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Serum uric acid levels and inflammatory markers with respect to dipping status: A retrospective analysis of hypertensive patients with or without chronic kidney disease

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ABSTRACT

Background: The aim of this study was to evaluate serum uric acid levels, inflammatory markers [C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)] and mean platelet volume (MPV) among hypertensive patients with or without chronic kidney disease (CKD) with respect to dipping status. *Methods*: A total of 432 hypertensive patients with (n = 340) or without (n = 92) CKD who had ambulatory blood pressure monitoring recordings were included. Correlation of serum uric acid levels with inflammatory markers (CRP, PLR, NLR) was evaluated as was the logistic regression analysis for determinants of nondipper pattern. *Results*: Nondipper pattern was noted in 65.2% and 79.7% of non-CKD and CKD patients, respectively. Multivariate logistic regression analysis revealed that only serum uric acid (OR, 2.69; 95% CI, 1.60 to 4.52; p = 0.000), MPV (OR, 1.81; 95% CI, 1.30 to 2.53; p = 0.000), PLR (OR, 0.98; 95% CI, 0.97 to 0.99; p = 0.000), and serum albumin (OR, 0.42; 95% CI, 0.19 to 0.93; p = 0.031) were significant determinants of nondipper pattern in the overall study population. *Conclusion*: In conclusion, our findings revealed higher prevalence of nondipper pattern in hypertensive patients with than without CKD and significantly higher levels for uric acid, CRP, MPV, PLR, and NLR among nondipper than dipper hypertensive patients with CKD. High levels for uric acid and MPV and lower levels for PLR and serum albumin were noted as significant determinants of nondipper pattern among hypertensive patients.

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Introduction

Chronic kidney disease (CKD) is emerging as a worldwide public health problem in relation to rising prevalence and incidence, while under-recognition of the disease at earlier stages has been associated with unfavorable outcomes (1,2). Thus, identification of risk factors and earlier detection of disease seem crucial to implement therapeutic interventions to prevent progression toward renal failure (3).

The nondipping phenomenon, defined as the lack of a nocturnal blood pressure (BP) decline ≥ 10% of daytime values (4), has been closely related to a high incidence of cardiovascular disease and a poor long-term survival in end-stage renal disease (ESRD) patients (5). Along with profound alterations in circadian BP (6,7), blunted fall in sleep BP (nondipping) occurs early in the course of disease among CKD patients (8–10). Hence, detection of altered circadian pattern via 24 h ambulatory blood pressure monitoring (ABPM) patterns, including blunting or loss of diurnal variation, has become important in hypertensive and CKD patients (3,10).

Although the exact mechanisms underlying the relationship between nondipper hypertension, increased target organ damage, and the higher frequency of cardiovascular events have not yet been clarified, a significant role has been attributed to the increased inflammation and high platelet activity (11,12).

Uric acid, the end product of purine catabolism in humans, is a component of the metabolic syndrome, while elevated levels were shown to be associated with increases in certain inflammatory markers and indicators of oxidative stress as well as with increased prevalence of nondipper hypertension and high-risk status of cardiovascular complications (12–17), while the exact role of hyperuricemia in the CKD progression and hypertension in humans is still a matter of controversy.

C-reactive protein (CRP), a member of the pentaxin family synthesized mainly in the liver under the influence of inflammatory cytokines (18), is considered to be an important indicator of increased inflammation and endothelial dysfunction associated with adverse events in cardiovascular diseases such as hypertension (12,19,20).

Increased total white blood cell (WBC) counts, increased neutrophil and platelet counts, and relative lymphocytopenia have been implicated as a biomarker of atherosclerosis in the general population, in patients with coronary artery disease as well as in ESRD patients (21–27). Additionally, higher levels of inflammatory markers were reported to be associated with faster progression of CKD, while total WBC count has been reported to predict deterioration of the kidney function (28–30).

Increased mean platelet volume (MPV) levels were reported to be related with left ventricular hypertrophy (LVH) in

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patients with essential hypertension (31,32). Recently, neutrophil-to-lymphocyte ratio (NLR) was introduced as a novel inexpensive and readily available indicator that reflects the severity and extension of systemic inflammation and atherosclerosis and predicts adverse clinical outcomes and estimates survival in cardiac and noncardiac disorders including ESRD (22,33–35). The platelet-to-lymphocyte ratio (PLR) has also recently been investigated as a new inflammatory marker that predicts major adverse outcomes in various cardiovascular and oncological diseases (36–39).

There is solid evidence that elevated CRP levels predict future cardiovascular events (40), while both PLR and NLR present simple and feasible novel prognostic inflammatory markers, providing better information than the total WBC count, for adverse cardiovascular outcomes in many types of cardiovascular diseases (36,37,41–44).

Despite the importance of nondipper hypertension on cardiovascular outcomes, there is a few data about the relationship between nondipper hypertension and uric acid, MPV, and new inflammatory markers in CKD. The present study was designed to evaluate serum uric acid levels, inflammatory markers (CRP, PLR, NLR), and MPV among hypertensive patients with or without CKD with respect to dipping status.

Methods

Study population and design

A total of 432 hypertensive patients with (n = 340) or without (n = 92) CKD who had ABPM recordings during their follow up at our clinic were included in this retrospective single-center study. Patients with diabetes mellitus, chronic liver disease, thyroid dysfunction, malignancy, acute infection, sleep disorder, and patients receiving allopurinol treatment were excluded from the study.

The study was conducted in full accordance with local Good Clinical Practice (GCP) guideline and current legislations, while the permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

Study parameters

Data on patient demographics, body mass index (BMI; kg/m^2), antihypertensive medication, ABPM recordings [daytime, nighttime, and 24 h systolic and diastolic BP, dipping status (%)], complete blood count [hemoglobin (g/dL), hematocrit (%), MPV, and automated differential counts for total WBCs, neutrophils, and lymphocytes], blood biochemistry [serum levels for urea, creatinine, uric acid, albumin, total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), electrolytes, parathormone, and ferritin], inflammatory markers (CRP, NLR, and PLR), and transthoracic echocardiography findings were recorded among dipper and nondipper patients in CKD and non-CKD groups. Correlation of serum uric acid levels with inflammatory markers was evaluated as were the univariate and multivariate logistic regression analyses for determinants of nondipper pattern.

Blood biochemistry analysis

All the laboratory test samples were obtained after an overnight fasting. All biochemical analyses including serum urea, creatinine, uric acid, albumin, total cholesterol, triglyceride, LDL, HDL, electrolytes, parathormone, and ferritin were measured standard enzymatic procedures by using Roche Cobas 6000 Modular analytics system. Serum CRP levels were measured by using nephelometric method (Siemens BN II system, Germany). Complete blood count with automated differential counts, which included total WBCs, neutrophils and lymphocytes, and the levels of MPV were obtained at the time of admission. NLR was calculated as ratio of neutrophil-to-lymphocyte counts and similarly PLR was calculated as the ratio of the platelet count-to-lymphocyte count, both obtained from the same blood sample. Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

ABPM recording

ABPM was recorded during a routine day by a SpaceLabs device osciometric unit (SpaceLabs, Hertford, UK). The device was applied to the nondominant arm and was applied for 24 h. BP was measured every 15 min during the daytime (7 am to 10 pm) and every 30 min at nighttime, which was between 10 pm and 7 am. The patients were instructed to maintain their usual activities during the monitoring process and stay calm when sensing the cuff inflation. Sleep and wake periods were assessed based on the information obtained from the patients. The recordings were analyzed from the study if >20% of the measurements were not recorded successfully. From the hourly averages of ambulatory BP recordings, daytime, nighttime, and 24 h averages of systolic and diastolic BPs were calculated for each patient. Nocturnal dipping (%) was defined by percent decrease in nighttime systolic BP compared to daytime systolic BP. When nocturnal dipping was less than 10%, it was defined as a nondipper pattern. For the dipping pattern, we defined the percentage decline in nocturnal systolic BP and diastolic BP from day to night by implementing the formula: [(daytime BP mean) – (nighttime mean)]/(daytime BP mean) × 100.

The definition on hypertension was 24 h ABP>135/85 mmHg or the active use of antihypertensive drugs.

Transthoracic echocardiography

All patients underwent standard transthoracic echocardiographic examination (Philips HD11 XE Ultrasound system, Bothel, USA) with a 1–5 MHz mHz transducer. Measurements of interventricular septal thickness, posterior wall thickness, and LV dimensions were performed at or just below the mitral valve tips, by the leading edge-to-leading edge method, according to the American Society of Echocardiography recommendations. LV end-diastolic and end-systolic and stroke volumes were calculated with the use of Teichholz's method.

Statistical analysis

SPSS 15.0 for Windows programs was used for statistical analysis. Parametric data were presented as mean ± standard deviation (SD). Student's *t* test was used for parametric variables and Mann–Whitney *U* test used for nonparametric variables. Spearman and Pearson tests were used for correlation analysis. Yates correction chi-square test and Fisher's exact test were used for comparison of qualitative data. Multivariate mutually adjusted logistic regression analysis was performed to determine risk factors for nondipper pattern. p-Value < 0.05 was considered as significant.

Results

Baseline demographic and clinical characteristics

Overall, nondipper pattern was noted in 65.2% of patients in non-CKD and 79.7% of patients in CKD group. No significant difference in demographics, anthropometrics, and antihypertensive treatments was noted between dipper and nondipper patients in CKD and non-CKD groups. Nighttime systolic and diastolic BP levels were significantly higher and average nocturnal dipping was significantly lower in nondipper than dipper patients in both CKD and non-CKD groups ($p < 0.001$ for each) (Table 1).

Laboratory findings

Uric acid, CRP, MPV, and PLR levels were significantly higher among nondipper than dipper patients in both CKD (6.9 ± 1.4 mg/dL vs. 5.6 ± 1.1 mg/dL, $p < 0.001$; 10.6 ± 13.7 mg/L vs. 6 ± 5.8 mg/L, $p < 0.001$; 10.2 ± 1.5 fL vs. 8.7 ± 1.0 fL, $p < 0.001$; and 157.3 ± 60.4 vs. 129.5 ± 65.3, $p < 0.001$, respectively) and non-CKD (5.4 ± 1.0 mg/dL vs. 4.6 ± 1.0 mg/dL, $p < 0.001$; 7.6 ± 4.4 mg/L vs. 4.7 ± 3.2 mg/L, $p < 0.001$; 9.5 ± 1.2 fL vs. 8.6 ± 0.8 fL, $p < 0.001$; and 121.1 ± 35.6 vs. 105.2 ± 25.7, $p = 0.02$, respectively) groups. NLR was significantly higher among nondipper than dipper patients (2.8 ± 1.1 vs. 2.2 ± 1.2, p < 0.001) only in the CKD group (Table 2, Figure 1).

No significant difference was noted in echocardiography findings with respect to dipping pattern in both CKD and non-CKD groups (Table 2).

Correlation of uric acid levels with inflammatory markers

Apart from no correlation to NLR in nondipper patients in the non-CKD group, serum uric acid levels were positively correlated with CRP, NLR, PLR, and MPV regardless of dipper pattern and CKD presence (Table 3, Figure 2).

Univariate analysis of correlates of nondipper pattern

Presence of CKD (OR, 2.17; 95% CI, 1.31 to 3.60; $p = 0.003$), increase in NLR (OR, 1.92; 95% CI, 1.39 to 2.65; $p = 0.000$), PLR (OR, 1.01; 95% CI, 1.00 to 1.02; $p = 0.000$), MPV (OR, 2.32; 95% CI, 1.86 to 2.89; $p = 0.000$), CRP (OR, 1.15; 95% CI, 1.08 to 1.22; $p = 0.000$), and serum uric acid (OR, 2.18; 95% CI, 1.76 to 2.70; $p = 0.000$) levels, while decrease in serum albumin levels (OR, 0.44; 95% CI, 0.22 to 0.85; $p = 0.015$) were associated with increased likelihood of nondipper pattern according to the univariate analysis (Table 4).

Multivariate linear regression analysis for determinants of nondipper pattern

Multivariate logistic regression analysis of mutually adjusted risk factors revealed that only serum uric acid (OR, 2.69; 95% CI, 1.60 to 4.52; $p = 0.000$), MPV (OR, 1.81; 95% CI, 1.30 to 2.53; $p = 0.000$), PLR (OR, 0.98; 95% CI, 0.97 to 0.99; $p = 0.000$), and serum albumin (OR, 0.42; 95% CI, 0.19 to 0.93; $p = 0.031$) were significant determinants of nondipper pattern in the overall study population (Table 4).

Discussion

Our findings revealed higher prevalence of nondipper pattern in hypertensive patients with than without CKD and significantly higher levels for uric acid, CRP, and MPV levels as well as higher PLR among nondipper than dipper hypertensive patients in both CKD and non-CKD groups. NLR was significantly higher among nondipper than dipper hypertensive patients only in the CKD group. Presence of CKD, higher levels for uric acid, MPV, CRP, PLR, and NLR, and lower serum albumin levels in the univariate analysis, whereas high levels for uric acid and MPV and lower levels for PLR and serum albumin in the multivariate analysis were noted as significant determinants of nondipper pattern.

Higher prevalence of nondipper pattern in hypertensive patients with than without CKD in our study, along with identification of presence of CKD to significantly predict the increased likelihood of nondipper pattern, supports the well-recognized fact that patients with CKD often have a nondipping BP pattern prevalence of which increases with degree of renal dysfunction (10,45). Similarly, data from a past study in nondiabetic hypertensive patients revealed higher frequency of patients with newly developed CKD in the nondippers than dippers on 24 h ABPM, while nondipper status was also shown to be a significant predictor of incident CKD independent of office BP or mean full-time/daytime BP (3).

Higher levels for uric acid, CRP, MPV, PLR, and NLR in nondipper than dipper hypertensives with CKD in our cohort seem notable given the association of nondipping pattern with a faster progression of renal insufficiency (4), and an increased risk of total mortality and the composite end point of incident ESRD and death in patients with CKD (46).

The association between higher nocturnal BP and endothelial inflammation was shown to be bidirectional with endothelial inflammation leading to higher BP, while higher BP worsening of the inflammatory process leading to higher levels of inflammatory markers such as CRP (12,47). Association of nondipping pattern with all inflammatory parameters (CRP, PLR regardless of kidney function, and NLR only in CKD patients) and MPV in our cohort supports that nondipping BP is associated with increased platelet activity and inflammatory response, which has been suggested to be one of the underlying plausible mechanisms of nondipping BP status among hypertensive patients (17).

Table 1. Baseline demographic and clinical characteristics.

	Chronic kidney disease					
	Absent (n = 92)			Present (n = 340)		
	Dipper (n = 32)	Nondipper (n = 60)	p-Value	Dipper (n = 69)	Nondipper (n = 271)	p-Value
	Mean (SD)			Mean (SD)		
Age (years)	56.6 (10.7)	56.9 (12.0)	0.904	58.0 (14.0)	58.3 (12.1)	0.813
Gender (M/F)	16/16	40/20	0.119	32/37	129/142	0.856
BMI (kg/m^2)	30.9 (2.9)	28.9 (5.0)	0.587	31.4 (5.2)	30.8 (5.4)	0.576
Drug use	*n* (%)			*n* (%)		
ACE inhibitors	7 (21.8)	13 (21.6)	0.98	14 (20.3)	57 (21.0)	0.75
AT1-R blockers	12 (37.5)	24 (40.0)	0.67	28 (40.6)	107 (39.5)	0.88
β-Blockers	7 (21.8)	13 (21.6)	0.85	16 (23.2)	61 (22.5)	0.56
CCBs	4 (12.5)	8 (13.3)	0.65	9 (13.2)	38 (14.0)	0.72
Diuretics	7 (21.9)	12 (20.0)	0.52	14 (20.3)	57 (21.0)	0.64
ABPM recordings (mmHg)						
Overall, 24 h	Mean (SD)			Mean (SD)		
Systolic BP	141.4 (13.5)	147 (18.1)	0.105	157.5 (20.5)	152.5 (20.3)	0.059
Diastolic BP	84.6 (10.7)	86.4 (12.3)	0.486	87.9 (14.9)	83.5 (14.6)	**0.029**
Daytime						
Systolic BP	147.1 (14.4)	147.6 (17.7)	0.837	163.5 (21.6)	152.5 (20.1)	**<0.001**
Diastolic BP	89 (11.9)	87.1 (12.9)	0.360	92.3 (16.0)	94.4 (14.7)	**<0.001**
Nighttime						
Systolic BP	124.6 (12.8)	144.9 (19.9)	**<0.001**	138.1 (17.9)	152.8 (23.2)	**<0.001**
Diastolic BP	71.5 (9.2)	83.6 (13.4)	**<0.001**	74.4 (13.1)	80.8 (15.3)	**0.001**
Average nocturnal dipping						
Systolic	15.3 (4.6)	1.8 (6.2)	**<0.001**	15.3 (5.4)	0.02 (6.6)	**<0.001**
Diastolic	19.4 (6.7)	4.1 (10.2)	**<0.001**	19.1 (7.6)	4.2 (8.4)	**<0.001**

ABPM: ambulatory blood pressure monitoring; ACE: angiotensin-converting enzyme; AT1-R: angiotensin II type 1 receptor; BMI: body mass index; BP: blood pressure; CCBs: calcium channel blockers.
Values in bold indicate statistical significance (p<0.05).

Table 2. Laboratory findings.

	Chronic kidney disease					
	Absent (n = 92)			Present (n = 340)		
	Dipper (n = 32)	Nondipper (n = 60)	p-Value	Dipper (n = 69)	Nondipper (n = 271)	p-Value
Blood biochemistry	Mean (SD)			Mean (SD)		
FBG (mg/dL)	94.0 ± 17.5	98 ± 15.0	0.42	103.3 ± 14.2	101.7 ± 11.0	0.62
Urea (mg/dL)	28.1 ± 8.1	26.2 ± 6.5	0.263	58.6 ± 35.5	64.2 ± 38.0	0.300
Creatinine (mg/dL)	0.8 ± 0.1	0.7 ± 0.1	0.061	1.8 ± 1.2	2.0 ± 1.6	0.672
Uric acid (mg/dL)	4.6 ± 1.0	5.4 ± 1.0	**<0.001**	5.6 ± 1.1	6.9 ± 1.4	**<0.001**
Sodium (mmol/L)	139.8 ± 2.4	139.7 ± 2.1	0.524	139.4 ± 4.2	139.9 ± 3.4	0.423
Potassium (mmol/L)	4.2 ± 0.9	4.2 ± 1.0	0.078	4.7 ± 0.6	4.7 ± 0.8	0.215
Calcium (mg/dL)	9.5 ± 0.3	9.4 ± 0.3	0.297	9.5 ± 0.6	9.4 ± 0.8	0.3
Phosphorus (mg/dL)	3.5 ± 0.7	3.5 ± 0.5	0.787	3.7 ± 0.9	3.7 ± 0.8	0.609
Albumin (g/dL)	4.5 ± 0.3	4.5 ± 0.3	0.862	4.4 ± 0.4	4.2 ± 0.5	**0.001**
Iron (μg/dL)	96.0 ± 83.8	76.7 ± 37.0	0.504	74.4 ± 33.2	74.0 ± 31.0	0.863
TIBC (μg/dL)	348.0 ± 66.1	367.7 ± 63.8	0.327	324.3 ± 66.8	316.1 ± 65.8	0.401
Ferritin (ng/mL)	110.7 ± 124.6	68.4 ± 81.5	0.165	137.1 ± 223.8	116.3 ± 122.9	0.881
Parathormone (pg/mL)	54.7 ± 16.2	63.7 ± 43.5	0.890	116.8 ± 153.4	111.6 ± 100.2	0.385
Total cholesterol (mg/dL)	195.3 ± 36.5	197.6 ± 41.4	0.803	205.4 ± 40.1	198.2 ± 44.6	0.152
Triglyceride (mg/dL)	133.4 ± 70.2	169.3 ± 120.1	0.400	181.4 ± 116.2	165.9 ± 105.0	0.382
LDL-cholesterol (mg/dL)	117.4 ± 32.6	117.9 ± 36.7	0.865	118.6 ± 38.3	117.7 ± 40.4	0.664
HDL-cholesterol (mg/dL)	52.5 ± 19.4	61.3 ± 98.0	0.311	49.1 ± 17.8	48.0 ± 16.1	0.738
Hemogram						
Hemoglobin (g/dL)	13.8 ± 1.7	13.4 ± 1.8	0.382	13.2 ± 1.9	13.0 ± 2.4	0.304
Hematocrit (%)	40.7 ± 4.7	40.1 ± 4.7	0.604	45.3 ± 50.4	38.5 ± 5.7	0.256
MPV (fL)	8.6 ± 0.8	9.5 ± 1.2	**<0.001**	8.7 ± 1.0	10.2 ± 1.5	**<0.001**
24 h proteinuria (g/day)	0.12 ± 0.08	0.14 ± 0.08	0.113	0.83 ± 1.25	1.70 ± 9.57	0.107
GFR (mL/min)	103.6 ± 10.9	102.8 ± 9.3	0.922	49.4 ± 25.4	46.5 ± 23.8	0.514
Inflammatory markers						
CRP (mg/L)	4.7 ± 3.2	7.6 ± 4.4	**<0.001**	6.0 ± 5.8	10.6 ± 13.7	**<0.001**
NLR	2 ± 0.9	2.1 ± 1.3	0.62	2.2 ± 1.2	2.8 ± 1.1	**<0.001**
PLR	105.2 ± 25.7	121.1 ± 35.6	**0.02**	129.5 ± 65.3	157.3 ± 60.4	**<0.001**
Echocardiography findings						
LV ejection fraction (%)	63.8 ± 2.6	63.4 ± 4.3	0.98	58.0 ± 8.2	59.8 ± 6.9	0.183
Left atrial diameter (cm)	3.5 ± 0.3	3.5 ± 0.4	0.99	3.8 ± 0.5	3.9 ± 0.5	0.951
LVED diameter (cm)	4.7 ± 0.2	4.6 ± 0.4	0.62	4.8 ± 0.6	4.7 ± 0.5	0.547
LVES diameter (cm)	3.0 ± 0.2	2.9 ± 0.3	0.64	3.4 ± 1.0	3.1 ± 0.5	0.088
IVST (cm)	1.0 ± 0.1	1.1 ± 0.1	0.72	1.2 ± 0.2	1.2 ± 0.2	0.676
PWT (cm)	0.9 ± 0.1	1.0 ± 0.1	0.88	1.1 ± 0.2	1.1 ± 0.2	0.990

CRP: C-reactive protein; FBG: fasting blood glucose; GFR: glomerular filtration rate; HDL: high-density lipoprotein; IVST: interventricular septum thickness; LDL: low-density lipoprotein; LV: left ventricle; LVED: left ventricle end-diastolic; LVES: left ventricle end-systolic; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PWT: posterior wall thickness; TIBC: total iron binding capacity.
Values in bold indicate statistical significance (p<0.05).

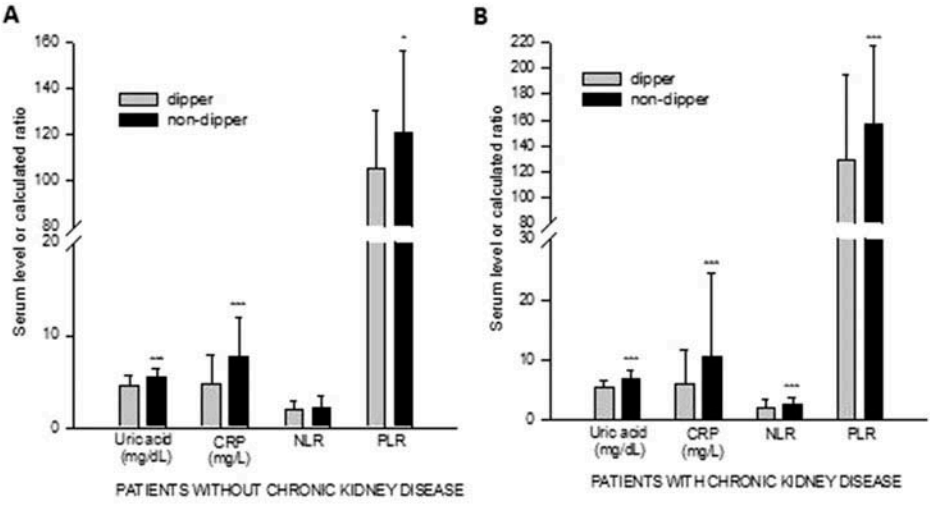

Figure 1. Serum uric acid levels and inflammatory markers in patients with and without CKD according to dipping status. *$p < 0.05$ and ***$p < 0.001$ compared to non-dipper patients.

Table 3. Correlation of uric acid levels with inflammatory markers.

	Chronic kidney disease							
	Absent				Present			
	Dipper (n = 32)		Nondipper (n = 60)		Dipper (n = 69)		Nondipper (n = 271)	
	Rho	p-Value	Rho	p-Value	Rho	p-Value	Rho	p-Value
CRP	0.787	**<0.001**	0.750	**<0.001**	0.663	**<0.001**	0.664	**<0.001**
NLR	0.774	**<0.001**	−0.023	0.860	0.831	**<0.001**	0.688	**<0.001**
PLR	0.726	**<0.001**	0.761	**<0.001**	0.755	**<0.001**	0.832	**<0.001**
MPV	0.748	**<0.001**	0.886	**<0.001**	0.565	**<0.001**	0.740	**<0.001**

CRP: C-reactive protein; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.
Values in bold indicate statistical significance (p<0.05).

Higher levels for CRP, MPV, and uric acid in nondipper hypertensives with or without CKD in our study are in agreement with published data on higher levels of CRP, serum uric acid (12,17), and MPV (17,48–50) levels in the nondipper hypertensive patients compared to dipper hypertensive patients and normotensive individuals.

Nondipper hypertension was associated with higher levels of uric acid levels and increased uric acid levels were shown to predict nondipper hypertension regardless of presence of CKD in our hypertensive patients. Presence of CKD was also amongst the significant predictors of nondipper pattern. This supports the fact that higher serum uric acid levels were an independent risk factor for chronic renal failure, which is in turn an independent risk factor for hypertension and nondipper hypertension (15,16). Increased serum uric acid levels were also reported to be associated with increases in certain inflammatory markers and indicators of oxidative stress (13,14). Accordingly, uric acid levels were positively correlated with CRP, MPV, and NLR regardless of the dipping pattern and kidney function in our cohort, whereas the correlation of uric acid levels to NLR in nondipper patients was only evident in case of hypertensive patients with CKD.

Increased levels of MPV predicted nondipper pattern in our cohort of hypertensives, which seems in agreement with increased platelet activation and reverse effect of antihypertensive medications on platelet functions reported in hypertensives as compared with normotensives (51,52). Notably, shear forces, renin–angiotensin system, endothelial dysfunction, elevated catecholamine levels, and presence of comorbidities have been suggested to promote increased activation of platelets in hypertensive settings (31,53).

Our findings indicate association of nondipper hypertension with higher levels PLR and positive correlation of serum uric acid levels with PLR independent from the decline in renal function, whereas association of nondipper hypertension with increased NLR and positive correlation of serum uric acid levels with NLR in nondippers only in hypertensive patients with CKD. Accordingly, owing to their significant correlation with nondipper status and serum uric acid levels in nondipper CKD patients in the present cohort, both NLR (combining the predictive risk of neutrophils and lymphocytes into a single risk factor) (41) and PLR (joining the predictive risk of platelet and lymphocyte counts into a single risk factor) (43) seem to be simple and feasible prognostic inflammatory markers in nondipper hypertensives with CKD.

We have previously shown the relationship between NLR, PLR, and inflammation in a cohort of ESRD patients on maintenance hemodialysis with higher values for NLR and PLR in patients with higher levels of inflammation along with a significant positive correlation of both NLR and PLR with hs-CRP levels (54).

Significantly higher levels for NLR and PLR in nondipper compared to dipper hypertension were also noted in a past

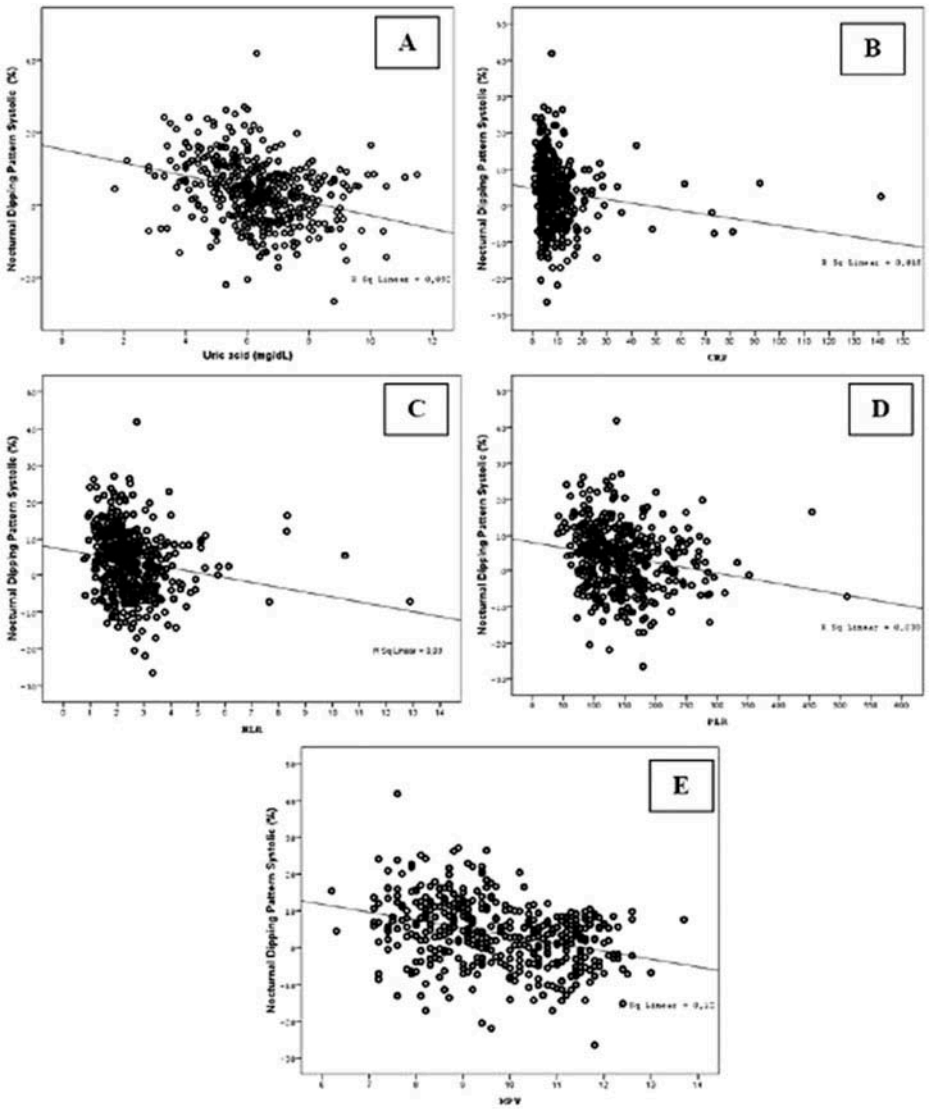

Figure 2. Correlation between nocturnal dipping pattern and serum uric acid, C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV).

Table 4. Univariate and multivariate logistic regression analysis for determinants of nondipper pattern.

	Univariate				Mutually adjusted multivariate			
Variables	OR	95% CI		*p*-Value	OR	95% CI		*p*-Value
CKD								
Negative	Reference				Reference			
Positive	2.17	1.31	3.60	**0.003**	0.51	0.22	1.16	0.109
NLR	1.92	1.39	2.65	**0.000**	1.18	0.82	1.71	0.368
PLR	1.01	1.00	1.02	**0.000**	0.98	0.97	0.99	**0.000**
MPV	2.32	1.86	2.89	**0.000**	1.81	1.30	2.53	**0.000**
CRP	1.15	1.08	1.22	**0.000**	1.00	0.95	1.07	0.899
Uric acid	2.18	1.76	2.70	**0.000**	2.69	1.60	4.52	**0.000**
Albumin	0.44	0.22	0.85	**0.015**	0.42	0.19	0.93	**0.031**

CI: confidence interval; CKD: chronic kidney disease; CRP: C-reactive protein; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; PLR: platelet-to-lymphocyte ratio.
Values in bold indicate statistical significance ($p<0.05$).

study conducted with Turkish hypertensive patients, which also revealed that higher PLR levels of ≥107 (OR, 2.62; CI, 1.13–6.06) but not NLR to predict nondipper status with a sensitivity of 66.3% and specificity of 68.7% based on logistic regression analysis (42).

However, while increased PLR and NLR were amongst the significant predictors of nondipper pattern in the univariate analysis, only PLR levels were confirmed to be a significant determinant of nondipper pattern in the multivariate analysis in our cohort. Besides, despite higher levels of PLR in

nondipper than dipper hypertensives and significant association of increased PLR levels with nondipper pattern in univariate analysis, multivariate analysis revealed lower levels of PLR to significantly predict increased likelihood of nondipping pattern in our cohort. Given that higher levels for MPV predicted the increased nondipping pattern, this seems to indicate the interaction between inflammatory markers in the pathogenesis of nondipper pattern to be much more multifaceted with likelihood of opposite predictive risk of platelet and lymphocytes.

Lower serum albumin levels in nondipper than dipper hypertensives with CKD and identification of lower serum albumin levels to predict increased likelihood of nondipper pattern in our study seem consistent with data on correlation of lower serum albumin levels with nondipping pattern (10,55). Although the mechanisms underlying the relation of nondipping pattern to serum albumin remain still inconclusive (10), reducing albuminuria has been suggested to be beneficial in terms of limiting progression of kidney disease and thus enabling consequent restoration of dipping (56,57).

Indeed, given that lower levels of both PLR and serum albumin levels predict increased likelihood of nondipper pattern, our findings may indicate the use of more composite markers such as the prognostic nutritional index, calculated based on the serum albumin concentration and peripheral blood lymphocyte count (58) and shown to be positively associated with PLR and NLR (59), to also be useful for predicting nondipper pattern in hypertensives.

Although some studies indicated higher prevalence of LV diastolic dysfunction parameters such as left atrial volume index, E/E', and the presence of LVH (3,60–62) in nondipper than dipper hypertensives, our findings revealed no difference in LV function in hypertensive patients with respect to dipping status both in CKD and non-CKD groups. Likewise, no difference in LVH was reported in hypertensive patients with respect to dipping status in other studies (53,63,64). In line with suggestion of similar average 24 h systolic and diastolic BP measurements in dipper and nondipper hypertensive patients to yield no difference in LVH with respect to dipping status (53), it is worth noting that dipper and nondipper hypertensives had similar average 24 h systolic BP in both CKD and non-CKD groups in our cohort.

In conclusion, our findings revealed higher prevalence of nondipper pattern in hypertensive patients with than without CKD and significantly higher levels for uric acid, CRP, MPV, PLR, and NLR among nondipper than dipper hypertensive patients with CKD. Presence of CKD, higher levels for uric acid, MPV, CRP, PLR, and NLR, and lower serum albumin levels in the univariate analysis, whereas high levels for uric acid and MPV and lower levels for PLR and serum albumin in the multivariate analysis were noted as significant determinants of nondipper pattern among hypertensive patients. Further large-scale randomized and controlled studies are needed to address the association of platelet activity and inflammation with nondipper pattern and renal dysfunction among hypertensive patients.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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