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Roles of spectral dual-layer CT, D-dimer concentration, and COVID-19 pneumonia in diagnosis of pulmonary embolism

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HIGHLIGHTS

- Using dual-energy CT reduces numbers of inconclusive pulmonary embolism findings.
- Greater extent of pulmonary embolism corresponds to higher D-dimer values.
- D-dimer cut-off of 1.0 mg/L in COVID-19 pneumonia maintains sensitivity for PE.

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ABSTRACT

Purpose: To demonstrate advantages of spectral dual-layer computed tomography (CT) in diagnosing pulmonary embolism (PE). To compare D-dimer values in patients with PE and concomitant COVID-19 pneumonia to those in patients without PE and COVID-19 pneumonia. To compare D-dimer values in cases of minor versus extensive PE.

Methods: A monocentric retrospective study of 1500 CT pulmonary angiographies (CTPAs). Three groups of 500 consecutive examinations: 1) using conventional multidetector CT (CTC), 2) using spectral dual-layer CT (CTS), and 3) of COVID-19 pneumonia patients using spectral dual-layer CT (COV). Only patients with known D-dimer levels were enrolled in the study.

Results: Prevalence of inconclusive PE findings differed significantly between CTS and CTC (0.8 % vs. 5.4 %, $p < 0.001$). In all groups, D-dimer levels were significantly higher in PE positive patients than in patients without PE (CTC, 8.04 vs. 3.05 mg/L; CTS, 6.92 vs. 2.57 mg/L; COV, 10.26 vs. 2.72 mg/L, $p < 0.001$). There were also statistically significant differences in D-dimer values between minor and extensive PE in the groups negative for COVID-19 (CTC, 5.16 vs. 8.98 mg/L; CTS 3.52 vs. 9.27 mg/L, $p < 0.001$). The lowest recorded D-dimer value for proven PE in patients with COVID-19 pneumonia was 1.19 mg/L.

Conclusion: CTPAs using spectral dual-layer CT reduce the number of inconclusive PE findings. Plasma D-dimer concentration increases with extent of PE. Cut-off value of D-dimer with 100 % sensitivity for patients with COVID-19 pneumonia could be doubled to 1.0 mg/L. This threshold would have saved 110 (22 %) examinations in our cohort.

1. Introduction

Pulmonary embolism (PE) is a life-threatening acute condition and one of the leading cardiovascular causes of death [1,2]. PE occurs in cases of thromboembolic disease, and the most used laboratory marker of thromboembolism is the plasma concentration of D-dimer. An elevated level of D-dimer can mark ongoing fibrinolysis [3]. A concentration of less than 0.5 mg/L is considered normal. This level can be affected not only by the intravascular presence of a blood clot but also by other conditions, such as ongoing systemic infection, cancer, or pregnancy [4]. Normal D-dimer level also increases with age [5].

During the recent COVID-19 pandemic, systemic viral infection

Abbreviations: COVID-19, coronavirus disease; CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; ROC, receiver operating characteristic.

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manifested predominantly as interstitial pneumonia. Apart from inflammatory lung disease, the development of PE is another complication accompanying COVID-19 pneumonia. Hypercoagulable state in patients with COVID-19 pneumonia, immune anti-inflammatory reaction, and vascular endothelial damage are involved in the development of PE [6,7].

The diagnostic method of choice when PE is suspected is computed tomography pulmonary angiography (CTPA), which visualizes the embolus itself [8]. The ongoing development of computed tomography technology is currently focused on spectral imaging. Dual-energy CT already is widely used in clinical practice. Generally, this technique works with the attenuation of two X-ray energy spectra and allows the creation of multiparametric image reconstructions, such as virtual monoenergetic reconstruction (for different keV values) or maps of iodine distribution in tissues. The specific technological details differ among manufacturers. Monoenergetic images with low keV values improve the distinction between the iodine contrast agent and soft tissues, and iodine maps allow assessment of tissue perfusion. Both can be used in assessing presence of PE [9,10].

Our study's main purpose was to demonstrate the potential use of spectral dual-layer CT in diagnosing PE. Another aim was to compare D-dimer values in patients with PE and concomitant COVID-19 pneumonia to those in patients without PE and without COVID-19 pneumonia. Moreover, we compared D-dimer values in cases of minor versus extensive PE.

2. Material and methods

This was a monocentric retrospective cross-sectional study approved by the local ethics committee.

The study enrolled 1500 consecutive patients backdated from 1 July 2021. They were divided into three equal groups of 500. All were over 18 years of age and had undergone CTPA in our hospital with clinical suspicion of acute pulmonary embolism. Specific thromboembolic risk scores were not routinely considered in indicating CTPA.

Included into the study were only those patients for whom D-dimer concentrations had been determined within 48 h prior to CT scan, 65 cases without this test were excluded to reach 1500 patients. The concentration of D-dimer was determined by latex enhanced immunoassay (LIA); at our hospital the maximum concentration measurable is limited to 20 mg/L for technical reasons.

COVID-19 infection was confirmed in all patients by reverse transcription polymerase chain reaction (RT-PCR) test. Individual virus variants were not identified.

The first group (CTC) consisted of patients COVID-19 negative who were examined on a conventional multidetector CT machine (Brilliance 64, Philips Healthcare). The recruitment period extended back to 27 January 2020.

The second group (CTS) consisted of patients COVID-19 negative, examined on a spectral CT scanner (IQon Spectral CT, Philips Healthcare). The recruitment period in their cases ended 1 September 2020.

These both groups represented general population, selection of CT scanner was based only on current availability of the machine.

The third group (COV) consisted of patients COVID-19 positive having CT imaging features consistent with COVID-19 pneumonia. They were examined by spectral CT. These CT findings typical for COVID-19 pneumonia consisted of bilateral ground-glass opacities, frequently in combination with patchy consolidations preferably in peripheral distribution [11]. To reach these 500 examinations according to these criteria, 52 cases COVID-19 positive but without signs of pneumonia had been excluded. The recruitment period dated back to 29 August 2020. The spectral CT scanner was chosen for this group because of its location within the hospital.

The different duration of the recruitment periods is due to the different caseload of individual CT scanners.

Acquisition parameters were as follow: tube voltage, 120–140 kV; automatic current modulation; reconstruction matrix, 512 × 512; slice thickness, 0.9 mm; caudocranial acquisition.

Contrast media administration can be characterized as follows: bolus tracking technique; region of interest, pulmonary truncus; difference, 60–90 Hounsfield units (HU); contrast medium, ≥350 mg iodine/mL; contrast medium volume, 60 mL (conventional CT) and 50 mL (spectral CT) followed by a 40 mL saline chaser; contrast medium flow, 4.5 mL/s.

PE was diagnosed based on the presence of intravascular pulmonary artery tree filling defects on CTPA. Diagnoses were further subdivided into extensive and minor. Minor PE was defined as presence of arterial contrast filling defects up to two lobes segmentally, respectively estimation of Qanadli CT obstruction index [12] lower than 10. This score assesses the thrombus location (20 for pulmonary trunk to 1 for segmental branches), and the degree of vessel obstruction (2 for complete, 1 for partial). The maximum value is 40, indicating complete obstruction of pulmonary trunk, and the lowest positive finding is 1, indicating the presence of a non-obstructing thrombus in one segmental artery. Considering the retrospective nature of the study, in some cases baseline submillimetre scans were no longer available in the archive, hence the accurate determination of the score, especially the sides of the obstruction level, or the possibility of volumetric analysis of thrombi was limited, therefore only a two-level stratification of PE findings was chosen.

Examination was inconclusive if it was not possible to decide about the presence of emboli in the vessel peripheral to the segmental branches. That was due either to motion artifacts or to insufficient or considerably inhomogeneous contrast filling of the peripheral circulation.

All CTPA scans were evaluated and reports completed according to consensus among two radiologists, at least one of whom was a board-certified radiologist with at least 6 years of clinical practice. The positive and inconclusive findings were further revised and graded by mutual agreement of two radiologists (TJ and VV). In all cases, the evaluators were aware of the D-dimer values.

The standardized report included assessment of contrast filling defects of the pulmonary arteries, width of the cardiac compartments and major pulmonary arteries, and pathology of the lung parenchyma.

In spectral CT scans, iodine perfusion maps and monoenergetic image reconstructions at 55 keV were routinely generated in all patients (Figs. 1,2). The criteria for the diagnosis of PE were the same as for conventional scans (pulmonary artery tree filling defects). Irregularities of parenchymal perfusion alone were neither evaluated as a positive PE finding nor quantified volumetrically.

Statistical analysis was performed using software TIBCO Statistica® in version 12. Statistical significance was regarded as existing at $p < 0.05$. Data were analysed using analysis of variance (ANOVA), receiver operating characteristics (ROC), chi-square test, Student's *t*-test, and Spearman correlation. The conditions requisite for the individual tests were verified.

3. Results

The age distributions of the three groups were not significantly different ($p = 0.29$–0.88, *t*-test). The gender distributions in the groups COVID-19 negative also were not significantly different (42.6 vs. 41.5 %, $p = 0.52$, chi-square test). Among patients with COVID-19 pneumonia, however, there was a significantly higher proportion of men ($p < 0.001$, chi-square test) (Table 1).

Pulmonary embolism was detected in 27 % (CTC) and 24 % (CTS) of patients within the groups COVID-19 negative and with no statistically significant difference between these two groups ($p = 0.125$, chi-square test). On the other hand, there was a significantly higher prevalence of PE in the CTS group compared to the COV group (24 % vs. 10.2 %, $p < 0.001$, chi-square test). The prevalence of inconclusive findings was significantly lower in examinations performed in the CTS group compared to the CTC examinations (0.8 % vs. 5.4 %, $p < 0.001$, chi-

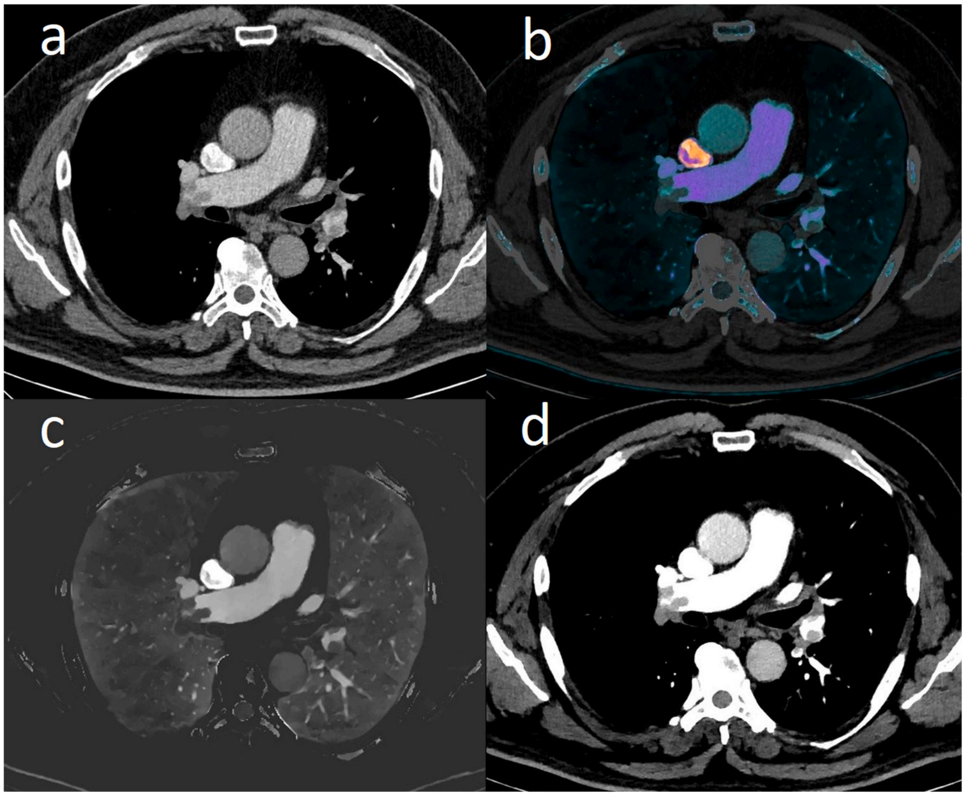

Fig. 1. CT image of pulmonary embolism in COVID-19 negative patient. a. Conventional (Hounsfield unit) CT image. b. Fusion of iodine density maps and conventional image. c. Iodine density – perfusion map. d. Virtual low-energy monoenergetic image (55 keV). Visible are contrast filling defects of main right pulmonary artery spreading to lobar branches and in the left lobar/segmental branches.

square test), (Table 2).

The ratios of minor to all PE diagnoses in the CTC, CTS, and COV groups, respectively, were 0.30, 0.42, and 0.33 (CTC vs. CTS, $p = 0.06$; CTS vs. COV, $p = 0.3$; chi-square test), (Table 2).

In all three groups, D-dimer levels were significantly higher in patients with PE than in patients without PE (CTC, 8.04 vs. 3.05 mg/L; CTS, 6.92 vs. 2.57 mg/L; COV, 10.26 vs. 2.72 mg/L; all $p < 0.001$, ANOVA). There were also significant differences in D-dimer values between the minor and extensive PE in the groups COVID-19 negative (CTC, 5.16 vs. 8.98 mg/L; CTS, 3.52 vs. 9.27 mg/L; $p < 0.05$, ANOVA). In patients with COVID-19 pneumonia (COV), the difference was not statistically significant (7.63 vs. 10.87 mg/L, $p = 0.35$, ANOVA). (Fig. 3)

According to the receiver operating characteristic (ROC) analysis, the optimal cut-off level of D-dimers for CTC was 2.96 mg/L with both sensitivity and specificity of 76.3 %, area under the curve (AUC) for PE was 0.8 (CI 95 %, 0.752–0.848). Optimal cut-off for CTS was 2.69 mg/L with sensitivity of 65 % and specificity of 79.6 %, AUC for PE was 0.78 (CI 95 %, 0.728–0.832). Cut-off for COV was 3.24 mg/L with sensitivity of 78.4 %, specificity of 81.1 %, and AUC for PE 0.84 (CI 95 %, 0.771–0.909). (Fig. 4, Table 3).

The lowest recorded D-dimer values for proven PE for each group were CTC, 0.69 mg/L; CTS, 0.53 mg/L; and COV, 1.19 mg/L.

Furthermore, a statistically significant correlation ($r = 0.1$, $p < 0.05$, Spearman correlation) for the increase of D-dimer levels with age was confirmed in the cumulative group of all patients without PE (Fig. 5).

4. Discussion

The innovative approach of this paper is a direct comparison of two or respectively three groups of patients with suspected acute pulmonary embolism, in terms of the technical advancement of the CT scanner and a clearly defined risk factor, COVID-19 pneumonia.

4.1. Role of spectral/dual-energy CT

Dual-energy computed tomography's advanced technology can improve the detection of small emboli as well as pulmonary artery intravascular contrast attenuation in cases of suboptimal intravascular opacification [13,14]. It could contribute to reducing the number of inconclusive findings [15]. In our cohort, there were statistically significantly fewer inconclusive findings in patients examined with spectral CT compared to the group examined with conventional (single energy spectrum) CT (0.8 % vs. 5.4 %). Therefore, we have verified those results also for the dual-layer detector CT, while most of the authors used dual-source CT. The relative proportions of minor PE, however, were similar across all three groups. Thus, spectral CT does not increase detection rate of small PEs.

In many cases of complete obstruction of the pulmonary artery, there were inhomogeneities or even defects in lung parenchymal perfusion within the corresponding lung segment. If no thrombotic vascular occlusion was detected, we did not consider these images as sign of PE. A similar picture may arise in the setting of advanced COVID-19 pneumonia with typical distribution of ground-glass opacities and consolidations at the periphery of the lung [16].

At our department, the examination protocol for PE includes reconstruction of iodine perfusion maps and virtual monoenergetic images at low keV. These are evaluated together with conventional CT images. In this setting, moreover, the amount of contrast agent administered can be reduced [17,18]. When using spectral CT at our department, we are currently testing a new protocol for pulmonary artery imaging utilizing a total 30 mL of iodine contrast agent as opposed to the established 50 mL.

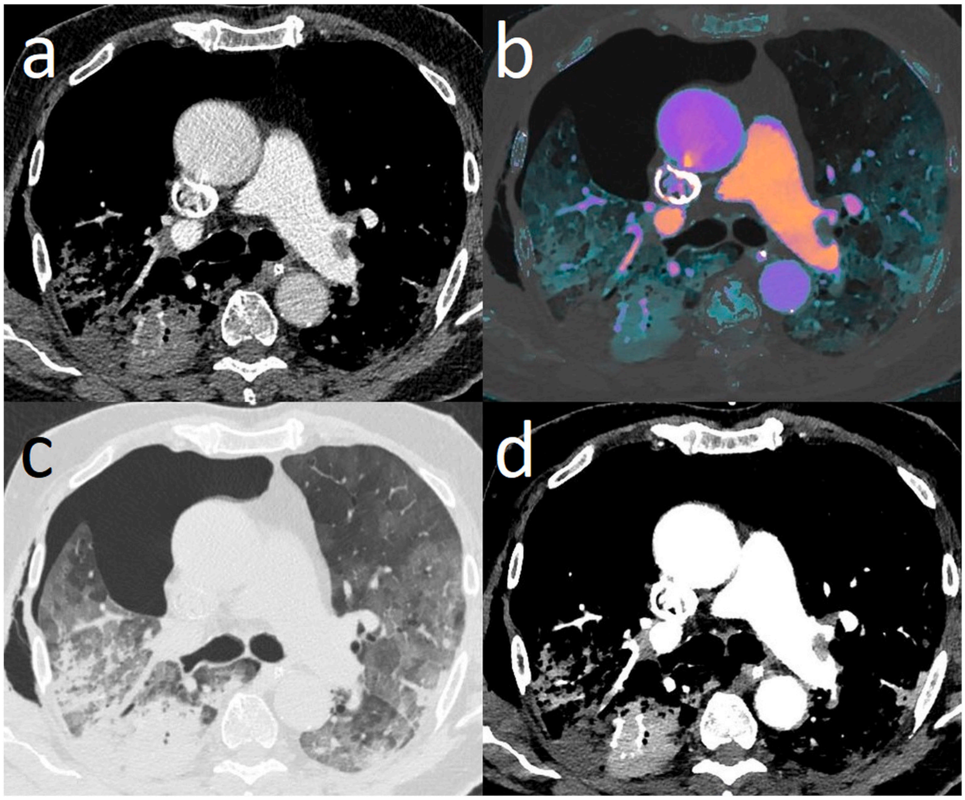

Fig. 2. CT image of pulmonary embolism in patient with complicated COVID-19 pneumonia. a. Conventional (Hounsfield unit) CT image. b. Fusion of iodine density maps and conventional image. c. Virtual non-contrast image, lung window. d. Virtual low-energy monoenergetic image (55 keV). Visible are contrast filling defects in pulmonary arteries (left in lobar/segmental branching, right in segmental branch). Wedge-shaped defect in perfusion (dorsal parts of right lung) in hyperaemic consolidation. Diffuse ground-glass opacities in both lungs, corresponding with COVID-19 pneumonia. Right side pneumothorax and thoracic wall emphysema.

Table 1
Gender, age and D-dimer level characteristics.

Characteristic	CTC	CTS	COV
Male [count]	213 (42.6 %)	206 (41.5 %)	298 (59.6 %)
Mean age [years]	65.6 (SD: 16.8)	64.5 (SD: 17)	64.6 (SD: 14.2)
D-dimer [mg/L]	4.4 (SD: 5.4)	3.6 (SD: 4.9)	3.6 (SD: 5)

Table 2
Absolute and relative prevalence of pulmonary embolism (PE).

Diagnosis	CTC	CTS	COV
Pulmonary embolism	135 (27 %)	120 (24 %)	51 (10.2 %)
Inconclusive	27 (5.4 %)	4 (0.8 %)	16 (3.2 %)
Minor PE	41 (8.2 %)	50 (10 %)	17 (3.4 %)
Extensive PE	94 (18.8 %)	70 (14 %)	34 (6.8 %)
Ratio minor PE/all PE	0.3	0.42	0.33

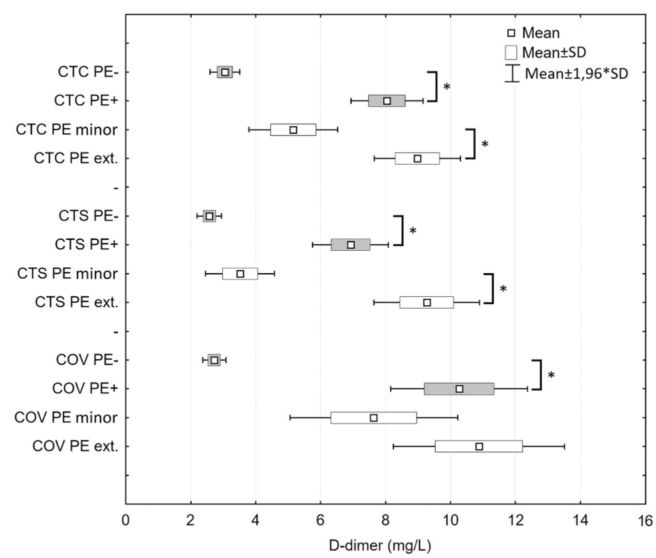

Fig. 3. Boxplots of D-dimer values for each subgroup. PE+, proven pulmonary embolism; PE-, patients without pulmonary embolism; PE minor and PE ext., minor or extensive PE. In case of extensive PE, contrast filling defects were evident in more than two lobes segmentally. *Indicates statistically significant difference ($p < 0.001$).

4.2. Role of COVID-19 pneumonia

Patients with COVID-19 pneumonia formed a sort of control group wherein D-dimer values were altered by the same external factor (infectious disease). There was greater proportion of uncertain findings in the COVID-19 pneumonia patients compared to the COVID-19 negative group examined on spectral CT (3.2 % vs. 0.8 %, $p < 0.05$, chi-square test). This may be related to inflammatory changes in the lung parenchyma (sometimes with extensive consolidations) and possible contribution of respiratory artifacts in patients with persisting dyspnoea.

In our cohort, the prevalence of PE was less than half in the COVID-19 pneumonia group (10 %) compared to the groups COVID-19 negative (CTC, 27 %; CTS, 24 %). Probably due to the clinical similarity and overlap of COVID-19 pneumonia symptoms and PE and the reported prothrombotic state [19], CTPA examination was indicated in relatively more cases.

The overall prevalence of PE in our cohort was very similar to pooled prevalence in non-ICU patients reported in a metanalysis by Suh [20]

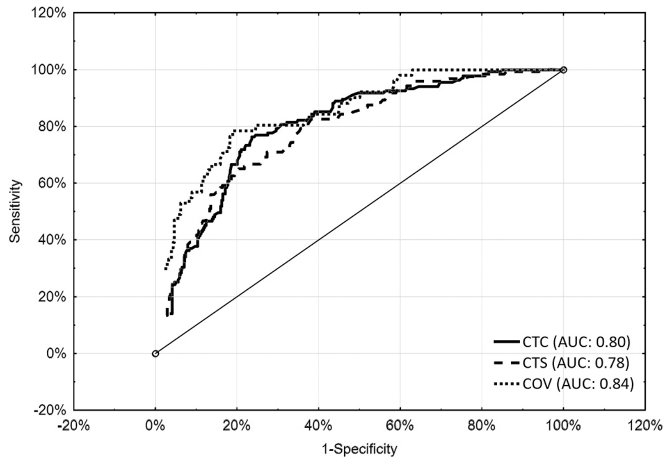

Fig. 4. Receiver operating characteristics of D-dimer values for CTC, CTS, and COV groups.

and to combined random effects estimate of PE in metanalysis by Gallastegui[21]. Another metanalysis by Kwee et al. [22] reports higher prevalence (23.9 %) in general wards versus in emergency departments (17.9 %) and intensive care units (48.6 %). Comparable monocentric study by Laounan Brem [23] shows slightly lower prevalence of PE (7.17 %).

4.3. Role of D-dimer

Various scoring systems (e.g. Wells score) are used to assess the risk of PE in the clinical examination. The test result in combination with the D-dimer value will aid in the decision to perform a CTPA [4]. At our hospital, information on the Wells score is not a standard part of the documentation and therefore its value is not considered in this paper.

D-dimer values are influenced not only by the presence of thromboembolic disease but also by other pathological conditions, which in practice limits their sensitivity in the diagnosis of PE. Given the size of the groups COVID-19 negative and the average age of the patients, the presence of these other factors was not considered.

The statistically significant difference between D-dimer concentrations in patients with and without pulmonary embolism and the results of ROC analysis confirm the clinical utility of D-dimer in diagnosing PE [24]. The AUC values (CTC, 0.8; CTS, 0.78; COV, 0.84) in our dataset using cut-off value of 0.5 mg/L are comparable to those in the literature [5,25].

Differences in D-dimer values between minor and extensive PE have already been observed [26,27], but comparison and actual quantification as to the extent of PE are problematic.

Increased level of D-dimer in patients with COVID-19 pneumonia already has been well described [28].

In our cohort, a common uncorrected cut-off value of 0.5 mg/L was used for all patients, even with COVID-19 pneumonia, whereas other authors more commonly report 1.0 mg/L for patients COVID-19 positive [29]. Using this cut-off value would have saved a total of 110 (22 %) examinations in the group COVID-19 positive when applied to our cohort. In such a reduced cohort, the prevalence of PE would be 13.1 %,

Table 3
Sensitivity and specificity ranges of D-dimer extracted from receiver operating characteristic curve.

	CTC		CTS		COV	
D-dimer	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
<1 mg/L	94 %	32 %	96 %	34 %	100 %	25 %
<1.5 mg/L	91 %	52 %	86 %	50 %	88 %	53 %
<2 mg/L	84 %	62 %	73 %	67 %	80 %	65 %

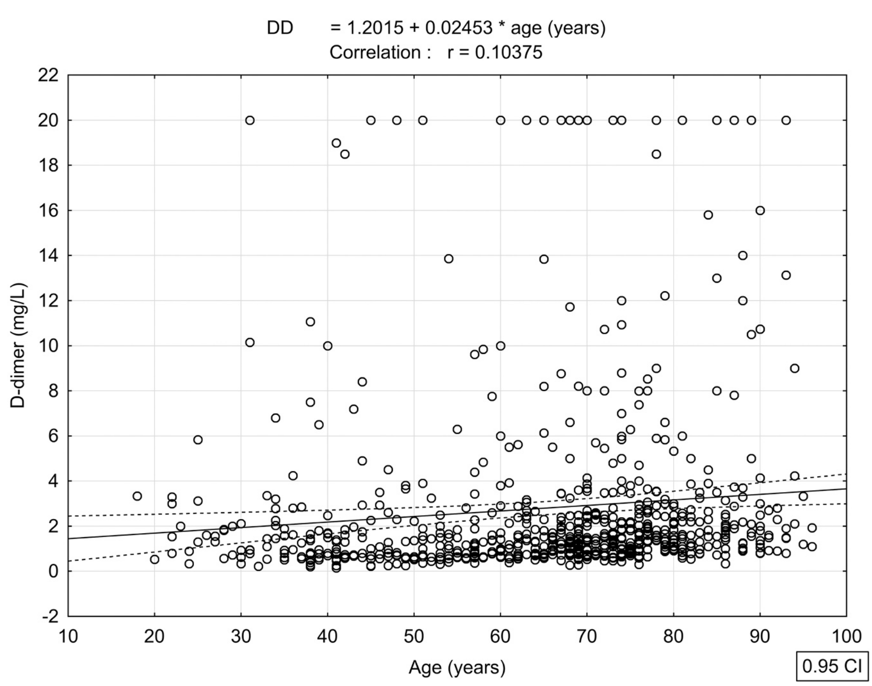

Fig. 5. Spearman correlation of D-dimer value and age in patients without PE.

and sensitivity would remain 100 %. Due to the nature of the CT examination, however, in addition to ruling out pulmonary embolism, we also evaluate the lung parenchyma for characteristic findings of COVID-19 pneumonia and possible complications. Based on the examination results, the therapy was eventually escalated (deployment of targeted medical therapy, invasive mechanical ventilation).

4.4. Limitations

D-dimer values were available for all patients prior to evaluation of the actual CTPA scans. This condition presented a potential scope for confirmation bias.

Evaluation of subsegmental defects brings a greater degree of subjectivity and can often lead to overdiagnosis of PE [30,31]. From a clinical point of view, the significance of such small findings is also disputed [32].

When assessing the cause of D-dimer elevation, other comorbidities such as cancer were not considered (apart from COVID-19 pneumonia). However, these comorbidities were very often not taken into account in clinical requests for CTPA or were not known at the time of the indication.

On the other hand, in some cases with an expected alteration of D-dimer levels, such as conditions after extensive recent surgery, this laboratory examination was not performed, so such patients were not included in our study population.

The evaluation of the CTPA itself included to assess the presence of signs of pulmonary hypertension. Due, however, to the study design and frequent presence of signs of hypertension even in patients without PE, the prevalence was not evaluated statistically.

Our spectral CT works with a dual-layer detector technology, which is quite different from the more commonly used dual-source CT technology. The inherent difference of the reconstructed multiparametric maps obtained by these techniques can be subject to debate, possibly limiting comparison with other studies.

5. Conclusions

CTPA using spectral dual-layer CT technology reduced the number of inconclusive PE findings. Moreover, the results confirmed the diagnostic utility of plasma D-dimer concentration in diagnosis of pulmonary embolism and that D-dimer values increase with age. D-dimer levels were significantly higher in cases of extensive PE compared to minor PE in patients COVID-19 negative. There was no statistically significant difference in the relative prevalence of minor PE among the three groups.

COVID-19 pneumonia generally increased D-dimer plasma concentration. Therefore, the cut-off for PE could be doubled to 1.0 mg/L while maintaining its 100 % sensitivity, thereby saving 22 % of those examinations conducted within our cohort.

Ethical statement

The study was approved by the local ethics committee (04–140922/EK), Ethical Committee of University Hospital Brno. Due to the retrospective nature of the study, informed consent was waived.

CRediT authorship contribution statement

Daniel Vlk: Writing – review & editing, Validation, Supervision. **Vlastimil Valek:** Writing – original draft, Validation, Investigation, Data curation, Conceptualization. **Tomáš Jůza:** Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marek Dostál:** Software, Resources, Methodology, Formal analysis. **Tomáš Andrašina:** Writing – review & editing, Supervision, Methodology.

Declaration of Competing Interest

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