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Research Article

The Relationship Between the Systemic Immune-Inflammation Index and Non-Dipper Hypertension in Patients with Newly Diagnosed Hypertension

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Abstract:

Background: It has been determined that there is an increase in mortality and morbidity rates due to cardiovascular diseases, which are observed more frequently in individuals with non-dipper hypertension (NDPHT). In this study, it was aimed to investigate whether there is a relationship between the systemic immune-inflammation index (SII), and NDPHT.

Materials and Methods: Patients who applied to the cardiology outpatient clinic between January 2022 to April 2022 with newly diagnosed HT were included in the study consecutively. Twenty-four hour ambulatory blood pressure (BP) measurement was performed for each patient, and the study population was divided into three groups as dipper hypertension (DPHT), NDPHT and normotensive. The patients were evaluated with their demographic characteristics, comorbidities and laboratory values. SII was calculated for each patient.

Results: There was no significant difference between the groups in demographic parameters. Left ventricular wall was thicker in the hypertensive group than the control group, and the left ventricular mass index (LVMİ) was higher in the hypertensive group. (p=0.017). Hs-CRP levels were significantly higher in the non-dipper hypertensive group than in the other groups (p=0.028). SII >347 had 69% sensitivity and 77% specificity in predicting NDPHT (area under the curve 0.789, p<0.001).

Conclusion: İt is feasible to develop a auxiliary diagnostic method with 69% sensitivity and 77% specificity (SII>347) to predict non-dipping status in newly diagnosed treatment-naive hypertensive patients.

Keywords: systemic ımmune-inflammation ındex; non-dipper hypertension; high sensitive c reactive protein

Introduction

Hypertension (HT) is one of the leading preventable cardiovascular risk factors. (1) It is known that cardiovascular mortality, cerebrovascular diseases, renal failure, and retinopathy are more common in hypertensive individuals compared to healthy people. (2-4) Although arterial blood pressure (BP) values are constantly changing during the normal day, they show a circadian rhythm. (5)

Due to the lifestyle and daily living activities of people in their normal daily lives, changes occur in BP values and blood pressure can exceed the target values. For this reason, it is reported that evaluation should not be made with only one measurement before diagnosing HT and it is more valid to take 24-hour BP averages. (6)

When BP values are examined, it has been determined that BP values changes with the circadian rhythm during the day. İn studies conducted in the literature, nighttime BP values are lower than daytime BP values and the decrease in BP differs between individuals. In a study conducted with healthy individuals, it was reported that ambulatory BP values reached the highest values in the morning, decreased during the day, and remained at the lowest values after sleeping. (7)

In classification created by ambulatory BP monitoring, it is stated that a decrease of 10% or more in BP values at sleep time compared to the daytime BP values is defined as Dipper HT (DHT) and a decrease of less than 10% is defined as Non-Dipper HT (NDPHT). (8,9)

DPHT and NDPHT are important in cardiovascular and cerebrovascular diseases in patients with HT and normotensive individuals. (10) Many studies have showed that target organ damage and cardiovascular events have been associated with circadian rhythm abnormalities such as increased morning BP (MBP), increased MBP surge (MBPS) and nondipping status. (5,11)

Different hypotheses have been proposed about the causes of the development of a Non-Dipper (NDP) pattern, including a renal mechanism due to high salt intake (12), alteration of the sleep-wake cycle (13), higher activity during night rest (14) and the relationship of the NDP pattern with a decrease in the parasympathetic nervous function and an increase in the sympathetic nervous function. (15) However, the causes of the development of the NDP pattern are still unclear.

When analyzed in terms of the pathophysiology of NDPHT, it was determined that the number of lymphocytes circulating in the peripheral blood in the inflammation region decreased. (16) It is stated that leukocytes, one of the blood components, perform a physiological response to stress in humans and the increase in the amount of this response is manifested by a decrease in the number of lymphocytes. (17) It is stated that one of the factors in the etiology of these events that occur in the body due to inflammation, ischemia, thrombosis and embolism in the development of DPHT is due to an increase in the number of platelets or an enlargement in volume. (18)

It is stated that SII is a new generation inflammation biomarker created with whole blood parameters. (17) This biomarker is a value that obtained by multiplying the neutrophil count by the platelet count and dividing the result by the lymphocyte count..

SII has been emerged to predict the prognosis and outcomes in cancer and cardiac patients based on peripheral blood cells such as platelet, neutrophil, and lymphocyte. (19-21) It has been reported that SII is an independent predictor of major adverse cardiovascular events in coronary artery disease patients (CAD). (20)

In this study, we aimed to evaluate the relation of SII with NDPHT in newly diagnosed HT patients with the homogenous cardiovascular risk profile.

Methods

Seventy patients with newly diagnosed HT admitted to the cardiology outpatient clinic between January 2022 and April 2022 were included. Thirty-five volunteers with similar demographic characteristics who applied to the cardiology outpatient clinic were included in the study as control group.

The diagnosis of HT was based on repeated measurements of systolic BP ≥140 and/or diastolic BP ≥90 mmHg at at least three separate visits. Twenty-four hour Ambulatory BP measurement (ABPM) was performed for each patient, and the study population was divided into three groups as DPHT, NDPHT and normotensive control groups according to whether there was a ≥10% decrease in nighttime BP values.

Those under 18 years of age or over 75 years of age and secondary HT, known CAD, peripheral artery disease, heart failure with EF < 40%, arrhythmia, significant valvular disease, shift workers, estimated glomerular filtration rate (eGFR) < 50 mL/ minute/1.73 m2 renal failure or those using antihypertensive drugs or catecholamines, α- or β-blockers and tranquilizers were not included in the study. Patients with reverse dipper or extreme dipper variations in ABPM were also excluded from the study.

This study was approved by the local ethics committee in accordance with the International Code of Ethics and the Declaration of Helsinki; All patients were informed about the aims of the study and their informed consent was obtained. Age, gender, smoking habit, echocardiographic data, laboratory results were obtained at the time of first application. To determine the hemogram, biochemistry, and high-sensitivity C-Reactive Protein (hs-CRP) levels, blood samples were taken between 8-10 am following a 12-hour fasting. SII was calculated by the formula; PlateletxNeutrophil/Lymphocyte (P x N)/L; where P, N, and L denote platelet, neutrophil, and lymphocyte counts in peripheral blood, respectively. Body Mass İndex (BMI) was calculated and glomerular filtration rate (GFR) was evaluated according to the MDRD (Diet Modification in Renal Disease) formula.

Office BP was measured every 6 months with an aneroid sphygmomanometer with a 36-42 cm wide cuff (ERKA Perfect-Aneroid; ERKA, BadTölz, Germany) calibrated using a mercury sphygmomanometer. Office BP measurements were made on 3 different days with the average of three measurements taken after 5 minutes of rest. HT was defined as blood pressure of 140/90 mmHg and/or above in all three measurements.

A fully automatic BP monitoring device (BR-102 Plus, Schiller, Baar, Switzerland) was used for 24-hour ambulatory blood pressure measurement. Daytime measurements were made every 15 minutes between 6:00 and 22:00 in the morning. Nighttime measurements were made every 30 minutes between 22:00 and 06:00. The recording was considered invalid if more than 30% of the measurements were missing. Daytime systolic BP, daytime diastolic BP, nighttime systolic BP and nighttime diastolic BP were recorded.

Echocardiography of the patients was performed by an experienced cardiologist who was unaware of the patient's clinical and laboratory data using the Vivid 9 (General Electric Healthcare, USA) system with a 2.5-3.5 MHz transducer. Echocardiographic examination was performed in all patients in the left decubitus position. Echocardiography showed interventricular septum (IVS) and posterior wall (PW) thicknesses. Left ventricular mass index (LVMİ) was calculated by dividing left ventricular mass (LVM) by body surface area. All measurements were repeated at least three times and averaged.

Statistical analysis

Statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) for Windows 21.0. The Kolmogorov-Smirnov test was used to determine whether the continuous variables were normally distributed. Normally distributed variables were given as mean±standard deviation, and non-normally distributed variables were given as median (minimum-maximum) values. Descriptive statistics are given as percentages and absolute values. Baseline features were compared with the chi-square test. When appropriate, one-way Analysis of Variance (ANOVA) or Kruskal-Wallis test was used to compare 3 groups for continuous variables. Differences between subgroups were revealed using the Dunn procedure (for data not normally distributed). Data were analyzed using univariate logistic and multivariate logistic regression models to determine whether SII was independently associated with the risk of NDPHT. Univariate analyzes considered the following variables: Hemoglobin, BMİ, hs-CRP, age, gender, LVMİ, smoking, fasting blood glucose, and creatinine. Covariates with $p<0.1$ from a univariate logistic regression were included for a multivariate analysis. We performed a Receiver Operating Characteristic (ROC) analysis to determine the most sensitive SII cutoff level to identify HT patients with non-dipper patterns. $p<0.05$ was considered statistically significant. Assuming the main distribution is a Laplace distribution, we performed a post hoc power analysis based on the SII results (effect size: 0.60, α: 0.05), which revealed a working power of 86%.

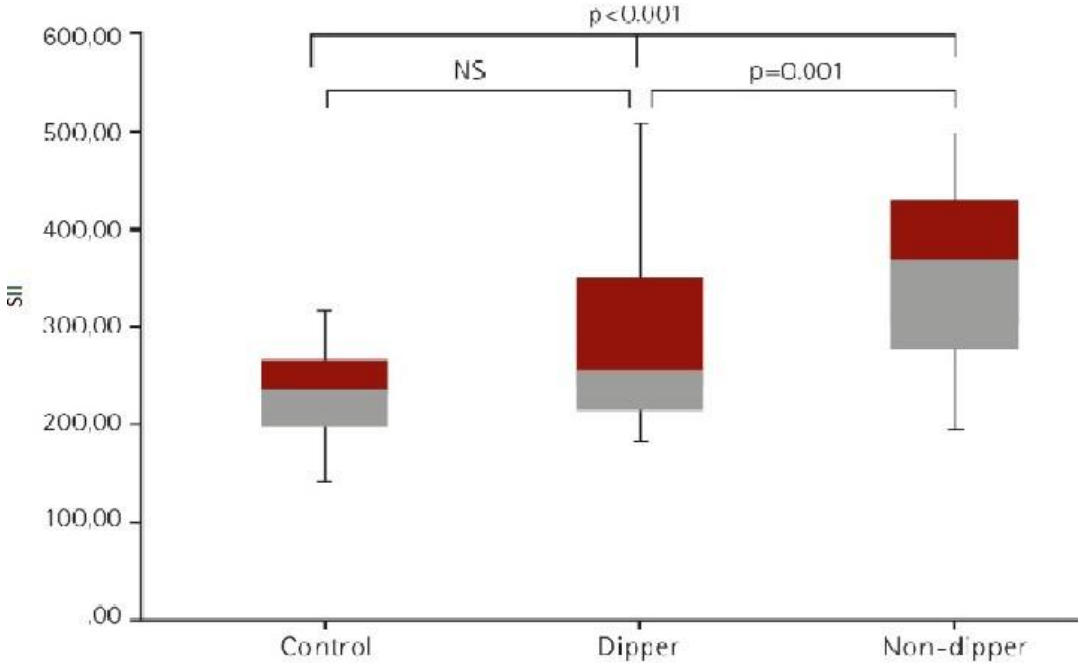
Results

Demographic, laboratory and echocardiographic characteristics of the study population are shown below. (Table 1) There was no significant difference between the groups in demographic parameters. In the

echocardiographic evaluation, it was determined that the left ventricular wall was thicker in the HT group than the control group, and the LVMİ was higher in the HT group. (p=0.017)

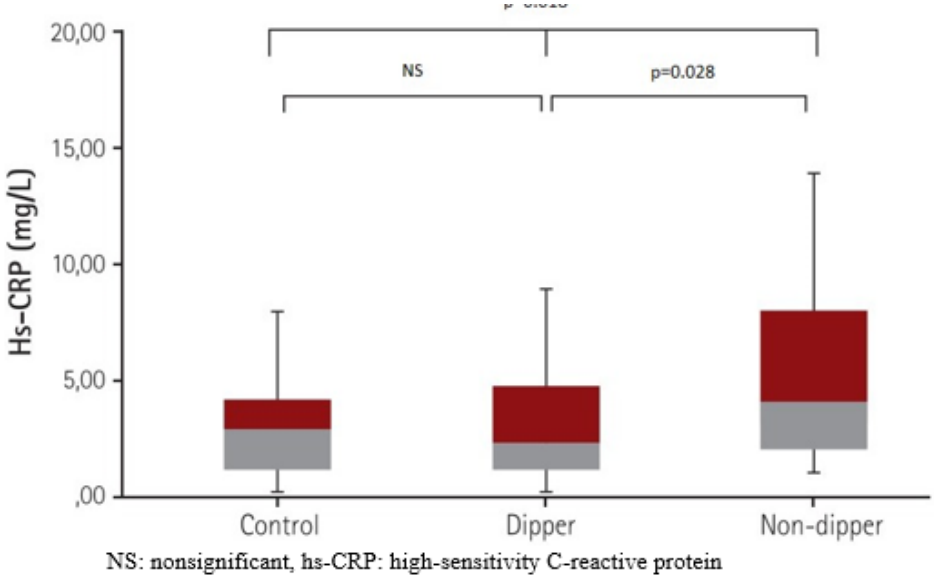
Daytime and nighttime BP averages of DPHT and NDPHT groups are given in Table 2. In the NDPHT group, a statistically significant decrease in BP was observed at night, and the nighttime mean values were higher compared to the DPH group.

Levels of SII were found to be significantly different between the three groups. (p<0.001). In binary comparison; While the NDPHT group had higher SII levels than both the DPHT and control groups (p<0.001), there was no significant difference between the DPHT and control groups' SII levels (p>0.05). (figure 1). Serum hs-CRP levels were significantly higher in the NDPHT group than in the other groups (p=0.028). However, there was no significant difference between the DPHT group and the control group (p>0.05). (Figure 2.) In HT patients, SII levels were positively correlated with hs-CRP levels (r=0.213, p=0.027). Subsequent multivariate regression analysis showed that high SII and hs-CRP levels could independently predict NDPHT (Table 3). In ROC analysis, SII >347 threshold; it had 69% sensitivity and 77% specificity in predicting disease (area under the curve 0.789, p<0.001). (Figure 3)



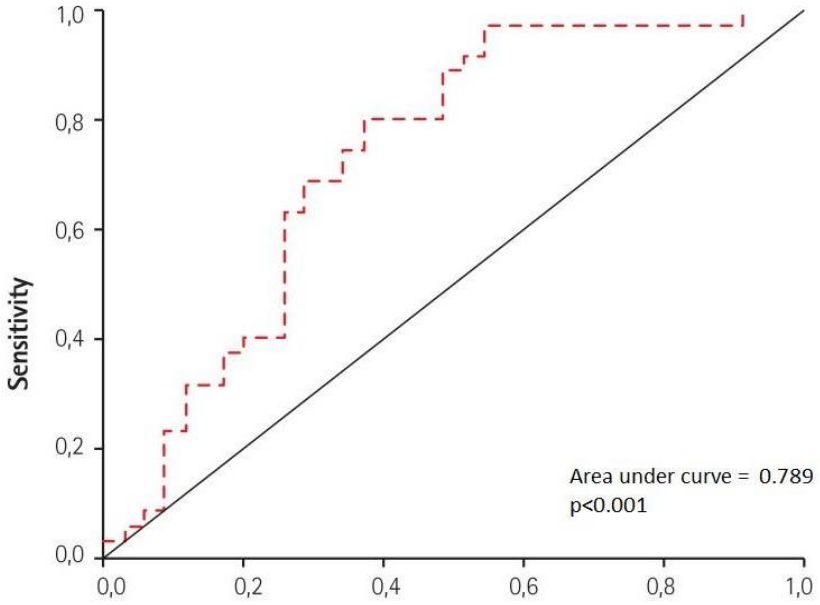
NS: nonsignificant

Figure 1: Comparison of the groups in terms of SII values



NS: nonsignificant, hs-CRP: high-sensitivity C-reactive protein

Figure 2: Comparison of the groups in terms of hs-CRP levels



NS: nonsignificant, hs-CRP: high-sensitivity C-reactive protein

Figure 2: Comparison of the groups in terms of hs-CRP levels

	Control (n=35)	Dipper (n=35)	Non dipper (n=35)	P
Age	51±6.4	47,2±9,3	47,4±5,2	0.125
Men, n (%)	15 (42)	21 (60)	16 (46)	0.307
Body mass index (kg/m2)	22,8 (19,3–25,9)	22,7 (19,5–26)	20,6(19,3-25,7)	0.105
Smokers	8 (22.9)	4 (11.4)	4 (11.4)	0.307
Total cholesterol (mg/dL)	184,9±39,4	197.4±48.6	192,3±39,4	0.469
Low-density lipoprotein cholesterol (mg/dL)	130.2±39.4	132.2±40,8	135.8±35,7	0.826
High-density lipoprotein cholesterol (mg/dL)	46 (30–76)	44 (30–72)	44 (30–95)	0.863
Triglycerides (mg/dL)	108 (48–294)	132 (46–223)	129 (55–300)	0.120
Creatinine (mg/dL)	0,8 (0,5–1,4)	0,8 (0,5–1,3)	0,7 (0,4–1,1)	0.421
Fasting glucose (mg/dL)	92 (77–116)	89 (69-109)	85 (51–112)	0.183
Hemoglobin g/dL	14,2±1,5	14,8±1,1	14,2±1,7	0.135
White blood cell count(103/mm3)	8.2 (4.8–11.4)	8,8 (5,8–12,6)	9,8 (6,0–15,4)	0.078
Platelet count(103/mm3)	157 (121–198)	168 (148–200)	180 (161–209)	0.086
hs-CRP (mg/L)	2,9 (0,1–15,0)	2.2 (0.1–11.0)	4.0 (1.0–13.84)	0.013
NLR	1.53 (1.33-1.81)	1.67 (1.49-1.89)	1.90 (1.77-2.09)	0.066
SII	267 (201-327)	311 (279-351)	577 (328-888)	<0,001
Echocardiographic parameters				
IVS (mm)	9,9 (7.3–11.8)	10.9 (8.9–14.2)	12,0 (10,9-13,9)	0.019
Posterior wall (mm)	9,5 (7.1–11.1)	10,4 (8,3–12,4)	10,9 (7,9–13,2)	0.024
LVEDD (mm)	46 (39–56)	45 (39–51)	46 (39-60)	0.667
LVMI (g/m2)2)	83,3 (56,9–156,2)	91,6 (47,8–137,1)	97,5 (63.8–151)	0.017

All values are presented as mean value, SD, median value (min - maximum), or n (%). hs-CRP: high sensitivity C-reactive protein, NLR: neutrophil lymphocyte ratio, SII: systemic inflammation index, IVS: inter ventricular septum, LVEDD: left ventricular end-diastolic diameter, LVMI: left ventricular mass index

Figure 3: Determination of the threshold SII parameter to predict non-dipper hypertensives, receiver operating characteristic curve

	Dipper	Non-dipper	p
Daytime SBP	151±6	152±8	0,874
Daytime DBP	92±4	94±5	0,678
Night SBP	132±7	143±5	<0,001
Night DBP	80±6	89±3	<0,001
24-hour SBP	146±7	149±6	0,234
24-hour SBP	93±4	94±5	0,884
Nocturnal base	%19	%7	<0,001

SBP: Systolic Blood Pressure DBP: Diastolic blood pressure

Table 1" Main characteristics of the study population

Variables	Univariate regression analysis	P	Multivariate regression analysis	p
Age	1.034 (0.975–1.097)	0.260	-	-
Female sex	0,561 (0,217–1.449)	0.233	-	-
Smoking	1.000 (0,229-4,361)	1.000	-	-
Hemoglobin	0,736 (0,522–1,038)	0.081	0,777 (0,532–1,137)	0.194
NLR	0,975 (0.940–1.011)	0.177	-	-
creatinine	0,209 (0,016–2.718)	0.231	-	-
LVMI	1.015 (0.991–1.040)	0.225	-	-
BMI	0.787 (0.608–1.018)	0.068	0,789 (0,589–1,056)	0.111
hs-CRP	1.221 (1.045–1.426)	0.012	1.201 (1.005–1.435)	0.044
SII	1.008 (1.003–1.014)	0.004	1.007 (1.001–1.013)	0.021

BMI: body mass index, LVMI: left ventricular mass index, hs-CRP: high-sensitivity Reactive Protein

Table 2: Daytime and 24-hour mean systolic and diastolic blood pressure readings between groups with dipper hypertension and non-dipper hypertension

Variables	Univariate regression analysis	P	Multivariate regression analysis	p
Age	1.034 (0.975–1.097)	0.260	-	-
Female sex	0,561 (0,217–1.449)	0.233	-	-
Smoking	1.000 (0,229-4,361)	1.000	-	-
Hemoglobin	0,736 (0,522–1,038)	0.081	0,777 (0,532–1,137)	0.194
NLR	0,975 (0.940–1.011)	0.177	-	-
creatinine	0,209 (0,016–2.718)	0.231	-	-
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BMI: body mass index, LVMI: left ventricular mass index, hs-CRP: high-sensitivity Reactive Protein

Table 3: Univariate and multivariate logistic regression analysis

Discussion

The current study shows that: SII is superior to platelet, neutrophil, lymphocyte, NLR, and PLR for identifying the presence of NDPHT. In association with increased serum hs-CRP levels and increased LVMI, increased SII levels may be suitable candidate to predict NDPHT. This study also shows that it is feasible to develop a auxiliary diagnostic method with 69% sensitivity and 77% specificity (SII>347) in predicting non-dipping status in newly diagnosed treatment-naive HT patients.

Inflammation plays a crucial role in the pathogenesis of HT and is associated with BP variability. (22) Inflammatory markers have been widely investigated for their usefulness in predicting high-risk patients with HT for adverse outcomes. Kim et al. demonstrated that inflammatory mediators including Tumor Necrosis Factor alfa (TNF-α), Interleukine-6 (IL-6), and hs-CRP were related to BP variability. (23) Kaya et al. reported that NDPHT patients had increased platelet activation than DPHT patients. (24) Neutrophil counts were found to be elevated before the development of HT in experimental models on mice. (25) Tatsukawa et al. observed that increased neutrophil count was significantly related to HT incidence in Japanese women. (26) Angeli et al. reported that neutrophil count was an independent predictor of HT and was a predictor of cardiovascular events. (27) Barhoumi et al. demonstrated that regulatory T lymphocytes, which is a subset of T lymphocytes, suppress the BP elevation and vascular injury mediated by angiotensin-II in an animal study. (28) Sunbul et al. found that hypertensive patients with non-dipper patterns had low lymphocyte counts as compared to dipper hypertensive patients. (29) Both NLR and PLR have been investigated in HT previously. Elevated NLR was related to the prevalence of HT and was associated with resistant HT. (30,31) Sun et al. reported that higher NLR was associated with all cause mortality in hypertensive patients. (32) NLR and PLR were found higher in NDPHT

than DPHT. (29) Song et al. showed that PLR was associated with concurrent HT in obstructive sleep apnea. (33) NLR was found to be significantly correlated with BP variability in a previous study reported by Kilicaslan et al. (34) In addition to this finding, Yildirim et al. showed that both NLR and PLR were associated with BP variability. (35) As mentioned above, all markers including neutrophil, lymphocyte, and platelet and combinations such as NLR and PLR were associated with the development of HT, BP variability, and adverse outcomes. Bolayır et al. found that hs-CRP levels were significantly higher in non-dippers and there was a positive and graded relationship between hs-CRP and average night-time BP. (36) İn Yucel et al.'s study non-dipper patients had significantly higher hs-CRP levels than dipper and normotensive patients. (37) In consistent with previous studies we found that serum hs-CRP levels were significantly higher in non-dipper group than the other groups, hs-CRP levels were also significantly higher in NDPHT than DPHT but there were no significant difference between dippers and the control group.

Previous studies have reported that patients with circadian abnormalities have significantly greater left ventricular hypertrophy (LVH). (38,39) İn Kılıc et al.'s study evaluating target organ damage in normotensive patients, non-dipping pattern was associated with an increase in LVMI. (40) İn another study it was shown that although there was no difference in systolic BP, dipping pattern was independently associated with an increase in LVMI. (41) Shibuya Y et al. showed increased myocardial thickness in normotensive individuals with NDPHT. (42) Howewer Cuspidi C et al. showed that left ventricular wall thickness, absolute LVM and LVM indexed by body surface area were slightly, but not signicantly higher in non-dippers. (43) It has already been commented that the greater prevalence of LVH reported by some studies in non-dippers may not be due to the non-dipping pattern, but probably to a higher BP level over 24 h. (44) In another study comparing dipping and non-dipping patterns in individuals with high-normal BP, LVMI was not different between groups. (45) İn our study although the left ventricle wall was thicker in the hypertensive group than the control group and higher LVMI was found in hypertensives there were no significant difference between NDPHT and DPHT .

İn the literature we across very few studies that have investigated the role of SII in hypertensive patients. Cirakcioglu et al. showed the significant association of SII with carotid intima-media thickness in HT patients. (46) Saylik, F., & Sarıkaya, R. showed the association between SII and exaggerated MBPS in newly diagnosed treatment-naive hypertensive patients. (47)

In our study, although there was no significant difference between NDPHT and DPHT in terms of platelet count, WBC count and NLR, there was a significant difference between the two groups in terms of SII. SII was better for identifying NDPHT than platelet, neutrophil, lymphocyte, NLR, and PLR. In this context, SII, which consists of all those markers, might better and widely reflects the immune status and its association with HT and also with non-dipper pattern.

Limitations

The major limitation was that we included newly diagnosed and treatment-naive hypertensive patients. So, we could not evaluate the effect of treatment on NDPHT, and our study cannot be generalized to all hypertensive patients, especially those on antihypertensive medication. Because the blood counts were measured on the admission day and were not measured on the following days, we could not test the effect of changes in peripheral blood cell counts on BP. The decision of times, including awaking and sleeping, was based on patients' selfreported times. Thus, the use of an objective method might be better to define those periods.

Conclusion

SII is superior to platelet, neutrophil, lymphocyte, NLR, and PLR for identifying the presence of NDPHT. In association with increased serum hs-CRP levels and increased LVMI, increased SII levels may be suitable candidate to predict NDPHT. This study also shows that it is feasible to develop a auxiliary diagnostic method with 69% sensitivity and 77% specificity (SII>347) in predicting non-dipping status in newly diagnosed treatment-naive hypertensive patients.

Declarations

Ethics approval and consent to participate: All patients were informed about the aims of the study and their Written/verbal informed consent for participation was obtained. This study was approved by Fırat University Ethics Committee in accordance with the International Code of Ethics and the Declaration of Helsinki

Consent for publication: Written/verbal informed consent was obtained from patients for anonymized information to be published.

Availability of data and materials: All needed data can be obtained from corresponding author.

Competing interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions: All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

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