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Comparison of diagnostic values of monocyte-lymphocyte ratio, neutrophil-lymphocyte ratio, red cell distribution width-lymphocyte ratio, and systemic inflammatory index in predicting patients with non-dipper hypertension

Serhat Günlü[1], Fethullah Kayan[1], Mehmet Zülkif Karahan[1]

[1] Mardin Artuklu University Faculty of Medicine, Department of Cardiology, Mardin, Türkiye

Abstract

Objective: Hypertension is related to myocardial ischemia, malignant arrhythmias, and cardiovascular mortality. However, inflammatory biomarkers are an important predictor of cardiovascular events. This study aimed to examine the diagnostic utility of inflammatory biomarkers in determining non-dipper hypertensive individuals and the relative superiority of the biomarkers.

Method: The research was carried out as a retrospective observational study. The patients with hypertension were classified into two groups: non-dipper (n=54) and dipper (n=143). The cut-off value of MLR (monocyte-lymphocyte ratio), NLR (neutrophil-lymphocyte ratio), SII (systemic inflammatory index), and RLR (red cell distribution width-lymphocyte ratio) for predicting non-dipper hypertension was determined using a receiver operating characteristic (ROC) analysis.

Results: A total of 197 patients, comprising 84 females (42.6%) and, 113 males (57.4%) with a median age of 62 (54-69) years, participated in the research. Age, FPG, CRP, WBC, NEU, LYM, MONO, RDW, NLR, MLR, RLR, and SII were higher in the non-dipper group ($p<0.05$). MLR, NLR, RLR, and SII were found to have acceptable diagnostic capabilities in identifying non-dipper hypertension patients (AUC: 0.70-0.76). When ROC analysis was performed to determine the main similarities, it was found that there were no differences between inflammatory indicators ($p>0.05$).When the odds ratios of putative variables were evaluated, it was found that increasing MLR (OR: 7.22; 95%CI: 3.52-14.78; $p<0.001$), NLR (OR: 8.63; 95%CI: 4.19-17.68; $p<0.001$), RLR (OR: 4.29; 95%CI: 2.18-8.54; $p<0.001$), and SII (OR: 6.31; 95%CI: 3.09-12.85; $p<0.001$) were independent predictors for non-dipper positivity.

Conclusion: In hypertensive patients, hematological inflammatory biomarkers MLR, NLR, RLR, and SII are valuable in determining non-dipper hypertension.

Keywords: Non-Dipper hypertension, Monocyte-Lymphocyte Ratio, Neutrophil-Lymphocyte Ratio, RDW-Lymphocyte Ratio, Systemic Inflammatory Index

INTRODUCTION

Hypertension is a prevalent systemic disease worldwide and is the leading potential cause of cardiovascular events (1). Despite many treatment methods, the expected degree of preventing organ damage from hypertension has not been achieved (2). Blood pressure (BP) is greatest in the morning, gradually drops during the day, and reaches its lowest level at night. Dipper hypertension is described when overnight BP lowers by more than 10% relative to daytime readings, while non-dipper hypertension is identified when nighttime BP reduces by less than 10% (3). Hypertension is related to harm to organs such as the cardiovascular system in non-dippers (4). The risk of atherosclerotic events is three times greater in people with non-dipper hypertension than those with dipper hypertension (5).

Inflammation plays a role in the pathogenesis of hypertension (6). Variation in BP is connected with inflammatory indicators. Recent research has revealed that inflammatory biomarkers, such as monocyte-lymphocyte

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Corresponding Author: Assoc. Prof. Dr. Serhat Günlü, Mardin Artuklu University Faculty of Medicine, Department of Cardiology, Mardin, Türkiye
Email: serhat8086@hotmail.com
ORCID iD: 0000-0001-6985-6112

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ratio (MLR), systemic inflammatory index (SII), and neutrophil-lymphocyte ratio (NLR) are useful for predicting the non-dipper pattern in hypertension (7). RDW-lymphocyte ratio (RLR) was compared with other markers in many diseases (8). The predictive value of RLR in estimating the non-dipper pattern remains unknown.

We aimed to examine the diagnostic utility of inflammatory biomarkers in determining non-dipper hypertensive individuals and the relative superiority of the biomarkers.

METHOD

This retrospective research was carried out between March 2021 and January 2023. Patients diagnosed with hypertension were enrolled in this study. Exclusion criteria were coronary artery disease, hyperthyroidism, hypothyroidism, valve disease, heart failure, renal failure, autoimmune disease, active infection or cancer, using steroids or anticoagulants, hepatic disease, morbidly obese, pulmonary disease, congenital heart disease, hematological disease. This research eliminated participants for whom data were unavailable and whose ambulatory BP monitoring analysis was ineffective. The local ethics committee (Gazi Yasargil Training and Research Hospital) approved the study protocol (No: 2023-371). It complied with the Helsinki Declaration's ethical criteria for human testing (Date: 03/03/2023) (2013). Patients' sociodemographic and clinical data were extracted from archival files. BP measurements of all patients were obtained from ambulatory Holter (Schiller BR-102 plus PWA, Baar, Switzerland) recordings. According to Holter recordings, patients were divided into dipper and non-dipper. Routine blood test results studied before ambulatory Holter BP wore were used. The formula used to calculate body mass index (BMI) was weight divided by height squared. The NLR value, which is the primary outcome variable and was utilized to calculate the reliability evaluation (post-study power) of counts of individuals enrolled in the groups, was by the cross-sectional research design. NLR was 7.34±5.61 in individuals with the non-dipper, whereas it was 3.11±2.36 in individuals with the dipper. The post-study power was 99% based on the disparity in NLR values between the independent group averages. The post-study power was over 80% based on the differences in the secondary outcome variables MLR, RLR, and SII. The skilled and experienced people wore the ambulatory BP device (DMS 300-3A Holter Recorder). Blood measures were obtained every 15 minutes between 07:00 and 23:00, and every 20 minutes between 23:00 and 07:00. Using short time intervals, the period from 10:00 to 22:00 was designated as daytime, while the period from 24:00 to 6:00 was designated as nighttime. Non-dipper hypertension was defined as lowering the mean blood pressure by less than 10% or staying constant. Dipper hypertension was defined as lowering mean systolic and diastolic blood pressure readings by more than 10%. The whole blood count was calculated using an automated hematology analyzer manufactured by Sysmex Corporation (Kobe, Japan). Total leukocyte count and differentiation, hemoglobin, hematocrit, platelet levels, RDW, NLR, MLR, and RLR values were documented as blood parameters. Multiplying the number of platelets by the NLR yields the SII (Platelet x NLR). Additionally, CRP levels were measured utilizing a Mindray Chemistry Analyzer instrument (BS-2000M, China). IBM SPSS software was used for the analysis (version 24.0).

Statistical analysis

The mean standard deviation or median are utilized to represent initial continuous variables (interquartile range). The Kolmogorov-Smirnov and Shapiro-Wilk tests were utilized to determine the normality of the variable distribution. Frequencies and percentages were utilized to represent categorical variables. The chi-squared or Fisher's exact test was employed for categorical variables. The Student's t-test or Mann-Whitney U-test was used to evaluate continuous variables. Statistical significance was stated at 0.05 for all tests.

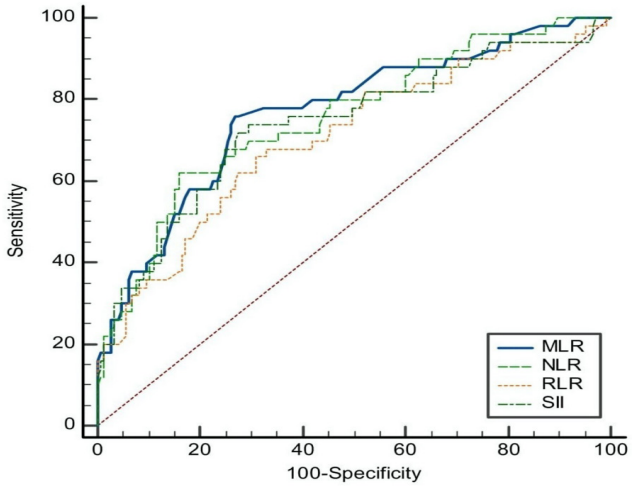

Figure 1. Comparison of the ROC curves for predicting dipper hypertension

RESULTS

A total of 197 patients, comprising 84 females (42.6%) and, 113 males (57.4%) with a median age of 62 (54-69) years, participated in the research. Individuals were classified into two groups: non-dipper (n=54) and dipper (n=143). The patient's clinical characteristics and laboratory results were expressed in Table 1. Age, FPG, CRP, WBC, NEU, LYM, MONO, RDW, NLR, MLR, RLR, and SII were higher in the non-dipper group ($p<0.05$). MLR, NLR, RLR, and SII were found to have the acceptable diagnostic capability in determining non-dipper hypertension (AUC: 0.70-0.76) (Figure 1, Table 2). When ROC

analysis was performed to determine the main similarities, it was found that there were no differences between inflammatory indicators (p>0.05). Put another way, we found that these biomarkers could be utilized interchangeably to predict hypertension in non-dippers (Table 3). When the odds ratios of putative variables were evaluated, it was found that increasing MLR (OR: 7.22; 95%CI: 3.52-14.78; p<0.001), NLR (OR: 8.63; 95%CI: 4.19-17.68; p<0.001), RLR (OR: 4.29; 95%CI: 2.18-8.54; p<0.001), and SII (OR: 6.31; 95%CI: 3.09-12.85; p<0.001) were independent predictors for non-dipper positivity (Table4).

Table 1. Clinical characteristics and laboratory tests of patients.

PARAMETERS	Total (n=197)		Dipper hypertension (n=143)		Non-dipper hypertension (n=54)		p-value*
	n	%	n	%	n	%	
Sex, female	84	42.6	58	40.6	25	46.3	0.43
Diabetes mellitus	86	43.6	62	43.3)	24	44.4	0.91
DL	79	40	55	38.8	24	44.4	0.48
Smoking	68	34.5	45	31.9	23	42.6	0.16
Age (years)	62 (54-69)		61 (53-66)		67 (57-74)		<0.001
BMI, (kg/m2)	31±4.5		31±4.4		30.8±4.9		0.54
FPG (mg/dL)	126.7±40.2		117.2±25.8		154.4±58.3		<0.001
Urea (mg/dL)	34 (29-39)		34 (28-39)		36 (29-49)		0.07
Creatinine (mg/dL)	0.85 (0.73-0.99)		0.83 (0.72-0.98)		0.87 (0.79-1.01)		0.11
Na (mmol/L)	139.14±2.96		139.13±2.98		139.14±2.89		0.98
K (mmol/L)	4.15±0.57		4.11±0.63		4.23±0.44		0.22
ALT (U/L)	20.59±10.51		19.8±9.63		22.4±12.5		0.09
AST (U/L)	21.76±8.95		21.21±8.34		21.24±10.19		0.15
LDL (mg/dl)	137±37		136±39		140±30		0.42
HDL (mg/dl)	39.8±8.4		40.1±8.3		38.6±9.3		0.24
CRP (mg/L)	3.86±3.89		3.21±2.35		5.75±4.96		0.02
WBC (103mcL)	9.82±3.16		9.21±2.51		11.42±2.71		0.001
HGB (g/L)	14.27±1.78		14.28±1.84		14.23±1.59		0.86
HCT (%)	42.33±4.41		42.43±4.48		42.12±4.23		0.56
NEU (103mcL)	6.96±3.25		6.06±2.45		9.59±3.76		<0.001
LYM (103mcL)	2.37±1.51		2.51±1.06		1.97±1.23		0.004
MONO (103mcL)	0.6±0.18		0.55±0.13		0.75±0.26		0.001
RDW (fL)	13.16±0.89		12.83±0.63		14.11±0.94		<0.001
PLT (103mcL)	258.22±72.86		258.38±70.5		257.74±80.06		0.96
NLR	4.29±3.79		3.11±2.36		7.34±5.61		<0.001
MLR	0.33±0.23		0.24±0.13		0.59±0.42		<0.001
RLR	7.38±5.01		6.28±3.08		10.57±7.57		<0.001
SII (PLT*NLR)	1108.19±989.8		779.8±641.53		2060.51±1350.99		<0.001
Systolic BP (mmHg)	110.64±12.50		108.82±12.58		123.48±18.32		<0.001
Diastolic BP (mmHg)	62.36±5.54		60.42±7.84		69.12±8.14		<0.001

* Student's t-test, Chi-Square test (p<0.005 significance). Values are presented as mean ± SD as appropriate. DL: Dyslipidemia, BMI: Body mass index, FPG: Fasting plasma glucose, Na: Sodium, K: Potassium, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TSH: Thyroid-stimulating hormone, fT3: free triiodothyronine, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, CRP:C-reactive protein, WBC: White blood cell, HGB: Haemoglobin, HCT: Haematocrit,NEU: Neutrophil, LYM: Lymphocyte, MONO: Monocyte, RDW: Red Cell Distribution Width, PLT: Platelets, NLR: neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, RLR: RDW to lymphocyte ratio

Table 2. Diagnostic accuracy of inflammatory biomarkers to predict non-dipper hypertension withcut-off values.

	AUC	Cut-off	Sensitivity %	Specificity %	%95CI	P-value	PPV %	NPV %
MLR	0.76	>0.25	75	73.1	0.70-0.82	<0.001	49.2	88.9
NLR	0.75	>4.53	62.1	83.9	0.67-0.82	<0.001	57.3	85.6
RLR	0.70	>6.85	65	69	0.63-0.76	<0.001	42.3	84.5
SII	0.73	>831.39	72.4	72.6	0.66-0.77	<0.001	47.2	87.2

AUC: Area under the curve, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval, MLR: monocyte to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, SII: systemic immune inflammation index

Table 3. Pairwise comparison of ROC curves and difference between areas.

	Difference between areas	95% Confidence Interval	P-value
MLR-NLR	0.01	0.056-0.081	0.71
MLR-RLR	0.06	0.021-0.145	0.15
MLR-SII	0.03	0.048-0.105	0.46
NLR-RLR	0.05	0.013-0.112	0.13
NLR-SII	0.02	0.015-0.046	0.34
SII-RLR	0.03	0.042-0.108	0.38

MLR: monocyte to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, SII: systemic immune inflammation index

Table 4. Multiple regression analysis of inflammatory biomarkers associated with non-dipper hypertension.

	Odds ratio	95% CI	P-value
MLR	7.22	3.52-14.78	<0.001
NLR	8.63	4.19-17.68	<0.001
RLR	4.29	2.18-8.54	<0.001
SII	6.31	3.09-12.85	<0.001

CI: confidence interval, MLR: monocyte to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, SII: systemic immune inflammation index

DISCUSSION

This study's primary finding is that MLR, RLR, NLR, and SII could be utilized to predict non-dipper patterns in individuals with hypertension. The ambulatory Holter BP, which is most frequently used to determine non-dippers in individuals presenting with hypertension, has a lengthy research duration. In contrast, because they are easily accessible and calculable, inflammatory indices may aid in predicting non-dipper hypertension that can cause major adverse events.

According to previous studies, patients with non-dipper hypertension had a more extensive inflammatory reaction, increased serious end-organ damage, and higher cardiac morbidity and mortality (9). The non-dipper BP pattern had a detrimental impact on cardiovascular risk irrespectively of whether the blood pressure was within or beyond the normal range (10). The harmful impact of non-dipper hypertension could be attributed to endothelial damage. Non-dipper hypertension individuals had lower endothelial progenitor cell counts than dipper hypertension individuals in previous research, which is crucial for endothelial stability and arterial regeneration (11). Numerous chronic disorders, including renal disease, coronary artery disease, hypertension, diabetes, connective tissue disease, and cancer, are related to theinflammatory process (12,13,14). Inflammation is related to BP fluctuation and plays a crucial role in the pathophysiology of hypertension (15). Specifically, high BP fluctuation may promote vascular inflammation (16). In Tanase et al. study, inflammatory cytokines including IL-6, hs-CRP, and TNF-α were related to BP fluctuation (17). In addition, Isayeva et al found that the non-dipper pattern of BP was linked to raised inflammatory markers (18).

The neutrophil-lymphocyte ratio (NLR) is a comprehensive inflammatory indicator that evaluates neutrophils and lymphocytes and indicates a pro-inflammatory state. Liu et al. found that increased NLR levels significantly correlated with a raised risk of developing hypertension (19). In another study, NLR was a surrogate marker for hypertension (20). Belen et al. revealed that NLR values were higher in resistant hypertension than in controlled and normotensive patients (21). NLR was independently associated with LVH in hypertensive patients (22). WANG et al. showed that there was a relationship between NLR and artery stiffness in non-dipper hypertension (23). Likewise, epicardial fat tissue thickness and NLR were higher in newly diagnosed hypertension patients (24). In the Taiwan population, NLR was found as an index for hypertension in males and the elderly (25). In Sun et al. study, higher NLR was associated with in-hospital mortality in hypertensive patients aged over 80 years (26).

Monocytes are a component of innate immunity and mature into macrophage and dendritic cells to maintain homeostasis, especially when the presence of inflammation and infection (27). Monocytosis was employed as a marker for several inflammatory disorders such as being essential in the formation of atherosclerosis in coronary artery disease (28). MLR was identified as an independent risk factor for carotid stenosis in hypertensive patients with ischemic stroke (29). Zhang et al. revealed that MLR was a predictor of chronic kidney disease in hypertensive patients (30). In a study, MLR found a new marker to identify target organ damage in children with primary and secondary hypertension (31). Xiang et al. showed that high MLR values better predict all-cause mortality in resistant hypertensive patients undergoing hemodialysis (32). On the other hand, Yıldırım et al. reported that MLR was not a diagnostic marker of preeclamptic patients (33).

In hypertensive individuals, elevated angiotensin II values may stimulate erythrocyte proliferative progenitors (34). Variation in erythrocyte size in circulation is measured by RDW. RLR is a novel inflammatory marker derived from the ratio of the red cell distribution width to the number of lymphocytes. Tanindi et al. found that higher RDW levels were correlated with non-dipper hypertension (35). Buyukkaya et al. stated that RDW was elevated in non-dipping BP in normotensive and hypertensive patients (36). Sarıkaya et al. observed that RDW values were higher in hypertension individuals with AF (37). In a study, RDW was associated with a higher possibility of adverse outcomes of hypertension (38). On the other hand, Sun et al. emphasized that RDW was not accompanied by an increased risk of all-cause mortality (26).

SII is a novel inflammatory index that thoroughly depicts the equilibrium between the immunological and inflammatory states of the organism. It has been established that a high SII value is connected with adverse consequences in individuals with cardiovascular disease and cancer (39). Akyüz et al. stated that SII was independently higher in non-dipper hypertension individuals (40). Saylik et al. observed that SII values were elevated in newly diagnosed, untreated hypertensive individuals with pronounced daytime BP increases (41). In addition, Çırakoğlu et al. demonstrated a strong association between carotid intima-media thickness and SII in non-dipper hypertension (42). In our study, we found that SII had similar diagnostic power to other parameters.

Limitations of the Study

This was a retrospective investigation at a single center. The study population was small. ECG and echocardiography analyses were not examined. No particular inflammatory markers, such as CRP, IL-6, and TNF-α, were examined to evaluate and compare the accuracy and efficacy of parameters.

CONCLUSION

In this study, MLR, NLR, SII, and RLR had the acceptable diagnostic capability in identifying non-dipper hypertension patients. These biomarkers could be utilized interchangeably to predict hypertension in non-dippers. In this field, large-scale studies are needed to determine the diagnostic importance of hematologic inflammation markers and to determine the limit values in predicting the non-dipper character in hypertensive patients.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Gazi Yaşargil Training and Research Hospital Clinical / Human Research Ethics Committee for this study with date March 3rd, 202 and number 2023-371, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: SG, FK Design: SG, FK, Supervising: SG, FK, Financing and equipment: SG, FK, MZK, Data collection and entry: SG, FK, Analysis and interpretation: SG, FK, Literature search: SG Writing: SG, Critical review: SG, FK, MZK

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