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The impact of smoking on inflammation indices: A cross-sectional study

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Abstract

We aim to investigate the association between smoking and systemic inflammation index (SII), the platelet-to-lymphocyte ratio (PLR), and the neutrophil-to-lymphocyte ratio (NLR) which are derivated from whole blood count. A total of 188 individuals who admitted to organ transplant outpatient polyclinics as donor candidates were included in this retrospective cross-sectional study. Donor candidates were divided into two groups; smokers and non-smokers. SII, PLR, and NLR were formulated from their hemogram during the preparation for donation. Serum C-reactive protein, uric acid, and creatinine levels were also compared between the two groups. P<0.05 was assumed as statistically significant. Seventy-five of 188 individuals (39.9%) were smokers. Smokers were older compared to nonsmokers and the mean smoking longevity was 21.14±12.92 years. SII, NLR, PLR, and CRP levels were higher in the smokers (p=0.020, p=<0.001, p=<0.001, and p=0.038, respectively). Smoking longevity had an impact on SII, PLR, NLR, and CRP (all p<0.001). Serum creatinine (and estimated glomerular filtration rate) had correlated with smoking and regression analysis indicated smoking was associated with high levels of serum creatinine (r=0.323, p<0.001, and r2=104). Smoking was a predictor for high levels of uric acid (p<0.001, r2=0.093). Smoking is associated with an increased inflammation status driven by changes in the immune response. The basic inflammation indices SII, NLR, and PLR, which can be derivated from whole blood count, and additionally CRP may be useful in the assessment of the inflammation status of smokers.

Keywords: Smoking, SII, NLR, PLR, CRP, inflammation

Introduction

Smoking is the second most common and preventable cause of diseases around the World. Smoking is associated with heart disease, stroke, and chronic lung disease, and if the trend of smoking remains similar in the near future to today, it will cause death to one in six people by 2030 [1].

The pieces of evidence obtained from previous studies have revealed that smoking is associated with elevated inflammatory biomarkers, C-reactive protein, interleukin-6, and interleukin-1β, tumor necrosis factor-α, interleukin-8, and decrease in anti-inflammatory interleukin-10 [2,3]. Additionally, smoking-induced inflammation has been found predictive of future cancer development [4,5].

The impact of smoking on innate and adaptive immunity can be described by laboratory measurements of various cytokines, however, those inflammatory biomarkers are not feasible for the risk assessment of inflammation for most centers since they are expensive and require an enhanced laboratory capacity [6,7]. A recent study demonstrated blood leukocyte, lymphocyte, and neutrophil counts elevated in smokers compared to non-smokers

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in monozygotic twins [8].

The systemic inflammation index (SII), the platelet-to-lymphocyte ratio (PLR), and the neutrophil-to-lymphocyte ratio (NLR) are the most common indices used to evaluate inflammatory status in various diseases such as cancer, rheumatological diseases, critically ill patients, and obesity [9-12]. The association between these indices and smoking has been scarcely evaluated in the literature.

In this study, we aim to assess the relationship between smoking and SII, NLR, and PLR in a large group of individuals who applied to our outpatient polyclinics to be kidney donors.

Material and Methods

Study Design

This single-center, retrospective, and cross-sectional study was conducted between 2021 and 2022 years in Medicana hospital organ transplantation outpatient polyclinic. The donor candidates who were accepted for donation following an in-depth evaluation were enrolled in the study. The individuals were divided into two groups; smokers and non-smokers. The participants' clinical and laboratory features, the longevity of smoking, and daily cigarette (package) use were noted.

Inclusion criteria were; > 20 years old, absence of recent or active inflammation, absence of chronic obstructive lung disease and coronary heart disease hindering to being a donor, and not being under pharmacotherapy which impacts inflammatory status. Participants with diabetes mellitus and hypertensive on polypharmacy were also excluded. Hypertensive individuals on mono antihypertensive therapy and with blood pressure < 140 mmHg systolic and <90 mmHg diastolic blood pressure are accepted for donation in our center.

Clinical and Laboratory Measurements

Body mass index (BMI) is calculated as follows; weight (kg)/ height (m) square (kg/m²).

The inflammation indices were calculated as follows; SII= absolute peripheral neutrophil count (x10³/ µL) x absolute peripheral platelet count (x10⁹/ µL) / absolute lymphocyte count, PLR= absolute peripheral platelet count (x10³/ µL) / absolute lymphocyte count, and NLR= absolute peripheral granulocyte count (x10³/ µL) / absolute lymphocyte count. Serum CRP level was measured by nephelometric assay (Behring Nephelometer Analyzer, Marburg, Germany). Serum creatinine, uric acid, and whole blood counts were studied. estimated glomerular filtration rates were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine formula (2009) using a website (www.mdrd.com).

Ethical Approval

This study was carried out in accordance with the Declaration of Helsinki. All participants have been informed. Consent of all participants was obtained. The study was approved by the Medicana Hospital ethics committee (Date: 01.12.2021, Approval number: BŞH-2021/24).

Statistical Analysis

A statistical package program for social sciences (SPSS for Windows version 15.0, IBM Corp., Armonk, NY, USA) was used to assess data. Kolmogorov-Smirnov test and skewness and kurtosis ranges were used to demonstrate the normality of continuous variables. The parametric and nonparametric descriptive data were given by mean ± standard deviation and median values (minimum and maximum), respectively. The Pearson Chi-Square test was utilized in the comparison of the categorical variables. The inflammatory indices SII, NLR, PLR, and CRP were compared between the two groups by using the Independent T-test. Pearson's correlation analyses were performed to demonstrate the correlation between the longevity of smoking and the inflammation indices. Linear regression analysis was used to demonstrate the interaction of study parameters. The ROC curve analysis was used to show the AUC, sensitivity, and specificity of the cut-off levels. Two-tailed p values <0.05 was accepted as statistically significant in the 95% confidence interval.

Results

A total of 188 participants were evaluated. 54.8% of those were males (n=103) and 45.2% were females (n=45.2). 75 of 188 (39.9%) individuals were smokers. The clinical and laboratory features of participants were given in Table 1.

Table 1. The clinical and laboratory features of participants

	N=188
Age, years	46.73±14.34
Sex, male/female, n, %	103(54.8%)/85(45.2)
BMI kg/m²	26.70±3.27
Smoker, n (yes/no)	61(32.4%)/127(67.6%)
Smoking duration, years	21.14±12.92
Hypertension (yes/no)	80/108
Hypertension longevity, year	9.2
Hypertensive, n (yes/no)	80(42.6%)/108(57.4%)
Serum creatinine, mg/dl	0.86±0.14
eGFR, ml/min/1.73 m²	93.77±18.13
Uric acid, mg/dl	5.77±1.21
Leukocytes, 10³ /µL	7371±1882
Lymphocytes, 10³ / µL	1544±1572
Platelets, 10³ / µL	263.547±88.210
SII	4.81±1.09
NLR	3.34±1.00
PLR	174.62±62.40
CRP, mg/L	0.82±0.62

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Table 2. Data of smokers compared to non-smokers

	Smokers, n=75	Non-smokers, n=113	P value
Age, years	51.90±14.45	44.25±13.66	**0.001**
Sex, male/female, n, %	13 (17.3%) / 62 (82.7%)	41 (36.3%) / 72 (63.7%)	**<0.001**
BMI kg/m²	26.76±2.49	26.68±3.60	0.875
Hypertension (yes/no), %	45 (60%) / 30 (40%)	35 (30.9%) / 78 (69.1%)	**<0.001**
Serum creatinine, mg/dl	0.95±0.13	0.81±0.13	**<0.001**
eGFR, ml/min/1.73 m²	87.04±15.62	97.00±18.43	**<0.001**
Uric acid, mg/dl	6.52±1.06	5.41±1.10	**<0.001**
Leukocytes, 10^3 / µL	7839±2235	7146±1649	**0.018**
Lymphocytes, 10^3 / µL	1556±262	1539±312	0.704
Platelets, 10^3 / µL	320.540±87.167	236.173±74.846	**<0.001**
SII	5.08±1.44	4.69±0.85	**0.020**
NLR	3.60±1.35	3.21±0.75	**<0.001**
PLR	208.91±62.71	158.15±55.35	**<0.001**
CRP, mg/L	0.98±0.66	0.75±0.60	**0.038**

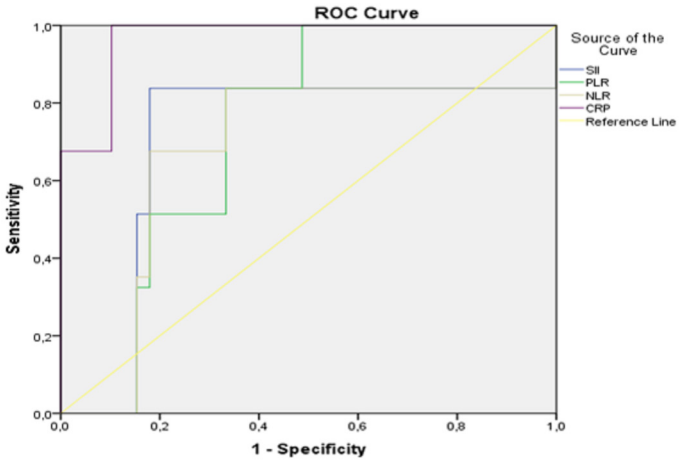

Figure 1. Roc curve diagram

Smokers were older and hypertensive compared to non-smokers (p=0.001 and p<0.001, respectively) (Table 2). However, linear regression analysis showed no impact of age on being a smoker (p= 0.166, r=0.101, and r2=0.10). Smoking had an impact on being hypertensive and has exhibited a positive correlation with HT (p<0.001, r2=0.083, and r=0.287, respectively). Serum creatinine (and eGFR) had correlated with smoking and regression analysis indicated smoking was associated with high levels of serum creatinine (r=0.323, p<0.001, and r2=104). A multivariate analysis model including HT, age, and being a smoker revealed that HT was not associated with higher sCr (p=0.066) while age and being a smoker had an impact on high sCr (p<0.001 for both parameters). Smoking was a predictor for high levels of uric acid (p<0.001, r2=0.093, and r=0.305), however, smoking had no impact on SII, NLR, and CRP (p=0.189, p=0.088, and p=0.075), except PLR (0.006). Although smoking longevity had an impact on SII, PLR, NLR, and CRP (p<0.001 and r2=0.253, p<0.001 and r2=0.231, p<0.001 and r2=0.251, and p<0.001 and r2=0.253, respectively). The sensitivity, specificity, and AUC of cut-offs of SII, NLR, PLR, and CRP for at least 20 years of smoking were demonstrated with the ROC curve diagram (Figure 1) and Table 3. Pearson's Chi-Square test revealed that at least 20 years of smoking was predictive for the cut-off values of SII, PLR, NLR, and CRP (p=0.002, p=0.001, p<0.001, nd p<0.001, respectively).

Table 3. The cut-off values of SII, PLR, NLR, and CRP and their sensitivity and specificity given at least 20 years of smoking

20 years of Smoking	Sensitivity	Specificity	AUC	P value	95% CI	
SII=5.26	83.8%	82.2%	.701	**.003**	.563	.838
PLR=187.930	84.0%	67.1%	.729	**.001**	.608	.850
NLR=3.23	83.8%	66.6%	.672	**.010**	.536	.807
CRP=0.94	100%	90.1%	.967	**.000**	.931	1.000

Discussion

Smoking affects both cellular and humoral immune responses which are associated with chronic inflammation at a systemic level. The alteration induced by smoking can be demonstrated by the changes in serum cytokine levels such as TNF-α, IL-1β,

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IL-6, IL-8, IL-10, and acute phase reactant CRP. This study indicates the systemic inflammation indices SII, NLR, and PLR reveal significant changes in smokers, and these alterations are associated with increased smoking duration.

The human immune system mobilizes a broad repertoire of innate and adaptive responses to protect against harmful agents. Smoking exhibits harmful impacts on both innate and adaptive immunity and expresses two features in the regulation of immunity; I)exacerbation of pathogenic responses, or II) attenuation of defensive immunity. T helper cells (Th1/Th2/Th17), CD4+ and CD25+regulatory T cells, B cells, and memory T/B lymphocytes are the adaptive immune cells, and leukocytes and NK cells are the innate immune cells are being affected by smoking [13]. Although smoking causes local and systemic inflammation, exposure to smoke also inhibits the inflammatory defense response of humans to various pathogens which is an additional source of acute and chronic inflammation [14]. However, recognizing the inflammation with practical methods which are available in every healthcare center, cheap and objective is the interest of the searches. Elisia reported in their study that red blood cells, hematocrits, hemoglobin levels, MCV, MCH, MCHC, platelet, and RDW levels were elevated while NK cells and T regulatory cells decreased in smokers. Additionally, total leukocytes were significantly higher, driven by increases in granulocytes and monocytes [15]. There are pieces of evidence demonstrating that the innate immune cells become more active than adaptive immune cells in smokers [8,15,16]. Given all, the use of blood cell ratios to create inflammation indices may be useful. According to our knowledge, this study demonstrates for the first time that SII, PLR, and NLR are elevated in smokers. The elevation in these parameters correlates with smoking longevity. The sensitivities of the cut-off values for SII (5.26), NLR (3.23), PLR (187.930 103/µL), and CRP (0.94 mg/dl) are more than 80% in people who have smoked for at least 20 years. The smokers were hypertensive, however, the smoking duration was apparently shorter than the smoking duration. This data supports the previous studies suggesting that blood pressure elevation in smokers or hypertensive smokers are more likely to develop severe forms of hypertension, including malignant and renovascular hypertension, an effect likely due to accelerated atherosclerosis [17-19]. CRP levels have been found elevated in smokers as we report in this study [20,21]. Following a 2-year smoking the sensitivity of and specificity of CRP for 0.9 mg/dl were 100% and 90.1%, respectively.

Uric acid has been considered a potential risk factor for the development, progression, and mortality of cardiovascular diseases, chronic kidney diseases, and autoimmune or inflammatory disorders [22,23]. However, the previous studies relevant to the association of smoking and uric acid is not clear [24,25]. This study shows uric acid level is higher among smokers. The relatively longer smoking duration compared to the previous studies, the higher numbers of hypertensive smokers and the higher percentage of males in smoker groups may have an impact on the results. Obesity and higher BMI are associated with increased systemic and local inflammation in humans [26,27]. However, BMI was similar between the two groups.

The adverse impact of active and passive smoking on renal function previously has been described [28-30]. Additionally, the association of longer smoking duration with a higher risk of CKD progression is evident, particularly in patients with eGFR <45 mL/min/1.73 m2 [31]. Similar to previous reports, our study exhibits that smoking is associated with high levels of sCr and low eGFR and this association is independent of accompanying HT. However, age was also strongly associated with higher sCr.

The major limitation of the study is the single measurement of inflammation indices. A longitudinal study with repeated measurement of inflammation indices will be more valuable. Additionally, despite the maximum effort to exclude the confounding factors, the environmental factors and the stressor nature of being an organ donor candidate may have effects on immune cells.

Conclusion

Smoking has been found to be associated with systemic inflammation indices in this well-described cohort. SII, NLR, PLR, and CRP are cheap, repeatable, and effective tools to be used in the assessment of inflammation in smokers. The impact of smoking on inflammation indices correlates with smoking longevity.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Ethics committee approval was obtained with the number of BŞH-2021/24 dated 01.12.2021.

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