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Is neutrophil/lymphocyte ratio a useful marker to predict the severity of pre-eclampsia?

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ABSTRACT

Objective: To evaluate the relationship of neutrophil/lymphocyte ratio (NLR) with proteinuria and blood pressure level in patients with pre-eclampsia and to investigate whether or not NLR has a role in predicting the severity of pre-eclampsia.

Study design: The study comprised 30 healthy pregnant females (Group 1), 37 females with mild pre-eclampsia (Group 2) and 40 with severe pre-eclampsia (Group 3). All the study participants were statistically compared in respect of demographic data, proteinuria levels, and blood pressure levels.

Result: Age, body mass index, and gestational weeks were similar in all the groups. Maternal NLR was determined to be significantly high in the pre-eclamptic patients (Groups 2 and 3) compared to the healthy pregnant patients (Group 1) ($p = 0.017$). NLR was significantly higher in the severe pre-eclampsia group than in the mild pre-eclampsia group ($p = 0.032$). A significant positive correlation was determined in correlation analysis between NLR and proteinuria ($p = 0.013$, $r = 0.319$). There was also a significant and positive correlation between NLR and systolic/diastolic arterial pressure ($p = 0.007$, $r = 0.285$; $p = 0.044$, $r = 0.213$, respectively).

Conclusion: In conclusion, while NLR was determined as significantly high in patients with pre-eclampsia, to be able to use this in the classification of the severity of pre-eclampsia, there is a need for further studies on a more extensive population.

1. Introduction

Pre-eclampsia (PE) is a pregnancy specific syndrome characterized by hypertension and proteinuria after 20 weeks gestation [1,2]. In pre-eclamptic patients there is inadequate placentation, due to a deficiency in trophoblastic invasion which causes placental hypoxia, pro-inflammatory cytokine secretion, angiogenic and anti-angiogenic factor release. Changes in the immune system are very important in the background of pre-eclampsia. In addition, pro-inflammatory cytokines, neutrophil activation and endothelial dysfunction are also associated with the pathophysiology of this disease [3].

Pregnancy is a controlled inflammatory state. It is believed that an excessive systemic inflammatory response is the basis of the clinical manifestations of PE, but the causes of this inflammatory response in normal pregnancy and PE have not yet been fully clarified [4,5].

Maternal circulating leukocytes are activated in pregnancy and further activated in pre-eclampsia [6]. All major leukocyte classes, including neutrophils, lymphocytes, and monocytes are activated. Lipids secreted by the placenta activate the leukocytes which are circulating through the intervillous space. As these activated leukocytes re-enter the maternal systemic circulation, they could be responsible for the vascular dysfunction associated with pre-eclampsia [7]. Neutrophils are usually thought to be the first line of defence against infection at the site of a wound, but as has been reported in recent studies, neutrophils also infiltrate systemic vascular tissue in women with pre-eclampsia, thus causing vascular inflammation [7,8].

Maternal neutrophil/lymphocyte ratio has come into current use to predict pre-eclampsia, but to the best of our knowledge, there has been no research on the use of the maternal neutrophil/lymphocyte ratio (NLR) to predict the severity of pre-eclampsia or the severity of proteinuria [9,10].

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Therefore, the aim of this study was to evaluate this hypothesis in groups of severe pre-eclampsia, mild pre-eclampsia and healthy pregnant cases. In the study, an examination was made of the correlation between the NLR ratio and the proteinuria and blood pressure levels of the patients in the three groups.

2. Materials and methods

This case–control study was conducted at the Obstetrics and Gynecology Clinic of the Medical Faculty of Sutcu Imam University (Kahramanmaras, Turkey) between December 2012 and April 2014. The study comprised 30 healthy pregnant females (Group 1), 37 pregnant females with mild pre-eclampsia (Group 2) and 40 pregnant females with severe pre-eclampsia (Group 3). Patients with any history of membrane rupture or any infection which could cause alterations in the maternal neutrophil/lymphocyte ratio, or multiple pregnancies were excluded from the study. The diagnosis of pre-eclampsia and severe preclampsia was made according to the recommendations of the most recent guidelines [11].

Venous blood samples were taken from all the participants and the neutrophil and lymphocyte levels were measured (Siemens, Advia 2120i, Hematology Systems, Germany). The demographic data of the patients were recorded and the protein amounts in spot urine, protein values in 24-h urine and NLR in the obtained blood samples were determined. Statistical comparison was made of the control group and all the pre-eclampsia patients in respect of NLR. As a result of this analysis, a significant difference was determined between the control group and the 77 pre-eclampsia patients, who were then sub-divided into 2 groups as mild pre-eclampsia ($n = 37$) and severe pre-eclampsia ($n = 40$). A comparison was made between these 2 groups in respect of NLR.

All statistical evaluations of the data obtained in the study were made with Statistical Program for Social Sciences (SPSS, Version 16.0; Chicago, IL, USA) software. The variables were stated as mean ± standard deviation. In the comparison of the data between the patient and control groups, the Mann Whitney and ANOVA tests were used. A value of $p < 0.05$ was accepted as statistically significant.

Approval for the study was granted by the Research Ethics Committee of Kahramanmaraş Sütçü İmam University School of Medicine.

3. Results

A statistical comparison was made of the demographic data (age, body mass index, gestational week) between Group 1 ($n = 30$, healthy pregnant females) and Groups 2 and 3 ($n = 77$, pregnant females with pre-eclampsia) (Table 1).

In the comparison between the 2 groups of patients, the mean maternal age was determined as higher in the pre-eclampsia group. When the patients in the pre-eclampsia group were separated into 2 groups of mild and severe pre-eclampsia, no statistically significant difference was determined between the 3 groups in respect of maternal age.

Table 1
A statistical comparison was made of the demographic data between Group 1 (healthy pregnant), Groups 2 and 3 (all preeclamptic patients).

	Group 1 (n: 30)	Groups 2 and 3 (n:77)	p Value
Age	28 ± 5,04	30.83 ± 6.21	0.028
BMI	27.4 ± 2.1	27.68 ± 2.2	0.89
Gestational age	36.2 ± 1.9	36 ± 2.1	0.91
N/L ratio	3.9 ± 2.3	5.68 ± 3.1	0.017
Proteinuria (24 h)	–	2754 ± 2.62 (230–11.322)	<0.001

Group 1: healthy pregnants, Group 2: mild preeclampsia, Group 3: severe preeclampsia, N/L ratio: neutrophil/lymphocyte ratio, BMI: body mass index.

The healthy pregnant females (Group 1) were compared with the pregnant patients with pre-eclampsia (Groups 2 and 3) in respect of maternal NLR. In the pre-eclamptic patients (Groups 2 and 3) the maternal NLR was determined to be statistically significantly higher than that of the healthy pregnant females ($p = 0.017$) (Table 1). The subsequent comparison of the two groups with pre-eclampsia determined NLR to be statistically significantly higher in the severe pre-eclampsia group than in the mild pre-eclampsia group ($p = 0.032$) (Table 2).

An important aspect of this study was the examination of the relationship of NLR with systolic and diastolic blood pressure levels used in the current guidelines and the proteinuria level used in the determination of the severity of pre-eclampsia. In the correlation analysis of NLR and proteinuria, a significant positive correlation was determined ($p = 0.013$ $r = 0.319$) and a significant and positive correlation between NLR and systolic/diastolic arterial pressure ($p = 0.007$, $r = 0.285$, and $p = 0.044$, $r = 0.213$ respectively).

4. Discussion

Pregnancy-related immunological changes include either local placental problems or broad systemic effects, such as an increase in the severity of certain infections during pregnancy [12,13].

In women with pre-eclampsia, it is likely that neutrophils are activated as they circulate through the intervillous space and are exposed to oxidized lipids secreted by the placenta [14,15]. Oxidized lipids are potent activators of neutrophils, leading to expression of COX-2 which regulates the release of thromboxane, TNF and superoxide [16,17]. Neutrophils obtained from pre-eclamptic females express significantly more COX-2 than neutrophils obtained from healthy pregnant females or healthy non-pregnant females [18]. However, the background of biochemical mechanisms responsible for these immunomodulatory changes has not been clearly described [19].

In many studies, macrophages in atherosclerotic plaque are considered to have a role as foam cells. Lymphocytes are a part of the adaptive immune system with the production of antibodies to overcome diseases. Neutrophils are usually thought to be the first line of defence against infection at the site of a wound, but as has been reported in recent studies, neutrophils infiltrate systemic vascular tissue in women with pre-eclampsia, thus causing vascular inflammation [7,8]. Other leukocyte types might also infiltrate the maternal vascular system in pre-eclamptic patients and may be responsible for vascular dysfunction.

Oylumlu et al. reported a significantly higher NLR in the pre-eclampsia group compared to the control group (7.3 ± 3.5 versus 3.1 ± 1.1; $p < 0.001$) [9]. In another study, although all classes of leukocytes were activated in the maternal circulation of females with pre-eclampsia, only neutrophils were found to significantly infiltrate the systemic vasculature. Staining for neutrophils was determined in 70% of vessels in pre-eclamptic women compared with only 33% of vessels for lymphocytes, and for those vessels with leukocytes present, there were three times more neutrophils per vessel than lymphocytes [20]. The number of neutrophils has been reported to increase 2.5-fold by 30 weeks of gestation in a normal pregnancy and to increase further in patients with pre-eclampsia [21]. This increase in neutrophil numbers in pregnancy is thought to be the result of increased levels of colony-stimulating factors [22].

Canzoneri et al. found that the total leukocyte count was significantly increased in women with severe PE compared with women with mild PE and normal pregnant controls: 10.66 ± 3.70 (p; 0.0001) versus 9.47 ± 2.59 and 8.55 ± 1.93 ($1 \times 10^3/\mu L$),