ORIGINAL RESEARCH

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Serum Neutrophil Gelatinase-Associated Lipocalin Levels in Patients with Non-Dipper Hypertension

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Abstract

Purpose: Neutrophil gelatinase-associated lipocalin (NGAL) is a protein belonging to the lipocalin superfamily and plays a role in atherosclerosis, renal injury and inflammation. The present study aimed to investigate serum NGAL concentrations in groups of patients with dipper and non-dipper hypertension (HT) and to characterize the relationship between NGAL concentration and circadian blood pressure in hypertensive patients.

Methods: A total of 41 (22 male, 19 female, mean age: 56.1 ± 8.9 years) non-dipper HT patients, 40 (19 male, 21 female, mean age: 54.0 ± 10.0 years) dipper HT patients and 42 age- and gender-matched healthy individuals were enrolled in the study. Dipper and non-dipper HT were diagnosed via ambulatory blood pressure monitoring. Serum NGAL concentrations were measured by enzyme-linked immunosorbent assay from blood samples obtained from patients.

Results: Serum NGAL concentrations were found to be significantly higher in the non-dipper and dipper HT patient groups in comparison with the control group (84.9 ± 23.0 ng/ml and 62.1 ± 17.8 vs. 46.6 ± 13.7 ng/ml, $p < 0.017$, respectively). Moreover, serum NGAL concentrations were significantly higher in the non-dipper HT group in comparison with the dipper HT group ($p < 0.017$). Serum NGAL concentration showed significant correlation with overall ambulatory BP levels both in non-dipper and dipper HT groups.

Conclusion: Serum NGAL concentrations increased significantly in non-dipper HT patients in comparison with dipper HT patients and normotensive patients and show significant correlation with ambulatory BP levels. Serum NGAL concentration might be a useful marker in identifying HT patients with higher risk for cardiovascular mortality.

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Hypertension (HT) is a disease that may lead to multiple target organ injury, and eventually to death due to related vascular system injury [1]. In addition to the presence of well recognized cardiovascular risk factors, alterations in circadian (nighttime-daytime) blood pressure level are also associated with disease prognosis. Blood pressure has been reported to decrease by 10-20% at night in a majority of HT patients (dipper) and by <10% at night in the remaining HT patients (non-dipper) [2-4]. Studies have demonstrated that non-dipper HT patients are at a higher risk for atherosclerotic events (myocardial and cerebral infarction), progressive nephropathy and cardiovascular mortality than dipper HT patients [5-8].

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein that belongs to the lipocalin superfamily and is released primarily from neutrophils, as well as from renal tubular cells and the endothelium, in response to inflammation and vascular injury [9,10]. Studies have demonstrated that NGAL is a good predictor of renal injury and prognosis [11,12]. Moreover, NGAL has been shown to play a role in atherosclerotic inflammation [13,14] and NGAL concentrations are significantly increased in coronary artery disease (CAD) and are closely associated with severity of CAD [15,16].

These results suggest that NGAL, which is both a renal and a cardiovascular predictor, might also play a role in altered nighttime blood pressure. In the present study, we investigate serum NGAL concentrations in dipper and non-dipper HT patient groups and determine the relationship of NGAL concentration with circadian blood pressure in hypertensive patients.

Materials and Methods

Study population

Our patient population consisted of dipper and non-dipper HT patients who were diagnosed via ambulatory blood pressure monitoring (ABPM). The patient population included 41 non-dipper HT patients (22 male, 19 female, mean age: 56.1 ± 8.9 years) and 40 age- and gender-matched dipper HT patients (19 male, 21 female, mean age: 54.0 ± 10.0 years). In addition, the study population included 42 age- and gender-matched healthy volunteers (20 male, 22 female, mean age: 54.4 ± 8.5 years).

Patients with secondary hypertension, coronary artery disease, renal insufficiency (creatinine-based estimated glomerular filtration rate (GFR) <90 ml/min/1.73 m² calculated by the Cockcroft-Gault formula), acute and chronic inflammatory disease, significant valvular disease, hematological disease, systolic heart failure (ejection fraction $<45\%$), diabetes mellitus,

atrial fibrillation and/or cerebrovascular disease were excluded. The local ethics committee approved the study protocol and informed consent was taken from all the patients.

Clinical BP measurements

BP measurements were taken for all patients after a 5 minute resting period and while the patients were sitting with their arm at heart level. The cuff of the blood pressure measuring device surrounded 80% of the upper arm and the distal end was 2.5-3 cm above the antecubital fossa [17]. Hypertension was defined by a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg during clinical BP measurements, or a history of taking antihypertensive medication [18].

Ambulatory blood pressure monitoring and dipping status

Twenty-four hour ABPM was performed using a portable digital recorder (Custo Med, Custo Screen 100, Germany). The device was set to take measurements at 15 minute intervals between 07:00 and 23:00 for daytime BP values and at 30 minute intervals between 23:00 and 07:00 for nighttime BP values. The recordings were analyzed by interactive software. Daytime, nighttime and 24 hour average SBP and DBP values and mean BP values were calculated for each patient using hourly averages of ambulatory BP recordings. Those with a 24 hour mean SBP >130 mmHg and/or DBP >80 mmHg were considered hypertensive [18]. Percentage decrease in nighttime blood pressure was calculated using the formula "Nighttime BP decrease (%) = (Daytime BP – Nighttime BP) $\times$ 100/Daytime BP". Hypertensive patients were dichotomized as dipper ($\geq 10\%$) or non-dipper ($<10\%$) according to the nighttime decrease in systolic and diastolic blood pressures [2-4].

Biochemical Measurements

Blood samples of selected individuals were collected between 8:00 and 10:00 am in the morning after 8-12 hours of fasting in order to avoid influences of diurnal rhythm. The samples were centrifuged and sera were separated. Routine biochemical and hematological parameters were analyzed on the same day. The sera were stored at -80°C until lipocalin-2/NGAL levels were analyzed using ELISA. Biochemical parameters were measured using commercial kits and a Abbott ARCHITECT c8000 (Abbott Laboratories, USA) auto-analyzer. Hematological parameters were analyzed by laser and impedance methods using the Abbott CellDyn 3700 (Abbott Laboratories, USA) device. High sensitive C-reactive protein (hs-CRP) (CardioPhase, hs-CRP) was measured quantitatively in a BN II

System Nephelometer (Dade Behring, Marburg, Germany) by immunonephelometric method from patients serum and results were reported in mg/L.

Serum lipocalin-2/NGAL levels were determined with ELISA and the Human lipocalin-2/NGAL kit (BioVendor-

Laboratorni Medicina a.s., Czech Republic) on the Triturus® ELISA analyzer (Grifols International, Spain) in accordance with the manufacturer's instructions. A standard curve was created using the four-parameter calculation method, and results were calculated in ng/ml according to the curve.

TABLE 1. Baseline laboratory and clinical characteristics of study population.

Variables	Non-dipper (n=41)	Dipper (n=40)	Control (n=42)	P
Age (years)	56.1±8.9	54.0±10.0	54.4±8.5	0.755
Male sex, n (%)	22 (53)	19 (48)	20 (47)	0.387
BMI (kg/m ²)	26.8±3.0	25.7±2.6	26.6±2.7	0.655
Smoking, n (%)	21 (51)	20 (50)	18 (42)	0.182
Clinical SBP (mmHg)	154.7±13.5 [‡]	152.3±13.2 [‡]	116.5±14.7	<0.001
Clinical DBP (mmHg)	95.8±9.5 [‡]	93.1±9.4 [‡]	71.1±10.7	<0.001
Fasting glucose (mg/dl)	89.7±9.0	88.1±10.5	92.1±19.9	0.583
Creatinine (mg/dl)	0.98±0.16	0.89±0.28	0.85±0.25	0.371
AST (U/L)	36.4±16.0	37.2±14.3	35.6±13.3	0.289
ALT (U/L)	32.2±13.8	31.1±14.5	28.7±11.2	0.394
Total cholesterol (mg/dl)	188.0±24.2	178.7±38.3	174.3±36.2	0.167
Low density lipoprotein (mg/dl)	115.4±27.4	109.9±31.1	104.6±27.1	0.112
High density lipoprotein (mg/dl)	38.1±9.9	37.2±7.8	36.7±10.7	0.153
Triglyceride (mg/dl)	174.3±75.2	163.9±65.1	164.4±57.6	0.182
Hemoglobin (mg/dl)	13.8±1.4	14.1±1.4	13.7±1.9	0.308
White blood cell (10 ³ /mm ³)	7.3±1.6	7.4±1.5	7.3±1.8	0.772
NGAL (ng/ml)	84.9±23.0 ^{‡,§}	62.1±17.8 [‡]	46.6±13.7	<0.001
Hs-CRP (mg/L)	4.83±1.64 ^{‡,§}	1.92±1.42	1.21±0.64	<0.001
GFR (ml/min/1.73 m ²)	101.55±11.52 [‡]	102.86±10.55 [‡]	112.1±12.05	0.063
Medical treatments				
ACE inhibitor, n (%)	16 (39)	14 (35)		0.562
ARB, n (%)	25 (61)	24 (60)		0.884
Ca-channel blocker, n (%)	26 (63)	24 (60)		0.754
Diuretic, n (%)	10 (24)	9 (23)		0.912

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NGAL, neutrophil gelatinase-associated lipocalin; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Hs-CRP, high-sensitive C-reactive protein; GFR, glomerular filtration rate.

[‡] p<0.017 compared with control subjects; [§] p<0.017 compared with dipper subjects

Statistical analysis

Statistical analyses were based on the SPSS 15.0 (Statistical Package for Social Sciences) program. The Kolmogorov-Smirnov test was used to check normal distribution of all the parameters. Categorical variables were expressed in percentage, whereas numerical variables were presented as mean $\pm$ standard deviation (SD). The basal characteristics of the patients were compared using the chi-square test. Comparison of groups was based on the Kruskal-Wallis test, and paired comparisons were made using either the Student's t-test or the Mann-Whitney U-test. Correlations between blood pressure and NGAL levels

were tested using Spearman's correlation analysis. Multivariate stepwise logistic regression analysis was performed to assess the parameters that are associated with a non-dipper BP pattern and age, BMI (body mass index), smoking and LDL (Low density lipoprotein) cholesterol, fasting glucose, serum hs-CRP and serum NGAL levels were included as the covariates in the multivariate regression model. A p-value of less than 0.05 was considered statistically significant. The two-way significance level for multiple comparisons between the groups was set at $p=0.017$.

Results

Baseline clinical characteristics

Baseline clinical characteristics of the patients are shown in Table 1. Clinical SBP and DBP values were significantly higher in the non-dipper and dipper patient groups as compared with the control group (SBP: 154.7 ± 13.5 and 152.3 ± 13.2 mmHg *vs.* 116.5 ± 14.7 mmHg, $p<0.017$; DBP: 95.8 ± 9.5 and 93.1 ± 9.4 mmHg *vs.* 71.1 ± 10.7 mmHg, $p<0.017$, respectively). On the contrary, clinical SBP and DBP values were similar in the non-dipper and dipper HT patient groups ($p>0.05$). In addition, no difference between the dipper and non-dipper HT groups was found regarding the different antihypertensive therapies that the patients had been taking ($p>0.05$). Also, serum hs-CRP levels were significantly higher in the non-dipper HT patient group in comparison with the dipper HT and control groups (4.83 ± 1.64 mg/L *vs.* 1.92 ± 1.42 mg/L and 1.21 ± 0.64 mg/L, $p<0.017$, respectively). There was no signifi-

FIGURE 1. Comparison of serum NGAL levels in non-dipper HT patients, dipper HT patients and normotensive controls

FIGURE 2. Correlation between serum NGAL levels and nighttime systolic BP values in non-dipper HT and dipper HT groups.

FIGURE 3. Correlation between serum NGAL levels and high-sensitive C-reactive protein (hs-CRP).

cant difference between the serum hs-CRP levels of dipper HT and control groups ($p>0.05$) (Table 1). Additionally, GFR values were significantly lower in the non-dipper and dipper HT patient groups in comparison with the control group (101.55 ± 11.52 and 102.86 ± 10.55 ml/min/ 1.73 m^2 vs. 112.1 ± 12.05 ml/min/ 1.73 m^2 , $p=0.063$) (Table 1).

Serum NGAL levels

Serum NGAL concentrations were significantly higher in the non-dipper and dipper HT patient groups than in the control group (84.9 ± 23.0 ng/ml and 62.1 ± 17.8 vs. 46.6 ± 13.7 ng/ml, $p<0.017$, respectively) (Table 1). Moreover, serum NGAL concentrations of the non-dipper HT group were significantly higher than those of the dipper HT group ($p<0.017$) (Figure 1).

Ambulatory blood pressure values

Although no significant differences were determined between non-dipper and dipper HT patient groups in terms of daytime SBP, DBP and mean BP values ($p=0.058$, $p=0.312$, $p=0.104$, respectively), nighttime SBP, DBP and mean BP values were significantly higher in the non-dipper than the dipper HT patient group (137.3 ± 15.2 vs. 124.7 ± 12.5 mmHg, $p<0.001$; 82.7 ± 10.8 vs. 76.7 ± 8.1 mmHg, $p<0.001$; 100.9 ± 11.8 vs. 92.7 ± 9.3 mmHg, $p<0.001$, respectively). Moreover, 24 hour SBP, DBP and mean BP values were also higher in the non-dipper than the dipper HT patient group (142.2 ± 12.7 vs. 132.8 ± 10.8 mmHg, $p=0.004$; 85.9 ± 9.9 vs. 81.3 ± 7.3 mmHg, $p=0.032$; and 104.7 ± 10.2 vs. 98.5 ± 8.2 mmHg, $p=0.009$, respectively) (Table 2).

TABLE 2. Comparison of ambulatory BP monitoring results of dipper and non-dipper groups

Variables (mmHg)	Non-dipper (n=41)	Dipper (n=40)	P
Daytime systolic BP	147.1±11.9	141.0±14.8	0.058
Daytime diastolic BP	89.1±11.4	85.9±11.0	0.312
Daytime mean BP	108.5±10.5	104.2±11.6	0.104
Nighttime systolic BP	137.3±15.2	124.7±12.5	<0.001
Nighttime diastolic BP	82.7±10.8	76.7±8.1	<0.001
Nighttime mean BP	100.9±11.8	92.7±9.3	<0.001
24 h systolic BP	142.2±12.7	132.8±10.8	0.004
24 h diastolic BP	85.9±9.9	81.3±7.3	0.032
24 h mean BP	104.7±10.2	98.5±8.2	0.009

Abbreviations: BP, blood pressure

TABLE 3. Correlation between NGAL levels and blood pressure in hypertensive patients

Variables (mmHg)	NGAL level			
	Non-dipper		Dipper	
	r	p	r	p
Daytime systolic BP	0.628	<0.001	0.555	<0.001
Daytime diastolic BP	0.483	0.002	0.449	0.004
Daytime mean BP	0.587	<0.001	0.515	0.001
Nighttime systolic BP	0.816	<0.001	0.708	<0.001
Nighttime diastolic BP	0.774	<0.001	0.622	<0.001
Nighttime mean BP	0.821	<0.001	0.675	<0.001
24 h systolic BP	0.711	<0.001	0.622	<0.001
24 h diastolic BP	0.632	<0.001	0.532	<0.001
24 h mean BP	0.702	<0.001	0.585	<0.001

Abbreviations: BP, blood pressure; NGAL, neutrophil gelatinase-associated lipocalin

Association of serum NGAL levels with ambulatory blood pressure levels and laboratory findings

Serum NGAL concentration showed significant correlation with overall ambulatory BP levels in both non-dipper and dipper groups (Table 3). Although NGAL concentrations were

strongly correlated with nighttime SBP, DBP and mean BP values, they were only moderately correlated with daytime SBP, DBP and mean BP values (Figure 2). There was a significant positive correlation between serum NGAL levels and hs-CRP levels ($r = 0.602$, $p < 0.001$, Figure 3) and a significant negative correlation between serum NGAL levels and GFR values in the non-dipper HT and dipper HT patient groups ($r = -0.489$, $p < 0.001$ and $r = -0.389$, $p < 0.001$, respectively).

Multivariate analysis demonstrated that the non-dipper BP pattern was associated with serum NGAL levels (standardized β coefficient = 0.054, $p < 0.001$), serum hs-CRP levels (standardized β coefficient = 0.042, $p = 0.005$) and LDL cholesterol levels (standardized β coefficient = 0.032, $p = 0.033$) in the multivariate stepwise logistic regression model (Table 4). Standardized β coefficients and P values were 0.706 and 0.369 for age, 0.048 and 0.743 for BMI, 0.569 and 0.356 for smoking, 0.031 and 0.501 for fasting glucose, respectively.

Discussion

In the present study, higher NGAL concentrations were identified in non-dipper HT patients in comparison with those in dipper HT and normotensive patients. Moreover, serum NGAL concentrations showed significant correlation with daytime, nighttime and 24 hour BP values.

HT is a well-known risk factor for cardiovascular diseases, renal insufficiency and stroke [1]. Clinical studies have demonstrated that the incidence of end-organ injury is higher in non-dipper HT patients, who are diagnosed based on a 24 hour ABPM that shows a nocturnal BP decrease $< 10\%$ [19, 20]. Even though the mechanism of non-dipper HT has not yet been determined, studies have demonstrated that autonomic dysfunction, increased sympathetic activity, a sedentary life style and volume-related factors play a role in the pathogenesis [21,22].

NGAL is a 25 kDa glycoprotein that was first isolated from neutrophils and has been found to be covalently bonded to the matrix metalloproteinase-9 (MMP-9) [9]. Studies have shown that serum and urinary NGAL concentrations are increased in the early phase of acute renal injury [23]. Moreover, it is thought that NGAL secreted from endothelial cells might play a role in inflammation that is associated with endothelial dysfunction and atherosclerosis [13,24]. Recent studies have demonstrated that serum NGAL concentrations are increased in CAD and might contribute to the atherosclerotic process [16,25].

HT is not only an increase in blood pressure, but is also a complex cardiovascular disease, where inflammation, endothelial dysfunction and platelet activation also play a role in pa-

TABLE 4. Multivariate logistic regression analysis to identify the independent determinants of non dipping blood pressure (BP) pattern

Variables	β coefficient	SE	OR (95%CI)	p
NGAL (ng/ml)	0.054	0.014	1.055(1.027-1.085)	<0.001
Age (year)	0.706	0.786	2.025(0.434-9.451)	0.369
BMI (kg/m ²)	0.048	0.147	1.049(0.786-1.400)	0.743
Smoking	0.569	0.465	1.495(0.789-2.365)	0.356
Fasting glucose (mg/dl)	0.031	0.046	1.031(0.943-1.129)	0.501
LDL-cholesterol (mg/dl)	0.032	0.015	1.032(1.003-1.063)	0.033
Hs-CRP (mg/L)	0.042	0.236	1.112(1.033-1.155)	0.005

Abbreviations: NGAL, neutrophil gelatinase-associated lipocalin; BMI, body mass index; LDL, low density lipoprotein; Hs-CRP, high-sensitive C-reactive protein.

thophysiology [26]. Increased inflammatory activity has been demonstrated in HT patients [27] and higher inflammatory activity in non-dipper than in dipper HT patients has been shown in studies investigating the relationship between circadian blood pressure and inflammatory markers such as C-reactive protein (CRP), gamma-glutamyltranspeptidase (GGT) and uric acid [2,28]. Clinical studies investigating the relationship between serum NGAL concentrations and inflammation demonstrated that levels of serum NGAL reflect the systemic inflammatory response in stroke, renal insufficiency and infection settings [29-31]. Kafkas *et al.* [32] determined that NGAL concentrations were higher in acute coronary syndrome (ACS) patients in comparison with stable angina patients. Moreover, serum NGAL concentrations were found to be correlated with neutrophil count and CRP concentrations. Linberg *et al.* [33] found that increased NGAL concentrations are associated with all-cause mortality and inflammation. Similarly, in our study serum hs-CRP levels were significantly higher in non-dipper HT patient group in comparison with dipper HT and control groups and there was a significant positive correlation between hs-CRP levels and serum NGAL suggesting that higher serum NGAL concentrations in the non-dipper HT group might be related to higher inflammatory activity in this group.

High blood pressure is known to lead to endothelial dysfunction [34]. A previous study detected impaired endothelium-dependent vasodilation through a decrease in levels of acetylcholine (Ach) and nitric oxide (NO), which arose from endothelial dysfunction in non-dipper HT patients compared with dipper HT patients [35]. Impaired endothelial function is associated with cardiovascular and cerebrovascular diseases, both of which are more prevalent in non-dipper HT

patients [35]. Kim *et al.* [36] reported that endothelial progenitor cells, which play a key role in endothelial homeostasis and vascular repair, are less prevalent in the circulation of non-dipper than dipper HT patients. In addition, aortic stiffness, which increases with atherosclerosis and endothelial dysfunction [37], has been shown to be increased in non-dipper HT patients compared with dipper HT patients [38,39]. Considering that NGAL, which is regarded as a plasma marker of neutrophil activation, increases in endothelial dysfunction and contributes to the development of atherosclerosis [13,40], the high serum NGAL concentrations found in non-dipper HT patients might be due to endothelial dysfunction, which is more prevalent in non-dipper HT patients.

A reduced nocturnal decrease in blood pressure has been associated with a higher incidence of end-organ injury and an unfavorable clinical outcome [41] and Ortiz *et al.* (LOD-RISK study) showed a higher incidence of renal injury among non-dipper HT patients than dipper HT patients [42]. Likewise, Timio *et al.* [5] conducted a long-term follow-up study of 48 HT patients with renal insufficiency and reported that renal insufficiency showed faster progression in the non-dipper than the dipper HT group. Previous studies have documented the relationship between serum NGAL concentrations and renal dysfunction [23]. Although patients with renal dysfunction were excluded from the present study, a significant negative correlation was observed between serum NGAL levels and GFR values. A subclinical renal damage due to decreased GFR levels may be contributing to the increased serum NGAL levels of non-dipper and dipper HT patient groups; therefore, higher serum NGAL concentrations detected in non-dipper HT patients in the present study may be an early sign of renal dysfunction.

Elneihoum *et al.* [29] investigated the relationship between plasma leukocyte activation markers and risk factors of atherosclerotic vascular disease. The researchers determined that plasma NGAL concentration shows positive correlation with blood pressure. Park *et al.* [43] found that serum NGAL levels were 85.0 ± 37.6 ng/ml in patients with essential HT and 43.8 ± 13.1 ng/ml in the normotensive control group; a statistically significant difference. Additionally, a significant correlation was found between serum NGAL levels and all blood pressure values (SBP, DBP and mean BP). These results are similar to those obtained in the present study. In their study on patients with advanced carotid artery stenosis, Giaginis *et al.* [44] demonstrated that serum NGAL levels were 64.21-118.29 (median: 81.71 ng/ml) in hypertensive patients, and 56.01-94.55 ng/ml (median: 75.41 ng/ml) in normotensive patients. The serum NGAL levels of patients were higher than those of our study; carotid atherosclerosis may contribute higher serum NGAL levels in these patients. Additionally, in our study, serum NGAL level was found by multivariate analysis to be an independent determinant factor of non-dipper blood pressure. Thus, serum NGAL levels may have promising predictive value in determining non-dipper blood pressure, which carries a high risk of cardiovascular mortality. In our study, serum NGAL concentrations showed the highest correlation with nighttime blood pressure values; in particular, a significant positive correlation between serum NGAL concentrations and nighttime blood pressure values suggests that there might be a relationship between the cardiovascular events caused by nighttime high blood pressure values and serum NGAL concentrations.

Study Limitations

A major limitation of our study was the small sample size of the study population, and as such we were not able to fully evaluate the prognostic value of serum NGAL levels in patients with HT; future studies could include using a larger patient cohort. Urinary NGAL levels were not determined, although measurement of urinary NGAL levels and comparison of urinary and serum NGAL levels may prove to play a complementary role in determining cardiovascular and renal damage in the hypertensive patient group. Although additional inflammatory and vascular markers, which could be indicators of endothelial dysfunction, were not measured in our study, their investigation would be a worthwhile area of research.

Conclusion

The present study is the first to demonstrate that serum NGAL concentrations increased significantly in non-dipper HT patients compared with both dipper HT patients and normotensive patients, and showed significant correlation with ambulatory blood pressure values. Increases in serum NGAL concentrations could be interpreted as a combined outcome of endothelial dysfunction, inflammation and renal injury in non-dipper HT patients. Moreover, serum NGAL concentrations might be a useful marker for determining HT patients with higher risk for cardiovascular mortality. Larger-scale prospective studies would help to validate our findings.

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