

## CROSS-SECTIONAL STUDY

# Association between the neutrophil to lymphocyte ratio and prehypertension

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**ABSTRACT**

**OBJECTIVES:** To explore the neutrophil-lymphocyte ratio (NLR) in patients with prehypertension (PHT).

**BACKGROUND:** Inflammation plays an important role in the development of cardiovascular diseases. A pathophysiological link also exists between inflammation and PHT. NLR is a simple marker for the assessment of inflammatory status. There is a lack of data regarding the association between NLR and pre-hypertensive state.

**METHODS:** The present cross-sectional study included 33 newly diagnosed PHT patients and 35 normotensive control subjects. Prehypertension was defined as a systolic blood pressure (BP) of 120–139 mm Hg and/or a diastolic BP of 80–89 mm Hg.

**RESULTS:** Patients were divided into tertiles based on NLR values: 1.17 (0.9–1.42) in tertile 1; 1.57 (1.43–1.78) in tertile 2; and 2.40 (1.82–4.5) in tertile 3. The frequency of PHT was significantly higher for patients in the upper NLR tertile compared to the middle and lower NLR tertiles (21 (91.3 %), 7 (30.4 %), and 5 (22.7 %), respectively;  $p < 0.001$ ). Systolic BP and diastolic BP were significantly higher among patients in the upper NLR tertile than among those in the other NLR tertiles.

**CONCLUSION:** An association exists between PHT and NLR. NLR measurement, as well as monocyte count, may be used to indicate increased risk of prehypertension (Tab. 2, Ref. 48). Text in PDF [www.elis.sk](http://www.elis.sk).

**KEY WORDS:** prehypertension, neutrophil-to-lymphocyte ratio, inflammatory.

**Introduction**

Prehypertension (PHT) has been defined as a systolic blood pressure (BP) of 120–139 mm Hg and/or a diastolic blood pressure of 80–89 mm Hg (1). The PHT designation serves to identify individuals who are potentially at higher risk for developing hypertension (HT) compared to those with optimal BP (< 120/80 mm Hg) (2, 3). In the past few years, several prospective and cross-sectional studies have reported an elevated risk of coronary vascular disease (e.g., coronary heart disease and myocardial infarction) in prehypertensive subjects (4–8). Thus, it is important to understand the pathogenesis of PHT, as PHT may be the first sign of cardiovascular disease (CVD) in some cases.

Several studies have shown that inflammation appears to play an important role in the development of cardiovascular diseases (9, 10). Elevated levels of systemic inflammatory markers have been found to be associated with the incidence of cardiovascular diseases, such as coronary artery disease, HT, and atrial fibrillation (4, 5, 11). White blood cell (WBC) count and its subtypes are related to enhanced cardiovascular risk factors (6, 12). The

neutrophil-lymphocyte ratio (NLR) has been evaluated as a new predictor for cardiovascular risk (6).

Despite the importance of PHT on cardiovascular outcomes, insufficient data exists on the potential association between the NLR and PHT. The NLR has never been investigated in prehypertensive patients. Therefore, the aim of this study was to explore the NLR in patients with PHT.

**Materials and methods**

The present study has a cross-sectional design. Power analysis suggested that a sample size of 25 was needed with an alpha of 0.05 for a power of 0.80. Thirty-three newly diagnosed PHT patients who had been admitted to our outpatient clinic for general check-up were selected. Thirty-five age- and sex-matched healthy volunteers were recruited for the control group. The investigation complied with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee, and all participants provided written informed consent before participating.

Prehypertension was defined as a systolic BP of 120–139 mmHg and/or a diastolic BP of 80–89 mmHg. BP measurements were performed on the right arm using a sphygmomanometer (Erka, Erlangen, Germany) after 10 minutes of rest in a seated position. The average of two blood pressure measurements obtained at least three minutes apart was recorded for each patient. The nurse specialist determined the mean BP. Ambulatory BP

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**Tab. 1. Clinical and hematological characteristics of patients by neutrophil-to-lymphocyte ratio tertiles.**

Variables	Neutrophil/lymphocyte ratio			p
	Tertile 1 (1.17±0.17) n=22	Tertile 2 (1.57±0.09) n=23	Tertile 3 (2.40±0.63) n=23	
Age, years	47±6	49±12	45±13	0.64
Prehypertensive, n (%)	5 (23)	7 (30)	21 (91)	
Body mass index, kg/m <sup>2</sup>	26.8±3.6	28.2±3.5	27.8±3.9	0.55
Female sex, n (%)	14 (63)	13 (56)	13 (56)	0.85
Smoking, n (%)	3 (13)	7 (30)	2 (9)	0.12
Mean SBP, mm Hg	112±11	114±12	127±6	<0.001
Mean DBP, mm Hg	72±9	75±8	83±5	0.001
Hemoglobin, g/L	14.0±1.2	13.9±1.3	14.0±1.7	0.98
Fasting glucose, mg/dL	99±13	99±11	100±12	0.98
LDL, mg/dL	122±27	111±32	110±19	0.41
Triglyceride, mg/dL	123±30	112±28	104±42	0.26
HDL, mg/dL	48±23	50±15	41±11	0.34
Creatinine, mg/dL	0.80±0.11	0.82±0.26	0.82±0.20	0.92
Red-cell distribution width, %	15.3±0.9	15.2±1.0	15.3±1.2	0.94
Platelet count, /mm <sup>3</sup>	262±66	252±59	262±57	0.82
Mean platelet volume, fL	8.29±1.40	8.11±1.03	8.28±1.29	0.93
White blood cell count, x10 <sup>3</sup> /μL	6.9±1.1	7.5±1.7	7.8±1.7	0.15
Neutrophil count, x10 <sup>3</sup> /μL	3.3±0.5	4.1±0.9	4.9±1.1	<0.001
Lymphocyte count, x10 <sup>3</sup> /μL	2.8±0.5	2.6±0.6	2.1±0.4	<0.001

DBP – diastolic blood pressure, HDL – high-density lipoprotein, LDL – low-density lipoprotein, SDB – systolic blood pressure

monitoring was not performed. Patients who had PHT but were otherwise healthy were included. Exclusion criteria included drug use, morbid obesity (body mass index  $\geq 35$  kg/m<sup>2</sup>), diabetes mellitus, metabolic syndrome, dyslipidemia, renal dysfunction (serum creatinine  $> 1.5$  mg/dl, blood urea nitrogen  $> 30$  mg/dl), heart failure, valvular diseases, asthma, chronic obstructive pulmonary disease, peripheral and cerebral vascular disease, hematological disorders, acute or chronic infection, cancer, inflammatory disease, and hepatic dysfunction.

#### Biochemical measurements

Venous blood samples were drawn at initial presentation from the antecubital vein. Total and differential leukocyte counts and routine biochemical tests were performed.

#### Statistical analysis

Data were analyzed using the SPSS software version 15.0 for Windows (SPSS Inc., Chicago, Illinois). The Kolmogorov-Smirnov test was used to verify the normality of the distribution for continuous variables. Continuous variables were defined as mean and standard deviation; categorical variables were given as percentages. The independent sample t test or the Mann-Whitney U test was used for continuous variables, and the chi-square test was used for categorical variables. One-way ANOVA or the Kruskal-Wallis test was performed for the comparison of multiple groups. Pearson analysis was used to evaluate correlations. Statistical significance was defined as  $p < 0.05$ .

#### Results

Patients were divided into tertiles based on NLR values: 1.17 (0.90–1.42) in tertile 1; 1.57 (1.43–1.78) in tertile 2; and 2.40

**Tab. 2. Baseline clinical and hematological characteristics of prehypertensive and normotensive patients.**

Variables	Prehypertensive	Control	p
Age, years	48±13	46±9	0.9
Body mass index, kg/m <sup>2</sup>	27.5±4.2	27.7±3.2	0.85
Female sex, n (%)	19 (58)	21 (60)	0.83
Smoking, n (%)	5 (15)	7 (20)	0.6
Mean SBP, mm Hg	129±4	107±5	<0.001
Mean DBP, mm Hg	85±3	70±4	<0.001
Hemoglobin, g/L	13.8±1.7	14.1±1.0	0.44
Fasting glucose, mg/dL	101±12	97±12	0.17
LDL, mg/dL	110±18	118±33	0.09
Triglyceride, mg/dL	111±37	115±32	0.61
HDL, mg/dL	46±21	47±10	0.19
Creatinine, mg/dL	0.85±0.20	0.77±0.19	0.13
Red-cell distribution width, %	15.4±1.2	15.1±0.9	0.25
Platelet count, /mm <sup>3</sup>	258±61	259±60	0.93
Mean platelet volume, fL	8.4±1.1	8.0±1.2	0.13
White blood cell count, x10 <sup>3</sup> /μL	7.4±1.6	7.4±1.5	0.88
Neutrophil count, x10 <sup>3</sup> /μL	4.4±1.2	3.8±0.9	0.03
Lymphocyte count, x10 <sup>3</sup> /μL	2.2±0.5	2.7±0.6	0.002
Neutrophil/lymphocyte ratio	2.07±0.74	1.41±0.29	<0.001

DBP – diastolic blood pressure, HDL – high-density lipoprotein, LDL – low-density lipoprotein, SDB – systolic blood pressure

(1.82–4.50) in tertile 3. Baseline demographic, hemodynamic, and biochemical and hematological characteristics of the study population tertiles are shown in Table 1. There were no statistically significant differences between the groups with respect to age, gender, body mass index, smoking, or hemoglobin.

The frequency of the prehypertensive state was significantly higher among patients in the upper NLR tertile compared to the middle and lower tertiles (21 (91.3 %), 7 (30.4 %), and 5 (22.7 %), respectively;  $p < 0.001$ ). There was no significant difference between the middle and lower NLR tertile groups in terms of pre-

hypertensive state ( $p = 0.559$ ). Systolic BP and diastolic BP were significantly higher among patients in the upper NLR tertile (systolic:  $127 \pm 6$  mm Hg,  $p < 0.001$ ; diastolic:  $83 \pm 5$  mm Hg) than among those in the middle (systolic:  $114 \pm 12$  mm Hg,  $p < 0.001$ ; diastolic:  $75 \pm 8$  mm Hg,  $p < 0.001$ ) and lower (systolic:  $112 \pm 11$  mm Hg,  $p < 0.001$ ; diastolic:  $72 \pm 9$  mm Hg,  $p = 0.002$ ) NLR tertiles. Table 2 demonstrates the characteristics of the prehypertensive patients compared to the normotensive controls. Biochemical and hematological parameters were comparable between groups except neutrophil and lymphocyte counts. In the PHT group, neutrophil count was significantly higher ( $4.4 \pm 1.2$  versus  $3.8 \pm 0.9$ ;  $p = 0.03$ ) and lymphocyte count was significantly lower ( $2.2 \pm 0.5$  versus  $2.7 \pm 0.6$ ;  $p = 0.002$ ) than in normotensive subjects. As a result, patients with PHT had significantly higher NLR values compared to the control group ( $2.07 \pm 0.74$  versus  $1.41 \pm 0.29$ ;  $p < 0.001$ ). Pearson analysis revealed a positive correlation between NLR and both systolic BP ( $r = 0.424$ ;  $p < 0.001$ ) and diastolic BP ( $r = 0.492$ ;  $p < 0.001$ ).

## Discussion

In the present study, a higher NLR, a reliable marker of inflammation, was found to be statistically associated with the presence of PHT. In addition, the NLR was significantly correlated with both systolic and diastolic BP.

Many prospective cohort studies have demonstrated an association between BP levels and risk of CVD, stroke, and premature death (1, 13). Increased CVD risk begins at systolic BP levels as low as 115 mm Hg (14). The longitudinal data from the Framingham Heart Study have clearly shown that individuals with BPs of 120–139/80–89 mm Hg are at increased risk of developing full-blown HT and CVD later in life than individuals with BPs less than 120/80 mm Hg (2). Studies in the United States and other populations have identified an association between increased WBC count and BP (15–17). The relationship between leukocytes and increased cardiovascular risk is well known. Inflammation is involved in the pathogenesis of several CVD (18, 19). Elevated WBC count is associated with deaths from cardiovascular causes, with the extent of coronary heart disease as well as with cardiovascular mortality, combined cardiovascular mortality and morbidity, myocardial infarction, congestive heart failure and stroke (20–25).

Horne et al. examined the predictive ability of total WBC count and its subtypes for risk of death and myocardial infarction. They found that high neutrophil and monocyte counts, low lymphocyte count, and high NLR are independently related to increased number of cardiovascular events (27). Leukocyte subtype counts and NLR are also indicators of systemic inflammation (27). Recent studies have demonstrated the predictive and prognostic significance of the NLR in a wide range of cardiovascular diseases (18, 19, 28–30). Atmaca et al. found that WBC counts were higher in patients with syndrome X than in control subjects (31). Demirkol et al. have found a significant positive correlation between carotid intima-media thickness values and plasma NLR values (32). These markers have prognostic importance in CVD (18, 19, 26).

Several recent studies have supported the hypothesis that inflammatory cells contribute to HT. The TNF- $\alpha$  antagonist etanercept reduces the HT caused by fructose feeding, prevents vascular dysfunction, and blunts the HT caused by angiotensin II. Etanercept was also determined to lower BP in an autoimmune model of chronic inflammation (33–35). In some cases, TNF- $\alpha$  antagonism prevents end-organ damage without lowering BP. For example, etanercept prevents renal injury in salt-dependent HT without lowering BP and reduces albuminuria and renal inflammation in transgenic hypertensive rats (36, 37). More recently, the novel, pro-inflammatory cytokine IL-17 was found to contribute to HT. IL-17 has been implicated in a variety of diseases, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, and airway inflammation (38). IL-17 is also produced by CD8 cells, neutrophils, and natural killer T cells (39–41). IL-17 promotes chemotaxis of other inflammatory cells, in part by stimulating the release of chemokines (42). The vascular accumulation of leukocytes (including T cells) caused by angiotensin II was determined to be markedly reduced in mice (42). Thus, IL-17 may contribute to the vascular pathophysiology of HT not only via its direct effects, but also by recruiting other inflammatory cells to the perivascular tissue.

Stimuli, such as angiotensin II, sodium, and others, cause a modest elevation in BP to values of approximately 135 to 140 mm Hg (43). These initial elevations in pressure are largely due to central actions, but also require the direct effects of angiotensin II on peripheral sites. This first phase of modest pressure elevation, often referred to as prehypertension, causes an inflammatory response, likely by generating neoantigens that activate T cells. The inflammatory response leads to entry of effector-like T cells into the perivascular fat and the kidneys. Macrophage infiltration is also promoted, in part because of signals from T cells (43).

In the NHANES III and REGARDS studies, individuals with PHT were found to have a higher level of C-reactive protein (44, 45). In the ATTICA study, a range of inflammatory markers, such as tumor necrosis factor- $\alpha$ , amyloid A, endothelin 1, homocysteine, advanced glycation products, and elevated WBC counts, were found to be significantly higher in prehypertensives compared to normotensives (46). Recently, Tian et al. investigated the association between specific circulating leukocyte types and BP and found that BP is related to both neutrophils and lymphocytes (47). Kawada et al. showed an independent relationship between neutrophil count and HT (48). Our findings were compatible with these study results.

To our knowledge, this is the first study to show an association between PHT and NLR. Further studies are needed to clarify the role of NLR in PHT patients, especially in relation to biochemical and clinical parameters, before we conclude that NLR may be used as a follow-up marker. This study was limited by a relatively small sample size.

## Conclusion

An association exists between PHT and NLR. NLR measurement, as well as monocyte count, may be used to indicate increased risk of prehypertension.

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Received July 7, 2014.  
Accepted March 8, 2015.