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ORIGINAL ARTICLE

Comparison of Multidetector Computed Tomography Findings with Clinical and Laboratory Data in Pulmonary Thromboembolism

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Summary

Background: Pulmonary thromboembolism (PTE) is a common disease with a high mortality rate that is difficult to diagnose and treat. Because of the variety of clinical symptoms and signs, it is difficult to diagnose. Therefore, the diagnosis of PTE is mainly confirmed by imaging techniques. The aim of this study was to evaluate whether there is any corelation of the Wells rule, D-dimer and LDH values with computerized tomography pulmonary angiography (CTPA) findings in PTE diagnosis.

Material/Methods: A consecutive series of 62 patients, which included 31 males and 31 females, with high/moderate/low risk of embolism according to Wells pulmonary embolism score, selected from the emergency service and/or outpatient clinic, enrolled in this prospective study. The patients with clinical or laboratory findings of elevated D-dimer level or elevated lactate dehydrogenase (LDH) level were suspected of embolism and underwent tomography.

Results: PTE was detected in 26 patients (42%). A significant difference was not detected between tomography finding positive and negative embolisms in the patient group in terms of age or gender distribution (P=0.221 and P=0.416, respectively).

No significant difference was detected between tomography finding positive and negative embolisms in the patient group in terms of elevated LDH or/and D-dimer levels (P=0.263 and P=1.000, respectively).

The distribution of low-risk-factor patients in the non-embolism group, and the distribution of high-risk-factor patients in the embolism-positive group was statistically significantly high (P<0.001). There was no statistically significant difference between the groups (P=0.053).

Correlation test showed no correlation between LDH and D-dimer levels. (r=0.214, P=0.180).

Conclusions: In conclusion, when a patient presents with chest pain, our carrying out LDH and D-Dimer tests will not exclude PTE without CTPA. However, we suggest that LDH isoenzymes should be studied in further research.

MeSH Keywords: Fibrin Fibrinogen Degradation Products • Lactate Dehydrogenases • Multidetector Computed Tomography • Pulmonary Embolism

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Background

Acute pulmonary thromboembolism (PTE) is a common disorder with high mortality and morbidity rates [1]. PTE accounts for 15% of hospital mortality. The annual incidence of PTE is thought to be 1.22 to 1.83 in 1000 cases. Most cases of PE that eventually cause fatalities are clinically unsuspected and therefore go untreated before death [2,3].
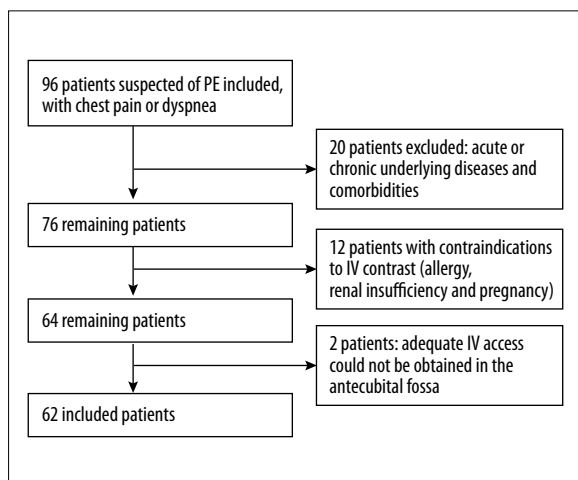
Figure 1. Participiant selections.

Due to the shortening of the screening period, parallel to the technological advancements, the thinning of the section thicknesses and the increase in the specificity and sensitivity, multi-detector row computed tomography (MDCT) angiography has been a part of the routine practice. The increasing availability of newer generations of multidetector CT scanners (16- and 64-slice) with rapid rotation speeds has made it possible to acquire thin-collimation images through large volumes of imaged tissue, allowing high-quality reconstructions using isometric voxels [4].

Patients in whom clinical symptoms are unrecognized or are attributed to other causes may undergo chest computed tomography (CT) with the use of protocols that are not tailored for the detection of pulmonary emboli, and use of such protocols leaves an uncertain number of patients who actually have PE without a diagnosis, untreated, and with a potential for increased mortality [5,6].

Clinical symptoms and findings, arterial blood gases, laboratory results such as D-dimer and LDH levels, chest X-rays, and venous Doppler ultrasonography (US) findings are all known to be inadequate in the diagnostics of pulmonary thromboembolism. CT angiography, with its non-invasive nature and accessibility, is an effective method of making or ruling out the diagnosis of pulmonary embolism.

The aim of this study was to evaluate whether there is any corelation of Wells rule, D-dimer and LDH values with computerized tomography pulmonary angiography (CTPA) findings in PTE diagnosis.

Material and Methods

This was a prospective study of consecutive patients evaluated for over 3 months, from May 2012 to July 2012. A total of 96 consecutive patients with suspected PE, included in the study, who had chest pain or dyspnea were clinically examined. The study was approved by the Ankara Education and Research Hospital (AERH) Ethics Board, and informed consent was obtained from all participants. All participants included in the study underwent a detailed physical examination, and a complete medical and family history was recorded. Clinical symptoms and findings of all

Table 1. Clinical probability classification according to Wells scoring.

Criteria	Points
Clinical finding for DVT	3
Most probable diagnosis of PTE	3
Heart rate >100/minute	1.5
Prior operation or immobilization in the last month	1.5
History of prior DVT of PTE	1.5
Hemoptysis	1
Malignancy	1
Scoring:	<2: Low clinical probability 2–6: Intermediate clinical probability >6: High clinical probability

DVT – deep venous thrombosis, PTE – pulmonary thromboembolism.

patients, presence of risk factors for PTE, patient age, history of recent surgical operation, prior PTE history, pulse rate, and history of malignancy were recorded using the computer database of the hospital. Of these patients, 20 were excluded for acute or chronic underlying diseases and comorbidities, 12 were with contraindications to IV contrast (allergy, renal insufficiency and pregnancy), and in 2 patients adequate IV access could not be obtained in the antecubital fossa (Figure 1). Symptomatic patients with a D-dimer cut-off value of 500 μg/L did not undergo CTPA and were left untreated and formally followed up for 3-months.

Finally, 62 patients, including 31 males and 31 females, underwent computed tomography pulmonary angiography (CTPA) at the CT unit of the Radiology Clinic with a preliminary diagnosis of low/intermediate/high probability for pulmonary thromboembolism as a result of clinical evaluation at the emergency service and/or outpatient clinic.

Wells clinical probability score for pulmonary thromboembolism was calculated for each patient using those data (Table 1). Patients were then divided into groups with high, intermediate, and low clinical probability of PTE.

The D-dimer (DD) level was tested using Innovance DD (Dade Behring, Marburg, Siemens Company, Germany), which is a latex-enhanced, turbidimetric test based on polystyrene particles covalently linked to a monoclonal antibody (DD5) to the cross-linkage region of cross-linked fibrin degradation products.

Lactate dehydrogenase (LDH) level was tested using Beckman Coulter AU 5800 (Mihsima, Beckman Coulter,Co., Ltd.,USA).

D-dimer (normal level <500 ug/dL) and LDH levels (range: 0–248) at the time of laboratory tests were also recorded using the same database. CTA sectional images that were performed using the same parameters were evaluated.

All CTA evaluations were performed using 64- and 16-detector CT equipment (Aquillon 64, Toshiba Medical Systems, Tochigi, Japan) and a spiral computed tomography scanner (Philips 16-section Brilliance system, Philips Healthcare, Holland), and intravenous contrast material

injections were performed using a CT automatic injector (Medrad Vistron and Ulrich Medikal).

In preparation for the pulmonary CTA evaluation, an intravenous line using an 18–20 G catheter through one of the forearm veins was inserted in each patient. Subsequently, 95–100 mL (1 mL/kg) of non-ionic contrast material was administered at a rate of 4 mL/sec by an automated injector. After a delay of 10 seconds following the injection of the contrast material, the sections were obtained (test dose was not administered to calculate the delay time; mean values reported in the literature were used).

Patients were asked to hold their breath during the evaluation. Imaging was obtained with the patient in the supine position with the arm of injection at the side of the patient to prevent subclavian vein compression, and the other hand at the level of the head.

Images were obtained through the apex of the lungs up to the level of the diaphragm with section thicknesses of 0.50 and 1.00 mm, and pitch value of 0.75. Variable dose parameters between 120 kVp and 250–300 mA were used according to the weight of the patient. CTA imaging was performed in the caudocranial direction and during a single breath-holding period.

CTA section images were transferred to the computer media and evaluated.The presence of PE on CTPA images was defined according to the established criteria (pulmonary arterial luminal filling defect on at least two consecutive axial images, associated with a crescent or ring of contrast enhancement surrounding partial filling defects) [7]. Potential confounding artifacts were excluded (respiratory or cardiogenic motion artifact, crossing unopacified pulmonary veins, bronchial wall thickening, and peribronchial lymph nodes) by careful analysis of the anatomy and adjacent lung parenchyma on both soft tissue and corresponding lung windows [8].

Statistical analyses

Data analysis was performed using the SPSS for Windows 11.5 package program. Distribution of continuous variables was analyzed with the Shapiro-Wilk test to determine whether it was close to normal distribution. The results of the descriptive statistics were expressed as mean ± standard deviation or median values (minimum-maximum) for continuous variables and number of cases and (%) for nominal variables.

The significance of the differences of means and medians between the groups was analyzed using the student's t-test and Mann-Whitney U-test, respectively. Nominal variables were analyzed using Pearson's chi-squared or Fisher's exact chi-squared test.

To evaluate whether LDH and D-dimer were predictive for diagnosing the groups with and without thromboembolism assessed using the CT results, sensitivity, specificity, positive and negative prediction values, and diagnostic accuracy rates were calculated. A value of P<0.05 was accepted as statistically significant.

Area Under the Curve (AUC) and 95% CI were calculated for both LDH and also D-dimer by using ROC analyses differentiating the groups with and without thromboembolism detected with pulmonary CT. The degree of association between continuous variables was evaluated by Spearman's rank correlation analysis.

Results

No significant differences in the mean ages and gender distribution were found between the groups with and without thromboembolism detected by pulmonary CT (P=0.221 and P=0.416, respectively). The percentage of cases with low risk and high risk were statistically higher in the groups that were positive and negative for thromboembolism, respectively (P<0.001). Although the number of cases with intermediate risk was higher in the group that was positive for thromboembolism, no statistical difference was found between the groups (P=0.053). The frequency of pleural fluid and consolidation in lung findings was statistically higher in the group that had thromboembolism compared to the group with no thromboembolism (P<0.001 and P=0.035, respectively). No statistical differences were found between the groups in the frequency of dyspnea and chest pain (P=0.960 and P=0.748, respectively) (Table 2).

No statistically significant differences were found in median LDH levels and frequency of high LDH levels between the groups with and without pulmonary thromboembolism detected with pulmonary CT (P=0.575 and P=0.263, respectively). Median D-dimer levels and frequency of high D-dimer levels were not significantly different between the groups with and without pulmonary thromboembolism detected with pulmonary CT, either (P=0.342 and P=1.000, respectively) (Table 3).

Roc analysis revealed that LDH values were not statistically significant in the differentiation between group with thromboembolism and group without thromboembolism. [AUC=0.550, 95% CI: 0.364-0.736, P=0.575].

Roc analysis revealed that D-Dimer levels were not statistically significantly different in discrimination between group with thromboembolism and group without thromboembolism. [AUC=0.550, 95% CI: 0.364-0.736, P=0.575].

Correlation test showed no correlation between LDH and D-dimer levels. (r=0.214, P=0.180).

The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, false negativity, and false positivity for LDH in predicting the presence of thromboembolism were 87.0%, 30.0%, 58.8%, 66.7%, 60.5%, 13.0%, and 70.0%, respectively.The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, false negativity, and false positivity for D-dimer in predicting the presence of thromboembolism were 96.0%, 3.0%, 42.9%, 50.0%, 43.1%, 4.0%, and 97.0%, respectively (Table 4).

LDH, alone or in combination with D-dimer, was not found to be significantly different between the groups in diagnosing PTE in this study (Table 5).

Table 2. Demographics and clinical features of cases with and without detection of thromboembolism according to pulmonary CT.

Variable	Thromboembolism negative (n: 36)	Thromboembolism positive (n: 26)	P-value
Age	54.1±19.6	59.9±16.7	0.221
Gender			0.416
Male	19 (52.8%)	11 (42.3%)	
Female	17 (47.2%)	15 (57.7%)	
Risk group			
Low	32 (88.9%)	11 (42.3%)	<0.001
Intermediate	4 (11.1%)	8 (30.8%)	0.053
High	0 (0%)	7 (26.9%)	<0.001
Pleural fluid	18 (50.0%)	1 (3.8%)	<0.001
Consolidation	9 (25.0%)	1 (3.8%)	0.035
Dyspnea	15 (41.7%)	11 (42.3%)	0.960
Chest pain	7 (19.4%)	4 (15.4%)	0.748

Table 3. Laboratory findings in the groups with and without detected thromboembolism according to pulmonary CT.

Variable	Thromboembolism negative	Thromboembolism positive	P-value
LDH	313 (64–800)	276 (179–814)	0.575
LDH level			0.263
Normal	6 (30.0%)	3 (13.0%)	
High	14 (70.0%)	20 (87.0%)	
D-Dimer	2.5 (0.14–606)	4.4 (0.23–399)	0.342
D-Dimer level			1.000
Normal	1 (3.0%)	1 (4.0%)	
High	32 (97.0%)	24 (96.0%)	

Table 4. Diagnostic performance indicators of LDH and D-dimer in differentiating the groups with and without thromboembolism detected with pulmonary CT.

Indicators	Definitions	LDH		D-dimer	
Number of cases	N	43		58	
Sensitivity	TP/(TP+FN)	20/23	(87.0%)	24/25	(96.0%)
Specificity	TN/(TN+FP)	6/20	(30.0%)	1/33	(3.0%)
PPV	TP/(TP+FP)	20/34	(58.8%)	24/56	(42.9%)
NTD	TN/(FN+TN)	6/9	(66.7%)	1/2	(50.0%)
Accuracy	(TP+TN)/(N)	26/43	(60.5%)	25/58	(43.1%)

TP – true positive; FN – false negative; TN – true negative; FP – false positive; PPV – positive predictive value; NPV – negative predictive value.

The presence and segmental location of incidental PE were recorded for each patient (Table 6).

PTEs in pulmonary CT angiography are in the form of vascular changes and parenchymal and pleural changes. The

Table 5. Frequency distribution of cases according to LDH and D-dimer levels associated with the risk groups among cases in which both LDH and D-dimer tests were performed.

Laboratory results	Low risk (n: 23)		Intermediate risk (n: 12)		High risk (n: 6)	
LDH (N) D-dimer (N)	–		–		–	
LDH (H) D-dimer (N)	1	(4.3%)	–		–	
LDH (N) D-dimer (H)	6	(26.1%)	2	(16.7%)	1	(16.7%)
LDH (H) D-dimer (H)	16	(69.6%)	10	(83.3%)	5	(83.3%)

(N) – normal; (H) – high.

Table 6. The frequency distrubution of thrombus and the location of clot in the pulmonary thromboembolism cases detected by pulmonary CT.

Variable	n=26	
Trombus		
Acute	15	(57.7%)
Chronic	7	(26.9%)
Acute and chronic	3	(11.5%)
Location of clots		
Right main	12	(46.2%)
Right lobar	11	(42.3%)
Right segmental	12	(46.2%)
Right subsegmental	3	(11.5%)
Left main	8	(30.8%)
Left lobar	11	(42.3%)
Left segmental	5	(19.2%)
Left subsegmental	1	(3.8%)

most reliable finding among the vascular changes is intraluminal filling defect. Defects are surrounded by a thin contrast material at least in one section. Less frequently, the vessel is totally obstructed. The circumferences of central and peripheral vessels in the lung parenchymal window are enlarged.

Discussion

Pulmonary thromboembolism, which is an obstruction of the pulmonary artery and its branches with clots emerging from the systemic veins, by definition, comprises 5–10% of all causes of in-hospital mortality [1]. Early diagnosis and treatment are important since the disorder is commonly seen and the response to treatment is good, in spite of the fact that mortality rate is high.

The first step in the diagnostics of a pulmonary embolus is clinical evaluation. The clinician must select an easily accessible algorithm with a high sensitivity. Several studies have investigated clinical probability assessment in patients with suspected PTE [9,10]. Other studies have examined the significance of the value of these clinical

probability systems in predicting PE [11,12]. Yuhai Gu et al. analyzed the clinical values of three commonly used scoring systems including Wells score, revised Geneva score, and Pisa score in predicting pulmonary thromboembolism (PTE) and reported that the Pisa score showed a relatively higher clinical value to predict clinical probability of PTE in patients, with its overall sensitivity and specificity being higher than the Wells and revised Geneva score in their country [13]. Wells score has statistically the highest diagnostic value in Turkey; for [14] this reason, physicians working at the departments of internal medicine, chest diseases and emergency medicine have been using Wells clinical probability scoring in our hospital. The rates of low probability, intermediate probability, and high probability for PTE were 88.9% (32/36), 11.1% (4/36), and 0%, respectively, in the group without PTE detected with CTA; and 42.3% (11/26), 30.8% (8/26), and 26.9% (7/26), respectively, in the group with PTE detected with CTA.

The presence of elevated levels of fibrin split products (FSPs) in patients with pulmonary embolism was reported by Wilson et al. in 1971 [15]. The D-dimer level lower than the threshold level (500 ug/mL) is a useful test to rule out PTE [16]. The enzyme-linked immunosorbent assay (ELISA) D-dimer test, and second-generation latex agglutination tests (immunoturbidimetric tests) have a remarkably high sensitivity and have been proven safe first-line tests in association with clinical probability to rule out PE in outcome studies [17,18]. ELISA is a more reliable method, while LATEX agglutination is a more rapid test. The diagnosis of PTE is confirmed or ruled out in 99% of the cases after obtaining the D-dimer result with ELISA [19,20]. The LATEX agglutination method might be inadequate to rule out PTE. However, the LATEX agglutination method, due to its rapidity, has been used in our hospital, as well as in many other health centers.

Normal D-dimer levels and a low clinical probability for PTE may rule out the diagnosis of PTE [21]. On the other hand, in patients with intermediate clinical probability, there is no consensus on the exclusion of the diagnosis of PTE when the D-dimer test results are normal. According to Righini et al. [22], compared with a fixed D-dimer cutoff of 500 μg/L, the combination of pretest clinical probability assessment with age-adjusted D-dimer cutoff was associated with a higher number of patients in whom PE could be considered ruled out with a low likelihood of subsequent clinical venous thromboembolism. In current study, we used the LATEX agglutination method, due to its rapidity, but this method might be inadequate to rule out the diagnosis of PTE with small sample sizes.

In the study of Solak et al., theD-dimer test had no diagnostic value in pulmonary emboli due to its low specificity. However, they concluded that it may be an auxiliary test to rule out the disease since it is easy and rapidly performed [23]. Kollef et al., reported that D-dimer is a useful test to exclude venous thromboembolic disease in cases admitted to intensive care units [24].

Lactate dehydrogenase (LDH) catalyzes the conversion of pyruvate to lactate and back, as it converts NADH to NAD$^+$ and back. A dehydrogenase is an enzyme that transfers a hydride from one molecule to another.

Atikcan et al. detected an elevation of transaminase and lactic dehydrogenase (LDH) enzyme levels in 30.9% of 42 cases with pulmonary emboli [25] LDH is the most frequently studied enzyme due to its metabolic and clinical importance and is the first enzyme proven to have isoenzymes. Mavioglu et al. [26] found significantly elevated pleural fluid LDH1 and LDH3 isoenzymes in pulmonary emboli, LDH3 and LDH5 isoenzymes in tuberculosis pleurisy, and LDH5 isoenzymes in malignant pleural effusions.

Babaoğlu et al.detected that LDH levels differed significantly in high- and intermediate-risk patients as compared with low-risk patients. While the average values differed among groups, the low-risk group had higher LDH values than the median LDH value in high-risk patients [27].

In this study, LDH alone or in combination with D-dimer, was not found to be significantly different between the groups in diagnosing PTE (Table 5). This might be due to the fact that total LDH elevation is nonspecific and that the sample size was small. On the other hand, in our hospital, isoenzymes of LDH are not studied because this examination is a too-detailed test for this second-stage hospital. LDH testing is not recommended for suspected PE.

The frequency of PTE in a study based on hospital medical records was found to be 12/100,000 among patients between 15–44 years of age, while the rate was 265/100,000 in patients older than 65 years of age [28]. The male/female ratio was reported to be 1.24 in the series reported by Guintini [29]. No significant differences were found between the genders in the current study, which may be due to the fact that the number of patients in the low-risk group was high.

The prevalence of embolus in CT pulmonary angiography was reported to be 9–35% in various studies [30,31]. The researchers of the current study detected embolus in 26 of 62 patients, which was attributed to the low number of cases.

The frequency of pleural fluid and consolidation among the lung findings was statistically significantly high in the group without thromboemboli compared to the group with detected thromboemboli. This is similar to the findings of the study by Karabulut N et al. [32].

Our study has several limitations. First, the sample size was small. Second, we used the LATEX agglutination method for D-Dimer test. Third, a fixed D-dimer cutoff of 500 μg/L was used; no age-adjusted D-dimer cutoff was used with the combination of Wells score. Fourth, isoenzymes of LDH were not studied.

Conclusions

In conclusion, when a patient presents with chest pain, our carrying out LDH and D-Dimer tests will not exclude PTE without CTPA. However, we suggest that LDH isoenzymes should be studied in further research.

Disclosure of conflict of interest

None.

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