Advances in CT pulmonary angiography for pulmonary embolism

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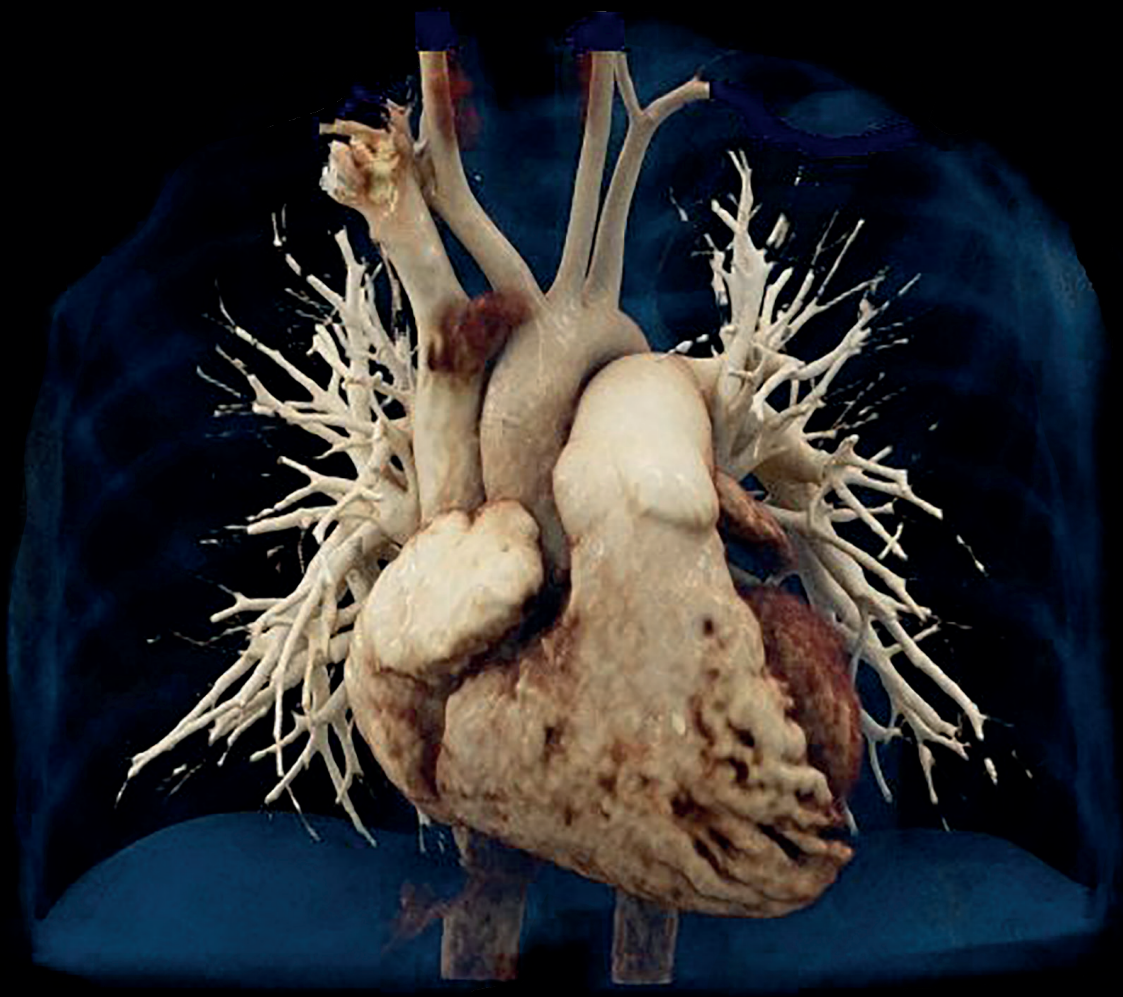

Ludovicus Franciscus Marie Beenen

Advances in CT Pulmonary Angiography for Pulmonary Embolism

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Advances in CT Pulmonary Angiography for Pulmonary Embolism

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in het openbaar te verdedigen in de Agnietenkapel
op donderdag 10 februari 2022, te 16.00 uur

door
Ludovicus Franciscus Marie Beenen
geboren te Delft

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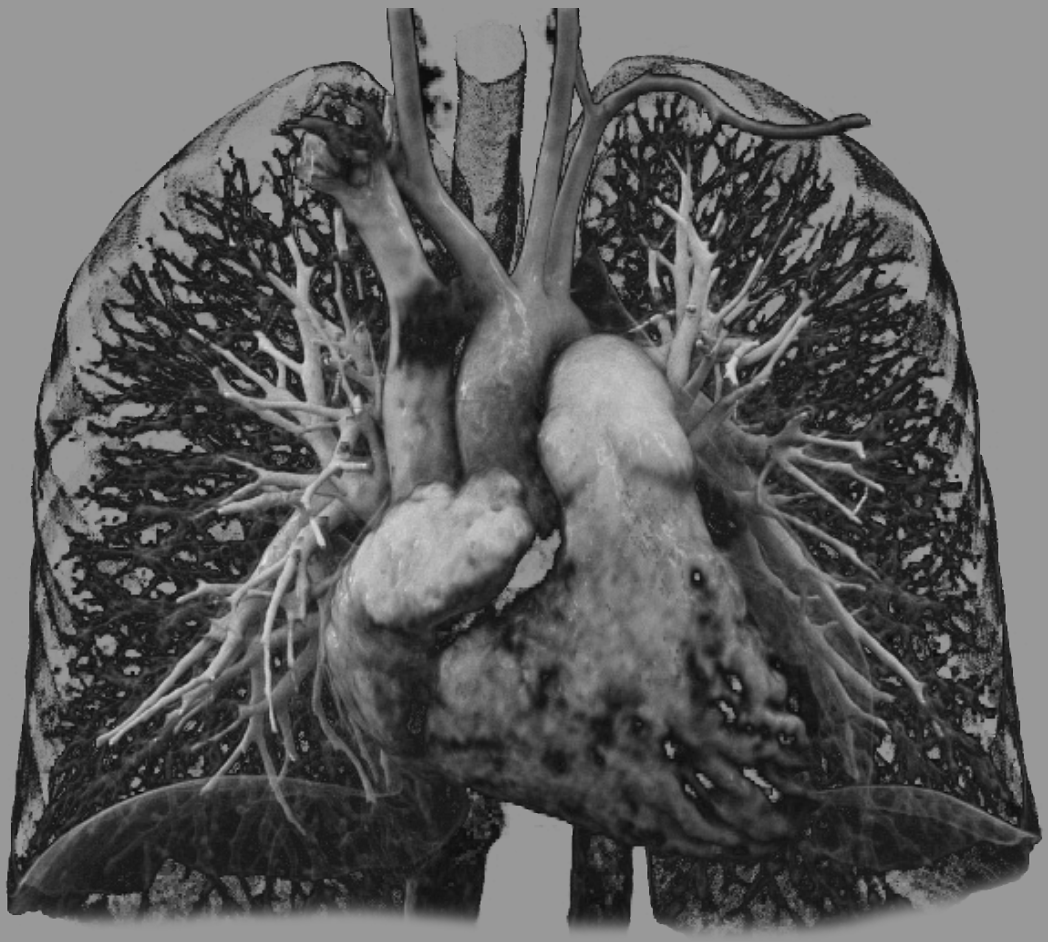
Table of contents



Chapter 1

Introduction & General Outline

Introduction

Pulmonary embolism (PE) is the third most frequent acute cardiovascular disease, after acute myocardial infarction and stroke.[1] The annual incidence of pulmonary embolism is 1 per 1000 people and increases sharply with age,[2] with an pulmonary embolism related mortality of 7 deaths per 100 000 people per year.[3] After diagnosis of acute pulmonary embolism up to 9.1% and 19.6% of patients die within 1 and 6 months, respectively,[4] with some attributable to associated comorbidities rather than to pulmonary embolism.

A large strain on the right ventricle caused by obstructing blood clots in the pulmonary circulation is thought to be the main mechanism for the occurrence of heart failure and mortality in pulmonary embolism.[5] It is of great importance to have the diagnosis pulmonary embolism established rapidly in order to start treatment as early as possible: a delay in timing of anticoagulation in the ED results in higher 30-day mortality.[6]

Presenting symptoms of pulmonary embolism range between vague discomfort of the chest until collapse for which cardiopulmonary resuscitation is needed, and can mimic many other diseases. The fear of missing such an important and potentially life-threatening diagnosis harbours the risk that often, or even too often, pulmonary embolism is considered by the treating physician, which will consequently lead to more imaging.

Request for imaging can be based on a general clinical impression but this has a relatively low specificity and lacks standardization.[7] To achieve a higher diagnostic efficiency, clinical decision rules (CDRs) have been developed, consisting of a number of clinical and medical parameters. After assessing a low probability of pulmonary embolism the diagnosis can be safely ruled out and redundant exposure to ionizing radiation and contrast medium can be avoided. The most well-known clinical decision rule contains the Wells criteria in which seven items are attributed with a specific value.[8] For scores above a certain threshold probability of pulmonary embolism is high and further imaging needs to be performed. In case of a low score, as a second step the D-dimer level, a fibrin degradation product, is determined. If the D-dimer level is not increased, pulmonary embolism can be safely excluded and imaging is not needed. Generally speaking, a clinical decision rule combined with a CT pulmonary angiography (CTPA) is a safe and reliable strategy to exclude pulmonary embolism.

This thesis is divided into three parts. Part I describes improvements in the diagnostic work-up of patients with a clinical suspicion of pulmonary embolism. Part II focuses on the additional value of findings on CTPA with regard to prognosis and risk stratification. Part III explores venous thrombo-embolism (VTE) diagnostic modalities in patients with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) linked to COronaVIrus Disease (COVID-19) admitted to the hospital, and particularly differences between ward and ICU patients.

PART I - DIAGNOSIS

Why don't physicians follow clinical guidelines? A clinical decision rule is less likely to be used when experienced as inconvenient or difficult to use.[9]

The *first part* of this thesis addresses the development, prospective validation and clinical impact of an improved diagnostic strategy for the evaluation of pulmonary embolism, called the YEARS algorithm. In daily clinical practice in busy emergency departments, during triage of patients suspected of pulmonary embolism d-dimer levels often are already measured even before assessment by the treating physician is performed. Hence, it would be logical to restructure this time-consuming two-step diagnostic strategy into one that integrates all assessments at presentation, and thus not only will prevent redundant CT-scanning for the patient, but also decreases the time spent in the emergency department.

PART II - PROGNOSIS

The *second part* of this thesis addresses the added value of findings other than pulmonary embolism on CTPA. CTPA is considered the reference standard imaging technique for the evaluation of pulmonary emboli. CTPA has several advantages above other modalities: it is non-invasive, robust, globally widely available, has a high sensitivity and specificity, and shows directly the distribution and extent of thrombi.[10,11] Furthermore, CTPA can provide additional information, which cannot be delivered by other modalities. Alternative diagnoses can be observed in approximately 50-70% of patients, mostly pneumonia, pleural fluid, heart failure, but also less frequent pathologies like pericardial fluid or abdominal pathology.[12] How co-existence of these pathologies with pulmonary embolism influences outcome is not exactly known, and will be addressed in this part. Also, modern CT scanners nowadays have several possibilities for advanced imaging, like dual energy (DECT) scanning. Hereby the amount of iodine can be established, resulting in an overall iodine mapping image, quite similar to the well-known ventilation-perfusion

scintigraphy images. Wedge shaped zones with less iodine suggests presence of an obstructing thrombus that otherwise possibly could have been missed. The total volume of these defects reflects the amount of lung tissue that is involved, which is associated with the development of pulmonary hypertension and mortality.[13]

Initial hemodynamic instability is an important marker of prognosis and occurs in approximately 5% of cases, with short term mortality exceeding 15%. For the remaining 95% of patients with acute pulmonary embolism, several prognostic scores consisting of simple clinical criteria have been proposed to estimate intermediate or low risk of an adverse outcome. Of these, the Pulmonary Embolism Severity Index (PESI) and the simplified-PESI (sPESI) are incorporated in the European Society of Cardiology (ESC)-guidelines to guide treatment.[5] To further estimate the risk of adverse outcome of pulmonary embolism, assessment of right ventricular dysfunction (RVD) is recommended, using biomarkers like NT-proBNP and echocardiography. Besides providing the diagnosis CTPA potentially could harbour such prognostic features. Many radiological parameters have been studied and proposed, including several scores that evaluate location and magnitude of clot distribution.[14] However, there is no consensus on the parameters that should be used, as the underlying evidence comes from low-quality studies and from different populations. Which of several potentially interesting parameters works best is addressed in this part: right ventricle/left ventricle ratio (RV/LV), enlarged pulmonary trunk, septal bowing, contrast medium reflux?

PART III - COVID

The *third part* of this thesis is dedicated to the interaction between COVID-19 and venous thromboembolism. In 2020 COVID-19 posed unprecedented health care problems, both on a global scale and for many individual patients. Acute respiratory failure is the most common reason for hospital admission. The mortality of these patients during the first wave of the pandemic was particularly high. Several hypotheses emerged on contributing factors, as e.g. imbalance of the bradykinin-kallikrein system with pulmonary oedema and inflammatory thrombotic micro-angiopathy. The differences between ICU and ward patients with regard to occurrence of pulmonary embolism and deep vein thrombosis, and consequences on pulmonary perfusion is explored in this part.

General outline

In **chapter 1** I present an overview of pulmonary embolism and the role of CTPA and advanced imaging in the diagnostic work-up and risk estimation of prognosis.

PART I - DIAGNOSIS

In *Part I* we explored improvements in diagnostic decision support and the appropriate use of CTPA for patients suspected of pulmonary embolism. First, in **chapter 2,** we evaluated the value of each of the items in the Wells criteria, in conjunction with a known elevated D-dimer. This resulted in the development of the YEARS decision rule, for which a multicentre clinical validation study is described in **chapter 3**.

PART I - PROGNOSIS

Part II focuses on the value of findings on CTPA in risk assessment and prognosis of patients with confirmed pulmonary embolism. I performed post hoc analyses in patients with pulmonary embolism who have been included in the Hokusai-VTE randomized clinical trial on anticoagulant therapy. In **chapter 4** the association between radiological parameters on CTPA and associated right ventricular dysfunction with short and long-term clinical outcome is investigated. The association of these parameters with body mass index is determined in **chapter 5**. The impact of co-existence of pulmonary embolism with several common pulmonary and cardiac pathologies on CTPA is described in **chapter 6**.

PART III - COVID

Part III is dedicated to COVID-19 and VTE. The incidence of pulmonary embolism and DVT in hospitalized patients with COVID-19 is described in **chapter 7**. In **chapter 8**, we describe the occurrence and possible significance of perfusion defects on dual energy CTPA in a sample of these patients during the first wave of the COVID-19 pandemic.

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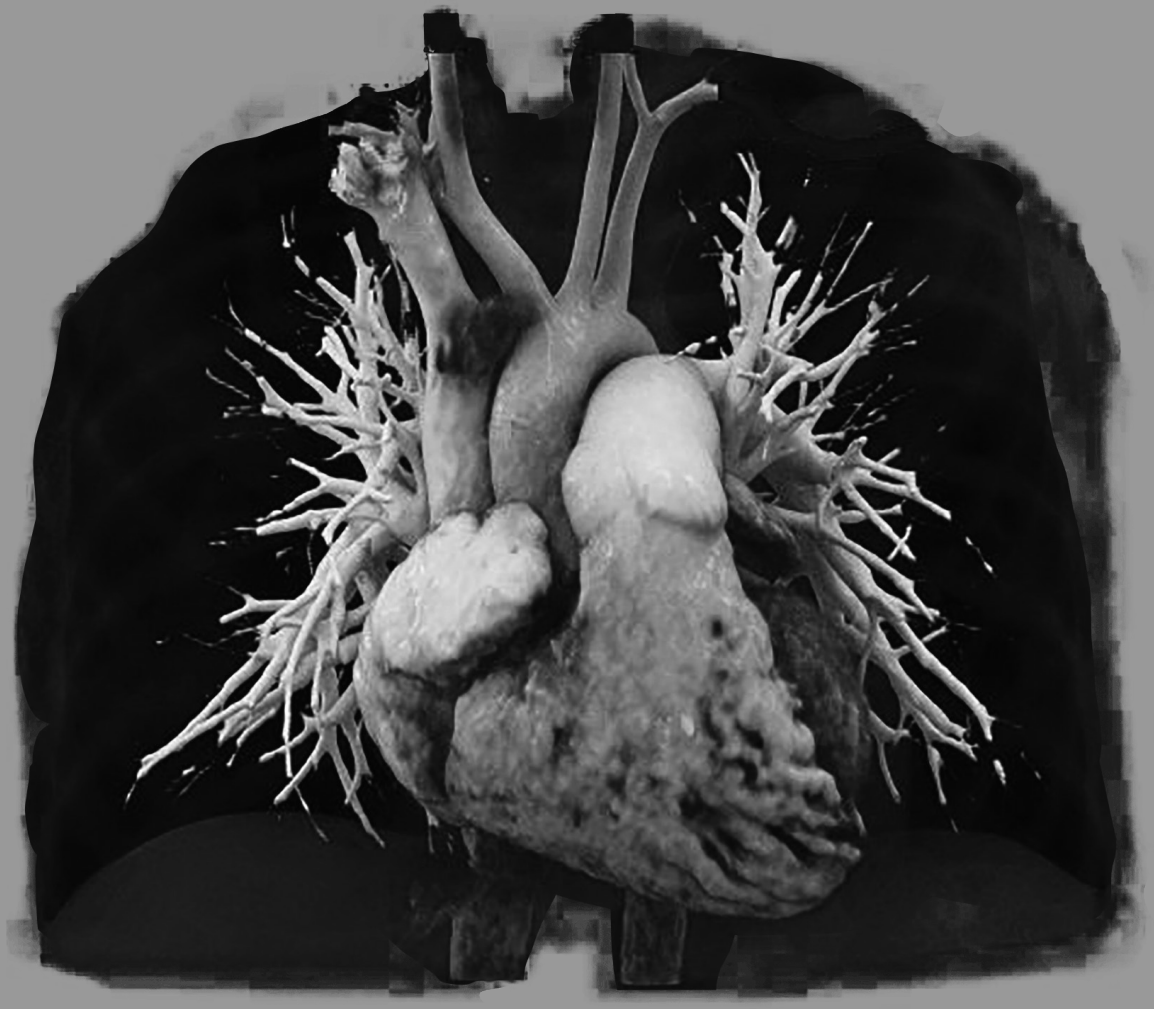
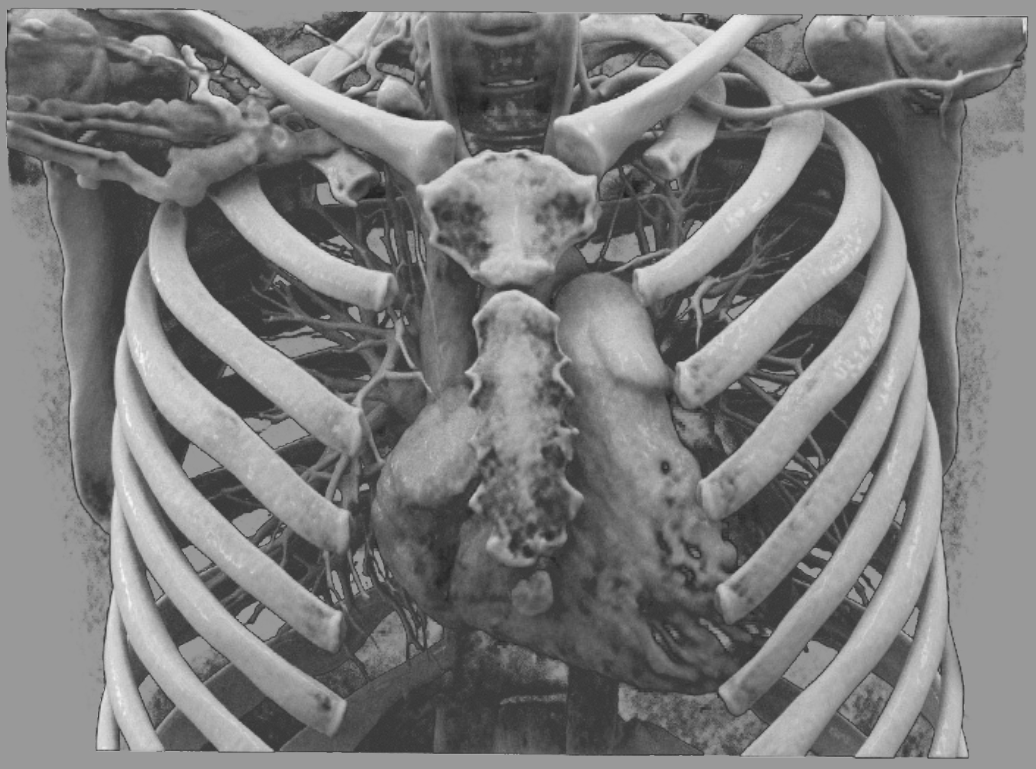


PART I

Optimising diagnosis of pulmonary embolism



Chapter 2

A simple decision rule including D-dimer to reduce the need for CT-scanning in patients with suspected pulmonary embolism

J. van Es, L.F.M. Beenen, R.A. Douma, P.L. den Exter, I.C.M. Mos, K. Kaasjager, M.V. Huisman, P.W. Kamphuisen, S. Middeldorp, P.M.M. Bossuyt

J Thromb Haemost. 2015 Aug;13(8):1428-35

Abstract

Background
An 'unlikely' clinical decision rule with a negative D-dimer result safely excludes pulmonary embolism (PE) in 30% of presenting patients. We aimed to simplify this diagnostic approach and to increase its efficiency.

Methods
Data of 723 consecutive patients with suspected PE were analysed (22% PE prevalence). After constructing a logistic regression model with the D-dimer test result and items from Wells' score, we identified the most prevalent combinations of influential items and selected new D-dimer positivity thresholds. The performance was separately validated in data from 2,785 consecutive patients with suspected PE.

Discussion
Three Wells items significantly added incremental value to the D-dimer test: haemoptysis, signs of deep vein thrombosis and 'PE most likely'. Based on the most frequent combinations of these three items, we identified two groups: (1) none of these three items positive (41%), (2) one or more of these items positive (59%). When applying a 1000 µg/L D-dimer threshold in group 1 and 500 µg/L in group 2, PE could be excluded without CT-scanning in 36%, at a false-negative rate of 1.2% (95% CI 0.04-3.3%). In the validation set, these proportions were 46% and 1.9% (95% CI 1.2-2.7%), respectively. Using the conventional Wells score with a normal D-dimer result, these rates were respectively 22% and 0.6% (95% CI 0.10-2.4%).

Conclusions
Combining Wells items with the D-dimer test resulted in a simplified decision rule, which reduces the need for CT-scanning in patients with suspected PE. A prospective validation is required before it can be implemented in clinical practice.

Introduction

The clinical presentation of patients with acute pulmonary embolism (PE) is non-specific and varies widely.[1,2] CT scanning has now become the first-line imaging modality in patients with suspected PE.[3] In the majority of these patients, computerized tomography pulmonary angiography (CTPA) does not show signs of PE.[4,5] As CTPA is also associated with an increased lifetime risk of malignancy from radiation exposure and the risk of contrast nephropathy,[6] clinicians are in need of a diagnostic strategy that safely reduces the number of required CTPAs.

In the past decade, standardized clinical decision rules have been derived and implemented in clinical practice. The most commonly used clinical decision rule in PE was developed by Wells *et al*.[7] It is based on calculating a score using six objective items from the clinical history and physical examination and one subjective item, inviting the physician to indicate whether or not an alternative diagnosis is more likely than the presence of acute PE.[7] The Wells score is used in combination with a highly sensitive D-dimer test.[5] The sensitivity of combining D-dimer at a 500 μg L^{-1} cut-off with the Wells score was estimated at nearly 100%. Its specificity, however, is only 30 to 40%.[8,9]

The combination of the Wells score and D-dimer leads to CT scanning in all patients with a slightly elevated D-dimer, even in patients with a Wells score of zero, although the accuracy of D-dimer testing has been demonstrated to be substantially different in this subgroup.[10] In clinical practice, D-dimer testing is often performed at a low clinical threshold, regardless of the Wells score,[8] and even routinely in some cases, ordered before clinical evaluation.[11] This results in even more patients being referred for CTPA.

The aim of this study was to derive a new clinical decision rule, combining Wells items and D-dimer testing, with a sensitivity similar to that of the original clinical decision rule but with an enhanced specificity, in order to safely reduce the number of (negative) CTPAs.

Methods

Development

We analyzed data from 807 patients with clinically suspected PE included in a prospective multicenter cohort study, the design of which has been reported in detail elsewhere.[12] Briefly, the study population consisted of consecutive in- and outpatients in whom acute PE was clinically suspected. Patients were identified in seven academic and non-academic hospitals in the Netherlands. For each included patient, the dichotomized Wells score and a high-sensitivity quantitative D-dimer test were performed in all patients (VIDAS D-dimer assay, bioMérieux, Marcy-l'

Étoile, France; Tina-quant assay, Roche Diagnostics, Mannheim, Germany; STA Liatest D-Di, Diagnostica Stago, Asnières-sur-Seine, France; or Innovance D-dimer, Siemens, Marburg, Germany).[12] The diagnosis of PE was confirmed by the presence of at least one filling defect in the pulmonary artery tree (either [sub-] segmental, lobar or central). Patients were followed for 3 months and objective, imaging diagnostic tests were done if PE or DVT was suspected.[12] The ethical review boards of all participating hospitals approved the study protocol and informed consent was obtained from all included patients.

Validation

For the validation, data from a large prospective multicenter cohort study were used.[5] This study had evaluated the clinical effectiveness of an algorithm based on the dichotomized Wells score, D-dimer testing and CTPA scanning in patients with suspected PE. The study design and results are reported elsewhere.[5] In short, the study group consisted of 3306 patients, who all underwent a sequential diagnostic work-up, consisting of clinical probability calculation (Wells score), a D-dimer test and CTPA scanning. PE was excluded by either an 'unlikely' Wells score (≤ 4) combined with a D-dimer test ≤ 500 µg L^{-1} (either VIDAS or Tinaquant D-dimer test) or a negative CTPA scan in all other patients. Patients were followed for 3 months.[5]

Statistical analysis

We aimed for a simple decision rule, with a sensitivity comparable to that of the original Wells-D-dimer strategy, but with an enhanced specificity. To identify the relevant variables, we used multivariable logistic regression to build a model with the original Wells items and the D-dimer test result, using PE as the dependent variable. To arrive at a parsimonious model, we then eliminated all Wells items not significantly associated with PE at a significance level of $P > 0.20$. The accuracy of the final model was evaluated by calculating the area under the receiver operating characteristics curve (AUC).

We then calculated the frequency of the informative Wells variables, the ones retained in the final model. Based on the most frequent combinations of these influential Wells items, we identified patient subgroups. In each of the resulting subgroups we then identified a D-dimer threshold that would lead to a sensitivity rate comparable to that of the original decision rule. Combing the items to define the subgroups with the new D-dimer thresholds resulted in a new decision rule. Additionally, we performed a subgroup analysis in in- and outpatients, because D-dimer is less specific in inpatients.[13]

The sensitivity of this new clinical decision rule was estimated as the proportion of patients with PE, as confirmed by CTPA, classified as positive with the clinical decision rule. Specificity was estimated as the proportion of patients without PE classified as negative with the clinical decision rule. The positive predictive value

(PPV) was defined as the proportion of patients with a positive clinical decision rule who had PE confirmed by CTPA; the negative predictive value (NPV) was defined as the proportion of patients with a negative clinical decision rule in whom PE was excluded by CTPA. Additionally, we calculated the false-negative rate, defined as the proportion of patients classified as negative with the rule who had PE during follow-up. We also assessed the number of patients who experienced DVT during follow-up.

Clinical utility was assessed by calculating the overall proportion of negatives: patients in whom further diagnostic testing could be safely withheld in principle, based on the new rule. The NPV and sensitivity, as well as the clinical utility of the new clinical decision rule, were compared with those of the original rule at a Wells score cut-off ≤ 4 in combination with a normal D-dimer result (≤ 500 μg L^{-1}). The 95% confidence interval (CI) for the 3-month incidence rate of PE with both decision rules was calculated. The new clinical decision rule, combined with a D-dimer test result, was considered acceptable if the confidence interval around the observed diagnostic failure rate did not exceed 3%.[14]

All p-values were two-tailed and statistical significance was defined as $P < 0.05$, except where indicated otherwise. All analyses were performed using SPSS software, version 19.0 (SPSS Inc, Chicago, Ill, USA).

Results

In 84 patients with clinically suspected PE in the derivation set no D-dimer test was available, and these patients were excluded. Of the remaining 723 patients, 156 (22%) had PE. The clinical characteristics of the two study groups are summarized in Table 1. When using the regular Wells score combined with the conventional D-dimer threshold, the number of patients in whom PE could be excluded was 160 (22%; 95% CI, 19%–25%). The corresponding PPV and NPV were 0.28 (95% CI, 0.24–0.31) and 0.99 (95% CI, 0.99–1.00), respectively.

Influential Items

Table 2 shows the multivariable logistic regression model, fitted to the data of the derivation set, using all the original Wells items. This table also shows the coefficients for a second model, one that additionally includes the D-dimer test result. When including the D-dimer test result, only three of the seven Wells items were significantly associated with PE (at $P < 0.2$): two clinical items (hemoptysis and clinical signs of DVT) and the subjective item (PE most likely). The other items (history of DVT or PE, malignancy and immobilization, and tachycardia) provided no or limited incremental value, conditional on the D-dimer test result. Figure 1 shows the receiver operating characteristic (ROC) curve for the corresponding model, with the three variables and the D-dimer test result, which had an AUC of 0.83 (95% CI, 0.80–0.87).

Table 1: Clinical characteristics.

	Derivation set, *n* = 723	Validation set, *n* = 2785
Mean age in years (SD)	52 (17)	52 (18)
Median D-dimer level in μg L^{-1} (IQR) In patients with PE In patients without PE	1000 (500–2200) 2695 (148–50000) 730 (400–1500)	700 (300–1830) 2647 (1470–50000) 520 (290–1255)
Female	441 (61%)	1580 (57%)
Active malignancy	90 (12%)	357 (13%)
COPD	67 (9%)	277 (10%)
Heart failure	38 (5%)	212 (7%)
Use of medication containing oestrogens	92 (13%)	375 (14%)
Outpatients	591 (82%)	2303 (83%)

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PE, pulmonary embolism; SD, standard deviation.

Table 2: Multivariable logistic regression models.

Wells items	Points	*N*	Wells items	Wells items and D-dimer test result
			OR (95% CI)	OR (95% CI)
Clinically suspected DVT	3	39 (5%)	3.94 (1.93–8.03)	2.99 (1.41–6.33)
Active malignant condition	1	90 (12%)	1.08 (0.91–1.90)	0.94 (0.51–1.74)
Previous DVT or PE	1.5	35 (5%)	3.30 (1.56–6.99)	2.25 (0.96–5.28)
Alternative diagnosis less likely than PE	3	399 (55%)	2.65 (1.76–3.98)	2.43 (1.56–3.77)
Heart rate ≥ 100 beats per minute	1.5	152 (21%)	1.59 (1.03–2.55)	1.29 (0.80–2.07)
Immobilization/surgery in past 4 weeks	1.5	145 (20%)	1.92 (1.23–3.00)	1.27 (0.77–2.09)
Haemoptysis	1	37 (5%)	2.86 (1.36–6.03)	2.84 (1.29–6.24)
D-dimer test result			–	1.58 (1.42–1.75)

Both models fitted to the data of 723 patients in the derivation set. DVT, deep venous thrombosis; PE, pulmonary embolism.

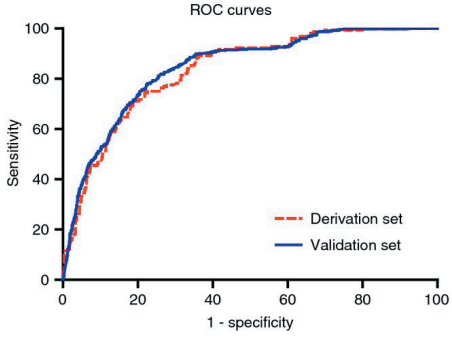


Figure 1:
Receiver operating characteristic curves illustrating the diagnostic performance of a logistic regression model with the two clinical items (hemoptysis and clinical signs of deep venous thrombosis) and the subjective item (pulmonary embolism most likely), and the D-dimer test result in the derivation and validation sets. The areas under the curve were 0.83 (95% confidence interval (CI), 0.80–87) and 0.84 (95% CI, 0.83–0.86), respectively.

Four combinations of the three remaining Wells items could be identified: (i) none of the three items positive (n = 298, 41%), (ii) only the subjective item positive, neither of the other two items positive (n = 354, 49%), (iii) one or two clinical items positive (n = 26, 3.6%), and (iv) the subjective item and one or more clinical items positive (n = 45, 6.2%). Based on these frequencies, we defined two groups: group 1, with none of the three items positive (41%), and group 2, with one or more items positive (59%).

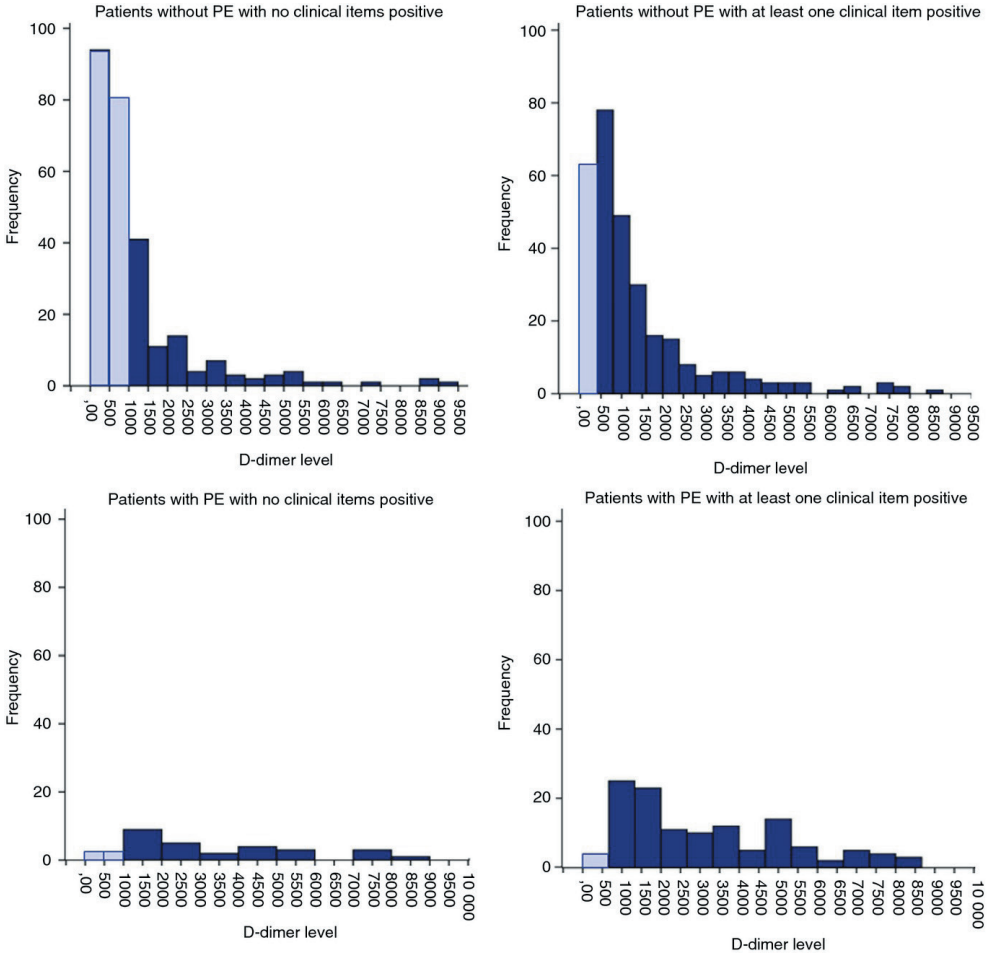


Figure 2:
The number of D-dimer levels in patients without PE and no clinical items positive, patients without PE and at least one *item positive, patients with PE with no clinical items positive and patients with PE with at least one* item positive. * 'PE is the most likely diagnosis', clinical signs of DVT or hemoptysis.

For patients with none of the three items present, the median D-dimer level was 725 μg L^{-1} (interquartile range [IQR], 400–1512). Patients in this group without PE had a median D-dimer level of 653 (IQR, 374–1237); in the patients with PE this median level was 2826 μg L^{-1} (IQR, 1648–4950). For patients with at least one of the items present, the overall median D-dimer level was 1170 μg L^{-1} (IQR 584–2587). These median levels were 821 μg L^{-1} (IQR 442–1704 μg L^{-1}) and 2690 μg L^{-1} (IQR 1445–5000 μg L^{-1}) for patients without and with PE, respectively. (See Figure 2 for the distribution of the D-dimer level in the different subgroups.)

We then calculated two D-dimer cut-off levels, one for group 1 and one for group 2, in steps of 100 μg L^{-1} and compared the clinical utility and safety. Considering the advantage of simple cut-off levels, we selected 1000 μg L^{-1} for group 1 and 500 μg L^{-1} for group 2. Using these cut-off levels we found the D-dimer result to be negative in 83 (12%) patients in group 1 (no items positive) and 176 (24%) patients in group 2.

The two different D-dimer cut-off levels, in patients with and without positive Wells items, translates into a new decision rule for patients with suspected PE (Figure 3).

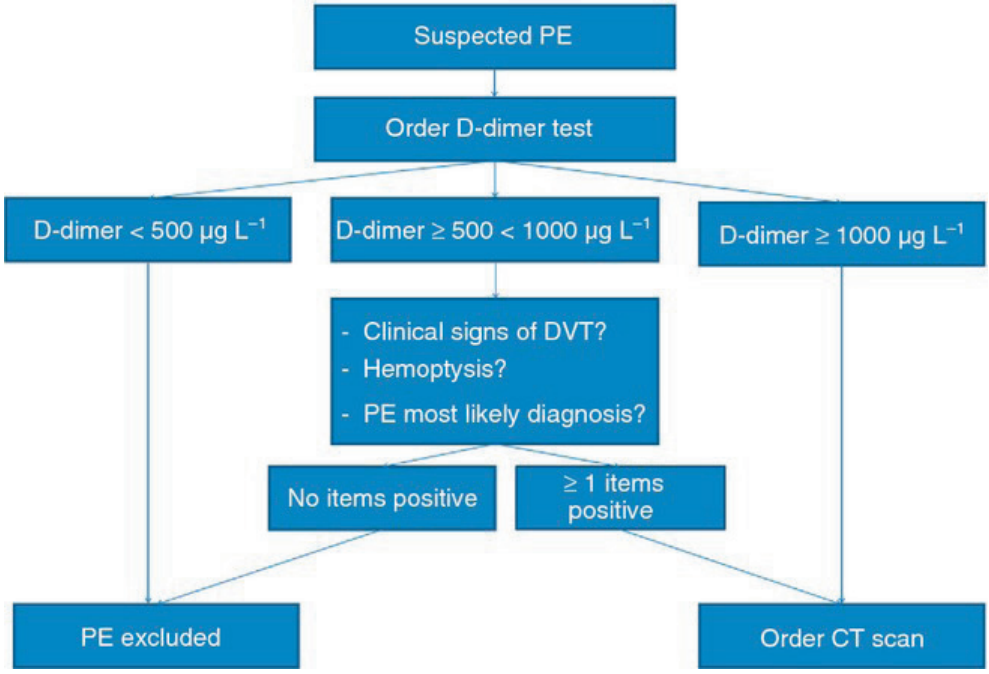


Figure 3:
Diagnostic work-up for suspected pulmonary embolism (PE), a combination of two cut-off levels of the D-dimer and three clinical items. DVT, deep venous thrombosis; PE, pulmonary embolism.

If the D-dimer result is ≥ 1000 µg L^{-1}, refer for CT scan. If the D-dimer result is < 500 µg L^{-1}, exclude PE. If the D-dimer result is ≥ 500 and < 1000 µg L^{-1}, order a CT scan only if PE is the most likely diagnosis, or if the patient has signs of DVT or hemoptysis. If none of these three items is present with a D-dimer result between 500 and 1000 µg L^{-1}, the diagnosis may be excluded. Consequently, in the case of a D-dimer lower than 500 µg L^{-1}, none of the Wells items seemed to be of importance, including clinical gestalt. The corresponding rule had an AUC of 0.87 (95% CI, 0.81–0.92) and 0.78 (95% CI, 0.76–84), respectively (Figure 4).

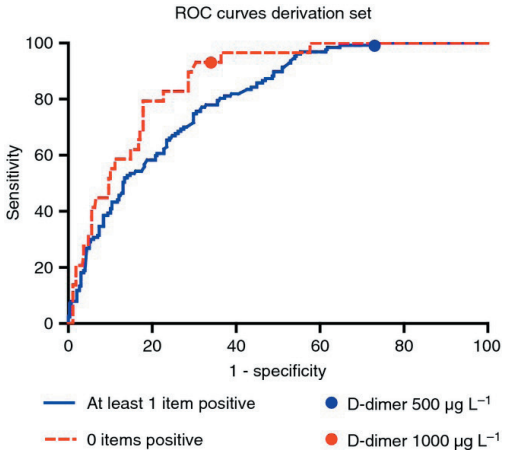


Figure 4:
The performance of D-dimer in patients with and without positive items. Items considered: two clinical items (hemoptysis and clinical signs of deep venous thrombosis) and the subjective item (pulmonary embolism most likely).

Table 3 shows additional information on the characteristics of patients who could be excluded by the new strategy and the original Wells score/D-dimer test combination.

With this new rule, PE could be excluded in 259 patients (36%; 95% CI, 32–39); CTPA would be needed in the remaining 64%. Compared with the conventional Wells rule with a 500 µg mL^{-1} D-dimer positivity threshold, the number of patients in whom PE could be excluded with the new rule increased from 160 to 259 (absolute increase 14%, relative increase of 62% [99/160]). The false-negative rate increased from 0.6% (1/160; 95% CI, 0.10–3.4%) to 1.2% (3/259; 95% CI, 0.04–3.3).

Table 3: Additional patients in whom PE could be ruled out by the new decision rule.

Cohort	PE additionally ruled out by new decision rule		
	Wells score >4.5 points	D-dimer > 500 µg L^{-1}	Total
Derivation	65	75	99
Validation	98	260	306

Numbers indicate patients qualifying for CT scanning based on the conventional Wells/D-dimer strategy but in whom PE could be ruled out with the new strategy.

One patient with a malignancy experienced DVT during follow-up; this patient had none of the items positive and a D-dimer test result of 980 μg mL^{-1}. Table 4 lists the characteristics of the rules in terms of sensitivity, specificity, PPV and NPV. An additional analyses on the in- and outpatients did not show significant differences (data not shown).

Table 4: Test characteristics of the new diagnostic strategy combined with D-dimer cut-off values 1000/500 μg L^{-1} and the conventional Wells score with the D-dimer test (cut-off 500 μg L^{-1}).

	New CDR including D-dimer cut-off levels 1000/500 μg L−1	Wells score 'unlikely' (≤ 4) and D-dimer < 500 μg L−1
Derivation set, *n* = 723		
Number (%) of patients in whom PE can be excluded	259 (36)	160 (22)
Sensitivity (95% CI)	0.981 (0.946–0.994)	0.994 (0.965–0.999)
Specificity (95% CI)	0.452 (0.411–0.493)	0.280 (0.245–0.319)
PPV (95% CI)	0.330 (0.289–0.374)	0.275 (0.240–0.314)
NPV (95% CI)	0.988 (0.967–0.997)	0.994 (0.966–0.999)
Validation set, *n* = 2785		
Number (%) of patients in whom PE can be excluded	1295 (46)	989 (36)
Sensitivity (95% CI)	0.951 (0.929–0.967)	0.990 (0.977–0.996)
Specificity (95% CI)	0.555 (0.535–0.575)	0.430 (0.409–0.450)
PPV (95% CI)	0.315 (0.292–0.339)	0.272 (0.252–0.294)
NPV (95% CI)	0.982 (0.973–0.986)	0.995 (0.988–0.998)

CDR, clinical decision rule; NPV, negative prospective value; PPV, positive prospective value; PE, pulmonary embolism.

Validation set

In 515 patients in the validation set with an 'unlikely' outcome of the Wells decision rule, D-dimer test results were recorded only qualitatively; these were excluded from this analysis. In another six patients, one of the Wells items was missing; these patients were also excluded. Of the remaining 2785 patients, 491 patients were diagnosed with PE (17.6%). The clinical characteristics were similar to those of the patients in the derivation set (Table 1).

For patients with none of the three Wells items positive, the overall median D-dimer level was 500 μg L^{-1} (IQR, 260–1241). Patients in this group without PE had a D-dimer median level of 430 (IQR, 240–1053) and in the patients with PE this median level was 2593 μg L^{-1} (IQR, 1330–4799). For patients with at least one of the items present, the overall median D-dimer level was 900 μg L^{-1} (IQR, 400–2303). These median levels were 633 μg L^{-1} (IQR, 300–1499 μg L^{-1}) and 2660 μg L^{-1} (IQR, 1497–5049 μg L^{-1}) for patients without and with PE, respectively. When using the original Wells score combined with a normal D-dimer test result, the number of patients in whom PE could be excluded was 989 (35%; 95% CI, 34 to 37%). The PPV of this new rule was 0.27 (95% CI, 0.25–0.29); the NPV was 0.99 (95% CI, 0.99–1.00) (Table 4).

The logistic regression model with the three influential Wells items and the D-dimer test result had an AUC of 0.84 (95% CI, 0.83–0.86) (Fig. 1). For 1135 (41%) patients in the validation set, none of the three informative Wells items was positive, whereas in the other 1649 patients (59%) one or more items were positive.

Applying the new rule, PE could be excluded in 1295 patients (46%; 95% CI, 45–48%), with a false-negative rate of 1.9% (24/1295; 95% CI, 1.2–2.7%). Compared with the conventional decision rule, the number of patients in whom PE could be excluded increased from 989 to 1295 (absolute increase 11%, relative increase of 31%). The false-negative rate increased from 0.5% (5/989; 95% CI, 0.2–1.2%) to 1.9% (24/1295; 95% CI, 1.2–2.7%) (Table 4). Subgroup analyses for in- and outpatients did not show significant differences (data not shown).

Discussion

We derived a simple clinical decision rule in which the D-dimer test and three Wells items were incorporated. Conditional on the D-dimer result, only three of the original Wells items proved to be informative. The new rule was based on these three informative items and on the D-dimer test result, with a different D-dimer threshold for those with no items positive, vs. those with one or more items positive. Combining the D-dimer test result with items of the Wells score resulted in a simple clinical decision rule with a high sensitivity and a significantly higher specificity, compared with the currently used diagnostic algorithm, consisting of the Wells score-D-dimer combination.

Based on two large prospective cohort studies of patients with suspected PE, with this new clinical decision rule, approximately 36% and 46% of patients with suspected PE can be withheld from further diagnostic imaging, a proportion substantially higher than that obtained with the original decision rule (22% and 36%). It is widely accepted that the confidence intervals of the diagnostic failure rate of a diagnostic strategy for PE should not exceed 3%.[14] This safety limit was not exceeded in the new strategy in the derivation set or the validation set. However, compared with the conventional strategy, the point estimate of the false-negative rate increased with this new rule, although it was still below 2%.[15,16]

In primary care, physicians already make use of a validated clinical decision rule for DVT, including seven clinical items and D-dimer testing.[17,18] A positive D-dimer result contributes six of the total 13 points. Using this rule, the proportion of patients with suspected DVT referred for imaging could be reduced from 100% to 77%, at the expense of not referring 0.7% of all DVT cases. However, it has only recently been demonstrated that for patients with suspected PE in primary care, the traditional Wells rule followed by a D-dimer test can safely exclude PE.[19] Several studies using a higher cut-off level of the D-dimer reported higher specificity

without a relevant fall in sensitivity.[20] Kline *et al*. recently doubled the threshold of the D-dimer, in a prospective study with 678 patients with suspected PE and an unlikely pretest probability.[21] They found the threshold of 1000 μg L^{-1} to be safe for excluding PE in patients with a Wells score of 4 points or less. Similarly, it has been shown that in 860 patients with a first episode of suspected DVT, with a low clinical probability, a D-dimer cut-off of 1000 μg L^{-1} is as safe as the conventional cut-off point of 500 μg L^{-1}.[22] Other studies also demonstrated that a D-dimer cut-off value that is adapted to the clinical probability category of the patient has greater utility for exclusion of PE compared with the use of a single D-dimer cut-off value, regardless of the clinical probability.[21,23] The proposed cut-off value was kept at 500 μg L^{-1} for patients with an intermediate clinical suspicion of PE, but was doubled in patients with a low clinical suspicion, and halved in patients with a high clinical suspicion of PE. In a study by Kabrhel et al,[23] the conventional cut-off of 500 μg L^{-1} had an overall sensitivity of 94% and a specificity of 58%. These rates were 88% and 75%, respectively, when probability-dependent cut-offs were used.

Some may wonder why some of the Wells items are no longer incorporated in the decision rule proposed here, despite the fact that additional evaluations have confirmed their association with PE. Apparently, when the D-dimer test result is already known, the additional value from items such as malignancy, immobilization, history of DVT or PE and tachycardia is less than that in the absence of D-dimer testing. The first three are risk factors, and their diagnostic value is more limited in the presence of objective laboratory testing, as is the case with D-dimer. It is known from other fields that risk factor information, known to be associated with the condition of interest, may have limited value in those presenting with signs and symptoms suggestive of that same condition.[24,25]

What then should take precedence: history taking and physical examination or objective testing? With the original rule, D-dimer testing was only needed in those with a 'PE unlikely' classification based on the Wells rule.[3] In current clinical practice, D-dimer testing is regularly ordered in all patients with suspected PE, often even before pretest probability is estimated.[11,26] Yet D-dimer should definitely not be used in isolation, as a standalone test; its accuracy is far from perfect and it may yield false-negative and false-positive results.[8]

With this new strategy, D-dimer takes a more prominent place in the diagnostic strategy and is necessary in all patients with suspected pulmonary embolism. Compared with the old strategy, this may come with extra costs and waiting time in clinical practice. On the other hand, our strategy predicts that fewer CT scans will be needed to exclude the diagnosis of PE in the patient population. Furthermore, PE can now be ruled out by only a low D-dimer (< 500 μg L^{-1}). We are aware that previous reports showed that D-dimer can lead to false-negatives in the case of a high clinical suspicion.[8,27] We believe that the value of our findings lies in two observations: first,

the specificity of the clinical decision rule, based on the Wells score, is increased, substantially reducing the need for CTPA with its associated potential for harm and over-diagnosis.[28] Second, our proposed strategy could be considerably easier to apply in a busy clinical practice, because fewer items need to be evaluated, counted and summed.

The conclusions of this study are strengthened by its large sample of patients and its multicenter design, which enhance the extrapolation of our findings to other clinics. Limitations include that a D-dimer test was not performed in some of the patients in the derivation set, and that other patients in the validation set had to be excluded because no qualitative D-dimer test was available.

Although our analysis was based on prospectively collected data and separately validated in an independent cohort, it was retrospective in design. We believe that the safety and efficiency of this new strategy have to be further validated in future studies before it can be implemented in clinical practice.

Addendum

J. van Es performed the analyses, wrote the manuscript and participated in designing the study. P. M. M. Bossuyt supervised and participated in the analyses, and writing and designing the study. R. A. Douma, S. Middeldorp, P. L. den Exter and L. F. M. Beenen helped in designing and writing the study. H. A. H. Kaasjager, I. C. M. Mos, P. W. Kamphuisen and M. V. Huisman participated in gathering the data. All authors reviewed the manuscript carefully.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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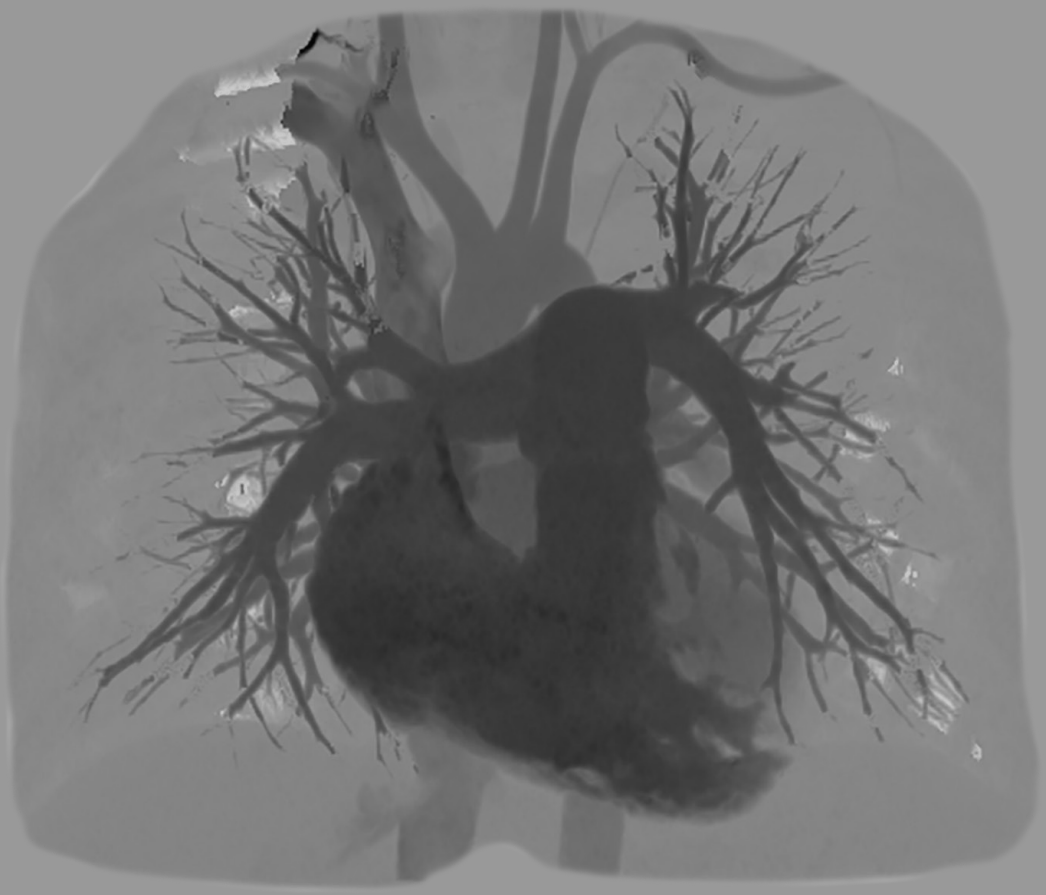

Chapter 3

Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study

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Abstract

Background
Validated diagnostic algorithms in patients with suspected pulmonary embolism are often not used correctly or only benefit subgroups of patients, leading to overuse of computed tomography pulmonary angiography (CTPA). The YEARS clinical decision rule that incorporates differential D-dimer cut-off values at presentation, has been developed to be fast, to be compatible with clinical practice, and to reduce the number of CTPA investigations in all age groups. We aimed to prospectively evaluate this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism.

Methods
We did a prospective, multicentre, cohort study in 12 hospitals in the Netherlands, including consecutive patients with suspected pulmonary embolism between Oct 5, 2013, to July 9, 2015. Patients were managed by simultaneous assessment of the YEARS clinical decision rule, consisting of three items (clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis), and D-dimer concentrations. In patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL, pulmonary embolism was considered excluded. All other patients had CTPA. The primary outcome was the number of independently adjudicated events of venous thromboembolism during 3 months of follow-up after pulmonary embolism was excluded, and the secondary outcome was the number of required CTPA compared with the Wells' diagnostic algorithm. For the primary outcome regarding the safety of the diagnostic strategy, we used a per-protocol approach. For the secondary outcome regarding the efficiency of the diagnostic strategy, we used an intention-to-diagnose approach. This trial is registered with the Netherlands Trial Registry, number NTR4193.

Results
3616 consecutive patients with clinically suspected pulmonary embolism were screened, of whom 151 (4%) were excluded. The remaining 3465 patients were assessed of whom 456 (13%) were diagnosed with pulmonary embolism at baseline. Of the 2946 patients (85%) in whom pulmonary embolism was ruled out at baseline and remained untreated, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up (0.61%, 95% CI 0.36–0.96) of whom six had fatal pulmonary embolism (0.20%, 0.07–0.44). CTPA was not indicated in 1651 (48%) patients with the YEARS algorithm compared with 1174 (34%) patients, if Wells' rule and fixed D-dimer threshold of less than 500 ng/mL would have been applied, a difference of 14% (95% CI 12–16).

Conclusions
In our study pulmonary embolism was safely excluded by the YEARS diagnostic algorithm in patients with suspected pulmonary embolism. The main advantage of the YEARS algorithm in our patients is the absolute 14% decrease of CTPA examinations in all ages and across several relevant subgroups.

Introduction

The clinical diagnosis of pulmonary embolism is non-specific and should therefore be followed by objective testing. Because of its diagnostic accuracy and wide availability, multidetector row computed tomography pulmonary angiography (CTPA) is the imaging test of choice to confirm acute pulmonary embolism in most patients. Increasing use of CTPA with diminishing prevalence of pulmonary embolism—to even less than 10%[1]—has led to overdiagnosis of mostly subsegmental pulmonary embolism and unnecessary risks of radiation exposure and contrast medium induced nephropathy.[2-6]To avoid these problems, validated diagnostic algorithms for suspected acute pulmonary embolism, using sequential testing, have been introduced.[7] In these algorithms, a normal D-dimer test result in patients with low probability safely excludes pulmonary embolism.[8] Correct application of these algorithms obviates the need for CTPA in 20–30% of patients, with an overall 3-month diagnostic failure rate of less than 1.5% after initial negative ruling of the algorithm.[7-9] An age-adjusted D-dimer threshold (age × 10 ng/mL for patients aged >50 years) has been validated prospectively, reporting an absolute reduction of 11.6% (95% CI 10.5–12.9) in the need for CTPA.[10] Importantly, only patients aged 50 years or older, and foremost those older than 75 years benefit from this strategy whereas when considering the life-time attributable cancer risk, the exposure to unnecessary radiation is considered more relevant to younger individuals, particularly women.[3]

Despite firm evidence of its safety and efficiency, adherence to recommended diagnostic strategies in clinical practice is variable. This variation might be partly due to complexity of these strategies, and insufficient time at busy emergency departments, which hampers the use of sequential tests.[11-14] In daily practice, D-dimer testing is frequently ordered and known at a low clinical threshold or even before the clinical assessment.[15,16] Improved adherence to the algorithm, for instance by implementation of a clinical decision support system, has been shown to significantly decrease the mean number of diagnostic tests used along with—and more importantly—the number of diagnostic failures.[17,18]

On the basis of a post-hoc derivation and validation study,[19] three items of the original Wells' clinical decision rule—i.e., clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis—were the most predictive for pulmonary embolism. They allowed the use of a differential D-dimer threshold based on the presence of one of these items, without losing sensitivity. Hence, this algorithm—which we call YEARS—involves the simultaneous assessment of only the three abovementioned items and a D-dimer test threshold of 500 ng/mL in presence, and 1000 ng/mL in absence of one of the YEARS items. The YEARS algorithm was designed to be more easily applied in a busy clinical practice than currently used diagnostic strategies, and to further

decrease the number of necessary CTPA examinations in patients of all ages. In this study, we aimed to prospectively evaluate this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism.

Materials and Methods

Study design and patients

We did a prospective, multicentre, cohort outcome study evaluating the safety and efficiency of the YEARS algorithm in patients with suspected acute pulmonary embolism between Oct 5, 2013, and July 9, 2015 (Figure 1).[19] The algorithm was implemented as standard diagnostic strategy in 12 participating hospitals in the Netherlands.

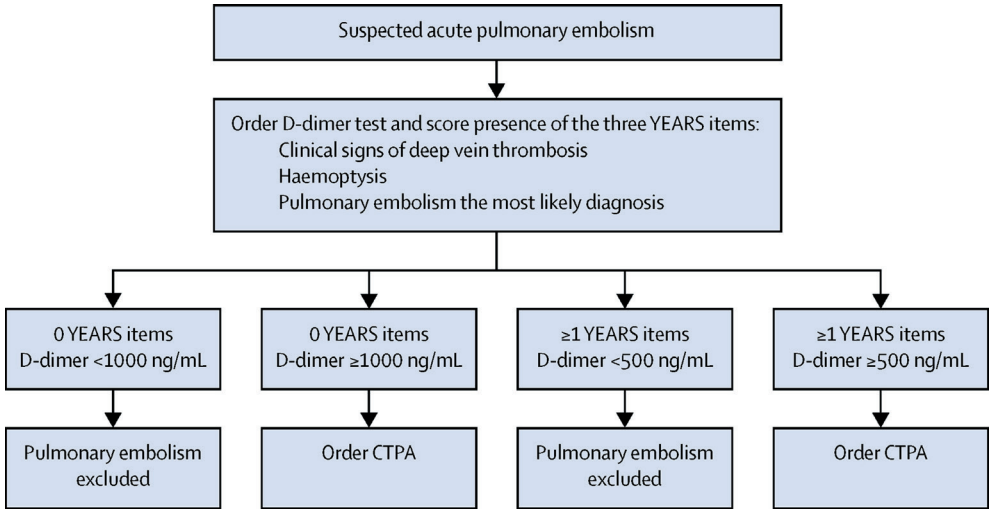

Figure 1: YEARS algorithm.
CTPA=computed tomography pulmonary angiography.

Patients

Consecutive outpatients and inpatients with clinically suspected acute (first or recurrent) pulmonary embolism were eligible for inclusion if they were aged 18 years or older. Exclusion criteria were treatment with therapeutic doses of anticoagulants initiated 24 hours or more before eligibility assessment, life expectancy less than 3 months or geographic inaccessibility precluding follow-up, pregnancy, or allergy to intravenous contrast agent. The protocol was centrally approved by the institutional review board of the Leiden University Medical Center, Leiden, Netherlands, which waived the need for informed consent; this decision was endorsed by the local institutional review board of each participating centre.

YEARS diagnostic algorithm

An attending physician who suspected acute pulmonary embolism assessed the patients, and then evaluated the YEARS score by assessing the presence or absence of each of the YEARS items—ie, symptomatic deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis—(scored as yes or no) with the pretest probability dependent threshold of the D-dimer test (Figure 1). D-dimer concentrations were measured upon presentation of the patient, according to local practice, with automated well validated high-sensitive quantitative D-dimer assays (Vidas D-dimer Exclusion, Biomerieux, Marcy-L'Étoile, France; Tinaquant, Roche Diagnostica, Mannheim, Germany; STA-LIA, DiagnosticaStago, Asnieres, France; and Innovance, Siemens, Marburg, Germany). Our study reflected daily clinical practice in which D-dimer concentrations are often determined at presentation to the emergency ward. Physicians were not blinded for the D-dimer test result when they assigned the YEARS items.

In patients with no YEARS items and a D-dimer concentration less than 1000 ng/mL, pulmonary embolism was considered excluded and further testing was withheld. In patients with one or more YEARS items and a D-dimer concentration less than 500 ng/mL, pulmonary embolism was also considered excluded and further testing was withheld. All other patients—ie, either with no YEARS item and a D-dimer concentration of 1000 ng/mL or more, or with one or more items and a concentration of 500 ng/mL or more—were referred for CTPA to show or exclude the diagnosis of pulmonary embolism. Patients in whom pulmonary embolism was ruled out were left untreated and followed up for 3 months. They were instructed to return to the hospital in the event of symptoms of venous thromboembolism, after which objective diagnostic tests were done to confirm or refute the disease. Follow-up consisted of a scheduled outpatient visit or telephone interview after 3 months. At this visit, information about complaints suggestive of venous thromboembolism was obtained. Patients in whom acute pulmonary embolism was confirmed at baseline were treated with anticoagulants according to international guidelines.

Outcomes

The primary outcome was the 3-month incidence of symptomatic venous thromboembolism in the overall population and in patients managed with and without CTPA separately. The diagnosis of pulmonary embolism or deep vein thrombosis was based on predefined criteria. In case of clinically suspected pulmonary embolism or deep vein thrombosis, objective diagnostic tests were required, including CTPA for suspected pulmonary embolism and compression ultrasonography for suspected deep vein thromboembolism. In case of death, information was obtained from the hospital records. Deaths were classified as caused by pulmonary embolism if it was confirmed by autopsy, was shown by objective testing before death, or could not be confidently

excluded as a cause of death. An independent adjudication committee assessed and adjudicated all suspected venous thromboembolism and deaths during follow-up.

The secondary outcome was the proportion of required CTPA examinations to complete the YEARS algorithm at baseline, as compared post hoc with the theoretical proportion of CTPA examinations that would have been required if the algorithm, using the two-level Wells' rule outcome and fixed D-dimer threshold of less than 500 ng/mL, would have been applied in the study population and to historical data.[20] Finally, we compared the efficiency to the scenario in which the age-adjusted D-dimer concentration would have been applied (calculated by age × 10 μg/L in patients >50 years). This comparison was done post hoc because the final evidence supporting this approach was not available at the moment of drafting of the protocol.10 The Wells' rule was calculated by an independent researcher (TvdH) based on the YEARS criteria entered in the case record form and information from the medical charts.

Statistical analysis

On the basis of derivation cohort of the YEARS algorithm, we expected a failure rate of 1.2% in patients managed without CTPA.[19] The sample size was based on this assumption, with the aim to keep the upper limit of the 95% CI of this point estimate below 2.7%.[21] This number reflects the 3-month incidence of venous thromboembolism after normal conventional pulmonary angiography. Any venous thromboembolism incidence with a complete confidence interval below this safety threshold was considered to be safe. We calculated that we needed to include 1333 patients managed without CTPA, with a two-sided α of 5% and a β of 80%. Because 44% of patients in the combined YEARS derivation and validation cohort could have been managed without CTPA and accounting for up to 7.5% loss to follow-up, a total of 3260 patients with suspected pulmonary embolism would be required.[19] For the primary outcome regarding the safety of the diagnostic strategy, we used a per-protocol approach. For the secondary outcome regarding the efficiency of the diagnostic strategy, we used an intention-to-diagnose approach. The difference between approaches was how to report the number of CTPA that were done but not indicated by the strategy. By using this approach, pulmonary embolism diagnosed at presentation on a CTPA that was not indicated was considered as failures of the diagnostic strategy.

For the secondary outcome analysis, we determined the absolute difference in the number of required CTPA examinations between the different clinical scenarios. Finally, we reported outcomes of not predefined post-hoc analyses for relevant subgroups: patients with malignancy, patients 50 years or older, patients with a history of venous thromboembolism, and inpatients and patients with complaints for more than 7 days. All descriptive parameters and exact 95% CIs around the observed incidences were calculated. All analyses were done with SPSS (version 23). This study is registered with the Netherlands Trial Register, number NTR4193.

Role of the funding source

This study was an academically sponsored trial. The steering committee, consisting of the authors, had final responsibility for the study design, oversight, and data verification and analyses. The sponsor was not involved in the study. All members of the steering committee contributed to the interpretation of the results, approved the final version of the manuscript, and vouch for the accuracy and completeness of the data reported. The final decision to submit the manuscript was made by the corresponding author on behalf of all coauthors.

Results

Study Patients

From Oct 5, 2013, to July 9, 2015, 3616 consecutive patients with clinically suspected pulmonary embolism were screened in the 12 participating hospitals, of whom 151 (4.2%) were excluded (Figure 2).

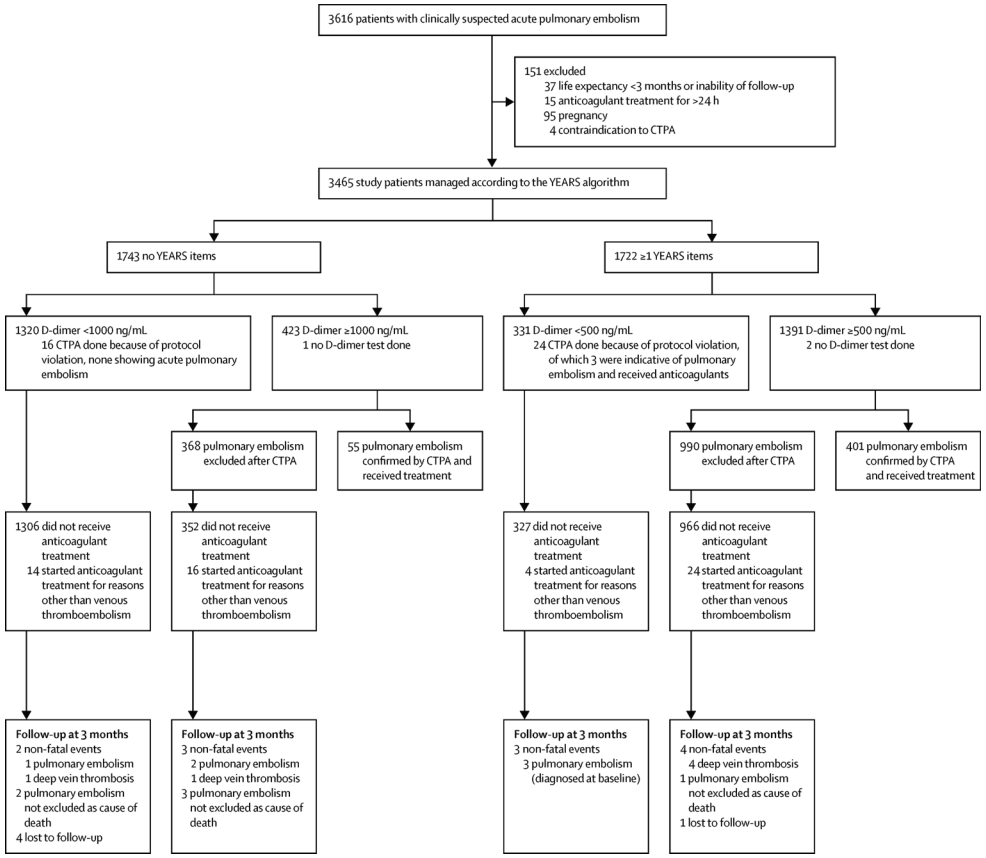

Figure 2: Flowchart of study patients.
CTPA=computed tomography pulmonary angiography.

Table 1 summarises the baseline characteristics. Overall, pulmonary embolism was detected in 456 (13%) of 3465 patients: in 55 (3.2%) of 1743 patients with none of the YEARS items and 401 (23%) of 1722 patients with one or more YEARS items.

Table 1: Baseline characteristics of patients with suspected pulmonary embolism.

	Patients (n=3465)
Mean age (years)	53 (18)
Women	2154 (62%)
Median duration of complaints (days)	3 (1–8)
COPD with treatment	423 (12%)
Heart failure with treatment	137 (4%)
Oestrogen use (% of women)	337 (16%)
Immobilisation or surgery in the past 4 weeks	407 (12%)
Outpatient	2996 (86%)
Heart rate greater than 100 beats per min	683 (20%)
History of pulmonary embolism or deep vein thrombosis	359 (10%)
Malignancy	336 (9.7%)

Data are mean (SD), n (%), or median (IQR). COPD=chronic obstructive pulmonary disease.

Safety of the overall YEARS algorithm

According to the intention-to-diagnose approach, of the 2946 (85%) patients in whom pulmonary embolism was ruled out at baseline, who remained untreated, and completed the follow-up period, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up, with an incidence of 0.61% (95% CI 0.36–0.96). The incidence of fatal pulmonary embolism was 0.20% (six patients, 95% CI 0.07–0.44; Table 2). In a worst case scenario, accounting the five patients who were lost to follow-up (four patients had pulmonary embolism excluded without CTPA and one patient had a negative CTPA) as recurrent venous thromboembolism, the 3-month incidence would have been 0.78% (23 of 2951 patients, 95% CI 0.49–1.2). For the per-protocol approach, the failure rate of the diagnostic algorithm was 0.51% (15 of 2943 patients, 95% CI 0.31–0.84) with a 0.20% 3-month risk of fatal pulmonary embolism (six of 2943, 0.08–0.46).

Table 2: Primary outcomes of venous thromboembolism events during 3-month follow-up.

	Patients (n)	Total venous thromboembolism (n [%, 95% CI])	Fatal pulmonary embolism* (n [%, 95% CI])
Completed algorithm	2946	18 (0.61%, 0.36–0.96)	6 (0.20%, 0.07–0.44)
Patients managed without CTPA	1629	7 (0.43%, 0.17–0.88)	2 (0.12%, 0.01–0.44)
Patients managed with CTPA	1317	11 (0.84%, 0.47–1.5)	4 (0.30%, 0.12–0.78)

Patients in whom pulmonary embolism was excluded by either a low YEARS score or CT scanning were left untreated. CTPA=computed tomography pulmonary angiography. * Patients who remained untreated and were not lost to follow-up.

Efficiency of the overall YEARS algorithm

In the intention-to-diagnose approach, CTPA was not done in 1611 (46%) patients and it was not indicated in 1651 (48%) patients following the per-protocol approach. If the standard diagnostic algorithm using Wells' rule and D-dimer with fixed threshold of <500 ng/mL would have been applied, 1174 (34%) patients could have been managed without CTPA at baseline, for an absolute difference of 13% (difference in intention-to-diagnose approach 437 CTPA examinations, 95% CI 10–15%) and 14% (difference in per-protocol approach 477 CTPA examinations, 12–16%) in favour of the YEARS algorithm.

If Wells' rule and the age-adjusted D-dimer threshold would have been applied, 1348 (39%) patients could have been managed without CTPA at baseline, an absolute difference of 8.7% (difference in per-protocol approach CTPA examinations 303, 95% CI 6.4–11%) and of 7.6% (difference in intention-to-diagnose approach CTPA examinations 263, 95% CI 5.3–9.9%).

In the subgroups of patients younger than 50 years and 50 years and older, a 14% absolute reduction in the number of required CTPA examinations was observed when the YEARS algorithm was applied compared with the standard diagnostic algorithm, with failure rates of 0.11% (one of 894, 95% CI 0.02–0.63) and 0.81% (six of 740, 0.37–1.8), respectively. Table 3 summarises the results for the other subgroups.

Table 3: Primary outcome and efficiency in subgroups of the total study population.

	Patients	PE at baseline	Managed without CTPA	Risk of VTE during 3-month follow-up						Efficiency compared with Wells' rule in combination with a D-dimer threshold of <500 ng/mL		
				Incidence in patients managed without CTPA		Incidence in patients managed with CTPA		Overall incidence after pulmonary embolism was excluded at baseline		Managed without CTPA (n)	Difference with YEARS algorithm	
				Events / patients	% (95% CI)	Events/ patients	% (95% CI)	Events/ patients	% (95% CI)		n/N	% (95% CI)
Malignancy	336	57 (17%)	62	2/61	3.2 (0.90–11)	5/211	2.4 (1.0–5.4)	7/272	2.6 (1.3–5.2)	37	25/336	7.4 (5.0–11)
No malignancy	3129	399 (13%)	1590	5/1573	0.32 (0.14–0.74)	6/1106	0.54 (0.25–1.2)	11 /79	0.41 (0.23–0.73)	1137	453/3129	15 (13–16)
Aged <50 years	1448	126 (8.7%)	900	1/894	0.11 (0.02–0.63)	1/415	0.24 (0.04–1.4)	2/1309	0.15 (0.04–0.56)	704	196/1448	14 (12–15)
Aged ≥50 years	2017	330 (16%)	752	6/740	0.81 (0.37–1.8)	10/902	1.1 (0.6–2.0)	16/1642	0.98 (0.6–1.6)	470	282/2017	14 (13–16)
History of VTE	359	107 (30%)	123	1/117	0.85 (0.15–4.7)	1/124	0.81 (0.14–4.6)	2/241	0.83 (0.23–3.0)	54	69/359	19 (15–24)
No history of VTE	3106	349 (11%)	1529	6/1517	0.40 (0.18–0.86)	10/1193	0.84 (0.46–1.5)	16/2710	0.59 (0.36–0.96)	1120	409/3106	13 (12–14)
Inpatient	469	66 (14%)	200	1/195	0.51 (0.09–2.9)	3/198	1.5 (0.52–4.4)	4/393	1.0 (0.40–2.6)	135	65/469	14 (11–17)
Outpatient	2996	390 (13%)	1452	6/1439	0.42 (0.19–0.91)	8/1119	0.71 (0.36–1.4)	14/2558	0.55 (0.33–0.92)	1039	413/2996	14 (13–15)
Complaints ≤7 days	2599	362 (14%)	1266	7/1253	0.56 (0.27–1.2)	9/942	0.96 (0.50–1.8)	16/2195	0.73 (0.45–1.2)	901	365/2599	14 (13–15)
Complaints >7 days	866	94 (11%)	386	0/381	0 (0–1.0)	2/375	0.53 (0.15–1.9)	2/756	0.26 (0.07–0.96)	273	113/866	13 (11–15)

Data are n or n (%), unless otherwise specified. PE=pulmonary embolism. CTPA=computed tomography pulmonary angiography. VTE=venous thromboembolism.

Table 4: Diagnostic failures in patients who were managed without CTPA at baseline.

	Sex	Age (years)	YEARS score	Wells' score*	D-dimer (ng/mL)	Interval (days)	Outcome	Circumstances of outcome event	Adjudicated as
Patient 1	F	59	0	0	609	54	Death	Patient developed cardiac arrest during admission for acute severe pancreatitis, and was known to have myotonic dystrophy type 1 with severe cardiomyopathy and arrhythmias; implantable cardioverter-defibrillator was deactivated after regular unjustified defibrillations; resuscitation was unsuccessful	Pulmonary embolism not excluded as cause of death
Patient 2	M	78	0	1	898	11	Death	Patient was diagnosed with end-stage metastasised oropharyngeal carcinoma; found deceased in nursing home	Pulmonary embolism not excluded as cause of death
Patient 3	F	89	0	1·5	610	18	Pulmonary embolism	Patient diagnosed on CTPA with subsegmental pulmonary embolism during admission for pneumonia and acute heart failure related to severe aortic valve stenosis and mitral valve insufficiency. Patient died 7 days after treatment, which was voluntarily withheld	Non-fatal pulmonary embolism
Patient 4	M	52	0	1	560	49	Deep vein thrombosis	Patient had deep vein thrombosis 14 days after surgery for glioblastoma multiforme	Deep vein thrombosis
Patient 5	F	21	2	5·5	380	0	Pulmonary embolism	CTPA done because of protocol violation at baseline	Non-fatal pulmonary embolism
Patient 6	M	58	1	3	420	0	Pulmonary embolism	CTPA done because of protocol violation at baseline	Non-fatal pulmonary embolism
Patient 7	F	71	1	6	410	0	Pulmonary embolism	CTPA done because of protocol violation at baseline	Non-fatal pulmonary embolism

CTPA=computed tomography pulmonary angiography. * Calculated post hoc. Patients managed without CTPA.

Table 5: Diagnostic failures in patients who were managed with CTPA at baseline.

	Sex	Age (years)	YEARS score	Wells' score*	D-dimer (ng/mL)	Interval (days)	Outcome	Circumstances of outcome event	Adjudicated as
Patient 1	M	50	0	1.5	1070	34	Deep vein thrombosis	Patient had vena cava superior syndrome caused by thrombosis at the site of the pacemaker leads	Thrombosis of the vena cava superior
Patient 2	F	73	0	3	1480	69	Death	Patient died in hospital under the clinical diagnosis of a pneumonia and acute heart failure	Pulmonary embolism not excluded as cause of death
Patient 3	F	79	0	3	2400	26	Pulmonary embolism	Initiation of anticoagulation because of suspected pulmonary embolism without CTPA confirmation after hospital admission because of heart failure and COPD exacerbation	Non-fatal pulmonary embolism
Patient 4	F	82	0	0	2550	?	Death	Patient died in nursing home after hospital admission because of acute heart failure and exacerbation of COPD	Pulmonary embolism not excluded as cause of death
Patient 5	F	57	0	1	4170	12	Pulmonary embolism	Patient was known to have recurrent sarcoma of the uterus; subsegmental pulmonary embolism diagnosed postoperatively; patient died 33 days after diagnosis of pulmonary embolism during palliative care in a hospice	Non-fatal pulmonary embolism
Patient 6	F	70	0	1	2400	17	Death	Patient died after sudden collapse followed by unsuccessful resuscitation 1 day after surgery for gastric carcinoma	Pulmonary embolism not excluded as cause of death

Table 5: Diagnostic failures in patients who were managed with CTPA at baseline.

	Sex	Age (years)	YEARS score	Wells' score*	D-dimer (ng/mL)	Interval (days)	Outcome	Circumstances of outcome event	Adjudicated as
Patient 7	F	73	1	5.5	2500	6	Deep vein thrombosis	Patient was known to have leukaemia; developed thrombosis of the brachial vein after superficial thrombophlebitis related to an intravenous catheter	Deep vein thrombosis
Patient 8	M	84	1	4	5000	32	Deep vein thrombosis	Patient was known to have metastasised prostate cancer; developed deep vein thrombosis after immobilisation during admission at the hospital	Deep vein thrombosis
Patient 9	F	66	1	7	1325	43	Death	Patient had curative treatment for lung cancer and a stent placed for post-radiation stenosis of the trachea; patient died at home after sudden haemoptysis	Pulmonary embolism not excluded as cause of death
Patient 10	M	70	1	3	5000	68	Deep vein thrombosis	Patient had subclavian vein thrombus associated with intravenous catheter	Deep vein thrombosis
Patient 11	F	48	1	3	747	78	Deep vein thrombosis	Patient developed deep vein thrombosis and was diagnosed with antiphospholipid syndrome	Deep vein thrombosis

Diagnostic failures in patients who were managed with CTPA at baselineCTPA=computed tomography pulmonary angiography. COPD=chronic obstructive pulmonary disease.
* Calculated post hoc.

Figure 2 shows the management of all 3465 included patients. Of the 1651 patients who should have been managed without CTPA, the protocol was violated in 40 patients. CTPA showed pulmonary embolism in three patients who were treated with anticoagulants. These observations were considered diagnostic failures and are included in the primary outcome. Furthermore, 18 (1.1%) of 1651 patients were treated with oral anticoagulants for other reasons (i.e., eight atrial fibrillation, one superficial thrombophlebitis, and nine other reasons including idiopathic pulmonary hypertension and peripheral arterial disease) and four (0.24%) of 1651 patients were lost to follow-up. Four of the remaining 1589 patients returned with symptomatic events of venous thromboembolism (Table 4). The 3-month incidence of venous thromboembolism in patients who did not have CTPA according to the YEARS algorithm was 0.43% (seven of 1629, 95% CI 0.17–0.88) and of fatal pulmonary embolism was 0.12% (two of 1629, 0.01–0.44; Table 2). Seven other patients (0.43%) died of non-venous-thromboembolism-related causes.

Patients managed with CTPA

Of the 1358 patients in whom CTPA ruled out pulmonary embolism, 40 patients (2.95%) were treated with anticoagulants for other reasons (i.e., 20 atrial fibrillation, three superficial thrombophlebitis, one splanchnic vein thrombosis, one thrombus in the left ventricle, one high-dose thrombosis prophylaxis, one suspected but later ruled out pulmonary vein thrombosis, one vena cava superior syndrome due to mediastinal mass, and 12 other reasons including idiopathic pulmonary hypertension and peripheral arterial disease) and one patient (0.07%) was lost to follow-up. Of the 1317 remaining patients, 11 patients returned with symptomatic events of venous thromboembolism (Table 5). The 3-month incidence of venous thromboembolism was 0.84% (11 of 1317, 95% CI 0.47–1.5) and incidence of fatal pulmonary embolism was 0.30% (four of 1317, 0.12–0.78; Table 2). 85 other patients (6.5%) died of non-venous-thromboembolism-related causes.

Discussion

Our study showed that the YEARS algorithm safely excluded acute pulmonary embolism. An absolute 14% decrease in the need for CTPA was achieved, compared with the standard algorithm. The 3-month incidence of venous thromboembolism in patients who did not undergo CTPA was in line with that observed in studies using algorithms with sequential diagnostic testing and traditional two-level Wells' score, and a fixed cutoff concentration of D-dimer of 500 ng/mL: 0.43% (95% CI 0.17–0.88) in our study versus 0.34% (0.036–0.96) reported by a meta-analysis.[20] Moreover, the risk of recurrent venous thromboembolism in patients with a normal CTPA was comparable to the risk observed in previous studies using standard algorithms: 0.84% (95% CI 0.47–1.5) versus 1.2% (0.8–1.8).[22] Additionally, fatal pulmonary embolism occurred in 0.30% (95% CI 0.12–0.78) of patients in our study compared with 0.6% (0.4–1.1) in another study using standard algorithms.[22]

The advantage of the YEARS algorithm over existing algorithms is the large reduction in the need for CTPA, which reduces radiation exposure and overdiagnosis,[1-4,23] and is achieved by using variable D-dimer thresholds depending on the clinical probability. This study is the first prospective outcome study that validated a D-dimer threshold of 1000 ng/mL in patients with a low clinical probability.

While our study was ongoing, another strategy to reduce the number of CTPA has been validated in a prospective outcome study: the age-adjusted D-dimer threshold.[10] If this strategy would have been applied to our study population, the YEARS algorithm would have led to an absolute reduction of 8.7% (95% CI 6.4–11) of CTPA. The main reason for this difference is the applicability of the YEARS algorithm to patients with suspected acute pulmonary embolism in all ages, and not only in patients older than 50 years. In patients younger than 50 years, the YEARS algorithm leads to a 14% absolute reduction of CTPA. Of note, reducing the number of CTPA is very relevant for young patients, particularly women, in whom concerns have been raised about long-term effects of radiation on the risk of breast cancer.

Methodological strengths of the study include the large number of consecutive patients, the near complete follow-up, and the independent adjudication of endpoints. Furthermore, by studying a real-world cohort of patients in daily practice, we expect that the YEARS algorithm can be easily implemented outside the participating study sites, and that our data for safety and efficiency are representative for non-trial conditions. Additionally, our results are in line with the numbers reported in the initial derivation and retrospective validation study of our algorithm.[19] Of note, although haemodynamic instability was not a formal exclusion criterion of this study, we have described a cohort of only haemodynamically stable patients.

Limitations of our the study are the absence of a control group because we

did not do a randomised study and could therefore not directly compare the risk of venous thromboembolism with a control group that would have been managed with traditional algorithms. However, the low observed 3-month risk of venous thromboembolism and near complete follow-up strongly support the chosen study design. Moreover, although an independent committee evaluated and adjudicated all endpoints, autopsy was hardly scarcely done. As a consequence, it was difficult to exclude pulmonary embolism as a possible cause of death in six patients during follow-up. These patients already had or developed extensive comorbidity, or went into the final stage of a terminal illness during the follow-up period, with most of them dying in an outpatient setting. Even so, although pulmonary embolism was conservatively adjudicated as the cause of death in these patients, the recurrence rate observed in our study remained well below the safety threshold, reinforcing the validity of our findings. Furthermore, the prevalence of pulmonary embolism was higher than observed in large cohorts in North America, but lower than observed in previous studies in Europe. The study patients were relatively young, but identical to those in an earlier large diagnostic management study by our group.[7] The results of the subgroup analyses, however, confirm the validity of applying the YEARS algorithm in a patient cohort with higher pulmonary embolism prevalence of up to 30% and provide evidence of the generalisability of our findings. Lastly, there were 43 violations of the study protocol, with a D-dimer test not done in three patients and a non-indicated CTPA done in 40 patients, of which three confirmed the presence of acute pulmonary embolism. This number is comparable to that in the Christopher study, in which two of 25 unjustified CTPA examinations revealed pulmonary embolism.[7] Finally, because of the small number of patients with cancer included in our study, the safety of this algorithm for patients with suspected pulmonary embolism in the presence of cancer remains to be determined.

In conclusion, the YEARS diagnostic algorithm safely ruled out acute pulmonary embolism in patients presenting with clinically suspected pulmonary embolism, with a low risk for venous thromboembolism during a 3-month follow-up. The main advantage of the YEARS algorithm is the absolute 14% decrease in the number of CTPA examinations that is applicable to all ages and was shown consistently across subgroups.

Contributors
TvdH, FAK, JvE, SM, and MVH designed the study. TvdH, FAK, and MVH managed the study with support and input from all other authors. TvdH, FAK, and MVH analysed the data, which were interpreted by all other authors. TvdH, FAK, and MVH wrote the first draft of the manuscript, which was reviewed, modified, and approved by all other authors. All authors vouch for the accuracy and completeness of the data reported and for keeping the study to the protocol.

Declaration of interests
We declare no competing interests.

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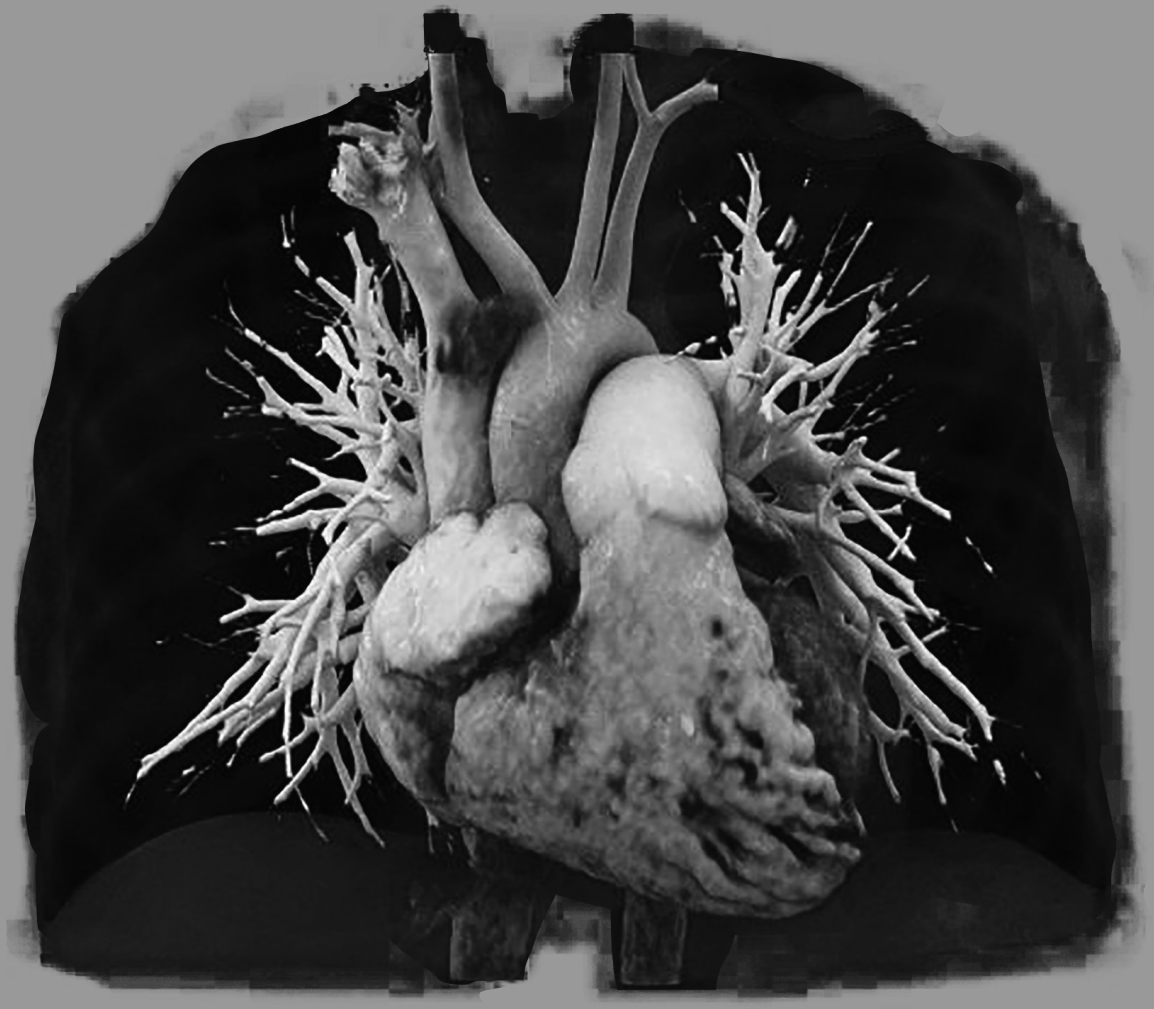
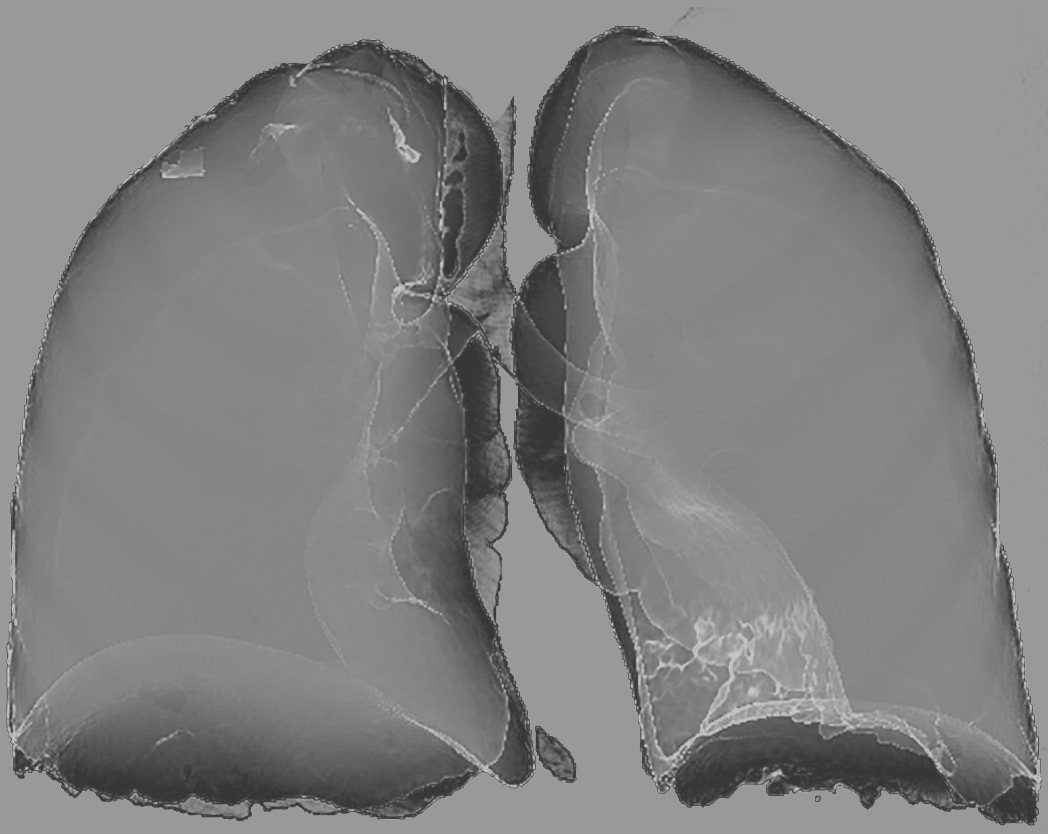


PART II

Radiology and prognosis of pulmonary embolism



Chapter 4

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

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Abstract

Background
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.

Methods
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 thrombo-embolism (VTE), hospitalisation, bleeding and adverse events were assessed over the short term (1 week and 1 month) and long term (12 months).

Results
Pulmonary trunk enlargement was the only parameter significantly associated with mortality over both the short and long term (odds ratio 4.18 (95%CI 1.04–16.8) at 1 week to OR 2.3 (95%CI 1.36–3.97) after 1 year, as well as with recurrent VTE and hospitalisation.

Conclusions
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.

Introduction

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

ESC guidelines categorize the risk of adverse outcome as high, intermediate or low. Risk calculations are based on 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, categorizing patients to intermediate-high 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 CT Pulmonary angiography (CTPA), the reference standard for the diagnosis of PE, 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-to-left ventricular ratio can be used as a predictor for mortality. As these studies did not investigate other potential predictive parameters, the unique position of the right-to-left ventricular 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 PE.

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 PE. [21] Our focus was on the evaluation of the predictive effects of baseline CTPA parameters on short and long term clinical outcome.

Materials and Methods

Patients and study design

Patient data and images were collected in the context of a large international randomized clinical trial comparing two anticoagulant regimens in patients with venous thrombo-embolism (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 or older

with acute, symptomatic venous thromboembolism (deep vein thrombosis and/or PE). 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 this was PE related. An independent committee adjudicated all predefined outcomes.

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

Data collection

All clinical and radiological data were anonymized, and centrally registered with double data entry by an independent trial data management agency. Clinical data were retrieved from the original CRFs. In all patients NT-proBNP levels were measured at baseline.

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 until high-end CT. For quality evaluation a 5-point Likert scale was used, anchored at 1 (unacceptable), 2 (poor), 3 (satisfactory), 4 (good) and 5 (excellent quality). The enhancement of the pulmonary trunk was assessed by measuring a 1 cm region of interest (ROI) and expressed in Hounsfield Units (HU).

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

A random sample of 50 patients was used to evaluate the intra-observer variability for the main study parameters, as assessed by Cohen's k-statistic. Intra-

observer agreement was graded according to Landis and Koch, with 0-20 indicating poor correlation, 20-40 moderate, 40-60 fair, 60-80 good, and 80-100 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 caval vein, azygos vein, 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. Pulmonary trunk was measured at its largest transverse diameter, the ascending aorta at the level of the carina, the caval veins were measured 2 cm from their entrance into the right atrium, and the azygos vein at its most cranial part. For the heart volume and the intrathoracic distance, the largest transverse diameters from pericardial contours and costal margins were taken.

The right-to-left ventricular (RV/LV), right-to-left ventricular short axis (RV/LVsa), and pulmonary trunk-to-aorta (TP/Ao) ratios were calculated by dividing the values of respective transverse diameters. All obtained values were then dichotomized at earlier reported thresholds (RV/LV > 1.0; RV/LVsa > 0.9; TP/A0 > 1.0, TP > 29 mm; cardiothoracic ratio > 0.50).

Ordinal measures were: bowing of the interventricular septum (negative, neutral, positive); reflux of contrast medium in the inferior caval vein (no, only into the IVC, intrahepatic < 3 cm, 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; only into the inferior caval vein was considered negative. Azygos vein reflux was considered present if it reached the crossing with the right main stem bronchus.

Events were analysed focusing on 4 time points: early (1 week and 1 month) and late (on treatment, mostly 3-6 months, and 12 month) period. For right ventricular dysfunction the reference standard was an increased value of NT-proBNP ≥ 600 pg/ml at baseline.[2]

Statistical analysis

Primary outcome for the study was mortality, secondary outcomes were recurrent VTE, hospitalization, bleeding and all adverse events. We calculated odds ratios with 95% confidence intervals (CI) 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 and specificity, PPV and NPV for mortality. Missing data were excluded from the analysis. No correction for multiple testing

was performed. Significance of differences were evaluated with two-sided p-values; a p-value < 0.05 was considered to imply statistical significance. All statistics were performed in SPSS version 23 (SPSS Inc, Chicago Ill).

Results

In the RCT, 3.481 patients had PE, 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 as e.g. insufficient coverage of heart and chest (Figure 1).

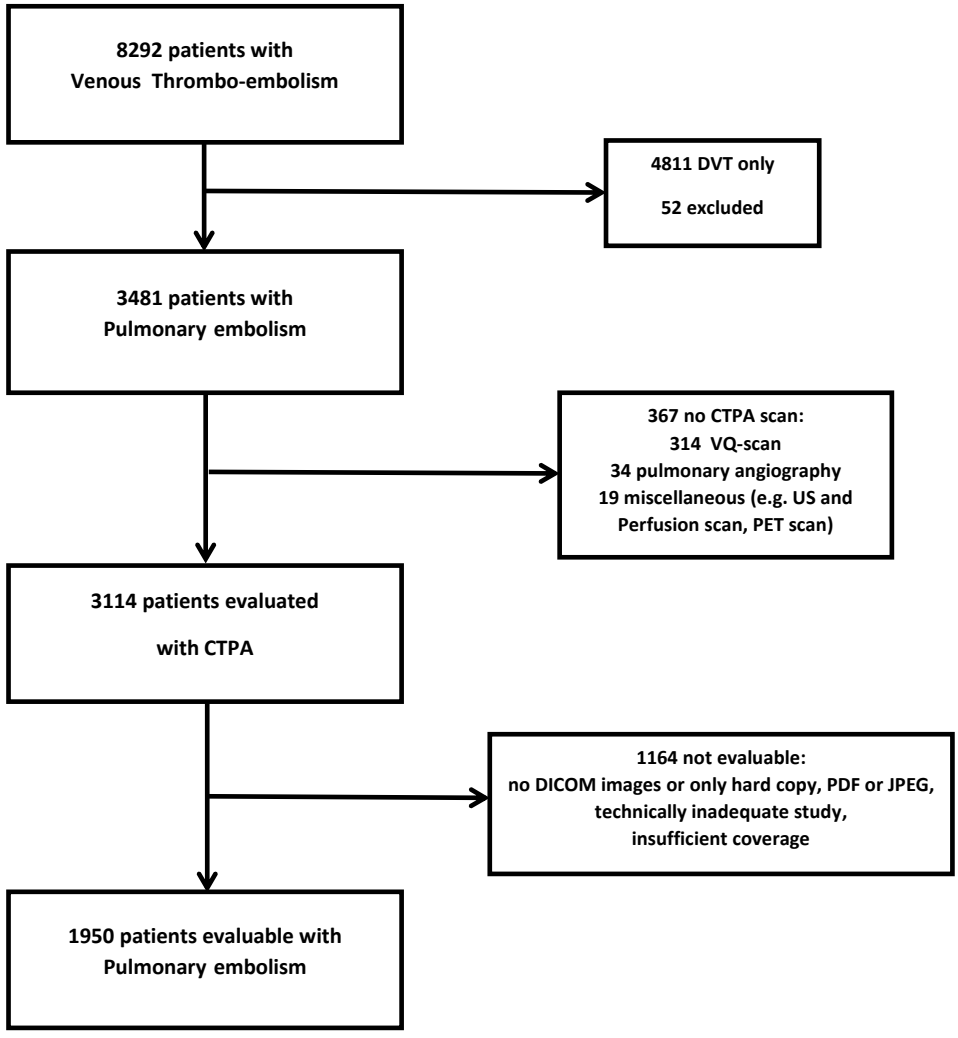

Figure 1: Inclusion flowchart.
CTPA: computed tomography pulmonary angiography; V/Q: ventilation/perfusion; PET: positron emission tomography.

To address possible selection bias, we compared baseline characteristics of included and excluded patients and found no relevant differences. One year outcomes also were not different, as mortality and recurrent VTE was 3.0 and 2.6% for the included 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. Mean age was 57 years. A summary of their characteristics is shown in Table 1. PE was provoked in 1288 patients, 456 patients had PE with concomitant DVT. In 565 patients the NT-proBNP level was > 600 pg/ml.

Table 1: Baseline characteristics.

	Included		Excluded	
	n	**% (or SD)**	**n**	**% (or SD)**
	1950	100	1531	100
Clinical				
Age (mean, SD)	57.0	16.6	57.5	16.5
Age > 65Y	714	36.6	560	36.6
Male	1049	53.8	793	51.8
Female	901	46.2	738	48.2
Weight (mean, SD)	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
US Right ventricular dimension *	37.2	28.2	31.8	22
Systolic Blood Pressure mmHg (mean, SD)	128	16.5	127	16.4
Diastolic Blood Pressure mmHg (mean, SD)	76	11	76	10.9
Heart Rate (mean, SD)	80	14	80	13.9
Respiratory Rate (mean, SD)	16	2.6	19.2	2
sPESI High Risk**	1051	53.9	990	64.8
Risk Factors				
Provoked PE	1288	66.1	959	62.6
Recent surgery, trauma, or immobilization	372	19.1	282	18.4
Sitting > 4 hours	185	9.5	121	7.9
Estrogen containing drugs use (Females)	196	21.8	103	6.7
Active cancer	56	2.9	34	2.2
Previous episodes of DVT/PE	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
CHF	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 number (%) or median (IQR), unless otherwise specified. CHF – Chronic heart failure; DVT –Deep Vein Thrombosis; PE – Pulmonary Embolus; sPESI – simplified pulmonary embolism severity index; US – Ultrasound. . * - 523/1950 included and 496/1531 excluded patients (mm: mean , SD); ** sPESI- item on O2 considered positive if patient needed oxygen administration.

Quality

Overall quality of the scans was good (3.7/5; SD=0.8). Mean Hounsfield Units in the pulmonary trunk was 325 (SD=118). Intra-observer agreement on a random sample from the complete database scored twice was excellent (kappa=0.9).

Table 2: CT Pulmonary Angiography diameters.

	n	missing	mean	SD	Min	Max	IQR
RV axial plane	1950	0	38.3	7.8	17	67	33 - 43
LV axial plane	1950	0	41.5	7.1	18	69	37 - 48
RV short axis	1906	44	39.7	7.7	20	71	34 - 45
LV short axis	1906	44	42.6	6.7	22	73	38 - 47
Aorta	1949	1	32.3	4.9	18	52	29 - 35
Pulmonary Trunk	1949	1	27.7	4.6	15	52	25 - 31
Azygos	1947	3	8.3	2.3	2	20	7 - 10
SVC	1949	1	18.9	4.1	8	33	16 - 22
RV Wall Thickness	1950	0	1.5	0.8	1	8	1 - 2
RA	1950	0	49.0	9.1	24	88	43 - 55
IVC	1942	8	22.7	4.3	8	41	20 - 25
Heart	1950	0	128.6	14.9	85	228	119 - 138
Chest	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
CTR	1950	0	0.50	0.06	0.34	0.97	0.46 - 0.54

Frequencies

The median right-to-left-ventricle ratio on CTPA was 0.89 (SD=0.27); 621 patients (32%) had a ratio >1 (Tables 2 and 3). Compared to those without RVD on CT, in patients with RV/LV>1 NT-proBNP more often was raised. The median short axis right-to-left-ventricle ratio was 0.88, of which 890 (47%) were > 0.90.

In 538 (28%) patients the septum was flattened, septal bowing occurred in 153 patients (7.9%). The pulmonary trunk was enlarged in 634 patients (33%). A pulmonary trunk/aorta ratio > 1 was present in 408 patients (20.9%). Backflow of contrast medium into the hepatic veins occurred in 261 (15%), and into the azygos vein in 445 (23%) patients.

Table 3: Frequency of abnormal cardiovascular radiological parameters.

	n	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/Aorta > 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

Short term outcomes

A summary of the investigated cardiovascular radiological parameters and their correlation with short and long term adverse events are displayed in Tables 4 and 5 (mortality) and Table 6 (recurrent VTE, hospitalization, major bleeding and all adverse events).

Table 4: Short and long term mortality: Odds ratios.

1 Week	n	no	%	present	%	OR	CI
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/Aorta > 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	n	no	%	present	%	OR	CI
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/Aorta > 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	n	no	%	present	%	OR	CI
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/Aorta > 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	n	no	%	present	%	OR	CI
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/Aorta > 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

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

1 Week	Sens	CI		Sens	CI		PPV	CI		NPV	CI
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
Pulm. 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/Aorta > 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
Cardiothor. 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	Sens	CI		Sens	CI		PPV	CI		NPV	CI
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
Pulm. 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/Aorta > 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
Cardiothor. 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	Sens	CI		Sens	CI		PPV	CI		NPV	CI
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/Aorta > 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	Sens	CI		Sens	CI		PPV	CI		NPV	CI
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
Pulm. 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/Aorta > 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
Cardiothor. 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

Table 6: 1 Month and 1 year recurrent VTE, hospitalization, major bleeding and adverse events.

Recurrent VTE

1 Month	n	no	%	present	%	OR	CI
RV/LV > 1	1950	7	53.8	6	46.2	1.84	0.62 - 5.51
RV/LVsa > 0,9	1914	5	38.5	8	61.5	1.85	0.60 - 5.67
Septal Bowing	1949	11	91.7	1	8.3	1.07	0.14 - 8.32
Septal flattening	1949	6	50.0	6	50.0	2.64	0.85 - 8.23
Aorta > 40 mm	1840	11	91.7	1	8.3	4.17	0.53 - 33.10
Pulmonary Trunk > 29 mm	1949	7	53.8	6	32.4	1.79	0.60 - 5.33
PT/Aorta > 1.0	1950	8	61.5	5	38.5	2.38	0.77 - 7.31
Cardiothoracic ratio > 0,50	1833	6	50.0	6	50.0	0.96	0.31 - 2.98
Backflow IVC	1754	7	63.6	4	36.4	0.97	0.28 - 3.34
Intrahepatic Reflux	1754	9	81.8	2	18.2	1.27	0.27 - 5.93
Backflow azygos vein	1947	12	92.3	1	7.7	0.28	0.04 - 2.16

1 Year	n	no	%	present	%	OR	CI
RV/LV > 1	1950	33	66.0	17	34.0	1.11	0.61 - 2.00
RV/LVsa > 0,9	1914	24	48.0	56	52.0	1.25	0.72 - 2.20
Septal Bowing	1949	45	91.8	4	8.2	1.05	0.37 - 2.94
Septal flattening	1949	35	71.4	14	28.6	1.05	0.56 - 1.97
Aorta > 40 mm	1840	45	95.7	2	4.3	2.05	0.48 - 8.77
Pulmonary Trunk > 29 mm	1949	35	70.0	15	30.0	0.89	0.48 - 1.64
PT/Aorta > 1.0	1950	41	82.0	9	18.0	0.83	0.40 - 1.71
Cardiothoracic ratio > 0,50	1833	25	51.0	24	49.0	0.92	0.52 - 1.62
Backflow IVC	1754	28	65.1	15	34.9	0.91	0.48 - 1.72
Intrahepatic Reflux	1754	34	79.1	9	20.9	1.53	0.73 - 3.23
Backflow azygos vein	1947	42	84.0	8	16.0	0.64	0.30 - 1.37

Hospitalisation

1 Month	n	no	%	present	%	OR	CI
RV/LV > 1	1950	62	68.9	28	31.1	0.97	0.61 - 1.52
RV/LVsa > 0,9	1914	47	52.2	43	47.8	1.06	0.69 - 1.61
Septal Bowing	1949	81	91.0	8	9.0	1.17	0.55 - 2.46
Septal flattening	1949	65	73.0	24	27.0	0.97	0.60 - 1.56
Aorta > 40 mm	1840	82	96.5	3	3.5	1.70	0.51 - 5.63
Pulmonary Trunk > 29 mm	1949	54	60.0	36	40.0	1.41	0.91 - 2.17
PT/Aorta > 1.0	1950	67	74.4	23	25.6	1.32	0.81 - 2.14
Cardiothoracic ratio > 0,50	1833	41	46.1	48	53.9	1.13	0.74 - 1.73
Backflow IVC	1754	48	61.5	30	38.5	1.07	0.67 - 1.70
Intrahepatic Reflux	1754	66	84.6	12	15.4	1.04	0.56 - 1.96
Backflow azygos vein	1947	76	84.4	14	15.6	0.61	0.34 - 1.09

1 Year	n	no	%	present	%	OR	CI
RV/LV > 1	1950	62	68.9	28	31.1	0.97	0.61 - 1.52
RV/LVsa > 0,9	1914	47	52.2	43	47.8	1.06	0.69 - 1.61
Septal Bowing	1949	81	91.0	8	9.0	1.17	0.55 - 2.46
Septal flattening	1949	65	73.0	24	27.0	0.97	0.60 - 1.56
Aorta > 40 mm	1840	82	96.5	3	3.5	1.70	0.51 - 5.63
Pulmonary Trunk > 29 mm	1949	54	60.0	36	40.0	1.41	0.91 - 2.17
PT/Aorta > 1.0	1950	67	74.4	23	25.6	1.32	0.81 - 2.14
Cardiothoracic ratio > 0,50	1833	41	46.1	48	53.9	1.13	0.74 - 1.73
Backflow IVC	1754	48	61.5	30	38.5	1.07	0.67 - 1.70
Intrahepatic Reflux	1754	66	84.6	12	15.4	1.04	0.56 - 1.96
Backflow azygos vein	1947	76	84.4	14	15.9	0.61	0.34 - 1.09

Table 6: Continued.

Major bleeding

1 Month	n	no	%	present	%	OR	CI
RV/LV > 1	1950	7	53.8	6	46.2	1.84	0.62 - 5.51
RV/LVsa > 0,9	1914	7	53.8	6	46.2	0.99	0.33 - 2.95
Septal Bowing	1949	12	92.3	1	7.7	0.98	0.13 - 7.57
Septal flattening	1949	9	69.2	4	30.8	1.17	0.36 - 3.81
Aorta > 40 mm	1840	13	100.0	0	0.0	0.99	0.99 - 1.00
Pulmonary Trunk > 29 mm	1949	6	46.2	7	53.8	2.44	0.82 - 7.28
PT/Aorta > 1.0	1950	7	53.8	6	46.2	3.27	1.09 - 9.79
Cardiothoracic ratio > 0,50	1833	3	23.1	10	76.9	3.22	0.88 - 11.73
Backflow IVC	1754	7	53.8	6	46.2	1.46	0.49 - 4.37
Intrahepatic Reflux	1754	9	69.2	4	30.8	2.57	0.78 - 8.40
Backflow azygos vein	1947	9	69.2	4	30.8	1.51	0.46 - 4.91

1 Year	n	no	%	present	%	OR	CI
RV/LV > 1	1950	18	60.0	12	40.0	1.43	0.69 - 3.00
RV/LVsa > 0,9	1914	15	51.7	14	48.3	1.08	0.52 - 2.24
Septal Bowing	1949	25	83.3	5	16.7	2.39	0.90 - 6.34
Septal flattening	1949	21	70.0	9	30.0	1.13	0.51 - 2.47
Aorta > 40 mm	1840	27	96.4	1	3.6	1.68	0.22 - 12.71
Pulmonary Trunk > 29 mm	1949	11	36.7	19	63.3	3.66	1.73 - 7.74
PT/Aorta > 1.0	1950	18	60.0	12	40.0	2.57	1.23 - 5.37
Cardiothoracic ratio > 0,50	1833	10	34.5	19	65.5	1.84	0.85 - 3.97
Backflow IVC	1754	16	57.1	12	42.9	1.28	0.60 - 2.73
Intrahepatic Reflux	1754	23	82.1	5	17.9	1.25	0.47 - 3.31
Backflow azygos vein	1947	24	80.0	6	20.0	0.84	0.34 - 2.07

All Adverse Events

1 Month	n	no	%	present	%	OR	CI
RV/LV > 1	1950	92	69.7	40	30.3	0.93	0.63 - 1.36
RV/LVsa > 0,9	1914	66	50.4	65	49.6	1.14	0.80 - 1.63
Septal Bowing	1949	121	92.4	10	7.6	0.97	0.50 - 1.89
Septal flattening	1949	96	73.3	35	26.7	0.95	0.64 - 1.42
Aorta > 40 mm	1840	120	96.8	4	3.2	1.56	0.55 - 4.44
Pulmonary Trunk > 29 mm	1949	75	56.8	57	43.2	1.63	1.14 - 2.34
PT/Aorta > 1.0	1950	96	72.7	36	27.3	1.46	0.98 - 2.17
Cardiothoracic ratio > 0,50	1833	58	45.0	71	55.0	1.19	0.83 - 1.70
Backflow IVC	1754	71	61.2	45	38.8	1.09	0.74 - 1.60
Intrahepatic Reflux	1754	94	81.0	22	19.0	1.37	0.84 - 2.22
Backflow azygos vein	1947	110	83.3	22	16.7	0.66	0.41 - 1.05

1 Year	n	no	%	present	%	OR	CI
RV/LV > 1	1950	92	69.7	40	30.3	0.93	0.63 - 1.36
RV/LVsa > 0,9	1914	66	50.4	65	19.6	1.14	0.80 - 1.63
Septal Bowing	1949	121	92.4	10	7.6	0.97	0.50 - 1.89
Septal flattening	1949	96	73.3	35	26.7	0.95	0.64 - 1.42
Aorta > 40 mm	1840	120	96.8	4	3.2	1.56	0.55 - 4.44
Pulmonary Trunk > 29 mm	1949	75	56.8	57	43.2	1.63	1.14 - 2.34
PT/Aorta > 1.0	1950	96	72.7	36	27.3	1.46	0.98 - 2.17
Cardiothoracic ratio > 0,50	1833	58	45.0	71	55.0	1.19	0.83 - 1.70
Backflow IVC	1754	71	61.2	45	38.8	1.09	0.74 - 1.60
Intrahepatic Reflux	1754	94	81.0	22	19.0	1.37	0.84 - 2.22
Backflow azygos vein	1947	110	83.3	22	16.7	0.66	0.41 - 1.05

During the first month 29 adverse events occurred, including 18 deaths, 12 recurrent VTEs, 13 bleedings. There were 26 hospitalisations.

During the first month 29 adverse events occurred, including 18 deaths, 12 recurrent VTEs, 13 bleedings. 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, CI=1.04-16.8; p=0.028, Table 2 and 3). The odds ratio at 1 month was lower and not statistically significant (OR 2.30, CI=0.97-5.45; p=0.051). All other parameters (RV/LV ratio, RV/LV short axis, septal bowing, pulmonary trunk/aorta ratio, cardiothoracic ratio and backflow to hepatic veins or azygos vein) were not significantly associated with mortality. Of the 9 patients that died within the first week, 6 (66.7%) had an enlarged pulmonary trunk. In total 18 patients died within one month, an enlarged pulmonary trunk was present in half of these 18 patients. In patients who survived one week or subsequently one month an enlarged pulmonary trunk was present in 628 and 625 patients (32.4%, p = 0.028 respectively 32.4%, p=0.11).

An enlarged pulmonary trunk diameter was also associated with recurrent VTE (OR 5.22, CI=1.01-26.7; p=0.028) at 1 week. Here also the odds ratio was lower and not significant at 1 month (1.8, CI=0.6-5.3; p=0.051). None of the evaluated radiological parameters, apart from enlarged pulmonary trunk diameter was associated with hospitalization. Sensitivities were low for all the researched parameters, as were the specificities and positive predictive values; however, all parameters showed a high negative predictive value.

Long term outcomes

The median on treatment time was 215 days (IQR 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 and 90 were hospitalized.

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 resp. 0.001). A TP/Aorta ratio > 1.0 was also significantly associated with mortality during treatment (p=0.002; Table 4) but not for the complete period (p=0.055). Of the 11 patients with interstitial lung disease, 2 patients that had an enlarged pulmonary trunk died. In 43 patients with a history of pulmonary hypertension, 21 had an enlarged pulmonary trunk of which 2 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 on both short and long term was associated with increased mortality and the risk of recurrent VTE and hospitalization.

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 in literature many parameters have been evaluated, 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 generally are preferred given the simplicity of analysis.[25] We evaluated observer agreement only for the main continuous variables, and not for the 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. Also, echocardiography can 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 randomized controlled trial do not necessarily reflect all those presenting in regular practice, and our results cannot be unconditionally generalized to those with exclusion criteria for the trial, such as hemodynamically unstable patients, patients with a limited life expectancy and pregnant women.

How do our findings fit into the current assessment of prognosis in patients with acute PE? 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 like an enlarged pulmonary trunk would probably facilitate such processes. In recent ESC guidelines primary categorization into low, intermediate or high risk is based on sPESI. In 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 are ranging from 0.9 until 1.8.[26]

Several studies have reported that RVD on CTPA is an indicator of the risk of adverse events.[13,27] Many studies however had a single centre, retrospective design, with short follow up and surrogate outcomes. As such, they have intrinsic methodological limitations that weaken their validity and generalizability. The larger series have shown conflicting results, either confirming or denying that right-to-left ventricular ratio is associated with an increased mortality.[14,28,29,30]

A recent systematic review stated that although RVD assessed by CT showed an association with an increased risk of mortality in patients with hemodynamically stable PE, it resulted in only small increases in the ability to classify risk.[31] Although additional publications confirmed this finding,[31,32] apparently, RV 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 RV dysfunction seems common, reflecting on 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 randomized clinical trial rather than a prospective cohort study of consecutive patients, and thus could reflect different study populations. Our finding that right-to-left ventricular 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 –recurrent VTE, hospitalization, 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 PE, for acute PE findings are contradictory, as an association with increased risk was not always observed in previous studies.[36-40] However, most of these studies were retrospective with limited number of patients. The assessment however is rather easy and not as time consuming as e.g. clot obstruction scores, 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 negative predictive value indicates that it may be useful for identification of those patients that have a low risk for adverse events who will not need for aggressive therapy, and can be discharged home early. However, for prognostication towards high risk measures like admission to ICU or thrombolysis a multifactorial risk-benefit analysis would be necessary.

One intriguing point is the apparent discrepancy between the relative high number of RVD observed in the earlier published studies, and the fortunately relatively low mortality percentages. In other words: although many patients are categorized as high risk, be it from radiological, biochemical, or combined, this does not translate in the same manner in mortality and adverse events. From this point it should be logical to better 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 PA diameter should be considered explorative findings, done in a trial population. The

findings are promising with regard to predict poor prognosis/mortality but should be confirmed in consecutive cohorts. Measurement of PA is quicker to perform than a RV/LV ratio assessment, and hence easier to integrate/accept/adopt in daily practice. Incorporation of enlarged pulmonary trunk diameters 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 like mortality, recurrent VTE, bleeding, hospitalization. Only an enlarged pulmonary trunk diameter was associated with an increased risk of mortality, recurrent VTE both on short as well as long term.

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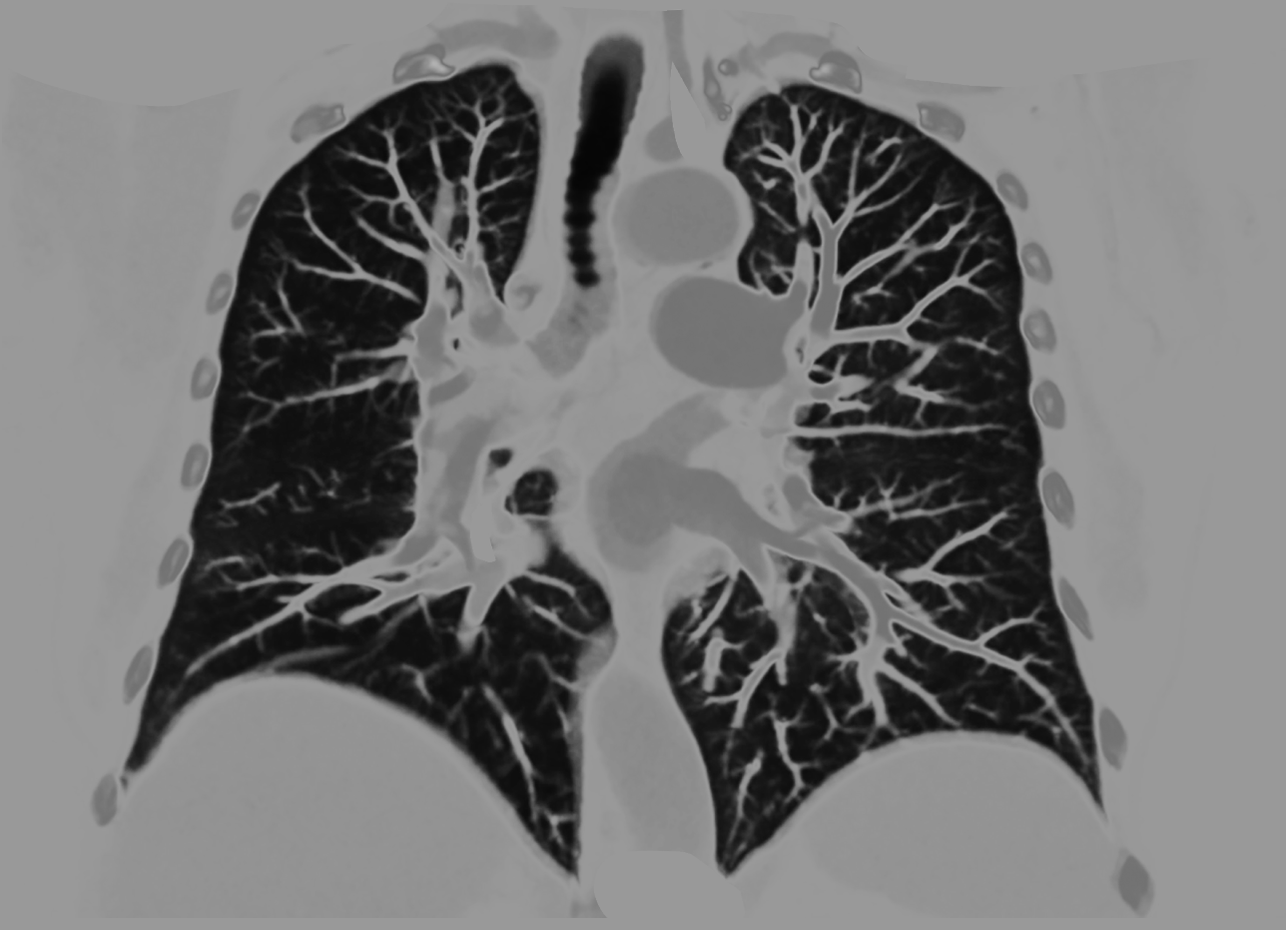

Chapter 5

Prognostic characteristics and body mass index in patients with pulmonary embolism: does size matter?

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Abstract

Background
The aim of this study was to explore the impact of body mass index (BMI) on prognostic indicators and clinical outcomes in patients with pulmonary embolism.

Methods
Patients with pulmonary embolism from the Hokusai venous thromboembolism (VTE) randomised clinical trial that compared two anticoagulant regimens were followed up for 1 year (n=1911). Patients were analysed with regard to World Health Organisation (WHO) BMI categories at baseline (underweight (<18.5), normal (18.5 to < 25), overweight (25 to <30), obese I (30 to <35), obese II (35 to <40), and obese III (≥40). Clinical and radiological prognostic characteristics for right ventricular dysfunction and adverse events were assessed with normal weight as reference. Clinical outcomes were mortality, recurrent VTE, hospitalisation, bleeding and overall adverse events.

Results
The relationship between BMI categories and both prognostic parameters and clinical outcomes showed U-shaped curves. Adjusted odds ratios (aOR) were highest in patients who were grade III obese for both clinical parameters (N-terminal pro-brain natriuretic peptide (NT-proBNP) >600 and simplified pulmonary embolism severity index (sPESI) ≥1; 2.9 and 1.6), and radiological parameters (pulmonary trunk>29 mm, right-to-left ventricular ratio>1.0, and central emboli; aOR = 4.3, 2.1 and 2.3). Bleeding was observed more frequently in the higher categories of obesity. In patients who were underweight, for NT-proBNP>600 and sPESI≥1 the aOR were 2.6 and 2.5, respectively; however, no major bleeding occurred in this category.

Conclusions
Several clinical and radiological prognostics characteristics and right ventricular dysfunction in pulmonary embolism are not evenly distributed among BMI categories. This is reflected in a trend toward worse outcomes in patienst who are overweight and underweight.

Introduction

Patients with pulmonary embolism at extremes of body weight pose specific clinical considerations with regard to diagnosis, treatment and prognosis. Obese patients are at increased risk for both deep vein thrombosis (DVT) and pulmonary embolism (PE) compared to patients with a normal Body Mass Index (BMI - weight in kilograms divided by height in meters squared). [1-3] This risk increases with increasing body mass index.[4,5] Potential causal mechanisms for increased risk of venous thrombosis by obesity are venous stasis, chronic inflammation, adipokines, increased coagulation activity, decreased fibrinolytic activity, and procoagulant microparticles.[6]

Regarding treatment, it is debated whether the extremes in body weight should receive modified treatment regimens.[7] Because of limited clinical data available for obese patients, the International Society on Thrombosis and Haemostasis (ISTH) guidance document advises against use of direct oral anticoagulants in patients with a body weight higher than 120 kg or a BMI higher than 40.[8] Although currently unfractioned heparin with aPTT monitoring for patients with severe obesity is recommended,[9] an expert panel recently expressed the urgent need for data on heparin regimens in all obese patients.[7] This becomes even more prominent with the alarming increase in overweight people worldwide.[10]

Remarkably, with regard to diagnosis and prognosis, knowledge of the impact of BMI on clinical presentation and clot characteristics and burden is even more limited. Unfortunately, even in large randomized trials on efficacy of anticoagulation in patients with venous thrombo-embolism (VTE) no subgroup analysis on body weight or BMI has been performed to provide methodologically robust data on this subject. Therefore, how this could reflect on work up and prognosis is not exactly known. Should BMI be a modifier for individual patient tailored care? Does body size matter?

Our hypothesis was that in patients with pulmonary embolism clot characteristics and prognosis are different at the extremes of BMI. The aim of this study was to explore the impact of body size on presentation, prognostic characteristics and outcome of patients with pulmonary embolism in CT pulmonary angiography. Therefore, we studied in a large cohort of patients with pulmonary embolism established clinical and radiological parameters associated with right ventricular dysfunction and mortality, and stratified them according to BMI categories.

Materials and Methods

Patients and study design

This present study is a post hoc analysis of the Hokusai-VTE study, a large international randomized clinical trial in which two anticoagulant regimens were

compared in patients with venous thrombo-embolism (ClinicalTrials.gov identifier: NCT00986154).[11,12] In short, eligible patients were aged 18 years or older and had acute symptomatic deep vein thrombosis and/or pulmonary embolism. Patients were excluded in case of contraindications to heparin or warfarin, severely impaired renal function or pregnancy. The Hokusai VTE trial did not exclude patients based on body weight. The institutional review board at each participating centre approved the general study protocol, and all patients provided written informed consent. Follow-up was 12 months, covering 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 this was PE related. An independent committee adjudicated all predefined outcomes. In the trial, in the two treatment arms there was no difference in hazard ratio between patients with a body weight of 100 kg or less, and those over 100 kg; no further detailed analyses were performed for high body weight groups.[11] For the current analysis all patients with PE, either with or without DVT, were included. Excluded were patients not evaluated by CT pulmonary angiography (CTPA), or when images were not available in DICOM format or inaccessible for reading in the image viewer.[12]

Data collection

All clinical and radiological data were anonymized, and centrally registered with double data entry by an independent trial data management agency. Clinical data were retrieved from the original CRFs. In all patients NT-proBNP levels were measured at baseline. All data for the present analysis had been collected and assessed prospectively before the trial data lock.

CT-data were acquired from the local participating centres, using local settings and protocols, with a wide variety of CT-scanners, from basic until high-end CT. Anonymized patient images from the central database were evaluated by a radiologist (LB) with 12 years of experience in cardiovascular imaging supported by a dedicated research assistant, both blinded for patient details and clinical information. For image reading a commercially available image viewer was used (eFilm Workstation for Windows Version 3.4.0, Build 10, Merge Technologies Inc., Milwaukee, USA). Images were primarily read in axial sections with additional support of multiplanar reformatting (MPR). Standard pulmonary angiography, mediastinal and lung parenchyma window settings were used, with individual adaptation if deemed necessary. Data were registered on a specially designed CRF.

We investigated body size according to the body mass index categories as classified by the World Health Organization (WHO): underweight (<18.5), normal (18.5 to < 25), overweight (25 to <30), obese I (30 to <35), obese II (35 to <40), and obese III (≥40).

Study outcomes: prognostic characteristics and clinical outcomes

Both clinical and radiological prognostic characteristics for right ventricular dysfunction and adverse events were assessed. For baseline NT-proBNP a value of ≥ 600 pg/ml at baseline was considered abnormal;[9] for sPESI calculation the arterial oxyhaemoglobin saturation <90% was not registered; this item was considered positive if patient required oxygen administration. The following radiological parameters for right ventricular dysfunction (RVD) were assessed: transverse diameter of right and left ventricle (axial view) and pulmonary trunk; bowing of the interventricular septum (negative, D-shaped/neutral, positive) and reflux of contrast medium in the intrahepatic veins). For the ventricular diameters, the largest cross-sectional distance between ventricular surfaces was taken. Pulmonary trunk was measured at its largest transverse diameter. All continuous variables were noted in millimetres where applicable. The right-to-left ventricular (RV/LV) ratios were calculated by dividing the values of respective transverse diameters. The obtained values were then dichotomized at regular used thresholds (RV/LV > 1.0; pulmonary trunk (PT) > 29 mm). 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 contrast medium reflux was into the intrahepatic veins; only into the inferior caval vein was considered negative.

Clinical outcomes for the study were mortality, recurrent VTE, hospitalisation, bleeding and overall adverse events. Outcome events were analysed after a follow up of one year.

Statistical analysis

Descriptive statistics are displayed as mean ± standard deviation (SD) for normally distributed variables and median ± interquartile ranges (IQR, 25th to 75th percentile) for not normally distributed variables. For comparison on binary outcomes the Chi-square test for dichotomous variables were used. Between the groups categorical variables were compared using the Chi-square test for trend; for continuous data by Students T test or Mann-Whitney U test if non-normally distributed. A p-value < 0.05 was considered statistical significant. We used logistic regression models to estimate odds ratios (OR) with 95% confidence intervals (CI) to investigate the association between the outcome variables and the BMI categories. In addition, where appropriate, we adjusted these analyses for age and sex. All statistical analyses were performed in SPSS version 23 (SPSS Inc, Chicago Ill), figures were designed in GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA.

Results

Baseline characteristics are displayed in Table 1. The initial study group consisted of 1950 patients with pulmonary embolism. In all 1950 patients baseline weight was available, but in 39 patients (2.0%) body height was not known. Hence baseline BMI could be calculated in 1911 patients, comprising the study group for further analyses. Of these 1911, 493 (25.8%) patients had a normal BMI (Table 2). The majority of patients, i.e. 1389 (72.7%) had a BMI>25 and obesity (BMI>30) was present in 670 (35.1%). A small proportion, i.e. 29 (1.5%) patients was underweight.

Table 1: Baseline characteristics.

	Total		**BMI <18.5**		**BMI 18.5-24.99**		**BMI >25**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Included	1911	100	29	1.5	493	25.8	1389	72.7
Clinical								
Age (mean, SD)	56.9	16.6	56.6	23.9	55.7	18.8	57.3	15.5
Weight (mean, SD)	84.6	20.1	49.9	8.0	66.7	10.0	91.7	18.2
SBP mmHg (mean, SD)	128	16.5	118	15.4	126	16.8	129	16.3
DBP mmHg (mean, SD)	76	11.0	69	8.8	74	10.6	77	11.1
Heart Rate (mean, SD)	80	14.2	85	10.0	80	14.7	80	14.1
Age <50Y	629	32.9	11	37.9	190	38.5	428	30.8
Age > 65Y	696	36.4	14	48.3	183	37.1	499	35.9
Weight < 60 kg	187	9.8	24	82.8	144	29.2	19	1.4
Current alcohol use	741	38.8	10	34.5	199	40.4	532	38.3
Smoking	834	43.6	15	51.7	235	47.7	584	42.0
NT-proBNP > 600	504	27.3	12	42.9	115	23.9	377	28.2
sPESI* High Risk ≥1	1028	53.8	21	72.4	251	50.9	756	54.4
Unprovoked PE	1266	66.2	21	72.4	327	66.3	918	66.1
Concurrent DVT	447	23.4	3	10.3	102	20.7	342	24.6
Risk Factors								
Recent surgery, trauma, or immobilisation	364	19.0	5	17.2	76	15.4	283	20.4
Sitting > 4 hours	182	9.5	1	3.4	58	11.8	123	8.9
Oestrogen drugs use	193	10.1	8	27.6	73	14.8	112	8.1
Previous DVT/PE	405	21.2	1	3.4	85	17.2	319	23.0
Thrombophilia	94	4.9	1	3.4	32	6.5	61	4.4
Concomitant Disease History								
Hypertension	793	41.5	11	37.9	136	27.6	646	46.5
Diabetes	194	10.2	3	10.3	18	3.7	173	12.5
Cardiovascular Disease	306	16.0	6	20.7	82	16.6	218	15.7
Chronic Heart Failure	34	1.8	2	6.9	6	1.2	26	1.8
Cerebrovascular Disease	71	3.7	1	3.4	20	4.1	50	3.6
Stroke	34	1.8	1	3.4	11	2.2	22	1.6
Renal Disease	128	6.7	2	6.9	30	6.1	96	6.9
Hepatic Disease	207	10.8	3	10.3	47	9.5	157	10.8
Pulmonary Disease	391	20.5	12	41.4	91	18.5	288	20.7
COPD	100	5.2	7	24.1	35	7.1	58	4.2
Pulmonary hypertension	43	2.3	2	6.9	6	1.2	35	2.5
Cancer	221	11.6	6	20.7	65	13.2	150	10.8

Data are number (%) or median (IQR), unless otherwise specified. CHF – Chronic heart failure; DBP – Diastolic Blood Pressure; DVT –Deep Vein Thrombosis; PE – Pulmonary Embolus; SBP – Systolic Blood Pressure; US – Ultrasound. * sPESI- item on O2 considered positive if patient needed oxygen administration.

Table 2: Distribution of patients according to WHO categories.

Total BMI	1911	%
<18,5	29	1.5
18,5-24,9	493	25.8
25-29,9	717	37.5
30-34,9	414	21.7
35-39,9	154	8.1
≥40	104	5.4
Complete	**1950***	

* Body height was not available in 39 (2.0%) of 1950 patients, so in these patients BMI could not be calculated.

With regard to risk factors for VTE, 372 patients (19.5%) had undergone recent surgery and 415 patients (21.7%) had a history of VTE. Arterial cardiovascular risk factors (e.g. smoking, hypertension) were present in a substantial proportion of patients: hypertension was present in 810 (42.4%) patients, 199 (10.4%) had diabetes mellitus, and 314 (16.4%) patients had a history of cardiovascular disease.

The overall trend, clinical, radiological and outcome parameters are displayed in Figure 1 for all patients according to the BMI categories. Both patterns for NT-proBNP, sPESI and enlarged pulmonary trunk showed a U-shaped curve, with lowest percentages in the normal BMI-range, and were higher for overweight as well as underweight patients. Other parameters like enlarged right-to-left ventricular ratio and central clot location showed a direct association with increasing BMI.

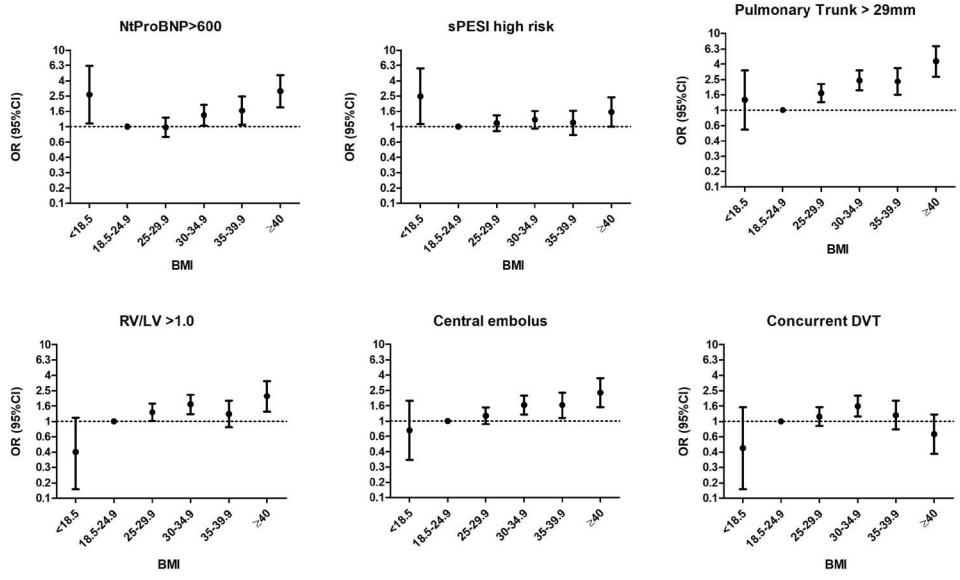

Figure 1:
Association between body mass index (BMI) categories and clinical and radiological parameters with BMI 18.5–24.9 kg·m−2 as a reference. Odds ratios for a) N-terminal pro-brain natriuretic peptide, b) high-risk simplified pulmonary embolism severity index score, c) pulmonary trunk >29 mm, d) right/left ventricular diameter ratio >1.0, e) central embolism and d) concurrent deep venous thrombosis are shown. Error bars present 95% confidence intervals.

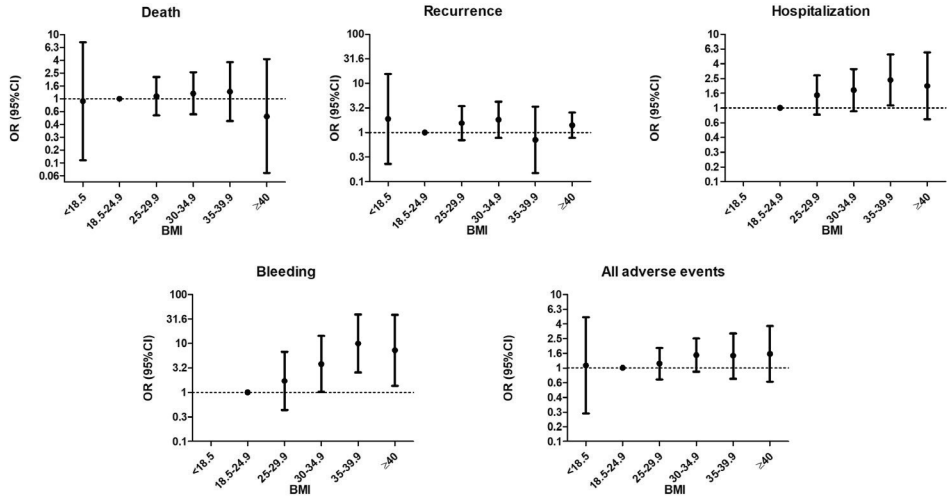

Figure 2:
Association between body mass index (BMI) categories and outcomes with BMI 18.5–24.9 kg·m−2 as reference. Odds ratios for a) death, b) recurrent venous thromboembolism, c) hospitalisation, d) bleeding and e) all adverse events are shown. Error bars represent 95% confidence intervals.

Table 3: Odds ratios for clinical and radiological parameters and outcomes according to BMI categories.

BMI	N (%)	OR	OR*
NTProBNP >600			
<18.5	12(42.8)	2.38 (1.09-5.18)	2.62 (1.10-6.23)
18.5-24.9	115 (24.0)	1 (reference)	1 (reference)
25.0-29.9	162 (23.4)	0.97 (0.74-1.28)	0.98 (0.74-1.31)
30.0-34.9	124 (31.2)	1.44 (1.07-1.94)	1.41 (1.03-1.93)
35.0-39.9	50 (34.0)	1.64 (1.10-2.44)	1.62 91.06-2.48)
>40	41 (41.0)	2.21 (1.41-3.46)	2.90 (1.79-4.70)
sPESI high risk			
<18.5	21 (72.4)	2.52 (1.10-5.80)	2.49 (1.08-5.75)
18.5-24.9	251 (51.0)	1 (reference)	1 (reference)
25.0-29.9	375 (52.4)	1.06 (0.84-1.33)	1.11 (0.88-1.40)
30.0-34.9	230 (55.7)	1.21 (0.93-1.57)	1.23 (0.95-1.60)
35.0-39.9	84 (54.5)	1.15 (0.80-1.66)	1.13 (0.78-1.62)
>40	66 (63.5)	1.67 (1.08-2.58)	1.55 (1.00-2.41)
Pulmonary trunk > 29 mm			
<18.5	8 (27.6)	1.39 (0.60-3.22)	1.36 (0.56-3.28)
18.5-24.9	106 (21.5)	1 (reference)	1 (reference)
25.0-29.9	232 (32.4)	1.75 (1.34-2.28)	1.66 (1.27-2.19)
30.0-34.9	168 (40.7)	2.50 (1.87-3.34)	2.44 (1.81-3.28)
35.0-39.9	59 (38.3)	2.26 (1.53-3.34)	2.37 (1.59-3.53)
>40	49 (47.1)	3.24 (2.09-5.04)	4.32 (2.73-6.83)
RV/LV>1.0			
<18.5	4 (13.8)	0.45 (0.15-1.31)	0.40 (0.13-1.12)
18.5-24.9	130 (26.4)	1 (reference)	1 (reference)
25.0-29.9	231 (32.3)	1.33 (1.03-1.71)	1.31 (1.01-1.70)
30.0-34.9	157 (38.0)	1.71 (1.29-2.27)	1.66 (1.24-2.21)
35.0-39.9	48 (31.2)	1.26 (0.85-1.88)	1.24 (0.83-1.85)
>40	41 (39.4)	1.81 (1.17-2.81)	2.12 (1.34-3.33)

Table 3: Continued.

BMI	N (%)	OR	OR*
Central Embolus			
<18.5	7 (24.1)	0.78 (0.33-1.86)	0.75 (0.31-1.82)
18.5-24.9	143 (29.1)	1 (reference)	1 (reference)
25.0-29.9	234 (32.7)	1.19 1.19-0.92)	1.17 (0.91-1.50)
30.0-34.9	167 (40.4)	1.66 (1.26-2.19)	1.61 (1.22-2.13)
35.0-39.9	62 (40.3)	1.65 (1.30-2.40)	1.61 1.10-2.36)
>40	49 (47.1)	2.17 1.41-3.35)	2.34 (1.51-3.62)
Concurrent DVT			
<18.5	3 (10.3)	0.44 (0.13-1.49)	0.45 (0.13-1.52)
18.5-24.9	102 (20.7)	1 (reference)	1 (reference)
25.0-29.9	170 (23.7)	1.19 (0.90-1.57)	1.15 (0.87-1.52)
30.0-34.9	121 (29.3)	1.58 (1.17-2.15)	1.57 (1.16-2.14)
35.0-39.9	36 (23.4)	1.17 (0.76-1.80)	1.20 (0.78-1.85)
>40	15 (14)	0.64 (0.36-1.16)	0.68 (0.38-1.23)
Death			
<18.5	1 (3.4)	1.22 (0.16-9.61)	0.92 (0.11-7.59)
18.5-24.9	14 (2.8)	1 (reference)	1 (reference)
25.0-29.9	22 (3.1)	1.08 (0.55-2.14)	1.09 (0.55-2.18)
30.0-34.9	14 (3.4)	1.20 (0.56-2.54)	1.21 (0.57-2.60)
35.0-39.9	5 (3.2)	1.15 (0.41-3.23)	1.29 (0.45-3.71)
>40	1 (1.0)	0.33 (0.04-2.55)	0.53 (0.07-4.18)
Recurrent VTE			
<18.5	1 (3.4)	1.92 (0.24-15.67)	1.90 (0.23-15.57)
18.5-24.9	9 (1.8)	1 (reference)	1 (reference)
25.0-29.9	21 (2.9)	1.62 (0.74-3.57)	1.55 (0.70-3.42)
30.0-34.9	14 (3.4)	1.88 (0.81-4.40)	1.82 (0.78-4.25)
35.0-39.9	2 (1.3)	0.71 (0.15-3.30)	0.71 (0.15-3.34)
>40	3 (2.9)	1.59 (0.42-5.99)	1.41 (0.78-2.53)
Hospitalisation			
<18.5	0 (0)	0	0
18.5-24.9	16 (3.3)	1 (reference)	1 (reference)
25.0-29.9	34 (4.7)	1.48 (0.81-2.72)	1.49 (0.81-2.75)
30.0-34.9	23 (5.6)	1.75 (0.91-3.37)	1.74 (0.90-3.35)
35.0-39.9	11 (7.1)	2.29 (1.04-5.04)	2.39 (1.08-5.32)
>40	5 (4.8)	1.50 (0.54-4.20)	1.99 (0.70-5.67)
Bleeding			
<18.5	0 (0)	0	0
18.5-24.9	3 (0.6)	1 (reference)	1 (reference)
25.0-29.9	7 (1.0)	1.61 (0.41-6.25)	1.72 (0.44-6.74)
30.0-34.9	9 (2.2)	3.63 (0.98-13.50)	3.82 (1.02-14.34)
35.0-39.9	8 (5.2)	8.93 (2.34-34.10)	9.99 (2.56-38.92)
>40	3 (2.9)	4.84 (0.96-24.33)	7.26 (1.37-38.32)
All Adverse Events			
<18.5	2 (6.9)	1.23 (0.279-5.43)	1.08 (0.24-4.90)
18.5-24.9	28 (5.7)	1 (reference)	1 (reference)
25.0-29.9	47 (6.6)	1.16 (0.72-1.89)	1.15 (0.70-1.87)
30.0-34.9	35 (8.5)	1.53 (0.92-2.57)	1.50 (0.89-2.52)
35.0-39.9	12 (7.8)	1.40 (0.69-2.83)	1.47 (0.71-2.94)
>40	7 (6.7)	1.20 (0.51-2.82)	1.55 (0.65-3.72)

Odds ratios for clinical and radiological parameters (3a) and outcomes (3b) according to BMI categories (BMI <18.5 (29 patients); 18.5-24.9 (492); 25.0-29.9(716); 30.0-34.9(413); 35.0-39.9 (154) and >40 (104 patients), with BMI 18.5-24.9 as reference. Proportion was calculated per BMI category with follow-up up to 12 months. BMI -Body Mass Index; DVT – deep venous thrombosis; PT – pulmonary trunk, sPESI – simplified pulmonary embolism severity index, RV/LV – right-to-left ventricular ratio; VTE – venous thrombo-embolism * Adjusted for age and sex; sPESI only adjusted for sex.

The associations between the prognostic characteristics and BMI categories are shown in Table 3. There was an apparent exposure-response relationship between BMI category and the proportion of patients with NT-ProBNP>600, sPESI high risk, pulmonary trunk > 29 mm, RV/VL>1 and presence of central emboli. The OR for NT-ProBNP>600 increased up to 2.90 (95%CI 1.79-4.70) at BMI>40. For the other prognostic characteristics the ORs for BMI>40 compared to normal BMI were OR 4.32 (95%CI 2.73-6.83) for pulmonary trunk>29mm, 2.12 (95%CI 1.34-3.33) for RV/LV>1.0, 2.34 (95%CI 1.51-3.62) for central location of the emboli and 1.55 (95%CI 1.00-2.41) for high sPESI risk category.

There were 57 deaths, 50 recurrent VTEs, 89 hospitalisations, 30 major bleedings, and 131 adverse events over all reported during one year. For the clinical outcomes an exposure-response relation for risk of hospitalisation, bleeding and adverse events was observed, with the risk of the event increasing with BMI (Table 3). The highest risk In the BMI category >40 was for bleeding (OR 7.26, 95%CI 1.37-38.3). Also for the other clinical outcomes, mortality and recurrent VTE, an increase for the higher BMI categories was observed, as well as for the overall risk of adverse events (Figure 1). Interestingly, risk of hospitalisation and major bleeding were not higher in patients with underweight, although the 95% CI for this point estimate was wide.

Discussion

We demonstrated that prognostic characteristics of pulmonary embolism on CTPA are associated with BMI in a category-dependent manner, with highest risk at the extremes of BMI. Also for the most important clinical outcomes mortality and VTE recurrence an unfavourable trend for the high BMI categories was present, though not statistically significant. Our study highlights the potential importance of assessing BMI as a prognostic indicator when diagnosing and treating patients with pulmonary embolism. Contrary to many other determinants, common demographics like body size and height are easily obtainable, without any effort or costs, for regular use in daily clinical practice.

A strength of our study is the prospective and rigorous collection of all included data as part of a large international randomized clinical trial. Both imaging data and clinical outcomes were assessed before the data lock and the assessors were blinded for treatment and outcome. We evaluated a broad range of parameters in order to provide a complete, integral picture rather than limiting to a single factor with concurrent restricted impact.

Our study has some limitations. Despite the fact that the number of all included patients is large, the relatively low frequency of events with associated statistical uncertainty prohibits us from drawing firm or definite conclusions, even more so

for the underweight category. We did not further adjust for potential confounders like comorbidities and risk factors, as the power to do so was limited by the relatively low number of outcome events. Because of the paucity of literature on this increasingly prominent issue however, we nevertheless think it of contributing value, as an incentive for further exploration of this topic. Also, we are aware that patients included in a randomized controlled trial do not necessarily reflect all those presenting in daily clinical practice, and our results cannot be unconditionally generalized to those with exclusion criteria for the trial, such as hemodynamically unstable patients and patients with a limited life expectancy. Lastly, we only used correlation with BMI categories. Although BMI as an obesity measure has been questioned, it is still the most widely used body-weight measurement, and easy to obtain. Apart from BMI also other measures for body size exists, such as body fat percentage, waist circumference or waist hip ratio (not registered in the trial).[5]

A classic U- or J-shaped curve for BMI categories has been reported in a wide variety of pathological and physiological conditions such as cardiovascular and respiratory disease, stroke, and cancer.[10,13,14] Our findings suggest that a similar pattern applies to prognostic indicators in patients with pulmonary embolism, with lowest prevalence of many investigated parameters for the normal weight group, and a higher prevalence at the extremes of body weight. BMI not only was predictive in several clinical and radiological prognostic characteristics associated with RV dysfunction, but also in a similar way with the relevant clinical outcomes. We are not aware of other studies that explored the association between a broad range of prognostic characteristics of pulmonary embolism and BMI categories; only for NT-proBNP one study reported that obese patients in general have reduced concentrations, despite higher left ventricular end diastolic pressures.[15] As such, it is even more interesting that in patients with pulmonary embolism, NT-proBNP levels tended to be higher in higher BMI categories. Notably, in obese patients adaptations in cardiac structure and function, more specifically differences of RV morphology could develop.[16] These alterations could e.g. be induced by increased RV afterload, increased blood volume, hormonal effects, or direct obesity-related myocardial effects.[17]

How do our findings fit into the current assessment of overweight patients with acute PE? In the Framingham study, women who had a fatal PE had higher body weight than those who died of other causes.[18] On the contrary, several investigators have reported a higher incidence of VTE in obese patients but a lower rate of mortality compared to non-obese patients, even despite the fact that obese patients have more comorbidities, a phenomenon referred to as the obesity paradox.[19-23] However, this is also in contrast with large autopsy studies where in each category of above-normal BMIs obese individuals were more likely to die from pulmonary embolism.[24,25]

Complex relationships exist between body mass indicators, metabolic function

and cardiovascular risk. Possibly, clot composition in obese individuals might be different from those with normal weight.[26] It has been hypothesized that these could become more resistant to fibrinolysis because of higher fibrinogen levels, polycythaemia, and other haematological changes related to obesity.[27,28] Our observation that patients with higher BMI categories had more central clots could also be a reflection of the different physical properties of the thrombi in obese.

For recurrent VTE several papers have been published, however also with conflicting results, as some found no association between obesity and the risk of VTE recurrence,[29-32] whereas others found a higher recurrence risk with higher BMI.[33,34] In our study confidence intervals for the estimates crossed unity and we therefore cannot give a definitive answer on this matter.

Reports on the other investigated clinical outcomes –hospitalisation, bleeding and overall adverse effects- are scarce, as most often they are used as a composite outcome, or focus on differences between treatment regimens.

Our finding of a trend for increased hospitalisation for obese patients is supported by the large Australian 45 and Up cohort study, where the risk of hospitalisation for a wide range of CVD subtypes increased with relatively fine increments in BMI. For PE, the age and sex adjusted hazard ratio was 1.39 (95% CI 1.25-1.55) compared to normal BMI.[35]

Bleeding complications during treatment of PE are more frequent than recurrent VTE.[36] In the current study a higher incidence of bleeding in the overweight was observed, underlining the importance of this complication. Both for weight and BMI, in the RIETE prospective registry,[19,37] as well as in subgroup analysis of the Matisse[29] and Einstein DVT/PE[31] anticoagulation RCT's no association between body weight or BMI and major bleeding was found. However, analysis was only performed using two or three large categories (patients weighing <50, 50–100 kg vs >100 kg, or BMI <30 vs ≥30 or <25, 25-30 and 30-35), and underweight patients were included in the normal weight category. Of note, in the RIETE study underweight patients with VTE(or weighing <50 kg) had a significantly higher rate of bleeding complications. This is in contradiction with our findings. A potential explanation could be the difference in selection of patients, or analysis and categorisation study.

For underweight patients studies on other clinical outcomes are scarce. For prognostic characteristics and RVD until now no data are published. Underweight patients had an increased mortality compared with those with normal weight,[19] but an equal number of fatal PE. Difficulty for this category is that it can reflect two different populations, those who have been always underweight, and those that due to underlying condition sustained a significant weight loss, such as in cancer, immobility or renal insufficiency making them susceptible to adverse events. As these people have less adipose tissue, probably drug pharmacokinetics could be different.

Our findings of a trend towards worse prognostics in obese patients underlines the importance of more patient centred care[38] in particular with respect to choosing the appropriate anticoagulant therapy for each individual patient. In this way, we can confirm the call for increased awareness on dedicated prophylactic and therapeutic anticoagulant regimens in obesity.[7] Reassuringly, a recent well-sized cohort study suggested similar efficacy and safety between direct oral anti-Xa inhibitors and warfarin in morbidly obese patients, although these retrospective findings warrant confirmation in prospective studies.[39]

Future directions for study should explore the interaction of obesity and other risk factors for VTE, both for development, presentation, therapeutics and outcomes.[40] Special attention should focus on clinical severity, RVD and risk stratification. As obesity can be regarded a pro-inflammatory condition, more fundamental research should be directed toward molecular, pathogenic and sex-specific mechanisms responsible for VTE onset, development, and recurrence.[41]

In conclusion, we found that several clinical and radiological prognostics characteristics and right ventricular dysfunction in pulmonary embolism are not evenly distributed among the BMI categories. This is reflected in a trend toward worse outcomes in the over- and underweight patients compared to normal weights. This could be an incentive toward dedicated patient tailored evaluation and treatment.

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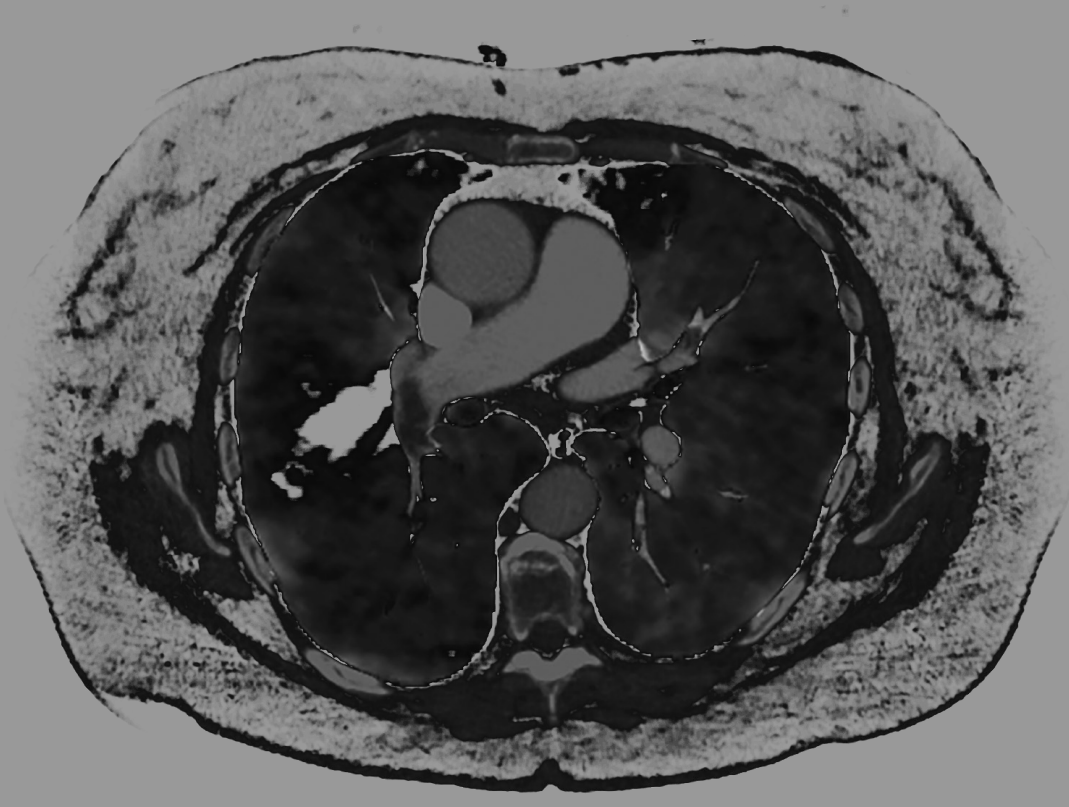

Chapter 6

Clinical impact of concomitant cardiopulmonary disease on CT pulmonary angiography in acute pulmonary embolism

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In preparation

Abstract

Background
The prognosis of acute pulmonary embolism varies depending on amongst other clot burden and concomitant conditions, usually assessed with prognostic scores of clinical variables. The aim of our study was to determine the impact of concomitant cardiopulmonary disease identified on the diagnostic CTPA on clinical outcome of acute pulmonary embolism.

Methods
We studied a post hoc sample of patients with pulmonary embolism included in the Hokusai-VTE randomized clinical trial that compared two anticoagulant regimens (n=1950). We assessed occurrence and severity of cardiopulmonary diseases on CT (pleural fluid, pericardial fluid, consolidations, coronary and aortic calcifications) and clinical and radiological prognostic characteristics for right ventricular dysfunction. Primary outcome was one-year mortality; secondary outcomes were recurrent VTE, hospitalization, bleeding and overall adverse events.

Results
Concomitant disease was present on CTPA in 1298 of 1950 patients (66.6%). One-year mortality was increased with presence of mild, moderate and severe disease on CTPA (OR 4.9, 10.4 and 32.2 (95%CI 1.4-16.8, 3.0-36.2 and 10.0-116)), also after adjustment for sPESI and age OR 3.4, 4.8 and 15.3 (0.99-11.9, 1.3-17.6 and 4.3-54.8)), compared to absence of concomitant disease. The exposure dependant association between disease severity and mortality was apparent in all evaluated CTPA findings.

Conclusions
In patients with acute pulmonary embolism, concomitant disease observed on the baseline CTPA impacts mortality and may be of additional value in risk stratification and prognosis.

Introduction

Computed tomography pulmonary angiography (CTPA) is the current state of the art diagnostic modality in the evaluation of patient with suspected pulmonary embolism (PE). The major advantage above other techniques is the ability to provide an alternative explanation for the patients' complaints, which can be encountered even more frequently than PE itself.[1] In clinical practice this can be very helpful, as signs and symptoms of PE are not specific and several other cardiopulmonary diseases can present with similar complaints. Also, the diagnosis of other cardiopulmonary diseases may have an impact on clinical course and outcome.

PE is a serious disease with overall mortality after 1 month of 9.1%.[2] The prognosis is determined by the impact it carries on the patients' cardiopulmonary status, more specifically how the clot burden affects right ventricular function, and by underlying diseases such as cancer.

Currently, risk assessment for pulmonary embolism is performed by first considering hemodynamic stability, followed by determination of several risk factors present in the simplified pulmonary embolism severity index (sPESI), and signs of right ventricular dysfunction as determined by NT-proBNP, echocardiography or on CTPA.[3] The additional burden of concomitant cardiopulmonary disease could negatively impact the chance for good recovery. Only a few, mostly retrospective single-centre studies have addressed this question, usually focusing on one aspect such as concomitant pleural effusion.[4-6] We investigated a variety of cardiopulmonary disease features on CTPA in a large prospective trial of patients with confirmed pulmonary embolism. The aim of our study was to determine the impact of concomitant cardiopulmonary disease as identified on the diagnostic CTPA on clinical outcome.

Materials and Methods

Patients and study design

The present study is a post hoc analysis of all patients that underwent CTPA for pulmonary embolism in the Hokusai-VTE study, a large multi-centre international randomized clinical trial in which two anticoagulant regimens were compared in patients with venous thromboembolism (VTE); ClinicalTrials.gov identifier: NCT00986154).[7] In this trial, eligible patients were aged 18 years or older and had acute symptomatic deep vein thrombosis (DVT) and/or PE. Patients were excluded in case of contraindication 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. Follow-up was 12 months, covering 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 these were PE-related. An independent committee adjudicated all predefined outcomes. For the current analysis all patients with PE, either with or without DVT, were included. Excluded were patients not evaluated by CTPA, or when images were not available in DICOM format or inaccessible for reading in the image viewer.

Data collection

All clinical and radiological data were anonymized and centrally registered with double data entry by an independent trial data management agency before the trial data lock. Clinical data were retrieved from the original CRFs. This included a broad range of risk factors at baseline as well as present and past diseases. In all patients NT-proBNP levels were measured at baseline. CTPA data were acquired from the participating centres, using local settings and protocols, with a wide variety of CT-scanners, from basic until high-end CT. Anonymized patient images from the central database were evaluated by a radiologist (LB) with 12 years of experience in cardiovascular imaging in cooperation with a dedicated research assistant, both blinded for patient details and clinical information. Data were registered on a CRF designed for the present analysis. For image reading a commercially available image viewer was used (eFilm Workstation for Windows Version 3.4.0, Build 10, Merge Technologies Inc., Milwaukee, USA). Images were primarily read in axial sections with additional support of multiplanar reformatting (MPR). Standard CTPA, mediastinal and lung window settings were used, with individual adaptation if deemed necessary.

Definitions and outcomes

We defined concomitant disease as all pleuro-parenchymal and cardiovascular pathologies visible on the baseline CTPA, in line with the Fleischner glossary terms:[8] pleural fluid, pericardial fluid, lung parenchymal opacities, interstitial lung disease (ILD), and calcifications in the aorta and coronary arteries. All concomitant disease was assessed semi-quantitatively using the 4-ordinal scale "none – mild – moderate – severe in line with common clinical practice. Pericardial fluid was regarded pathological if > 5 mm. When all pathologies were regarded together, the highest graded pathology determined the overall severity grade.

Additionally, clinical (NT-proBNP, sPESI) and radiological prognostic characteristics for right ventricular dysfunction and adverse events were registered.[9] For NT-proBNP a value of ≥ 600 pg/ml at baseline was considered abnormal. For sPESI calculation the arterial oxyhaemoglobin saturation <90% was not registered; this item was considered positive if patient required oxygen administration. Radiological parameters assessed for right ventricular dysfunction (RVD) were: right-to-left ventricular (RV/LV) ratio >1.0 (transverse diameter of right and left ventricle (axial view), pulmonary trunk (PT) > 29 mm; bowing of the interventricular

septum (D-shaped/ straightened or curved toward the left ventricle) and reflux of contrast medium in the intrahepatic veins. All continuous variables were noted in millimetres were applicable.

The primary outcome for the present analysis was mortality after one year. Secondary outcomes were recurrent VTE, hospitalization, bleeding and overall adverse events during one year follow up.

Statistical analysis

Descriptive statistics are displayed as mean ± standard deviation (SD) for normally distributed variables and median ± interquartile ranges (IQR, 25th to 75th percentile) for not normally distributed variables. For comparison on binary outcomes the Chi-square test for dichotomous variables were used. Between the groups categorical variables were compared using the Chi-square test for trend; for continuous data by Students T test or Mann-Whitney U test if non-normally distributed. A p-value < 0.05 was considered statistically significant. We used logistic regression models to estimate odds ratios (OR) with 95% confidence intervals (CI) to investigate the association between the outcome variables. In addition, we adjusted odds ratios for sPESI. All statistical analyses were performed in SPSS version 23 (SPSS Inc, Chicago Ill).

Results

Baseline characteristics are displayed in Table 1. The study group consisted of 1950 patients with pulmonary embolism. Concomitant disease on CTPA was present in 1298 patients (66.6%), and was mild in 810 (41.5%), moderate in 327 (16.8%) and severe in 161 (8.3%) (Table 2). The odds ratios for mortality of sPESI≥1 was 4.3 (CI 2.1-8.5).

There was a severity-dependent increase both in occurrence as well as in odds ratios of mortality. When no concomitant disease was present, the 1-year mortality was 0.5%, which increased to 2.2% in mild, 4.6% in moderate, and to 13.7% in severe concomitant disease. With no concomitant disease as reference, the odds ratios and adjusted odds ratios for mortality in mild disease were 4.9 (CI 1.4-16.7) and 3.4 (1.0-11.9), and for moderate disease 10.4 (3.0-36.2) and 4.8 (1.3-17.6), respectively (Table 3). With absence of concomitant disease as reference (OR 1), the odds ratio for mortality with presence of any severe concomitant disease on CTPA was 32.24 [95%CI 10.0-116], and adjusted for sPESI 15.3 (4.3-54.8).

The stepwise association between concomitant disease severity and mortality was apparent in all evaluated CTPA findings. After adjustment for sPESI, the odds ratio for mortality in the most severe pathologies were 27.9 (CI 7.6-102.8) for ILD, 10.99 (CI 2.7-45.6) for pleural fluid and 8.4 (CI 1.6-44.5) for pulmonary consolidations.

Table 1: Baseline characteristics.

	All patients		Concomitant disease on CTPA	
	n	%	n	%
Included	1950	100	1298	66.6
Clinical				
Age (mean, SD)	57.0	16.6	60.0	16.4
Weight (mean, SD)	84.5	20.1	82.8	18.9
SBP mmHg (mean, SD)	128	17	129	17
DBP mmHg (mean, SD)	76	11	76	11
Heart Rate (mean, SD)	80	14	80	14
Age <50Y	638	32.7	355	26.0
Age > 65Y	154	7.9	143	10.5
Weight < 60 kg	190	9.7	144	10.5
Current alcohol use	754	38.7	528	38.7
Smoking	854	43.8	635	46.5
NT-proBNP > 600	515	27.4	378	28.8
sPESI* High Risk ≥1	1051	53.9	807	59.1
Concurrent DVT	456	23.4	275	20.1
Risk Factors				
Recent surgery, trauma, or immobilisation	372	19.1	273	20.0
Sitting > 4 hours	185	9.5	114	8.3
Oestrogen drugs use	196	10.1	100	7.3
Previous DVT/PE	415	21.3	282	20.6
Thrombophilia	94	4.8	62	4.5
Concomitant Disease History				
Hypertension	810	41.5	635	46.5
Diabetes	199	10.2	153	11.2
Cardiovascular Disease	314	16.1	256	18.7
Chronic Heart Failure	35	1.8	28	2.0
Cerebrovascular Disease	73	3.7	60	4.4
Stroke	35	1.8	29	2.1
Renal Disease	129	6.6	93	6.8
Hepatic Disease	212	10.9	155	11.3
Pulmonary Disease	401	20.6	322	23.6
COPD	103	5.3	96	7.0
Pulmonary hypertension	43	2.2	39	2.9
Cancer	228	11.7	190	13.9

Data are number (%) or median (IQR), unless otherwise specified. CHF – Chronic heart failure; DVT –Deep Vein Thrombosis; PE – Pulmonary Embolism; sPESI – simplified pulmonary embolism severity index; US – Ultrasound; * - 523/1950 included and 496/1531 excluded patients (mm: mean , SD); ** sPESI- item on O2 considered positive if patient needed oxygen administration.

Table 2: Association between concomitant disease severity on CTPA and clinical outcomes.

	N (%)	OR	OR Adjusted for sPESI
Mortality			
Concomitant disease			
No	3 (0.5)	1 (reference)	1 (reference)
Mild	18 (2.2)	4.9 (1.4-16.8)	3.4 (0.99-11.9)
Moderate	15 (4.6)	10.4 (3.0-36.2)	4.8 (1.3-17.6)
Severe	22 (13.7)	32.2 (10.0-115.9)	15.3 (4.3-54.8)
Total	58 (3.0)		
Recurrent VTE			
Concomitant disease			
No	12 (1.8)	1 (reference)	1 (reference)
Mild	21 (2.6	1.4 (0.69-2.9)	1.3 (0.62-2.7)
Moderate	14 (4.3)	2.4 (1.1-5.2)	2.0 (0.82-4.7)
Severe	3 (1.9)	1.0 (0.28-3.6)	0.8 (0.21-3.1)
Total	50 (2.6)		
All Bleeding			
Concomitant disease			
No	6 (0.9)	1 (reference)	1 (reference)
Mild	12 (15)	1.6 (0.60-4.4)	1.1 (0.39-3.1)
Moderate	8 (2.4)	2.7 (0.93-7.9)	1.2 (0.37-3.9)
Severe	4 (2.5)	2.7 (0.77-9.8)	1.3 (0.32-5.1)
Total	30 (1.5)		
Hospitalisation			
Concomitant disease			
No	15 (2.3)	1 (reference)	1 (reference)
Mild	35 (4.3)	1.9 (1.04-3.5)	1.4 (0.76-2.7)
Moderate	26 (8.0)	3.4 (1.9-7.0)	2.0 (0.97-4.0)
Severe	14 (8.7)	4.0 (1.9-8.6)	2.2 (0.98-5.0)
Total	90 (4.6)		
All Adverse Events			
Concomitant disease			
No	20 (3.1)	1 (reference)	1 (reference)
Mild	50 (6.2)	2.1 (1.2-3.5)	1.6 (0.95-2.8)
Moderate	34 (10.4)	3.7 (2.8-6.5)	2.2 (1.2-4.0)
Severe	28 (17.4)	6.7 (3.6-12.2)	3.9 (2.0-7.4)
Total	132 (6.8)		

Odds ratios for concomitant disease severity and different clinical outcomes, with no disease as reference. Proportion was calculated per disease severity with follow-up up to 12 months. CI – confidence intervals, OR –Odds ratio; sPESI – simplified pulmonary embolism severity index, VTE – venous thromboembolism.

Table 3: Association between concomitant cardiopulmonary diseases on CTPA and mortality.

		N (%)	OR	OR Adjusted for sPESI
Concomitant disease				
No	652	3 (0.5)	1 (reference)	1 (reference)
Mild	810	18 (2.2)	4.9 (1.4-16.8)	3.4 (0.99-11.9)
Moderate	327	15 (4.6)	10.4 (3.0-36.2)	4.8 (1.3-17.6)
Severe	161	22 (13.7)	32.2 (10.0-115.9)	15.3 (4.3-54.8)
Total	1950	58 (3.0)		
Coronary calcifications				
No	1136	24 (1.8)	1 (reference)	1 (reference)
Mild	426	16 (3.8)	2.1 (1.1-4.1)	0.98 (0.49-2.0)
Moderate	161	15 (9.3)	5.6 (2.9-11.0)	2.0 (0.95-4.4)
Severe	27	3 (11.1)	6.8 (1.9-24.2)	2.9 (0.75-11.0)
Aorta calcifications				
No	1177	17 (1.4)	1 (reference)	1 (reference)
Mild	564	22 (3.9)	2.8 (1.5-5.3)	1.4 (0.65-2.8)
Moderate	192	15 (7.8)	5.8 (2.8-11.8)	1.9 (0.81-4.7)
Severe	17	4 (23.5)	21.0 (6.2-71.0)	5.5 (1.32-22.8)
Pericardial fluid				
No			1 (reference)	1 (reference)
Moderate/severe	52	6 (8.3)	3.2 (1.3-7.7)	2.3 (0.9-5.8)
Pleural Fluid				
No	1578	38 (2.4)	1 (reference)	1 (reference)
Mild	300	10 (3.3)	1.4 (0.69-2.8)	1.2 (0.6-2.6)
Moderate	59	7 (11.9)	5.5 (2.3-12.8)	4.3 (1.7-10.5)
Severe	13	3 (23.1)	12.2 (3.2-45.9)	11.0 (2.7-45.6)
Consolidation				
No	1121	25 (2.2)	1 (reference)	1 (reference)
Mild	604	25 (4.1)	1.9 (1.1-3.3)	1.8 (0.99-3.2)
Moderate	211	6 (2.8)	1.3 (0.52-3.2)	1.5 (0.58-3.8)
Severe	14	2 (14.3)	7.3 (1.6-34.4)	8.4 (1.6-44.5)
Emphysema				
No	1513	29 (1.9)	1 (reference)	1 (reference)
Mild	291	14 (4.8)	2.6 (1.4-4.9)	1.7 (0.9-3.3)
Moderate	109	8 (7.3)	4.1 (1.8-9.1)	2.4 (1.02-5.6)
Severe	37	7 (18.9)	11.9 (4.8-29.4)	4.5 (1.6-12.6)
ILD				
No	1905	50 (2.6)	1 (reference)	1 (reference)
Mild	21	1 (4.8)	1.9 (0.24-14.1)	1.2 (0.15-9.5)
Moderate	13	1 (7.7)	3.1 (0.4-24.2)	2.9 (0.35-24.1)
Severe	11	6 (54.5)	44.5 (13.2-150.1)	28.0 (7.6-102.8)

Odds ratios for different concomitant diseases and 1 year mortality, with no disease as reference. Proportion was calculated per disease severity with follow-up up to 12 months. CI – confidence intervals, OR –Odds ratio; sPESI – simplified pulmonary embolism severity index, VTE – venous thromboembolism * Adjusted for sPESI.

For the secondary outcomes hospitalisation and overall adverse events association was apparent ($p<0.001$) (Table 4), but recurrent VTE ($p=0.165$) and bleeding ($p=0.244$) were not associated with presence of concomitant disease.

Discussion

In this study we showed that in patients with acute pulmonary embolism concomitant disease present on the baseline CTPA is associated with poor clinical outcome. Both pulmonary and cardiovascular manifestations of disease were associated with mortality in a severity-dependent manner, also when adjusted for sPESI.

A strength of our study is the prospective and rigorous collection of all included data as part of a large international randomized clinical trial. Both imaging data and clinical outcomes were assessed before the data lock and the assessors were blinded for allocation of treatment and for clinical outcome during follow-up. We evaluated a broad range of parameters and biomarkers in order to provide a complete radiological assessment rather than limiting us to a single factor.

Our study has some limitations. We did not further adjust for potential confounders like known comorbidities. Yet, we think that with age and sPESI parameters the most important confounders are covered. Also, we are aware that patients included in a randomized controlled trial do not necessarily reflect all those presenting in daily practice, and our results cannot be unconditionally generalized to those with exclusion criteria for the trial, such as hemodynamically unstable patients and patients with a limited life expectancy.

Acute PE can interfere with both circulation and gas exchange. It therefore seems biologically plausible that concomitant pathology affects primary cardiopulmonary reserve, and consequently could lead to worse clinical outcomes of acute PE[3].

Although sPESI has been validated as risk assessment tool, its ingredients represent to a great deal static information on known diseases. The imaging findings assessed in this study can be regarded as a more direct reflection of the actual health status of the individual patient. As this is supplementary information not present in other scores, additional value can be derived which could possibly impact on prognostics of the individual patient.

This is reflected in our findings of a general higher odds ratio for mortality with increasing severity of concomitant disease, even after correcting for sPESI. Interestingly, the odds ratios were even a little bit higher for the overall radiological pathologies than for overall sPESI, although confidence intervals did overlap. It seems logical that also with higher degrees of disease severity, the number of adverse events and hospitalisation increase.

In our study manifestations of concomitant pathology apparently had no effect on the risk of major bleeding or recurrent VTE.

A variety of cardiopulmonary pathologies had impact on mortality, each with a different pathophysiological background, which will be discussed shortly.

Pleural fluid is the pulmonary manifestation most widely studied in conjunction with pulmonary embolism, with widely varying estimates of prevalence between 2 and 50%. [4,10-16] Conversely, pulmonary embolism should be considered as a possible cause of any pleural effusion, as it is the most commonly overlooked disorder in patients with pleural effusion. [17] In our study mortality was about 11-fold higher in patients with large effusions.

Consolidations and atelectasis are frequent diagnoses in patients presenting to the emergency department with chest pain or dyspnoea.[1] However, it does not exclude presence of PE. In fact, in our study severe consolidations were associated with increased mortality, whereas for less severe consolidations and atelectasis no impact on mortality was found.

COPD and PE can both present with dyspnoea. Mortality and length of hospital admission seem to be increased in patients with unexplained acute exacerbation of COPD and PE. [18,19] Also, in patients with ILD and pulmonary hypertension a RV/LV ratio ≥1 is predictive for mortality or transplantation.[20]. This is in line with our observations of increasing odds ratios for mortality in the more severe cases of emphysema and ILD.

Pericardial fluid had a moderate effect on mortality in our study, which is in line with other studies in different settings.[21,22] Occurrence of pericardial fluid during PE ranges between 3-9%. Presence of pericardial fluid may lead to hemodynamic deterioration during both acute right ventricular pressure load and subsequent volume loading, and has been proposed as contributing factor for risk estimation in prognostic scores.[23,24]

Coronary and aortic calcifications may not have implications for acute clinical management but may be important for incident cardiovascular risk prediction[25]. Prevalence in CTPA is rather high with ranges between 44 - 54%.[4,26] Of note, these findings are often not reported.[26] We observed higher mortality with increasing severity of coronary and/or aorta calcifications, which underlines the need for adequate reporting.

How do our findings fit into the current assessment of patients with acute PE?

Many parameters have been suggested as potentially valuable for prognostication, yet are not integrated in clinical practice as they are too difficult for regular handling.[27] Concomitant abnormalities on CTPA are not yet incorporated, and can probably be regarded as risk modifiers for both the intermediate and low risk categories of the ESC guidelines on PE, with impact on either the decision for home treatment or on the other spectrum close monitoring. In this perspective, standardized reporting of radiological, clinical and biochemical parameters into a format which could be integrated into an artificial intelligence algorithm could be of

additional value. Future directions for study should explore imbedding these findings in artificial intelligence algorithms.

In conclusion, we found that in patients with acute pulmonary embolism concomitant disease observed on CTPA is associated with mortality and may be of additional value in risk stratification and prognosis.

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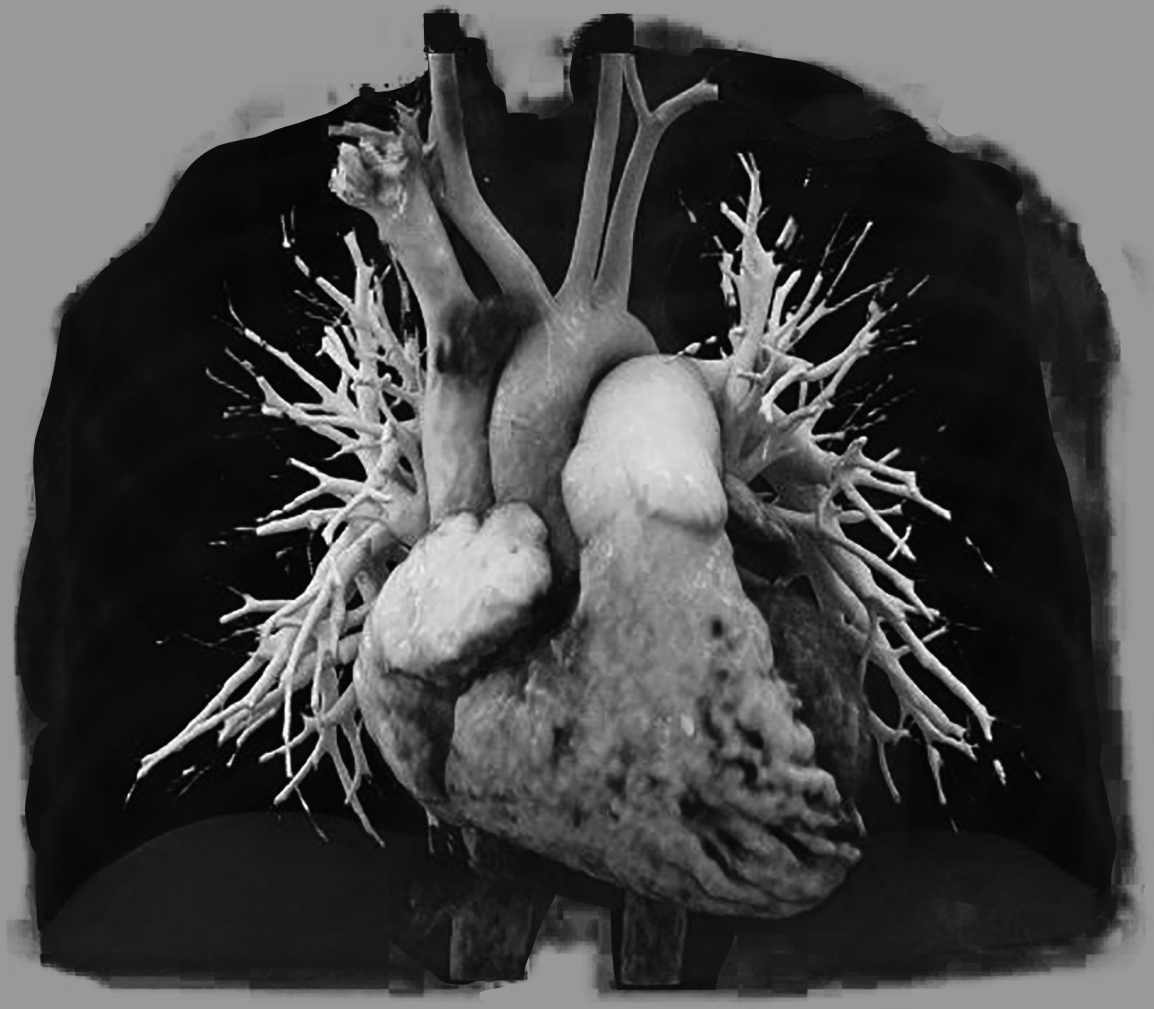
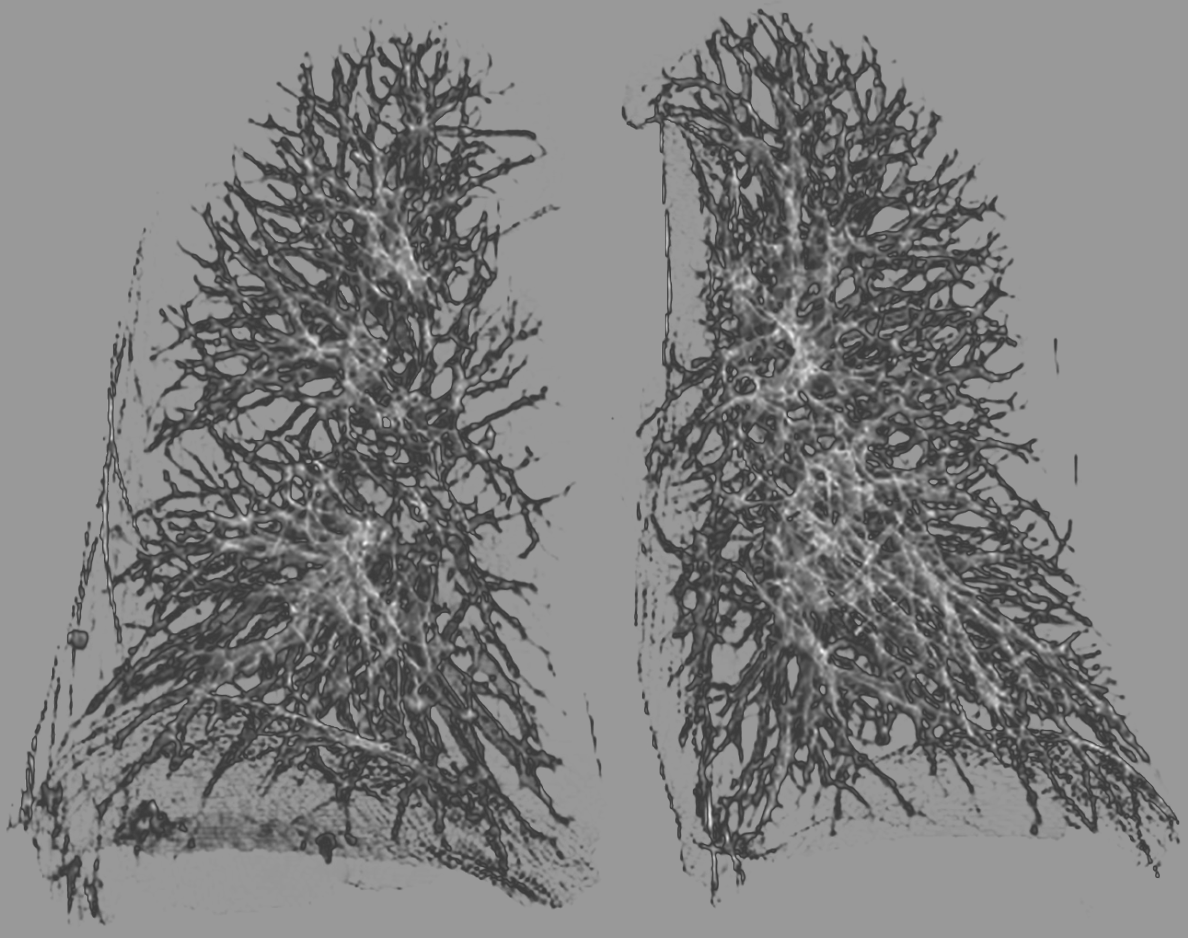


PART III

Venous thromboembolism and COVID-19



Chapter 7

Incidence of venous thromboembolism in hospitalized patients with COVID-19

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Abstract

Background
Coronavirus disease 2019 (COVID-19) can lead to systemic coagulation activation and thrombotic complications. Objective of this study was to investigate the incidence of objectively confirmed venous thromboembolism (VTE) in hospitalized patients with COVID-19.

Methods
Single-centre cohort study of 198 hospitalized patients with COVID-19.

Results
Seventy-five patients (38%) were admitted to the intensive care unit (ICU). At time of data collection, 16 (8%) were still hospitalized and 19% had died. During a median follow-up of 7 days (IQR, 3-13), 39 patients (20%) were diagnosed with VTE of whom 25 (13%) had symptomatic VTE, despite routine thrombosis prophylaxis. The cumulative incidences of VTE at 7, 14 and 21 days were 16% (95% CI, 10-22), 33% (95% CI, 23-43) and 42% (95% CI 30-54) respectively. For symptomatic VTE, these were 10% (95% CI, 5.8-16), 21% (95% CI, 14-30) and 25% (95% CI 16-36). VTE appeared to be associated with death (adjusted HR, 2.4; 95% CI, 1.02-5.5). The cumulative incidence of VTE was higher in the ICU (26% (95% CI, 17-37), 47% (95% CI, 34-58), and 59% (95% CI, 42-72) at 7, 14 and 21 days) than on the wards (any VTE and symptomatic VTE 5.8% (95% CI, 1.4-15), 9.2% (95% CI, 2.6-21), and 9.2% (2.6-21) at 7, 14, and 21 days).

Conclusions
The observed risk for VTE in COVID-19 is high, particularly in ICU patients, which should lead to a high level of clinical suspicion and low threshold for diagnostic imaging for DVT or PE. Future research should focus on optimal diagnostic and prophylactic strategies to prevent VTE and potentially improve survival.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and can lead to systemic coagulation activation. Initial studies from China report increased D-dimers (0.5 mg/L or higher) in 46% to 63% of patients, as well as other signs of coagulation activation including mild thrombocytopenia and a moderately prolonged prothrombin time.[1,2] Additionally, more pronounced coagulation activation seems to be correlated with a severe disease course, including admission to the intensive care unit (ICU) and death. For example, patients who died of COVID-19 had higher D-dimers on admission compared with those who survived, whereas D-dimer levels increased further during hospital stay in patients who died, but not in survivors.[3] In another study, patients with D-dimer levels of 1.0 µg/L or higher had an 18-fold increased risk of death.[2] One study used the International Society on Thrombosis and Haemostasis definition of disseminated intravascular coagulation and found that a score of ≥5 points was present in 71% of those who died compared with 0.6% in survivors.[4] None of these studies reported on the number of patients with thrombotic complications.

Since the pandemic spread of SARS-CoV-2, there have been several anecdotal reports from colleagues on a high incidence of thrombotic complications, including thrombosis of extracorporeal circuits for continuous veno-venous hemofiltration, central venous catheter-associated thrombosis, and deep venous thrombosis (DVT) and pulmonary embolism (PE). Most but not all of these complications occurred in patients admitted to the ICU, with most patients receiving routine thrombosis prophylaxis.

Diagnosis of DVT and PE may be particularly challenging in patients with COVID-19. Symptoms of PE overlap with symptoms of COVID-19 and mild symptoms may be overlooked in a patient already suffering from shortness of breath. Similarly, clinical signs and symptoms of DVT may be harder to detect, especially in ICU patients, and when treating clinicians primarily focus on respiratory status and do not systematically assess lower extremities for signs of DVT.

In early April 2020, a large number of venous thromboembolic events were diagnosed in COVID-19 patients admitted to our ICU, based on a clinical suspicion of DVT in the lower extremities. These observations have led us to intensify the dose of low-molecular-weight heparin to prevent VTE in COVID-19 patients in the ICU. In the present study, we report on the incidence and risk factors of VTE in COVID-19 patients admitted to the ICU or general ward.

Methods

Patients

We identified consecutive patients admitted for COVID-19 to the Amsterdam University Medical Centres, location Academic Medical Centre, until April 12, 2020. COVID-19 was confirmed by a reverse transcription polymerase chain reaction (RT-PCR) test on a nose/throat swab or sputum sample positive for SARS-CoV-2. Given the sensitivity of RT-PCR of only 50% to 80%,[5] a daily multidisciplinary team also considered COVID-19 confirmed in patients with a negative RT-PCR but with symptoms and disease course consistent with COVID-19, the absence of an alternative diagnosis, as well as a computed tomography (CT) scan of the chest showing abnormalities highly suspicious of typical pulmonary involvement of COVID 19 (COVID-19 Reporting and Data System [CO-RADS] 4 or 5 per the Dutch Radiology Society).[6,7] We did not include patients who were diagnosed with COVID-19 during hospital stay for other medical conditions.

Hospitalized patients were categorized as ICU patients or as ward patients. Patients were categorized as ward patients if they had not been transferred to the ICU at any time during the course of their disease. All ICU patients were admitted on the ICU for mechanical ventilation.

Thrombosis prophylaxis was part of standard of care in all COVID-19 patients. Ward patients received thrombosis prophylaxis with nadroparin 2850 IU once daily or 5700 IU for patients with a body weight of ≥100 kg. From April 3 onwards, patients in ICU received a double dose of nadroparin compared with patients on the wards, which was nadroparin 2850 IU twice daily for patients with a body weight <100 kg and 5700 IU twice daily for those ≥100 kg.

Outcomes

The primary outcome was an objectively confirmed diagnosis of distal or proximal DVT, PE, or venous thrombosis at other sites including catheter-related thrombosis. The secondary outcome was symptomatic VTE, excluding events detected by bilateral leg ultrasound screening. All outcomes were adjudicated by two of the authors (M.C. and N.v.E.). We did not adjudicate deaths to identify fatal PE because almost all deaths were due to hypoxemic respiratory failure, which can be indistinguishable from fatal PE, whereas autopsies were rarely performed in COVID-19 patients.

Data collection

Patient data were retrospectively reviewed from the day of admission to our hospital (also in case a patient was transferred from another hospital) until death, hospital discharge, transfer to another hospital, or end of data collection on April 30, 2020. We collected data on demographics and blood tests on admission. D-dimer levels

were included if measured on or within 72 hours of admission. Formal approval from the Medical Ethics Review Committee was not required as the Medical Research Involving Human Subjects Act does not apply for this observational study.

Statistical analysis

Patient characteristics were compared between ICU and ward patients using standard descriptive statistics. The proportion of ICU and ward patients with VTE was assessed, with 95% confidence intervals (CI) calculated using Wilson's score interval. In addition, the cumulative incidence, overall and for symptomatic VTE only, was calculated at 7, 14, and 21 days using a competing risk approach considering death as a competing risk. Risk factors for VTE were evaluated by calculating subdistribution hazard ratios (SHR) in Fine & Gray competing risk regression models. A sensitivity analysis was performed in which missing values were imputed 20 times using multiple imputation with chained equations, assuming a missing at random pattern. The multiple imputation model included all patient characteristics, laboratory values, radiology information, and outcome data. Estimates across the imputation datasets were combined using Rubin's rule. The association between VTE and mortality and between ICU stay and VTE were analysed by calculating a time-varying hazard ratio in Cox proportional hazards model. Analyses were performed in R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

Results

Between March 2 and April 12, 2020, 199 patients who were hospitalized because of COVID-19 were identified. One patient was excluded because he was immediately transferred to another hospital from the emergency department. Of the remaining 198 patients, 148 (75%) were hospitalized after an emergency department visit, whereas 50 (25%) were transferred from another hospital. Seventy-five patients (38%) were admitted to the ICU after being transferred from the ICU of another hospital (n = 44), our general ward (n = 20), or directly from the emergency department (n = 11). COVID-19 was confirmed by a positive RT-PCR in 173 patients (87%) and considered confirmed by clinical features consistent with COVID-19 in combination with a CT of the chest with highly suspicious or typical features (CO-RADS 4 or 5) and no alternative diagnosis in 25 (13%).

Characteristics

Patient characteristics are shown in Table 1. Mean age was 61 years (standard deviation, 14) and 130 (66%) were male. Median body mass index was 27 kg/m^2 (interquartile range [IQR], 24, 31). Compared with ward patients, ICU patients were more often male (77% vs 59%; P = .011) and had higher D-dimer levels on

admission (median 2.0 vs 1.1 mg/L; $P = .006$). The median time between symptom onset and admission to our hospital was 7 days (IQR, 5, 10) for patients presenting at the emergency department and 11 days (IQR, 6, 14) for those transferred from another hospital. Thrombosis prophylaxis was initiated in 167 patients (84%), whereas 19 (9.6%) continued therapeutic anticoagulation for an indication that was present at the time of admission (e.g., atrial fibrillation).

Table 1: Baseline characteristics.

	All Patients N = 198	**Patients Admitted to ICU N = 75**	**Patients Admitted to Regular Ward N = 123**	***P* value**
Mean age, y (SD)	61 (14)	62 (10)	60 (16)	0.28
Male sex, n (%)	130 (66)	58 (77)	72 (59)	0.011
Body weight ≥ 100 kg, n (%)	22/157 (14)	12/73 (16)	10/84 (12)	0.56
Median body mass index, kg/m^2 (IQR)	27 (24, 31)	27 (24, 29)	28 (25, 31)	0.17
History of venous thromboembolism, n (%)	11 (5.6)	2 (2.7)	9 (7.3)	0.27
Active cancer, n (%)	7 (3.5)	3 (4.0)	4 (3.3)	1.0
Anticoagulant therapy at admission	19 (9.6)	7 (9.3)	12 (9.8)	1.0
Antiplatelet therapy at baseline	29 (15)	8 (11)	21 (17)	0.30
Platelet count				
Mean, ×109/L (SD)	239 (93)	251 (89)	231 (95)	0.15
<150 × 109/L, n (%)	27/196 (14)	7 (9.5)	20/122 (16)	0.23
D-dimer				
Median, mg/L (IQR)	1.1 (0.7, 2.3)	2.0 (0.8, 8.1)	1.1 (0.7, 1.6)	0.006
>0.5 mg/L, n (%)	110/131 (84)	40/48 (83)	70/83 (84)	1.0
>1.0 mg/L, n (%)	75/131 (57)	31/48 (65)	44/83 (53)	0.27

Table 2: Clinical outcomes.

	All Patients (N = 198) n (%)	**ICU Patients (N = 75) n (%)**	**Patients in Wards (N = 123) n (%)**
Venous thromboembolism	39 (20)	35 (47)	4 (3.3)
Pulmonary embolism	13 (6.6)	11 (15)	2 (1.6)
Central or lobar	1 (0.5)	1 (1.3)	0
Segmental	10 (5.1)	9 (12)	1 (0.8)
Subsegmental	2 (1.0)	1 (1.3)	1 (0.8)
DVT	26 (13)	24 (32)	2 (1.6)
Proximal leg DVT	14 (7.1)	14 (19)	0
Distal leg DVT	11 (5.6)	9 (12)	2 (1.6)
Upper extremity DVT	1 (0.5)	1 (1.3)	0
Symptomatic VTE	25 (13)	21 (28)	4 (3.3)
Pulmonary embolism	13 (6.6)	11 (15)	2 (1.6)
Proximal DVT	8 (4.0)	8 (11)	0
Distal DVT	4 (2.0)	2 (2.7)	2 (1.6)

At the end of data collection (April 30, 2020), 136 patients (69%) had been discharged, 8 (4.0%) transferred to another hospital, 38 had died (19%), and 16 (8%) were still hospitalized. All patients still hospitalized were followed for at least 17 days. The median times from admission to discharge or death were 5 days (IQR, 3, 9) and 9 days (IQR, 5, 14), respectively. Thirteen patients (6.6%) were re-hospitalised after a median of 4 days (IQR, 2, 16) after discharge.

Venous thromboembolism

During a median follow-up of 7 days (IQR, 3, 13; range, 1-43), 39 patients (20%; 95% CI, 15-26) were diagnosed with VTE and 2 (1.0%; 95% CI, 0.28-3.6) with extensive symptomatic thrombophlebitis for which therapeutic anticoagulation was initiated. Type of VTE was PE with or without DVT in 13 patients (6.6%), proximal DVT in 14 (7.1%), distal DVT in 11 (5.6%), and upper extremity DVT in 1 (0.5%) (Table 2). VTE was symptomatic in 25 patients (13%) and detected incidentally or by screening in 14 (7.1%). Of note, screening for lower extremity DVT was performed in 55 patients (28%) during hospital stay (ICU, n = 38; ward, n = 17), whereas CT pulmonary angiography for PE was only performed on indication (e.g., sudden worsening hypoxemia). VTE was diagnosed after a median of 7 days after admission (IQR, 4, 10) and symptomatic VTE also after a median of 7 days (IQR, 5, 9).

In the competing risk model, the cumulative incidences of VTE at 7, 14, and 21 days were 16% (95% CI, 10-22), 33% (95% CI, 23-43), and 42% (95% CI, 30-54), respectively (Figure 1A). When only considering symptomatic VTE, the cumulative incidences were 10% (95% CI, 5.8-16), 21% (95% CI, 14-30), and 25% (95% CI, 16-36) at 7, 14, and 21 days, respectively (Figure 1B). When analysed as a time-varying variable, VTE was significantly associated with death (hazard ratio [HR], 2.7; 95% CI, 1.3-5.8), also when adjusted for age, sex, and ICU stay as time-varying variable (adjusted HR, 2.4; 95% CI, 1.02-5.5).

All VTE were diagnosed in patients receiving thrombosis prophylaxis. The risk of VTE in ICU patients was not lower during the period when the standard dose of nadroparin prophylaxis was doubled (58%) vs in the first follow-up period (41%).

ICU vs ward patients

Median follow-up duration was 15 days in ICU patients (IQR, 9, 20) and 4 days in ward patients (IQR, 2, 7). The proportion of patients with VTE was significantly higher in ICU patients (47%; 95% CI, 36-58) than in ward patients (3.3%; 95% CI, 1.3-8.1), corresponding to an SHR of 7.9 (95% CI, 2.8-23). The cumulative incidences of any VTE in ICU patients at 7, 14, and 21 days were 26% (95% CI, 17-37), 47% (95% CI, 34-58), and 59% (95% CI, 42-72), respectively (Figure 2A).

Symptomatic VTE was detected in 21 (28%) ICU patients and 4 (3.3%) ward patients (SHR, 3.9; 95 CI, 1.3-12). The cumulative incidences of symptomatic VTE in ICU patients at 7, 14, and 21 days were 15% (95% CI, 8.0-24), 28% (95% CI, 18-39), and 34% (95% CI, 21-46) (Figure 2B). The cumulative incidences of both any VTE and symptomatic VTE in ward patients at 7, 14, and 21 days were 5.8% (95% CI, 1.4-15), 9.2% (95% CI, 2.6-21), and 9.2% (2.6-21) (Figure 2).

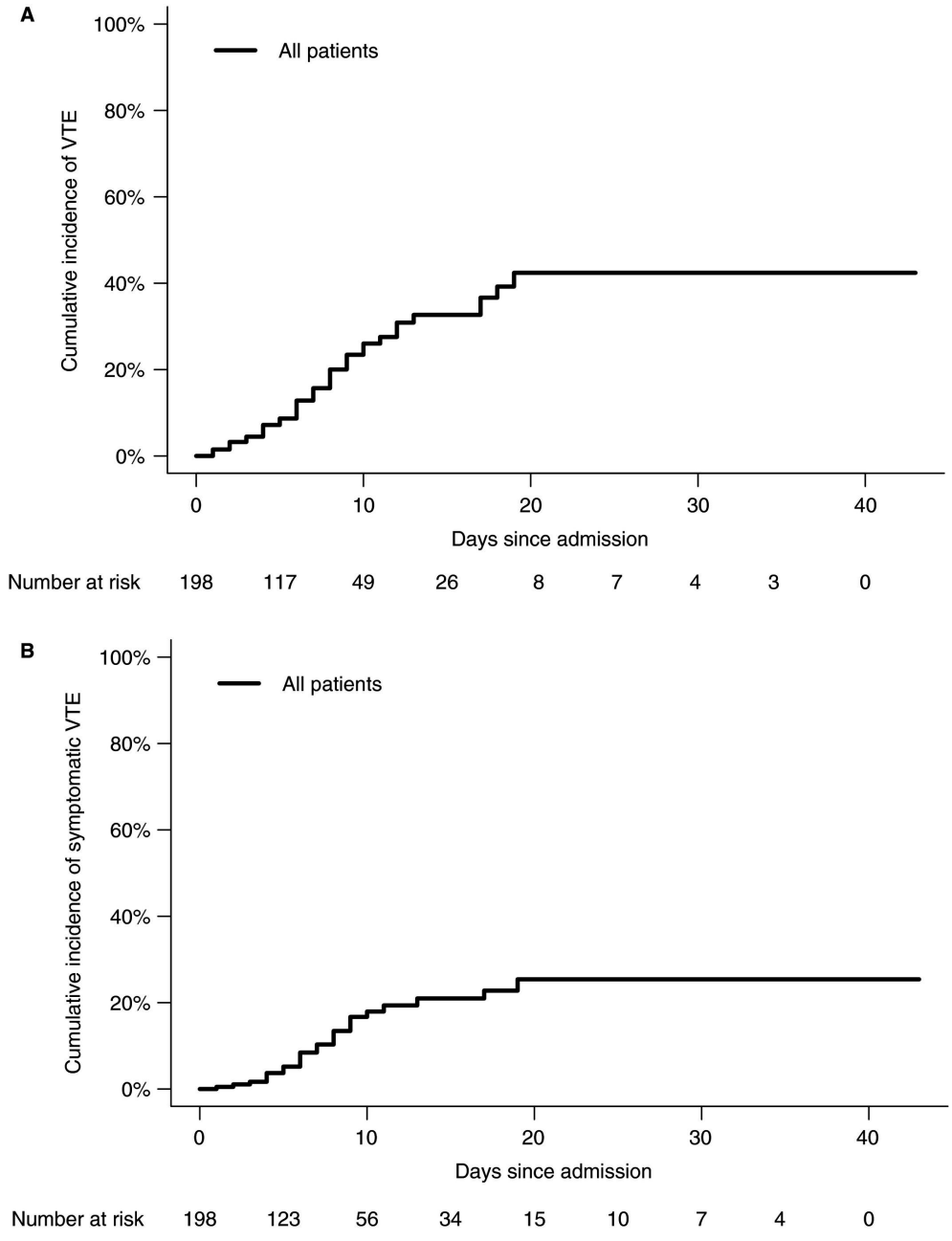

Figure 1:
A, Venous thromboembolism. B, Symptomatic venous thromboembolism. ICU, intensive care unit; VTE, venous thromboembolism.

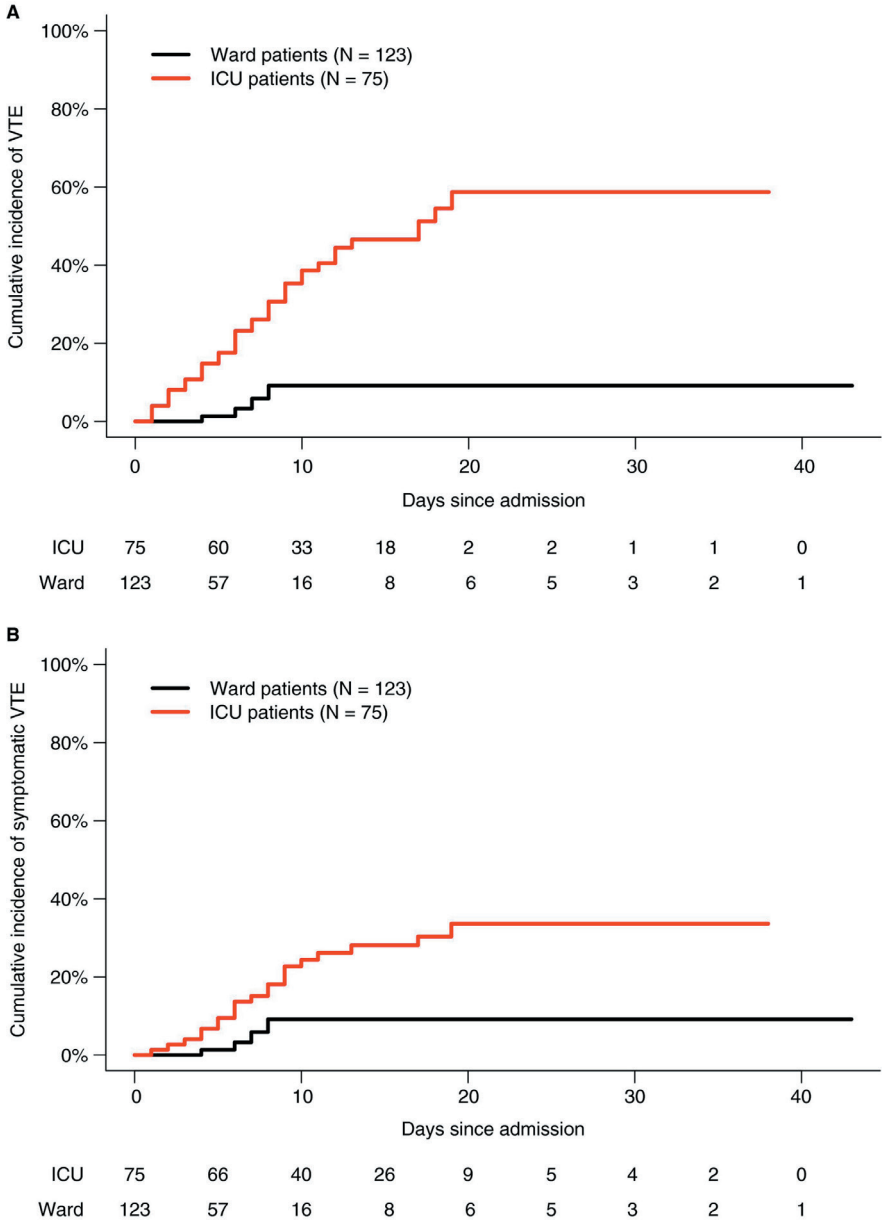

Figure 2:
A, Venous thromboembolism in ICU and ward patients. B, Symptomatic venous thromboembolism in ICU and ward patients. ICU, intensive care unit; VTE, venous thromboembolism.

The difference between ICU and ward patients was comparable when ICU stay was modelled as a time-varying variable (HR for any VTE, 7.1; 95% CI, 3.1-16). The higher risk in ICU patients was consistent in the sensitivity analysis excluding patients transferred from another hospital (50% vs 3.4%; SHR, 7.2; 95% CI, 2.3-23).

Table 3: Risk factors for venous thromboembolism.

	VTE (N = 39)	No VTE (N = 159)	Univariable SHR (95% CI)[c]	Multivariable SHR (95% CI)[d]
Mean age, years (SD)	62 (10)	60 (15)	0.98 (0.8-1.2)[a]	1.05 (0.82-1.4)[a]
Male sex	27 (69)	103 (65)	0.7 (0.4-1.5)	0.53 (0.27-1.0)
Intensive care unit	35 (89)	40 (25)	7.9 (2.8-23)	8.9 (3.2-25)
Median body weight, kg/m^2 (IQR)	82 (74, 93)	84 (75, 95)	0.6 (0.2, 2.3)[b]	0.9 (0.2, 3.9)[b]
History of venous thromboembolism	3 (7.9)	8 (5.2)	1.1 (0.3-3.0)	1.6 (0.4-7.2)
Anticoagulant use at admission	0 (0)	19 (12)		
Mean hemoglobin, mmol/L (SD)	8.0 (1.4)	7.9 (1.2)	1.04 (0.8-1.4)[b]	1.1 (0.8-1.5)[b]
Median white blood cell count, $\times10^9$/L (IQR)	7.6 (5.9, 11)	6.9 (5.4, 9.3)	1.9 (1.1, 3.2)	1.9 (0.9, 4.1)[b]
Median neutrophil count, $\times10^9$/L	6.0 (4.4-8.1)	5.2 (3.8-7.1)	2.0 (0.99-4.0)	1.7 (0.8-3.7)[b]
Median lymphocyte count, $\times10^9$/L	0.59 (0.47-0.83)	1.0 (0.8-1.3)	0.66 (0.43-1.02)	0.7 (0.4-0.95)[b]
Median neutrophil-to-lymphocyte ratio	11 (7.0-15)	5.4(3.5-8.1)	2.0 (1.3-3.1)[b]	1.7 (1.2-2.5)[b]
Mean platelet count, $\times10^9$/L	246 (87)	237 (95)	1.02 (0.99-1.1)[a]	1.002 (0.97-1.04)[a]
Median D-dimer, mg/L (IQR)	2.6 (1.1, 18)	1.0 (0.7, 1.7)	1.6 (1.2, 2.1)[b]	1.4 (1.1, 1.9)

Abbreviations: IQR, interquartile range; SD, standard deviation; SHR, subdistribution hazard ratio; VTE, venous thromboembolism. [a] Per 10-unit increase. [b] Per 1-unit increase. [c] Variables with a non-normal distribution (i.e., body weight, white blood cell count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, and D-dimer) were analysed log-transformed. [d] Multivariable analysis were adjusted for age, sex, and intensive care unit admission.

Risk factors for venous thromboembolism

Besides ICU stay, other risk factors associated with VTE in univariable regression analyses were a higher white blood cell count (SHR, 1.9 for every log-transformed unit increase; 95% CI, 1.1-3.2), higher neutrophil-to-lymphocyte ratio (SHR, 2.0 for every log-transformed unit increase; 95% CI, 1.3-3.1), and a higher D-dimer level (SHR, 1.6 for every log-transformed unit increase; 95% CI, 1.2-2.1) (Table 3). These associations remained materially unchanged when adjusted for age, sex, and ICU stay (Table 3), when excluding patients transferred from another hospital (data not shown), and when missing values were imputed (data not shown). Notably, none of the 19 patients (0%) who continued therapeutic anticoagulation that they used for other indications developed VTE compared with 39 of 179 of the remaining patients (22%; SHR, not estimable; Fisher exact test $P = 0.03$).

Discussion

We observed a very high risk of VTE in patients with COVID-19. Although the profound coagulopathy associated with COVID-19 has been described soon after start of the pandemic, few data on clinical VTE have been reported. In a cohort of 81 ICU patients in China, in which routine thromboprophylaxis was not the standard of care, the proportion of patients who were diagnosed with DVT was 25%; a follow-up

duration or cumulative incidence was not reported.[8] In a study of 184 ICU patients in 3 Dutch hospitals, where routine low-molecular-weight heparin prophylaxis was applied, 68 (37%) patients had VTE, with a reported cumulative incidence of 49%.[9] Similar observations have now been reported in ICU patients in France and Italy.[10,11] In our hospital, where thrombosis prophylaxis in patients admitted with COVID-19 is standard of care, VTE was observed in 35 of 75 (47%) ICU patients, with a cumulative incidence of 59% at 21 days. The very high incidence in ICU patients in the present study may partially be explained by the initiation of a screening approach, although the risk remained high if only symptomatic VTE was considered (28% of patients; cumulative incidence 34% at 21 days). In non-ICU COVID-19 patients admitted to the regular ward, 4 of 123 patients (3%) were diagnosed with symptomatic VTE despite thrombosis prophylaxis.

Our study has some limitations and strengths. First, this was a single-centre cohort study with a relatively small sample size, and 8% of patients were still hospitalized at the time of data collection. Second, including patients transferred from other hospitals may lead to immortal time bias because they need to survive until transfer, thereby potentially biasing the VTE cumulative incidence. However, restricting the analysis to patients admitted directly from our own emergency department did not substantially affect the results. Although immortal time bias could also have been introduced by placing patients who were transferred from the ward to the ICU in the ICU group, results were consistent when analysing ICU stay in a time-varying model. There appeared to be a considerable difference between the crude proportion of patients with VTE and the cumulative incidence estimate from the survival model, despite the use of a competing risk model to mitigate the influence of death. Likely explanations include the relatively short median follow-up duration, the number of patients still hospitalized, and the (informative) censoring of patients when discharged from the hospital; the risk of VTE in the latter group is likely to be lower than that of patients remaining in the cohort. Finally, based on concerns of a high risk of (fatal) VTE following early observations, we changed our practice during the follow-up period by performing screening compression ultrasound in the ICU every 5 days, while also performing a single cross-sectional round of compression ultrasounds at the ward in the 10 days before data collection. This screening led to diagnosis of asymptomatic DVT, all in the ICU group, which may be clinically less relevant than symptomatic DVT. Strengths include the inclusion of consecutive patients, the follow-up duration of at least 17 days, no loss to follow-up, and the objectively confirmed and adjudicated diagnosis of VTE.

Whether the high incidence of VTE observed in the ICU justifies higher or therapeutic doses of pharmacological prophylaxis at an acceptable bleeding risk and whether this would improve the outcome of severe COVID-19 pneumonia is unknown. One observational study from China that included 449 hospitalized

COVID-19 patients suggested that thrombosis prophylaxis was associated with a 56% to 63% reduction in mortality in patients with sepsis-induced coagulopathy, but not in other patients.[12] Only 22% of COVID-19 patients received thrombosis prophylaxis, which is much less than expected according to guidelines on thrombosis prophylaxis in medical patients.[13] Currently, several randomized controlled trials are being planned or have started in which the optimal dose of thrombosis prophylaxis will be investigated. Some of these trials use an elevated D-dimer level as an entry criterion (e.g., Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care [RAPID COVID COAG]; clinicalTrials.gov identifier NCT04362085). This approach is supported by the present observation that higher D-dimer levels at baseline are associated with VTE during follow-up. It is not known whether VTE contributes to respiratory deterioration or death in COVID-19 pneumonia, although VTE during the course of disease appeared to be associated with mortality in an exploratory analysis in our cohort. Interestingly, none of the patients who were receiving therapeutic anticoagulation at admission (for other indications) developed VTE.

The 3% risk of VTE among patients who were not admitted to ICU is considerable, despite the standard use of thrombosis prophylaxis. In an Italian single-centre retrospective cohort study, the proportion of COVID-19 patients with VTE was 6% in ward patients, corresponding to a cumulative incidence of 7%.[11] These reported risks appear to be higher than expected in medical hospitalized patients who are not critically ill.[13]

Based on the present findings, we believe the threshold of suspicion of VTE in COVID-19 patients should be low and elicit appropriate diagnostic testing and treatment if VTE is diagnosed. The clinical value of ultrasound screening of the lower extremities in ICU patients with COVID-19 is a matter of debate. However, given the high risk of symptomatic VTE in ICU patients, screening followed by initiating therapeutic anticoagulation may be justified in patients diagnosed with asymptomatic (proximal) DVT to prevent extension and embolization. It is possible that a higher intensity of thrombosis prophylaxis, both in ICU and ward patients, not only decreases VTE but also decreases mortality. Future research should therefore focus on optimal diagnostic and prophylactic strategies for VTE in hospitalized patients with COVID-19.

Aknowledgements

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Conflict of interest

Dr. Middeldorp reports grants and fees paid to her institution, outside the present work, from Abbvie, BMS/Pfizer, Aspen, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Sanofi, and Portola. Dr. Coppens reports research support and lecturing or consultancy fees, outside the present work, from Bayer, CSL Behring, Daiichi Sankyo, Novo Nordisk, Sanquin Blood Supply, Sobi, and Portola. Dr. van Es reports fees paid to his institution, outside the present work, from Bayer, LEO Pharma, and Daiichi Sankyo. The other authors have no disclosures.

Author contributions

All authors contributed substantially to the study design, acquisition, analysis, and interpretation of the data. Saskia Middeldorp, Michiel Coppens, and Nick van Es drafted the first version of the manuscript. All authors revised the manuscript critically and approved the final version.

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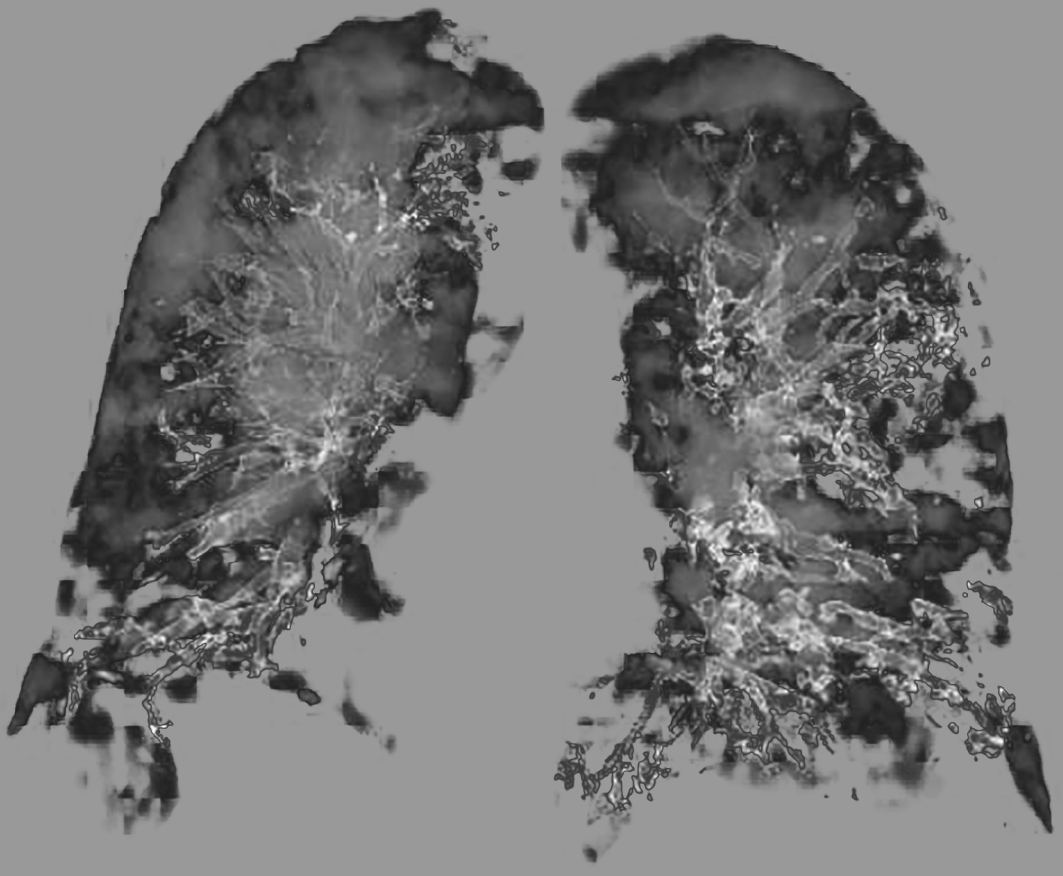

Chapter 8

Extensive pulmonary perfusion defects compatible with microthrombosis and thromboembolic disease in severe Covid-19 pneumonia

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Abstract

Background

It is unclear why some patients with progression to severe COVID-19 pneumonia require invasive mechanical ventilation while others can be managed with supplemental oxygen. We hypothesized that pulmonary perfusion defects consistent with microthrombosis are common in COVID-19 patients requiring mechanical ventilation.

Methods

We studied 20 consecutive PCR confirmed COVID-19 pneumonia patients who were admitted to the hospital due to acute respiratory failure and who had a clinical suspicion of pulmonary embolism. We compared 10 ICU patients who required invasive mechanical ventilation to 10 patients who were managed on the ward. All patients underwent dual energy CT Pulmonary Angiography (CTPA). Lung analysis for iodine distribution maps was used to evaluate pulmonary perfusion and were compared between groups.

Results

Median duration between disease onset and CTPA was 16 (IQR 11) vs. 13.5 (IQR 10) days for the ICU and ward-groups, respectively. Pulmonary emboli were diagnosed in 8 ICU patients and 2 ward patients ($p<0.005$). All ICU patients showed bilateral extensive scattered perfusion defects while ward patients only showed small perfusion defects near the pleura or directly associated with a pulmonary embolism (mean area 52.5%±14.8 vs. 17.5%±7.5 of total lung volume; $p<0.0001$). No significant differences in right ventricular dysfunction signs were observed.

Conclusions

Mechanically ventilated ICU patients with severe COVID-19 pneumonia associated respiratory failure have both a high incidence of pulmonary embolism as well as scattered large areas of severely diminished lung perfusion, resulting in a pulmonary ventilation perfusion mismatch, most likely reflecting pulmonary microcirculatory dysfunction due to inflammatory response with microthrombosis.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) can result in severe COVID-19 pneumonia and poses unprecedented health care problems, both on a global scale and for many individual patients.[1,2] Acute respiratory failure is the most common reason for hospital admission. Many patients can be managed with supplementary oxygen on the ward, but in up to 20% respiratory failure progresses and requires admission to an intensive care unit (ICU) for mechanical ventilation.[3] The mortality of these patients is particularly high, ranging up to 50%.[4]

Several hypotheses have been proposed to explain the differences in clinical course between patients. One hypothesis is that pulmonary embolism results in severe hypoxemia. Observational studies suggest a high incidence of deep vein thrombosis in COVID-19, up to 25% in ICU patients compared to 6.5% in ward patients,[5] which may progress to pulmonary embolism. Pulmonary oedema as a result of dysbalance of the bradykinin-kallikrein system is also suggested to contribute.[6] Another hypothesis is the onset of local thrombosis in the pulmonary microvasculature due to an inflammatory thrombotic microangiopathy.[7,8] All entities are observed in some autopsy reports of COVID-19 patients.[9-11] A better understanding of why gas exchange worsens is important as this could set the stage for intervention studies.[12,13]

We performed a cross-sectional study comparing advanced functional imaging findings on dual energy CT Angiography (CTPA) between patients with COVID-19 pneumonia who were admitted to the ICU for invasive ventilation and patients who were admitted to the ward with supplemental oxygen. We hypothesized that patients requiring invasive mechanical ventilation for COVID-19 related acute respiratory failure have more extensive perfusion defects compared to patients not requiring invasive ventilation.

Materials and Methods

Patients and study design

This was an observational study in 20 patients who were admitted after March 15th 2020 to a university hospital in the Netherlands with RT-PCR confirmed COVID-19 and in the course of the disease had a clinical suspicion of pulmonary embolism. We compared 10 consecutive patients with severe COVID-19 pneumonia who were admitted to the ICU requiring mechanical ventilation to 10 consecutive patients who were managed on the COVID-19 ward with supplemental oxygen with a maximum of 15 L/min via non-rebreathing mask but no need for positive pressure ventilation. All ICU patients were admitted because of type I respiratory failure. We do not perform high flow nasal oxygen therapy or continuous positive airway pressure ventilation in patients with severe COVID-19 pneumonia and all ICU-patients are

intubated and mechanically ventilated. All patients had radiological characteristics of COVID-19, scored as CORADS 5 according to the CO-RADS system, the "COVID-19 Reporting and Data System".[14] CO-RADS 5 implies a very high level of suspicion for pulmonary involvement of COVID-19 based on typical CT findings (multifocal bilateral ground-glass opacities, with or without consolidations, in lung regions close to visceral pleural surfaces). All patients underwent a dual energy CT Pulmonary Angiography for clinical suspicion of pulmonary embolism, for the ICU patients primarily on clinical grounds, for the ward patients according to the YEARS-criteria.[15] Informed consent was waived by the institutional ethics committee.

Data collection

Clinical data were obtained through review of medical records. Patient characteristics (age, gender, comorbidities), clinical follow up, including multidisciplinary conferences, and RT-PCR results were extracted from electronic patient records. The data reported here are those available through May 15th , 2020. Results are reported according to the STROBE guideline.

Imaging

CT-images were acquired from a high-end dual source CT (CT Somatom Force, Siemens Healthineers, Forchheim, Germany) in the emergency department solely dedicated to COVID-19 (suspected) patients. A non-enhanced Chest CT (NECT) scan followed by a dual energy CT Pulmonary Angiography (CTPA) in deep inspiration was obtained from all 20 patient with the following scan parameters: for NECT: 100/Sn150 kVp, Qref mAs 200 mA, pitch 1.8, rotation time 0.25 sec, careDose4D, and for CTPA: collimation 2 *192 * 0.6 mm, 80/Sn150 kVp, Qref mAs 90/50, pitch 0.55, rotation time 0.25 sec, after injection of 50 mL contrast medium (Iomeron 300, Bracco Imaging, Germany) at 5 mL/s in the right antecubital vein. Reconstructions were done in 1 and 3 mm lung and soft kernel. Post-processing was performed on a dedicated software platform (Syngo via, VB30, Siemens Healthineers, Forchheim, Germany). Iodine maps were constructed from Lung Analysis; both axial, sagittal and coronal iodine multiplanar reconstructions (MPR) were made with 1 and 5 mm slice thickness and increment.

All images were evaluated independently by two radiologists (LB and MS) with respectively 15 and 7 years of experience in chest imaging, differences were settled in consensus. Images were primarily read in PACS (Enterprise Imaging, AGFA-Gevaert, Mortsel, Belgium) in 3 orientations (axial, coronal and sagittal) with additional MPR if deemed necessary. Standard pulmonary angiography, mediastinal and lung parenchyma window settings were used, with individual adaptation when necessary. Pulmonary embolism was defined as a constant intravascular filling defect on CTPA. Location of a filling defect was registered for each lobe until

most distal subsegmental levels, occurrence of an isolated subsegmental defect and central emboli were also noted separately. Severity of the COVID-19 pneumonia was assessed semi-quantitatively, scored for each lobe in steps of 25% (0: normal; 1: < 25%; 2: <50%; 3: <75% and 4>75% of lobe volume involved) with a maximum score of 20. Iodine maps were calculated for Pulmonary Blood Volume (PBV) using a dedicated software program (Lung analysis).[16] Pulmonary blood volume perfusion defects were visually assessed semi-quantitatively on the orange coloured iodine distribution maps in steps of 10% for each lung, and a composite volume for both lungs. The following parameters suggestive of right ventricular dysfunction were assessed: right-to-left ventricular (RV/LV) ratio, pulmonary trunk diameter, bowing of the interventricular septum and reflux of contrast medium into intrahepatic veins > 3 cm.[17] All data were registered on a specially designed CRF.

Statistical analysis

Data are presented as mean ± standard deviation (SD) for normally distributed variables and median ± interquartile ranges (IQR, 25th to 75th percentile) for non-normally distributed variables. For comparison on binary outcomes Chi-square or Fisher's exact test for dichotomous variables was used and for continuous data between groups by Students T test or Mann-Whitney U test where applicable. Significance of differences were evaluated with two-sided p-values; a p-value <0.05 was considered to imply statistical significance. All statistics were performed in SPSS version 26 (SPSS Inc, Chicago Ill).

Results

Patients demographics are displayed in Table 1. The mean (±SD) age of patients was 63.9±7.8 for patients admitted to the ICU and 61.7±9.1 years for patients who were managed on the ward.

Duration of symptoms to the moment of CTPA imaging was not different between the two groups (16 vs. 13.5 days, P=0.24). CT severity scores indicative of the extent of parenchymal involvement were higher in the ICU patient compared to the ward patients (17.7±2.0 vs 8.5±3.8 of max. 20 points; p<0.001).

Table 1: Patient characteristics of ICU and ward patients with severe COVID-19 pneumonia.

	ICU N=10		Ward N=10		*p*-value
Baseline					
Age *years* (Mean; SD)	63.6	8.2	61.7	10.2	0.60
Sex (N; %)					0.37
Male	6	(60)	5	(50)	
Female	4	(40)	5	50)	
Weight *kg* (Median; IQR)	87.0	(25.0)	97.0	(32.0)	0.21
BMI (Median; IQR)	28.3	(4.8)	33.3	(18.8)	0.081
Co-morbidities					
Obesity (N; %)	4	(40)	4	(40)	
Diabetes (N; %)	3	(30)	3	(30)	
Hypertension (N; %)	2	(20)	4	(40)	
Cancer (N; %)	0	(0)	0	(0)	
Cardiovascular Disease (N; %)	2	(20)	1	(10)	
Cerebrovascular Disease (N; %)	2	(20)	0	(0)	
Obstructive Pulmonary Disease (N; %)	3	(30)	2	(20)	
History of DVT/PE (N; %)	1	(10)	2	(20)	
Clinical course of COVID-19					
Duration symptoms to hospitalization *days* (Median; IQR)	6	(5)	8	11	0.03
Duration symptoms to CTPA *days* (Median; IQR)	16	(11)	13.5	10	0.24
Mortality (N; %)	6	(60)	0	(0)	0.003
Discharged (N; %)	0	(0)	8	(80)	0.000
Use of anticoagulation					
Use of therapeutic anticoagulation at time of CTPA (N; %)	1	(10)	0	(0)	
Antiplatelet use (N; %)	3	(30)	0	(0)	
LMWH prophylaxis (N; %)	9	(90)	9	(90)	
Concomitant DVT (N; %)	6	(60)	1	(10)	
Laboratory values at day of CTPA					
CRP *mg/L* (median; IQR)	227.9	(138.5)	77.5	(147.6)	0.27
Hb *mmol/L* (mean; SD)	6.9	(1.1)	7.9	(2.3)	0.74
WBC $x10^9/L$ (median; IQR)	7.8	(9.8)	4.9	(2.5)	0.006
Lymphocytes $x10^9/L$ (median; IQR)	0.49	(0.09)	0.68	(0.36)	0.11
Platelet count $x10^9/L$ (median; IQR)	261	(212)	148	(67)	0.016
Fibrinogen *gl/L* (median; IQR)	8.3	(2)	NA		0.37
APTT *seconds* (median; IQR)	44.5	(23)	23	(4)	0.002
PT *seconds* (median; IQR)	11.3	(0.74)	10.9	(0.6)	0.64
D-dimer *mgl/L* (median; IQR)	7.4	(10.5)	1.3	(3.7)	0.017
Creatinin *umol/L* (median; IQR)	77.0	(25)	81.0	(64)	0.65
LDH *Ul/L* (median; IQR)	616	(180)	353	(298)	0.09
Ventilation parameters					
PEEP *cmH2O* (Median; IQR)	8.9	(2.9)			
Driving pressure *cmH2O* (Median; IQR)	12.2	(8.1)			
Plateau pressure *cmH2O* (Median; IQR)	21.1	(8.0)			
Tidal Volume *mL/kg* (Median; IQR)	5.8	(2.1)			
PaO2/Fio2 *mmHg* (Median; IQR)	114	(39)			
Compliance *mL/cmH2O* (Median; IQR)	56.6	(33.9)			

Table 2: Radiological characteristics of ICU and ward patients with severe COVID-19 pneumonia who underwent CT Pulmonary Angiography.

	ICU N=10		Ward N=10		*p*-value
CORADS & Disease Severity					
CORADS	5		5		1
CT Severity points (max20; mean, SD)	17.7	(2.0)	8.5	(3.8)	<0.001
Ascending aorta *HU* (median, IQR)	261	(109)	256	(151)	0.65
Pulmonary trunk *HU* (median, IQR)	295	(156)	365	(138)	0.33
Aorta/pulmonary trunk *HU* (mean, SD)	0.94	(0.48)	0.74	(0.36)	0.35
CT angiography results					
Pulmonary embolism					
Present (N; %)	8	(80)	2	(20)	0.007
Bilateral (N; %)	5	(50)	1	(10)	<0.001
Most proximal clot location					
Central (N; %)	2	(20)	1	(10)	
Segmental (N; %)	4	(40)	0	(0)	
Subsegmental (N; %)	1	(10)	1	(10)	
Isolated subsegmental (N; %)	1	(10)	0	(0)	
Signs of right ventricular dysfunction					
Right/Left Ventricular ratio > 1.0 (N; %)	3	(30)	3	(30)	1
Pulmonary Trunk > 29 mm (N; %)	4	(40)	2	(20)	0.068
Septal flattening (N; %)	2	(20)	1	(10)	0.53
Reflux of contrast medium (N; %)	2	(20)	1	(10)	0.53
Perfusion defects Iodine map					
Right lung % *of lung* (mean, SD)	52.0	(16.2)	21.0	(5.7)	0.009
Left lung % *of lung* (mean, SD)	52.0	(16.2)	20.0	(10.5)	<0.001
Total % *of both lungs* (mean, SD)	52.5	(14.8)	17.5	(7.5)	<0.001
Total perfusion defect >1/3 lung volume (N; %)	10	(100)	0	(0)	<0.001
Pulmonary blood volume right lung	838	(669)	1209	1527	0.049
Pulmonary blood volume left lung	536	(490)	895	(1289)	0.023
Pulmonary blood volume lungs	1404	(1423)	2039	(2934)	0.034

Pulmonary embolism was found more often in ICU patients compared to patients managed on the ward: 80% (n=8) versus 20% (n=2; p<0.005; Table 2). Central emboli were observed in 2 ICU patients and 1 ward patient.

Analysis of the iodine pulmonary blood volume maps showed strikingly different appearances between the two groups (Figure 1).

ICU patients displayed large areas of scattered perfusion defects throughout both lungs, not only at the subpleural regions but also in the deeper parts of the lungs remote from the pleura or fissures. The areas with perfusion defects were anatomically not completely explainable by pulmonary embolism and parenchymal involvement. Estimated mean percentage of perfusion defects was 52.5%±14.8 in ICU patients and 17.5%±7.5 in COVID-19 ward patient (p<0.001; Figure 2).

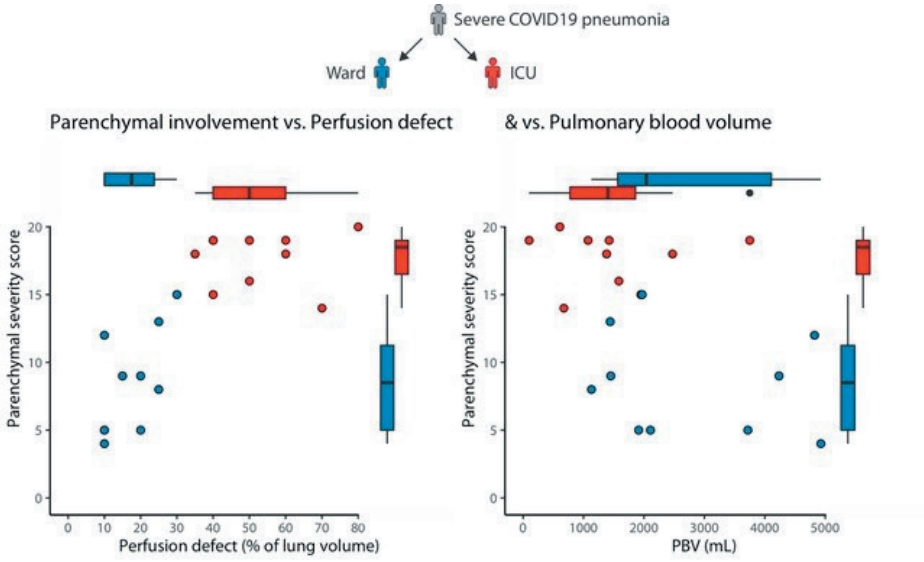

Figure 1:
Relationship between parenchymal involvement, perfusion defect, pulmonary blood volume for intubated ICU patients (red) and ward patients (blue). Y-axis: Parenchymal involvement with maximal score 20. Left panel, x-axis: perfusion defect as percentage of lung volume. Right panel, x-axis: pulmonary perfused blood volume (PBV) in mL.

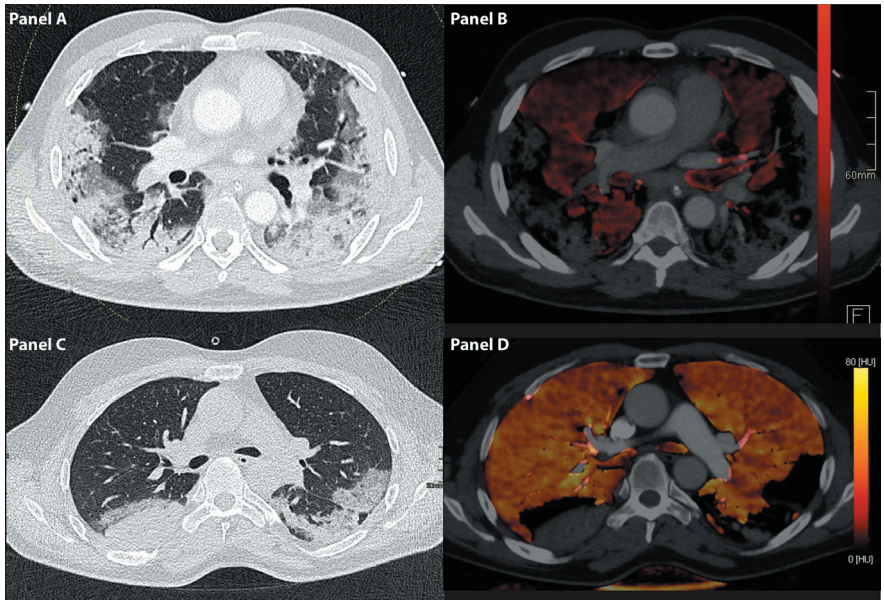

Figure 2:
CT and Dual energy CTPA Pulmonary Blood Volume maps in two COVID-19 patients. Top panels: ICU patient with mechanical ventilation. Bottom panels: ward patient. Left panels: CT images in lung setting. Right panels: Perfusion reconstructions. (a) example of extensive involvement of the lung parenchyma (b) pulmonary embolus in the right lower lobe, with bilateral large areas of perfusion defects, also without associated pulmonary emboli. Note the limited areas of normal perfusion (orange) even in visually rather normal appearing lung zones. (c) bilateral posterior consolidations and areas of ground glass. (d) CTPA showed no pulmonary embolism. Homogeneous perfused blood volume in both lungs, with restriction only in the consolidated areas.

A lower pulmonary blood volume was seen in ICU patients (1404 mL) compared to patients managed on the ward (2039 mL, p=0.03; Figure 3, Table 2). Enhancement of pulmonary trunk and aorta was not different between the 2 groups. No significant differences were present between the groups with respect to signs of right ventricular dysfunction.

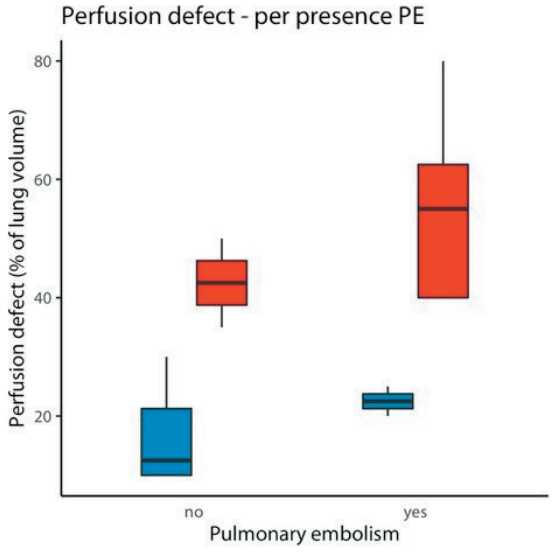

Figure 3:
Perfusion defect as percentage of lung volume stratified for the presence of pulmonary embolism for intubated ICU patients (red) and ward patients (blue).

Discussion

The main findings of our study can best be summarized as follows: (1) intubated and mechanically ventilated ICU patients with COVID-19 related acute respiratory failure show extensive bilateral patchy areas of perfusion defects, which are not seen in patients who do not require invasive mechanical ventilation; (2) pulmonary embolism is also more frequent in ICU patients (3) perfusion defects occur also in normally aerated areas without adjacent pulmonary embolism, possibly due to microthrombi. The observed extensive pulmonary perfusion defects might contribute to the severity in respiratory failure in concert with increased shunt due to the loss of aeration as a result of parenchymal involvement.

The remarkably higher incidence of pulmonary embolism we observed is in line with the reported incidences of venous thromboembolic events in several cohorts of COVID-19 patients.[18-20] Deep vein thrombosis, both in the distal and proximal veins of the lower extremities as well as in the upper limbs or jugular veins, is frequently observed in COVID-19 patients on the ICU.[5,21-23] Despite this fact, our

observation that the minority of cases had central pulmonary embolism suggest that the pulmonary emboli are not all the result of deep vein thrombosis migrating to the pulmonary vasculature. Local microthrombi might better explain our observations and might result from diffuse alveolar damage and local thrombotic microangiopathy, which is in line with a case series of post mortem COVID-19 sections of the lungs.[11,24] This is not unique for COVID-19 pneumonia as acute infections in general are associated with a transient increased risk of venous thromboembolic events. The pathophysiology of thrombotic coagulopathy is complex and multifactorial, involving an interplay between cellular and plasmatic elements of the haemostatic system and components of the innate immune response to the infecting pathogen.[25,26] This study emphasized the need for a better understanding of this interplay in severe COVID-19 pneumonia.[27]

The scattered areas of diminished pulmonary perfusion as encountered in the COVID-19 ICU patients included in this study are strikingly different from the perfusion defects that are commonly seen on these scans.[28-30] The currently available evidence suggests that these perfusion defects cannot only be attributed to acute lung injury or mechanical ventilation, [31,32] but are rather unique for severe COVID-19 pneumonia. Peripheral perfusion defects were also seen in the included ward patients with pulmonary embolism but occurred adjacent to the embolism. Pulmonary embolism only partly explained the perfusion defects in ICU patients, as these also occurred without any adjacent intravascular filling defects. Perfusion defects have long been known to emerge after pulmonary embolism as they were frequently observed on regular nuclear V/Q scans.[33] Clinically, over the last decade dual energy CT scanners proved to provide comparable functional imaging by iodine density maps as surrogates of lung perfusion.[28,29,34] In pulmonary embolism the imaging defects are regularly confined to the periphery, and only infrequently cover more than a third of the normal pulmonary area.

In our study perfusion defects extended in some areas beyond the boundaries of consolidations and ground glass opacities into quite normal appearing lung tissue. Absent perfusion in normally aerated lung tissue is detrimental, certainly in the context of pneumonia, as it will cause additional dead space ventilation and may redirect pulmonary blood flow to poorly- or non-aerated lung tissue resulting in additional shunt and therefore hypoxemia. In pulmonary embolism outside the context of COVID-19, the thrombotic burden and diminished lung perfusion areas could result in an increase in the afterload of the right ventricle, which then could lead to right ventricular dysfunction and acute heart failure,[17,35] however between our two groups no significant differences were seen with regard to signs of right ventricular dysfunction. A possible explanation may be that regulatory vasodilatation occurs in other regions, which aggravates shunt, although we are uncertain about the mechanism through which this is regulated. The large areas of severely diminished

perfusion most likely reflect diffuse pulmonary microcirculation dysfunction that is irrespective of the presence of pulmonary embolism. Pinpointing the exact location of the microcirculatory blood flow disturbances is challenging, yet important to better understand the pathophysiological substrate of our findings. Our findings are consistent with a recent case report that also suggested vascular and perfusion abnormalities in severe COVID-19 pneumonia,[7] although the extent of the perfusion defects is much more evident in this present study.

The strength of our study is that all patients underwent advanced imaging using a high-end dual source CT-scanner dedicated to COVID-19 patients. This limits the chance of measuring artefacts, although even then technical challenges remain. Our study also has several limitations. First, this is a single centre study using a cross sectional design which does not allow to make any causal inferences with regard to the pathophysiology or order of events. Second, we used semi-quantitative scores for single pass CT perfusion evaluation. Quantitative measurements for image analysis require a time-consuming procedure, and above that are not validated for the investigated questions. Also, we did not prospectively calculate the dead-space and shunt fractions in the included patients and were unable to link the imaging results with gas-exchange.[36] Finally, we cannot assess the impact of positive pressure ventilation on the observed perfused blood volumes and perfusion defects. Although the effect of positive pressure ventilation on lung perfusion is well known, little data is available on the changes in regional perfusion defects like we observed. Two animal studies applying positive pressure ventilation did not report any perfusion defects similar to what we describe here.[31,37]

In conclusion, Invasively mechanically ventilated ICU patients with severe COVID-19 frequently develop pulmonary embolism and also show large scattered areas of severely diminished perfusion consistent with diffuse pulmonary microcirculatory dysfunction. These defects are independent of the presence of pulmonary embolism, possibly reflective of microthrombi in the pulmonary circulation. The combination of extensive parenchymal involvement with diffuse perfusion abnormalities may explain the occurrence of severe and persistent respiratory failure that is frequently seen in patients with severe COVID-19 pneumonia who require mechanical ventilation.

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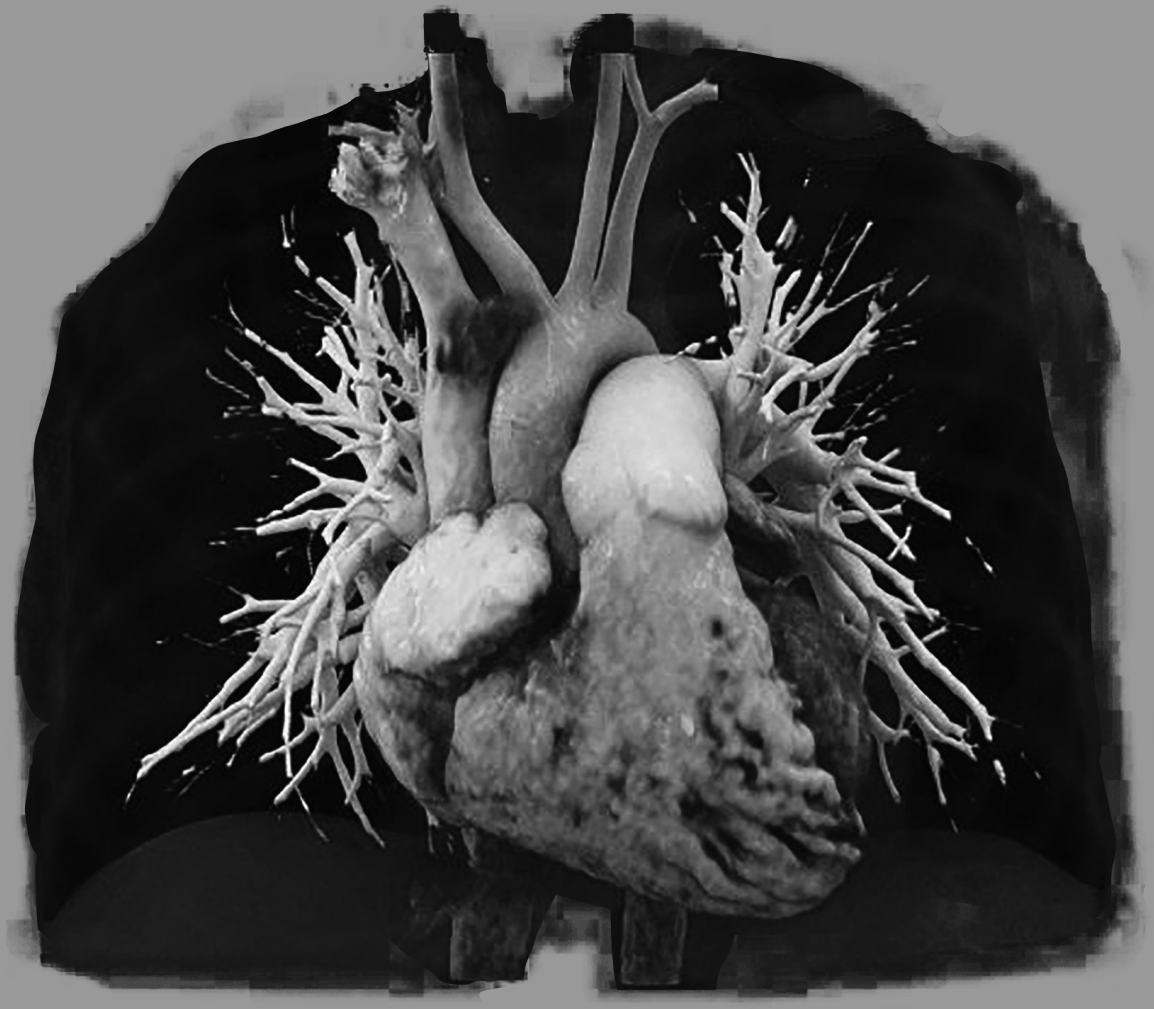
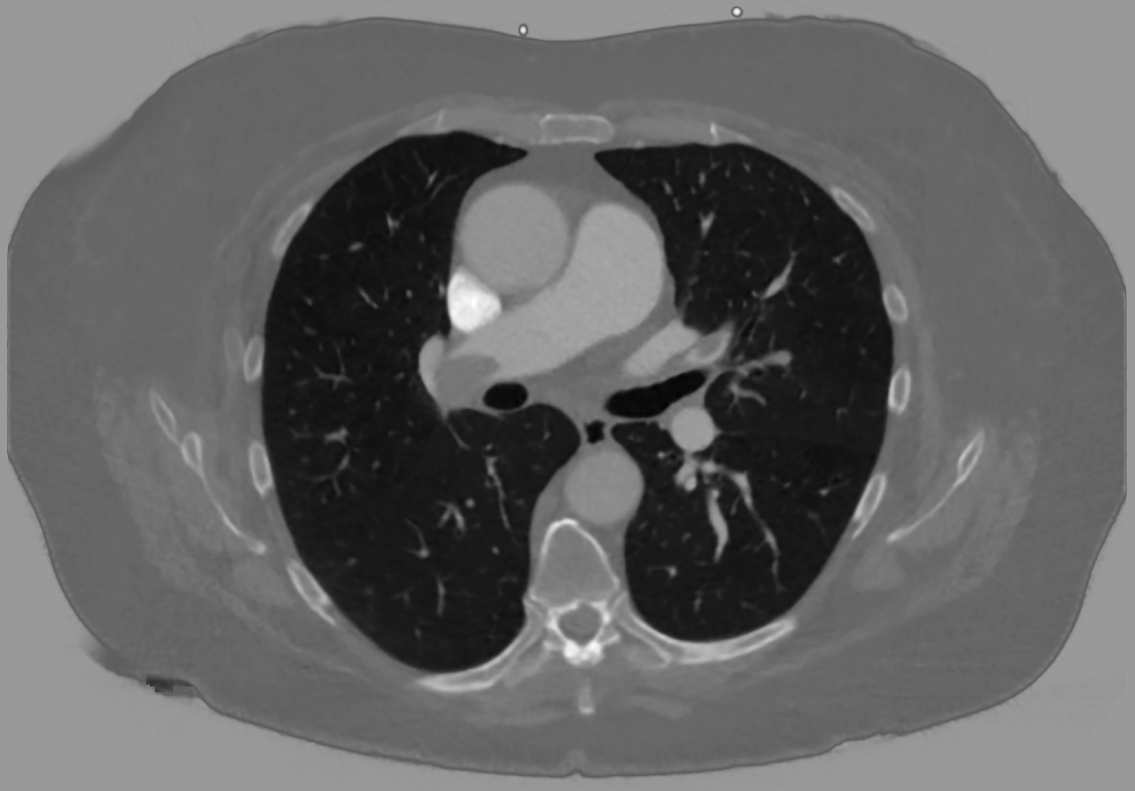


PART IV

General Discussion and Appendix



Chapter 9

General discussion & future aspects

General discussion

In this thesis I examined the possibilities of improving the diagnostic management strategy and risk assessment of patients suspected to have pulmonary embolism (PE). With computed tomography pulmonary angiography (CTPA) not only the presence of pulmonary emboli can be established, but also risk estimation can be derived from various radiological parameters. In this way, use of imaging can be further optimized.

This thesis is divided into three parts. *Part I* focuses on the improvements in diagnostic decision support for patients with the suspicion of a pulmonary embolism. In *Part II*, for patients with confirmed pulmonary emboli the additional value of findings on CTPA in risk assessment and prognosis is explored. In *Part III*, the interaction between COVID-19 and VTE is discussed.

PART I - DIAGNOSIS

An important step in the evaluation of the suspicion of pulmonary embolism is the decision whether a patient has to undergo imaging to confirm or exclude the diagnosis. To this end, several diagnostic strategies have been developed, that include both a clinical decision rule and d-dimer test to assess the probability of pulmonary embolism. A 'pulmonary embolism unlikely' clinical decision rule with a negative D-dimer result safely excludes pulmonary embolism in 30% of presenting patients.

In **chapter 2** we aimed to simplify this diagnostic approach and to increase its efficiency. Data of two large prospective multicentre cohort studies in the Netherlands with consecutive patients suspected of pulmonary embolism were used for derivation and subsequent validation. After constructing a logistic regression model with the known D-dimer test result and items from the Wells clinical decision rule, we identified the most prevalent combinations of informative items and selected new D-dimer thresholds. In addition to a given D-dimer test result only three Wells items showed significant incremental value: haemoptysis, signs of deep vein thrombosis and 'pulmonary embolism most likely diagnosis'. Two groups were identified in whom pulmonary embolism could be excluded without CTPA: (1) none of these three items positive and a d-dimer lower than 1000 ng/mL D-dimer; (2) one or more of these items positive and a d-dimer lower than 500 ng/mL. In this post-hoc analysis, pulmonary embolism could be excluded without CTPA in 36%, at a false-negative rate of 1.2%. (95% CI 0.04-3.3%). Combining the D-dimer test result with items of the Wells score resulted in a simple clinical decision rule with a high sensitivity and a significantly higher specificity compared to the previously most widely used diagnostic algorithm, i.e. the Wells score-D-dimer combination. We called this algorithm the YEARS algorithm, after Café De Jaren (Dutch for "years")

where the investigators met to discuss these findings.

This newly developed YEARS clinical decision rule that incorporates differential D-dimer cut-off values at presentation has been developed to reduce the number of CTPA investigations in all age groups. Before its implementation in clinical practice could be considered, a prospective validation study of this clinical decision rule was needed; the results are described in **chapter 3**. In this prospective multicentre study in 12 hospitals in the Netherlands 3465 patients were assessed of whom 13% were diagnosed with pulmonary embolism. Of the 85% in whom pulmonary embolism was ruled out according to the YEARS algorithm and remained untreated, 0.6% (95% CI 0.36–0.96) of these patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up. CTPA was not indicated in 48% of patients, i.e. a 14% absolute decrease of CTPA examinations compared to the Wells' rule and fixed D-dimer threshold of less than 500 ng/mL.

PART II - PROGNOSIS

Prognosis of pulmonary embolism is determined primarily by the hemodynamic status of the patient. In general, the burden of embolic clots exerts a negative impact on the heart leading to right ventricular dysfunction (RVD). According to the ESC guidelines, in intermediate and low risk patients, prognosis is further refined by assessing the (simplified) PESI- pulmonary embolism severity index, combined with signs of right ventricular dysfunction. Apart from laboratory tests (NT-pro BNP) or echocardiography, information on right ventricular dysfunction also can be derived from the CTPA establishing the diagnosis of pulmonary embolism, although no general consensus exists on which of the parameters should be used.

In **chapter 4** the value of various cardiovascular CTPA parameters for prognosis and risk stratification on short- and long-term clinical outcomes were evaluated. Radiological and clinical data of 1950 patients with acute pulmonary embolism who participated in an international randomized clinical trial on anticoagulants (Hokusai VTE) were used. Studied parameters were 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, hospitalization, bleeding and adverse events were assessed over the short term and long term. Pulmonary trunk enlargement was the only parameter significantly associated with mortality over both the short and long term, as well as with recurrent VTE and hospitalization.

In **chapter 5** the association of body mass index (BMI) with prognostic indicators and clinical outcomes in patients with pulmonary embolism was studied. Patients were analysed with regard to World Health Organization (WHO) BMI categories at the time of inclusion in the trial. We found that several clinical and radiological prognostics characteristics and right ventricular dysfunction in pulmonary embolism

were not evenly distributed among BMI categories. The relationship between BMI categories and both prognostic parameters and clinical outcomes showed U-shaped curves, reflected in a trend towards worse outcomes in patients who are either overweight or underweight.

Apart from excluding or confirming a diagnosis of pulmonary embolism, CTPA also can provide an alternative diagnosis. When such a pathology is present together with pulmonary embolism this could increase the disease burden a patient has to cope with, and potentially could negatively influence survival. In **chapter 6** we aimed to determine the impact of concurrent cardiac and pulmonary disease identified on the diagnostic CTPA on clinical outcome of acute pulmonary embolism. We assessed occurrence and severity of a variety of comorbidities (pleural fluid, pericardial fluid, consolidations, coronary and aortic calcifications) and clinical and radiological prognostic characteristics for right ventricular dysfunction. Concomitant disease was present in 66.6% of all patients. Compared to patients without concomitant diseases, the odds for mortality with presence of mild, moderate and severe disease on CTPA was 4.9, 10.4 and 32 (95% CI 1.4-16.8, 3.0-36.2 and 10.0-115.9; and adjusted for sPESI and age 3.4, 4.8 and 15.3; (95% CI 1.0-11.9, 1.3-17.6 and 4.3-54.8). This stepwise association between disease severity and mortality was apparent in all evaluated CTPA findings. Concomitant disease observed on the baseline CTPA in patients with acute pulmonary embolism thus impacts mortality and may be of additional value in risk stratification and prognosis.

PART III - COVID

At present, Coronavirus disease 2019 (COVID-19) is dominating medicine and the world. Thrombosis, both VTE and arterial has proven to be a striking complication of COVID-19, as a consequence of marked coagulation activation and coagulopathy. In **chapter 7** we investigated the incidence of venous thromboembolism in 198 hospitalized patients with COVID-19 during the first wave of the pandemic. During a median follow-up of seven days 20% of patients were diagnosed with VTE, of whom 13% had symptomatic VTE, despite routine thrombosis prophylaxis. The cumulative incidence of VTE at 21 days was 42%, and was much higher in the ICU than on the wards. So, the observed risk for VTE in COVID-19 is high, particularly in ICU patients, which should lead to a high level of clinical suspicion and low threshold for diagnostic imaging for DVT or pulmonary embolism.

In **chapter 8** we evaluated pulmonary perfusion characteristics of COVID-19 patients with a suspicion of pulmonary embolism using dual energy CTPA. We found that invasively mechanically ventilated ICU patients with severe COVID-19 not only can develop pulmonary embolism but also show large scattered areas of severely diminished perfusion consistent with diffuse pulmonary microcirculatory dysfunction. These defects seem to be independent of the presence of pulmonary

embolism, possibly reflecting microthrombi in the pulmonary circulation. The combination of extensive parenchymal involvement with diffuse perfusion abnormalities may explain the occurrence of severe and persistent respiratory failure that is frequently seen in patients with severe COVID-19 pneumonia who require mechanical ventilation.

Future aspects

A clinical decision rule should be robust, reliable, intuitive, and easy to use. The YEARS algorithm allows the physician to exclude pulmonary embolism in a large proportion of patients without using imaging. For the future it seems however challenging to further optimize this algorithm. To further increase efficiency, probably more parameters should be incorporated, which in turn would complicate the decision process, and thus compromises the user-friendliness and willingness to use it in clinical practice. The role of the YEARS algorithm in different subgroups and populations is of interest, such as inpatients, patients with cancer and patients with COPD. Also for critical care patients it would be of value, as in this population an additional downside of the need for imaging is the disadvantage of transporting such patients with associated risk for complications. After publication of the YEARS algorithm, it has been investigated for pregnant women in the Artemis study and confirmed to be a safe and useful strategy, with a small adaptation with compression ultrasonography in case of signs of DVT. At present the multicentre HYDRA study is including patients with cancer and a suspicion of pulmonary embolism.

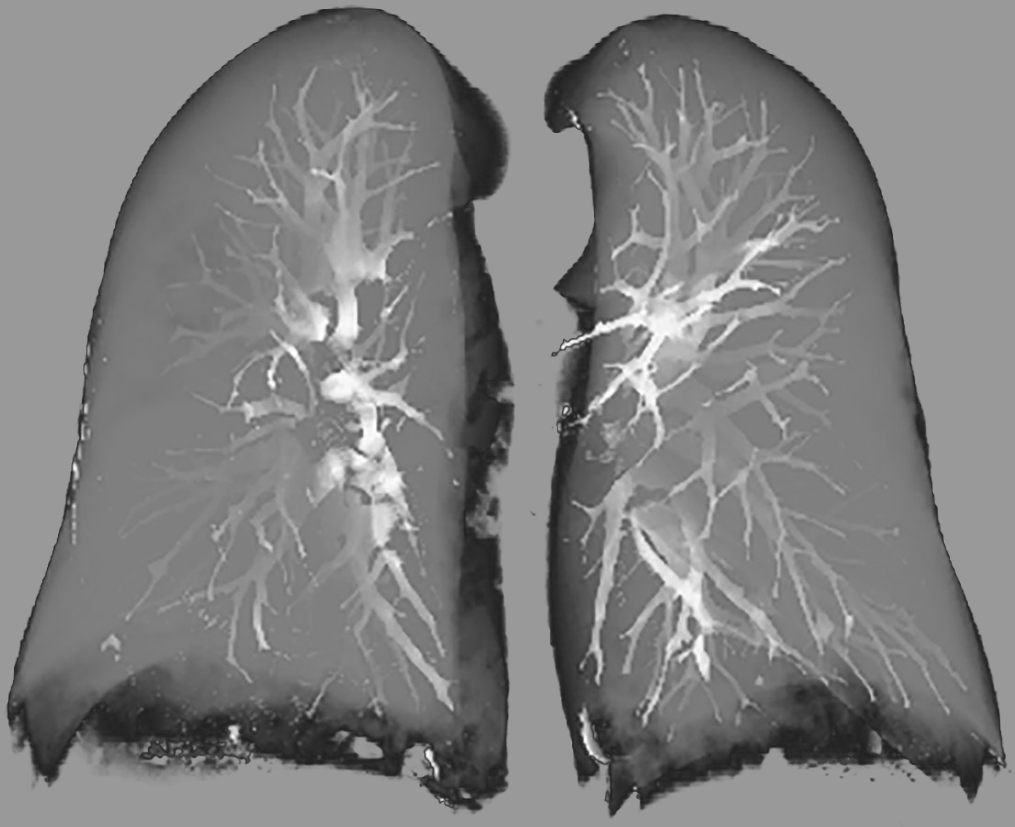
With respect to assessing prognosis, large scale prospective studies on the role of radiological cardiovascular parameters in risk stratification, both separately as well as in combination with other biomarkers, will be needed to confirm the findings and clinical impact presented in this thesis. This could be approached from two sides: looking at the negative predictive value, or focussing on the prognostic value: which patients carry a very low risk and can be discharged home safely, and in which patients is a more aggressive therapeutic approach be warranted?

Concomitant pathologies on CTPA can probably be regarded as modifiers in risk estimation for both the intermediate and low risk categories, with impact on either the decision about home treatment, or close clinical monitoring on the other side of the spectrum.

Many potential parameters have been suggested for prognostication, yet are not integrated in clinical practice as these are too difficult in the daily work flow. Meta-analyses of individual patient data with pooling of (un)published results from large registries and clinical trials could potentially provide opportunities for subgroup analyses and adjustment for confounders in prognostication. Standardized reporting

of radiological, clinical and biochemical parameters into an integral format could be of additional value. Future studies should explore imbedding these uniformly reported findings in artificial intelligence programmes integrated into electronic patient data programs.

In Covid-19, future research should focus on optimal diagnostic and prophylactic strategies of VTE that may potentially improve survival of patients. Characterization of the different pulmonary and extra-pulmonary manifestations on CT both with and without associated pulmonary embolism could be supported by AI algorithms to better understand the time course of the disease. Evaluation of the prevalence and the extent of pulmonary perfusion defects observed in CTPA and their effect on physiology and outcome should be studied both in ward and ICU patients. Its influence on microcirculation and gas exchange could be a factor in choosing the appropriate ventilation strategy in critical care patients, but this has to be proven in larger prospective studies. Even though the pandemic of COVID-19 is improving, the lessons learned may be of benefit to optimize use of radiological assessments in other pneumonias.



Chapter 10

Appendix

Summary

In this thesis the possibilities of improving the clinical workflow and risk assessment of patients with the suspicion of a pulmonary embolism in general, and in specific populations and circumstances have been explored.

Part I of this thesis focuses on the improvements in diagnostic decision support for patients with the suspicion of a pulmonary embolism. In Part II, for patients with proven pulmonary embolism, the additional value of findings on CTPA in risk assessment and prognosis is explored. In Part III, the interaction between COVID-19 and pulmonary embolism and deep vein thrombosis is discussed.

Part I

In **chapter 2** we aimed to simplify the diagnostic approach for the use of CTPA in patients with a suspicion of pulmonary embolism. Data of 723 consecutive patients were analysed post hoc, and the results validated in 2785 consecutive patients suspected of pulmonary embolism of two prospective multicentre cohort studies in the Netherlands, respectively. Of the regular used clinical decision rule, only three Wells items significantly added incremental value to the D-dimer test: haemoptysis, signs of deep vein thrombosis and 'pulmonary embolism most likely'. We identified two groups: (i) none of these three items positive and a 1000 ng/L D-dimer threshold; (ii) one or more of these items positive and 500 ng/L threshold. Combining Wells items with the D-dimer test resulted in a simplified decision rule, which reduces the need for CTPA in patients with suspected pulmonary embolism.

This YEARS algorithm that incorporates differential D-dimer cut-off values at presentation has been developed to be fast, to be compatible with clinical practice, and to reduce the number of CTPA investigations in all age groups. In **chapter 3** we prospectively evaluated this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism in 3465 patients in 12 hospitals in the Netherlands. We concluded that pulmonary embolism could be safely excluded by the YEARS diagnostic algorithm in patients with suspected pulmonary embolism. The main advantage of the YEARS algorithm in our patients was the absolute 14% decrease of CTPA examinations in all ages and across several relevant subgroups.

Part II

In part II different perspectives on prognostication of patients with pulmonary embolism were studied, by using radiological and clinical data of 1950 patients with acute pulmonary embolism who participated in the Hokusai VTE-trial, an international randomized clinical trial on anticoagulants.

In **chapter** 4 we evaluated the impact of specific cardiovascular radiological parameters on short and long-term clinical outcomes. Most of the evaluated

radiological parameters did not have strong effects on outcome in patients with acute pulmonary embolism. Only an enlarged pulmonary trunk diameter had an increased risk of mortality with odds ratio after 1 week of 4.2 (95% CI 1.04–16.8) and recurrent VTE up to 12 months, and can be used for risk stratification.

In **chapter 5** we explored the impact of body mass index (BMI) on prognostic indicators and clinical outcomes in patients with pulmonary embolism. We observed that several clinical and radiological prognostics characteristics and right ventricular dysfunction in pulmonary embolism are not evenly distributed among the BMI categories. This is reflected in a trend towards worse outcomes in patients who are overweight and those who are underweight, giving it an impression of U-shaped curves.

In **chapter 6** the impact of concurrent cardiopulmonary disease identified on the diagnostic CTPA on clinical outcome of acute pulmonary embolism was determined. Concomitant disease observed on the baseline CTPA in patients with acute pulmonary embolism impacts mortality in a severity dependent manner, and may be of additional value in risk stratification and prognosis.

Part III

Coronavirus disease 2019 (COVID-19) can lead to systemic coagulation activation and thrombotic complications. In **chapter 7** we investigated the incidence of objectively confirmed venous thromboembolism in 198 hospitalized patients with COVID-19. The observed risk for VTE in COVID-19 is very high, particularly in ICU patients, which should lead to a high level of clinical suspicion and low threshold for diagnostic imaging for DVT or pulmonary embolism.

In **chapter 8** we observed that invasively mechanically ventilated ICU patients with severe COVID-19 not only can develop pulmonary embolism but also show large scattered areas of severely diminished perfusion on dual energy CTPA, consistent with diffuse pulmonary microcirculatory dysfunction. These defects seem to be independent of the presence of pulmonary embolism, possibly reflective of micro thrombi in the pulmonary circulation. The combination of extensive parenchymal involvement with diffuse perfusion abnormalities may explain the occurrence of severe and persistent respiratory failure that is frequently seen in patients with severe COVID-19 pneumonia who require mechanical ventilation.

Samenvatting

In dit proefschrift heb ik mogelijkheden voor de verbetering van de klinische evaluatie en risicoschatting bij patiënten die van een longembolie verdacht worden onderzocht. Dit niet alleen in algemene zin, maar ook voor specifieke subgroepen en omstandigheden.

Deel I van het proefschrift richt zich op de verbeteringen in de beslisondersteuning bij patiënten met verdenking op een longembolie. In deel II werd bij patiënten met een bewezen longembolie de aanvullende waarde van CT voor de inschatting van de prognose bekeken. In deel III werd de samenhang tussen COVID-19 en longembolie en diepe veneuze trombose onderzocht.

Deel I

In **hoofdstuk 2** hebben we ons gericht op de verbetering van de diagnostiek met behulp van een CT bij patiënten met de verdenking op een longembolie. Daarbij werden uit twee grote Nederlandse cohorten data van 723 patiënten achteraf geanalyseerd, en vervolgens gevalideerd in 2785 opeenvolgende patiënten die verdacht werden van een longembolie. Van de regulier gebruikte Wells criteria bleken slechts drie een toegevoegde waarde te hebben als een d-dimeer reeds bekend was: bloed ophoesten, tekenen van een trombosebeen, en inschatting dat een longembolie de meest waarschijnlijke diagnose was. Daarbij konden twee groepen onderscheiden worden: 1) geen enkele van deze items was aanwezig; hierbij was een grens van 1000 ng/mL d-dimeer gesteld; of 2) een of meer van de drie items aanwezig, waarbij er een grens van 500 ng/mL voor de d-dimeer gehanteerd wordt. Op deze manier kon door een combinatie van de d-dimeer met genoemde items een makkelijk toepasbare beslisregel worden ontwikkeld.

Dit YEARS algoritme met verschillende D-dimeer afkapwaardes bij presentatie heeft tot doel om vlot, de klinische praktijk volgend, het aantal onnodige CT-scans te reduceren voor alle leeftijdscategorieën. In **hoofdstuk 3** werd deze simpele beslisregel prospectief gevalideerd in 3465 patiënten met de verdenking op een longembolie in 12 Nederlandse ziekenhuizen. We zagen dat longembolie veilig kon worden geëxcludeerd door YEARS. Het belangrijkste voordeel was de absolute afname met 14% van het aantal CT-scans in alle leeftijdscategorieën en in de verschillende subgroepen.

Deel II

In deel II werden verschillende gezichtspunten t.a.v. het prognosticeren van patiënten met bewezen longembolie bestudeerd. Daartoe werden data gebruikt van 1950 patiënten uit een grote internationale gerandomiseerde trial van anticoagulantia, de Hokusai-VTE.

In **hoofdstuk 4** werd de impact van specifieke cardiovasculaire parameters bestudeerd op zowel de korte als de lange termijn uitkomsten. De meeste van de onderzochte parameters bleken niet van waarde te zijn bij de prognosevorming. Alleen een verbrede longslagader bleek geassocieerd met een verhoogde sterftekans (na 1 week Odds ratio van 4.2 met 95% betrouwbaarheidsinterval 1.04-16.8) en recidief trombo-embolie tot 12 maanden, en kan dus voor risicostratificatie ingezet worden.

In **hoofdstuk 5** werd de impact van de lichaamscompositie op basis van de BMI (body mass index) op de prognostische indicatoren en klinische uitkomsten bij longembolie bestudeerd. We zagen dat enkele klinische en radiologische prognostische karakteristieken en dysfunctie van de rechterhartkamer niet gelijkmatig verdeeld waren tussen de verschillende BMI-categorieën. Slechtere uitkomsten werden vaker gezien bij mensen met overgewicht of ondergewicht, resulterend in U-vormige curve.

In **hoofdstuk 6** werd de invloed van diverse andere cardiopulmonale afwijkingen op de CT longembolie ten aanzien van de klinische uitkomsten geanalyseerd. Het bleek dat gelijktijdige aanwezigheid van deze afwijkingen en longembolie op de CT effecten hebben op de sterfte, met een sterker effect bij ernstiger afwijkingen. Dit kan van belang zijn bij de risico stratificatie en prognose.

Deel III

Coronavirus ziekte-19 kan leiden tot stollingsstoornissen en trombotische complicaties. In **hoofdstuk 7** onderzochten we het voorkomen van trombosebenen en longembolieën bij 198 opgenomen patiënten met COVID-19. Het risico op veneuze trombo-embolie is zeer hoog, met name bij IC-patiënten, en zal derhalve tot een hoge mate van verdenking moeten leiden, en tot een laagdrempelig gebruik van aanvullende diagnostiek.

In **hoofdstuk 8** stelden we vast dat bij beademde IC-patiënten met ernstige COVID-19 op een zogenaamde dual energy CT er niet alleen longembolieën maar ook grote perfusiedefecten zichtbaar zijn. Dit bleek ook los van longembolieën op te treden, vermoedelijk door stoornissen in de microcirculatie van de longen. De combinatie van uitgebreide doorbloedingsdefecten en grote afwijkingen in het longweefsel kan de ernstige en aanhoudende ademhalingsproblemen verklaren zoals die vaak optreden bij beademde patiënten met een ernstige COVID-19 longontsteking.

List of abbreviations

CDR	Clinical Decision Rule
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CTPA	CT Pulmonary Angiography
DECT	Dual Energy CT
DVT	Deep Venous Thrombosis
ESC	European Society of Cardiology
IQR	Interquartile Range
LV	Left Ventricle
NPV	Negative Predictive Value
OR	Odds Ratio
PE	Pulmonary Embolism
PESI	Pulmonary Embolism Severity Index
PET	Positron Emission Tomography
PPV	Positive Predictive Value
PT	Pulmonary Trunk
RA	Right Atrium
RV	Right Ventricle
RVD	Right Ventricular Dysfunction
sPESI	Simplified PESI
US	Ultrasound
V/Q	Ventilation/perfusion
VTE	Venous Thromboembolism

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PhD portfolio

Name PhD student: Ludo F.M. Beenen
PhD period: 2014-2021
Name PhD supervisors: prof.dr. S. Middeldorp, prof.dr. J. Stoker

PhD training

	Institute/location	Year	Workload (ECTS)
General courses – 8.4 ECTS			
AMC World of Science	AMC Graduate School	2014	0.7
Embase/Medline via OVID	AMC Graduate School	2014	0.1
Endnote	AMC Graduate School	2014	0.1
Medical Literature: Searching for a Systematic Review	AMC Graduate School	2014	0.1
Clinical Epidemiology: Evaluation of Medical Tests	AMC Graduate School	2014	0.9
Practical Biostatistics	AMC Graduate School	2014	1.4
Randomized Controlled Trials		2014	0.6
Clinical Epidemiology 2: Observational Epidemiology, Effects and Effectiveness	AMC Graduate School	2014	0.6
Evaluation of Medical Tests	AMC Graduate School	2014	0.1
Systematic Reviews	AMC Graduate School	2014	0.7
The Art of Scientific Writing	AMC Graduate School	2014	1.5
Oral Presentation in English	AMC Graduate School	2014	0.5
Specific courses			
BROK-GCP Herregistratie	VUMC	2015	0.1
EBRO Cursus	Utrecht	2016	0.2
Sprekerstraining Spies	NVVR, Nijmegen	2017	0.2
Teach The Teacher Good Practice Opleiden	Laren	2018	0.1
Teach the Teacher - KPB	AMC Amsterdam	2018	0.1
Teach the Teacher - Voortgangsgesprek	AMC Amsterdam	2019	0.1
Symposium Update Regelgeving Klinisch Onderzoek - Herregistratie BROK	AMC Amsterdam	2019	0.1
Sprekerstraining Herrebout	NVVR, Hilversum	2020	0.2
Conferences and symposia (selected) – 34.4 ECTS			
RSNA 100th Scientific Assembly & Annual meeting	RSNA, Chicago	2014	1.4
ECR	ESR, Wenen	2015	1.0
16th European Congress of Trauma & Emergency Surgery	ECTES, Amsterdam	2015	0.5

4th Congress International Society of Forensic Radiology and Imaging	Isfri, Leicester	2015	0.6
Ultra-Low Dose Cardiopulmonary CT Imaging – The State of the Art	UMC Utrecht	2015	0.1
26th ASER Postgraduate Course in Emergency and Trauma Radiology	ASE, Miami	2015	1.1
Platform Medisch Leiderschap Tweede Masterclass	Schola Medica, Utrecht	2015	0.1
Sectiedag Cardiovasculaire Radiologie, Cardiale beeldvorming middels CT en MRI: stand van zaken uitgelicht	Utrecht	2015	0.1
DECT in Radiology and Radiobiology	Maastricht	2015	0.2
5e NTVG-Dag. Kunst en Kunde	NTvG Amsterdam	2015	0.1
RSNA 101th Scientific Assembly & Annual meeting	Chicago, USA	2015	1.4
Symposium Heart for women	Radboud UMC Nijmegen	2016	0.2
Sectiedag MSK	NVvR, Amersfoort	2016	0.1
9e Symposium Complicaties in de Traumachirurgie	AMC Amsterdam	2016	0.2
Radiologie Festival CT en de toekomst: CT bij MCI	VUmc Amsterdam	2016	0.2
Jaarlijkse sectiedag Acute Radiologie	NVvR,Hilversum	2016	0.1
5th Congress International Society of Forensic Radiology and Imaging	ISFRI, Amsterdam	2016	0.5
27th ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, San Francisco	2016	1.1
Patient symposium World Thrombosis Day	AMC Amsterdam	2016	0.1
Openingssymposium SEH van de Toekomst	AMC Amsterdam	2016	0.1
ESGAR Workshop Acute Abdomen	ESGAR Amsterdam	2016	0.4
Rembrandt symposium Longembolie	Amsterdam	2016	0.4
LNAZ symposium Improving trauma care: trauma system evaluations in an international perspective	Utrecht	2016	0.2
6e NTVG-Dag. Kunst en Kunde	NTvG, Amsterdam	2016	0.1
Sectievergadering Cardiovasculaire Radiologie	NVVR, Utrecht	2016	0.1
Symposium Advances in Intra-arterial Treatment of Acute Ischemic Stroke	Amsterdam	2016	0.1
Sectievergadering Abdomen Radiologie oncologische beeldvorming een handleiding voor de dagelijkse praktijk	AvL, Amsterdam	2016	0.1
Sectiedag thorax	NVVR, Utrecht	2016	0.1
RSNA 102nd Scientific Assembly & Annual meeting	RSNA, Chicago	2016	1.4
ESER/BSER Annual Scientific Meeting	ESER, Londen	2017	0.5
6th ISFRI Congress	ISFRI, Denemarken	2017	0.6
Symposium Mens in Beeld: Beeldvorming van infectie en inflammatie in de longen.	UMC Utrecht	2017	0.1
28th ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, Toronto	2017	1.1

Sectiedag Cardiovasculaire Radiologie	NVVR, Utrecht	2017	0.1
RSNA 103rd Scientific Assembly & Annual meeting	RSNA, Chicago	2017	1.4
Jaarlijkse sectiedag Thorax Radiologie	NVvR, Utrecht	2017	0.1
SWC op weg naar de toekomst - stip op de horizon	NVVR, Utrecht	2018	0.1
KNMG Masterclass Calamiteiten in de regio	UMC Utrecht	2018	0.1
Congres opgeschaalde zorg	LNAZ, Amsterdam	2018	0.2
ESTI/ESCR Joint Meeting	ESTI/ESCR Geneve	2018	0.6
ESSR Annual Scientific Meeting	ESSR, Amsterdam	2018	0.5
4th Annual ACS symposium, Oosterkerk	ACS Amsterdam	2018	0.2
Sectiedag Forensische Radiologie	NVVR, Den Bosch	2018	0.1
Amstol symposium	AMC Amsterdam	2018	0.2
28th ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, Virginia	2018	1.1
Jaarlijkse sectiedag Thorax Radiologie	NVvR, Utrecht	2018	0.1
Sectiedag Cardiovasculaire Radiologie	NVVR Amsterdam	2018	0.1
Sectiedag Abdomen Radiologie	NVVR, Den Haag	2018	0.1
RSNA 104th Scientific Assembly & Annual Meeting	RSNA, Chicago	2018	1.4
Hora Est Minisymposium	AMC Amsterdam	2018	0.1
Sandwichcursus Nucleaire geneeskunde	NVvR. Ede	2019	0.2
ECR	ESR, Wenen	2019	1.0
Sectiedag Cardiovasculaire Radiologie	NVvR, UMC Utrecht	2019	0.1
Contrast Stroke consortium meeting	UMCG Groningen	2019	0.2
Sectiedag MSK NL-BE Radiologie	NVvR, Leiden	2019	0.2
Spoedzorgnet Thema avond reanimatie ECMO en eCPR		2019	0.1
ESCR 2019 Cardiac Imaging Annual Scientific Meeting	ESCR, Antwerpen	2019	0.6
Sectiedag thorax	NVVR, Utrecht	2019	0.1
RSNA 105th Scientific Assembly & Annual meeting	RSNA, Chicago	2019	1.4
Trauma Complicatiecongres2.9	AMC, Amsterdam	2020	0.2
SWC Zichtbaar Leiderschap	NVVR, Ede	2020	0.1
Sandwichcursus Thoraxradiologie	NVVR, Ede	2020	0.2
31st ESGAR Annual Meeting and Postgraduate Course	ESGAR Amsterdam	2020	0.7
Radiologendagen bij je thuis	NVVR	2020	0.3
Postcovid care Live Event: Post-COVID-19 care and research at Amsterdam UMC	Amsterdam UMC	2020	0.2
ISTH 2020 Virtual Congress	ISTH, Online	2020	0.2

ECR European Congress of Radiology	ESR, Online	2020	1.0
ECR Highlights AI	ESR, Online	2020	0.2
ESC Congress 2020- The Digital Experience.	ESC, Online	2020	0.9
ECR Highlights: Abdomen, MSK, Cardio, Chest, Radiation, Children, Radiographers, Emergency Radiology, Interventional Radiology	ESR, Online	2020	1.4
Sectie Forensische en Postmortale Radiologie	NVVR, Online	2020	0.1
29th ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, Online	2020	1.2
43rd Annual Meeting ESNR	ESNR, Online	2020	0.5
ESCR Congress	ESCR, Online	2020	0.5
Sectiedag Cardiovasculaire Radiologie	NVVR, Online	2020	0.1
FMS Symposium zorgevaluatie: de oogst van 5 jaar zorgevaluatie	FMS, Online	2020	0.1
Sectiedag Thorax Radiologie	NVvR, Online	2020	0.1
Amsterdam UMC & COVID-19: unorthodox teams, accelerating science	Amsterdam UMC	2020	0.2
EACVI online	ESC, Online	2020	0.2

Seminars & Webinars

ISTH Academy Webinar Acute PE: Administering Reperfusion Therapy	2016
ESCR Webinar Pulmonary Hypertension	2017
ACS Symposium The Female Factor in Thrombosis and Pulmonary Hypertension	2017
Venticare Live 2018, Jaarbeurs Utrecht	2018
Webinar ESR Artificial Intelligence	2019
Webinar FMS: COVID-19	2020
Webinar NIV: Dilemma rond behandeling en plaats CT-thorax bij COVID-19	2020
Webinar ISTH:Thrombosis, Thromboprophylaxis and Coagulopathy in COVID 19 Infections,	2020
Webinar ISTH thrombotic and hemostatic issues in critical care units managing COVID-19	2020
Webinar ESER | Post-Peak COVID: Where are we now	2020
Webinar ESCR "The role of the cardiovascular radiologist during the COVID-19 pandemic	2020
Webinar ISTH/EHA Coagulopathy in COVID-19 Patients: Latest Data, Recommendations, and Perspectives	2020
Webinar BIR: COVID-19 imaging	2020
Webinar ESCR Advanced Webinar "Imaging in vasculitis: MR, CT and more	2020
Webinar ISTH /Royal Society of Medicine.COVID-19 Series: Thrombotic complications	2020

ESCR Webinar Panta Rei		2020	
Webinar Kansen voor machine learning in de acute keten		2020	
ESCR Webinar Upcoming trends and techniques in cardiac CT		2020	
Presentations (selected)			
Sandwichcursus Acute & NeuroRadiologie	NVVR, Ede	2016	0.5
Radiologie Festival CT en de toekomst: CT bij MCI	VUMC Amsterdam	2016	0.2
27th ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, San Francisco	2016	1.0
ESGAR Workshop Acute Abdomen	Amsterdam	2016	0.4
Rembrandt symposium Longembolie	Amsterdam	2016	0.4
28th ASER Postgraduate Course in Emergency and Trauma Radiology	Toronto, Canada	2017	1.1
Rembrandt symposium Longembolie CTEPH	Amsterdam	2017	0.4
Vaatlabcursus IVG	AMC Amsterdam	2017	0.2
Sandwichcursus Kinder - & Acute Radiologie	NVvR. Ede	2017	0.4
Sandwichcursus Acute & interventieradiologie	NVvR. Ede	2019	0.4
Radiologendagen NVVR	NVvR. Hilversum	2019	0.4
ECR	ESR, Wenen	2019	1.0
29th ASER Postgraduate Course in Emergency and Trauma Radiology	ASER, Scottsdale	2019	1.1
Sandwichcursus Cardiovasculaire Radiologie	NVVR, Ede	2020	0.4
ACS Symposium Pulmonary hypertension, Update on the derivation and validation of the CO-RADS classification	AMC Amsterdam	2020	0.1
Amstel academie CTP/DECT	Amsterdam	2020	0.2
Nationale antistollingsdag,	Online	2020	0.1
NVTH COVID and VTE, PE and pulmonary perfusion	NVTH, Online	2020	0.2
RSNA 106th Scientific Assembly & Annual meeting;	Online	2020	1.5

Teaching

	Year
Teaching	
Residents, students, technicians, radiologists, other physicians	2014-2021
Supervising	
Residents, students, technicians	2014-2021

Awards/recognitions

	Year
Awards and Prizes	
ASER Best oral presentation “cum laude”	2016
Fellow of American Society of Emergency Radiology	2020

List of Publications

1990

1. Beenen LF, Scholten HG.
   Guillain-Barré syndrome following Campylobacter jejuni enteritis.
   Ned Tijdschr Geneeskd. 1990 May 19;134(20):1010-2.

1997

2. Roos YB, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M.
   Timing of surgery in patients with aneurysmal subarachnoid haemorrhage: rebleeding is still the major cause of poor outcome in neurosurgical units that aim at early surgery.
   J Neurol Neurosurg Psychiatry. 1997 Oct;63(4):490-3. doi: 10.1136/jnnp.63.4.490.

1999

3. Beenen LF, Lindeboom J, Kasteleijn-Nolst Trenité DG, Heimans JJ, Snoek FJ, Touw DJ, Adèr HJ, van Alphen HA.
   Comparative double blind clinical trial of phenytoin and sodium valproate as anticonvulsant prophylaxis after craniotomy: efficacy, tolerability, and cognitive effects.
   J Neurol Neurosurg Psychiatry. 1999 Oct;67(4):474-80. doi: 10.1136/jnnp.67.4.474.

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4. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M.
   Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands.
   J Neurol Neurosurg Psychiatry. 2000 Mar;68(3):337-41. doi: 10.1136/jnnp.68.3.337.

5. Postma TJ, Heimans JJ, Luykx SA, van Groeningen CJ, Beenen LF, Hoekstra OS, Taphoorn MJ, Zonnenberg BA, Klein M, Vermorken JB.
   A phase II study of paclitaxel in chemonaïve patients with recurrent high-grade glioma.
   Ann Oncol. 2000 Apr;11(4):409-13. doi: 10.1023/a:1008376123066.

6. Beenen LF, Touw DJ, Hekker TA, Haring DA.
   Pharmacokinetics of intraventricularly administered teicoplanin in Staphylococci ventriculitis.
   Pharm World Sci. 2000 Aug;22(4):127-9. doi: 10.1023/a:1008719806949.

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7. Roos YB, Levi M, Carroll TA, Beenen LF, Vermeulen M.
Nimodipine increases fibrinolytic activity in patients with aneurysmal subarachnoid hemorrhage.
Stroke. 2001 Aug;32(8):1860-2. doi: 10.1161/01.str.32.8.1860.

8. Thomeer M, Vanbeckevoort D, Bielen D, Beenen L, Gevers A, Rutgeerts R, Marchal G.
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9. Roos YB, Dijkgraaf MG, Albrecht KW, Beenen LF, Groen RJ, de Haan RJ, Vermeulen M.
Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis.
Stroke. 2002 Jun;33(6):1595-9. doi: 10.1161/01.str.0000016401.49688.2f.

2008

10. Saltzherr TP, Fung Kon Jin PH, Bakker FC, Ponsen KJ, Luitse JS, Scholing M, Giannakopoulos GF**,** Beenen LF, Henny CP, Koole GM, Reitsma HB, Dijkgraaf MG, Bossuyt PM, Goslings JC.
An evaluation of a Shockroom located CT scanner: a randomized study of early assessment by CT scanning in trauma patients in the bi-located trauma center North-West Netherlands (REACT trial).
BMC Emerg Med. 2008 Aug 22;8:10. doi: 10.1186/1471-227X-8-10.

2009

11. Saltzherr TP, Goslings JC; multidisciplinary REACT 2 study group.
Effect on survival of whole-body CT during trauma resuscitation.
Lancet. 2009 Jul 18;374(9685):198; author reply 198-9. doi: 10.1016/S0140-6736(09)61324-6.

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13. Rosmulder RW, Krabbendam JJ, Kerkhoff AH, Schinkel ER, Beenen LF, Luitse JS. ['Advanced triage' improves patient flow in the emergency department without affecting the quality of care].
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14. Aukema TS, Hietbrink F, Beenen LF, Leenen LP.
Does thoracic injury impair the predictive value of base deficit in trauma patients?
Injury. 2010 Apr 26. doi: 10.1016/j. injury.2010.04.003.

15. Saltzherr TP, Beenen LF, Reitsma JB, Luitse JS, Vandertop WP, Goslings JC.
Frequent computed tomography scanning due to incomplete three-view X-ray imaging of the cervical spine.
J Trauma. 2010 May;68(5):1213-7. doi: 10.1097/TA.0b013e3181b28aa4.

16. Lemmers M, Saltzherr TP, Beenen LF, Ponsen KJ, Goslings JC.
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Emerg Med J. 2010 Jul;27(7):522-5. doi: 10.1136/emj.2009.078519. Epub 2010 Apr 1.

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17. Saltzherr TP, van der Vlies CH, van Lienden KP, Beenen LF, Ponsen KJ, van Gulik TM, Goslings JC.
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HPB (Oxford). 2011 May;13(5):350-5. doi: 10.1111/j.1477-2574.2011.00293.x. Epub 2011 Mar 29.

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Am J Emerg Med. 2011 Jun;29(5):572.e1-2. doi: 10.1016/j.ajem.2010.05.006. Epub 2010 Aug 1.

19. Douma RA, Mos IC, Erkens PM, Nizet TA, Durian MF, Hovens MM, van Houten AA, Hofstee HM, Klok FA, ten Cate H, Ullmann EF, Büller HR, Kamphuisen PW, Huisman MV; Prometheus Study Group.
Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study.
Ann Intern Med. 2011 Jun 7;154(11):709-18. doi: 10.7326/0003-4819-154-11-201106070-00002.

20. Paulus F, Veelo DP, de Nijs SB, Beenen LF, Bresser P, de Mol BA, Binnekade JM, Schultz MJ.
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21. Aukema TS, Beenen LF, Hietbrink F, Leenen LP.
Validation of the Thorax Trauma Severity Score for mortality and its value for the development of acute respiratory distress syndrome.
Open Access Emerg Med. 2011 Aug 23;3:49-53. doi: 10.2147/OAEM.S22802. eCollection 2011.

22. Fung Kon Jin PH, Dijkgraaf MG, Alons CL, van Kuijk C, Beenen LF, Koole GM, Goslings JC.
Improving CT scan capabilities with a new trauma workflow concept: simulation of hospital logistics using different CT scanner scenarios.
Eur J Radiol. 2011 Nov;80(2):504-9. doi: 10.1016/j.ejrad.2009.11.026. Epub 2010 Mar 12.

23. Kruyt ND, Beenen LF, van den Berg Vos RM, Dippel DW, Imanse JG, Kwa VI, de Leeuw FE, Luijckx GJ, Nederkoorn PJ, van Oostenbrugge RJ, Visser MC, van der Worp HB, Wermer MJ, Zinkstok SM, Roos YB
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24. Wittenberg R, Berger FH, Peters JF, Weber M, van Hoorn F, Beenen LF, van Doorn MM, van Schuppen J, Zijlstra IA, Prokop M, Schaefer-Prokop CM.
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Br J Surg. 2012 Jan;99 Suppl 1:105-13. doi: 10.1002/bjs.7705.

26. Sierink JC, Saltzherr TP, Edwards MJ, Beuker BJ, Patka P, Goslings JC; REACT-2-studiegroep.
[Direct total body CT scan in multi-trauma patients].
Ned Tijdschr Geneeskd. 2012;156(30):A4897.

27. Aukema TS, Beenen LF, Hietbrink F, Leenen LP.
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31. Giannakopoulos GF, Saltzherr TP, Beenen LF, Reitsma JB, Bloemers FW, Goslings JC, Bakker FC; REACT Study Group.
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Injury. 2012 Sep;43(9):1517-21. doi: 10.1016/j.injury.2011.07.012. Epub 2011 Aug 4.

32. Fahmi F, Marquering HA, Streekstra GJ, Beenen LF, Velthuis BK, VanBavel E, Majoie CB.
Differences in CT perfusion summary maps for patients with acute ischemic stroke generated by 2 software packages.
AJNR Am J Neuroradiol. 2012 Dec;33(11):2074-80. doi: 10.3174/ajnr.A3110. Epub 2012 May 3.

33. van Es J, Beenen LF, Gerdes VE, Middeldorp S, Douma RA, Bossuyt PM.
The accuracy of D-dimer testing in suspected pulmonary embolism varies with the Wells score.
J Thromb Haemost. 2012 Dec;10(12):2630-2. doi: 10.1111/jth.12037.

34. Purmer IM, van Iperen EP, Beenen LF, Kuiper MJ, Binnekade JM, Vandertop PW, Schultz MJ, Horn J.
Brain computer tomography in critically ill patients--a prospective cohort study.
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Eur Radiol. 2013 Jan;23(1):148-55. doi: 10.1007/s00330-012-2593-0. Epub 2012 Aug 11.

37. Lucassen WA, Beenen LF, Büller HR, Erkens PM, Schaefer-Prokop CM, van den Berk IA, van Weert HC.
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A large soft tissue mass of the chest wall.
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43. Boers AM, Marquering HA, Jochem JJ, Besselink NJ, Berkhemer OA, van der Lugt A, Beenen LF, Majoie CB; MR CLEAN investigators.
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Clinical impact of findings supporting an alternative diagnosis on CT pulmonary angiography in patients with suspected pulmonary embolism.
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