 % (Table 2).

Table 2: Overall deaths and survivals in patients with pulmonary embolism, comparison with respect to the alveolar-arterial gradient.

$AaDO_2$ n (%)	≥ 42.38	< 42.38	Total
Dead (%)	14 (93%)	1 (7%)	15
Alive (%)	38 (26)	71 (74)	109
Total (%)	38 (35)	86 (65)	124

$AaDO_2$: alveolar arterial gradient.

Alveolar-arterial gradient ($AaDO_2$)

The mean $AaDO_2$ was 39.9 (95% CI: 36.8-42.9) for all of the submassive PE patients. The mean $AaDO_2$ was 56.5 ± 13.3 mmHg (range, 26-82) for patients who died and 37.6 ± 16.1 mmHg (range, 7-78) for PE patients who survived.

The area under the ROC curve was 0.83 (% CI: 0.73-0.94, p<0.0001) for all mortality at 90 days (Figure 1). 14 of 15 patients who died had $AaO_2 \geq 42.38$ and 71 of 109 patients who survived had a AaO_2 lower than 42.38 with a sensitivity specificity and NPV for overall deaths of $AaDO_2 \geq 42.38$ mmHg were 93.3%, 65.1% and 98.6% respectively (Table 2). Accuracy of test for overall deaths was found to be 68.5%. The cutoff value of $AaDO_2$ < 42.38 defined by ROC showed significant survival differences for overall mortality in the Kaplan–Meier survival analysis (p<0.012; Figure 2).

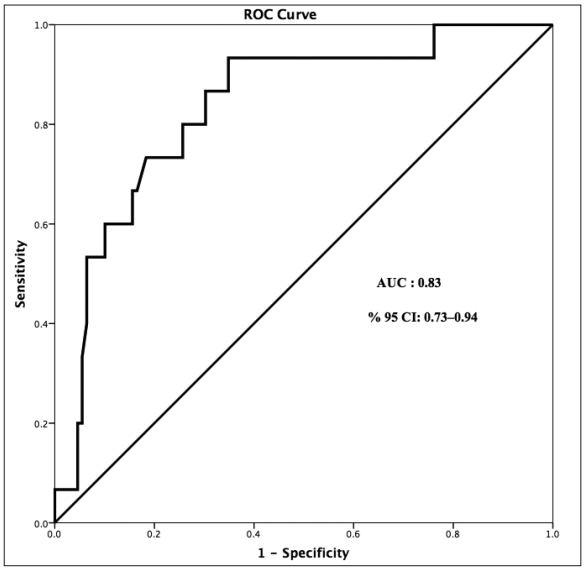

Figure 1: Receiver-operating characteristic curve of ability of alveolar-arterial gradient ($AaDO_2$) to predict overall mortality.

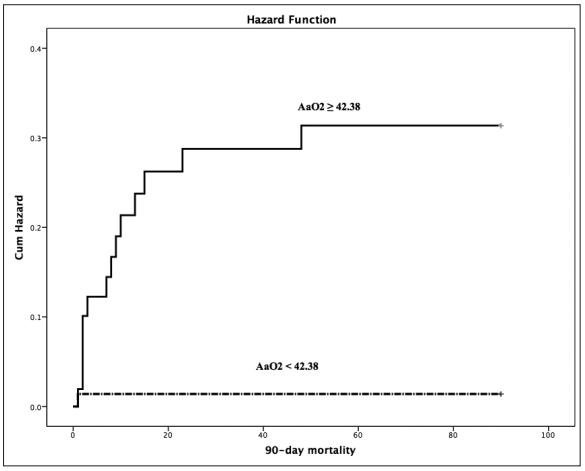

Figure 2: Cumulative proportional 90-day survival (Kaplan-Meier) of 124 patients with submassive pulmonary embolism, grouped according to the cutoff values: alveolar-arterial gradient (AaO_2) ≥ 42.38 or AaO_2 <42.38.

Troponin

Troponin levels were high in 81.8% of patients who died while it was high in 45.6% of patients who survived (p<0.026). High troponin levels showed sensitivity of 81.8% specificity of 54.4% and NPV of 95% in the prediction of deaths.

Pulmonary artery pressure (PAP)

The Mean PAP was 46.4 ± 13.5 mmHg for all submassive patients. The mean PAP was 56.3 ± 16.9 mmHg (range: 26-82) for patients who died and 45.1 ± 12.4 mmHg (range: 7–78) for patients who survived.
The area under the ROC curve was 0.75 (% CI: 0.74-0.87, p<0.002) for all mortality at 90 days. Sensitivity specificity and NPV for overall deaths of 47.5 mmHg were 60%, 77% and 93.3% respectively. Accuracy of test for overall deaths was found to be 75%.

CT findings

All CT findings including RV/LV ratio, interventricular septum and ancillary pulmary ct findings[1] were evaluated. Pulmonary thrombi showed a tendency to settle in the main pulmonary arteries in patients who died whereas it showed a predilection for peripheral pulmonary arteries in patients who survived (p<0.01).

Discussion

The present study suggest that alveolar-arterial gradient, is of significant prognostic value in patients with

submassive PE so that this tool may be used in risk stratification of patients who may need more careful follow up and therapy such as thrombolytic therapy.

Normotensive patients with acute PE and evidence of RV dysfunction are classified as having submassive PE, constitute a large population at increased risk for adverse events, and warrant consultation from cardiovascular medicine specialists[7]. Although advanced therapy with fibrinolysis is considered a life-saving intervention in massive PE, the decision to select advanced therapy for submassive PE or to maintain anticoagulation alone it remains controversial in patients with submassive PE, because of a paucity of trials to help guide management[9]. Thrombolytic therapy is able to directly dissolve clots to accelerate the resolution of PE, which may appear to be more effective compared with the use of anti- coagulants. A study by Konstantinides et al[11] revealed that thrombolytic therapy significantly reduced mortality in submassive PE compared with heparin anticoagulation alone[2,11]. In another study by Fei et all[3,23] showed that thrombolytic therapy can rapidly relieve dyspnea, reduce pulmonary arterial pressure and revascularize the embolized blood vessels[4,24]. However, it is necessary for physicians to assess the thrombolytic benefits against the significantly increased hemorrhagic risks[5,6,25]. The bleeding complications of thrombolytic therapy have been demonstrated to be notably higher than those of anticoagulant therapy; the overall major bleeding rate may reach up to 20%, while the risk of catastrophic intracranial hemorrhage is 1.9%[2,26]. Taking plus and minus aspects of thrombolytic therapy into account, thrombolytic agents may be beneficial in a carefully selected subgroup of patients with submassive pulmonary embolism[8]. At this point, the problem is that which parameters should be used for prognostic stratification. In our study, we tried to stratify patients with submassive pulmonary embolism with help of $AaDO_2$.

Gas exchange abnormalities seen in patients with PE are associated with the size of the emboli, degree of obstruction, embolization time and the underlying cardiopulmonary disease[2,10,27]. The transfer of oxygen and carbon dioxide across lungs is impaired in patients with Acute PE. Decreased arterial PO_2 (hypoxemia) and increased $AaDO_2$ gradient are the most common gas exchange abnormalities which are due to large shunts in pulmonary vascular bed[12,13,27]. The $AaDO_2$ is used as good index of gas exchange abnormalities, and the factors influencing it are diffusion gradient, ventilation–perfusion imbalance and true shunt. The prognostic role of alveolar-arterial oxygen pressure differences with an acute PE has been demonstrated in the literature[14-16,28].

The combination of AaDO2 and pulmonary artery pressure has been used for classifying PE[17,29]. Additionally, Masami et al have documented that inverted T waves have prognostic significance in acute PE. Therefore, the combination of initial $AaDO_2$ and ECG findings may provide another approach for predicting clinical prognosis. Aggressive thrombolytic therapy should be considered for patients with high $AaDO_2$ levels.

The present study further assessed the utility of using $AaDO_2$ to predict mortality, and with help of the ROC curves, we found that the optimal cut-off value for was 42.4 mmHg for 90-day mortality in patients with submassive PE. It had a high sensitivity and negative predictive rate and moderate specificity. Figure 2 represents the relevant 90-day survival curves for mortality. These curves demonstrate a significant difference between 90-day mortality and survival, based on the cutoff value for $AaDO_2$ after adjusting for other significant interfering factors. Mortality was uncommon for any patient with $AaDO_2 < 42.4$ mmHg during the first 24 hours of admission. To verify this result, future research will require an increased number of both hemodynamically stable and instable PE patients. Thus, $AaDO_2$ can be used in combination with other parameters, such as hypotension, high troponin, RVD, to improve the accuracy of prognostic evaluation.

Arterial blood gases have been extensively evaluated in the diagnostic work-up of patients with suspected PE. It has been reported that there is a linear association between PE severity and PaO2 levels[18,30]. Our study demonstrated that hypoxemia was significantly different in mortality vs survival groups. Yet PO2 alone had lower sensitivity for risk stratification of patients than $AaDO_2$.

The risk determination with the help of $PaO_2/PaCO_2$ ratio in PE is very important because it reflects oxygenation and ventilation. Ozsu at all[2,31] demonstrated that $PaO_2/PaCO_2 > 1.8$ values provided the survival advantage. Accordingly in our study 10 out of 15 patients who died had $PaO_2/PaCO_2 \leq 1.83$. However $PaO_2/PaCO_2$ ratio had lower sensitivity and NPV comparing with $AaDO_2$.

RVD detected by echocardiography or CT is a consequence of severe PE that is associated with poor prognosis and higher mortality rates[19,32]. Since echocardiography has some technical limitations, is expensive and not widely available in all medical centers, cardiac troponin testing may assist in determining the management of haemodynamically stable patients with acute PE. Reviewing recent studies, Becattini and colleagues[16,20] found that high troponin concentrations were associated with a higher mortality rate. We found that increased median Troponin-T levels and RV/LV ratio on CT were significantly higher in patients experiencing adverse events which was in agreement with previous studies[21,33-35].

Our study has several limitations. First, the number of adverse events was small and the stability of the prognostic model is therefore debatable. Second, we excluded from the analysis 10 normotensive patients receiving thrombolytic therapy. The benefit of thrombolytic treatment and its role on prognosis in these patients remains unclear, and current guidelines recommend against the use of thrombolytic therapy for patients with normotensive PE[2,21]. Therefore, we decided a priori to exclude from the analysis patients with normotensive PE who received thrombolytic treatment to be able to analyze properly prognostic factors in these patients without any

influence of a treatment on prognosis.

Conclusion

The results of this study suggest that alveolar-arterial gradient is useful and simple measurement for predicting short-term outcome of patients with submassive PE, together with CTPA. It has high sensitivity, negative predictive value and moderate specificity for 90-day death. If validated in independent cohorts, parameter of $AaDO_2 \geq 42.4$ mmHg may be an attractive tool as being an easily applicable and inexpensive diagnostic tool for identifying patients requiring more careful follow-up at hospital, for whom additional treatment such as thrombolytic therapy may be necessary.

Conflict of Interest

Authors declare no conflict of interest.

Acknowledgements

This study was presented as a poster presentation in European Respiratory Society Congress 2014 in Munich, Germany.

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