ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 28(4): 679-685, 2023
DOI: 10.5505/ejm.2023.57355

Prognostic Value of Serum Neuron Specific Enolase and Pentraxin-3 In Acute Pulmonary Embolism

Muhammed İkbal Şaşmaz[1*], Cumhur Murat Tulay[2], Ekim Saglam Gurmen[1], Ahmet Angin3, Cevval Ulman[3]

[1]Department of Emergency Medicine, Manisa Celal Bayar University, Turkey
[2]Department of Thoracic Surgery, Manisa Celal Bayar University, Turkey
[3]Department of Biochemistry, Manisa Celal Bayar University, Turkey

ABSTRACT

The aim of this study is to investigate whether serum neuron-specific enolase (NSE) and pentraxin-3 (PTX-3) values are effective in the diagnosis and prognosis of acute pulmonary embolism. In addition, in the light of significant results, we aimed to determine a cut-off value for NSE and PTX-3 in acute pulmonary embolism and to try to determine the sensitivity - specificity in the diagnosis of pulmonary embolism according to these values.

In this prospective study, patients who applied to the Emergency Department of Manisa Celal Bayar University School of Medicine between September 2019 and January 2021 and were diagnosed with acute pulmonary embolism constituted the study group and healthy volunteers without any chronic disease or drug use constituted the control group. Serum NSE and PTX-3 values of the patient and control groups were compared. In addition, demographic data, vital signs, laboratory findings, PESI (pulmonary embolism severity index) scores and prognoses of the patients were investigated.

In this study 70 patients diagnosed with pulmonary embolism were included to the patient group. 36 (51.4%) of them were women and the mean age was 67.01 ± 14. 74 healthy volunteers were included to the control group; 45 of them (60.8%) were women and the mean age was 44.99 ± 12.85. In patient group the mean PTX-3 value of the was 1.753±1.91 ng/ml, the mean NSE value was 182.13±14.99 ng/ml. In control group, the mean PTX-3 value was 0.429±0.035 ng/ml, the mean NSE value was 166.51±5.14 ng/ml. While there was a statistical difference between two groups in terms of pentraxin-3 value, there was no difference in terms of NSE value. When the cut-off value of 1.115 ng/ml for serum pentraxin-3 in the ROC analysis in order to distunguish the patients with pulmonary embolism from the control group, sensitivity was found to be 58.6% and specificity to be 96%.

In our study, we found that serum PTX-3 level is a powerful biomarker with high specificity in the diagnosis of acute pulmonary embolism and is positively associated with the severity and prognosis of the disease. Therefore, we believe that serum PTX-3 may be a guiding biomarker in the diagnosis and prognosis of acute pulmonary embolism in clinical practice.

Keywords: Pulmonary embolism, neuron-specific enolase, pentraxin-3

Introduction

Pulmonary embolism (PE) is the third most common cardiovascular disease after acute coronary syndrome and stroke (1,2). Clinical signs and symptoms of pulmonary embolism may vary depending on the size, number (single/multiple), and localization of blood clot. Diagnosis of PE can be difficult for the clinician due to the low specificity of clinical signs and diagnostic tests (3). Therefore, the most important issue in the diagnosis of PE is clinical suspicion.

Some clinical scoring systems are used to evaluate the probability of PE according to the clinical status of the patient. The two most common and accepted scoring systems are Wells and modified Genova scoring systems (4). After risk assessment using the scoring system, it is recommended to measure the plasma D-dimer level (5). D-dimer is the product of lysis of cross-linked fibrin and the levels of D-dimer are increased in patients with acute PE. Plasma D-dimer level is a nonspecific biomarker, because the level of D-dimer can be increased in many other conditions such as malignancy, pregnancy, inflammatory conditions, and infections. Since plasma D-dimer measurement has a high negative predictive value, a normal plasma D-dimer level may be useful in excluding the diagnosis of acute PE or deep vein thrombosis (DVT) (6). On the other hand, high D-dimer levels have low positive predictive value and D-dimer testing is not useful for confirming the diagnosis of PE (6,7). Cardiac troponins are useful biochemical parameters that indicate

***Corresponding Author:** Dr. Muhammed İkbal Şaşmaz, Manisa Celal Bayar University Faculty of Medicine, Emergency Department
E-mail: ikbalsasmaz84@gmail.com, phone: +90 (536) 550 50 31
ORCID ID: Muhammed İkbal Şaşmaz: 0000-0002-3267-3184, **Cumhur Murat Tulay:** 0000-0001-8593-9233, **Ekim Saglam Gurmen:** 0000-0002-8672-6181, **Ahmet Angin:** 0000-0003-2933-2183, **Cevval Ulman:** 0000-0002-0345-0264
Received: 06.04.2023, **Accepted:** 26.08.2023

myocardial injury and poor prognosis in PE patients. Studies have shown that mortality rates are significantly higher in PE patients with high troponin levels (8,9).

In this study, we aimed to investigate whether neuron-specific enolase (NSE) and pentraxin-3 (PTX-3) levels are effective biomarkers in the diagnosis and prognosis of the disease in patients diagnosed with acute PE in the emergency department.

Material and Method

Study Design: This study was conducted prospectively on 80 patients diagnosed with acute PE who applied to Manisa Celal Bayar University Faculty of Medicine Emergency Medicine Department between 01.09.2019 - 01.01.2021 and a control group of 80 healthy volunteers who had no chronic disease and did not use any medication. During the study period, 10 patients with acute PE and 6 healthy volunteers were excluded from the study due to the detection of COVID-19 PCR positivity. The study was completed with 70 patients with acute PE and 74 healthy volunteers.

Ethical approval for the study was obtained from the Health Sciences Ethics Committee of Manisa Celal Bayar University Faculty of Medicine (Approval date 19 June 2019, approval number 20478486). Written informed consent was obtained from patients or first-degree relatives of patients and healthy participants who volunteered to participate in the study.

Patients diagnosed with acute PE on admission to the emergency department were included in the study. The exclusion criteria were as follows: patients transferred from other healthcare facilities with the diagnosis of acute PE, COVID-19 PCR positivity, pregnant patients, patients who did not consent to participate in the study**,** patients under the age of 18. The inclusion criteria for the control group were as follows: patients who did not have any chronic diseases and medication in the history, absence of signs and symptoms of deep vein thrombosis, absence of tachycardia (pulse >100/min.), no history of immobilization or surgery in the last 4 weeks, no previous history of deep vein thrombosis or pulmonary embolism and absence of previous or ongoing COVID-19 disease.

Data Analysis and Evaluation Techniques: For the diagnosis of acute PE, filling defect in the pulmonary artery or its branches in computed tomography pulmonary angiography, which is the gold standard imaging method, was accepted as the gold standart. In addition to routine laboratory tests in patients with suspected PE, 5 cc of venous blood was drawn and filled into a serum tube for the measurement of serum NSE and PTX-3. 5 cc of venous blood was taken from the healthy volunteers in the control group and filled into the serum tube.

The complaints, vital signs, localization of the artery with filling defect, PESI (pulmonary embolism severity index) scores, laboratory findings (blood gas, D-dimer, troponin), and serum NSE and PTX-3 values of patients diagnosed with acute PE were recorded. In addition, the risk classification of the patients, and one-month prognosis were also recorded.

Venous blood samples taken from the patients were placed in tubes with coagulation activator without anticoagulant. Blood samples were centrifuged at 3000 rpm for 15 minutes, their serums were separated and stored at -80 °C until analysis. Serum NSE, PTX-3 concentrations were analyzed by ELISA (Enzyme Linked Immunoassay) method. ELISA washing processes were performed with an automatic washing device (BioTek ELx50 BioTek Instruments Inc. Highland Park, Winooski, VT, USA), absorbance readings were performed on an ELISA reader (BioTek Epoch, BioTek Instruments Inc. Highland Park, Winooski, VT, USA).

Serum NSE levels were analyzed with the Human NSE (Neuron Specific Enolase) ELISA Kit (Elabscience, USA) according to the procedures specified in its manual. The kit sensitivity is 1.4 ng/mL. The measuring range of the kit is 2.34-150 ng/ml. The intra-assay precision CV values of the kit were calculated in the range of 3.99%-5.41%, and the inter-assay precision CV values were calculated in the range of 4.55%-6.58%. The positive control range of the Human NSE ELISA Kit was between 39.29-110.45 ng/mL, and the negative control range was ≤4.89 ng/mL. The control values we reached during the study were within the specified ranges.

Serum Pentraxin-3 levels were analyzed with the Human PTX 3/TSG-14 (Pentraxin 3) ELISA Kit (Elabscience, USA) according to the procedures specified in its manual. The precision of the kit was 0.19 ng/mL; the measuring range was 0.31-20 ng/mL. The intra-assay precision CV values of the kit were calculated in the range of 3.83%-7.21%, and the inter-assay precision CV values were calculated in the range of 4.37%-6.48%. The positive control range of the Human PTX 3/TSG-14(Pentraxin 3) ELISA Kit was between 6.98-13.88ng/mL, and the negative control range was

≤0.38ng/mL. The control values we obtained during the study were within the specified ranges.

Statistical Analysis: SPSS 22 (Statistical Packagefo the Social Sciences) program was used for statistical analysis. Mean and standard deviation were used for descriptive statistics, while numbers and percentages were used for categorical data. The Shapiro-Wilk goodness of fit test was used to check if the assumptions of the parametric test statistic were achieved. In the comparison of two independent groups, Student T test was used if the data were parametric and normally distributed, otherwise Mann Whitney U test was used. Spearman correlation test was used for correlation analysis. If there was a significant difference between the patient group and the control group in terms of serum NSE and PTX-3 values, sensitivity and specificity were calculated by ROC curve analysis. A p value of <0.05 was considered statistically significant.

Results

In our study, 70 patients diagnosed with acute PE formed the study group. In the study group the mean age was 67.01±14 years and 36 (51.4%) were female. In the control group, there were 74 healthy volunteers, 45 (60.8%) of whom were women, and the mean age was 44.99±12.85. While there was a statistical difference between the groups in terms of mean age (p<0.001), there was no difference in terms of gender (p=0.257). The mean vital signs and laboratory values of the patients diagnosed with PE are given in Table 1.

The most common complaint at the time of admission was shortness of breath (n=36), and the second most common complaint was chest pain (n=10). The mean PESI score of the patients was 115.24±44.93. Computed tomography pulmonary angiography revealed filling defects in the main pulmonary artery in 26 (37.1%) patients, in segmental branches in 30 (42.9%) patients, and in subsegmental branches in 14 (20%) patients. There were 18 (25.7%) patients diagnosed with high-risk pulmonary embolism. Thrombolytic therapy was applied to 11 (15.7%) patients. It was determined that 8 (11.4%) patients died in the 30-day prognosis. The reasons for admission, risk classification and outcomes of the patients are given in Table 2.

The mean PTX-3 value of the patient group was 1.753±1.91 ng/mL, while the mean NSE value was 182.13±14.99 ng/mL. In the control group, the mean PTX-3 value was 0.429±0.035 ng/mL, while the mean NSE value was 166.51±5.14 ng/mL. While there was a statistical difference between the groups in terms of PTX-3 value (p<0.001), there was no difference in terms of NSE value (p=0.496). In the patient group, the mean PTX-3 values of 18 patients diagnosed with high-risk pulmonary embolism and 52 patients with non-high-risk pulmonary embolism were 2.60±1.74 and 1.46±1.45 ng/ml, respectively (p=0.008). The mean PTX-3 and NSE values of the patient and control groups are given in Table 3.

When the cut-off value for serum PTX-3 is taken as 1.115 ng/ml in the ROC analysis in order to distinguish the patient group from the control group; the sensitivity was 58.6% and specificity was 96% (AUC: 0.793, 95% CI: = 0.718-0.869). The positive predictive value was found to be 100% and the negative predictive value was 71.4% (figure 1).

According to Spearman correlation analysis, a moderate positive correlation was found between serum PTX-3 level and PESI score in the patient group (r=0.538; p<0.001). The relationship between serum PTX-3 level and PESI score is given in Figure 2.

Discussion

Acute PE causes a wide clinical findings ranging from mild symptoms such as weakness and palpitations to sudden death, depending on the regions where the main pulmonary artery or its branches are involved. Contrary to acute myocardial infarction, the diagnostic value of ECG and laboratory tests is low in acute PE. Therefore, the most important issue in the diagnosis of acute PE is clinical suspicion. (10). D-dimer, a fibrin degradation product, is a biochemical marker with a high negative predictive value in patients with suspected acute PE, in other words, it is effective in excluding the diagnosis. Also, in many recent studies, cardiac biomarkers such as BNP and cTNT have also been evaluated in acute PE, and both have been found to be important prognostic markers, although not helpful in the diagnosis of acute PE (11,12).

Pentraxin-3, a molecule of the same origin as serum reactive protein (CRP), is a multifunctional protein with complex regulatory roles in inflammation and remodeling (13,14). Recently, it has been revealed that PTX-3 may have a functional role in some vascular diseases such as atherosclerosis and myocardial infarction. It is thought that PTX-3 has a regulatory role in the

Table 1. Mean Vital Findings, PESI Score and Laboratory Values of the Patient Group

	N	Minimum	Maximum	Mean (SD)
Systolic blood pressure (mmHg)	70	81,00	180,00	125,04 (23,63)
Diastolic blood pressure (mmHg)	70	48,00	97,00	74,30 (12,21)
Heart rate (min)	70	68,00	140,00	106,32 (18,35)
O2 saturation (%)	70	60,00	98,00	88,35 (8,01)
PESI score	70	46,00	263,00	115,24 (44,93)
NSE (ng/mL)	70	116,04	205,90	182,13 (14,99)
PTX-3 (ng/mL)	70	0,033	6,24	1,75 (1,91)
pH	70	7,12	7,58	7,40 (0,084)
Lactate (mmol/L)	70	,73	9,58	2,65 (2,03)
pO2 (mmHg)	70	38,27	136,20	71,51 (21,75)
pCO2 (mmHg)	70	20,47	50,00	33,36 (6,27)
HCO3 (mmol/L)	70	14,60	29,79	22,42 (3,02)
Troponin (ng/L)	61	2,00	2838,00	283,28 (680,94)
D-dimer (ng/mL)	54	466,00	13356,00	3283,00 (3353,10)

N: number, **SD:** Standard Deviation

Table 2. Reasons for Application, Risk Classifications and Outcomes of the Patients

		N	%
Complaint	• Shortness of breath	36	51,4
	• Chest pain	10	14,3
	• Syncope	6	8,6
	• Hemoptysis	2	2,9
	• Altered mental status	7	10,0
	• Fatigue	2	2,9
	• Leg pain / leg swelling	7	10,0
Filling defect	• Main pulmonary artery	26	37.1
	• Segmentary branch	30	42.9
	Sub segmental branch	14	20
Pulmonary embolism classification	• High risk PE	18	25.7
	• Non-high risk PE	52	74.3
Treatment	Thrombolytic therapy	11	15.7
	Anticoagulant therapy	59	84.3
Result	Admission to hospital	44	62.9
	Admission to intensive care units	18	25.7
	Transfer to other facilities	8	11.4
30-day prognosis	Death	8	11.4
	Discharge	62	88.6
Total		70	100

immunoinflammatory response, especially in cardiovascular diseases. However, increased serum PTX-3 level as a protective physiological response in cardiovascular diseases was found to be correlated with the severity of the disease (15-17).

Studies investigating the efficacy of serum PTX-3 levels in acute pulmonary embolism are limited. Yang et al., in their study with 117 patients with acute PE, showed that serum pentraxin-3 levels are an effective biomarker in the risk classification and prognosis of the patients (18). The results we obtained in our study showed that serum PTX-3 levels in PE patients were significantly higher than in the healthy volunteer group. More importantly, when we took the cut-off value of 1,115 ng/mL for serum PTX-3 in the detection of acute PE, we

Table 3. Mean PTX-3 and NSE Values of the Patient and Control Groups

*	Patient group (n=70) (Mean±SD)	Control group (n=74) (Mean±SD)	p value
PTX-3 (ng/mL)	1.753±1.91	0.429±0.035	0.001
NSE (ng/mL)	182.13±14.99	166.51±5.14	0.496

* The mean PTX-3 and NSE values of the patient group and control group were compared

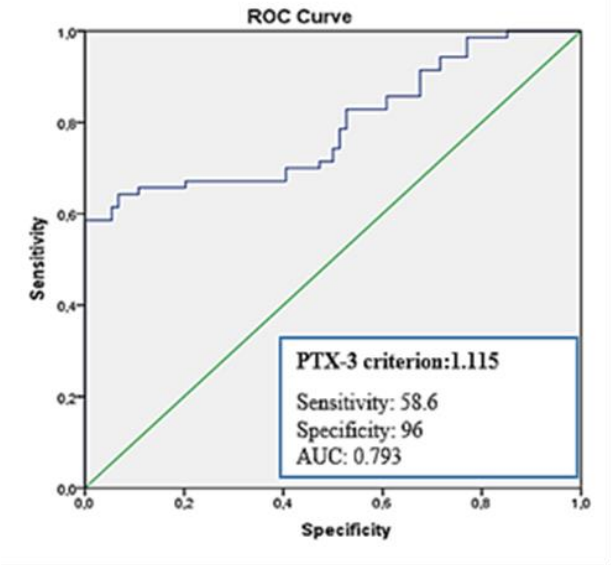

Fig. 1. ROC curve for the PTX-3 value used to differentiate the patient group from the control group

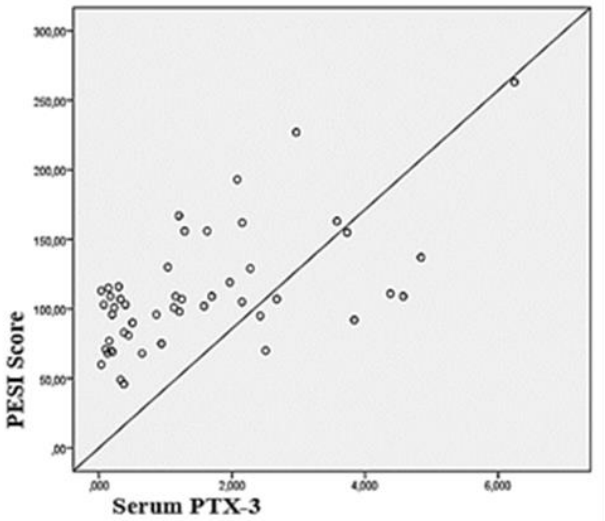

Fig. 2. The Relationship Between Serum PTX-3 Level and PESI Score

found that the sensitivity was 58.6% and the specificity was 96%.

In the light of these results, we believe that serum PTX-3 can be used clinically as a strong biomarker to confirm the diagnosis of PE in patients with suspected acute PE. In other words, PTX-3 can reveal the diagnosis of pulmonary embolism in the results above 1.115 cut-off value in suspected pulmonary embolism. Contrary to D-dimer, PTX-3 has a low negative predictive value and is insufficient to exclude the disease. Therefore, in clinical practice, the combined use of PTX-3 and D-dimer in suspected acute PE may guide the diagnosis or exclusion of the disease.

Pulmonary embolism severity index (PESI) is a scoring method used to evaluate the severity of the disease in patients with acute PE. There are many studies showing that the PESI score has high sensitivity and specificity in predicting acute PE prognosis and mortality (19,20). For this reason, it is frequently used in the management of patients with acute PE. In our study, a moderate correlation was found between serum PTX-3 value and PESI score. In addition, in our study, the mean PTX-3 value of high-risk PE patients was significantly higher than that of low-risk PE patients. Therefore, we think that serum PTX-3 value is a guiding biomarker in the risk classification and prognosis of APE patients in our study, as in Yang et al. studies (18).

Neuron-Specific Enolase is an enzyme found mainly in neurons and neuroectodermal cells that anaerobically converts glucose into metabolites suitable for oxidation. In healthy individuals, serum NSE levels are low. After neuronal tissue damage such as brain injury or stroke, a strong increase in blood NSE levels is observed, and therefore NSE is an important biomarker in indicating brain damage (21).

Serum NSE level is effective in predicting neurological outcomes and risk of death, especially in cardiac arrest patients (22,23). It has been shown that serum NSE levels are correlated with poor prognosis in systemic diseases such as small cell lung cancer, prostate cancer, and diabetic ketoacidosis, in addition to disorders with neuronal damage (24-26). In the study conducted by Li et al. in 2018, the relationship between serum NSE level and Chronic Obstructive Pulmonary Disease (COPD) was investigated, and it was observed that serum NSE level increased in COPD exacerbation (27). These studies reveal that serum NSE levels increase not only in central nervous system diseases, but also in conditions such as shock and hypoxia.

To our knowledge, there is no study in the literature investigating the effectiveness of NSE in predicting the severity of acute PE. At the beginning of this study, we hypothesized that neuronal damage may occur secondary to hypoxia in acute PE and that the NSE level may increase, and that this increase may be associated with prognosis. However, we found that there was no significant difference in serum NSE levels between acute PE patients and healthy volunteers.

Limitations: We selected the control group from healthy volunteers who did not have a chronic disease and did not use any medication. Therefore, the mean age of the control group was significantly lower than the patient group. In addition, the patient population of our study is limited and more comprehensive studies are needed.

In our study, we found that serum PTX-3 level is a powerful biomarker with high specificity in the diagnosis of acute pulmonary embolism. Therefore, in clinical practice, the combined use of PTX-3 and D-dimer in suspected acute PE may guide the diagnosis or exclusion of the disease.

Funding Information: This work was supported by the Scientific Research Project Office of Manisa Celal Bayar University (Project Number: 2019-129).

Informed consent: Informed consent was obtained from all individual participants included in the study.

Prior presentation: Absent.

Contributors' list: Contributorship and data collection: MIS, ESG, and CMT; Served as scientific advisors: MIS and CMT. Writing and statistical study: MIS. Analysis of the samples: CU and AA.

Declaration of Competing Interest: The authors declare that they have no conflict of interest.

References

1. Hess EP, Campbell RL, White RD. Epidemiology, trends, and outcome of out-of-hospital cardiac arrest of non-cardiac origin. Resuscitation. 2007, 72, 200-206
2. Deasy C, Bray JE, Smith K, Harriss LR, Bernard SA, Cameron P. Out-of-hospital cardiac arrests in young adults in Melbourne, Australia-adding coronial data to a cardiac arrest registry. Resuscitation. 2011, 82, 1302-6
3. Konstantinides SV, Meyer G, Becattini C, et al. ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). EurHeart J. 2020,41,4:543-603. doi: 10.1093/eurheartj/ehz405. PMID: 31504429.
4. Barco S, Ende-Verhaar YM, Becattini C, et al. Differential impact of syncope on the prognosis of patients with acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2018,39:4186-4195.
5. Agnelli G, Becattini C. Acute pulmonary embolism. N Engl J Med. 2010, 363: 267.
6. De Monyé W, Sanson BJ, Mac Gillavry MR, et al. Embolus location affects the sensitivity of a rapid quantitative D-dimer assay in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med. 2002,165: 345-8.
7. Gibson NS, Sohne M, Gerdes VE, Nijkeuter M, Buller HR. The importance of clinical probability assessment in interpreting a normal d-dimer in patients with suspected pulmonary embolism. Chest. 2008, 134: 789-93.
8. Janata K, Holzer M, Laggner AN, Mullner M. Cardiac troponin T in the severity assessment of patients with pulmonary embolism: cohort study. BMJ. 2003,326:312-3. 36.
9. Janata K, Holzer M, Laggner AN, Mullner M. Cardiac troponin T in the severity assessment of patients with pulmonary embolism: cohort study. BMJ. 2003,326:312-3. 36.
10. Kline JA. "Diagnosis and exclusion of pulmonary embolism, "Thrombosis Research, 2018, 163, 207–220.
11. Kohn MA, Klok FA, and van Es N. "D-dimer interval likelihood ratios for pulmonary embolism," Academic Emergency Medicine, 2017, 24(7) 832–837.
12. Giannitsisand E, Katus HA. Biomarkers for clinical decision-making in the management of pulmonary embolism, Clinical Chemistry, 2017, (1). 91–100.
13. Garlanda C, Bottazzi B, Magrini E, Inforzato A, Mantovani A. Ptx3, a Humoral pattern recognition molecule, in innate immunity, tissue repair, and cancer. Physiol Rev. 2018, 98:623–39. doi: 10.1152/physrev.00016.2017.
14. Jaillon S, Peri G, Delneste Y, et al. The humoral pattern recognition receptor PTX3 is stored in neutrophil granules and localizes in extracellular traps. J Exp Med. 2007, 204:793–804.doi: 10.1084/jem.20061301
15. Ristagno G, Fumagalli F, Bottazzi B, et al. Pentraxin 3 in cardiovascular disease. Frontiers in immunology, 2019,10, 823.
16. Jenny NS, Blumenthal RS, Kronmal RA, Rotter JI, Siscovick DS, Psaty BM. Associations of pentraxin 3 with

cardiovascular disease: the Multi-Ethnic Study of A therosclerosis. Journal of Thrombosis and Haemostasis, 2014, 12(6), 999-1005.

17. Norata GD, Garlanda C, Catapano AL. The long pentraxin PTX3: a modulator of the immunoinflammatory response in atherosclerosis and cardiovascular diseases. Trends in cardiovascular medicine, 2010, 20(2), 35-40.
18. Yang H, Zhang J, Huan Y, Xu Y, Guo R. Pentraxin-3 Levels Relate to the Wells Score and Prognosis in Patients with Acute Pulmonary Embolism. Disease Markers, 2019.
19. Donzé J, Le Gal G, Fine MJ, et al. Prospective validation of the pulmonary embolism severity index. Thrombosis and haemostasis, 2008, 100(05), 943-948.
20. Righini M, Roy PM, Meyer G, Verschuren F, Aujesky D, Le Gal G. The Simplified Pulmonary Embolism Severity Index (PESI): validation of a clinical prognostic model for pulmonary embolism. Journal of thrombosis and haemostasis: JTH, 2011, 9(10), 2115-2117.
21. Isgrò MA, Bottoni P, Scatena R. Neuron-specificenolase as a biomarker: biochemical and clinical aspects. Advances in Cancer Biomarkers, 2015, 125-143.
22. Luescher T, Mueller J, Isenschmid C, et al. Neuron-specificenolase (NSE) improves clinical risk scores for prediction of neurological outcome and death in cardiac arrest patients: Results from a prospective trial. Resuscitation, 2019,142, 50-60.
23. Streitberger KJ, Leithner C, Wattenberg M, et al. Neuron-specific enolase predicts poor outcome after cardiac arrest and targeted temperature management: a multicenter study on 1,053 patients. Critical care medicine, 2017, 45(7), 1145-1151.
24. Tian Z, Liang C, Zhang Z, et al. Prognostic value of neuron-specific enolase for small cell lung cancer: a systematic review and meta-analysis. World journal of surgical oncology, 2020, 18, 1-8.
25. Muoio B, Pascale M, Roggero E. The role of serum neuron-specific enolase in patients with prostate cancer: a systematic review of the recent literature. The International journal of biological markers, 2018, 33(1), 10-21.
26. Hamed S, Metwalley KA, Farghaly HS, Sherief T. Serum levels of neuron-specific enolase in children with diabetic ketoacidosis. Journal of child neurology, 2017, 32(5), 475-481.
27. Li J, Kong X, Shu W, Zhang W. The association of serum neuron-specific enolase with other disease markers in chronic obstructive pulmonary disease: A case-control study. Pakistan journal of medical sciences, 2018, 34(5), 1172.