DÜSTAD
Dünya Sağlık ve Tabiat Bilimleri Dergisi
JOGHENS
Journal of Global Health & Natural Science
ISSN: 2687-637X Yıl: 2021 Cilt: 4 Sayı: 1

The Clinical Significance of d-Dimer/Troponin T Ratio in Patientswith Pulmonary Thromboembolism

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Abstract: d-Dimer and hsTT are biochemical markers used for pulmonary thromboembolism (PTE). There are very few studies on the clinical significance of the ratio between these two parameters. Our aim is finding new parameter d-Dimer/hsTT ratio for PTE. So this new ratio can be important to distinguish from other thromboembolic events. The study included patients who were admitted to the EmergencyDepartment of Ankara Numune Training and Research Hospital and underwent CT pulmonary angiogram (CTPA) with pre-diagnosis of PTE between 2014-2017. The computed tomography reports of the patients were also evaluated. The detected pathologies and pulmonary thromboembolism presence were recorded. The ratio of d-dimer and hsTT values of the patients were calculated and mortality were recorded. While there was a statistically significant difference between the two groups in terms of d-Dimer and hsTT ($p = 0.001$ and $p < 0.001$, respectively), there was no differencein terms of d-Dimer/hsTT ($p = 0.199$). Compared with the literature, we have found that different cardiac troponins are examined for d-Dimer/Troponin ratio and that there is no standard. However, most of the studies have emphasized the significance of cardiac enzyme results in terms of poor prognosis.

Key words: d-Dimer, troponin, pulmonary thromboembolism.

Pulmoner Tromboemboli Hastalarında d-Dimer/Troponin T Oranının Klinik Önemi

Özet: d-Dimer ve hsTT, pulmoner tromboembolizm (PTE) için kullanılan biyokimyasal belirteçlerdir. Bu iki parameter arasındaki oranın klinik önemi üzerine çok az çalışma vardır. Amacımız, PTE için yeni parametre d-Dimer / hsTT oranı bulmaktır. Dolayısıyla bu yeni oran, diğer tromboembolik olaylardan PTE'yi ayırt etmek için önemli olabilir. Çalışmaya 2014-2017 yılları arasında Ankara Numune Eğitim ve araştırma Hastanesi Acil Servisi'ne başvuran ve PTE ön tanısıyla BT pulmoner anjiyografi (BTPA) çekilen hastalar dahil edildi. Hastaların bilgisayarlı tomografi raporları değerlendirildi. Saptanan patolojiler ve pulmoner tromboembolizm varlığı kaydedildi. Hastaların d-Dimer ve hsTT değerlerinin oranı hesaplandı ve mortalite durumu kaydedildi. İki grup arasında d-Dimer ve hsTT açısından istatistiksel olarak anlamlı fark varken (sırasıyla $p=0.001$ ve $p<0.001$), d-Dimer / hsTT oranı açısından fark yoktu ($p=0.199$). Litertür ile karşılaştırıldığında, farklı kardiyak troponinlerin d-Dimer / Troponin oranı için incelendiğini ve bir standart olmadığını bulduk. Bununla birlikte, çalışmaların çoğu kötü prognoz açısından kardiyak enzim sonuçlarının önemini vurgulamıştır.
Anahtar Kelimeler: d-Dimer, troponin, pulmoner tromboemboli

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INTRODUCTION

Pulmonary thromboembolism (PTE) is a clinical condition usually caused by thrombi of thedeep calf veins that occlude the pulmonary artery or its branches. The diagnosis is challenging due to its various clinical presentations (1). Venous thromboembolism (VTE), clinically presenting as deep venous thrombosis (DVT) or PTE, is the third most common acute cardiovascular disease following myocardial infarction and stroke (2). The 30-day mortality rates exceed 15% with a sudden cardiac death rate of 11%. Right ventricular dysfunction is also seen in approximately 27-56% of the patients (3).

While the low plasma level of d-Dimer has a high predictive value in excluding PTE, it is widely accepted that high d-Dimer level has a low predictive value in diagnosing PTE (4). PTE is excluded if the d-dimer level is below 1000 ng/mL in the absence of any clinical condition (according to Wells score) or below 500 ng/mL in the presence of one or more clinical conditions. Moreover, elevated cardiac Troponin values (≥14 pg/mL) igh sensitivity Troponin T (hsTT)in patients aged <75 years and ≥45 pg/mL in patients aged ≥75 years) have been reported to indicate poor prognosis in PTE, especially in normotensive patients (2).

It is a known fact that early diagnosis and treatment are important in PTE, thus the mortalityis reduced. d-Dimer and hsTT are biochemical markers used for this purpose. There are veryfew studies on the clinical significance of the ratio between these two parameters. Kim et al.
(5) published an article on this topic in the Korean Journal of Internal Medicine in 2019. Thecorrelation between d-Dimer/Troponin I (TnI) ratio was investigated in patients withpulmonary thromboembolism and non-ST-elevation myocardial infarction (NSTEMI). In conclusion, it was found to be higher and more significant in PTE than in NSTEMI. The aim of our study was to demonstrate the clinical significance of d-Dimer/hsTT ratio betweenthe patient groups with and without pulmonary embolism and to evaluate the prognosis witha new perspective.

MATERIAL AND METHODS

Study design and participants

The study was conducted retrospectively after obtaining the ethics committee (decision of the Ankara Numune Training and Research Hospital Clinical Research Ethics Committee, dated 13/09/2017 and numbered E-17-1474) approval. The study included patients who were admitted to the Emergency Department of Ankara Numune Training and Research Hospital and underwent CT pulmonary angiogram (CTPA) with pre-diagnosis of PTE between 2014-2017. The records of these patients were scanned through the information processing systemof our hospital. The records of 453 patients were reviewed retrospectively. 270 patients wereexcluded from the study due to missing data, pregnancy and being under 18 years of age. Epidemiological data of 183 patients were used in the study (Figure 1). 183 patients were divided into 2 groups as those with or without pulmonary thromembolism. Of these patients,those under 18 years of age, pregnant women, had no troponin value or could not be measured numerically (expressed by <) and who had tomography without checking d-Dimerlevel were excluded from the study.

Data collection

Of the data of the patients, age, gender, hsTT, d-dimer and CTPA results were recorded. Patients who were thought to have acute pulmonary embolism and who underwent CTPA for diagnosis were included in the study. The hsTT and d-Dimer values of the patients wererecorded through the system. In addition, computed tomography images were examined. Diseases detected in radiology reports were

recorded. Among these patients, those under theage of 18, pregnant, and those without hsTT and d-Dimer values were excluded from the study. The ratio of d-dimer and hsTT values of the patients were calculated. In addition, other thromboembolic and pulmonary pathologies detected other than pulmonary embolism were also recorded. Finally, the 30-day mortality status of the patients was examined from the hospital records. The data were recorded by 2 specialist doctors. A third specialist checked this data. The computed tomography reports of the patients were also evaluated. The detected pathologies and pulmonary thromboembolism presence were recorded.

Sample collection

It was determined that the hsTT values of the patients were measured using the electrochemiluminescence immunological test (ECLIA) with the sandwich principle in a Cobas device (Roche Diagnostics, Mannheim, Germany). The reference values were as follows: Limit of Blank (LoB) = 3 ng/L (pg/mL), Limit of Detection (LoD) = 5ng/L (pg/mL)and Limit of Quantitation (LoQ) = 13 ng/L (pg/mL). It was determined that d-dimer was measured with immuno-turbodimetric STA - Liatest D - Di PLUS method (Diagnostica Stago S.A.S. Seine, France). The reference value for d-dimer was <0.5 microg/ml. The computed tomography device was a Toshiba Aquilion 64-slice CT (Toshiba Medical SystemCorporation, Shimoishigami, Otawara-Shi, Japan). The CT scans were performed in accordance with the PTE protocol.

Statistical analysis

The Kolmogorov-Smirnov test was used to determine whether the data of the patients included in the study are normally distributed. The age, d-Dimer, hsTT, and d-Dimer/hsTT data were non-normally distributed. Therefore, the Mann-Whitney U test was used for comparisons between groups. The Chi-square test was used to compare categorical variables.Non-normally distributed data were expressed as median (interquartile range) - (median (IQR)). A p-value of <0.05 was considered statistically significant

RESULTS

The data of the patient group with PTE on CTPA and the control group without PTE are summarized in Table 1. There was no significant difference between the patient and controlgroups in terms of age and gender (p = 0.135 and p = 0.717, respectively). The two groups were similar in terms of age and gender. While there was a statistically significant differencebetween the two groups in terms of d-Dimer and hsTT (p = 0.001 and p <0.001, respectively), there was no difference in terms of d-Dimer/hsTT (p=0.199).

The results of the comparison of the presence of PTE with mortality are shown in Table 2. Accordingly, there was a statistically significant difference between the PTE and non-PTE groups in terms of mortality (p = 0.005). However, the mortality rate was 4.5% in the non- PTE group. We think that this mortality is associated with non-embolic diseases.

The distribution of patients with and without PTE according to d-dimer positive and negativestatus was adapted in Table 3. Negative d-dimer level shows positive results towards normallung ventilation.

In terms of comorbid diseases other than PTE, of the patients, 18.5% had pneumonia, 11.1% had malignancy, 3.7% had pneumonia and effusion. Moreover, of the patients, 4 had muralthrombus, 2 had acute coronary syndrome, 1 had mesenteric ischemia, 1 had pneumothorax,1 had acute respiratory distress syndrome (ARDS), 1 had acute pulmonary edema, 1 had aortic dissection and 1 had peripheral artery disease.

DISCUSSION

In PTE, the right ventricle is affected when more than 50% of the vascular bed is obstructedby thrombus. Right ventricular dysfunction occurs with increased pulmonary artery pressure. Increased need for oxygen may lead to microinfarctions in the heart, elevating cardiac enzymes. This is expected to extend up to 6-12 hours and return to normal at 40 hours (1).

Considering that, the ratio of hsTT to d-dimer was evaluated. When the d-dimer and hsTT values of the patients with PTE and without PTE were examined, the difference between thetwo groups was significant ($p = 0.001$, $p < 0.001$, respectively). However, the d-Dimer/hsTTratio was not significant ($p = 0.199$). In the study of Kim et al. (5), the d-Dimer/TnI ratio was found to be significantly higher in patients with PTE than in patients with NSTEMI. The cut-off value was 1.12 mg/L for d-Dimer (AUC 0.860, sensitivity 81.1%, specificity 70.2%), 0.72 ng/mL for TnI (AUC 0.875, sensitivity 80.6%, specificity 78.9%), and the d-Dimer/TnI ratio was 1.82 (AUC 0.951, sensitivity 93.3%, specificity 86.6%). d-Dimer/TnI ratio was found to show better sensitivity and specificity than d-Dimer or TnI in the differential diagnosis between PTE and NSTEMI. The most important difference between the two studies was that the study by Kim et al. was conducted between patients with PTE and NSTEMI. Our study was conducted between PTE and other non-PTE causes. We thinkthat the difference between the two studies is due to that. Because only 2 patients had acutecoronary syndrome in our study. Another difference between the studies was in terms of troponin parameters studied. Kim et al. examined Troponin I level, while we measured hsTT. These two important differences can be summarized as follows: the troponin level below theequation would naturally be higher in the NSTEMI group than in patients with PTE. The study of Kim helps us in selecting patients to schedule coronary angiography (CAG) with the cut-off level that they established for d-Dimer/TnI, which is simple and inexpensive, andperhaps prevents unnecessary CAG procedures. In order to compare this ratio more effectively, it is actually necessary to make a comparison with conditions that do not increasecardiac enzymes as much as NSTEMI. Since our study was conducted retrospectively, the number of PTE patients was small due to patients with incomplete data. We think that furtherstudies to be conducted on a larger number of patients diagnosed with PTE by excluding NSTEMI will provide statistically more valuable data.

High levels of d-dimer, a degradation product of fibrin, have been reported to be a risk indicator for future VTE in the healthy population, as well as predictive of poor cardiac prognosis (6-7). In the study by Hajsadeghi et al. on d-dimer/fibrinogen ratio in intensive care patients, the d-Dimer/fibrinogen (DDFR) ratio was found to be significantly higher in patients with PTE ($p=0.003$) (DDFR in PTE positive patients $=9.13 \pm 7.16$) (8). In addition d-dimer levels were significantly higher compared to the non-PTE group ($\mu g/ml=4.65 \pm 3.46$). In our study, d-dimer levels were significantly higher in the PTE group than in the non-PTE group ($p = 0.001$). PTE was detected only in 1 patient with negative d-Dimer level. This aspect of our study was in line with the literature (9-11).

Cardiac troponin is a highly sensitive and specific biochemical marker of myocardial injury. High levels of troponin may be observed in patients with acute PTE, especially in those with massive PTE. Since it reflects right ventricular dysfunction, it has prognostic significance (12). In our study, hsTT values were significantly higher in the PTE group ($p < 0.001$). When the studies in the literature were reviewed in the light of these results, d-Dimer and cardiac troponin values were significant and valuable in the diagnosis in terms of thrombus load (14), complications (15,16) and imaging findings (17,18). In the meta-analysis of Hamedani et al. (13) including 45 studies, it was reported that biomarkers studied after heavy exercise

were significant in recognizing pulmonary embolism and cardiac injury, and it was demonstrated that these biomarkers even mimic pulmonary embolism and cardiac injury after heavy exercise. Martinez et al. (14) measured higher levels of d-Dimer and troponin in central pulmonary embolism. Vuilleumier et al. (15) found a 3.5-fold increase in complications in the last 3 months of elevated troponin I (death, VTE, acute dyspnea, pulmonary infarction, heart failure, and myalgia), while Kline et al. (16) found it significantin predicting right ventricular hypokinesis. Klok et al. (17) found low troponin T levels to be better to determine low complication rates than those with high right and left ventricularratios on CT and high d-Dimer levels. Jeebun et al. (18) found a high correlation between right and left ventricular ratios on tomography and elevated d-Dimer and troponin I values in pulmonary embolism.

Unless untreated, the mortality rate of PTE may rise up to 30-34%, while it can be reduced to 2-8% with early diagnosis and appropriate treatment (2,19). In our study, we found that 6(22.2%) of the 27 patients with PTE died. This was similar to the mortality rate found in thestudy by Jose et al. (20). In the non-PTE group, the mortality rate was 4.5%. There was a significant difference between the two groups in terms of mortality ($p = 0.005$). We think that the mortality in the non-PTE group is associated with comorbid diseases of the patients.

CONCLUSION

The retrospective nature of our study and the small number of patients with PTE were significant limitations. Compared with the literature, we have found that different cardiac troponins are examined for d-Dimer/Troponin ratio and that there is no standard. However, most of the studies have emphasized the significance of cardiac enzyme results in terms of poor prognosis. This suggests that cardiac troponin parameters should be evaluated with a standard cut-off, such as the INR level. In other words, a specific cut off value can be determined between each cardiac enzyme studied and the d-Dimer ratio. This may help obtain more significant data on predicting prognosis in prospective analysis studies to be conducted on larger patient groups. We are of the opinion that there is a need for multicenter, prospective studies on the use of d-Dimer/troponin ratio in PTE, which is simple, calculableand cost-effective.

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TABLES

Table 1. Age, gender, d-dimer, troponin T and d-dimer / troponin T data of patient andcontrol groups

Parameter	No PTE	There is PTE	P value
Age	70 (25)	74 (21)	0,135
Gender (Male) (n)	75	14	0,717
Gender (Female) (n)	81	13	
D-dimer (mg/L)	1,48 (2,04)	2,33 (2,25)	0,001
Troponin T (ng/mL)	0,021 (0,041)	0,055 (0,175)	<0,001
D-dimer/Troponin T	58,66 (139,49)	41,54 (93,58)	0,199

* Data are given as median (interquartile range) for numerical variables and number forgender

Table 2. Comparison of patient and control groups by mortality status

Pulmonary embolism	No mortality	There is mortality	P value
No	149 (%95,5)	7 (%4,5)	0,005
There is	21 (%77,8)	6 (%22,2)	

Table 3. Comparison of patient and control groups by d-dimer positivity and negativity (d-dimer positivity-negativity was adapted by age (9).

D-dimer	No PTE yok	There is PTE	P value
Negative	38 (%24,4)	1 (%3,7)	0,016
Positive	118 (%75,6)	26 (%96,3)	
Total	156 (%100)	27 (%100)	

Figure 1. Flow chart of patients who underwent CTPA with suspected PTE