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The platelet-to-lymphocyte ratio as an indirect outcome predictor in primary hypertension: a retrospective study

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ABSTRACT

Background: Nondipper hypertensive patients have higher levels of platelet-to-lymphocyte ratio, a new studied inflammatory biomarker in primary hypertension. Furthermore, these patients have a higher risk of cardiovascular morbidity and mortality. This study aimed to assess the relationship between platelet-to-lymphocyte ratio and hypertensive pattern (dipper vs nondipper) and the association between the hypertensive pattern and major adverse cardiovascular events.

Methods: A retrospective analysis was performed. One hundred fifty-three patients were included and classified as dipper or nondipper according to 24-hour ambulatory blood pressure measurements. Platelet-to-lymphocyte ratio was calculated based on complete blood count data.

Results: The dipper group included 109 patients, and the nondipper group included 44 patients. Nondipper patients have 2.11 more risk of presenting a higher platelet-to-lymphocyte ratio than dipper individuals (odds ratio [OR] = 2.11; 95% CI, 1.220–3.664; $P = .007$). Nondipper patients also registered earlier cardiovascular events, such as acute myocardial infarction and stroke ($P < .001$).

Conclusions: Nondipper hypertensive individuals registered higher levels of platelet-to-lymphocyte ratio and earlier cardiovascular events than dipper patients. Therefore, platelet-to-lymphocyte ratio could be used as an indirect predictor of cardiovascular risk in primary hypertension and contribute to optimize preventive strategies.

Keywords: platelet-to-lymphocyte ratio, nondipper hypertension, cardiovascular events

Introduction

Hypertension is a major cause of cardiovascular morbidity and mortality.[1] Despite the fact that its etiopathogenesis remains uncertain, it is believed that primary hypertension interacts intimately with chronic inflammation.[2] Indexes calculated from complete blood count parameters, such as neutrophil-to-lymphocyte ratio, mean platelet volume, red cell distribution width, and platelet-to-lymphocyte ratio (PLR), have been described as potential inflammatory biomarkers.[3-6]

PLR was firstly and extensively studied in malignant diseases, coronary and valvular heart disease, pulmonary thromboembolism, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, and more recently in primary hypertension.[6-13]

According to the circadian variation of blood pressure (BP), systolic blood pressure (SBP) and diastolic blood pressure are expected to decrease more than 10% during sleep, compared with daytime, which happens in dipper hypertensive individuals; in nondipper hypertensive individuals, this variation does not occur.[14]

Nondipper hypertensive individuals have a higher risk of cardiovascular morbidity and mortality, independently of the mean BP, and PLR is significantly higher in these hypertensive individuals.[6,14,15]

This study aimed to evaluate the relationship between PLR and dipper and nondipper primary hypertension and the association between dipping pattern and major cardiovascular events.

Methods

This retrospective study included 153 consecutive patients diagnosed with primary hypertension and referred to internal medicine outpatient clinic, from January 2017 to December 2021.

Demographic characteristics, cardiovascular risk factors (as body mass index, smoking status, cholesterol levels, duration of hypertension, and presence of diabetes mellitus), medication used, and other systemic diseases were collected through the access to clinical files.

Diabetes mellitus was defined according to 2011 American Diabetes Association diagnostic criteria or receiving antidiabetic therapy. Renal failure was defined through the glomerular filtration rate that was calculated using the 2021 CKD-EPI Creatinine formula.

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TABLE 1

Baseline characteristics and clinical data of the study population

Variables	All patients (n = 153)	Nondipper (n = 44)	Dipper (n = 109)	*P*
Age (years)	54.9 ± 17.4	60.0 ± 18.2	52.8 ± 16.6	.023
Female (n)	76	22	54	.959
Body mass index (kg/m^2)	28.4 ± 3.9	28.7 ± 3.7	28.3 ± 4.1	.624
Smoking (n)	23	5	18	.951
Diabetes mellitus (n)	34	14	20	.080
Hyperlipidemia (n)	80	29	51	.091
Antihypertensive agents				.350
ACE inhibitors (n)	41	10	31	
ARBs (n)	5	2	3	
β-Blockers (n)	4	2	2	
Calcium antagonists (n)	4	3	1	
Diuretics (n)	4	0	4	

Data are expressed as mean ± standard deviation or as number of patients; $P < .05$ is considered statistically significant for all tests.
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; n, number.

Patients with secondary hypertension, acute or chronic infection, acute renal failure, malignant or hematological diseases, collagen tissue disease, thrombocytopenia ($<150 \times 10^9$/uL), thrombocytosis ($>450 \times 10^9$/uL) or with use of antiplatelet, and anticoagulant or immunosuppressive agents were excluded from this study.

For each included patients, previously performed 24-hour ambulatory blood pressure monitoring (ABPM) and blood test were selected. The ABPM assessed had more than 70% valid BP measurements and was performed with the cuff placed on the nondominant arm and with device programmed to measure BP every 15 minutes between 07:00 and 23:00 (daytime) and every 20 minutes between 23:00 and 07:00 (night-time). Individuals with a decrease of more than 10% in the mean of SBP and diastolic blood pressure during the night were grouped as dipper hypertensive patients and those without this drop as nondipper hypertensive patients.

The blood sample was collected in the day before the ABPM after overnight fasting. Complete blood count and general chemistry values were collected. PLR was calculated as the ratio between platelet count and lymphocyte count was present in complete blood count. In addition, urine was assessed to evaluate the presence of moderately increased albuminuria.

The study protocol was approved by an independent Ethics Committee (Comissão de Ética para a Saúde—Centro Hospitalar de São João [Ethics Committee of São João Hospital Center]) with code number 107/2022 and complies with the principles outlined in the Declaration of Helsinki. The anonymity of patients was guaranteed.

Statistical analyses

Statistical analyses were performed using SPSS 27.0 statistical package for Windows (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was performed to determine whether data followed a normal distribution. Numerical data with a normal distribution were expressed as mean ± standard deviation, whereas numerical data not normally distributed were presented as median (range). The independent samples *t* test was used to analyze normally distributed parameters, and the Mann-Whitney *U* test was used to analyze parameters without a normal distribution. High PLR was defined as cases presenting a PLR ≥115.09 based on the median values for this ratio. To assess the relationship between these parameters, crosstabs and chi-square test were used. Furthermore, odds ratio (OR) was

TABLE 2

Hemodynamic data of the study population

Variables	All patients (n = 153)	Nondipper (n = 44)	Dipper (n = 109)	*P*
Systolic BP, 24-hour (mmHg)	132.2 ± 15.2	135.1 ± 16.6	131.1 ± 14.6	.177
Systolic BP, awake (mmHg)	141.3 ± 16.5	138.1 ± 16.6	142.4 ± 16.4	.166
Systolic BP, asleep (mmHg)	123.3 ± 15.7	132.1 ± 17.2	120.0 ± 13.8	<.001
Diastolic BP, 24-hour (mmHg)	77.8 ± 11.4	77.3 ± 11.5	77.9 ± 11.4	.774
Diastolic BP, awake (mmHg)	85.5 ± 12.4	81.0 ± 12.2	87.2 ± 12.1	.008
Diastolic BP, asleep (mmHg)	71.1 ± 10.5	73.7 ± 11.3	70.1 ± 10.1	.076

Data are expressed as mean ± standard deviation; $P < .05$ is considered statistically significant for all tests.
BP, blood pressure.

TABLE 3

Laboratory findings of the study population

Variables	All patients (n = 153)	Nondipper (n = 44)	Dipper (n = 109)	*P*
Fasting glucose (mg/dL)	97.0 (67–526)	104.0 (67–356)	95.0 (73–526)	.136
HbA1C (%)	5.5 (4.8–11.3)	5.7 (4.8–8.6)	5.5 (4.8–11.3)	.029*
Creatinine (mg/dL)	0.83 ± 0.29	0.86 ± 0.31	0.83 ± 0.29	.562
Albumin (mg/dL)	43.4 ± 4.8	42.6 ± 3.4	43.8 ± 5.2	.257
Triglyceride (mg/dL)	102.0 (38–211)	123.0 (42–211)	97.5 (38–314)	.131
Total cholesterol (mg/dL)	176.8 ± 35.5	177.1 ± 35.9	176.7 ± 35.5	.954
LDL cholesterol (mg/dL)	100.8 ± 30.8	100.1 ± 33.2	101.1 ± 30.0	.860
HDL cholesterol (mg/dL)	51.8 ± 10.9	51.1 ± 10.5	52.1 ± 11.1	.629
Moderately increased microalbuminuria (n)	35	9	26	.653
Lymphocytes ($\times 10^9$/L)	2.1 (0.9–5.6)	1.9 (0.9–3.7)	2.2 (0.9–5.6)	.027*
Platelet ($\times 10^9$/L)	244.9 ± 58.9	252.5 ± 58.0	241.5 ± 59.3	.301
PLR	115.1 (37.1–259.8)	140.4 (69.9–254.2)	108.6 (37.1–259.8)	<.001*

Data are expressed as median (min-max), mean ± standard deviation, or as number of patients; $P < .05$ is considered statistically significant for all tests (*).
HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number; PLR, platelet-to-lymphocyte ratio.

calculated as a measure of association between an exposure (high PLR) and an outcome (nondipper status). *P* values less than .05 were considered statistically significant. Finally, the hazard ratio (HR) was calculated to determine the temporal relationship between cardiovascular events and hypertensive pattern.

Results

The study population was consisted of 153 consecutive patients diagnosed with primary hypertension. The mean age of the patients was 54.9 ± 17.4 years, and most (75.8%) were diagnosed with hypertension less than 15 years ago.

All patients were divided into two groups according to the status of dipper or nondipper hypertension in 24-hour ambulatory BP monitoring. The dipper group included 109 patients, and the nondipper group included 44 patients.

Demographic and clinical characteristics were similar in both groups (Table 1). No differences were found between the two groups relatively to body mass index, active smoking, and

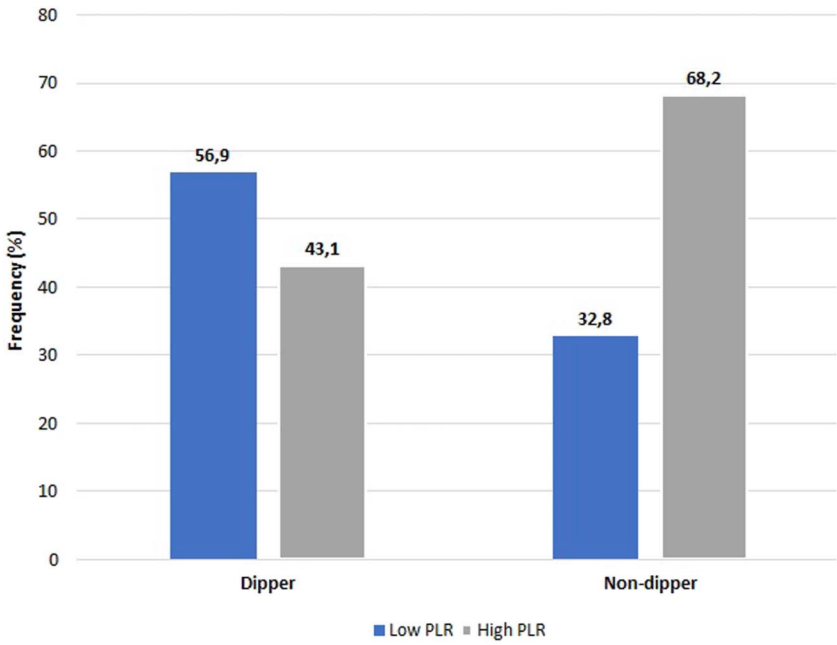

Figure 1. The relationship between PLR and hypertensive pattern.

TABLE 4

Cardiovascular events and number of deaths according to the hypertensive pattern

Variables	All patients (n = 153)	Nondipper (n = 44)	Dipper (n = 109)	*P*
Acute myocardial infarction (n)	17	13	4	<.001*
Stroke (n)	23	12	11	.004*
Death—cardiovascular cause (n)	1	1	0	.116
Death—other cause (n)	3	1	2	.860

Data are expressed as number of patients; $P < .05$ is considered statistically significant for all tests (*).
n, number.

chronic diseases such as hyperlipidemia and diabetes mellitus. Approximately 112 of the 153 patients were taking antihypertensive agents: 26 were taking one drug, 31 were taking two drugs, and 55 were taking three or more drugs. The patients took their pills at fixed hours.

The mean asleep SBP was significantly higher in the nondipper group than in the dipper group (132.1 ± 17.2 mmHg versus 120.0 ± 13.8 mmHg, $P < .0001$). The mean awake DSP was significantly higher in the dipper group (87.2 ± 12.1 mmHg versus 81.0 ±12.2 mmHg, $P = .008$) (Table 2). No differences between the two groups were found relatively to the other BP measures.

Laboratory findings were similar between the dipper and nondipper groups (Table 3), with few exceptions: The median level of glycated hemoglobin (HbA1C) was significantly higher in the nondipper group (5.7% [4.8–8.6] versus 5.5% [4.8–11.9], P=.029); lymphocyte count was significantly lower in the nondipper group (1.9×10^9/uL [0.9–3.7] versus 2.2×10^9/uL [0.9–5.6], $P = .027$); and the median PLR was significantly higher in the nondipper group than in the dipper group (140.4 [69.9–254.2] versus 108.6 [37.1–259.9], P<.001) (Table 3).

In addition, the PLR variable was subdivided, using as cutoff median, in other two categories—low PLR (<115.09) and high PLR (≥115.09)—and its association with hypertensive pattern was expressed in a bar chart (Fig. 1). A crosstab and chi-square test were performed, and a higher PLR was significantly associated with the nondipper pattern. In fact, these patients have 2.11 more risk of presenting a higher PLR than dipper individuals (OR = 2.11; 95% CI, 1.220–3.664; $P = .007$).

Regarding cardiovascular events, the number of patients with a history of acute myocardial infarction and stroke was significantly higher in the nondipper group when compared with the dipper individuals ($P < .001$ and $P = .004$, respectively) (Table 4). The hazard curves were plotted, and nondipper patients registered earlier cardiovascular events when compared with the dipper individuals ($P < .001$) (Fig. 2.) This association persisted after logistic regression analysis with variables such as age, sex, diabetes, and chronic renal failure.

In addition, no significant differences were found between myocardial infarction and stroke and PLR categories—low or high PLR ($P = .209$ and $P = .071$, respectively) (Table 5). The

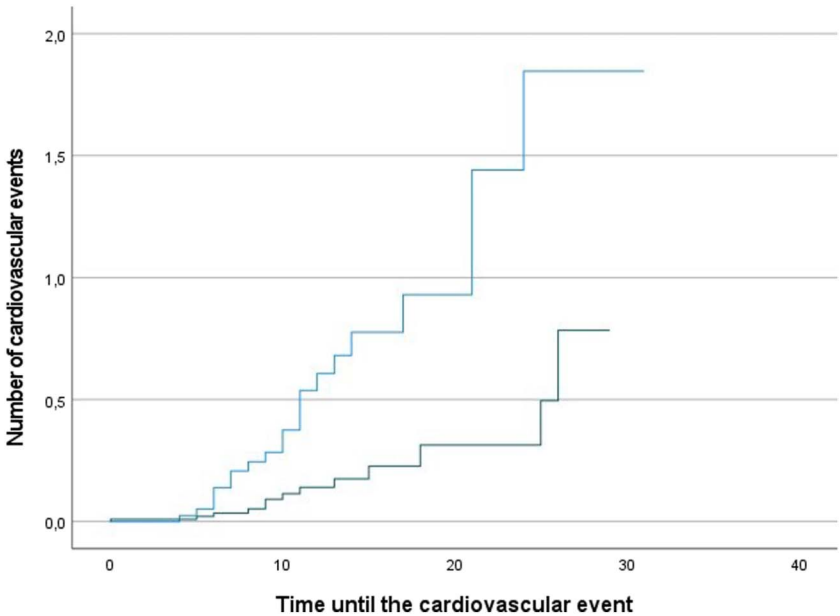

Figure 2. The association between hypertensive pattern and major cardiovascular events: hazard curves. Legend: hypertension pattern. Light blue: nondipper pattern. Dark blue: dipper pattern.

TABLE 5

Cardiovascular events and number of deaths according to PLR categories

Variables	All patients (n = 153)	Low PLR (n = 76)	High PLR (n = 77)	*P*
Acute myocardial infarction (n)	17	6	11	.209
Stroke (n)	23	12	11	.071
Death—cardiovascular cause (n)	1	1	0	.313
Death—other cause (n)	3	1	2	.568

Data are expressed as number of patients; $P < .05$ is considered statistically significant for all tests (*).
n, number.

hazard curves were plotted too, and no significant association was verified (Fig. 3).

Discussion

Hypertension is a major cause of cardiovascular morbidity and mortality, and it is believed to be associated with inflammatory process.[1,2] Inflammation promotes platelet activation, which stimulates thrombus formation in consequence of rupture of atherosclerotic plaques or endothelial cell erosion, promoting atherothrombotic disease and cardiovascular events.[16-18] PLR has been studied as a biomarker of inflammation in proinflammatory diseases as in primary hypertension.[6]

The literature suggests that PLR is higher in nondipper patients when compared with dipper hypertensive individuals.[6,14,15] Bayracki also suggested that PLR is an independent risk factor for the nondipper hypertension. In fact, in this study, a higher PLR predicted a nondipper pattern.[6]

In addition, in this study, lower lymphocyte count showed significant association with the nondipper pattern. In fact, lower lymphocyte count in the presence of high PLR could be explained by the elevated level of endogenous cortisol that is associated with inflammatory response.[19] In addition, HbA1c has significantly higher in the nondipper group, probably due to the susceptibility of these patients to have several vascular risk factors. Despite this, these results did not confirm the influence of diabetes on the association between nondipper pattern and cardiovascular events.

Nondipper hypertensive patients have a higher risk of adverse cardiovascular events.[1] In fact, left ventricular hypertrophy and heart failure are more associated with nondipper hypertension.[20,21] Furthermore, nondipper hypertension is considered an independent risk factor for all-cause of mortality.[1] In this study, nondipper individuals registered higher levels of PLR and earlier cardiovascular events than dipper patients. Therefore, PLR could be used as an indirect predictor of cardiovascular risk in primary hypertension and contribute to optimize preventive strategies.

This study has some limitations because of its retrospective design and the small size of the sample, and in this way, generalizations should be performed with caution. It included patients with diabetes mellitus; dyslipidaemia and chronic renal failure; diseases associated with inflammatory

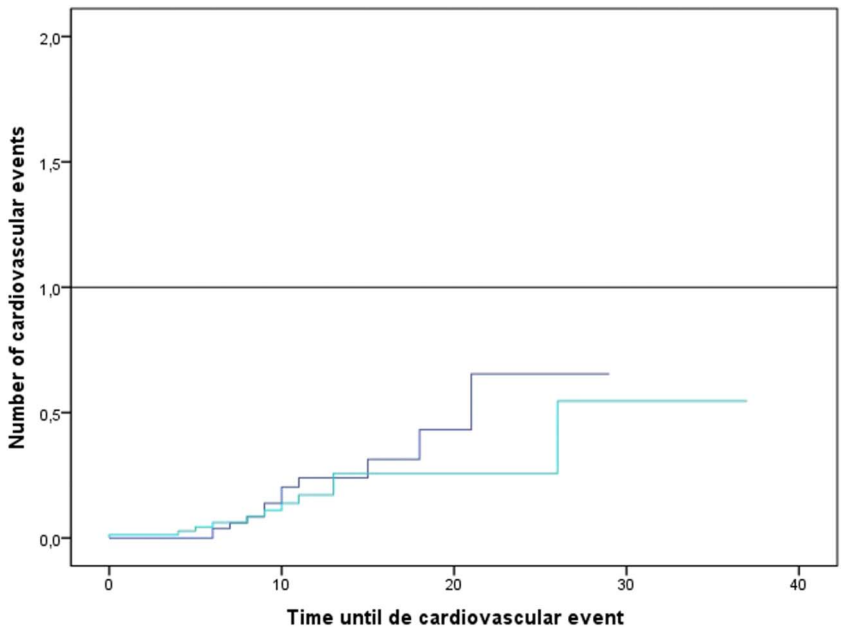

Figure 3. The association between PLR categories and major cardiovascular events: hazard curves. Legend: low/high PLR. Light blue: high PLR. Dark blue: low PLR.

processes, which could influence the levels of platelets; and lymphocytes. Furthermore, future studies must consider other inflammatory biomarkers associated with primary hypertension, such as neutrophil-to-lymphocyte ratio. Finally, regarding mortality, the collected data were not sufficient to be relevant because of the low number of patients and short length of follow-up. Therefore, no conclusions could be done about the relationship between mortality and hypertensive pattern and mortality and PLR categories.

In conclusion, nondipper hypertensive individuals registered higher levels of PLR. Furthermore, these patients had earlier cardiovascular events, such as acute myocardial infarction and stroke. PLR can be used in the daily practice to estimate the cardiovascular risk in nondipper hypertensive patients and contribute to optimize preventive strategies. In addition, PLR is easily calculated through the access to hemogram parameters, which is a cost-effective examination.

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None.

Conflicts of interest statement

The authors declare no conflicts of interest.

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