Original Article

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Contrast reflux into the inferior vena cava on computer tomographic pulmonary angiography is a predictor of 24-hour and 30-day mortality in patients with acute pulmonary embolism

Nikolaos Bailis[1], Marianne Lerche[2], Hans Jonas Meyer[1], Andreas Wienke[3] and Alexey Surov[1]

Abstract

Background: Acute pulmonary embolism (PE) is a common disease with a high mortality. Computed tomographic pulmonary angiography (CTPA) represents the current gold standard for the evaluation of patients with suspected PE.

Purpose: To search possible CTPA predictors of 24-h and 30-day mortality in PE.

Material and Methods: Overall, 224 patients with PE (46.4% women, mean age 64.7 ± 16.7 years) were acquired. CTPA was performed on a multi-slice CT scanner. The following radiological parameters were estimated: thrombotic obstruction index; diameter of the pulmonary trunk (mm); short axis ratio of right ventricle/left ventricle; diameter of the azygos vein (mm); diameter of the superior and inferior vena cava (mm); and reflux of contrast medium into the inferior vena cava (IVC).

Results: Patients who died within the first 24 h after admission (n = 32, 14.3%) showed a reflux grade 3 into IVC more often than survivors (odds ratio [OR] 7.6, 95% confidence interval [CI] 3.3–17.7; $P < 0.001$). Other relevant CTPA parameters were diameter of IVC (OR 1.1, 95% CI 1.01–1.21; $P = 0.034$) and diameter of the pulmonary trunk (OR 0.91, 95% CI 0.82–1.01, $P = 0.074$), whereas the Mastora score showed nearly no influence (OR 1.01, 95% CI 0.99–1.02, $P = 0.406$). Furthermore, 61 (27.2%) patients died within the first 30 days after admission. These patients showed a reflux grade 3 into IVC more often than survivors (OR 3.4, 95% CI 1.7–7.0; $P = 0.001$). Other CTPA parameters, such as diameter of IVC (OR 1.04, 95% CI 0.97–1.12; $P = 0.277$) and diameter of the pulmonary trunk (OR 0.96, 95% CI 0.89–1.04; $P = 0.291$), seem to have no relevant influence, whereas Mastora score did (OR 0.99, 95% CI 0.976–0.999, $P = 0.045$).

Conclusion: Subhepatic contrast reflux into IVC is a strong predictor of 24-h and 30-day mortality in patients with acute PE.

Keywords
Pulmonary embolism, computed tomography, mortality

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Introduction

Acute pulmonary embolism (PE) is a common disease with a high mortality (1,2). It is very important to stratify the mortality risk of patients with PE at the time of presentation. Computed tomographic pulmonary angiography (CTPA) represents the current gold standard for the evaluation of patients with suspected PE (1).

[1]Department of Radiology, University of Leipzig, Leipzig, Germany
[2]Department of Respiratory Medicine, University of Leipzig, Leipzig, Germany
[3]Institute of Medical Epidemiology, Biostatistics, and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany

Corresponding author:
Alexey Surov, Department of Diagnostic and Interventional Radiology, University Hospital of Leipzig, Liebigstrasse 20, 04103 Leipzig, Germany.
Email: Alexey.Surov@medizin.uni-leipzig.de

Previously, numerous studies also analyzed CTPA signs as possible outcome predictors in patients with PE. There are different parameters such as pulmonary vessel obstruction, interventricular septum deviation, diameter of the pulmonary trunk, diameter of the azygos and/or superior vena cava, reflux into the inferior vena cava, and so on (3–11).

However, there are several problems to address. First, most results were based on small samples of up to 100 patients. Second, different endpoints were analyzed. This made a direct comparison of the reported data impossible. In addition, studies analyzing relationships between CTPA findings and mortality in PE used different terms. Finally, the published data were contradictory. While some authors found associations between several CTPA parameters and severity of PE, others did not (3–11). For instance, some studies did not find associations between mortality and thrombotic obstruction index (7,8). However, other authors suggested that thrombus burden could predict mortality in patients with PE (3). Similarly, discrepant results were also published for other CTPA parameters. So far, Zhao et al. (10) found that patients with severe PE showed larger diameter of the pulmonary trunk than patients with non-severe PE. Furthermore, it has also been reported that the ratio of right ventricle (RV) to left ventricle (LV) showed a positive correlation with the severity and/or mortality of PE (5,7).

However, other investigators did not find associations between cardiac CT measurements and/or the diameter of the pulmonary trunk or main pulmonary arteries and mortality in PE (13).

Another problem is that most previous investigations analyzed relationships between several CTPA parameters and a 30-day mortality in PE. However, 30 days represent a relatively large time period and the mortality can be influenced by multiple factors. There were no studies that investigated an ultra-short mortality within the first 24 h after clinical manifestation in PE. If CTPA might really stratify an immediate mortality risk in PE, so CT parameters can select patients with PE, who need more intensive treatment.

Therefore, the aim of the present study was to search possible CTPA predictors of 24 h mortality in PE.

Material and Methods

This retrospective study was approved by the institutional review board and informed consent was waived.

In the time period from 2012 to 2017, 246 patients with acute PE were retrospectively identified in the database of our emergency department. Patients with terminal oncologic diseases (n = 2) were excluded. Furthermore, cases with injection of contrast medium via a central venous catheter were also excluded from the study (n = 13). In addition, patients with administration of contrast medium via leg veins (n = 7) were excluded. Overall, 224 patients with acute PE (104 [46.4%] women, 120 [53.6%] men; mean age = 64.7 ± 16.7 years) were acquired for the study. In all patients, the diagnosis of PE was confirmed by CTPA. The presence of endoluminal clots on CT scans were considered diagnostic of embolism. The observation time of the patients was 30 days.

All patients presented with chest pain and dyspnea. The estimated Simplified Pulmonary Embolism Severity Index (sPESI) was in the range of 0–6 points (mean value = 2 ± 1.2 points, median = 2 points).

CTPA was performed on a multi-slice CT scanner (Ingenuity 128, Philips, Hamburg, Germany). In all cases, intravenous administration of an iodine-based contrast medium (60 mL Imeron 400 MCT, Bracco Imaging Germany GmbH, Konstanz, Germany) was given at a rate of 4.0 mL/s via peripheral venous line. Automatic bolus tracking was performed in the pulmonary trunk with a trigger of 100 Hounsfield units (HU). Typical imaging parameters were: 100 kVp; 125 mAs; slice thickness = 1 mm; and pitch = 0.9. CTPA was performed in every case in deep inspiration level.

The following radiological parameters were calculated in the patients: thrombotic obstruction index; diameter of the pulmonary trunk (in mm); RV to LV diameter ratio (RV/LV); diameter of the azygos vein (in mm); diameter of the superior and inferior vena cava (in mm); and reflux of contrast medium into the inferior vena cava (IVC).

The distance from wall to wall was regarded as the vessel diameter (Fig. 1). The pulmonary trunk was measured on an axial slice on which it showed its maximal diameter. On the same slice, the diameter of the superior vena cava (SVC) was measured. RV and LV diameters were measured on axial images at the largest points between the inner margins of the interventricular septum and the free wall. The diameter of the IVC was measured on axial slices between the liver and the heart.

Thrombotic obstruction of the pulmonary arteries was calculated according to Mastora et al. (14) (Mastora score). The obstruction of the mediastinal, lobar, and segmental arteries was quantified after visual analysis of each artery of interest on the CT section enabling the most accurate delineation of the arterial branch. The scoring system includes the five mediastinal, six lobar, and 20 segmental arteries, each scored for the degree of luminal obliteration in the range of 0%–100% (14). The sum of the mediastinal, lobar, and segmental artery scores leads to a global obstruction score. In brief, the percentage of the pulmonary artery circulation obstructed by endoluminal clots was calculated by dividing the observed CT

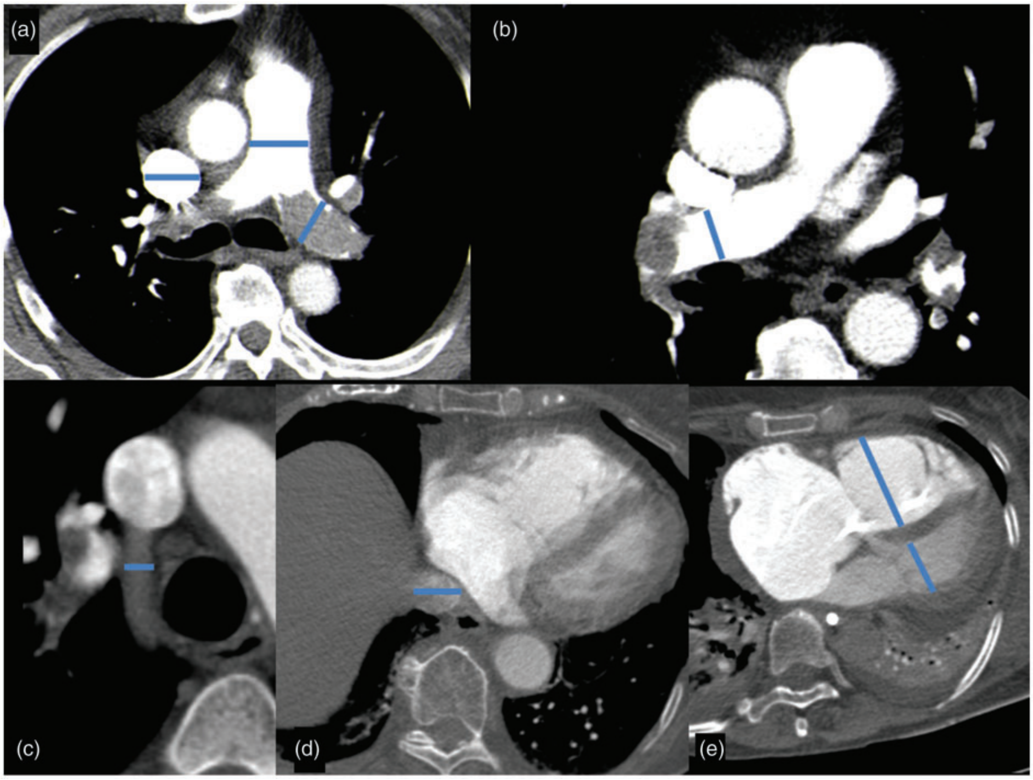

Fig. 1. Measurements on CTPA performed for the present study on axial CT pulmonary angiograms in a 73-year-old woman with proved PE. (a) Diameter of the pulmonary trunk, left pulmonary artery, and superior vena cava; (b) diameter of the right pulmonary artery; (c) diameter of the azygos vein; (d) diameter of the inferior vena cava; (e) RV/LV diameter ratio and ventricular septal bowing. CTPA, computed tomographic pulmonary angiography; LV, left ventricle; PE, pulmonary embolism; RV, right ventricle.

severity score at a given anatomical level by the maximal CT score of obstruction for this anatomical level. This procedure led to the determination of the percentage of obstruction of the central pulmonary arterial bed (corresponding to the obstruction of both mediastinal and lobar pulmonary arteries), the peripheral pulmonary arterial bed (namely, the segmental pulmonary arteries), and the entire pulmonary arterial bed (including central and peripheral pulmonary arteries) (14). Thereafter, the sum of the percentages of all arteries was calculated as the global obstruction score with a maximum of 300%.

Reflux into the IVC was estimated on coronal images and was quantified in a 4-point scale: grade 0 = no reflux; grade 1 = subcardial reflux into the IVC; grade 2 = intrahepatic reflux into the IVC; and grade 3 = subhepatic reflux into the IVC (Fig. 2).

All measurements were performed in consensus by two radiologists with 3 and 16 years of experience in general radiology, and 2 and 11 years of experience of CTPA evaluation, respectively. The readers were blinded regarding clinical outcome. The images were analyzed in digital format on a picture archiving and communication system (PACS) workstation (Syngo Plaza, Siemens Healthineers, Erlangen, Germany) in axial, coronal, and sagittal views with a slice thickness of 3.0 mm.

Statistical analysis

Statistical analysis was performed using the SPSS package (IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, NY, USA). The collected data were evaluated by descriptive statistics (mean, median, and SD for continuous variables, absolute and relative frequencies for categorical variables). Continuous variables were compared between survivors and non-survivors by t-test whereas categorical variables were compared by χ^2 test. A backward algorithm in a multiple logistic regression model was used to identify relevant risk factors of 24-h mortality as well as 30-day mortality characterized by odds ratios (OR) with 95% confidence intervals (CI) and *P* values with an exploratory interpretation.

Results

The mean value of Mastora score was 79.6% ± 25.6, the median value was 84%, and the range was 11%–137%.

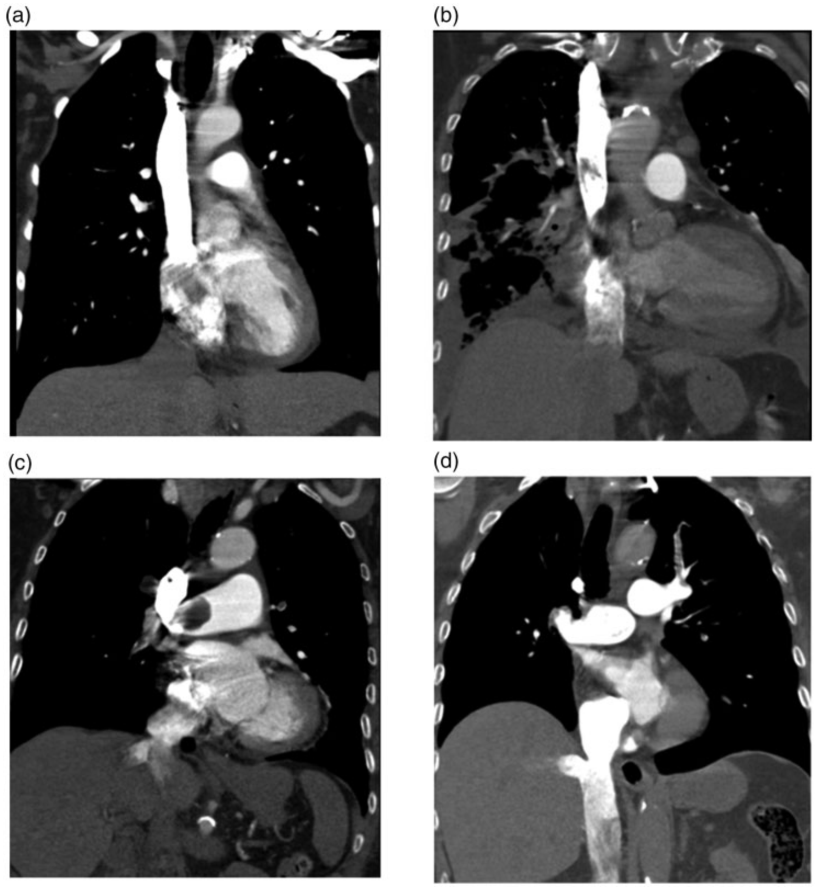

Fig. 2. Estimation of contrast medium reflux into the IVC: (a) Grade 0 = no reflux; (b) Grade 1 = reflux into the suprahepatic IVC only; (c) Grade 2 = reflux into the intrahepatic IVC as well and into the hepatic veins; (d) Grade 3 = subhepatic reflux.

Other CTPA parameters were as follows: mean diameter of the pulmonary trunk = 29.8 ± 4.3 mm; mean diameter of the left pulmonary artery = 23.6 ± 3.7 mm; mean diameter of the right pulmonary artery = 24.8 ± 4.4 mm; mean diameter of the SVC = 23.5 ± 3.7 mm; mean diameter of the IVC = 30.4 ± 4.5 mm; and diameter of the azygos vein = 11.0 ± 2.5 mm. Ventricular septum bowing was identified in 88 (39.3%) of the patients. The mean RV/LV ratio was 1.13 ± 0.25. Reflux of administrated contrast medium into the IVC was detected in 180 (80.4%) of 224 patients.

Of the analyzed 224 patients, 32 (14.3%) died within the first 24 h after admission. Table 1 gives comparison results of CTPA variables between survivors and patients who died within the first 24 h after admission. Patients who died within the first 24 h after admission showed a reflux grade 3 versus grades 0–2 into the IVC more often than survivors (OR = 7.6, 95% CI = 3.3–17.7; $P < 0.001$). Other relevant CTPA parameters were diameter of the IVC (OR = 1.1, 95% CI = 1.01–1.21; $P = 0.034$) and diameter of the pulmonary trunk (OR = 0.91, 95% CI = 0.82–1.01; $P = 0.074$), whereas the Mastora score showed nearly no influence (OR = 1.01, 95% CI = 0.99–1.02; $P = 0.406$).

Furthermore, 61 (27.2%) patients died within the first 30 days after admission. These patients showed a reflux grade 3 into the IVC more often than survivors (Table 2, OR = 3.4, 95% CI = 1.7–7.0; $P = 0.001$). Other CTPA parameters such as diameter of the IVC (OR = 1.04, 95% CI = 0.97–1.12; $P = 0.277$), and diameter of the pulmonary trunk (OR = 0.96, 95% CI = 0.89–1.04; $P = 0.291$) seems to have no relevant influence, whereas Mastora score did (OR = 0.99, 95% CI = 0.976–0.999; $P = 0.045$).

Discussion

As mentioned above, many previous studies analyzed relationships between CTPA parameters and morbidity/mortality in PE with controversial results. The discrepancy of the reported data may be explained by the fact that different morbidity and/or mortality terms were used. So far, most frequently, 30-day mortality

Table 1. Comparison of CTPA parameters between 24-h survivors and non-survivors in the present study.

Parameters	24-h survivors (n = 192)	24-h non-survivors (n = 32)	*P* values
Diameter of the pulmonary trunk	30.0 ± 4.3	28.9 ± 4.5	0.183
Diameter of the right PA	24.8 ± 4.4	24.7 ± 4.4	0.902
Diameter of the left PA	23.6 ± 3.6	23.6 ± 4.2	0.964
Diameter of the SVC	23.3 ± 3.7	24.7 ± 3.2	0.054
Diameter of the azygos vein	10.9 ± 2.50	11.8 ± 2.6	0.065
Diameter of the IVC	30.2 ± 4.6	31.3 ± 4.2	0.235
Mastora score	78.6 ± 25.4	85.3 ± 26.3	0.169
Ventricular septal bowing (%)	40.2	37.5	0.772
RV/LV ratio > 1 (%)	66.7	75.0	0.350
RV/LV ratio	1.12 ± 0.26	1.19 ± 0.21	0.175
Reflux into the IVC (%)			
None	20.9	15.6	< 0.001
Grade 1	29.8	12.5	
Grade 2	34.6	18.8	
Grade 3	14.7	53.1	

Values are given as mean ± SD unless otherwise specified.
CTPA, computed tomographic pulmonary angiography; IVC, inferior vena cava; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; SVC, superior vena cava.

Table 2. Comparison of CTPA parameters between 30-day survivors and non-survivors in the present study.

Parameters	30-days survivors (n = 163)	30-day non-survivors (n = 61)	*P* values
Diameter of the pulmonary trunk	30.0 ± 4.2	29.3 ± 4.7	0.254
Diameter of the right PA	24.7 ± 4.5	25.0 ± 4.2	0.691
Diameter of the left PA	23.6 ± 3.6	23.7 ± 3.9	0.822
Diameter of the SVC	23.3 ± 3.6	24.0 ± 3.9	0.202
Diameter of the azygos vein	10.9 ± 2.4	11.3 ± 2.8	0.300
Diameter of the IVC	30.3 ± 4.7	30.6 ± 4.1	0.674
Mastora score	81.4 ± 24.4	74.8 ± 28.1	0.111
Ventricular septal bowing (%)	40.0	39.3	0.929
RV/LV ratio > 1 (%)	68.7	65.6	0.654
RV/LV ratio	1.12 ± 0.24	1.17 ± 0.29	0.214
Reflux into the IVC (%)			
None	20.4	19.7	0.009
Grade 1	30.9	18.0	
Grade 2	34.0	27.9	
Grade 3	14.8	34.4	

Values are given as mean ± SD unless otherwise specified.
CTPA, computed tomographic pulmonary angiography; IVC, inferior vena cava; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; SVC, superior vena cava.

was analyzed (9,13,15,16). However, 48-h (7), three-month (17), and 180-day mortality (18) were also investigated. Furthermore, numerous studies calculated only simple correlations between CTPA and echocardiographic and/or clinical parameters.

In our point of view, the essential question is whether CTPA parameters can predict immediate risk for patients with PE or not. To the best of our knowledge, this is the first study to analyze the prognostic role of CTPA in the prediction of immediate mortality in PE. As shown, reflux into the IVC, diameter of the IVC, and diameter of the pulmonary trunk can predict 24-h and 30-day mortality in PE. However, OR values for the diameter of the IVC and pulmonary trunk were very low. Only IVC reflux grade 3 can be really used for the prediction of immediate mortality in acute PE.

Interestingly, other parameters did not play an important role here. In addition, the pulmonary vessel obstruction index was not associated with immediate mortality in PE. This finding supports the results of a recently published study that thrombotic vessel obstruction does not influence severity and mortality in PE (19). Furthermore, similar data were also reported by other authors (5,20,21).

Some reports indicated that the diameter of the pulmonary trunk and/or main pulmonary arteries as a sign of pulmonary hypertension may also be predictors of severity and/or mortality in PE. For example, Zhao et al. (10) showed that patients with severe PE had a larger diameter of the pulmonary trunk than patients with non-severe PE. However, in the present study, the diameter of the pulmonary trunk or main pulmonary arteries did not correlate with mortality. Our results are in agreement with those of Araoz et al. (13) and Aviram et al. (22). Moreover, in the present study, survivors had a larger diameter of the pulmonary trunk in comparison to non-survivors. This finding is difficult to ascertain.

According to the literature, other radiological parameters, especially signs of RV dysfunction/decompensation (RVD), are of more importance and can be used as morbidity biomarkers in PE (22). The following CTPA parameters reflect RVD: diameter of the SVC; diameter of the azygos vein; reflux into the azygos vein; reflux into the IVC; and RV/LV ratio (7,8,10,11,15,22–24). In fact, according to Collomb et al. (8), patients with severe PE had a larger SVC diameter in comparison to patients with non-severe PE. Similarly, the diameter of the SVC was larger in patients with hemodynamically unstable PE than in those with hemodynamically stable PE (23). Furthermore, Ghaye et al. (7) showed that patients with PE, who died within 48 h after admission, had a larger diameter of the SVC in comparison to survivors. However, other authors did not identify differences in the diameter of the SVC between survivors and non-survivors (12).

Furthermore, numerous studies analyzed the associations between mortality and RV/LV ratio in PE. Many reports indicated that this parameter can be used as a predictor of mortality (5,7). For example, Furlan et al. (5) found in their meta-analysis that the RV/LV ratio was associated with short-term mortality in PE. Similar results were reported by Meinel et al. (24). Furthermore, it has also been shown that the RV/LV ratio correlated with the level of troponin in PE (25). According to Moroni et al. (26), a RV/LV diameter ratio >1 was predictive of death ($OR = 3.83$; $P < 0.01$) only when we also took into account the value of the embolic burden ($< 40\%$).

However, some studies identified no correlation between cardiac CT measurements and mortality rate in PE (12,13,15,16). So far, Atasoy et al. (12) did not find any relationships between the RV/LV ratio and 30-day mortality in PE. Similarly, in the study by Araoz et al. (13), the RV/LV ratio was also not associated with mortality. The data from the present study indicate that the short axis RV/LV ratio does not predict immediate mortality in PE.

In addition, ventricular septal bowing could not predict short-term mortality in the present study. Similarly, Aviram et al. (22) found that this sign showed excellent specificity (100%) in predicting RVD, but a very low sensitivity (26.5%) for clinical application.

IVC reflux is another important CTPA parameter. According to the literature, it correlates well with tricuspid regurgitation and echocardiographic signs of RVD (27). Furthermore, IVC reflux is also associated with level of troponin and N-terminal natriuretic peptide (11). However, Yeh et al. (28) suggested a low sensitivity and specificity of IVC reflux for the prediction of RVD. Previously, few studies analyzed the role of IVC reflux in the prediction of mortality in PE. In the study by Aviram et al. (22), patients with substantial IVC reflux showed a higher mortality rate within 30 days in comparison to patients with no or minimal reflux. Similar results were reported also by Bach et al. (9). Moreover, in contrast to other CT parameters, IVC reflux has a well inter-observer agreement (29). In the present study, only subhepatic reflux into the IVC, i.e. grade 3, was the predictor of immediate mortality in PE. Other refluxes, such as grade 1 and/or grade 2, did not differ substantially between survivors and non-survivors. This result is in good agreement with those of Aviram et al. (22), who also found that only high IVC reflux can predict mortality in PE. This finding is very important. In fact, immediate visual estimation of subhepatic reflux on CTPA directly identifies patients at risk in PE without calculation of complex scores or additional measurements.

The present study is limited by its retrospective nature. Furthermore, although it analyzed a relatively large cohort, the subgroup of patients who died within 24 h is small. Furthermore, we did not use the ECG gating method. Therefore, the RV and LV diameters might not be precise because it depends on a cardiac cycle. Clearly, further prospective and eligible multicenter large studies should prove our preliminary results.

In conclusion, the present study showed that subhepatic contrast reflux into the IVC can be used as a predictor of 24-h and 30-day mortality in patients with acute PE.

Author's note

Alexey Surov is also affliated with Department of Radiology and Nuclear Medicine Otto-von-Guericke-University Magdeburg, Magdeburg, Germany.

Declaration of conflicting interests

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ORCID iD

Alexey Surov https://orcid.org/0000-0002-9273-3943

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