



Pentraxin 3: a new biomarker for determining the probability of acute pulmonary embolism

PTX3 in pulmonary embolism

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Abstract

Aim: Pentraxin 3 (Ptx3) is a new biomarker in inflammatory disorders and thromboembolic events. Several studies showed elevated levels of Ptx3 in acute coronary syndrome, infectious diseases, and malignancies. In our study, we aimed to evaluate the relationship between Well's Score and Ptx 3 levels in Pulmonary embolism (PE) patients for determining the probability and severity of the disease. **Material and Method:** Twenty-two PE patients diagnosed with CT angiography presented to our emergency department and 20 healthy adults as a control group were enrolled in the study. Age, gender, Ptx3, CRP, D-dimer levels and Well's Scores of the patients were noted. After one month, Ptx3, CRP and quantitative D-Dimer levels of the patients were tested again. **Results:** Mean 1st Ptx3 level of the PE group was higher than the 2nd Ptx3 level and the Ptx3 level of the control group. In the PE group, mean 1st Ptx3 level of the females was 1.87 ± 0.48 and 2.37 ± 0.96 in males and was not significantly different. The 1st Ptx3 levels and the 2nd Ptx3 levels of the PE groups were significantly different ($p=0.001$). The 1st Ptx3 levels of the PE group and the Ptx3 levels of the control group were significantly different ($p=0.001$). The 2nd Ptx3 level of the PE group and Ptx3 levels of the control group were significantly different ($p=0.001$). In the PE group, 1st Ptx3 levels were significantly related with Well's Score of the patients ($p=0.001$). **Discussion:** Ptx3 is an important inflammatory marker and secreted from a wide range of cells including adipocytes, cardiomyocytes, brain cell, endothelial cells, and alveolar epithelial cells and may be helpful in determining the probability of PE in suspicious patients in the emergency department.

Keywords

Pentraxin 3; Well's Score; Pulmonary Embolism; D-Dimer

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Introduction

Pulmonary embolism (PE) is one of the important causes of sudden, non-traumatic death all over the world. The incidence of this disease is 1 in 1500 per year, commonly seen in the geriatric population and females [1]. In the emergency department, clinicians usually use Well's scoring system for calculating the probability of PE. According to this scoring system risk score interpretation (probability of PE) is following: > 6 points is a high risk (78.4%); 2-6 points is a moderate risk (27.8%); < 2 points is a low risk (3.4%). Suspected deep venous thromboses (3 points), alternative diagnosis less likely than PE (3 points), heart rate >100 beats/min (1.5 points), prior venous thromboembolism (1.5 points), immobilization within prior 4 week (1.5 points), active malignancy (1 point), hemoptysis (1 point) [2].

Ptx3 has been reported as a biomarker of different immunopathological diseases and its relevance with the resolution of infections and diseases has also been studied. The level of circulating Ptx3 is low in healthy human condition, but increases in inflammatory states starting from very early stages [3]. In recent studies, Ptx3 level changes in lung diseases (chronic obstructive lung disease, acute lung injury, asthma, lung cancer, pulmonary infections) have been reported [4-7].

In our study, we aimed to evaluate the relationship between Well's Score and Ptx3 levels in PE patients for determining the probability and severity of the disease.

Material and Method

Patient Selection

Twenty-two PE patients diagnosed with CT angiography [8], presented to our emergency department between 01.06.2014 and 01.06.2015 and 20 healthy adults as a control group were enrolled in this prospective study. Ethical approval for this study was obtained from the ethics committee. Age, gender, Ptx3, C-reactive protein (CRP), D-dimer levels, and Well's Scores of the patients were noted. All patients were admitted and 5 patients died during treatment. After one month we tested Ptx3, CRP and quantitative D-Dimer levels of the patients again. These blood tests were performed once in the control group. Patients with active infection and comorbid diseases (excluding malignancy and deep venous thrombosis), rheumatologic disorders, smokers, drug users, and pregnant patients were excluded.

Ptx3 Level Measurement

Levels of Ptx3 were determined by an enzyme-linked immunosorbent assay kit (R&D Systems, Catalogue No. DPTX 30, Minneapolis, MN, USA) according to the manufacturer's instructions. The absorbance of samples was measured at 450 nm using VERSA max tuneable microplate readers (designed by Molecular Devices, CA, USA). The results were expressed as ng/ml. All fluid samples were collected in tubes without anticoagulant, centrifuged at 1811 g for 10 min, and the supernatants stored at -80°C until Ptx3 assay was performed.

Statistical analysis

The normal distribution and homogeneity of each parameter were tested using the Shapiro-Wilk test. The homogeneity of variance is determined with the Levene's test. Values were presented as mean \pm standard deviations. One way ANOVA test

was used to determine the relationship between Well's score (low risk-moderate risk-high risk groups) and Ptx3 levels. Paired Sample T-test was used to compare the 1st and 2nd Ptx3 levels of the PE group. Student's T-test was used to compare the control group and PE patients. In all tests, the significance level is $p < 0.05$ and the confidence interval was 95%. SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) software 20.0 was used for all analyses.

Results

In our study, 16 (72.7%) females, 6 males (27.3%) totally 22 patients and a control group consisting of 20 healthy volunteers (12 females (60%), 8 males (40%) were enrolled. Mean age of the PE group was 66.22 ± 10.55 (min: 48, max: 82), and the control group was 31.2 ± 9.66 (min: 18, max: 56).

Mean 1st Ptx3 level of the PE group was higher than the 2nd Ptx3 level and the Ptx3 level of the control group. Detailed Ptx3, CRP, D-Dimer levels of the groups were detailed in Table 1.

In the PE group, mean 1st Ptx3 level of the females was 1.87 ± 0.48 ng/ml and 2.37 ± 0.96 ng/ml in males and was not significantly different ($p=0.436$; CI:-2.6-1.38). In the PE group, the mean of 2nd Ptx3 was 0.78 ± 0.20 ng/ml in females, 0.75 ± 0.43 ng/ml in males and were not significantly different ($p=0.268$; CI:-0.97-1.12). In the control group, the mean of Ptx3 levels 0.56 ± 0.20 ng/ml in females, 0.44 ± 0.15 ng/ml in males and was not significantly different ($p=0.389$; CI:-0.77-0.32).

Table 1. Ptx, CRP, and D-Dimer levels of the groups.

	1 st	2 nd	Control Group
Ptx3 (ng/ml)	5.31 ± 1.98 (min:2.4,max:9.1)	1.29 ± 0.75 (min:0.2,max:3)	1.06 ± 0.5 (min:0.2,max:2.1)
CRP (mg/L)	27.72 ± 18.76 (min:8,max:86)	8.64 ± 4.12 (min:2,max:21)	8.25 ± 4.1 (min:3,max:16)
D-Dimer	707.3 ± 121.8 (min:525,max:987)	174.6 ± 84.3 (min:45,max:341)	179.5 ± 76.4 (min:80,max:321)

The 1st Ptx3 levels and the 2nd Ptx3 levels of the PE groups were significantly different ($p=0.001$; CI: 3.22-4.66). The 1st Ptx3 levels of the PE group and the Ptx3 levels of the control group were significantly different ($p=0.001$; CI: 4.41-6.22). The 2nd Ptx3 level of the PE group and Ptx3 levels of the control group were significantly different ($p=0.001$; CI: 0.90-1.68). In the PE group, 1st ($p=0.01$) (Figure 1) and 2nd ($p=0.01$) Ptx3 levels were significantly related to Well's Score of the patients (Table 2). Patients with high probability had higher Ptx3 levels. But 1st D-Dimer ($p=0.171$) and 1st CRP levels ($p=0.459$) were not related to Well's score in the patient group ($p > 0.05$). In both groups there was no correlation between age and Ptx3 levels ($p=0.40$).

Discussion

Ptx3 is an important inflammatory marker and secreted from a wide range of cells including adipocytes, cardiomyocytes, brain cell, endothelial cells, and alveolar epithelial cells [9-13]. See comment in PubMed Commons below Ptx3 has different functions and provides immuno-protection. It binds to the surface of pathogens and apoptotic inflammatory cells and promotes

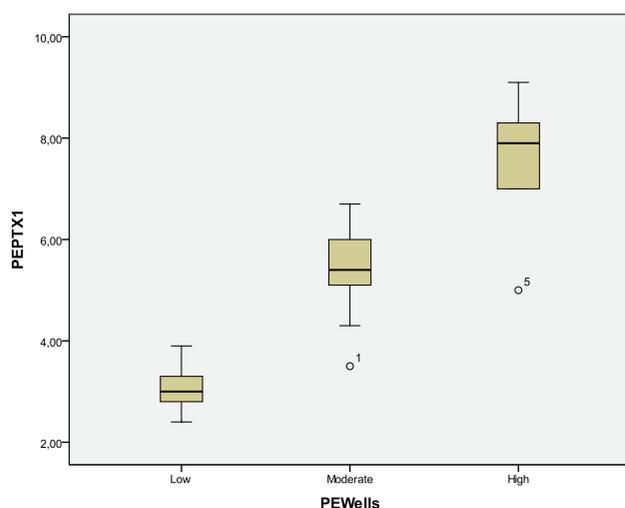


Figure 1. Pentraxin3 levels due to the Well's scores of the patient group. (One Way ANOVA).

Table 2. The Relation Between 1st/2nd Ptx3 Levels and Well's Scores of the PE Patients.

	N	Mean	Std. Deviation	95% CI for Mean				
				Lower Bound	Upper Bound	Min.	Max.	
PEPTX1	Low	6	3.0667	0.50465	2.5371	3.5963	2.40	3.90
	Moderate	9	5.3444	0.98883	4.5844	6.1045	3.50	6.70
	High	6	7.5333	1.42782	6.0349	9.0317	5.00	9.10
	Total	21	5.3190	1.98938	4.4135	6.2246	2.40	9.10
PEPTX2	Low	5	0.7000	0.28284	0.3488	1.0512	0.20	0.90
	Moderate	7	1.2429	0.61606	0.6731	1.8126	0.50	2.30
	High	5	1.9600	0.78294	0.9878	2.9322	0.80	3.00
	Total	17	1.2941	0.75206	0.9074	1.6808	0.20	3.00

*One Way ANOVA.

their opsonization and clearance early in the infection process. This role is important to avoid inducing a deleterious hyper-inflammatory state that could arise due to activation of the adaptive arm of the immune response. Although the N-terminal domain of Ptx3 is suggested to be required for pathogen binding, the full-length protein is required for opsonization. Also, Ptx3, when bound to pathogenic components, activates dendritic cells, which is instrumental in initiating an appropriate T cell response. Another mechanism by which Ptx3 initiates the thread of innate immunity is activating the complement cascade [3, 14, 15].

Ptx3 is also reported to upregulate tissue factor expression in endothelial cells and play a role in thrombogenesis [16]. All of these may elevate Ptx3 levels in angina pectoris, acute myocardial infarction heart failure, and sepsis/systemic inflammatory response syndrome [10, 17-20]. Several inflammatory mediators such as platelet activating factor, thromboxane, and endothelins have also been implicated in the pathogenesis of acute PE [21]. However, whether Ptx3 could be one of the biomarkers in patients with PE is unclear.

In our study, The Ptx3 levels did not differ between females and males. The 1st and the 2nd Ptx3 levels in the PE group were higher than in the control group. After the treatment and after one-month recovery period, the Ptx3 levels did not decrease to normal ranges. Ptx3 levels were significantly correlated with

Well's score of the patients, high levels demonstrated high probability.

Recently, Ptx3 has been studied in several lung diseases [4, 5, 7]. Ozsu et al. reported high Ptx3 levels in parapneumonic effusions rather than the non-parapneumonic effusions [22]. Relevant to our study, Ptx3 level was found to be the most sensitive biomarker of chronic thromboembolic pulmonary hypertension (CTEPH). Although plasma Ptx3 levels did not correlate with the severity of the pulmonary hemodynamics, high levels in clinically stable patients following PE should prompt a further work-up for CTEPH, which may lead to an early diagnosis [23]. Seventy patients with CTEPH and 20 clinically stable PE patients were enrolled in their study, and they measured plasma Ptx3, CRP, heart-type fatty acid-binding protein (H-FABP), and brain natriuretic peptide (BNP) levels in the patients. We measured the 2nd Ptx3 levels after one-month recovery period and the levels did not decrease to normal ranges.

Similarly, Noriaki et al. showed that Ptx3 was a sensitive and specific biomarker for the diagnosis of acute coronary syndrome (ACS) and had diagnostic values when measured in combination with Troponin T. They compared ST-elevated and non-ST patients. Circulating Ptx3 (0.36 pg/mL versus 0.015 pg/mL), Troponin T, and H-FABP levels were significantly higher in ACS than non-ACS [24].

In another thromboembolic issue, acute stroke, Ptx3 was not correlated with the disease's prognosis. In the study, researchers compared the Ptx3 levels with the scoring system but couldn't find a relation between the scoring system and Ptx3 levels [25].

Ptx3 is a new important inflammatory biomarker and it may be helpful in determining the probability of PE in suspicious patients. Further comprehensive studies are required in this issue. We included patients with malignancy and deep venous thrombosis in our study because they are important factors of Well's scoring system.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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