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Original Article

Leukocyte and lipid-based inflammation indices as predictors of asymptomatic organ damage in treatment-naive and newly diagnosed hypertension patients

Yeni tanı almış tedavi almamış hipertansiyonlu hastalarda asemptomatik organ hasarının öngörücüsü olarak lökosit ve lipid bazlı enflamasyon indeksleri

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ABSTRACT

Introduction: Low-grade inflammation is known to facilitate the development of hypertensive organ damage. This study aimed to investigate the relationship between the leukocyte and lipid-based inflammation indices and asymptomatic organ damage (AOD) in treatment-naive and newly diagnosed hypertension patients (TNNDH).
Methods: The study included 200 patients with TNNDH who are treating by the Cardiology Clinic and 100 healthy controls. Left venriculer mass index (LVMI) of >95 g/m^2 in women and >115 g/m^2 in men, and carotis intima media thickness (CIMT) of >0.9 mm or presence of plaque in the carotid artery and microalbuminuria of >30 mg/day were evaluated as AOD indicators. Platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), systemic immune-inflammation index (SII), monocyte to HDL ratio (MHR), and atherogenic index of plasma (AIP) levels were calculated based on the complete blood count.
Results: Positive correlations were found between all inflammation indices and AOD indicators. AOD was detected in 66.7% of the TNNDH patients. The mean PLR (143.0±37.9 vs. 138.0±36.2; p<0.05), mean NLR (2.1±0.5 vs. 1.8±0.5; p<0.05), mean SII (608.5±125.6 vs. 462.9±60.7; p<0.05) and mean AIP (0.7±0.2 vs. 0.5±0.2; p<0.05) levels were higher in the AOD group. Increasing SII and AIP levels were independent predictors of AOD. SII had superior diagnostic discrimination compared to other leukocyte and lipid-based inflammatory indices in predicting AOD (AUC=0.872; p<0.001).
Conclusion: High SII and API levels are independent predictors of AOD. However, SII exhibits superior diagnostic performance in discrimination of AOD. SII can be a useful screening tool in detecting AOD in HDTND patients.

Keywords: Atherosclerosis, end organ damage, hypertension, inflammation index

ÖZ

Giriş: Düşük dereceli enflamasyonun hipertansif organ hasarının gelişimini kolaylaştırdığı bilinmektedir. Bu çalışma, yeni tanı almış tedavi görmemiş hipertansiyonu (TNNDH) olan hastalarda lökosit ve lipid bazlı enflamasyon indeksleri ile asemptomatik organ hasarı (AOD) arasındaki ilişkiyi araştırmayı amaçlamıştır.
Yöntem ve Gereçler: Çalışmaya Kardiyoloji Kliniğinde takipli TNNDH'li 200 hasta ve 100 sağlıklı kontrol dahil edildi. Kadınlarda LVMI >95 g/m^2 ve erkeklerde LVMI >115 g/m^2 ve CIMT >0.9 mm veya karotiste plak varlığı ve mikroalbüminüri >30 mg/gün AOD göstergeleri olarak değerlendirildi. Tam kan sayımından trombosit/lenfosit oranı (PLR), nötrofil/lenfosit oranı (NLR), sistemik immün-enflamasyon indeksi (SII), monosit/HDL oranı (MHR), aterojenik plazma indeksi (AIP) seviyeleri hesaplandı.
Bulgular: Tüm enflamasyon indeksleri ile AOD göstergeleri arasında pozitif korelasyonlar bulundu. TNNDH hastalarının %66.7'sinde AOD tespit edildi. Ortalama PLR (143.0±37.9 - 138.0±36.2; p<0.05), ortalama NLR (2.1±0.5 - 1.8±0.5; p<0.05), ortalama SII (608.5±125.6 - 462.9±60.7; p<0.05)) ve ortalama AIP (0,7±0,2'ye karşı 0,5±0,2; p<0,05) seviyeleri AOD grubunda daha yüksekti. Artan SII ve AIP seviyeleri, AOD'nin bağımsız

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prediktörü idi. SII, AOD'yi öngörmede diğer lökosit ve lipid bazlı enflamatuar indekslere kıyasla daha üstün tanısal ayrımcılığa sahipti (AUC=0,872; p<0,001).
Sonuç: Yüksek SII ve API seviyeleri, AOD varlığının bağımsız öngörücüleridir. Bununla birlikte, SII, AOD'nin ayırt edilmesinde üstün tanısal performans sergiler. SII, HDTND hastalarında AOD'yi saptamada yararlı bir tarama aracı olabilir.

Anahtar kelimeler: Ateroskleroz, uç organ hasarı, hipertansiyon, enflamasyon indeksi

INTRODUCTION

Hypertension (HTN), which has an increasing prevalence globally, is an important risk factor for morbidity and mortality (1). Late diagnosis of HTN, which has an asymptomatic nature, may result in the development of asymptomatic organ damage (AOD) (2). High blood pressure, which is involved in the development or acceleration of atherosclerosis, can cause cardiac and vascular tissue damages. This is suggested to be an important mechanism underlying the pathology of AOD (3). Since the progression of AOD may result in organ dysfunction, the evaluation of AOD at the first hospital admission of these patients is important for prognosis (4).

High blood pressure plays a role in increasing oxidative stress and reactive oxygen species (5). Atherogenic lipids play roles in cellular dysfunction and cause low-grade inflammation in endothelial cells (6). These factors cause damage to endothelial tissues and result in an inflammatory response (7). In the inflammatory microenvironment, high-density lipoprotein (HDL) undergoes oxidation. HDL is also involved in the proliferation and differentiation of progenitor cells in leukocytes (8). Leukocytes are important indicators of circulating immune-inflammatory cells. They can accelerate the atherosclerotic process due to increased inflammation. In experimental studies of HTN, the migration of T cells to the kidneys and endothelial tissues was associated with organ damage (9,10). These findings suggest that atherogenic lipids and the related immune system-mediated inflammatory response have important roles in hypertensive organ damage.

Recent studies have suggested that leukocyte or lipid-based inflammation indices may be potential screening tools for target organ damage in patients with HTN. However, we could not find any studies investigating the diagnostic performance superiority of leukocyte and lipid-based inflammation indices in patients with newly diagnosed treatment-naive HTN (TNNDH). Therefore, this study aimed to investigate the relationship between leukocyte and lipid-based inflammation indices and AOD in TNNDH.

MATERIALS AND METHODS

This study has a single-center retrospective design. Patients who applied to Cardiology Clinic in Istanbul Research and Training Hospital between January 2018 to January 2021 were evaluated. This study was approved by the local ethics committee (Decision Date/No: 01.07.2022/224).

Study population

The study included 200 patients with TNNDH who are treating by the Cardiology Clinic and 100 healthy controls. The control group consisted of healthy individuals who applied to the clinic for a check-up and did not have any chronic diseases and were not on drugs.

Previously known or documented diagnosis of primary or secondary HTN, obesity, smoking and alcohol use, documented coronary artery disease, acute or chronic kidney disease, heart failure, liver diseases, diabetes mellitus, rheumatic diseases, malignancy, active or chronic infection, peripheral arterial disease, cerebrovascular disease, nephrotic-level proteinuria, and the use of antioxidant substances or lipid drugs were exclusion criteria.

Body mass index (BMI) was calculated as follows: body weight (kg) / height^2 (m^2). Microalbuminuria of >30 mg/day or proteinuria of >150 mg/day, left ventricular mass index (LVMI) of >95 g/m^2

in women and >115 g/m^2 in men, and carotid intima-media thickness (CIMT) of >0.9 mm or presence of plaque in the carotid were evaluated as AOD indicators (11). Patients with any of these indicators were identified as AOD (+).

Biochemical parameters

Fasting laboratory parameters were measured for the hospital admission. Lipid parameters (by enzymatic colorimetric methods), and microalbuminuria in 24 hours (by turbidimetric methods) were performed with a Hitachi Modular P800 autoanalyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Erythrocytes and thrombocytes were performed by impedance (resistance) method, leukocytes were measured by optical laser scattering (light scattering), and other complete blood count parameters were measured with a Sysmex XE 2100 hematology analyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Hemoglobin was measured photometrically. The leukocyte and lipid-based inflammation indices were calculated as follows: SII = neutrophil count × platelet count / lymphocyte count, PLR = platelet count / lymphocyte count, NLR = neutrophil count / lymphocyte count, MHR = monocyte count / HDL value, AIP = log(triglyceride/HDL) value.

Blood pressure measurement

Resting for 5 minutes after hospital admission, all patients underwent 3 different BP measurements at 5-minute intervals and their average was taken. BP measurements were made with an Omron M3 automatic sphygmomanometer (Omron Healthcare, Tokyo, Japan). The diagnosis of hypertension was evaluated according to the 2018 ESC criteria (12). HTN was defined as systolic BP (SBP) of ≥140 mmHg and diastolic BP (DBP) of ≥90 mmHg.

Echocardiographic examination

Echocardiographic imaging was performed by a cardiologist blinded to the study using an echocardiography device (2.5 MHz transducer, Vivid 7, GE-Vingmed Ultrasound AS, Horten, Norway). Left ventricular mass was computed with the Devereux formula via 2D echocardiographic measurements. The Devereux formula of LVM = $1.04 \times [(IVST + PWT + LVDd)^3 - (LVDd)^3] - 13.6$ was used and was indexed to body surface area. LVMI of >95 g/m^2 in women and >115 g/m^2 in men was evaluated as an indicator of left ventricular hypertrophy.

Carotid ultrasonography

CIMT was performed with patients in supine position and both hands under the head. CIMT values were measured with a high-resolution B-mode device (Logiq 7, GE Med Inc., Chicago, IL, USA) by a radiologist blinded to the clinical status of the patients. All measurements were taken from the right and left main carotid arteries using a linear probe with an automatic system. Measurements were performed at 3 points: the right carotid artery branches from the brachiocephalic trunk, the left carotid arteries from the aorta at 2 cm away, and the bifurcation of the internal carotid arteries. Longitudinal measurements were performed from distances of media-adventitia echogenicity and vessel lumen echogenicity. CIMT was calculated by taking the average of 3 measurements made for each carotid artery.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 26 for Windows (IBM Corp., Armonk, NY, USA). The extent to which the data followed a normal distribution was evaluated using the Kolmogorov–Smirnov test. Numerical variables with and without normal distribution were plotted as mean ± standard deviation and median (25th and 75th interquartile range (IQR)), respectively. Numerical and percentile values of categorical variables were presented. Correlations between numerical parameters were analyzed via Pearson and Spearman correlation analysis. Chi-square, Yates correction, and Fisher exact tests were used for the comparison of categorical data. The Student t-test or Mann–Whitney U test were

used for the comparison of numerical variables between two groups, and ANOVA (post hoc: Bonferroni test) or the Kruskal–Wallis H test (post hoc: Dunn test) were used for the comparisons made among the three groups according to the distribution of normality. Stepwise multivariable logistic regression analysis was used to predict AOD. Diagnostic performance assessment of the inflammation indices was performed by ROC curve analysis. The optimal threshold value of the inflammation indices in predicting AOD was determined by the Youden index method. Values of $p<0.05$ were considered to be significant in statistical analyses.

RESULTS

Hypertensive patients with a mean age of 51.5±11.4 years and who were mostly female (65%) were included in the study. Demographic characteristics were similar in the control and TNNDH group ($p>0.05$). The levels of AOD indicators were higher in the TNNDH group (Table 1).

The mean neutrophil and mean platelet, mean PLR levels were higher in the TNNDH group compared to the control group respectively, while mean lymphocyte levels were lower. In terms of leukocyte-based inflammatory indices, the

Table 1. Demographic and laboratory findings.

Variables	Control group n=100	TNNDH group n=200	p
Age, years	51.2±9.2	51.5±11.4	0.819
Gender, n (%)			
Female	65(65.0)	129(64.5)	0.999
Male	35(35.0)	71(35.5)	
BMI, kg/m^2	27.8±4.1	28.2±5.1	0.496
SBP, mm Hg	126.2±17.3	160±13.3	<0.001*
DBP, mm Hg	77.7±16.4	98.8±10.1	<0.001*
CIMT, mm	0.6±0.1	0.8±0.2	<0.001*
LVMI, g/m^2	75.1±10.2	88.3±17.4	<0.001*
Microalbuminuria, mg/24h	6.0(1.2-27.4)	13(1.1-247.5)	0.023*
Hemoglobin, g/dL	14.2±1.8	14.1±1.5	0.672
FBG, mg/dL	96.4±13.2	97.9±13	0.384
WBC, x10^9/L	6.8±1.4	7.3±2.1	<0.001*
Neutrophil, x10^9/L	3.3±0.6	4.1±1.2	<0.001*
Platelet, x10^9/L	231.0±48.3	290.0±62.2	<0.001*
Lymphocyte, x10^9/L	2.4±0.7	2.2±0.7	0.012*
Monocyte, x10^9/L	0.5±0.1	0.5±0.2	0.186
PLR	98.4±24.0	140.9±37.2	<0.001*
NLR	1.4±0.4	1.9±0.5	<0.001*
SII	315.6±50.6	548.1±126.0	<0.001*
Total cholesterol, mg/dL	193.4±42.8	205.8±47.7	0.028*
LDL, mg/dL	112(36-208)	122(40-255)	0.277
HDL, mg/dL	55.5±13.6	46.7±11.2	<0.001*
Triglyceride, mg/dL	108(37-310)	163(70-551)	<0.001*
MHR	8.4(3.2-31.6)	11.2(1.5-40.7)	<0.001*
AIP	0.2±0.1	0.6±0.2	<0.001*

** p<0.05 was considered statistically significant.*
Abbreviations: AIP, atherogenic index of plasma; BMI, body mass index; CIMT, carotid intima media thickness; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVMI, left ventricular mass index; MHR, monocyte to HDL ratio; NDHTN, newly diagnosed treatment-naïve hypertension; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SBP, systolic blood pressure; SII, systemic immune-inflammation index; WBC, white blood cell.

Table 2. The relationship between inflammation indices and asymptomatic organ damage indicators in patients with newly diagnosed treatment-naive HTN.

Variables	CIMT		LVMI		Microalbuminuria	
	r	p	r	p	r	p
Age	0.292	<0.001*	0.280	0.026*	0.053	0.456
BMI	0.120	0.191	0.100	0.210	0.073	0.303
SKB	0.045	0.525	0.048	0.527	0.051	0.476
DKB	0.092	0.195	0.099	0.164	0.002	0.977
Hemoglobin	0.132	0.161	0.034	0.633	0.009	0.896
FBG	0.055	0.442	0.011	0.879	0.100	0.158
WBC	0.298	<0.001*	0.296	<0.001*	0.270	0.032*
Neutrophil	0.295	<0.001*	0.290	<0.001*	0.293	0.006*
Platelet	0.290	0.007*	0.287	0.011*	0.296	<0.001*
Lymphocyte	-0.286	0.025*	-0.278	0.043*	-0.280	0.018*
Monocyte	0.188	0.208	0.183	0.219	0.169	0.350
PLR	0.311	<0.001*	0.324	<0.001*	0.306	<0.001*
NLR	0.320	<0.001*	0.336	<0.001*	0.313	<0.001*
SII	0.441	<0.001*	0.409	<0.001*	0.400	<0.001*
LDL	0.100	0.157	0.070	0.326	0.042	0.559
HDL	-0.284	0.020*	0.299	0.005*	0.294	0.001*
Triglyceride	0.280	0.038*	0.277	0.040*	0.273	0.046*
MHR	0.304	<0.001*	0.309	<0.001*	0.311	<0.001*
AIP	0.418	<0.001*	0.405	<0.001*	0.393	<0.001*

** p<0.05 was considered statistically significant.*
Abbreviations: AIP, atherogenic index of plasma; BMI, body mass index; CIMT, carotid intima media thickness; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVMI, left ventricular mass index; MHR, monocyte to HDL ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SBP, systolic blood pressure; SII, systemic immune-inflammation index; WBC, white blood cell.

mean PLR (140.9±37.2 vs. 98.4±24.0; p<0.001), mean NLR (1.9±0.5 vs. 1.4±0.4; p<0.001) and mean SII (548.1±126.0 vs. 315.6±50.6; p<0.001) levels were higher in the TNNDH group than in the control group. In terms of lipid-based inflammatory indices, median MHR (11.2 vs. 8.4; p<0.001) and mean AIP (0.6±0.2 vs. 0.2±0.1; p<0.001) levels were higher in the TNNDH group (Table 1).

All inflammation indices levels positively correlated with the AOD indicators (Table 2). AOD was detected in 66.7% of the patients with TNNDH. The distribution of demographic and laboratory findings according to the presence of AOD is shown in Table 3. The mean PLR (143.0±37.9 vs. 138.0±36.2; p<0.05), mean NLR (2.1±0.5 vs. 1.8±0.5; p<0.05), mean SII (608.5±125.6 vs. 462.9±60.7; p<0.05) and mean AIP (0.7±0.2 vs. 0.5±0.2; p<0.05) levels were higher in the group with AOD (+) compared to the group without AOD, while median MHR levels were similar. These inflammation indices were higher in the group without AOD compared to the control group, while MHR was lower in the control group (Table 3).

Variables associated with the presence of AOD were included in the multivariable regression model. Increased of SII and AIP levels were identified as independent predictors of AOD. It was determined that an increase by one unit of SII levels increased the probability of AOD by 1.03 folds (OR=1.03, p<0.001), while an increase by one unit of AIP levels increased by 6.01 folds (OR=6.01; p<0.001) (Table 4).

Table 3. Distribution of demographic and laboratory findings by presence asymptomatic organ damage.

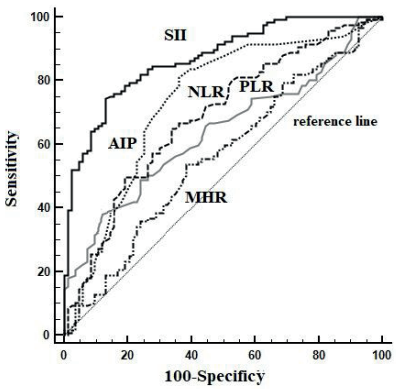
Variables	Control group n=100	TNNDH group		p
		AOD (-) n=83	AOD (+) n=117	
Age, years	51.2±9.2	50.8±12.0	51.8±10.8	0.643
Gender, n (%)				
Female	65(65.0)	49(59.0)	80(68.4)	0.407
Male	35(35.0)	34(41.0)	37(31.6)	
BMI, kg/m²	27.8±4.1	27.5±5.0	28.7±5.2	0.326
SBP, mm Hg	**126.2±17.3**	160.7±14.4	159.5±12.5	<0.001*
DBP, mm Hg	**77.7±16.4**	98.9±12.6	98.7±8.0	<0.001*
CIMT, mm	0.6±0.1	0.7±0.1	**0.9±0.1**	<0.001*
LVMI, g/m²	75.1±10.2	79.7±12.9	94.3±17.7	<0.001*
Microalbuminuria, mg/24h	6.0(1.2-27.4)	8.1(1.8-28)	**20.5(1.1-247.5)**	<0.001*
Hemoglobin, g/dL	14.2±1.8	14.3±1.6	13.9±1.5	0.302
FBG, mg/dL	96.4±13.2	100.3±12.2	96.1±13.0	0.059
WBC, x10⁹/L	6.8±1.4	7.0±2.2	**7.4±2.0**	<0.001*
Neutrophil, x10⁹/L	3.3±0.6	3.6±1.1	**4.5±1.1**	<0.001*
Platelet, x10⁹/L	**231±48.3**	**271.7±59.7**	**303.1±61**	<0.001*
Lymphocyte, x10⁹/L	**2.4±0.7**	2.1±0.8	2.2±0.6	0.021*
Monocyte, x10⁹/L	0.5±0.1	0.5±0.1	0.5±0.2	0.342
PLR	**98.4±24**	**138.0±36.2**	**143.0±37.9**	<0.001*
NLR	**1.4±0.4**	**1.8±0.5**	**2.1±0.5**	<0.001*
SII	**315.6±50.6**	**462.9±60.7**	**608.5±125.6**	<0.001*
Total cholesterol, mg/dL	193.4±42.8	195.6±44.6	**212.7±48.6**	0.019*
LDL, mg/dL	112(36-208)	120(40-229)	124(53-255)	0.493
HDL, mg/dL	**55.5±13.6**	47.0±10.3	46.5±11.7	<0.001*
Triglyceride, mg/dL	**108(37-310)**	**146(70-400)**	**196(87-551)**	<0.001*
MHR	**8.4(3.2-31.6)**	10.4(1.5-32.3)	11.8(1.8-40.7)	<0.001*
AIP	**0.2±0.1**	**0.5±0.2**	**0.7±0.2**	<0.001*

** p<0.05 was considered statistically significant. Bold characters show the difference between groups.*
Abbreviations: AIP, atherogenic index of plasma; BMI, body mass index; CIMT, carotid intima media thickness; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVMI, left ventricular mass index; MHR, monocyte to HDL ratio; NDHTN, newly diagnosed treatment-naïve hypertension; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SBP, systolic blood pressure; SII, systemic immune-inflammation index; WBC, white blood cell.

Table 4. Factors associated with asymptomatic organ damage in patients with newly diagnosed treatment-naive hypertension.

Variables	Univariable Regression				Multivariable Regression			
	OR	95% CI		p	OR	95% CI		p
		lower	upper			lower	upper	
WBC	1.05	1.01	1.1	<0.001*	-	-	-	-
Neutrophil	2.10	1.54	2.87	<0.001*	-	-	-	-
Platelet	1.09	1.04	1.14	0.001*	-	-	-	-
PLR	1.04	1.01	1.08	<0.001*	-	-	-	-
NLR	3.18	1.91	7.59	<0.001*	-	-	-	-
SII	1.02	1.01	1.03	<0.001*	1.03	1.01	1.05	<0.001*
Total cholesterol	1.05	1.01	1.12	0.040*	-	-	-	-
Triglyceride	1.09	1.05	1.13	<0.001*	-	-	-	-
AIP	10.15	2.85	36.08	<0.001*	6.01	1.22	29.73	<0.001*
					Nagelkerke R^2=0.617; p<0.001			

**p<0.05 is considered significant for statistical analyses.*
Abbreviations: AIP, atherogenic index of plasma; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; OR, odds ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; WBC, white blood cell.



	AUC	SE	95% CI
SII	0.870	0.02	0.815 to 0.913
AIP	0.735	0.04	0.668 to 0.795
NLR	0.685	0.04	0.616 to 0.749
PLR	0.638	0.04	0.567 to 0.704
MHR	0.558	0.04	0.487 to 0.628

Pairwise comparison of ROC curves

	ΔAUC	p
SII vs		
AIP	0.135	0.001*
NLR	0.185	<0.001*
PLR	0.232	<0.001*
MHR	0.312	<0.001*
AIP vs		
NLR	0.05	0.286
PLR	0.097	0.047*
MHR	0.177	0.001*

Figure 1. Diagnostic performance assessment of leukocyte and lipid-based inflammatory indices in predicting AOD.

The SII levels higher than 512.7 with 74.4% sensitivity and 86.8% specificity were found to be a predictor of AOD (AUC±SE= 0.870±0.02, +PV= 88.0%, -PV= 71.0%, p< 0.001). The AIP levels higher than 0.7 with 81.2% sensitivity and 63.8% specificity were found to be a predictor of AOD (AUC±SE= 0.735±0.04, +PV= 76%, -PV= 70.7%, p< 0.001). The SII had superior diagnostic discrimination compared to other leukocyte and lipid-based inflammatory indices in predicting the presence of AOD (Figure 1).

DISCUSSION

To the best of our knowledge, this study is the first to report the diagnostic performance of leukocyte- and lipid-based inflammatory indices in TNNDH patients compared to healthy controls. In patients with TNNDH, there was a positive correlation between all inflammatory index values and all indicators of AOD. Excluding MHR, the levels of all inflammation indices were higher in patients with AOD. SII and AIP values were independent predictors of AOD, and SII showed superior diagnostic performance compared to all other inflammation indices in predicting AOD.

In HTN, overt organ damage may develop silently. TNNDH patients may be at high risk due to late diagnosis particularly. We detected AOD in approximately 59% of our TNNDH patients. In a recent study of TNNDH patients, the prevalence of target organ damage was reported as 60.7% (13). Current results support the lack of awareness of organ damage in cases of TNNDH. Requiring a multidisciplinary approach, hypertensive organ damage is determined by CIMT, LVMI, urinary microalbuminuria, and urinary protein excretion. However, doing so requires advance expertise (14). Inflammatory indices obtained from complete blood count measurements, which are easily and economically evaluated in every hospital, may be important screening tools for AOD. The underlying mechanism is the low-grade inflammation that facilitates the development of hypertensive organ damage (15).

The increased level of mechanical or shear stress in HTN is an important factor in accelerating atherosclerosis. This causes an inflammatory response by the immune system (16). In this process, inflammatory mediators play a role in leukocyte activation. This activation, which is actually an adaptive mechanism, can exacerbate inflammatory responses through the secretion of various inflammatory mediators (17). Progression of atherosclerosis can result in tissue damage. This causes an accumulation of macrophages in the damaged tissues. The inflammatory process proceeds with increased release of IL-6 and TNF-α in the circulation together with increased CRP production (18). These inflammatory mediators have been associated with hypertensive organ damage in previous studies (19,20).

The fact that HTN is an atherosclerotic and chronic inflammatory disease is consistent with the finding that leukocyte-based inflammatory index values are higher among these patients. Increased inflammation is associated with the impaired endothelial and renal function (21,22). Previous studies reported increased PLR and NLR levels as predictors of endothelial and kidney dysfunction (16,24). Elevated SII levels are associated with both increased urinary albumin excretion and CIMT (22,23). Increased PLR and NLR levels in TNNDH patients showed a positive correlation with both endothelial and renal function indicators, and increased PLR and NLR levels were found to be important potential markers for AOD. However, the inclusion of SII in the multiple regression model of the present study resulted in PLR and NLR losing their statistical significance. The SII formula contains all components of NLR and PLR. Therefore, it may have emerged as a more important marker in the multivariable regression model. This result was also supported by ROC curve analysis; SII showed superior diagnostic performance compared to PLR and NLR.

Atherogenic lipids that cause low-grade inflammation in endothelial cells are closely related to endothelial dysfunction and atherosclerosis (6). The MESA Study performed with a healthy multiethnic population showed that combined hyperlipidemia and simple hypercholesterolemia were associated with elevated CIMT and prevalent coronary artery calcium (24). Recent studies have suggested that AIP is an important predictor of cardiovascular events and atherosclerosis (25,26). The combination of low HDL and high triglycerides is defined as atherogenic dyslipidemia. Atherogenic dyslipidemia has been associated with increased cardiovascular events, heart rate, systolic blood pressure, and decreased insulin sensitivity (27). It has been suggested that there is increased infiltration of atherogenic lipid molecules into vascular plaques due to increased mechanical stress and endothelial permeability in HTN patients (4). This mechanism is consistent with the results of a previous study reporting that MHR predicted AOD in primary hypertension patients (28). In our study, MHR was higher in both HTN patients and those who developed AOD. However, it lost statistical significance in multivariate regression analysis. This may be due to a stronger relationship of AIP and SII levels with the development of AOD. However, we could not find any studies evaluating the relationship between AIP and hypertensive organ damage with a multidisciplinary approach. In TNNDH patients, AIP was associated with both endothelial and renal function indicators. Although AIP had a lower diagnostic performance than SII, it was found to be an independent predictor of AOD. The sustained inflammation observed in cases of HTN may cause more severe inflammatory responses, while lipids are known to play roles in leukocyte activation. Therefore, the combination of leukocyte- and lipid-based inflammatory indices may play a prognostic role in the risk stratification of TNNDH patients.

This study has several important limitations. First, it has a retrospective, cross-sectional design. Second, a larger patient population would better support the results. The consistency of leukocyte and lipid-based inflammatory indices could be supported by data on overt organ damage in hypertensive patients with long-term follow-up. Finally, highly sensitive inflammatory markers, including cytokines, were not studied.

CONCLUSIONS

TNNDH patients have higher leukocyte and lipid-based inflammatory index values. High SII and API levels are independent predictors of AOD. However, SII exhibits superior diagnostic performance in the discrimination of AOD. SII may be a useful screening tool in the detection of AOD in TNNDH patients. This is consistent with the role of lower levels of inflammation in the development of AOD.

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REFERENCES

1. Dai H, Bragazzi NL, Younis A, Zhong W, Liu X, Wu J et al. Worldwide Trends in Prevalence, Mortality, and Disability-Adjusted Life Years for Hypertensive Heart Disease From 1990 to 2017. Hypertension 2021; 77: 1223-33. https://doi.org/10.1161/HYPERTENSIONAHA.120.16483
2. Gauer R. Severe Asymptomatic Hypertension: Evaluation and Treatment. Am Fam Physician 2017; 95: 492-500.
3. Rubattu S, Pagliaro B, Pierelli G, Santolamazza C, Castro SD, Mennuni S et al. Pathogenesis of target organ damage in hypertension: role of mitochondrial oxidative stress. Int J Mol Sci 2014; 16: 823-39. https://doi.org/10.3390/ijms16010823
4. Lawler PR, Hiremath P, Cheng S. Cardiac target organ damage in hypertension: insights from epidemiology. Curr Hypertens Rep 2014; 16: 446. https://doi.org/10.1007/s11906-014-0446-8
5. Rodrigo R, Gonzalez J, Paoletto F. The role of oxidative stress in the pathophysiology of hypertension. Hypertens Res 2011; 34: 431-40. https://doi.org/10.1038/hr.2010.264
6. Malekmohammad K, Bezsonov EE, Rafieian-Kopaei M. Role of Lipid Accumulation and Inflammation in Atherosclerosis: Focus on Molecular and Cellular Mechanisms. Front Cardiovasc Med 2021; 8: 707529. https://doi.org/10.3389/fcvm.2021.707529
7. McMaster WG, Kirabo A, Madhur MS, Harrison DG. Inflammation, immunity, and hypertensive end-organ damage. Circ Res 2015; 116: 1022-33. https://doi.org/10.1161/CIRCRESAHA.116.303697
8. Harslof M, Pedersen KM, Nordestgaard BG, Afzal S. Low High-Density Lipoprotein Cholesterol and High White Blood Cell Counts: A Mendelian Randomization Study. Arterioscler Thromb Vasc Biol 2021; 41: 976-87. https://doi.org/10.1161/ATVBAHA.120.314983
9. Kirabo A, Fontana V, de Faria AP, Loperena R, Galindo CL, Wu J et al. DC isoketal-modified proteins activate T cells and promote hypertension. J Clin Invest 2014; 124: 4642-56. https://doi.org/10.1172/JCI74084
10. Loperena R, Van Beusecum JP, Itani HA, Engel N, Laroumanie F, Xiao L et al. Hypertension and increased endothelial mechanical stretch promote monocyte differentiation and activation: roles of STAT3, interleukin 6 and hydrogen peroxide. Cardiovasc Res 2018; 114: 1547-63. https://doi.org/10.1093/cvr/cvy112
11. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34: 2159-219. https://doi.org/10.1093/eurheartj/eht151
12. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39: 3021-104. https://doi.org/10.1093/eurheartj/ehy339
13. Prakash D. Target organ damage in newly detected hypertensive patients. J Family Med Prim Care 2019; 8: 2042-6. https://doi.org/10.4103/jfmpc.jfmpc_231_19
14. Ates I, Ozkayar N, Akyel F, Topcuoglu C, Akyel S, Barca AN et al. The relationship between asymptomatic organ damage, and serum soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) and Interleukin-17A (IL-17A) levels in non-diabetic hypertensive patients. BMC Nephrol 2014; 15: 159. https://doi.org/10.1186/1471-2369-15-159
15. Liu X, Zhang Q, Wu H, Du H, Liu L, Shi H et al. Blood Neutrophil to Lymphocyte Ratio as a Predictor of Hypertension. Am J Hypertens 2015; 28: 1339-46. https://doi.org/10.1093/ajh/hpv034
16. Sun HJ, Wu ZY, Nie XW, Bian JS. Role of Endothelial Dysfunction in Cardiovascular Diseases: The Link Between Inflammation and Hydrogen Sulfide. Front Pharmacol 2019; 10: 1568. https://doi.org/10.3389/fphar.2019.01568
17. Arbel Y, Finkelstein A, Halkin A, Birati EY, Revivo M, Zuzut M et al. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis 2012; 225: 456-60. https://doi.org/10.1016/j.atherosclerosis.2012.09.009
18. Krayem I, Bazzi S, Karam M. The combination of CRP isoforms with oxLDL decreases TNF-alpha and IL-6 release by U937-derived macrophages. Biomed Rep 2017; 7: 272-6. https://doi.org/10.3892/br.2017.949
19. Patrick DM, Van Beusecum JP, Kirabo A. The role of inflammation in hypertension: novel concepts. Curr Opin Physiol 2021; 19: 92-8. https://doi.org/10.1016/j.cophys.2020.09.016
20. Xiao L, Harrison DG. Inflammation in Hypertension. Can J Cardiol 2020; 36: 635-47. https://doi.org/10.1016/j.cjca.2020.01.013
21. Bartoloni E, Alunno A, Valentini V, Luccioli F, Valentini E, La Paglia G et al. Role of Inflammatory Diseases in Hypertension. High Blood Press Cardiovasc Prev 2017; 24: 353-61. https://doi.org/10.1007/s40292-017-0214-3

22. Qin Z, Li H, Wang L, Geng J, Yang Q, Su B et al. Systemic Immune-Inflammation Index Is Associated With Increased Urinary Albumin Excretion: A Population-Based Study. Front Immunol 2022; 13: 863640. https://doi.org/10.3389/fimmu.2022.863640
23. Cirakoglu OF, Yilmaz AS. Systemic immune-inflammation index is associated with increased carotid intima-media thickness in hypertensive patients. Clin Exp Hypertens 2021; 43: 565-71. https://doi.org/10.1080/10641963.2021.1916944
24. Paramsothy P, Knopp RH, Bertoni AG, Blumenthal RS, Wasserman BA, Tsai MY et al. Association of combinations of lipid parameters with carotid intima-media thickness and coronary artery calcium in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2010; 56: 1034-41. https://doi.org/10.1016/j.jacc.2010.01.073
25. Kim SH, Cho YK, Kim YJ, Jung CH, Lee WJ, Park JY et al. Association of the atherogenic index of plasma with cardiovascular risk beyond the traditional risk factors: a nationwide population-based cohort study. Cardiovasc Diabetol 2022; 21: 81. https://doi.org/10.1186/s12933-022-01522-8
26. Yin J, Li M, Yu L, Hu F, Yu Y, Hu L et al. The relationship between the atherogenic index of plasma and arterial stiffness in essential hypertensive patients from China: a cross-sectional study. BMC Cardiovasc Disord 2021; 21: 245. https://doi.org/10.1186/s12872-021-02049-8
27. Kutkiene S, Petrulioniene Z, Laucevicius A, Matuzeviciene G, Kasiulevicius V, Petrulionyte E et al. Cardiovascular risk profile of patients with atherogenic dyslipidemia in middle age Lithuanian population. Lipids Health Dis 2018; 17: 208. https://doi.org/10.1186/s12944-018-0851-0
28. Aydin E, Ates I, Fettah Arikan M, Yilmaz N, Dede F. The ratio of monocyte frequency to HDL cholesterol level as a predictor of asymptomatic organ damage in patients with primary hypertension. Hypertens Res 2017; 40: 758-64. https://doi.org/10.1038/hr.2017.36