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Assessment of relationships between novel inflammatory markers and presence and severity of preeclampsia: Epicardial fat thickness, pentraxin-3, and neutrophil-to-lymphocyte ratio

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ABSTRACT

Objective: The aim of this study was to evaluate the relation of three new inflammatory markers with presence and severity of preeclampsia and to compare the predictive values of all markers for presence of this setting.

Methods: In this study, a total of 100 consecutive pregnants with a diagnosis of preeclampsia and 40 healthy pregnants between October 2014 and April 2015 were included. Epicardial fat tissue was calculated by two-dimensional transthoracic echocardiography, and pentraxin-3 and neutrophil-to-lymphocyte ratio were measured by using an enzyme-linked immunosorbent assay method and routine blood count analysis, respectively.

Results: Epicardial fat thickness ($p < 0.001$), pentraxin-3 ($p < 0.001$), and neutrophil-to-lymphocyte ratio ($p < 0.001$) were found to be significantly increased in the preeclampsia as compared to the healthy pregnants. Furthermore, epicardial fat thickness ($p = 0.002$), pentraxin-3 ($p < 0.001$), and neutrophil-to-lymphocyte ratio ($p < 0.001$) were significantly elevated in the severe preeclampsia compared to mild preeclampsia. In the multivariate analysis, epicardial fat thickness ($p = 0.013$), pentraxin-3 ($p = 0.04$), and neutrophil-to-lymphocyte ratio ($p < 0.001$) were found as significant independent predictors of presence of preeclampsia after adjusting for other risk factors.

Conclusion: Epicardial fat thickness, neutrophil-to-lymphocyte ratio, and pentraxin-3 are important markers that provide an additional information beyond that provided by conventional methods in predicting presence and severity of preeclampsia.

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Epicardial fat thickness; neutrophil-to-lymphocyte ratio; pentraxin-3; preeclampsia

Introduction

Preeclampsia (PE) is one of the leading causes of maternal and fetal major adverse events including death and iatrogenic preterm birth (1). Although it is defined as proteinuria and hypertension after 20 weeks of gestational stage by current guidelines, early and accurate diagnosis of this disease remains a challenge. Recent study reported a presence of maternal adverse events including eclampsia without any traditional clinical and laboratory findings such as hypertension and proteinuria (2). Hence, there is an urgent need to investigate practical, routinely used, and inexpensive markers for early and accurate diagnosis and risk stratification of PE.

Epicardial fat tissue (EFT) is a visceral adipose depot of heart, which is located on the cardiac surface between myocardium and visceral pericardium and along large coronary arteries. It is a source of many endocrine and inflammatory mediators, also termed as "new cardiometabolic risk factor" (3,4). A significant relation between an increased EFT and presence of PE was reported in recent studies (5). Moreover, Can et al. demonstrated a positive relation between EFT and both presence and severity of PE (6). Similar associations

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Original Investigation

Assessment of Relationships Between Novel Inflammatory Markers and Presence and Severity of Preeclampsia: Epicardial Fat Thickness, Pentraxin-3, and Neutrophil-to-Lymphocyte Ratio.

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were presented in some other diseases such as type 2 diabetes mellitus, gestational diabetes mellitus, and obese polycystic ovary syndrome (7–9).

Pentraxin 3 (PTX3) is a new pro-inflammatory molecule belonging to classic C-reactive protein (CRP) family. It is either synthesized and expressed locally by vascular endothelial cells, smooth muscle cells, fibroblasts, and macrophages at the inflammatory sites or by monocytes/macrophages upon exposure to primary inflammatory signals such as tumor necrosis factor-, interleukin(IL)-1, oxidized low-density lipoprotein, and bacterial products (10,11). An increased plasma level of PTX3 has been demonstrated in acute myocardial infarction (12), chronic heart failure (13), and pregnancy failure (14), suggesting that PTX3 may have clinical utility for early diagnosis and appropriate treatment. Moreover, a significant relation was reported between raised PTX3 level and both presence of PE and intrauterine growth restriction in a recent study (15).

Neutrophil-to-lymphocyte ratio (NLR), which is calculated as the ratio of the neutrophils and lymphocytes both obtained from the same automated blood sample at admission, is a new marker of systemic inflammation. Predictive and prognostic values of NLR in many cardiovascular diseases such as non-dipper hypertension, stable coronary artery disease, acute myocardial infarction undergoing primary percutaneous coronary intervention, peripheral arterial occlusive disease, acute pulmonary embolism, and cardiac syndrome X were demonstrated in recent studies (16–22). Furthermore, an important association between NLR and presence of PE with significant predictive values was reported (5).

Since some information is available about the relation between EFT, PTX3, and NLR and presence and severity of PE, which were reported seperately, we aimed to evaluate the relation and predictive role of three new inflammatory markers with presence and severity of PE at the same time. The secondary aim of the present study was to compare the predictive values of all study markers for presence of this setting.

Methods

Study participants

In this observational case-control study, a total of 100 consecutive pregnant patients, who were admitted to obstetric and gynecology clinic of high volume research and training hospital with hypertension and edema after 20 weeks of gestational period, hospitalized and eventually delivered nulliparous with a diagnosis of PE, between October 2014 and April 2015, were included. Moreover, 40 pregnant subjects, who had no known hypertension, and an uncomplicated pregnancy, presented to the obstetrics and gynecology outpatient clinic for routine prenatal screening, were recruited as the control group.

The diagnosis of PE was based on the American College of Obstetricians and Gynecologists guideline as follows (23): a systolic blood pressure of ≥140 mmHg or diastolic blood pressure ≥90 mmHg, measured twice in four-hour intervals while resting, after the 20th gestational week, as well as 300 mg proteinuria detected in a 24-hour urine sample, or in the absence of proteinuria, hypertension together with evidence of systemic disease, including thrombocytopenia, increased levels of liver transaminases, renal failure, pulmonary edema, and visual or cerebral disturbances. Moreover, severe PE was defined as the presence of any of the following criteria: systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on two separate measurements, performed at six-hour intervals at the least, elevated serum creatinine level (>1.1 mg/dL), headache, visual impairment, epigastric pain or pain in the right upper quadrant, elevated hepatic transaminases (≥ 40 IU/ml), thrombocytopenia (Plt<100,000/μL), or pulmonary edema. The study participants were divided into two groups as PE and control subjects. In addition, preeclamptic pregnants were subdivided into two categories such as severe (n = 45) and mild (n = 55) PE.

The exclusion criteria of the present study were as follows: the patients who had a history of structural heart disease, heart failure, coronary artery disease, chronic hypertension, type 1 or 2 diabetes, gestational diabetes, multiple gestation, active labor, polyhydramnios, premature rupture of membrane, severe liver or kidney failure, obesity (body mass index ≥ 30), malignancy, hypo-hyperthyroidism, hematological disease, acute or chronic infectious or systemic inflammatory conditions, and autoimmune disease.

Demographic, clinical, and laboratory characteristics of patient and control groups including maternal age, gestational week at delivery, smoking habits, and medical treatments on admission were recorded by systematic review of patient files. Height and weight were recorded, and body mass index (BMI) was calculated as the weight divided by the square of height (kg/m^2).

Eligible patients were between 18 and 40 years old, and all were able to provide written informed consent, which was a prerequisite for enrollment. The study complies with the Declaration of Helsinki, and the trial protocol was approved by the local Ethics Committee.

Biochemical measurements

Blood samples were taken after a 12-hour overnight fast from the antecubital vein with the patient in a sitting position, using the vacutainer system (Franklin Lakes, N.J.) into tubes containing anticoagulant EDTA. They were also taken before betamethasone administration. The serum was obtained by centrifugation at 3,000 rpm at 4°C for 15 min. Obtained sera were stored at −80°C until analysis. All routine biochemical and hematological parameters were measured on the day of blood draw. Biochemical parameters, including fasting blood glucose, creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG), were measured using an Abbott Diagnostics C8000i (Abbott, Wiesbaden, Germany) auto-analyzer with commercial kits. The LDL cholesterol was assayed by applying Friedewald's formula for samples with TG ≤ 400 mg/dl. Hematological parameters were obtained using the Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland, Inc., Mervue, Galway, Ireland). The NLR was calculated from the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count.

Serum PTX3 concentrations were measured with a commercially available kit using an enzyme-linked immunosorbent assay (ELISA) method (Perseus Proteomics Inc., Tokyo, Japan). This assay can measure plasma PTX3 concentration linearly between 0.1 and 20 ng/mL. The coefficient of variation for the PTX3 assay was 3.7% at 0.2 ng/mL and 1.4% at 2.2 ng/mL. All samples were assessed in duplicate, and the mean values were used in subsequent calculations.

Echocardiographic examination

All study participants underwent comprehensive two-dimensional (2D) transthoracic echocardiographic examinations to determine EFT with a Vivid S5 (GE Vingmed, Horten, Norway) device using a 2.5- to 3.5-MHz probe. The echocardiographic images were digitally recorded into a computerized database (EchoPac, Hopewell Jct., NY) and analyzed by an experienced cardiologist blinded to patients' data in order to avoid interobserver variability. The EFT was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, and its thickness was measured perpendicularly on the free wall of the right ventricle at the end of systole in three cardiac cycles. Measurements were obtained from the parasternal long- and short-axis views. The average value of three cardiac cycles from each echocardiographic view was taken into account (24,25). The maximum EFT was measured from the point on the free wall of the right ventricle along the midline of the ultrasound beam perpendicular to the aortic annulus. For the midventricular parasternal short-axis assessment, maximum EFT was measured from the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the interventricular septum at mid-chordal level and the tip of the papillary muscles, as the anatomic landmark. Three days after the first measurement, echocardiographic images of 28 patients were randomly selected, and EFT was measured a second time to evaluate intraobserver variability. The intraobserver variability coefficient was 0.84. Measurements of the left ventricle diameter, interventricular septum, and posterior wall thickness were performed on M-mode traces recorded from the parasternal long axis view according to the established standards (26). The left ventricular mass index (LVMI) was calculated using the Devereux Formula as described (27).

Statistical analysis

Continuous, normally distributed variables were expressed as mean ± standard deviation and non-normally distributed variables as median (interquartile range). Categorical variables were expressed as frequencies and/or percentages. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov) to determine if they are normally distributed. Kruskal-Wallis and Mann-Whitney U-tests were used for continuous non-normally distributed variables, and student t-test for continuous normally distributed variables. Categorical variables were compared by the likelihood ratio chi-square test. Correlations between variables were assessed using Spearman rank correlations test. A receiver operating curve (ROC) analysis was done to investigate the discriminative role of EFT, PTX3, and NLR for presence of PE. A univariate and backward stepwise multivariate logistic regression analysis was performed to identify independent predictors for PE. An overall 5% type-I error level was used to infer statistical significance, and a two-sided p-values <0.05 were considered to be statistically significant. All statistical analyses were carried out using SPSS statistical software, version 21.0 (SPSS Inc., Chicago, Illinois, USA).

Results

One hundred forty pregnants were enrolled in this study. The study groups were classified into either a preeclamptic group (n = 100) or a healthy pregnant group (n = 40) according to the presence of well-defined PE criteria. Baseline demographic, clinic, and laboratory characteristics of the study groups were presented in Table 1. There was no difference between two groups in terms of age, gestational age, and body mass

Table 1. Baseline demographic, clinic, and laboratory characteristics of the preeclampsia and control groups.

	Preeclampsia (n = 100)	Control (n = 40)	p
Age, years	27 ± 5	28 ± 5	0.532
Gestational Age At Delivery, day	251.1 ± 21.4	254 ± 13.7	0.387
BMI, kg/m^2	30 ± 4.4	29.4 ± 3.3	0.433
Pentraxin 3, ng/ml	3.9 ± 3.5	1.5 ± 0.8	**0.001**
Epicardial Fat Thickness, mm	6.8 ± 0.7	5.9 ± 0.7	**0.001**
Glucose, mg/dL	90.8 ± 16.8	91.4 ± 13.9	0.493
Urea, mg/dL	10.1 ± 3.2	11 ± 3.4	0.142
Creatinine, mg/dL	0.6 ± 0.1	0.5 ± 0.1	0.135
HDL, mg/dL	47.2 ± 8.4	47.8 ± 7.2	0.675
Hemoglobin, g/dL	11.6 ± 1.4	11.5 ± 1.3	0.711
NLR	5.3 ± 1.4	3 ± 0.8	**0.001**
LVEDD, mm	48 ± 3.4	48.9 ± 3.7	0.187
LVESD, mm	29.8 ± 2.8	29.6 ± 2.7	0.771
LA diameter, mm	30.2 ± 3	29.9 ± 3.1	0.541
EF, %	57.5 ± 4.8	57.3 ± 4.4	0.831
LVMI, g/m^2	83.4 ± 9.9	79.5 ± 9.4	**0.022**

BMI: body mass index; EF: ejection fraction; HDL: high-density lipoprotein; LA: left atrium; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVMI: left ventricular mass index; NLR: neutrophil to lymphocyte ratio.

index. As it was expected, preeclamptic group was more likely to have higher systolic and diastolic blood pressures. Moreover, EFT (6.8 ± 0.7 vs. 5.9 ± 0.7 mm, $p < 0.001$), PTX3 (3.9 ± 3.5 vs. 1.5 ± 0.8 ng/ ml; $p < 0.001$), NLR (5.3 ± 1.4 vs. 3.0 ± 0.8, $p < 0.001$), and LVMI (83.4 ± 9.9 vs. 79.5 ± 9.4 mm, $p = 0.022$) were found to be significantly increased in the PE group as compared to the healthy pregnants.

Baseline demographic, clinic, and laboratory characteristics of the mild and severe PE groups were summarized in Table 2. Systolic and diastolic blood pressures and proteinuria were found to be raised as severity of the disease increased. Furthermore, EFT (7.0 ± 0.8 vs. 6.6 ± 0.6 mm, $p = 0.002$), PTX3 (6.0 ± 4.1 vs. 2.2 ± 1.3 ng/ml; $p < 0.001$), and NLR (6.3 ± 1.1 vs. 4.5 ± 1.0, $p < 0.001$) were significantly elevated in the severe PE group as compared to the mild preeclamptic pregnants.

Table 2. Baseline demographic, clinic, and laboratory characteristics of the mild and severe preeclampsia groups.

	Mild Preeclampsia (n = 55)	Severe Preeclampsia (n = 45)	p
Age, years	27 ± 6	27 ± 5	0.769
Gestational Age At Delivery, day	251.9 ± 21.4	250.2 ± 16.2	0.661
BMI, kg/m^2	29.9 ± 4	30 ± 4.8	0.905
Pentraxin 3, ng/ml	2.2 ± 1.3	6 ± 4.1	**0.001**
Epicardial Fat Thickness, mm	6.6 ± 0.6	7 ± 0.8	**0.002**
Glucose, mg/dL	91.2 ± 16	90.3 ± 17.9	0.586
Urea, mg/dL	10.1 ± 2.9	10.1 ± 3.5	0.939
Creatinine, mg/dL	0.6 ± 0.1	0.6 ± 0.1	0.873
Proteinuria, mg/day	703.3 ± 248.3	3746.7 ± 1585.2	**0.001**
HDL, mg/dL	47.2 ± 8.2	47.2 ± 8.7	0.991
Hemoglobin, g/dL	11.7 ± 1.3	11.5 ± 1.6	0.508
NLR	4.5 ± 1	6.3 ± 1.1	**0.001**
LVEDD, mm	48.9 ± 3.6	48.9 ± 3.9	0.972
LVESD, mm	29.5 ± 2.7	29.8 ± 2.8	0.674
LA diameter, mm	29.7 ± 3.1	30.2 ± 3.2	0.379
EF, %	57.3 ± 4.3	57.2 4.4	0.923
LVMI, g/m^2	82.7 ± 10.2	84.4 ± 9.4	0.347

BMI: body mass index; EF: ejection fraction; HDL: high-density lipoprotein; LA: left atrium; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVMI: left ventricular mass index; NLR: neutrophil to lymphocyte ratio.

EFT was significantly positively correlated with PTX3 ($r = 0.307$, $p < 0.001$), NLR ($r = 0.448$, $p < 0.001$), proteinuria ($r = 0.305$, $p = 0.002$), systolic and diastolic blood pressures ($r = 0.496$, $p < 0.001$ and $r = 0.508$, $p < 0.001$ respectively). In addition, significant direct correlations were found between PTX3 and NLR ($r = 0.563$, $p < 0.001$), proteinuria ($r = 0.551$, $p < 0.001$), systolic and diastolic blood pressures ($r = 0.507$, $p < 0.001$ and $r = 0.457$, $p < 0.001$ respectively). NLR was also significantly positively correlated with proteinuria ($r = 0.592$, $p < 0.001$), systolic, and diastolic blood pressures ($r = 0.701$, $p < 0.001$ and $r = 0.614$, $p < 0.001$ respectively).

A receiver operating curve (ROC) was generated for sensitivity and specificity, with the respective areas under the curve (AUC), to investigate the predictive value of EFT, PTX3, and NLR for presence of PE (Figure 1). EFT with a cut of value of 6.15 mm had 76.0% sensitivity and 70.0% specificity (ROC area under curve: 0.812, 95% CI: 0.729–0.894, $p < 0.001$), PTX3 with a cut of value of 1.75 had 76.0% sensitivity and 67.5% specificity (ROC area under curve: 0.792, 95% CI: 0.718–0.866, $p < 0.001$) and NLR with a cut of value of 3.5 had 93.0% sensitivity and 80.0% specificity (ROC area under curve: 0.930, 95% CI: 0.887–0.973, $p < 0.001$) in precisely predicting a PE diagnosis.

In a univariate regression analysis, PTX3, EFT, NLR, and LVMI were significantly related with PE. In the multivariate analysis, EFT ($p = 0.013$), PTX3 ($p = 0.04$) and NLR ($p < 0.001$) were found as significant independent predictors of presence of PE after adjusting for other risk factors (Table 3).

Discussion

The main findings of the present study were as follows: 1) Elevated new inflammatory markers levels such as EFT, PTX3, and NLR were related to PE, 2) Significant direct correlations were demonstrated between them, 3) A significant discriminative role of EFT, PTX3, and NLR for presence of PE, with cut of values of 6.15 mm, 1.75 ng/ml, and 3.5, respectively, were reported in a ROC curve analysis, 4) EFT, PTX3, and NLR were significant independent predictors of PE after adjusting for other risk factors.

PE affects and complicates approximately 3–14% of pregnancies (1). The main pathophysiologic mechanisms of PE, which are not fully elucidated and similar to

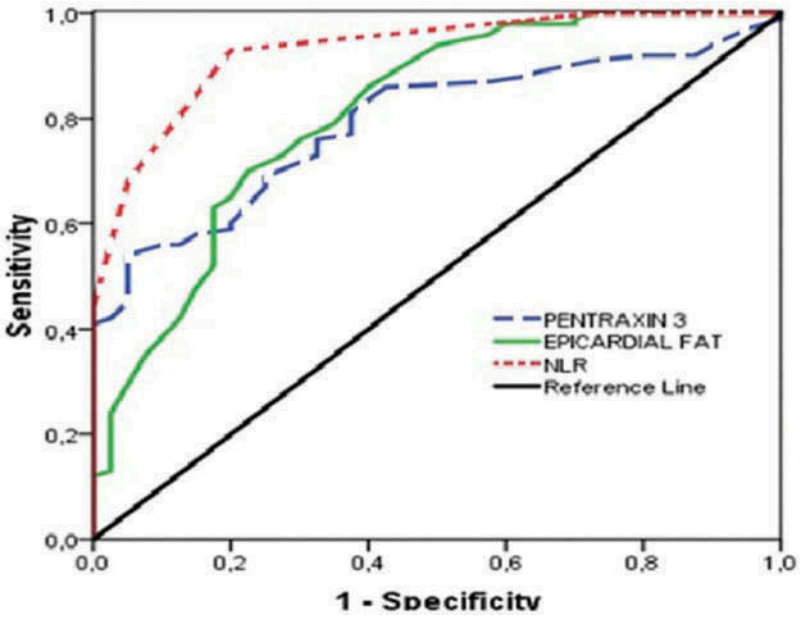

Figure 1. Receiving operating characteristics (ROC) curves for the predictive value of EFT, PTX3, and NLR for presence of preeclampsia.

Table 3. Results of Univariate and Multivariate Regression Analysis.

	Univariate			Multivariate		
	p	OR	(95% CI)	*p*	OR	(95% CI)
Gestational Age At Delivery	0.385	0.991	0.970–1.012			
BMI	0.483	1.034	0.942–1.134			
Hb	0.709	1.053	0.804–1.378			
Urea	0.144	0.919	0.821–1.029			
HDL	0.672	0.990	0.945–1.037			
LVMI	**0.033**	1.043	1.003–1.085	0.425	1.027	0.962–1.096
PTX3	**0.001**	2.479	1.611–3.817	**0.040**	1.929	0.911–4.085
NLR	**0.001**	9.154	4.139–20.247	**0.001**	8.161	3.091–21.548
EFT	**0.001**	6.614	3.215–13.608	**0.013**	3.771	1.316–10.810

BMI: body mass index ; CI: confidence interval; EFT: epicardial fat thickness; Hb: Hemoglobin; HDL: high-density lipoprotein; LVMI: left ventricular mass index; NLR: neutrophil to lymphocyte ratio; OR: odss ratio; *p: p* value; PTX3: pentraxin 3.

cardiovascular diseases such as atherosclerosis and coronary and peripheral arterial diseases, are severe inflammation, increased cytokines and pro-inflammatory molecules release, endothelial dysfunction and dysregulation, angiogenesis, inappropriate placentation, oxidative stress, and immunological and genetic factors (2). Variable clinical presentation, limitations of available blood pressure level and proteinuria measurement methods, and early and fast progression of disease before precise diagnosis are unique and major issues of PE (1,2,28). Therefore, novel, easy measured, and cheap markers are needed to increment early diagnosis and treatment for PE. In our study, we investigated relationships between novel inflammatory markers such as EFT, PTX3, and NLR and presence and severity of PE.

EFT, which is one of the significant indicator of severe inflammation, may play a crucial role in the pathophysiological pathway of cardiovascular diseases via secretion of many proinflammatory and atherogenic molecules. Its elevated value was found to be related with many cardiovascular diseases such as coronary artery disease, coronary artery calcification, hypertension, PE, type 2 diabetes mellitus, gestational diabetes mellitus, and obese polycystic ovary syndrome (3,4,7–9,29). Gastaldelli et al. presented an association between raised EFT and increased mean blood pressure (30). Moreover, a significant impaired effect of elevated EFT on diurnal blood pressure was demonstrated by the study of Ertas et al (31). Can et al. reported a significant relation between raised EFT and presence and severity of PE (6). They suggested that EFT may affect endothelial function and sympathetic activity with its paracrine function in this acute setting. Oylumlu et al. also demonstrated a similar association between EFT and only presence of PE (5). In our study, different from Oylumlu et al. study, raised EFT was significantly related to both presence and severity of PE. Moreover, concordant with these previous studies indicated above, EFT was found as a significant predictor for PE in pregnant women.

A significant predictive and prognostic role of PTX3 in terms of major adverse cardiovascular events including mortality was reported in cardiovascular diseases (10,12,13). Furthermore, an independent relation of PTX3 with presence of PE was presented by the study of Turkmen et al (32). Cozzi et al. demonstrated a significant

independent association between raised maternal PTX3 and presence and severity of PE (15). Our study, concordant to these previous studies, has demonstrated a similar association between PTX3 and PE. PTX3, for the first time, was reported as significantly directly correlated with other new inflammatory markers such as EFT and NLR. These study findings confirm the relevance of PTX3 in support the hypothesis that PE is a systemic disease related with impaired maternal endothelial function and severe inflammation.

NLR combines the predictive risk of these two leukocyte subtypes into a single risk factor (33). It was suggested to be an indirect indicator of systemic inflammation in various recent studies. Moreover, raised NLR was demonstrated to be a predictor of major adverse cardiovascular events in acute myocardial infarction, peripheral arterial occlusive disease, and coronary artery disease (16–22). In the studies by Sunbul et al. (34) and Demir et al. (19), elevated NLR was demonstrated in non-dipper hypertensives compared to those in dipper hypertensive patients. Neutrophilic leukocytosis, which has been reported in recent studies in the settings of both normal pregnancy and PE (35), was suggested due to increased levels of arachidonic. An elevated neutrophil and decreased lymphocyte and eosinophil counts were reported in preeclamptic pregnants (36). Oylumlu et al. reported firstly a significant independent association between increased NLR and PE. It was also significantly correlated with EFT (5). In our study, concordant with Oylumlu et al. study, concomitant relationship among the echocardiographic EFT, NLR, and PE was presented. In addition, similar to Oylumlu et al. study, EFT and NLR were significantly correlated with each other.

Limitations of the study

The present study has some limitations. First, it has a non-randomized study design that arose from a single center, and hence, it was subject to selection bias. Second, the study population was relatively small; however, we were still able to demonstrate a significant independent relationship between EFT, PTX3, NLR and presence and severity of PE. Third, substantial overlap in data point, commonly seen in case-control study, lowers the relationship between EFT, PTX3, NLR and presence and severity of this setting. Last, since these inflammatory markers were measured and calculated only once during admission, we could not assess the changes in EFT, PTX3, and NLR in response to treatment due to lack of serial measurements.

Conclusion

We demonstrated, for the first time, significant relations of all three elevated new inflammatory markers such as EFT, PTX3, and NLR with both the presence and the severity of PE at the same time in this study. Moreover, they were reported as significant independent predictors of PE after adjusting for other risk factors. EFT, PTX3, and NLR, which show the patient's inflammatory status, are markers that provide an additional information beyond that provided by conventional in predicting presence and severity of PE. Larger prospective cohort studies with more participants will be required to elucidate the exact pathophysiologic relation between these markers and PE.

Declaration of interest

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper. The authors have had full control of all primary data, and they agree to allow the journal to review their data if requested.

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