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IN FOCUS

Management of suspected pulmonary embolism (PE) by D-dimer and multi-slice computed tomography in outpatients: an outcome study

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Summary. *Objectives:* A prospective outcome study designed to evaluate a simple strategy for the management of outpatients with suspected pulmonary embolism (PE), based on clinical probability, D-dimer, and multi-slice computed tomography (MSCT). *Methods:* A cohort of 432 consecutive patients admitted to the emergency department with suspected PE was managed by sequential non-invasive testing. Patients in whom PE was ruled out were not given anticoagulants, but were followed-up for 3 months. *Results:* Normal D-dimer and low-intermediate clinical probability ruled out PE in 103 patients [24% (95% CI 20–28)]. Seventeen patients had normal D-dimer, but high clinical probability and proceeded to MSCT. All patients proved negative for PE. A total of 329 (76%) patients underwent MSCT examination. Pulmonary embolism was diagnosed in 93 patients [21.5% (95% CI 18–26)] and was ruled out by negative MSCT in 221 patients [51% (95% CI 46–56)]. MSCT scans were determined as inconclusive in 15 (4.5%) patients. No patient developed objectively verified venous thromboembolism (VTE) during the 3-month follow-up period. However, the cause of death was adjudicated as possibly related to PE in two patients, resulting in an overall 3-month VTE risk of 0.6% (95% CI 0–2.2%). The diagnostic algorithm yielded a definite diagnosis in 96.5% of the patients. *Conclusions:* This simple and non-invasive strategy combining clinical probability, D-dimer, and MSCT for the management of outpatients with suspected PE appears to be safe and effective.

Keywords: clinical probability assessment, D-dimer, multi-slice CT, pulmonary embolism, venous thromboembolism.

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Introduction

Pulmonary embolism (PE) remains a challenging diagnostic problem in which clinical assessment alone is unreliable and objective testing is necessary. The introduction of D-dimer testing and spiral computed tomography scanning has considerably modified the diagnostic approach to PE [1,2].

As no single test is sufficiently sensitive or specific for the diagnosis of PE, most algorithms involve a combination of two or more tests in order to increase the diagnostic accuracy, and to minimize the exposure to ionizing radiation and the use of invasive tests.

D-dimer is generally considered a sensitive, but non-specific marker for the presence of venous thromboembolism (VTE). Raised levels are commonly found in hospitalized patients, in pregnant women, and in patients with cancer [3]. Its role is therefore mainly limited to the exclusion of VTE in outpatients [4]. Depending on the assay, D-dimer can reliably exclude PE in up to 30% of outpatients [5,6].

There is still considerable debate about the optimal diagnostic imaging modality in patients with suspected PE. Spiral computed tomography (CT) is becoming increasingly accepted as the first-line imaging test [7]. The advantages of CT scanning are not only limited to the high diagnostic accuracy and high diagnostic yield, but also to its ability to disclose alternative pathologies [8–10].

The role of spiral CT in the diagnosis of PE has been extensively evaluated in recent years [6,9,11–14]. The main impediment for single slice spiral CT has been the limitation of this modality to detect small peripheral emboli [2,15]. Thus, negative CT examinations are often questioned, and call for further diagnostic tests to confirm the absence of PE. The new generation spiral CT scanners, known as multi-slice CT, are characterized by high image acquisition speed and have significantly improved the detection rate of peripheral emboli [7,16–18].

This study was therefore designed to assess the safety and the efficacy of a simple and non-invasive diagnostic strategy in outpatients referred with suspected PE by combining clinical probability assessment, D-dimer testing, and multi-slice computed tomography (MSCT). A negative MSCT examination was accepted to rule out the presence of PE without the need for further testing.

Methods

Patients

A total of 495 consecutive patients with suspected PE, referred to the Emergency Department of Østfold Hospital Trust in Fredrikstad, Norway between February 1, 2002, and December 31, 2003, were considered for inclusion. Patients were eligible for inclusion if there was clinical suspicion of PE defined as acute onset of dyspnea, chest pain, palpitation, or syncope, and if they were ≥18 years of age. Outpatients were characterized by an interval of <48 h between hospital admission and the onset of clinical suspicion of PE. The study protocol was approved by the regional ethics committee, and written informed consent was obtained from all participants in accordance with the revised Declaration of Helsinki.

A total of 492 patients met the inclusion criteria. Sixty (12%) patients were excluded from the study. The causes for exclusion were: protocol violations in 23 patients (clinical probability was not assessed in eight patients with normal D-dimer and CT was not performed in the remaining 15 patients); anticoagulation prior to ($n = 13$) or during the follow-up period ($n = 9$); contraindication to i.v. iodinated contrast medium ($n = 6$); refusal to consent ($n = 5$); pregnancy ($n = 2$); expected survival <3 months ($n = 1$); and incomplete data ($n = 1$). The cause of anticoagulation after inclusion was atrial fibrillation in six patients and the diagnosis of deep vein thrombosis (DVT) in three patients.

Study design

The study was designed as a prospective management trial with a 3-month follow-up period. Patients with suspected PE were managed by the physician in charge according to the study algorithm (Fig. 1). Data including sign and symptoms, risk factors for VTE, arterial blood gas analysis, and chest X-ray findings were filled in a standardized form. D-dimer test was performed as the initial diagnostic test in all patients. The D-dimer cut-off level was 0.4 mg L^{-1} and values less than or equal to the cut-off level were deemed to rule out PE in patients with low-intermediate clinical probability. Patients with high

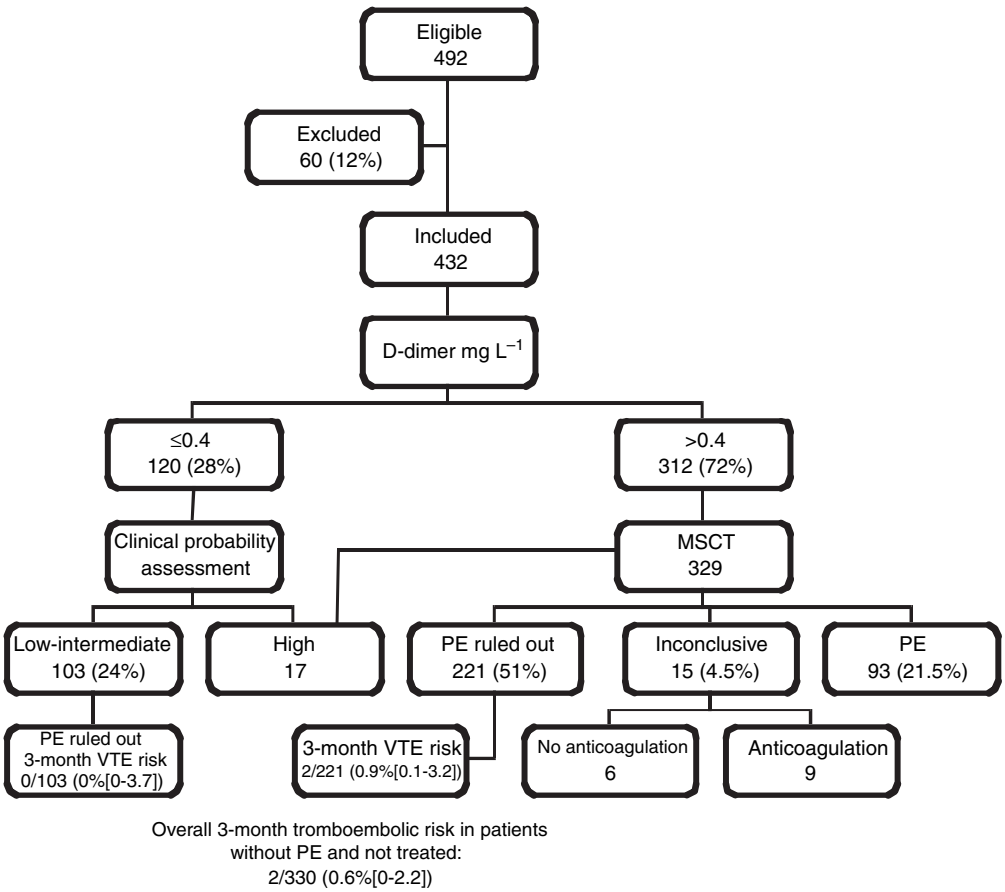

Fig. 1. Results of the diagnostic process. CPA, Clinical probability assessment; AC, Anticoagulation.

clinical probability and a normal D-dimer as well as those with elevated D-dimer proceeded to MSCT. In case of an inconclusive MSCT, bilateral compression ultrasonography of the lower extremities to rule out DVT was recommended followed by perfusion scintigraphy and/or pulmonary angiography if no DVT was revealed.

Diagnostic tests

Clinical probability assessment Clinical probability was assessed by the attending physician based on the presence of risk factors, chest X-ray findings, arterial blood gas analysis, and the likelihood for alternative diagnosis according to the criteria proposed by Hyers (Table 1) [19].

Plasma D-dimer This was assayed with an immunoturbidimetric method (STA Liatest D-Di, Diagnostica Stago, Asnières, France) run on an automated coagulation analyzer (STA-R, Diagnostica Stago, Asnières, France) at the central laboratory.

Multi-slice spiral CT A 4-detector row CT scanner (MX 8000; Marconi, Cleveland, OH, USA) was used. A total volume of 120 mL non-ionic contrast medium (Iomeron, Bracco, Milan, Italy) containing 300 mg iodine mL^{-1} was injected intravenously. An automated bolus tracking system initiated scanning 4 s after the contrast medium reached the aortic arch. Scanning was done with 2.5 mm collimation, a pitch of 1.25, 120 kV, and 175 mAs with a gantry rotation time of 0.5 s. Elevated levels of serum creatinine were not considered an absolute contraindication to MSCT; protective measures as hydration were taken in these cases. The patients were examined with a single breath-hold technique from the lung apex to the lowest hemidiaphragm.

Dual readings on the work station were routinely carried out on all CT examinations. The primary evaluation was performed by the on-call radiologist, while secondary evaluations were carried out by consultant radiologists before the final report was issued. PE was diagnosed if a filling defect or complete occlusion was seen in proximal, segmental or subsegmental arteries. PE was considered absent when the pulmonary vasculature, including subsegmental branches, was visualized and was free of filling defects. The diagnosis was considered inconclusive when poor opacification or major motion artefact was observed or due to the ambiguity of findings as irregular arterial walls or the presence of an adjacent pulmonary abnormality.

Table 1 Clinical probability assessment for PE according to the criteria proposed by Hyers [19]

High clinical probability:
Risk factor present
Otherwise unexplained dyspnea, tachypnoe, or pleuritic pain
Otherwise unexplained radiographic or gas-exchange abnormality
Intermediate clinical probability:
Neither high nor low clinical probability
Low clinical probability:
Dyspnea, tachypnoea, or pleuritic pain possibly present but explainable by another disorder.
Radiographic or gas-exchange abnormality possibly present but explainable by another disorder

Ultrasonography Bilateral compression ultrasonography of the lower extremities consisting of B-mode examination of the common femoral and popliteal veins was recommended to be performed on patients with inconclusive CT scan; lack of vein compressibility was considered as the main criterion for the diagnosis of DVT [20].

Outcomes

The safety of the management strategy was assessed by the 3-month thromboembolic risk, which was defined as an objectively verified VTE or death from PE in those patients who initially were diagnosed not to have a PE and had not received anticoagulation for >48 h during the follow-up period. The efficacy of the diagnostic strategy was assessed in terms of the proportion of patients in whom a definite diagnosis was made according to the diagnostic algorithm.

Deaths were adjudicated by an independent committee on the basis of autopsy reports, death certificates and hospital charts as definitely caused by PE, definitely unrelated to PE, or possibly related to PE if the cause of death could not be clearly established.

3-month follow-up

Patients were interviewed at the end of the follow-up period by telephone. The interviews were carried out by one of the study coordinators. The follow-up information was obtained by mail whenever telephone interviews were not possible. For patients who could not be reached by telephone or mail ($n = 2$), hospital charts and laboratory and radiology archives were reviewed and family physicians were consulted. Multiple contacts with the family physician were registered on both patients in the subsequent 3–12 months following inclusion; patients charts revealed no indication for VTE diagnosis or treatment with anticoagulation.

Statistical analysis

The 95% confidence interval (CI) was calculated from the binomial distribution by means of CI analysis software (Epi-Info, version 6, Atlanta, GA, USA). An apriori acceptable upper limit of the 95% CI for the 3-month thromboembolic risk was 4%, a limit accepted in similar outcome studies on PE [5,6,9].

Results

The final study population comprised 432 patients (males/females = 201/231) (Fig. 1). Median age was 58 years (range

Table 2 Characteristics of study population

Males/females – N (%)	201/231 (47/53)
Median age – years (range)	58 (18–94)
Risk factors – N (%)	
Family history of VTE	37 (8.6)
Previous VTE	43 (10.0)
Known cancer	31 (7.2)
Known thrombophilia	5 (1.2)
Immobilization >3 days or recent surgery with 12 weeks	38 (8.8)
Oral contraceptives or HRT	36 (8.4)
Recent air travel >4 h during the last 2 weeks	8 (1.9)
Post partum	5 (1.2)
Clinical presentation – N (%)	
Central chest pain	159 (36)
Pleuretic chest pain	217 (50)
Dyspnea	252 (58)
Syncope	27 (6.2)
Vital signs – median (25%–75% quartiles)	
Pulse rate – beats min^{-1}	83 (71–97)
Systolic blood pressure – mmHg	139 (125–154)
Diastolic blood pressure – mmHg	79 (70–88)
Respiratory rate min^{-1}	18 (15–20)
Blood gas analysis – median (25%–75% quartiles)	
O_2 saturation %	95 (92–97)
PaO_2 (kPa)	9.6 (8.3–11.3)
$PaCO_2$ (kPa)	4.8 (4.4–5.3)

18–94 years). No patients were lost to follow-up. Patient characteristics are summarized in Table 2.

Negative findings according to the diagnostic algorithm

A total of 120 patients [28% (95% CI 24–32)] had D-dimer value ≤0.4 mg L^{-1}. The clinical probability for PE was low-intermediate in 103 of these patients [24% (95% CI 20–28)] and these patients were considered not to have PE and anticoagulation was not given. The 3-month thromboembolic risk in these patients was 0% (95% CI 0–3.7). In the remaining 17 patients with normal D-dimer, but high clinical probability for PE, additional MSCT examination did not reveal PE in any of the patients. A total of 329 (76%) patients underwent MSCT examination. PE was ruled out by negative CT in 221 patients [51% (95% CI 46–56)].

Of the 324 patients who did not receive anticoagulant therapy either on the basis of negative D-dimer or on the basis of an unequivocally negative CT, none developed an objectively verified VTE in the subsequent 3 months resulting in a 3-month non-fatal thromboembolic risk of 0% (95% CI 0–1.2).

Five of the patients, in whom PE was excluded, died during the follow-up period. All deaths occurred in patients with elevated D-dimer. The cause of death was adjudicated as: certainly unrelated to PE in three patients (two were autopsied and the third died on the first postoperative day following surgery for aortic dissection) and possibly related to PE in the other two patients. One 75-year-old male had metastasizing prostate cancer and thrombocytopenia (platelet count $60{\cdot}10^9$ L^{-1}) died at home 8 weeks after inclusion. The other 89-year-old woman was found dead three weeks after inclusion, on the second postoperative day following surgical fixation of a supracondylar fracture of the arm. As the cause of death was adjudicated as possibly related to PE in those two patients, the 3-month thromboembolic risk after a negative CT scan was 0.9% (95% CI 0.1–3.2) and the overall 3-month thromboembolic risk for patients with no PE and who did not receive anticoagulation during the follow-up period 0.6% (95% CI 0–2.2).

A total of 23 patients were excluded because of violation of the study protocol; 10 patients had a normal D-dimer value. None of these developed VTE or died during the 3-month follow-up period. The remaining 13 patients had elevated D-dimer, but MSCT was not performed due to the emergence of an alternative diagnosis during the diagnostic work-up. Of these, one patient was re-admitted 5 weeks later and PE occluding the main pulmonary arteries was disclosed by MSCT.

Three patients were excluded from the study as treatment with anticoagulation was initiated due to the diagnosis of DVT despite a negative MSCT examination. Compression ultrasonography was performed the same day following CT examination, demonstrating the lack of compressibility in a single calf vein distal to the trifurcation in all three patients.

Positive findings according to the diagnostic algorithm

Pulmonary embolism was diagnosed in 102 [23.6% (95% CI 20–28)] patients. The MSCT images were unequivocally positive in 93 patients [21.5% (95% CI 18–26)]. In nine patients, the interpretations were less conclusive, but they were anticoagulated either on the basis of positive ultrasound finding of DVT in two cases or on the basis of clinical judgment supported by highly suggestive MSCT finding in the absence of an alternative diagnosis in the remaining seven patients.

The most proximal extension of the detected clots were the main pulmonary arteries in 49 (48%), the lobar arteries in 20 (20%), the segmental vessels in 26 (25%) and the subsegmental vessels in seven patients (7%).

The clinical probability for PE was estimated in 398 (92%) patients. PE was diagnosed in 47 of 305 patients (15%) with low-intermediate clinical probability and in 41 of 79 patients (52%) with high clinical probability.

D-dimer values in patients with PE ranged from 0.5 mg L^{-1} to values >20 mg L^{-1}. Four patients (3.8%) receiving anticoagulation for PE died during the follow-up period. Autopsy was performed in one patient confirming the presence of PE.

Inconclusive results

The CT examinations were determined as inconclusive in 15 (4.5%) patients. Nine patients received anticoagulant therapy. Only three of these patients were further examined with

bilateral compression ultrasonography of the lower extremities revealing the presence DVT in two of them.

Anticoagulation was withheld in the remaining six patients. Bilateral compression ultrasonography was performed in four patients. Two of those were further examined by other means: one by perfusion lung scan and pulmonary angiography and the other by perfusion lung scan alone; all examinations were negative. In the remaining two patients, the decision to withhold anticoagulation was based on the establishment of an alternative diagnosis.

Discussion

Several strategies for managing patients with suspected PE have been validated in recent years [21]. However, most of these strategies are complicated and involve multiple rounds of tests and are thus time consuming, costly and difficult to apply in clinical practice [5,6,9,11,22].

Our intention was to develop a simple and effective algorithm that can provide rapid and accurate diagnosis. To achieve this objective, we chose the combination of D-dimer as a first step test due to its high negative predictive value, low cost and feasibility to rule out the presence of VTE, followed by MSCT as a stand-alone imaging test for the direct visualization of the pulmonary vasculature.

The algorithm proved to be safe and effective. The combination of these diagnostic modalities yielded a definite diagnosis in 96.5% of patients in whom the protocol was met. The overall 3-month thomboembolic risk was 0.6% (95% CI 0–2.2). These results are in keeping with those reported in previous outcome studies (Table 3) [5,6,9,11,22,23].

The practical relevance of these results is supported by the prevalence of PE in the study population, which is similar to that in other large studies [5,6,9,12]. Moreover, the overall exclusion rate in this study was acceptable (12%) and is lower than that reported in many large multi-center trials [5,6,11]. We believe that these two points compensate for the limitation caused by the study design as a single-center trial.

Adherence to the protocol was high with only 23 patients (5%) being excluded because of incomplete investigations, confirming the feasibility of this analysis-based decision strategy. The algorithm was applicable in the vast majority of patients; MSCT was contraindicated only in eight patients either due to intolerance of contrast agent, or because of pregnancy.

D-dimer was performed as a first step test in this study. Normal D-dimer safely ruled out PE in one-quarter of the patients without the need for further testing. However, we chose to add clinical probability assessment and consequently performed CT in patients with high clinical probability and normal D-dimer largely because the D-dimer assay used in this study had not been previously validated in an outcome study and even more importantly the optimal cut-off value of this assay was not yet clearly defined. Failing to assess the clinical probability in patients with normal D-dimer was thus considered as a protocol violation and led to the exclusion of these patients. The clinical probability had in fact no implications on the management of patients with elevated D-dimer values. However, we must admit that the prior knowledge of the D-dimer value may have influenced the physician's assessment of clinical probability, as low D-dimer values automatically infer a reduced possibility of VTE.

The clinical probability assessment scheme used in this study has previously not been properly validated. The test is easy to apply in clinical practice. In contrast to the standardized prediction rules such as the Geneva [24] and Wells' score [25], this scheme is not based on a scoring system. In addition, the scheme depends heavily on the identification of an alternative disorder that can explain the abnormal finding. Although highly logical, this component imposes a subjective element on the conclusion.

None of the 17 patients with normal D-dimer but high clinical probability, who subsequently underwent MSCT examination, had PE, neither did any of them develop VTE during the 3-month follow-up period. Moreover, none of the 10 patients with normal D-dimer who were excluded because of protocol violations developed VTE in the subsequent 3 months. Pooling those to patients with low-intermediate clinical probability, the overall diagnostic yield of D-dimer would have been increased to 30% had the clinical probability assessment testing been omitted, a result comparable to the diagnostic yield of the ELISA based VIDAS test shown in other studies [5,6]. Although the number of patients in the high

Table 3 Comparison of various diagnostic strategies applying CT for managing suspected PE

Study	Population	Rate of PE (%)	Criteria for exclusion of PE	No. of patients	3-m VTE risk – % (95% CI)
Musset *et al.* [11]	In- and outpatients	34.6	Low or intermediate clinical probability, negative spiral CT and ultrasound	507	1.8 (0.8–3.3)
Van Strijen *et al.* [9]	In- and outpatients	24.3	Normal or inconclusive spiral CT and and negative serial ultrasonography	376	0.8 (0.3–2.3)
Perrier *et al.* [6]	Outpatients	23	Normal D-dimer, or negative US, negative spiral CT and Low or intermediate CP, or normal pulmonary angiography	685	1.0 (0.5–2.1)
Present study	Outpatients	23.6	Normal D-dimer and low or intermediate CP or unequivocally negative MSCT	330	0.6 (0–2.2)

risk group is too small and the 95% CIs are too wide to draw definitive conclusions, these data suggest that further investigation and treatment can be withheld in patients with high clinical probability and normal D-dimer. However, owing to the heterogeneous nature of the different assays, these results cannot be extrapolated to other less sensitive D-dimer assays. Because of the many advantages of D-dimer testing like feasibility, low cost and safety, it is tempting to apply it as a first step test regardless of the clinical probability. Although it seems safe enough, the main disadvantage of using D-dimer to rule out PE in high risk patients is the large number of patients needed to be tested in order to rule out one PE.

The recommendations concerning the safety to withhold anticoagulation after a negative spiral CT are contradictory, and most of these recommendation are based on studies using imaging with single slice CT [1,3,26,27]. In this study, MSCT was applied as a stand-alone imaging test and negative results were considered to rule out PE. This notion has not been sufficiently validated in outcome trials. The 3-month thromboembolic risk after a negative MSCT was 0.9% (95% CI 0.1–3.2) in that subgroup, a rate that is acceptable and reliably proves the safety of this approach. The elimination of further testing after negative CT makes the approach less complicated and more feasible in addition to reducing costs and time required to reach the diagnosis.

The proportion of inconclusive CT interpretations in this study falls within the range of those reported in other studies ranging from 1.6%–7.9% [6,9,11,28]. Adherence to the protocol concerning the work-up of patients with equivocal CT examinations was surprisingly low. Compression ultrasonography was only performed in half of these patients, and only the minority of patients with negative ultrasound underwent further evaluation with perfusion scan or pulmonary angiography. Pulmonary angiography was only performed in one patient, reflecting the reluctance of radiologists to perform the test on the one hand and the physicians to order it on the other hand. However, we lack a reasonable explanation for not performing perfusion scans. We believe that the high clinical suspicion of PE in these patients reinforced by the persistence of symptoms in the absence of an alternative explanatory diagnosis, and complemented by highly suggestive radiological findings did contribute to the decision to treating these patients without further verification.

Regarding the optimal approach to patients with inconclusive MSCT, we believe that ultrasound of the lower limbs should be first performed to search for a DVT as an indirect indication of the presence of PE. A negative examination should be further verified by isotope scanning or pulmonary angiography. Repeating MSCT examination using thinner collimation could be an alternate, as evidence already exists that the diagnostic accuracy and the inter-observer agreement are improved with thinner collimation scans [18].

An isolated calf vein thrombosis was revealed in three patients despite the unequivocal finding of negative MSCT. All three patients were however referred to compression ultrasound examination because of the co-existing clinical evidence of DVT manifested by localized pain or swelling indicating the possible presence of DVT. According to the study protocol, lack of compressibility above the trifurcation was demanded to establish the diagnosis of DVT, a criteria largely applied in studies using compression ultrasonography [5,6,9,11]. The accuracy of the diagnosis in these patients is therefore questionable and cannot be relied on to advocate the need for compression ultrasonography following a negative MSCT. However, it is recommended to perform ultrasonography prior to CT if the patient has co-existing manifestations of DVT [3]. In a worst case scenario, the 3-month thromboembolic risk would have increased to 1.8% (95% CI 0.7–4.0) if the DVT had gone unnoticed and the patients had returned back with VTE in the subsequent 3 months.

Ultrasonography is positive in 10%–15% of all patients without leg symptoms who undergo evaluation for suspected PE [6,11]. Applying compression ultrasonography prior to MSCT would have obviated the need for a CT scan in those patients. On the other hand, a negative test cannot rule out PE. Consequently, 85%–90% of the examined patients would have to undergo MSCT if ultrasonography was performed prior to MSCT. This approach is more resource intensive and time consuming. We therefore believe that the higher proportion of patients exposed to ionizing radiation in our proposed algorithm can be justified. An added benefit is the possibility of MSCT to detect other pathologies.

As the proposed algorithm includes D-dimer, our study was designed for and was conducted in outpatients. Thus, our results and in particular those concerning the diagnostic yield of D-dimer cannot be generalized to include hospitalized patients as D-dimer is commonly elevated and is hence of less value in these patients.

In conclusion, our study shows that the diagnostic strategy combining D-dimer as a first step test followed by multi-slice spiral CT, as a lone imaging test, in patients with elevated D-dimer is safe and effective in outpatients with suspected PE.

Contributors

W. Ghanima and P.M. Sandset designed and coordinated the study and drafted the manuscript. V. Almaas, S. Aballi and C. Dörje supervised daily field activities, patient recruitment and follow-up. B.E. Nielssen and L.O. Holmen coordinated the radiological examinations. M. Abdelnoor and R. Almaas contributed in the design and statistics. All authors contributed to the planning of the study, reviewed the report and approved its final version.

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