Prognostic value of cardiovascular parameters in computed tomography pulmonary angiography in patients with acute pulmonary embolism

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In CTPA only an enlarged pulmonary trunk is associated with an increased risk for mortality and recurrent VTE http://ow.ly/EfDv30k408r

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ABSTRACT The value of various computed tomography parameters for prognosis and risk stratification in acute pulmonary embolism is controversial. Our objective was to evaluate the impact of specific cardiovascular computed tomography pulmonary angiography parameters on short- and long-term clinical outcomes.

We analysed radiological and clinical data of 1950 patients with acute pulmonary embolism who participated in an international randomised clinical trial on anticoagulants. Parameters included right/left ventricular ratio, septal bowing, cardiothoracic ratio, diameters of pulmonary trunk and aorta, and intrahepatic/azygos vein contrast medium backflow. Associations with mortality, recurrent venous thromboembolism (VTE), hospitalisation, bleeding and adverse events were assessed over the short term (1 week and 1 month) and long term (12 months).

Pulmonary trunk enlargement was the only parameter significantly associated with mortality over both the short and long term (OR 4.18 (95% CI 1.04–16.76) at 1 week to OR 2.33 (95% CI 1.36–3.97) after 1 year), as well as with recurrent VTE and hospitalisation.

Most of the evaluated radiological parameters do not have strong effects on the short- or long-term outcome in patients with acute pulmonary embolism. Only an enlarged pulmonary trunk diameter carries an increased risk of mortality and recurrent VTE up to 12 months, and can be used for risk stratification.

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Introduction

Pulmonary embolism is the third most common cardiovascular disease worldwide with mortality ranging up to 25% [1]. Calculating the risks of adverse outcome for a patient can guide therapeutic decision making (home therapy, hospitalisation or thrombolysis) [2–4]. This risk can be based on clinical, biochemical and imaging parameters [5–7]. The detrimental consequences from pulmonary embolism are thought to be mainly associated with the development of right ventricular dysfunction (RVD), which could cause an increase of cardiac biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) [8]. The burden to the heart would lead to overall heart failure and subsequent death.

European Society of Cardiology (ESC) guidelines categorise the risk of adverse outcome as high, intermediate or low. Risk calculations are based on the simplified pulmonary embolism severity index (sPESI) and are suggested to guide treatment accordingly [2]. For the large intermediate-risk group, fine tuning can be done on the presence of RVD, categorising patients to intermediate/high risk or intermediate/low risk as assessed by biomarkers or imaging [9]. In daily practice, however, additional tests such as ultrasound or NT-proBNP are frequently not performed [10]. It would be ideal if computed tomography pulmonary angiography (CTPA), the reference standard for the diagnosis of pulmonary embolism, could also be used to assess the prognosis [11]. So far, heterogeneity in study groups, definitions and outcomes prohibits consensus on the prognostic performance of CTPA [12]. Two multicentre prospective studies have suggested that the right/left ventricular (RV/LV) ratio can be used as a predictor for mortality. As these studies did not investigate other potential predictive parameters, the unique position of the RV/LV ratio can be questioned [13, 14]. Other reported radiological findings such as cardiovascular diameters, backflow or clot burden have been evaluated, but findings on their value are inconsistent [15–20]. Consequently, it is unclear if one or more CTPA parameters can contribute to risk stratification in patients with acute pulmonary embolism.

To add strong evidence to the debate on the value of CTPA parameters in risk stratification we analysed imaging, clinical and follow-up data collected in a prospective multicentre trial in patients with acute pulmonary embolism [21]. Our focus was on the evaluation of the predictive effects of baseline CTPA parameters on short- and long-term clinical outcomes.

Materials and methods

Patients and study design

Patient data and images were collected in the context of a large international randomised clinical trial comparing two anticoagulant regimens in patients with venous thromboembolism (VTE). The results, design and methods of the Hokusai-VTE study have been described in detail previously (ClinicalTrials.gov identifier NCT00986154) [21]. In short, eligible patients were patients aged ⩾18 years with acute, symptomatic VTE (deep vein thrombosis (DVT) and/or pulmonary embolism). Patients were excluded in case of contraindications to heparin or warfarin, severely impaired renal function, or pregnancy. The institutional review board at each participating centre approved the general study protocol and all patients provided written informed consent.

Patients were enrolled between January 2010 and October 2012 at 439 centres in 37 countries. All data for the present analysis had been collected and assessed prospectively before the trial data lock. Follow-up was 12 months, covering both the in-hospital period as well as regular outpatient clinic controls, and patients on and off anticoagulant treatment. Adverse events were noted on separate forms, as well as whether they were pulmonary embolism related. An independent committee adjudicated all predefined outcomes.

For this additional study all patients with pulmonary embolism, either with or without DVT, were selected. Patients with DVT only, patients not evaluated by CTPA, or images not available in DICOM format or inaccessible for reading in the image viewer used (*e.g.* hard copy, corrupted discs) were excluded.

Data collection

All clinical and radiological data were anonymised and centrally registered with double data entry by an independent trial data management agency. Clinical data were retrieved from the original case report forms. NT-proBNP levels were measured at baseline in all patients.

CT data were acquired from the local participating centres, using local settings and protocols. This means that a wide variety of CT scanners were used, from basic to high-end CT scanners. A five-point Likert scale was used for quality evaluation, anchored at 1 (unacceptable), 2 (poor), 3 (satisfactory), 4 (good) and 5 (excellent). Enhancement of the pulmonary trunk was assessed by measuring a 1-cm region of interest and expressed in Hounsfield units.

Anonymised patient images from the central database were evaluated by a radiologist (L.F.M.B.) with 12 years of experience in chest imaging supported by a dedicated research assistant. Both were unaware of patient details and clinical information. A commercially available image viewer was used for image reading (eFilm Workstation for Windows version 3.4.0, Build 10; Merge Technologies, Milwaukee, WI, USA). Images were primarily read in axial sections with additional support of multiplanar reformatting. Standard pulmonary angiography, mediastinal and lung parenchyma window settings were used, with individual adaptation if deemed necessary. Data were registered on a specially designed case report form.

A random sample of 50 patients was used to evaluate the intra-observer variability for the main study parameters, as assessed by Cohen's κ. Intra-observer agreement was graded according to the Landis–Koch criteria, with 0–0.20 indicating poor correlation, 0.21–0.40 indicating moderate correlation, 0.41–0.60 indicating fair correlation, 0.61–0.80 indicating good correlation and 0.81–1.00 indicating excellent correlation. No additional readers were engaged as intra-observer agreement for the selected parameters is reportedly high [22–24].

All continuous variables were noted in millimetres where applicable. The following parameters were assessed: transverse diameter of right ventricle, left ventricle (both on axial and reformatted short axis view), pulmonary trunk, ascending aorta, inferior and superior cava veins, azygos vein and right atrium, and heart and intrathoracic diameters. For the ventricular diameters, the largest cross-sectional distance between ventricular surfaces was taken. The right atrium was measured at its largest transverse diameter. The pulmonary trunk was measured at its largest transverse diameter, the ascending aorta at the level of the carina, the cava veins were measured 2 cm from their entrance into the right atrium, and the azygos vein at its most cranial part. For heart volume and intrathoracic distance, the largest transverse diameters from pericardial contours and costal margins were taken.

The RV/LV, RV/LV short axis (RV/LVsa) and pulmonary trunk/aorta (PT/Ao) ratios were calculated by dividing the values of the respective transverse diameters. All values obtained were then dichotomised at earlier reported thresholds (RV/LV >1.0, RV/LVsa >0.9, PT/Ao >1.0, PT >29 mm and cardiothoracic ratio >0.50) [11–18].

Ordinal measures were: bowing of the interventricular septum (negative, neutral or positive), and reflux of contrast medium in the inferior vena cava (IVC) (no, only into the IVC, intrahepatic veins <3 cm or and intrahepatic veins>3 cm) and in the azygos vein (yes or no). Interventricular septum bowing was considered present when the septum was curved to the left ventricle, or flattened if the septum was straightened or bowed. Backflow was considered positive if reflux was into the intrahepatic veins; reflux only into the IVC was considered negative. Azygos vein reflux was considered present if it reached the crossing with the right mainstem bronchus.

Events were analysed focusing on four time-points: early (1 week and 1 month) and late (on-treatment (mostly 3–6 months) and 12 months). For RVD, the reference standard was an increased value of NT-proBNP $\geqslant$600 pg·mL^{-1} at baseline [2].

Statistical analysis

The primary outcome for the study was mortality; secondary outcomes were recurrent VTE, hospitalisation, bleeding and all adverse events. We calculated odds ratios with 95% confidence intervals to express the strength of the association between cardiovascular CTPA parameters and mortality, as well as other clinical outcomes. We also calculated estimates of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for mortality. Missing data were excluded from the analysis. No correction for multiple testing was performed. Significance of differences was evaluated with two-sided p-values; a p-value <0.05 was considered to imply statistical significance. All statistical analyses were performed in SPSS version 23 (IBM, Armonk, NY, USA).

Results

In the randomised clinical trial, 3481 patients had pulmonary embolism, of which 3114 had been diagnosed using CTPA. After screening, 1164 of these were excluded because images were presented on hard copies, JPEG or PDF only, no DICOM images were available, or because of a technically inadequate study, *e.g.* insufficient coverage of heart and chest (figure 1). To address possible selection bias, we compared baseline characteristics of included and excluded patients, and found no relevant differences. The 1-year outcomes also were not different, as mortality and recurrent VTE were 3.0% and 2.6% for the included group and 3.1% and 2.7% for the excluded group, respectively. Hence, data of 1950 patients were included in this evaluation. Of these, 1049 (54%) were male and the mean age was 57 years. A summary of their characteristics is shown in table 1. Pulmonary embolism was provoked in 1288 patients; 456 patients had pulmonary embolism with concomitant DVT. 565 patients had NT-proBNP >600 pg·mL^{-1}.

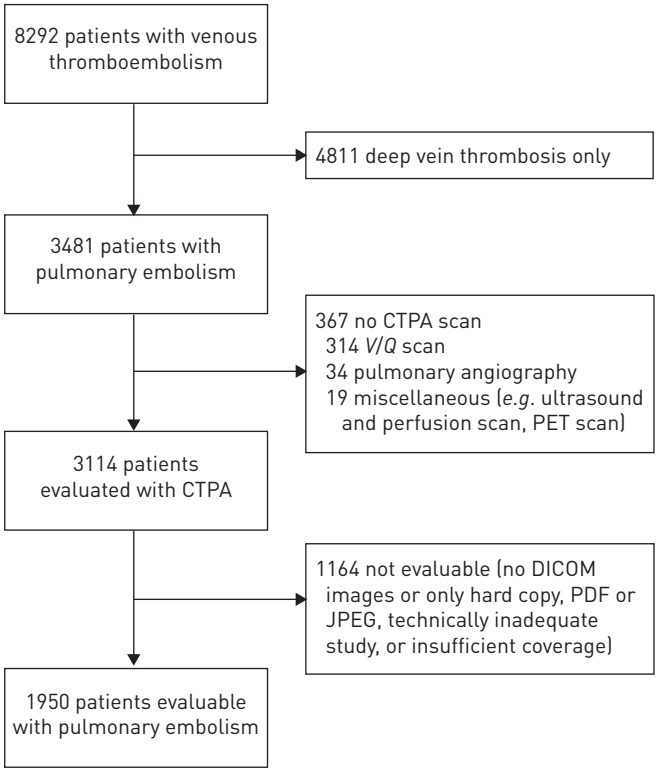

FIGURE 1 Inclusion flowchart. CTPA: computed tomography pulmonary angiography; *V/Q*: ventilation/perfusion; PET: positron emission tomography.

Quality

Overall quality of the scans was good (mean±SD 3.7±0.8 out of 5). Enhancement in the pulmonary trunk was mean±SD 325±118 HU. Intra-observer agreement on a random sample from the complete database scored twice was excellent (κ=0.9).

Frequencies

The median RV/LV ratio on CTPA was 0.89; 621 patients (32%) had a ratio >1 (tables 2 and 3). Compared with those without RVD on CT, NT-proBNP was more often raised in patients with RV/LV >1. The median RV/LVsa ratio was 0.88, of which 890 patients (46%) had a ratio >0.90.

In 538 patients (27.6%) the septum was flattened; septal bowing occurred in 153 patients (7.9%). The pulmonary trunk was enlarged in 634 patients (32.5%). PT/Ao >1 was present in 408 patients (20.9%). Backflow of contrast medium into the hepatic veins occurred in 261 patients (14.9%) and into the azygos vein in 445 patients (22.9%).

Outcomes

A summary of the investigated cardiovascular radiological parameters and their correlation with short- and long-term adverse events is given in tables 4 and 5 (mortality) and supplementary table S1 (recurrent VTE, hospitalisation, major bleeding and all adverse events).

Short-term outcomes

29 adverse events occurred during the first month, including 18 deaths, 12 recurrent VTEs and 13 episodes of bleeding. There were 26 hospitalisations.

Of all the radiological parameters evaluated, only pulmonary trunk diameter >29 mm was significantly associated with mortality at 1 week (OR 4.18, 95% CI 1.04–16.76; p=0.028) (tables 2 and 3). The odds ratio at 1 month was lower and not statistically significant (OR 2.30, 95% CI 0.97–5.45; p=0.051). All other parameters (RV/LV ratio, RV/LVsa ratio, septal bowing, PT/Ao ratio, cardiothoracic ratio and backflow to hepatic veins or azygos vein) were not significantly associated with mortality. Of the nine patients who died within the first week, six (66.7%) had an enlarged pulmonary trunk. In total, 18 patients died within 1 month; an enlarged pulmonary trunk was present in half of these 18 patients. In patients who survived 1 week or subsequently 1 month, an enlarged pulmonary trunk was present in 628 and 625 patients, respectively (32.4%; p=0.028 *versus* 32.4%; p=0.11).

TABLE 1 Baseline characteristics

	Included	Excluded
Subjects	1950	1531
Clinical		
Age years	57.0±16.6	57.5±16.5
Age >65 years	714 (36.6)	560 (36.6)
Male	1049 (53.8)	793 (51.8)
Female	901 (46.2)	738 (48.2)
Weight kg	84.5±20.1	79.8±19.9
Concomitant DVT	456 (23.4)	363 (23.7)
Smoking	854 (43.8)	635 (41.5)
Alcohol	754 (38.7)	446 (29.1)
Ultrasound right ventricular diameter mm	37.2±28.2 (n=523)	31.8±22 (n=496)
Systolic blood pressure mmHg	128±16.5	127±16.4
Diastolic blood pressure mmHg	76±11	76±10.9
Heart rate beats·min^{-1}	80±14	80±13.9
Respiratory rate breaths·min^{-1}	16±2.6	19.2±2
sPESI high risk[#]	1051 (53.9)	990 (64.8)
Risk factors		
Provoked pulmonary embolism	1288 (66.1)	959 (62.6)
Recent surgery, trauma or immobilisation	372 (19.1)	282 (18.4)
Sitting >4 h	185 (9.5)	121 (7.9)
Oestrogen-containing drugs use (females)	196 (21.8)	103 (6.7)
Active cancer	56 (2.9)	34 (2.2)
Previous episodes of DVT/pulmonary embolism	415 (21.3)	305 (19.9)
Thrombophilic condition	94 (4.8)	59 (3.9)
Concomitant disease history		
Hypertension	810 (41.5)	645 (42.2)
Diabetes	199 (10.2)	155 (10.1)
Cardiovascular disease	314 (16.1)	274 (17.9)
Chronic heart failure	35 (1.8)	62 (4.1)
Cerebrovascular disease	73 (3.7)	65 (4.3)
Stroke	35 (1.8)	38 (2.5)
Renal disease	129 (6.6)	132 (8.6)
Hepatic disease	212 (10.9)	195 (12.8)
Pulmonary disease	401 (20.6)	446 (29.2)
COPD	103 (5.3)	116 (7.6)
Interstitial lung disease	11 (0.6)	3 (0.2)
Pulmonary hypertension	43 (2.2)	56 (3.7)
Cancer	228 (11.7)	148 (9.7)

Data are presented as n, n (%) or mean±SD. DVT: deep vein thrombosis; sPESI: simplified pulmonary embolism severity index; COPD: chronic obstructive pulmonary disease. [#]: item on oxygen considered positive if patient needed oxygen administration.

An enlarged pulmonary trunk diameter was also associated with recurrent VTE (OR 5.22, 95% CI 1.01–26.7; p=0.028) at 1 week. Here also the odds ratio was lower and not significant at 1 month (OR 1.8, 95% CI 0.6–5.3; p=0.051). None of the evaluated radiological parameters, apart from enlarged pulmonary trunk diameter, were associated with hospitalisation. Sensitivities were low for all the evaluated parameters, as were the specificities and PPVs; however, all parameters showed high NPVs.

Long-term outcomes

The median (interquartile range) on-treatment time was 215 (178–358) days. During the complete 1-year period, 143 adverse events were registered in 131 patients. In total, 58 patients died, 49 had recurrent VTE, 30 had a major bleeding episode and 90 were hospitalised.

An enlarged pulmonary trunk diameter was significantly associated with mortality during the on-treatment time as well as for the complete 12 months (p=0.004 and p=0.001, respectively). PT/Ao >1.0 was also significantly associated with mortality during treatment (p=0.002), but not for the complete period (p=0.055). Of the 11 patients with interstitial lung disease, two patients who had an enlarged pulmonary trunk died. In 43 patients with a history of pulmonary hypertension, 21 had an enlarged

TABLE 2 Radiological diameters and ratios

	Total	Missing	Mean±SD	Minimum	Maximum	Interquartile range
RV axial plane mm	1950	0	38.3±7.8	17	67	33–43
LV axial plane mm	1950	0	41.5±7.1	18	69	37–48
RV short axis mm	1906	44	39.7±7.7	20	71	34–45
LV short axis mm	1906	44	42.6±6.7	22	73	38–47
Aorta mm	1949	1	32.3±4.9	18	52	29–35
Pulmonary trunk mm	1949	1	27.7±4.6	15	52	25–31
Azygos vein mm	1947	3	8.3±2.3	2	20	7–10
SVC mm	1949	1	18.9±4.1	8	33	16–22
RV wall thickness mm	1950	0	1.5±0.8	1	8	1–2
Right atrium mm	1950	0	49.0±9.1	24	88	43–55
IVC mm	1942	8	22.7±4.3	8	41	20–25
Heart mm	1950	0	128.6±14.9	85	228	119–138
Chest mm	1950	0	259.1±24.2	126	344	242–276
RV/LV axial	1950	0	0.95±0.27	0.39	2.61	0.78–1.00
RV/LV short axis	1950	0	0.96±0.26	0.47	2.11	0.80–1.02
PT/Ao	1950	0	0.87±0.15	0.42	2.08	0.77–0.96
Cardiothoracic ratio	1950	0	0.50±0.06	0.34	0.97	0.46–0.54

Data are presented as n, unless otherwise stated. RV: right ventricular; LV: left ventricular; SVC: superior vena cava; IVC: inferior vena cave; PT/Ao: pulmonary trunk/aorta.

pulmonary trunk, of which two died. All other evaluated cardiovascular parameters were not significantly associated with mortality or other adverse events.

Discussion

Our study showed that most of the investigated cardiovascular radiological parameters, including RV/LV ratio, septal bowing, cardiothoracic ratio and contrast medium backflow, have no prognostic value for short- or long-term mortality. The exception was an enlarged pulmonary trunk diameter, which over both the short and long term was associated with increased mortality and the risk of recurrent VTE and hospitalisation.

A strength of our study is that data were prospectively collected in a large international trial, and both imaging data and clinical outcomes were assessed blinded for treatment and outcome.

Our study also has limitations. Although many parameters have been evaluated in the literature, we only analysed the most frequently used radiological parameters and cut-off values as these would be most easily implementable, had we found any of these to be of value. As reconstructed views yield comparative values but are more time consuming, plain axial transverse images are generally preferred given the simplicity of analysis [25]. We evaluated observer agreement only for the main continuous variables and not for the

TABLE 3 Frequency of abnormal cardiovascular radiological parameters

	Total	Missing	Normal	Abnormal
RV/LV >1	1950	0	1329 (68.2)	621 (31.8)
RV/LVsa >0.9	1914	36	1024 (53.5)	890 (46.5)
Septal bowing	1949	1	1796 (92.1)	153 (7.9)
Septal flattening	1949	1	1411 (72.4)	538 (27.6)
Aorta >40 mm	1840	110	1800 (97.8)	40 (2.2)
Pulmonary trunk >29 mm	1949	1	1315 (67.5)	634 (32.5)
PT/Ao >1.0	1950	0	1542 (79.1)	408 (20.9)
Cardiothoracic ratio >0.50	1833	117	897 (48.9)	936 (51.1)
Backflow IVC	1754	196	1105 (63)	649 (37)
Intrahepatic contrast reflux	1754	196	1493 (85.1)	261 (14.9)
Backflow azygos vein	1947	3	1502 (77.1)	445 (22.9)

Data are presented as n or n (%). RV/LV(sa): right/left ventricular (short axis); PT/Ao: pulmonary trunk/aorta; IVC: inferior vena cava.

TABLE 4 Short- and long-term mortality: odds ratios

	Total	No	Present	OR (95% CI)
1 week				
RV/LV >1	1950	6 (66.7)	3 (33.3)	1.07 (0.27–4.29)
RV/LVsa >0.9	1914	4 (44.4)	5 (55.6)	1.44 (0.39–5.38)
Septal bowing	1949	8 (100.0)	0 (0.0)	
Septal flattening	1949	5 (62.5)	3 (37.5)	1.58 (0.38–6.62)
Aorta >40 mm	1840	9 (100.0)	0 (0.0)	
Pulmonary trunk >29 mm	1949	3 (33.3)	6 (66.7)	4.18 (1.04–16.76)
PT/Ao >1.0	1950	6 (66.7)	3 (33.3)	1.90 (0.47–7.62)
Cardiothoracic ratio >0.50	1833	2 (22.2)	7 (77.8)	3.37 (0.70–16.28)
Backflow IVC	1754	5 (62.5)	3 (37.5)	1.02 (0.24–4.29)
Intrahepatic reflux	1754	6 (75.0)	2 (25.0)	1.91 (0.38–9.53)
Backflow azygos vein	1947	7 (77.8)	2 (22.2)	0.96 (0.20–4.66)
1 month				
RV/LV >1	1950	15 (71.4)	6 (28.6)	0.86 (0.33–2.21)
RV/LVsa >0.9	1914	8 (38.1)	13 (61.9)	1.88 (0.78–4.56)
Septal bowing	1949	20 (100.0)	0 (0.0)	
Septal flattening	1949	13 (65.0)	7 (35.0)	1.42 (0.56–3.57)
Aorta >40 mm	1840	20 (100.0)	0 (0.0)	
Pulmonary trunk >29 mm	1949	10 (47.6)	11 (52.4)	2.30 (0.97–5.45)
PT/Ao >1.0	1950	14 (66.7)	7 (33.3)	1.91 (0.76–4.75)
Cardiothoracic ratio >0.50	1833	7 (33.3)	14 (66.7)	1.93 (0.78–4.81)
Backflow IVC	1754	12 (60.0)	8 (40.0)	1.14 (0.46–2.80)
Intrahepatic reflux	1754	15 (75.0)	5 (25.0)	1.92 (0.69–5.34)
Backflow azygos vein	1947	18 (85.7)	3 (14.3)	0.56 (0.16–1.91)
Complete on-treatment period				
RV/LV >1	1950	20 (66.7)	10 (33.3)	1.07 (0.50–2.30)
RV/LVsa >0.9	1914	12 (40.0)	18 (60.0)	1.74 (0.83–3.63)
Septal bowing	1949	29 (100.0)	0 (0.0)	
Septal flattening	1949	20 (69.0)	9 (31.0)	1.18 (0.54–2.62)
Aorta >40 mm	1840	29 (100.0)	0 (0.0)	0.98 (0.98–0.99)
Pulmonary trunk >29 mm	1949	13 (43.3)	17 (56.7)	2.76 (1.33–5.72)
PT/Ao >1.0	1950	17 (56.7)	13 (43.3)	2.95 (1.42–6.13)
Cardiothoracic ratio >0.50	1833	10 (33.3)	20 (66.6)	1.94 (0.90–4.16)
Backflow IVC	1754	17 (60.7)	11 (39.3)	1.10 (0.51–2.37)
Intrahepatic reflux	1754	21 (75.0)	7 (25.0)	1.93 (0.81–4.59)
Backflow azygos vein	1947	26 (86.7)	4 (13.3)	0.52 (0.18–1.48)
1 year study period				
RV/LV >1	1950	42 (72.4)	16 (27.6)	0.81 (0.45–1.45)
RV/LVsa >0.9	1914	28 (48.3)	30 (51.7)	1.24 (0.74–2.09)
Septal bowing	1949	55 (96.5)	2 (3.5)	0.42 (0.10–1.74)
Septal flattening	1949	43 (75.4)	14 (24.6)	0.85 (0.46–1.57)
Aorta >40 mm	1840	52 (94.5)	3 (5.5)	2.73 (0.81–9.13)
Pulmonary trunk >29 mm	1949	23 (39.7)	35 (60.3)	2.33 (1.36–3.97)
PT/Ao >1.0	1950	40 (69.0)	18 (31.0)	1.73 (0.98–3.06)
Cardiothoracic ratio >0.50	1833	23 (40.4)	34 (59.6)	1.43 (0.94–2.45)
Backflow IVC	1754	28 (54.9)	23 (45.1)	1.41 (0.81–2.48)
Intrahepatic reflux	1754	40 (78.4)	11 (21.6)	1.60 (0.81–3.16)
Backflow azygos vein	1947	51 (87.9)	7 (12.1)	0.46 (0.21–1.01)

Data are presented as n or n (%), unless otherwise indicated. RV/LV(sa): right/left ventricular (short axis); PT/Ao: pulmonary trunk/aorta; IVC: inferior vena cava.

ordinal measurements. We also did not perform separate assessments for treatment allocation to edoxaban or enoxaparin followed by warfarin, as this subgroup analysis was done in the original dataset [21]. We did not perform a multivariable analysis, as we first aimed to assess the prognostic value of each parameter separately. Echocardiography can also be a useful tool for short-term mortality risk stratification [12]. As only 523 (26.8%) of the evaluated patients received this test, this was not analysed in the present study. We are aware that patients included in a randomised clinical trial do not necessarily reflect all those presenting in regular practice and our results cannot be unconditionally generalised to those with exclusion criteria for the trial, such as haemodynamically unstable patients, patients with a limited life expectancy and pregnant females.

TABLE 5 Short- and long-term mortality: sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
1 week				
RV/LV >1	0.33 (0.03–0.64)	0.68 (0.66–0.70)	0.00 (0.00–0.01)	1.00 (0.99–1.00)
RV/LVsa >0.9	0.56 (0.23–0.88)	0.54 (0.51–0.56)	0.01 (0.00–0.01)	1.00 (0.99–1.00)
Septal bowing	0.00 (0.00–0.00)	0.92 (0.91–0.93)	0.00 (0.00–0.00)	1.00 (0.99–1.00)
Septal flattening	0.38 (0.04–0.71)	0.72 (0.70–0.74)	0.01 (0.00–0.01)	1.00 (0.99–1.00)
Aorta >40 mm	0.00 (0.00–0.00)	0.98 (0.97–0.98)	0.00 (0.00–0.00)	1.00 (0.99–1.00)
Pulmonary trunk >29 mm	0.67 (0.36–0.97)	0.68 (0.66–0.70)	0.01 (0.00–0.02)	1.00 (1.00–1.00)
PT/Ao >1.0	0.33 (0.03–0.64)	0.79 (0.77–0.81)	0.01 (0.00–0.02)	1.00 (0.99–1.00)
Cardiothoracic ratio >0.50	0.78 (0.51–1.05)	0.49 (0.47–0.51)	0.01 (0.00–0.01)	1.00 (0.99–1.00)
Backflow IVC	0.38 (0.04–0.71)	0.63 (0.61–0.65)	0.00 (0.00–0.01)	1.00 (0.99–1.00)
Intrahepatic reflux	0.25 (0.00–0.55)	0.85 (0.83–0.87)	0.01 (0.00–0.02)	1.00 (0.99–1.00)
Backflow azygos vein	0.22 (0.00–0.49)	0.77 (0.75–0.79)	0.00 (0.00–0.01)	1.00 (0.99–1.00)
1 month				
RV/LV >1	0.29 (0.09–0.48)	0.68 (0.66–0.70)	0.01 (0.00–0.02)	0.99 (0.98–0.99)
RV/LVsa >0.9	0.62 (0.41–0.83)	0.54 (0.51–0.56)	0.01 (0.01–0.02)	0.99 (0.99–1.00)
Septal bowing	0.00 (0.00–0.00)	0.92 (0.91–0.93)	0.00 (0.00–0.00)	0.99 (0.98–0.99)
Septal flattening	0.35 (0.14–0.56)	0.72 (0.70–0.74)	0.01 (0.00–0.02)	0.99 (0.99–1.00)
Aorta >40 mm	0.00 (0.00–0.00)	0.98 (0.97–0.98)	0.00 (0.00–0.00)	0.99 (0.98–0.99)
Pulmonary trunk >29 mm	0.52 (0.31–0.74)	0.68 (0.66–0.70)	0.02 (0.01–0.03)	0.99 (0.99–1.00)
PT/Ao >1.0	0.33 (0.13–0.53)	0.79 (0.77–0.81)	0.02 (0.00–0.03)	0.99 (0.99–1.00)
Cardiothoracic ratio >0.50	0.67 (0.47–0.87)	0.49 (0.47–0.51)	0.01 (0.01–0.02)	0.99 (0.99–1.00)
Backflow IVC	0.40 (0.19–0.61)	0.63 (0.61–0.65)	0.01 (0.00–0.02)	0.99 (0.98–1.00)
Intrahepatic reflux	0.25 (0.06–0.44)	0.85 (0.84–0.87)	0.02 (0.00–0.04)	0.99 (0.98–1.00)
Backflow azygos vein	0.14 (0.00–0.29)	0.77 (0.75–0.79)	0.01 (0.00–0.01)	0.99 (0.98–0.99)
On-treatment period				
RV/LV >1	0.33 (0.16–0.50)	0.68 (0.66–0.70)	0.02 (0.01–0.03)	0.98 (0.98–0.99)
RV/LVsa >0.9	0.60 (0.42–0.78)	0.54 (0.51–0.56)	0.02 (0.01–0.03)	0.99 (0.98–0.99)
Septal bowing	0.00 (0.00–0.00)	0.92 (0.91–0.93)	0.00 (0.00–0.00)	0.98 (0.98–0.99)
Septal flattening	0.31 (0.14–0.48)	0.72 (0.70–0.74)	0.02 (0.01–0.03)	0.99 (0.98–0.99)
Aorta >40 mm	0.00 (0.00–0.00)	0.98 (0.97–0.98)	0.00 (0.00–0.00)	0.98 (0.98–0.99)
Pulmonary trunk >29 mm	0.57 (0.39–0.74)	0.68 (0.66–0.70)	0.03 (0.01–0.04)	0.99 (0.98–1.00)
PT/Ao >1.0	0.43 (0.26–0.61)	0.79 (0.78–0.81)	0.03 (0.01–0.05)	0.99 (0.98–0.99)
Cardiothoracic ratio >0.50	0.67 (0.50–0.84)	0.49 (0.47–0.52)	0.02 (0.01–0.03)	0.99 (0.98–1.00)
Backflow IVC	0.39 (0.21–0.57)	0.63 (0.61–0.65)	0.02 (0.01–0.03)	0.98 (0.98–0.99)
Intrahepatic reflux	0.25 (0.09–0.41)	0.85 (0.84–0.87)	0.03 (0.01–0.05)	0.99 (0.98–0.99)
Backflow azygos vein	0.14 (0.01–0.26)	0.77 (0.75–0.79)	0.01 (0.00–0.02)	0.98 (0.98–0.99)
1 year				
RV/LV >1	0.28 (0.16–0.39)	0.68 (0.66–0.70)	0.03 (0.01–0.04)	0.97 (0.96–0.98)
RV/LVsa >0.9	0.52 (0.39–0.65)	0.54 (0.51–0.56)	0.03 (0.02–0.05)	0.97 (0.96–0.98)
Septal bowing	0.04 (0.00–0.08)	0.92 (0.91–0.93)	0.01 (0.00–0.03)	0.97 (0.96–0.98)
Septal flattening	0.25 (0.13–0.36)	0.72 (0.70–0.74)	0.03 (0.01–0.04)	0.97 (0.96–0.98)
Aorta >40 mm	0.05 (0.00–0.11)	0.98 (0.97–0.99)	0.08 (0.01–0.16)	0.97 (0.96–0.98)
Pulmonary trunk >29 mm	0.52 (0.39–0.65)	0.68 (0.66–0.70)	0.05 (0.03–0.06)	0.98 (0.97–0.99)
PT/Ao >1.0	0.31 (0.19–0.43)	0.79 (0.78–0.81)	0.04 (0.02–0.06)	0.97 (0.97–0.98)
Cardiothoracic ratio >0.50	0.60 (0.47–0.72)	0.49 (0.47–0.52)	0.04 (0.02–0.05)	0.97 (0.96–0.98)
Backflow IVC	0.45 (0.31–0.59)	0.63 (0.61–0.66)	0.04 (0.02–0.05)	0.97 (0.97–0.98)
Intrahepatic reflux	0.22 (0.10–0.33)	0.85 (0.84–0.87)	0.04 (0.02–0.07)	0.97 (0.97–0.98)
Backflow azygos vein	0.12 (0.04–0.20)	0.78 (0.76–0.80)	0.02 (0.00–0.03)	0.97 (0.96–0.98)

RV/LV(sa): right/left ventricular (short axis); PT/Ao: pulmonary trunk/aorta; IVC: inferior vena cava.

How do our findings fit into the current assessment of prognosis in patients with acute pulmonary embolism? We need better tools to identify high-risk patients with a favourable risk/benefit ratio from thrombolysis or, alternatively, to identify those who would benefit from close clinical monitoring in order to provide them with rescue thrombolysis. As the beneficial effect of thrombolysis primarily reflects the first days, an easily applicable modifier such as an enlarged pulmonary trunk would probably facilitate such processes. In recent ESC guidelines primary categorisation into low, intermediate or high risk is based on sPESI. In the second instance either biomarkers, RV/LV ratio or echocardiography can be used for further stratification on RVD. However, no consensus exists on its usefulness, as well as on the threshold, as RVD values reported in the literatures range from 0.9 to 1.8 [26].

Several studies have reported that RVD on CTPA is an indicator of the risk of adverse events [13, 27]. However, many studies had a single-centre, retrospective design, with short follow-up and surrogate outcomes, and, as such, they have intrinsic methodological limitations that weaken their validity and generalisability. The larger series have shown conflicting results, either confirming or denying that the RV/LV ratio is associated with an increased mortality [14, 28–30].

A recent systematic review stated that although RVD assessed by CT showed an association with an increased risk of mortality in patients with haemodynamically stable pulmonary embolism, it resulted in only small increases in the ability to classify risk [31]. Although additional publications confirmed this finding [31, 32], apparently right ventricular enlargement alone is not sufficient to indicate a poor short-term prognosis and other factors should also be taken into consideration [33]. For the long term, persistent RVD seems common, reflecting diminished exercise capacity and reduced quality of life [34]. One of the differences with the published cohorts is the fact that our study contains a population that was included in a randomised clinical trial rather than a prospective cohort study of consecutive patients and thus could reflect different study populations. Our finding that the RV/LV ratio is not associated with an increased mortality could thus be an incentive to reconsider the risk stratification algorithm.

Reports on the other investigated outcomes, *i.e.* recurrent VTE, hospitalisation, bleeding and adverse effects, are scarce, as most often they are used as a composite outcome or focus on differences between treatment regimens [35].

Although an enlarged pulmonary trunk diameter is an established feature in the work-up of chronic pulmonary embolism, findings are contradictory for acute pulmonary embolism, as an association with increased risk was not always observed in previous studies [36–40], although most of these studies were retrospective with limited numbers of patients. However, the assessment is rather easy and not as time consuming as clot obstruction scores, for example, and thus could be used easily in daily practice. Sensitivity for enlarged pulmonary trunk diameter may be low, but as specificity was high, we may be able to better identify specific risk groups. Its high NPV indicates that it may be useful for identification of those patients that have a low risk for adverse events who will not have a need for aggressive therapy and can be discharged home early. However, for prognostication towards high-risk measures, such as admission to the intensive care unit or thrombolysis, a multifactorial risk/benefit analysis would be necessary.

One intriguing point is the apparent discrepancy between the relative high occurrence of RVD observed in the earlier published studies and the fortunately relatively low mortality percentages. In other words, although many patients are categorised as high risk, be it from radiological, biochemical or combined parameters, this does not translate in the same manner in terms of mortality and adverse events. From this point it should be logical to further investigate the role of radiological cardiovascular parameters in risk stratification, both separately as well as in combination with other biomarkers. At present, in patients with an intermediate-risk profile the ESC guidelines recommend to use an increased RV/LV ratio either in CT or echocardiographic evaluation, after patients have been stratified by clinical parameters (sPESI) [2]. No statement has been made on the use of enlarged pulmonary trunk diameters. Our results on the pulmonary trunk diameter should be considered explorative findings, done in a trial population. The findings are promising with regard to prediction of poor prognosis/mortality, but should be confirmed in consecutive cohorts. Measurement of the pulmonary trunk is quicker to perform than a RV/LV ratio assessment and hence easier to integrate/accept/adopt in daily practice. Enlarged pulmonary trunk diameter is an attractive radiological marker to be further investigated in clinical management studies.

In conclusion, we found that several of the widely suggested radiological cardiovascular parameters did not show an association with short- or long-term adverse events such as mortality, recurrent VTE, bleeding or hospitalisation. Only an enlarged pulmonary trunk diameter was associated with an increased risk of mortality and recurrent VTE over both the short as well as long term.

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organising thrombosis masterclasses (paid to institution) from Aspen, research grants and personal fees for advisory board participation (paid to institution) from Daiichi Sankyo, and personal fees for steering committee work (paid to institution) from Portola, outside the submitted work.

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