

New inflammatory indicators: association of high eosinophil-to-lymphocyte ratio and low lymphocyte-to-monocyte ratio with smoking

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Abstract

Objective: Smoking has been proven to increase systemic inflammation in previous studies using different biomarkers. The eosinophil-to-lymphocyte ratio (ELR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR) are new indicators of systemic inflammation that are used as predictors of systemic inflammation, morbidity, and mortality associated with many diseases. We investigated the effects of smoking on these inflammatory indicators.

Methods: In total, 616 consecutive smoking healthy subjects and 387 age-matched nonsmoking healthy subjects were enrolled. White blood cell counts (neutrophils, lymphocytes, basophils, eosinophils, and monocytes) were determined by electrical impedance with an automatic blood cell counting device. The ELR, LMR, and NLR were calculated based on these cell counts. Smoking habits of participants were calculated as pack/year.

Results: The NLR and ELR were significantly higher and the LMR was significantly lower in smokers than nonsmokers. The pack-years were positively correlated with the NLR and ELR and negatively correlated with the LMR.

Conclusion: A high NLR and ELR and low LMR are associated with cigarette smoking and may be useful indicators of systemic inflammation activity, even in healthy smokers. Smokers with a high NLR and ELR and low LMR can easily be identified during routine blood analysis and might benefit from preventive treatment.

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Keywords

Cigarette smoking, systemic inflammation, complete blood cell count, biomarkers, eosinophil-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio

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Introduction

Cigarette smoking is a leading cause of morbidity and mortality associated with cardiovascular disease and has been implicated in the pathogenesis of atherosclerosis and thrombotic events.^{1,2} Smoking has been proven to increase systemic inflammation in previous studies using different biomarkers.^{3–5} Smoking has also been shown to increase the leukocyte and eosinophil counts in peripheral blood, although the underlying mechanism remains unknown. Blood test parameters reportedly return to the reference range after 5 years of smoking cessation.⁶ Several studies have shown that various types of white blood cells (WBCs) are damaged by smoking.^{7,8} WBCs are the principal cells affected by inflammation and are considered responsible for undesirable situations in patients with cardiovascular disease. Various WBC types are known as indicators of the inflammatory status.^{9,10} Increased neutrophil, basophil, and eosinophil counts and low lymphocyte counts induced by stress signalize alterations in the immune system.^{11–13}

Several studies have shown that smoking is associated with changes in various hematological parameters such as the neutrophil, lymphocyte, monocyte, and eosinophil counts, all of which are active in inflammation, as well as with the neutrophil-to-lymphocyte ratio (NLR).^{14–16} In addition to these known parameters, the eosinophil-to-lymphocyte ratio (ELR) and lymphocyte-to-monocyte ratio (LMR) have recently been used as new indicators

of systemic inflammation, morbidity, and mortality.^{17–19}

To the best of our knowledge, however, the connection among smoking, the LMR, and the ELR has not been studied. A complete blood cell (CBC) count can be easily and inexpensively performed in all laboratories. Thus, the NLR, LMR, ELR, and various whole blood cell counts can be evaluated by clinicians using a rapid, low-cost method. The present study was performed to analyze the effects of smoking on the following inflammatory indicators: the ELR, LMR, NLR, and several whole blood cell counts.

Methods

Study population

This cross-sectional observational study involved consecutive smoking healthy subjects and age-matched, nonsmoking healthy subjects with no smoking history who were treated at the cardiology outpatient clinics of Dr. Ersin Arslan Education and Research Hospital in Gaziantep, Turkey from June 2017 to August 2018. None of the participants had any systemic diseases or risk factors for atherosclerosis with the exception of hyperlipidemia. Cardiac ischemia and other cardiac pathologies were detected by an exercise stress test and transthoracic echocardiography. Smokers were defined as those who consumed at least one cigarette per day. The number of pack-years was calculated by multiplying

the number of cigarettes smoked with the number of smoked years and then dividing this total by 20. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg and treatment with antihypertensive drugs. Diabetes was defined as treatment with an oral antidiabetic drug and/or insulin or a fasting blood glucose level of ≥ 126 mg/dL. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee (Presidency of R. T. Gaziantep University Ethics Committee). All participants in the study provided written informed consent.

Exclusion criteria

The exclusion criteria in this study were diabetes mellitus, coronary artery disease, hypertension, heart failure, chronic kidney disease, chronic lung disease, connective tissue disease, metabolic syndrome, anemia, thyroid dysfunction, nonsteroidal anti-inflammatory drug use within the previous week, steroid use within the previous 6 months (including steroid creams), upper respiratory tract infection diagnosed within the previous 3 weeks, pregnancy, leukocytosis, leukopenia or any other hematological, biochemical, or serological abnormalities, routine alcohol intake, marijuana intake, consumption of other tobacco products, ex-smokers, and a body mass index of >30 kg/m².

Echocardiography

A Vivid 5 ultrasound system (GE Medical Systems, Milwaukee, WI, USA) was used to perform transthoracic echocardiography. A 2.5-MHz transducer and harmonic imaging were used in accordance with the recommendations of the American Society of Echocardiography. M-mode echocardiography was applied to obtain the diastolic

and systolic diameters of the left ventricle. The Teichholz method was applied to assess the left ventricular ejection fraction.²⁰

Exercise stress test

The Bruce or modified Bruce treadmill protocol was used to perform the stress test (Cardiosis TEPA Exercise Stress Test device; TEPA Medical and Electronic Products Industry and Trade Company, Ankara, Turkey). Bruce treadmill protocols were performed as non-invasive measurements of functional capacity tolerance for exercise and for existence of cardiovascular disorders in participants.²¹

Laboratory measurements

Ante-cubital vein was used to gain 6 mL for full biochemistry and 5 mL for total blood count (CBC) samples following 12 hours of fasting. The blood samples were collected in vacuum tubes filled with 15% K3 ethylene diamine tetraacetic acid as an anticoagulant (Sarstedt, Essen, Belgium). CBC parameters were evaluated using a Sysmex XN-1000 hematology analyzer (Sysmex Europe GmbH, Sysmex Corporation, Hamburg, Germany) according to the manufacturer's instructions. Venous blood samples were taken after a 12-hour fast to measure biochemical parameters using a cobas device (Roche Diagnostics, Basel, Switzerland).

Statistical evaluation

SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was performed to check whether data were normally distributed. The Mann-Whitney U-test was then applied to analyze continuous data with non-normal distributions. Non-normally distributed variables are shown as median (25th–75th percentile). Pearson's correlation test was used for

correlation analyses. All p -values were two-tailed, and $p < 0.05$ was accepted as statistically significant.

Results

In total, 1003 consecutive subjects were initially included. After application of the exclusion criteria, the study population comprised 616 smokers (male, $n = 489$) and 387 nonsmokers (male, $n = 289$) ranging in age from 17 to 70 years. The nonsmoking group exhibited a significantly lower total WBC count ($p < 0.0001$), monocyte count ($p < 0.0001$), eosinophil count ($p < 0.0001$), basophil count ($p < 0.0001$), neutrophil count ($p < 0.0001$), NLR ($p = 0.001$), ELR ($p < 0.0001$), triglyceride

concentration ($p < 0.0001$), low-density lipoprotein cholesterol (LDL-C) concentration ($p = 0.001$), hematocrit ($p < 0.0001$), and hemoglobin ($p < 0.0001$) than the smoking group (Table 1, Figure 1, and Figure 2). However, the nonsmoking group exhibited a significantly higher LMR ($p < 0.0001$) and high-density lipoprotein cholesterol (HDL-C) concentration ($p < 0.0001$) than the smoking group (Table 1 and Figure 3). Positive correlations were found between the pack-years and the total cholesterol concentration ($p = 0.005$), triglyceride concentration ($p < 0.0001$), LDL-C concentration ($p = 0.003$), basophil count ($p < 0.0001$), neutrophil count ($p = 0.030$), eosinophil count ($p < 0.0001$), monocyte count ($p < 0.0001$), NLR

Table 1. Intergroup comparison of demographic data.

| Variable | Smokers ($n = 616$) | Nonsmokers ($n = 387$) | p value |
|--|-----------------------|--------------------------|-----------|
| Age, years | 35.9 (24.0–45.0) | 36.0 (23.0–46.0) | 0.594 |
| Platelets, $\times 10^3/\text{mm}^3$ | 261.8 (223.0–295.0) | 259.0 (218.0–286.0) | 0.185 |
| Mean platelet volume, fL | 10.4 (9.7–11.0) | 10.4 (9.8–11.0) | 0.465 |
| Glucose, mg/dL | 94.5 (86.4–100.0) | 95.4 (89.0–99.0) | 0.29 |
| Triglycerides, mg/dL | 149.4 (91.0–168.0) | 134.1 (75.0–154.0) | <0.0001 |
| LDL cholesterol, mg/dL | 108.0 (87.0–126.0) | 104.1 (82.0–120.0) | 0.001 |
| Total cholesterol, mg/dL | 181.0 (154.0–200.0) | 178.1 (151.2–198.0) | 0.95 |
| HDL cholesterol, mg/dL | 43.4 (42.0–49.0) | 48.6 (40.0–57.0) | <0.0001 |
| Hemoglobin, g/dL | 15.1 (13.9–14.7) | 14.5 (13.3–15.3) | <0.0001 |
| Hematocrit, % | 45.4 (41.6–47.1) | 43.6 (39.9–45.9) | <0.0001 |
| White blood cells, $\times 10^3/\text{mm}^3$ | 7.94 (6.40–8.99) | 7.35 (6.05–8.51) | <0.0001 |
| Neutrophils, $\times 10^3/\text{mm}^3$ | 4.80 (3.57–5.54) | 4.28 (3.25–5.19) | <0.0001 |
| Lymphocytes, $\times 10^3/\text{mm}^3$ | 2.24 (1.83–2.65) | 2.27 (1.86–2.64) | 0.696 |
| Eosinophils, $\times 10^3/\text{mm}^3$ | 0.20 (0.12–0.24) | 0.172 (0.100–0.220) | <0.0001 |
| Basophils, $\times 10^3/\text{mm}^3$ | 0.040 (0.030–0.046) | 0.343 (0.200–0.400) | <0.0001 |
| Monocytes, $\times 10^3/\text{mm}^3$ | 0.65 (0.53–0.77) | 0.599 (0.437–0.660) | <0.0001 |
| NLR, % | 2.42 (1.52–2.82) | 2.07 (1.43–2.41) | 0.001 |
| LMR, % | 3.62 (2.68–4.45) | 4.31 (3.02–5.13) | <0.0001 |
| ELR, % | 0.10 (0.50–1.12) | 0.78 (0.42–0.100) | <0.0001 |
| Urea, mg/dL | 27.9 (22.3–33.0) | 28.0 (22.0–33.0) | 0.750 |
| Creatinine, mg/dL | 0.69 (0.60–0.87) | 0.70 (0.61–0.86) | 0.674 |
| Sodium, mmol/L | 139.4 (138.0–142.0) | 139.8 (138.0–142.0) | 0.157 |
| Potassium, meq/L | 4.31 (4.00–4.58) | 4.29 (4.00–4.56) | 0.738 |
| Calcium, mg/dL | 9.64 (9.10–9.77) | 9.48 (9.14–9.80) | 0.269 |

Data are presented as median (25th–75th percentile). LDL, low-density lipoprotein; HDL, high-density lipoprotein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; ELR, eosinophil-to-lymphocyte ratio.

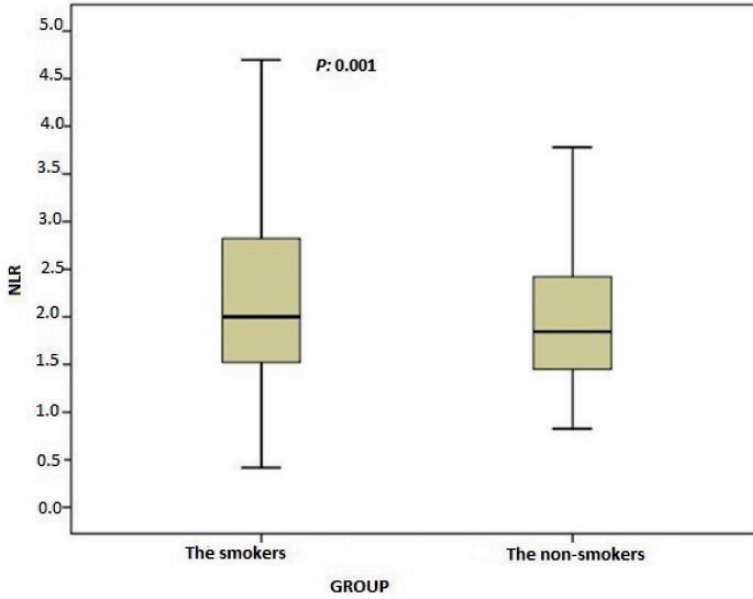


Figure 1. Comparison of neutrophil-to-lymphocyte ratio (NLR) between the smokers and nonsmokers. The box-whisker plots show the NLR for the smokers and nonsmokers. The heavy black horizontal lines for each group represent the means, the extremities of the box are the 25th and 75th percentiles, and the error bars are the minimum and maximum outliers.

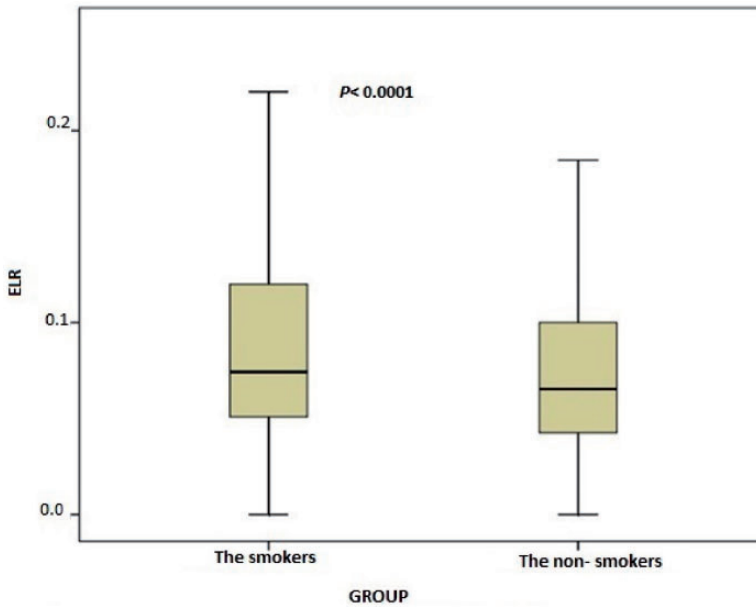


Figure 2. Comparison of eosinophil-to-lymphocyte ratio (ELR) between the smokers and nonsmokers. The box-whisker plots show the ELR for the smokers and nonsmokers. The heavy black horizontal lines for each group represent the means, the extremities of the box are the 25th and 75th percentiles, and the error bars are the minimum and maximum outliers.

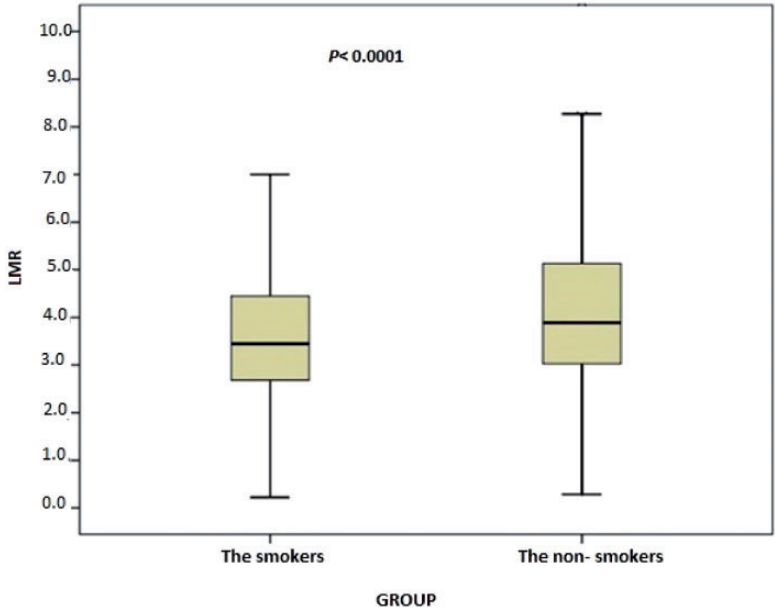


Figure 3. Comparison of lymphocyte-to-monocyte ratio (LMR) between the smokers and nonsmokers. The box-whisker plots show the LMR for the smokers and non-smokers. The heavy black horizontal lines for each group represent the means, the extremities of the box are the 25th and 75th percentiles, and the error bars are the minimum and maximum outliers.

($p < 0.0001$), and ELR ($p < 0.0001$) (Table 2, Figures 3–5). Negative correlations were found between the pack-years and the HDL-C concentration ($p = 0.009$) and LMR ($p < 0.0001$) (Table 2, Figure 6). No statistically significant differences were found in hyperlipidemia, age, or other investigated laboratory parameters between the smokers and nonsmokers (Table 1).

Discussion

This study was performed to calculate the LMR, NLR, and ELR (recently established inflammatory, morbidity, and mortality markers) in healthy smokers and determine whether a correlation exists between smoking and these values. This study revealed that the ELR and NLR were higher in smokers than nonsmokers with a weak and positive correlation with pack-years and that the LMR was lower in smokers

Table 2. Pearson correlation analysis between smoking (pack-years) and the NLR, LMR, ELR, and various laboratory parameters.

| | Pack-years | |
|--|------------|---------|
| | r | p |
| Triglycerides, mg/dL | 0.149 | <0.0001 |
| Total cholesterol, mg/dL | 0.118 | 0.005 |
| LDL-C, mg/dL | 0.126 | 0.003 |
| HDL-C, mg/dL | -0.111 | 0.009 |
| WBC count, $\times 10^3/\text{mm}^3$ | 0.096 | 0.018 |
| Neutrophils, $\times 10^3/\text{mm}^3$ | 0.087 | 0.030 |
| Lymphocytes, $\times 10^3/\text{mm}^3$ | -0.049 | 0.226 |
| Monocytes, $\times 10^3/\text{mm}^3$ | 0.178 | <0.0001 |
| Eosinophils, $\times 10^3/\text{mm}^3$ | 0.311 | <0.0001 |
| Basophils, $\times 10^3/\text{mm}^3$ | 0.158 | <0.0001 |
| NLR, % | 0.185 | <0.0001 |
| LMR, % | -0.151 | <0.0001 |
| ELR, % | 0.296 | <0.0001 |

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; ELR, eosinophil-to-lymphocyte ratio.

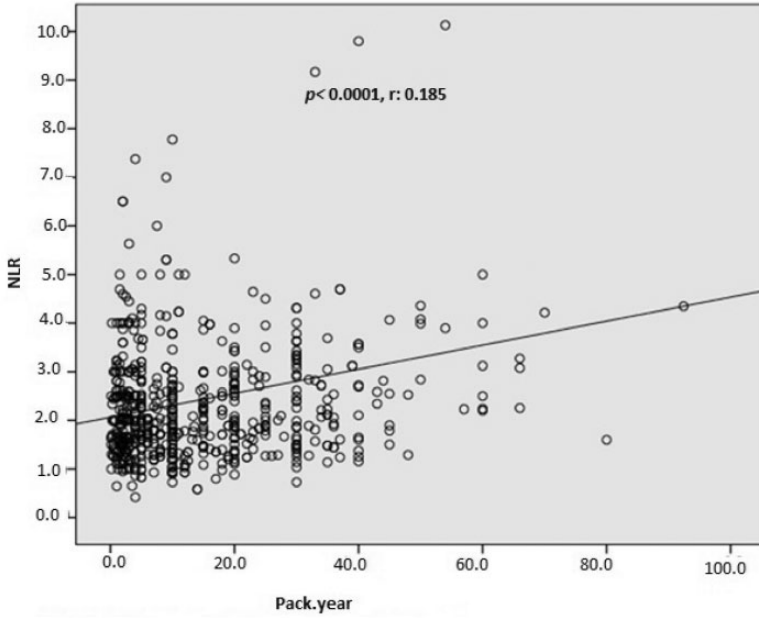


Figure 4. Pearson's correlation analysis between the neutrophil-to-lymphocyte ratio (NLR) and pack-years.

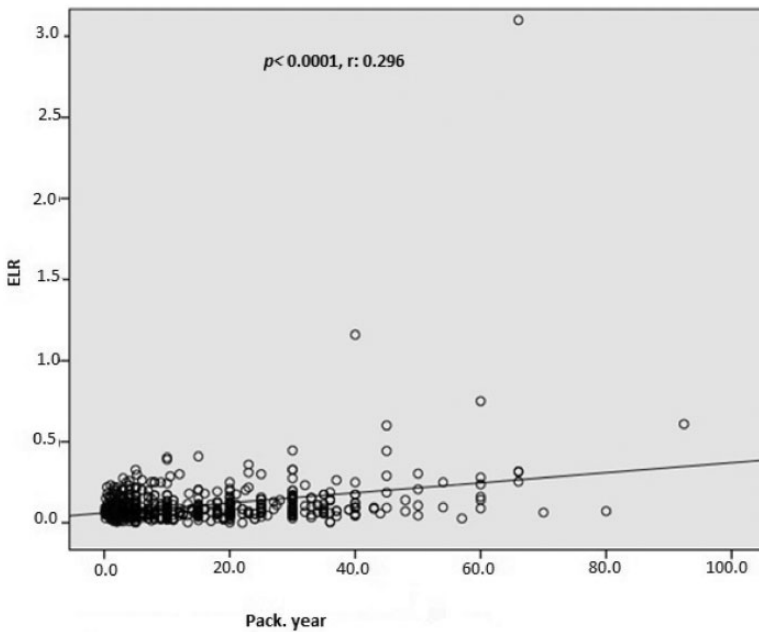


Figure 5. Pearson's correlation analysis between the eosinophil-to-lymphocyte ratio (ELR) and pack-years.

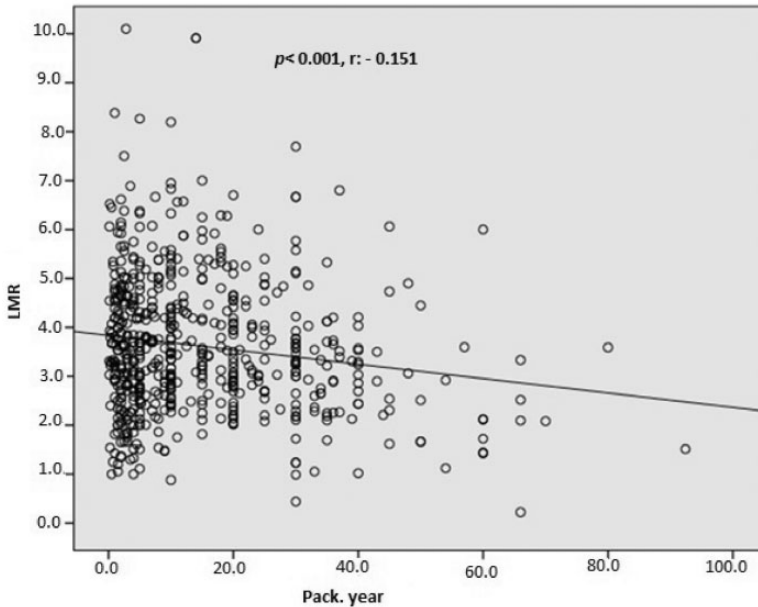


Figure 6. Pearson's correlation analysis between the lymphocyte-to-monocyte ratio (LMR) and pack-years.

than nonsmokers with a weak and negative correlation with pack-years (Tables 1 and 2; Figures 1–6). These data indicate a possible association between a high WBC count, monocyte count, eosinophil count, basophil count, neutrophil count, NLR, and ELR and a low LMR with existing systemic inflammation in the pathophysiology of cigarette smoking. Our results also suggest a relationship between high hemoglobin and hematocrit concentrations and dyslipidemia in cigarette smokers.

Smoking causes chronic systemic inflammation even in individuals without additional health problems, and various biomarkers have been used to detect systemic inflammation in these individuals.^{3–5,22,23} Several recent studies have focused on the NLR as a systemic inflammatory marker in smokers.^{11,14} Although many studies have been performed to assess the correlations of CBC parameters with smoking, we are unaware of any

studies evaluating the effect of smoking on the LMR and ELR.^{15,24,25}

Lymphocytes, neutrophils, eosinophils, and monocytes are associated with the immune response and inflammation. Leukopenia is associated with cardiovascular adverse events.^{26,27} Additionally, elevated monocyte, neutrophil, and eosinophil counts are associated with cardiovascular disease. Both high monocyte, eosinophil, and neutrophil counts and a low lymphocyte count reflect systemic inflammation and physiologic stress and contribute to the development of cardiovascular disease.^{28–33}

The relationships between the LMR, ELR, and NLR and adverse events in patients with oncological and cardiac diseases have been revealed in several recent studies. The NLR, ELR, and LMR, which are easily calculated from the CBC count, have been shown to be potential diagnostic and prognostic indicators of some

malignant subtypes and cardiac diseases.^{17,19,30,31,34-38}

Previous studies have also shown that the total WBC, neutrophil, monocyte, lymphocyte, basophil, and eosinophil counts, which are hematologic parameters, play important roles in the inflammatory process; these parameters are also used as indicators of inflammation and are closely related to smoking.^{11,39} Although many studies have been performed to explore the effects of smoking on hemogram parameters, few have focused on how smoking affects the NLR. Moreover, to the best of our knowledge, the relationship between smoking and the LMR and ELR has not been previously studied.

Similar to previously conducted studies, we found that while the WBC, neutrophil, eosinophil, and basophil counts were significantly higher in the smokers than nonsmokers, the lymphocyte count was not significantly different between the two groups.^{11,39} Additionally, we determined that the NLR and ELR were significantly higher in the smokers than nonsmokers (Table 1). However, the LMR was lower in the smokers than nonsmokers (Table 1). Although a positive and significant correlation was detected between the pack-years and the NLR and ELR (Table 2; Figures 3-5) and a negative and significant correlation was detected between the pack-years and the LMR, we found that these correlations were weak (Table 2, Figure 6). This result might be explained by the subjects included in the study being selected from among healthy individuals and being relatively young. In addition, three parameters (triglyceride, LDL-C, and HDL-C concentrations) were remarkably different between the two groups (Table 1). These data are in agreement with previous studies showing higher serum triglyceride and LDL-C concentrations along with a lower plasma HDL-C concentration in smokers than nonsmokers.⁴⁰

Recent researches have clearly established that smoking causes an increase in cardiovascular events, morbidity, and mortality.⁴¹⁻⁴³ Many studies have shown that the LMR, ELR, and NLR are closely related to systemic inflammation, morbidity, and mortality.^{17,19,34,35} The higher ELR and NLR and lower LMR in the smokers of the present study, even smokers with no health problems, may serve as indicators of systemic inflammation and many cardiovascular and other diseases caused by systemic inflammation.

Limitations

Second-hand smoking and exposure to environmental pollutants may increase systemic inflammation and affect the blood levels of biomarkers of systemic inflammation.⁴⁴⁻⁴⁷ In addition, studies have shown that decreasing the energy intake and increasing the physical activity level may be effective therapies for reducing overall inflammation; therefore, physical inactivity contributes to an enhanced proinflammatory burden.^{48,49} In the present study, second-hand smoking and environmental pollution exposure could not be controlled, and the participants were not questioned regarding their physical activities. The obtained data should thus be interpreted with caution.

Conclusions

The ELR, NLR, and LMR are indicators of systemic inflammation and are used as predictors of morbidity and mortality associated with many diseases. Both healthy and clinically asymptomatic smokers may either develop inflammatory conditions or undergo worsening of their existing inflammatory conditions by smoking. The NLR, LMR, and ELR are simple, cost-effective parameters that can be used to predict systemic inflammatory responses in smokers.

The detection of a high NLR and ELR and a low LMR by a simple CBC count during routine laboratory testing might help to intercept the development of inflammation. For this reason, these three indices should be given more attention when examining smokers to enhance both prevention and intervention of inflammatory conditions.

Contributorship statement

Study conception: Çekici Y, Yılmaz M, Seçen Ö.

Study design: Çekici Y, Yılmaz M, Seçen Ö.

Data acquisition: Çekici Y.

Data analysis: Yılmaz M, Seçen Ö.

Data interpretation: Çekici Y, Yılmaz M, Seçen Ö.

Writing of the manuscript: Çekici Y, Yılmaz M, Seçen Ö.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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