





Computed Tomography Pulmonary Perfusion for Prediction of Short-Term Clinical Outcome in Acute Pulmonary Embolism

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Abstract

Background Computed tomography pulmonary angiography (CTPA) is the imaging modality of choice for the diagnosis of acute pulmonary embolism (PE). With computed tomography pulmonary perfusion (CTPP) additional information on lung perfusion can be assessed, but its value in PE risk stratification is unknown. We aimed to evaluate the correlation between CTPP-assessed perfusion defect score (PDS) and clinical presentation and its predictive value for adverse short-term outcome of acute PE.

Patients and Methods This was an exploratory, observational study in 100 hemodynamically stable patients with CTPA-confirmed acute PE in whom CTPP was performed as part of routine clinical practice. We calculated the difference between the mean PDS in patients with versus without chest pain, dyspnea, and hemoptysis and 7-day adverse outcome. Multivariable logistic regression analysis and likelihood-ratio test were used to assess the added predictive value of PDS to CTPA parameters of right ventricle dysfunction and total thrombus load, for intensive care unit admission, reperfusion therapy and PE-related death.

Results We found no correlation between PDS and clinical symptoms. PDS was correlated to reperfusion therapy ($n = 4$ with 16% higher PDS, 95% confidence interval [CI]: 3.5–28%) and PE-related mortality ($n = 2$ with 22% higher PDS, 95% CI: 4.9–38). Moreover, PDS had an added predictive value to CTPA assessment for PE-related mortality (from Chi-square 14 to 19, $p = 0.02$).

Conclusion CTPP-assessed PDS was not correlated to clinical presentation of acute PE. However, PDS was correlated to reperfusion therapy and PE-related mortality and had an added predictive value to CTPA-reading for PE-related mortality; this added value needs to be demonstrated in larger studies.

Keywords

- ▶ pulmonary embolism
- ▶ diagnosis
- ▶ diagnostic imaging
- ▶ perfusion
- ▶ prognosis

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Introduction

Computed tomography pulmonary angiography (CTPA) is the current imaging modality of choice for the diagnosis of pulmonary embolism (PE).¹ In recent years, technical advances have been made in the diagnostic management of PE including the introduction of computed tomography pulmonary perfusion (CTPP) imaging. With CTPP additional information of hemodynamic and functional impact of the PE as expressed by measures of pulmonary perfusion can be assessed.²

Available studies using CTPP have mostly focused on its diagnostic performance for acute PE. The addition of CTPP to CTPA has been reported to improve the specificity for a PE diagnosis³ and to improve the detection rate of small, subsegmental emboli.^{4,5} Also, perfusion defects on CTPP were found to be correlated to PE thrombus load and signs of right ventricular dysfunction on CTPA.⁶⁻¹⁰ Therefore, perfusion defects on CTPP may be relevant for prognostication of PE patients as well, although this is less well studied. For instance, the quantification of perfusion defects may predict PE-related death, hemodynamic collapse, or need for oxygen therapy. This information is relevant for initial risk stratification and treatment or to consider home treatment in patients with good prognosis.¹¹

In this study, we aimed to evaluate the correlation between perfusion defects on CTPP and clinical symptoms at presentation and its predictive value for adverse short-term outcome of acute PE.

Patients and Methods

Study Design and Population

This was a prospective observational study in a convenience sample of 100 consecutive hemodynamically stable adult patients (≥ 18 years) with CTPA-confirmed acute symptomatic PE, diagnosed between July 2017 and October 2019 in the Leiden University Medical Center in whom CTPP was performed as part of routine clinical practice. Patients were excluded in case of nonassessable CTPP scan due to imaging artifacts. The diagnostic management of patients with suspected acute PE started with assessment of the clinical pretest probability in combination with D-dimer testing, following the YEARS algorithm.^{12,13} In patients with CTPA-confirmed acute PE, anticoagulant treatment was started or modified in patients already on anticoagulant treatment according to international standards. The Hestia rule, consisting of 11 clinical criteria, was used to identify low-risk PE patients for outpatient treatment.^{11,14,15} This study was approved by the institutional review board of the Leiden University Medical Center, and informed consent requirement was waived due to its observational nature.

Primary and Secondary Aim

The primary aim was to investigate the correlation between quantification of CTPP-measured perfusion defects with clinical symptoms at presentation and its predictive value for adverse short-term 7-day outcome. The secondary aim was to investigate the added value of CTPP reading to right ventricle to left ventricle diameter ratio (RV/LV ratio),

pulmonary artery trunk diameter and total thrombus load on CTPA for prediction of intensive care unit (ICU) admission, reperfusion therapy, and PE-related mortality. Furthermore, the correlation between PDS on CTPP and total thrombus load on CTPA was evaluated.

Outcomes

For the primary outcome, clinical symptoms at presentation and adverse short-term outcome were evaluated. Clinical symptoms included (non)pleural chest pain, dyspnea, and hemoptysis. Adverse short-term outcome included hospital or ICU admission, need for supplemental oxygen therapy or intravenous pain medication >24 hours, reperfusion therapy, vasopressor or inotropic therapy, and PE-related death within 7-day follow-up. All symptoms and outcomes were assessed from digital patient files.

For the secondary outcome, we assessed prognostic imaging signs on CTPA including RV/LV ratio, pulmonary artery trunk diameter, and total thrombus load. The predictive capacity of these CTPA clinical imaging signs and of PDS for the outcome of ICU admission, reperfusion therapy, and PE-related mortality was evaluated.

Image Acquisition and Analysis

Since June 2017, CTPP is part of the standard CT angiography protocol in adult patients with suspected PE at our hospital. CT examinations were performed on a 320-multislice detector row CT scan (Canon). CTPP images were acquired by using subtraction technique, in which the precontrast image is subtracted from the contrast-enhanced image. The subtraction image is then color coded and fused with the CTPA images; normal perfusion: yellow to orange, moderately decreased perfusion: red to pink, and severely decreased or absent perfusion: purple to dark blue/black (**Fig. 1**).

For this analysis, CTPP and CTPA image reading was performed independently by two different readers, who were unaware of presenting symptoms and occurrence of adverse events. CTPP assessment was performed by a researcher (L.F.V.D) trained by an expert thoracic radiologist (L.J.M.K.). Perfusion defects were quantified per segment by using the score proposed by Chae et al and expressed as mean PDS in percentage.¹⁰ To assess the interobserver agreement for PDS reading, CTPP images of 25 consecutive patients were independently evaluated by a second reviewer (L.J.M.K.). RV/LV ratio, pulmonary artery trunk diameter, and total thrombus load on CTPA were evaluated by one expert thoracic radiologist (L.J.M.K.) with over 20 years of experience in pulmonary CTPA reading. The maximum diameters of both the right and left ventricle were measured in the standard axial view with measurement of the maximal distance between the ventricular endocardium and the interventricular septum. The pulmonary artery trunk was measured at its largest transverse diameter. The total thrombus load was assessed by using the CT obstruction index according Qanadli et al.¹⁶

Definitions

Acute PE was defined as at least one filling defect in the pulmonary artery tree on CTPA.¹⁷⁻¹⁹ Pleural chest pain was

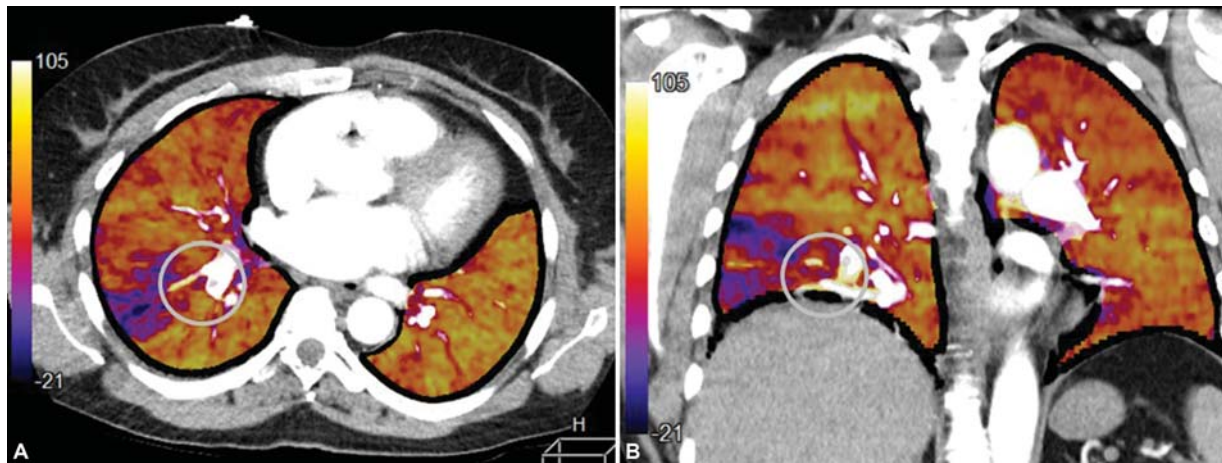


Fig. 1 (A) Fused parametric perfusion map with computed tomography pulmonary angiography, axial and (B) coronal image in a patient with an acute thrombus in the right lower lobe pulmonary artery (encircled) with subsegmental reduced lung perfusion in the laterodorsal segment of the right lower lobe.

defined as sharp chest pain that worsens during breathing. Nonpleural chest pain was defined as pressure on or squeezing sensation in the chest. PE-related death was defined as objectively confirmed clinically severe PE before death in the absence of an alternative diagnosis.²⁰

Statistical Analysis

Baseline characteristics are described as mean with standard deviation (SD) or median with interquartile range. To evaluate the correlation between PDS to clinical symptoms and adverse outcomes, the difference between the mean PDS with corresponding 95% confidence interval (CI) in patients with versus without chest pain, dyspnea, and hemoptysis and adverse short-term outcome was calculated. To evaluate the agreement in PDS scoring between the two reviewers, the mean difference between PDS assessed by reviewer 1 and 2 was calculated.

The added predictive value of PDS to CTPA assessment for ICU admission, reperfusion therapy, and PE-related death was assessed by comparing two prediction models. In the first prediction model, CTPA parameters including RV/LV ratio, pulmonary artery trunk diameter, and total thrombus load were included. In the second prediction model, PDS assessment was added to these CTPA parameters. Multivariable logistic regression analysis and the likelihood-ratio test were performed to assess the predictive value of the two models for ICU admission, reperfusion therapy, and PE-related death and whether PDS assessment significantly improved the predictive value of the model. Additionally, to quantify the performance of the prediction models, we determined the discrimination and calibration. Discrimination refers to the ability to discriminate between those with and those without the outcome and calibration to the agreement between observed outcomes and predictions. Discrimination was expressed with the concordance (c) statistic, by calculating the area under the receiver operating characteristic curve (AUC) with a 95% CI, with discrimination considered perfect if AUC of 1, good if AUC >0.8, moderate if AUC 0.6 to 0.8, poor if AUC <0.6, and no better than chance if AUC = 0.5. Calibration was assessed by using the Brier score, which ranges from 0 to 0.25, with a score of zero

signifies a perfect prediction model and a score of 0.25 a noninformative model.²¹

The correlation between PDS and total thrombus load was evaluated by using the Pearson's correlation test. A two-sided *p*-value of *p* <0.05 was considered as statistical significant. All statistical analyses were performed in SPSS version 25 (IBM, Armonk, New York, United States).

Results

Study Population

A total of 100 patients with CTPA proven acute PE were eligible for analysis. The baseline characteristics of the 100 included patients are shown in **Table 1**. Four patients were transferred to another hospital within 48 hours because of

Table 1 Baseline characteristics of 100 patients with acute pulmonary embolism

Mean age (\pm SD), y	62 (16)
Male, <i>n</i> (%)	53 (53)
Median duration of complaints (IQR), d	2.0 (1–7)
Recurrent VTE, <i>n</i> (%)	17 (17)
Active malignancy, <i>n</i> (%)	27 (27)
Immobility for >3 d or recent long travel >6 h in the past 4 weeks, <i>n</i> (%)	24 (24)
Trauma/surgery during the past 4 wk, <i>n</i> (%)	22 (22)
Active inflammation/infection	3 (3)
Hormone (replacement) therapy, <i>n</i> (%)	7 (7)
Known genetic thrombophilia, <i>n</i> (%)	0 (0)
Outpatient	80 (80)
Mean PDS score (\pm SD), %	27 (13)
Mean Qanadli score (\pm SD), %	30 (23)
RV/LV ratio > 1, <i>n</i> (%)	49 (49)

Abbreviations: IQR, interquartile range; PDS, perfusion defect score; RV/LV ratio, right ventricle to left ventricle diameter ratio; SD, standard deviation; VTE, venous thromboembolism.

logistical reasons. Results for adverse short-term outcome were thus available for 96 patients. The mean PDS of all included patients was 27% (SD = 13%) and mean Qanadli score was 30% (SD = 23%). Forty-nine patients (49%) had a RV/LV ratio >1 (►Table 1). The agreement in PDS scoring between the two reviewers was good with a mean difference in PDS of 4.2% (SD = 6.9%).

Primary Outcome

The prevalence of symptoms at presentation and adverse short-term outcome with associated mean PDS are presented in ►Table 2. Of the 100 patients, dyspnea was present in 84 (84%), pleural chest pain in 55 (55%), nonpleural chest pain in 25 (25%) and hemoptysis in 6 patients (6.0%). A total of 60 patients (60%) were admitted to the hospital, of whom 7 patients (7.3%) were admitted to the ICU. Twenty-five patients (26%) were treated with oxygen >24 hours, 6 patients (6.3%) received intravenous pain medication >24 hours, 4 patients (4.2%) received reperfusion therapy, and 3 patients (3.1%) needed vasopressor/inotropic therapy. We did not find a relevant correlation between PDS and clinical presentation (►Table 2). The PDS was associated with reperfusion therapy (16% higher PDS, 95% CI: 3.5–28%) and PE-related mortality (22% higher PDS, 95% CI: 4.9–39%; ►Table 2). The PDS was not associated with the need for oxygen therapy, pain medication, or vasopressor/inotropic therapy nor with ICU admission.

Secondary Outcome

The results from logistic regression and likelihood-ratio test are shown in ►Table 3. The first model including CTPA parameters alone was correlated to ICU admission (Chi-square [χ^2] = 17.1, degrees of freedom [df] = 3, $p = 0.001$). Model 2 was also correlated to ICU admission ($\chi^2 = 17.9$, df = 4, $p = 0.001$), but the predictive capacity hardly improved when PDS was added

to CTPA parameters ($\chi^2 = 0.799$, df = 1, $p = 0.371$). Model 1 including CTPA parameters and model 2 with addition of PDS assessment were both able to predict reperfusion therapy ($\chi^2 = 20.9$, df = 3, $p < 0.001$ and $\chi^2 = 24.1$, df = 4, $p < 0.001$, respectively). However, the predictive capacity of the model did not improve when PDS was added to CTPA parameters ($\chi^2 = 3.22$, df = 1, $p = 0.073$). Model 1 including CTPA parameters alone was able to predict PE-related mortality ($\chi^2 = 13.8$, df = 3, $p = 0.003$). Model 2 was also able to predict PE-related mortality ($\chi^2 = 19.3$, df = 4, $p = 0.001$) and the addition of PDS scoring also increased the predictive capacity of the model ($\chi^2 = 5.44$, df = 1, $p = 0.020$). The odds ratios including 95% CI of each CTPA parameter and PDS within prediction model 2 for each adverse outcome are provided in ►Table 3.

The AUC for CTPA parameters to predict ICU admission was 0.852 (95% CI: 0.647–1.00), 0.976 (95% CI: 0.938–1.00) for reperfusion therapy and 0.989 (95% CI: 0.965–1.00) for PE-related mortality. When PDS was added to the prediction model, these AUCs were 0.876 (95% CI: 0.725–1.00), 0.984 (95% CI: 0.951–1.00), and 1.00 (95% CI: 1.00–1.00), respectively (►Table 3). The prediction model including CTPA parameters had a Brier score of 0.042 for ICU admission, 0.021 for reperfusion therapy, and 0.010 for PE-related mortality. Prediction model 2 had a Brier score of 0.043 for predicting ICU admission, 0.013 for reperfusion therapy, and <0.001 for PE-related mortality (►Table 3).

With the use of the Pearson correlation test, a positive correlation between the total PDS and CTPA-assessed total thrombus load was found ($r = 0.523$, $p < 0.001$).

Discussion

We showed that perfusion defects on CTPP are correlated to reperfusion therapy and PE-related mortality, and that the

Table 2 Perfusion defect score in 100 acute pulmonary embolism patients and correlation to presenting symptoms and short-term adverse outcome

	Prevalence (%)	Mean (SD) PDS in % in patients with:	Mean (SD) PDS in % in patients without:	Difference (95% CI)
Symptoms at presentation ($n = 100$) and 7-day outcome ($n = 96$)				
Pleural chest pain ^a	55 (55)	28 (14)	27 (12)	1.5 (–3.7 to 6.7)
Nonpleural chest pain ^a	25 (25)	32 (12)	26 (13)	5.5 (–0.41 to 11)
Dyspnea	84 (84)	28 (13)	25 (13)	3.4 (–3.7 to 11)
Hemoptysis	6 (6.0)	27 (14)	27 (13)	–0.74 (–12 to 10)
Hospital admission	60 (60)	28 (14)	27 (11)	0.92 (–4.4 to 6.2)
ICU admission	7 (7.3)	32 (19)	26 (12)	5.7 (–3.9 to 15)
Oxygen therapy >24 h	25 (26)	28 (15)	26 (12)	1.4 (–4.3 to 7.2)
IV pain medication >24 h	6 (6.3)	23 (12)	27 (12)	–4.6 (–15 to 5.7)
Reperfusion therapy	4 (4.2)	42 (14)	26 (12)	16 (3.5–28) ^b
Need for vasopressor therapy	3 (3.1)	34 (32)	27 (12)	7.6 (–6.8 to 22)
PE-related death	2 (2.1)	49 (19)	27 (12)	22 (4.9–39) ^b

Abbreviations: CI, confidence interval; CTPP, computed tomography pulmonary perfusion; ICU, intensive care unit; PDS, perfusion defect score; PE, pulmonary embolism; SD, standard deviation.

^aPatients could have either pleural chest pain or nonpleural chest pain, or both at the same time.

^bSymptoms/outcome correlated to PDS on CTPP.

Table 3 Predictive value, area under the receiver operating characteristic curve and Brier score of model 1 (CTPA parameters including RV/LV ratio, pulmonary artery trunk diameter, and total thrombus obstruction score) and model 2 (CTPA parameters and perfusion defect score) and odds ratios for each parameter within model 2 for ICU admission, reperfusion therapy, and PE-related mortality

	Chi-square	df	Sign.	AUC (95% CI)	Brier score	Odds ratio (95% CI)
ICU admission						
Model 1	17.1	3	0.001	0.852 (0.647–1.00)	0.042	
Model 2	17.9	4	0.001	0.876 (0.725–1.00)	0.043	6.27 (0.880–44.6) 1.03 (0.832–1.28) 1.07 (0.999–1.15) 0.955 (0.859–1.06)
Difference between model 1 and 2	0.799	1	0.371			
Reperfusion therapy						
Model 1	20.9	3	<0.001	0.976 (0.938–1.00)	0.021	
Model 2	24.1	4	<0.001	0.984 (0.951–1.00)	0.013	65.4 (0.243–1.76 ^E + 4) 1.51 (0.866–2.63) 1.21 (0.975–1.49) 1.19 (0.947–1.49)
Difference between model 1 and 2	3.22	1	0.073			
PE-related mortality						
Model 1	13.8	3	0.003	0.989 (0.965–1.00)	0.010	
Model 2	19.3	4	0.001	1.00 (1.00–1.00)	<0.001	Not applicable due to low number of events
Difference between model 1 and 2	5.44	1	0.020			

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; Df, degrees of freedom; ICU, intensive care unit; RV/LV ratio, right ventricle to left ventricle diameter ratio.

addition of PDS assessment to CTPA assessment of RV/LV ratio, pulmonary artery trunk diameter, and total thrombus load improved the predictive value of the model to predict PE-related mortality, but not ICU admission nor reperfusion therapy. Moreover, perfusion defects on CTPA did not correlate to clinical symptoms at presentation.

Risk stratification of patients with acute PE is crucial for deciding on the optimal treatment, including hospitalization, close hemodynamic monitoring, and reperfusion therapy.^{1,22,23} Previous studies found that right ventricle enlargement (RV/LV ratio > 1.0) is associated with an increased risk for PE-related mortality.^{24–26} Current European guidelines therefore recommend the assessment of right ventricular dimensions or function as part of initial risk stratification.²² As previous publications have shown that CTPA-assessed PDS is correlated to RV/LV ratio and total thrombus load,^{6–10} perfusion imaging may play a role in this risk stratification. Although our results showed an improvement in the predictive capacity for PE-related mortality when PDS was added to CTPA-reading, the improvement in AUC was only marginal. Furthermore, we could not confirm an added value of PDS over CTPA assessment to predict ICU admission nor reperfusion therapy. A possible explanation may be the low incidence of these adverse outcomes (range between two and seven patients).

We also evaluated whether perfusion defects on CTPA were correlated to clinical symptoms at presentation. This is relevant, as pain and dyspnea for which treatment with intravenous pain medication, and oxygen therapy may be needed are also relevant for the decision for hospitalization or home treatment.^{27,28} However, an association between PDS and presenting symptoms could not be established. Of note, as the generation of dyspnea and chest pain involve multiple underlying (complex and not fully understood) mechanisms, a discrepancy between chest pain and dyspnea and extent of perfusion defects in acute PE is possible.²⁹ PDS was also not correlated to hospital admission. However, the decision to admit a patient to the hospital is often based on multiple variables, some not included in this analysis, including pregnancy, active bleeding and the presence of a social reason for treatment in hospital.

In current literature, the addition of CTPA to CTPA was found to improve the specificity in the PE detection from 94% (95% CI: 89–97%) to 100% (95% CI: 100–100%) and the detection of occlusive (sub)segmental pulmonary emboli.³⁰ CTPA was also evaluated for PE prognostication and was shown to be correlated to adverse clinical outcome including ICU admission, all-cause and PE-related mortality,^{7,31} but had no added value to RV/LV ratio to predict mortality.^{32,33} Hence, based on our results and

available literature, the application of CTPP seems to be mostly relevant for the diagnostic management of acute PE rather than for prognostication.

Limitations of the study are its observational design and the use of a convenience cohort without a specific sample size calculation. This latter may have resulted that the study was underpowered to detect a correlation between PDS and clinical symptoms and some adverse outcomes. On the other hand, the predictive value of perfusion defects for reperfusion therapy and PE-related mortality may be overestimated due to the low incidence of these adverse events and should therefore be interpreted with caution. Furthermore, the presence of clinical symptoms was self-reported and not assessed in a standardized manner, what may have introduced relevant bias. Bias may also be present in the perfusion defect quantification as perfusion defects may not only be the result of a PE but also of other pathology such as pneumonia. The strengths of this study are its prospective design and the inclusion of all comers, which supports the external validity of our findings. Also, CTPA and CTPP assessment was performed by independent readers who were unaware of the clinical presentation and course.

In conclusion, PDS was not associated with clinical presentation of acute PE. However, our data showed that CTPP-assessed PDS was correlated to reperfusion therapy and PE-related mortality and improved the predictive value of CTPA reading for PE-related mortality, but not for ICU admission or reperfusion therapy. Due to the limited number of adverse events and the design of our study, our observations should be considered hypothesis generating. Future larger studies including an upfront determined sample size calculation are needed to determine the clinical relevance of PDS quantification on top of CTPA assessment of right ventricle dysfunction in risk stratification of acute PE.

Authors' Contributions

L.F.V.D. and F.A.K. had full access to all data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. L.F.V.D., L.J.M.K., and F.A.K. performed analysis and interpretation of the data. L.F.V.D. and F.A.K. drafted the manuscript. L.F.V.D., L.J.M.K., M.V.H., M.K.N., and F.A.K. acquired the data, carried out critical revision of the manuscript, and approved the manuscript.

Conflict of Interest

None declared.

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References

- Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. *Nat Rev Dis Primers* 2018;4:18028
- Cai XR, Feng YZ, Qiu L, et al. Iodine distribution map in dual-energy computed tomography pulmonary artery imaging with rapid kVp switching for the diagnostic analysis and quantitative evaluation of acute pulmonary embolism. *Acad Radiol* 2015;22(06):743–751
- Grob D, Smit E, Prince J, et al. Iodine maps from subtraction CT or dual-energy CT to detect pulmonary emboli with CT angiography: a multiple-observer study. *Radiology* 2019;292(01):197–205
- Weidman EK, Plodkowski AJ, Halpenny DF, et al. Dual-energy CT angiography for detection of pulmonary emboli: incremental benefit of iodine maps. *Radiology* 2018;289(02):546–553
- Mao X, Wang S, Jiang X, Zhang L, Xu W. Diagnostic value of dual-source computerized tomography combined with perfusion imaging for peripheral pulmonary embolism. *Iran J Radiol* 2016;13(02):e29402
- Kong WF, Wang YT, Yin LL, Pu H, Tao KY. Clinical risk stratification of acute pulmonary embolism: comparing the usefulness of CTA obstruction score and pulmonary perfusion defect score with dual-energy CT. *Int J Cardiovasc Imaging* 2017;33(12):2039–2047
- Meinel FG, Graef A, Bamberg F, et al. Effectiveness of automated quantification of pulmonary perfused blood volume using dual-energy CTPA for the severity assessment of acute pulmonary embolism. *Invest Radiol* 2013;48(08):563–569
- Zhou Y, Shi H, Wang Y, Kumar AR, Chi B, Han P. Assessment of correlation between CT angiographic clot load score, pulmonary perfusion defect score and global right ventricular function with dual-source CT for acute pulmonary embolism. *Br J Radiol* 2012;85(1015):972–979
- Thieme SF, Ashoori N, Bamberg F, et al. Severity assessment of pulmonary embolism using dual energy CT - correlation of a pulmonary perfusion defect score with clinical and morphological parameters of blood oxygenation and right ventricular failure. *Eur Radiol* 2012;22(02):269–278
- Chae EJ, Seo JB, Jang YM, et al. Dual-energy CT for assessment of the severity of acute pulmonary embolism: pulmonary perfusion defect score compared with CT angiographic obstruction score and right ventricular/left ventricular diameter ratio. *AJR Am J Roentgenol* 2010;194(03):604–610
- Zondag W, Kooiman J, Klokk FA, Dekkers OM, Huisman MV. Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. *Eur Respir J* 2013;42(01):134–144
- van der Hulle T, Cheung WY, Kooij S, et al;YEARS study group. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet* 2017;390(10091):289–297
- van der Pol LM, Tromeur C, Bistervels IM, et al;Artemis Study Investigators. Pregnancy-adapted YEARS algorithm for diagnosis of suspected pulmonary embolism. *N Engl J Med* 2019;380(12):1139–1149
- den Exter PL, Zondag W, Klokk FA, et al;Vesta Study Investigators * Efficacy and safety of outpatient treatment based on the Hestia clinical decision rule with or without n-terminal pro-brain natriuretic peptide testing in patients with acute pulmonary embolism. a randomized clinical trial. *Am J Respir Crit Care Med* 2016;194(08):998–1006
- Zondag W, Mos IC, Creemers-Schild D, et al;Hestia Study Investigators. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. *J Thromb Haemost* 2011;9(08):1500–1507
- Qanadli SD, El Hajjam M, Vieillard-Baron A, et al. New CT index to quantify arterial obstruction in pulmonary embolism: comparison with angiographic index and echocardiography. *AJR Am J Roentgenol* 2001;176(06):1415–1420
- Huisman MV, Klokk FA. How I diagnose acute pulmonary embolism. *Blood* 2013;121(22):4443–4448
- Huisman MV, Klokk FA. Diagnostic management of clinically suspected acute pulmonary embolism. *J Thromb Haemost* 2009;7(Suppl 1):312–317
- Huisman MV, Klokk FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. *J Thromb Haemost* 2013;11(03):412–422

- 20 Kraaijpoel N, Tritschler T, Guillo E, Girard P, Le Gal G. Definitions, adjudication, and reporting of pulmonary embolism-related death in clinical studies: a systematic review. *J Thromb Haemost* 2019;17(10):1590–1607
- 21 Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;21(01):128–138
- 22 Konstantinides SV, Meyer G, Becattini C, et al;ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;41(04):543–603
- 23 Klok FA, Meyer G, Konstantinides S. Management of intermediate-risk pulmonary embolism: uncertainties and challenges. *Eur J Haematol* 2015;95(06):489–497
- 24 Meinel FG, Nance JW Jr, Schoepf UJ, et al. Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. *Am J Med* 2015;128(07):747–59.e2
- 25 Klok FA, Van Der Bijl N, Eikenboom HC, et al. Comparison of CT assessed right ventricular size and cardiac biomarkers for predicting short-term clinical outcome in normotensive patients suspected of having acute pulmonary embolism. *J Thromb Haemost* 2010;8(04):853–856
- 26 van der Bijl N, Klok FA, Huisman MV, et al. Measurement of right and left ventricular function by ECG-synchronized CT scanning in patients with acute pulmonary embolism: usefulness for predicting short-term outcome. *Chest* 2011;140(04):1008–1015
- 27 van der Wall SJ, Hendriks SV, Huisman MV, Klok FA. Home treatment of acute pulmonary embolism: state of the art in 2018. *Curr Opin Pulm Med* 2018;24(05):425–431
- 28 Klok FA, Huisman MV. When I treat a patient with acute pulmonary embolism at home. *Hematology (Am Soc Hematol Educ Program)* 2020;2020(01):190–194
- 29 Burki NK, Lee LY. Mechanisms of dyspnea. *Chest* 2010;138(05):1196–1201
- 30 Grob D, Oostveen LJ, Prokop M, Schaefer-Prokop CM, Sechopoulos I, Brink M. Imaging of pulmonary perfusion using subtraction CT angiography is feasible in clinical practice. *Eur Radiol* 2019;29(03):1408–1414
- 31 Apfaltrer P, Bachmann V, Meyer M, et al. Prognostic value of perfusion defect volume at dual energy CTA in patients with pulmonary embolism: correlation with CTA obstruction scores, CT parameters of right ventricular dysfunction and adverse clinical outcome. *Eur J Radiol* 2012;81(11):3592–3597
- 32 Im DJ, Hur J, Han K, et al. Prognostic value of dual-energy CT-based iodine quantification versus conventional CT in acute pulmonary embolism: a propensity-match analysis. *Korean J Radiol* 2020;21(09):1095–1103
- 33 Im DJ, Hur J, Han KH, et al. Acute pulmonary embolism: retrospective cohort study of the predictive value of perfusion defect volume measured with dual-energy CT. *AJR Am J Roentgenol* 2017;209(05):1015–1022