

Multidetector computed tomography for acute pulmonary embolism: diagnosis and risk stratification in a single test

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Aims

In patients with acute pulmonary embolism (PE), right ventricular dysfunction at echocardiography is associated with increased in-hospital mortality. The aims of this study in patients with acute PE were to identify a sensitive and simple criterion for right ventricular dysfunction at multidetector computed tomography (MDCT) using echocardiography as the reference standard and to evaluate the predictive value of the identified MDCT criterion for in-hospital death or clinical deterioration.

Methods and results

Right ventricular dysfunction at MDCT was defined as the right-to-left ventricular dimensional ratio and was centrally assessed by a panel unaware of clinical and echocardiographic data. A right-to-left ventricular dimensional ratio ≥ 0.9 at MDCT had a 92% sensitivity for right ventricular dysfunction [95% confidence interval (CI) 88–96]. Overall, 457 patients were included in the outcome study: 303 had right ventricular dysfunction at MDCT. In-hospital death or clinical deterioration occurred in 44 patients with and in 8 patients without right ventricular dysfunction at MDCT (14.5 vs. 5.2%; $P < 0.004$). The negative predictive value of right ventricular dysfunction for death due to PE was 100% (95% CI 98–100). Right ventricular dysfunction at MDCT was an independent predictor for in-hospital death or clinical deterioration in the overall population [hazard ratio (HR) 3.5, 95% CI 1.6–7.7; $P = 0.002$] and in haemodynamically stable patients (HR 3.8, 95% CI 1.3–10.9; $P = 0.007$).

Conclusion

In patients with acute PE, MDCT might be used as a single procedure for diagnosis and risk stratification. Patients without right ventricular dysfunction at MDCT have a low risk of in-hospital adverse outcome.

Keywords

Pulmonary embolism • Venous thrombo-embolism • Echocardiography • Computed tomography

Introduction

Patients with acute pulmonary embolism (PE) have a wide spectrum of clinical presentation and outcome and require different intensities of clinical care. Therefore, risk stratification for adverse outcome is essential to drive decisions about the optimal management strategies.¹ Admission to intensive care unit and treatment with thrombolysis could be necessary in patients with estimated high risk for adverse outcome.² Early hospital

discharge or even home treatment could be possible in patients with estimated low risk for adverse outcome.³ The proportion of patients with less severe PE is increasing, due to the reduced threshold of clinical suspicion and the increased availability of facilities for diagnosis.⁴ This makes essential to identify patients with relatively low risk for adverse outcome. Risk stratification in patients with acute PE is mainly based on the clinical presentation and the assessment of right ventricular dysfunction and injury. Right ventricular dysfunction is commonly assessed by

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echocardiography and myocardial injury by serum troponin.⁵ Right ventricular dysfunction at echocardiography is associated with an increased risk of in-hospital adverse outcome.^{6,7} However, echocardiography requires experienced personnel on an around-the-clock basis. Multidetector contrast-enhanced computed tomography (MDCT) is widely used for the diagnosis of PE.^{1,8–10} Multidetector computed tomography allows the visualization and measurement of the heart chambers and thus has the potential to be an alternative to echocardiography to assess right ventricular dysfunction.^{11–14}

We performed a prospective study in patients with acute PE to identify a sensitive and simple criterion for right ventricular dysfunction at MDCT and to evaluate the prognostic value of the identified MDCT criterion for in-hospital death and clinical deterioration.

Methods

Patients

Consecutive patients with symptomatic acute PE confirmed by 4- or 16-detector CT were considered for inclusion in the study. To be included in the study, patients should have had transthoracic echocardiography and serum troponin performed before or after 6 h from the diagnostic MDCT. Patients were excluded from the study if they had inadequate echocardiography or MDCT due to poor-quality images. Any decision about treatment was in charge of the attending physician. Data on demographic features, medical history, laboratory and echocardiographic findings, and anticoagulant treatment were collected.

The study was approved by local Institutional Review Boards. Written informed consent was obtained from all patients.

Study design

This is a prospective study in patients with acute PE performed in 12 centres in Italy, Poland, Germany, and The Netherlands. The objectives of the study were: (i) to evaluate the accuracy of MDCT in the assessment of right ventricular dysfunction, by using echocardiography as the reference standard; (ii) to assess the rate of in-hospital death, death due to PE, and clinical deterioration in patients with or without right ventricular dysfunction assessed by MDCT.

As in a previous study, clinical deterioration was defined as the occurrence of one or more among shock, need for thrombolysis, endotracheal intubation, catecholamine infusion, or cardiopulmonary resuscitation for sustained hypotension or recurrent PE.¹⁵ In case of death, the presumed cause was reported. Autopsy was not mandatory. As in previous studies, PE was considered the cause of death if there was an objective documentation or if death could not be attributed to a documented cause and PE could not be confidently ruled out.¹⁶

Transthoracic echocardiography

All patients underwent standard two-dimensional echocardiography. The diagnosis of right ventricular dysfunction required the presence of at least two among right-to-left ventricular end-diastolic diameter ratio >0.9 in the apical four-chamber view, or right-to-left ventricular end-diastolic diameter ratio >0.7 in the parasternal long-axis or subcostal four-chamber views, or paradoxical interventricular septal motion, or systolic pulmonary artery pressure over 30 mmHg.^{17,18} All these were to be in the absence of right ventricular hypertrophy. Echocardiography was locally adjudicated by physicians unaware of MDCT adjudication concerning right ventricular dysfunction.

Multidetector computed tomography angiography

Standard contrast-enhanced protocols for the diagnosis of PE were used (image acquisition beginning with a scanning delay of ~ 15 – 20 s after the start of the injection of contrast medium). Multidetector computed tomographies were recorded on CDs and were centrally evaluated by a panel (M.D., M.C.V., and C.B.) which included a radiologist expert in lung CT reading. Disagreement was resolved by consensus. The panel was unaware of the echocardiography results.

Right ventricular dysfunction was assessed by measuring the ratio of the right-to-left ventricular short-axis diameters. Ventricular diameters were measured by identifying the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis of the heart.¹³ Measurements were performed at the valvular plane in the two-dimensional axial transverse images, taking into account that the maximum dimension of the right and left ventricles may be found at slightly different levels (Figure 1).

Statistical analysis

Data were reported as proportion or as mean \pm SD or median (first–third inter-quartile range) as appropriate. Continuous data were compared with Student's *t*-test. Qualitative variables were compared by χ^2 test. *P*-values of <0.05 were considered to indicate statistical significance in all the analyses. All *P*-values are two-sided, and the 95% confidence intervals (CIs) were also reported.

The receiver-operating characteristic analysis was used to assess the diagnostic performance of MDCT for right ventricular dysfunction by using echocardiography as the reference standard and to identify a high-sensitivity cut-off for right ventricular dysfunction. We estimated that a sample of 250 patients would be needed to determine an accuracy of MDCT [measured as the area under the curve (AUC)] of at least 0.80 with a 95% CI of at most $\pm 5\%$, assuming a 40% disease prevalence.

Agreement among panel members for the right-to-left ventricular ratio at MDCT was assessed by the intra-class correlation coefficient

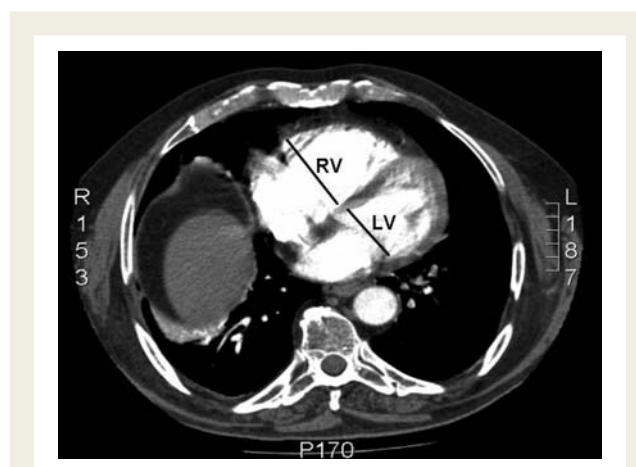


Figure 1 Measurement of right ventricular dysfunction at multidetector computed tomography. Ventricular diameters were measured by identifying the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis of the heart. Measurements were performed at the valvular plane in the two-dimensional axial transverse images. RV, right ventricle; LV, left ventricle.

(right-to-left ventricular ratio as a continuous variable) and by Cohen's κ -statistic (right-to-left ventricular ratio as a dichotomous variable).

The Kaplan–Meier statistic and log-rank test were used to estimate the cumulative probability of death, death due to PE, and death or clinical deterioration in patients with and without right ventricular dysfunction at MDCT. The Cox proportional hazard model was used to calculate the hazard ratio (HR) of clinical variables and MDCT measurements to assess for predictors of death or clinical deterioration. Multivariable analysis was then performed to identify predictors of death and death or clinical deterioration using the proportional hazards model with the calculation of 95% CIs. The following variables were considered: demographic features (age and gender), co-morbidities (cancer and cardiac disease), laboratory (troponin), echocardiographic (right ventricular dysfunction), and MDCT (right-to-left ventricular dimensional ratio) findings. We avoided to include in the same multivariable model variables that were closely related the one to the other. Assumption of proportional hazard was assessed and satisfied by visual inspection of the log-minus-log survival curves for right ventricular dysfunction at MDCT present/absent.

All analyses were performed by using SPSS 11.0.

We assumed an incidence of death or clinical deterioration of 10 and 2%, respectively, in patients with and without right ventricular dysfunction at MDCT.^{11–13} Given these assumptions, we needed 200 patients per group to detect a difference in this magnitude between the two groups, with a power of 90% and a type I error rate of 5%.

Results

Overall, 630 patients with acute PE were managed in the study centres during the study period. Of them, 113 were excluded because MDCT was not performed or was not available for central assessment and 57 were excluded because echocardiography and/or troponin assessment was not obtained in the time frame required by the study design. No statistically significant difference was observed between included and excluded patients regarding demographics, medical history, and clinical presentation.

Overall, 460 consecutive patients with acute PE confirmed by MDCT who had transthoracic echocardiography and serum troponin performed before or after 6 h from the diagnostic MDCT were evaluated for inclusion in the study. Three patients were excluded due to inadequate images at MDCT (0.7%). Thus, 457 patients were included in the analyses; mean age was 67 ± 16 , 209 patients were males (45.7%). Baseline features of the study population are reported in *Table 1*. Four hundred and eleven patients (90%) were haemodynamically stable and 230 patients (50%) had right ventricular dysfunction at echocardiography at the time of the diagnosis of PE.

The mean duration of the hospital stay was 9 ± 4 days, ranging from a minimum of 3 days to a maximum of 28 days.

Accuracy of multidetector computed tomography for assessing right ventricular dysfunction

The accuracy analysis was based on the first 260 consecutive patients. Among these patients, 149 (58%) were found to have right ventricular dysfunction at echocardiography. At MDCT evaluation, the mean right-to-left ventricular diameter ratio was $1.1 \pm$

0.3. The mean right-to-left ventricular ratio at MDCT was higher in patients with right ventricular dysfunction at echocardiography than in those without it (1.25 ± 0.27 compared with 0.89 ± 0.19 ; $P < 0.001$).

The diagnostic accuracy of MDCT for detecting right ventricular dysfunction, by using echocardiography as the reference standard, shown by the AUC was 0.86 (95% CI 0.82–0.91; *Figure 2*). Sensitivity and specificity for a right-to-left ventricular ratio ≥ 0.9 were 92% (95% CI 89–95) and 56% (95% CI 46–66), respectively. Sensitivity and specificity for a right-to-left ventricular ratio ≥ 1 at MDCT were 85% (95% CI 81–89) and 72% (95% CI 67–77), respectively. A right-to-left ventricular ratio ≥ 0.9 was identified as a high-sensitivity cut-off for right ventricular dysfunction at MDCT and then used in the clinical outcome analysis.

The intra-class correlation coefficient for right-to-left ventricular ratio assessment at MDCT among the panel members was 0.91, $P < 0.001$. Inter-observer agreement as assessed by Cohen's κ -statistic was 0.88.

Clinical outcome by multidetector computed tomographic assessment

The prognostic value of right ventricular dysfunction as assessed by MDCT was evaluated in the overall study population (457 patients). Fifty-two patients (11.3%) died or had clinical deterioration while in hospital. In-hospital death occurred in 25 patients (5.5%). Death was deemed to be due to PE by the attending physician in 17 patients (3.7%). In the remaining eight patients, death was due to pneumonia (four patients), sepsis (two patients), cancer (one patient), and intracranial haemorrhage (one patient). In-hospital clinical deterioration occurred in 40 patients (8.8%), of which 13 died. Death occurred in 10 patients (4%) within 3 days and in 18 patients (7%) within 1 week from the diagnosis of PE; all but one of the deaths due to PE occurred within 1 week from the diagnosis of PE.

Three hundred and three patients (66%) were found to have right ventricular dysfunction at MDCT. Baseline features of patients with and without right ventricular dysfunction at MDCT are reported in *Table 1*. Forty-four of 303 patients (14.5%) with right ventricular dysfunction at MDCT and 8 of 154 patients (5.2%) without right ventricular dysfunction at MDCT died or had clinical deterioration (HR 3.5, 95% CI 1.6–7.7; $P = 0.002$; *Table 2*). In-hospital death was more common in patients with right ventricular dysfunction at MDCT than in patients without it (6.9 vs. 2.6%; HR 2.8, 95% CI 0.9–8.1; $P = 0.06$; *Figure 3*). In-hospital death due to PE occurred in 5.6% of the patients with and in none of the patients without right ventricular dysfunction at MDCT ($P < 0.001$). Thus, the negative predictive value of right ventricular dysfunction at MDCT for death due to PE was 100% (95% CI 98–100; $P = 0.004$).

In univariate analysis, right ventricular dysfunction at echocardiography (HR 2.8, 95% CI 1.5–5.3; $P = 0.001$) as well as elevated serum troponin (HR 2.1, 95% CI 1.2–3.6; $P = 0.01$) were also associated with an increased risk for death or clinical deterioration.

In multivariable analysis, right ventricular dysfunction as assessed by MDCT was associated with an increased risk for death or clinical deterioration (HR 3.0, 95% CI 1.4–6.8) after adjusting for age

Table 1 Main features of study patients

	Overall population (457 patients)	Right-to-left ventricular ratio ≥ 0.9 at MDCT		P
		Present (303 patients)	Absent (154 patients)	
Age				
Mean (SD)	67 (16)	69 (15)	62 (19)	0.04
Range	18–97	18–97	18–96	
Male, n (%)	209 (45.7)	131 (43.2)	78 (50.6)	NS
Cancer, n (%)	91 (19.9)	62 (20.5)	29 (18.8)	NS
COPD, n (%) ^a	39 (11)	20 (10)	15 (10)	NS
Chronic heart failure, n (%)	21 (4.6)	15 (5.0)	6 (4.0)	NS
Immobilization for medical illness, n (%)	178 (38.9)	122 (40.3)	56 (36.4)	NS
Dyspnoea, n (%)	360 (79)	254 (83.8)	106 (68.8)	0.004
Chest pain, n (%)	159 (35)	99 (32.7)	60 (39.0)	NS
Tachycardia, n (%)	179 (39)	136 (44.9)	43 (27.9)	0.02
Systolic BP ≥ 90 mmHg, n (%)	411 (90)	262 (86.5)	149 (96.8)	0.002
Thrombolytic therapy, n (%)	45 (9.8)	40 (13)	5 (3.2)	<0.001
Echo-RVD, n (%)	230 (50)	207 (68.3)	23 (14.9)	<0.001
Elevated troponin, n (%)	177 (39)	152 (50.2)	25 (26.2)	<0.001

Features are reported with respect to the overall study population and to the two groups of patients with and without right ventricular dysfunction at MDCT. BP, blood pressure; echo, echocardiography; RVD, right ventricular dysfunction.

^aData available on 357 patients.

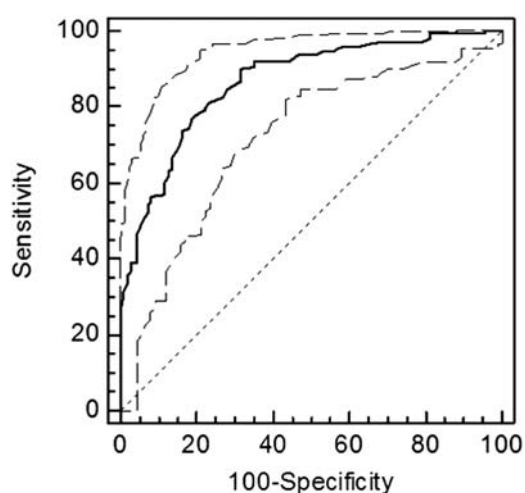


Figure 2 Receiver-operating characteristic curve with 95% confidence interval (dashed lines) illustrating the diagnostic performance of multidetector computed tomography to detect right ventricular dysfunction when compared with the reference standard echocardiography. The area under the curve was 0.86 (95% confidence interval 0.82–0.91).

and gender. In the same model, elevated troponin was not an independent predictor of death or clinical deterioration (HR 1.4, 95% CI 0.8–2.5). Right ventricular dysfunction as assessed by MDCT was also associated with an increased risk for death due to PE or clinical deterioration (HR 3.4, 95% CI 1.25–9.0).

At time of the diagnosis of PE, 262 (63.7%) of the patients which were haemodynamically stable had right ventricular dysfunction at MDCT. Of the haemodynamically stable patients, 28 died or had clinical deterioration while in hospital (6.8%). Right ventricular dysfunction at MDCT was associated with an increased risk for death or clinical deterioration in patients who were haemodynamically stable at the time of the diagnosis of PE at univariate (HR 3.8, 95% CI 1.3–10.9; $P = 0.007$). In multivariate analysis, right ventricular dysfunction at MDCT (HR 3.8, 95% CI 1.3–11.0) was an independent predictor of death or clinical deterioration in patients who were haemodynamically stable at the time of the diagnosis of PE after adjusting for age and gender. In this analysis, elevated troponin was not an independent predictor of death or clinical deterioration (HR 1.2, 95% CI 0.6–2.5).

Discussion

This study shows that the right-to-left ventricular dimensional ratio at MDCT has a good accuracy when compared with echocardiography for the assessment of right ventricular dysfunction in patients with acute PE. Right ventricular dysfunction at MDCT is an independent predictor for death or clinical deterioration and can be used for risk stratification for adverse outcome. Thus, MDCT has the potential to provide both diagnosis and prognostic stratification in patients with acute PE.

A simple criterion was used for the assessment of right ventricular dysfunction at MDCT. In previous studies, right ventricular dysfunction was measured by a quite complex procedure which required reformatted images.^{11,12} In our study, right ventricular dysfunction was assessed at MDCT by using two-dimensional axial transverse images. This measurement does not require

Table 2 Clinical outcome events according to the presence or absence of right ventricular dysfunction at multidetector computed tomography

	Right ventricular dysfunction at MDCT		HR (95% CI)	P-value	PPV (95% CI)	NPV (95% CI)
	Present	Absent				
Overall study population (n = 457)	n = 303	n = 154				
Death or clinical deterioration, n (%)	44 (14.5)	8 (5.2)	3.5 (1.6–7.8)	<0.01	15 (12–18)	95 (93–97)
Clinical deterioration, n (%)	34 (11.2)	6 (3.9)	4.0 (1.4–11.5)	<0.01	11 (8–14)	96 (94–98)
Death, n (%)	21 (6.9)	4 (2.6)	2.8 (0.9–8.2)	0.06	7 (5–9)	97 (95–99)
Death due to PE, n (%)	17 (5.6)	0	—	<0.01	NV	100 (98–100)
Haemodynamically stable patients (n = 411)	n = 262	n = 149				
Death or clinical deterioration, n (%)	24 (9.1)	4 (2.7)	3.8 (1.3–10.9)	0.01	9 (5–12)	97 (94–100)
Clinical deterioration, n (%)	15 (5.7)	3 (2.0)	4.0 (0.9–17.6)	0.06	6 (3–9)	98 (96–100)
Death, n (%)	14 (5.3)	3 (2.0)	2.9 (0.9–10.3)	0.08	5 (2–8)	98 (96–100)
Death due to PE, n (%)	9 (3.4)	0	—	<0.01	NV	100 (98–100)

HR, hazard ratio; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; PE, pulmonary embolism; NV, not valuable.

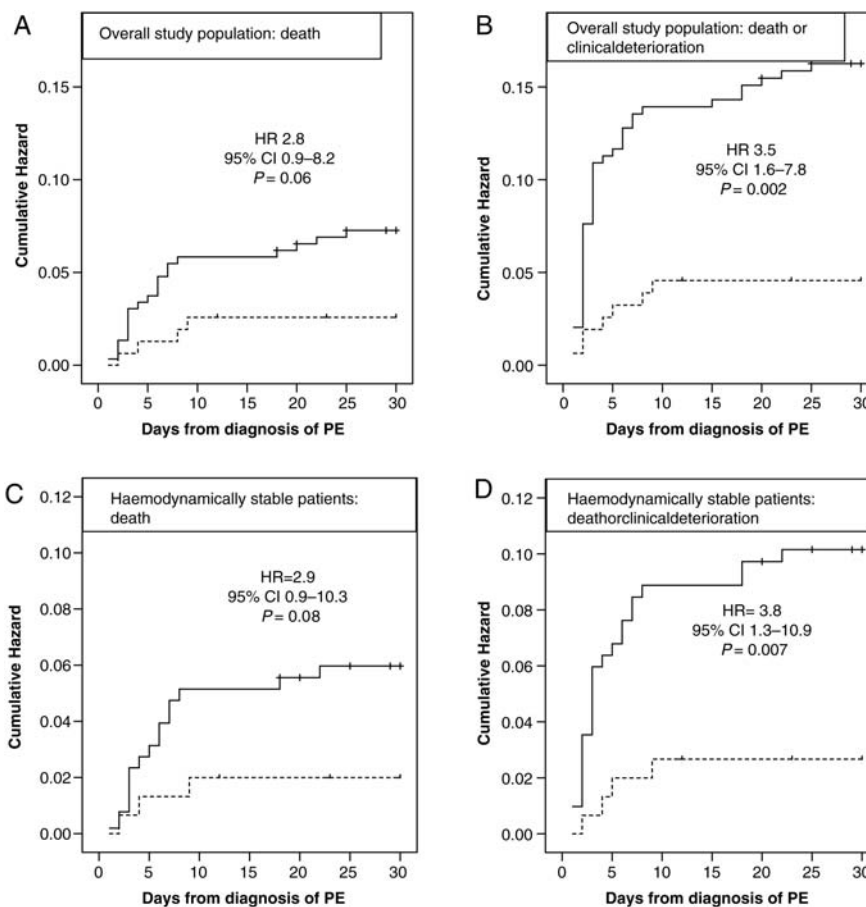


Figure 3 Cumulative incidence of overall death (A) and death or clinical deterioration (B) in patients with (solid lines) and without (dashed lines) right ventricular dysfunction at multidetector computed tomography. Cumulative incidence of death (C) and death or clinical deterioration (D) in haemodynamically stable patients with (solid lines) and without (dashed lines) right ventricular dysfunction at multidetector computed tomography. HR, hazard ratio; CI, confidence interval; PE, pulmonary embolism.

multiplanar reconstruction as it is performed in the same images used for the diagnosis of PE. By following this approach, the assessment of right ventricular dysfunction at MDCT is made easy and rapid and promptly available every-day in the urgent setting. Based on the results of our study, MDCT could potentially replace echocardiography to assess right ventricular dysfunction in patients with acute PE.

Risk stratification should be performed to categorize patients with acute PE according to their risk for in-hospital adverse outcome.¹ Based on this stratification, patients are candidates to a different clinical management concerning admission to intensive care unit and treatment with thrombolysis.¹⁹ Right ventricular dysfunction at MDCT was found to be an independent predictor for adverse outcome in the overall study population and in haemodynamically stable patients. In these patients, risk stratification can be particularly useful due to the wide variability in the rate of adverse outcome.^{20,21}

The prognostic value of right ventricular dysfunction at MDCT was evaluated by assessing death or clinical deterioration during the hospital stay. In our study, a right-to-left ventricular dimensional ratio <0.9 at MDCT was found in about one-third of the patients and was shown to have a 100% negative predictive value for death due to PE. The high negative predictive value could be useful to identify those patients at low risk of death who are candidates to early discharge or home treatment. The assessment of right ventricular dysfunction at MDCT could avoid further testing for risk stratification in about one-third of the patients. The prevalence of right ventricular dysfunction was 66% in our study, compared with 64% found by Schoepf *et al.*¹¹ and 58% by van der Meer *et al.*¹³ The low positive predictive value of a right-to-left ventricular dimensional ratio ≥ 0.9 cannot be used to justify treatment upgrading.

In our study, a good correlation was found between measurements made by an expert radiologist and physicians with experience on MDCT reading for PE. This finding supports the reliability of the right-to-left ventricular dimensional ratio at MDCT as a criterion for right ventricular dysfunction.

Whether further risk stratification by using additional testing could help to identify those patients with right ventricular dysfunction requiring intensive monitoring or thrombolysis is unclear. In this study, the additive prognostic value of serum troponin did not reach a statistical significance over right ventricular dysfunction at MDCT, although the results were directionally consistent. Although individual studies and meta-analyses showed that troponin is a predictor for adverse outcome in patients with acute PE,^{22,23} the additive prognostic value of troponin over right ventricular dysfunction at echocardiography needs to be confirmed.^{24,25}

None of the MDCT in this study was electrocardiogram (ECG)-gated. Electrocardiogram-gated MDCT allows more accurate evaluation of the heart. However, this technique requires longer acquisition times and higher radiation doses. Moreover, ECG-gated CT is not routinely used for the evaluation of chest pain or suspected PE in the emergency department. Four- and 16-detector CTs were used in this study. More sophisticated CT scanners are currently available in advanced medical centres. Such scanners could allow a further increase in the accuracy of right ventricular evaluation in patients with acute PE.

Multidetector computed tomography is not able to provide functional evaluation of the right ventricle (such as hypokinesia or estimation of pulmonary artery pressure) easily obtained by echocardiography. However, right ventricular dilatation at echocardiography is the most reliable predictor of adverse clinical outcome in patients with acute PE.

This study has some limitations. The study design required to have echocardiography and serum troponin performed within 6 h from MDCT and this could have led to unintentional patient selection. We could have included patients with severe PE as suggested by the higher than expected proportion of patients with right ventricular dysfunction at echocardiography. The cause of death was adjudicated by the attending physician who was not blinded concerning the echocardiography assessment. Indeed, no central assessment of the echocardiography was performed.

However, our study also has some strengths. In this prospective study, right ventricular dysfunction at MDCT was centrally adjudicated by a panel unaware of the results of echocardiography, clinical presentation, and outcome. The rate of inadequate MDCT images was extremely low, despite the multicentre nature of the study. Of interest, right ventricular dysfunction at MDCT showed a high negative predictive value in the large group of haemodynamically stable patients.

In conclusion, our study supports the hypothesis that in patients with acute PE, MDCT can be used as a single procedure for diagnosis and risk stratification. Patients without right ventricular dysfunction at MDCT have a low risk of in-hospital adverse outcome. Both these hypotheses should be assessed in further validation studies.

Conflict of interest: none declared.

Appendix

List of participants who contributed to the study

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