Introduction

Blood pressure (BP) normally decreases during sleep, and certain metabolic and cardiovascular alterations may affect this circadian pattern. Leading reasons for a non-dipping BP pattern are obesity, sleep disorders, obstructive sleep apnea, chronic kidney disease, excessive salt consumption, diabetes mellitus, orthostatic hypotension, autonomic dysfunction, and advanced age. An arbitrary cut-off point has been proposed to define patients as “dippers” if their nocturnal BP falls by ≥10% of the daytime mean BP value. A non-dipper BP pattern is associated with high cardiovascular mortality and morbidity in people with both normal BP and hypertension.

In recent years, hematological parameters such as the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to high-density lipoprotein (HDL) cholesterol ratio (MHR), and systemic immune-inflammation index (SII) have been investigated in different systemic diseases as indicators of inflammation. Although studies are searching for...
the relationship between inflammation and nocturnal BP pattern in hypertensive patients.\textsuperscript{13,14} to the best of our knowledge, these easily accessible parameters have not been used in studies with normotensive individuals. Hence, in this study we aimed to investigate the relationship between inflammation-based indexes and nocturnal BP pattern in normotensive individuals.

\section*{Materials and Methods}

\subsection*{Study Population}

Patients admitted to the outpatient cardiology clinic at Hospital were retrospectively screened. Those who were evaluated with ambulatory BP monitoring (ABPM) to confirm/reject a hypertension diagnosis were enrolled. Our sample represented patients aged 18 years or older, without a history of hypertension or treatment with antihypertensives, and with ABPM findings compatible with normotension in consistence with the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines\textsuperscript{2}(daytime threshold for hypertension: systolic BP [SBP] ≥ 135 mmHg and/or diastolic BP [DBP] ≥85 mmHg; nighttime: SBP ≥120 mmHg and/or DBP ≥70 mmHg; overall 24-hour mean: SBP≥130 mmHg and/or DBP≥80 mmHg). Exclusion criteria were pregnancy; history of drug/alcohol abuse; having a night shift job; chronic inflammatory disease; kidney failure; thyroid function disorders; connective tissue disease; chronic liver disease; acute infection; sleep disorders; malignancy; use of antinflammatory drugs, statins, or drugs that may increase BP (such as steroids); and intolerance to ABPM. The sample size was defined for convenience. A total of 131 patients were included. Participants represented a consecutive series of patients fulfilling these exclusion/inclusion criteria and were divided into 2 groups (dippers vs non-dippers) according to the decline in nighttime SBP. The dipper group was defined as patients with a nocturnal dip of ≥10\% in SBP. The non-dipper group was defined as patients with a nocturnal dip of <10\% in SBP.\textsuperscript{2}

This study was approved by the local ethics committee of Istanbul Bakirkoy Dr Sadi Konuk Training and Research Hospital (20.05.2019, 2019-10-10).

\subsection*{ABPM Assessment}

A portable recording device (Suntech Bravo 24-HR ABP) was used to record 24-h ABPM values. The cuff was placed on the patient’s non-dominant arm. Overall, the nighttime and daytime SBP and DBP of each participant were automatically measured every 20 min between 07:00 and 23:00 h and every 30 min during the night. Daytime and nighttime periods were defined using fixed time periods for all patients. Participants were asked to continue performing their usual activities. Data was analyzed using SunTech AccuWin Pro v3 ABPM software. Mean SBP and DBP values, as well as mean arterial pressure (MAP), were separately calculated for nighttime and daytime periods. BP series were excluded if ≤70\% of the measurements were valid. The percentage of nocturnal BP decline was calculated using the following formula: nocturnal BP decline (\%)=(daytime BP- nocturnal BP)×100 / daytime BP.

\subsection*{Study Parameters}

Data regarding patient demographics, blood biochemistry (total cholesterol, triglycerides, low-density lipoprotein cholesterol, HDL), complete blood count at admission, and ABPM results were obtained from the medical records. The 24-hour, nighttime, and daytime ABPM values of SBP, DBP and MAP, as well as the mean nocturnal declines in SBP, DBP, and MAP, were recorded for all patients.

SII (calculated as platelet count x neutrophil count / lymphocyte count), NLR, PLR, and MHR were constructed as inflammation-based indexes in accordance with previous studies.\textsuperscript{9-12,15,16}

\subsection*{Statistical Analysis}

Our statistical analysis was performed using IBM SPSS Statistics version 21 and MedCalc version 12.3.0.0. The normality of the data was tested with the Shapiro-Wilk test. Normally distributed variables were presented as means ± standard deviations (SDs); non-normally distributed variables were reported as median (interquartile range [IQR]) values. Independent samples t-tests and Mann-Whitney U tests were used for comparing normal and non-normal variables, respectively, between the 2 independent groups. Categorical variables were presented as frequencies and percentages (n, \%), and Pearson’s chi-squared tests were used to compare categorical variables between groups. The Spearman’s correlation coefficient was used to examine the relationships between variables. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performances of inflammation-based
indexes. The Youden’s J index was used to obtain the optimal cut-off value. The level of statistical significance adopted for our analyses was 5%.

**Results**

This single-center, retrospective study included 131 patients (mean±SD age 49.20±15.09 years, 58 (76.0%) of which were women). Among these 131 patients, 55 (42.0%) were included in the dipper group and 76 (58.0%), in the non-dipper group. Baseline characteristics and laboratory findings of the groups are summarized on Table-1. No significant differences were noticed between groups in terms of patient characteristics.

ABPM results of both groups were summarized on Figures-1 and -2. A significant difference was observed between dippers and non-dippers in terms of daytime and nighttime SBP and DBP. The difference between dippers and non-dippers in terms of daytime SBP was (mean±SD) 121.24±7.43 vs 114.25±7.46, respectively, p<0.001, while for daytime DBP it was (mean±SD) 73.20±6.11 vs 68.46±5.68, p<0.001. The difference between dippers and non-dippers in terms of nighttime SBP was (median [IQR]) 102 (15.0) vs 109 (9.8), respectively, p<0.001, and in terms of nighttime DBP it was (median [IQR]) 60.0 (8.0) vs 63 (5.8), p<0.001. The difference between dippers and non-dippers in terms of daytime MAP was (median [IQR]) 73.33 (9.0) vs 78.5 (6.5), p<0.001; these were also statistically significant.

MHR, PLR, and NLR were similar between dippers and non-dippers (p=0.929, p=0.110, and p=0.152, respectively). However, SII was significantly higher in the non-dipper group than in the dipper group (median [IQR]): 457.4 (233.5) vs 391.4 (266.6), respectively, p=0.033 (Table-2). When we investigated the correlations between the change in systolic BP (ΔSBP) and inflammation-based indexes, we found significant negative correlations between ΔSBP and SII (r=-0.172, p=0.049) and between ΔSBP and PLR (r=-0.179, p=0.040) in non-dipper normotensives. On the other hand, correlations between ΔSBP and MHR (p=0.768) and between ΔSBP and NLR (p=0.320) were not significant in non-dipper normotensives.

| Table 1 – Baseline characteristics and laboratory findings of dipper and non-dipper groups |
|---------------------------------------------------------------|
| **Dipper (n=55)** (mean±standard deviation) | **Non-dipper (n=76)** (median [IQR]) | **p-value** |
| Age (years) | 49.7±14.1 | 48.8±15.9 | 0.743 |
| Gender (female) | 40 (41.7) | 56 (58.3) | 1.000 |
| Total cholesterol (mg/dL) | 202.1±42.1 | 206.1±37.6 | 0.570 |
| TG (mg/dL) | 133 (103) | 105 (82.3) | 0.408 |
| HDL (mg/dL) | 50 (16) | 51 (17.8) | 0.879 |
| LDL (mg/dL) | 123.7±36.7 | 128.7±29.7 | 0.390 |
| WBC (×10^9/L) | 7.59 (3.29) | 7.45 (2.45) | 0.928 |
| Neutrophil (×10^9/L) | 406 (186) | 419.50 (204.3) | 0.509 |
| Monocyte (×10^9/L) | 61 (39) | 59 (27) | 0.946 |
| Lymphocyte (×10^9/L) | 244 (131) | 241.50 (84.3) | 0.475 |
| RDW % | 13.40 (1.3) | 13.50 (1.6) | 0.931 |
| PLT (×10^9/L) | 256.6±82.9 | 269.7±88.3 | 0.223 |
| MPV (fL) | 10.20 (1.3) | 10.25 (1.18) | 0.814 |

Data presented as *mean±standard deviation*, median (interquartile range [IQR]), or *n(%)* values.
LDL: low-density lipoprotein; TG: triglyceride; HDL: high-density lipoprotein; WBC: white blood cell; PLT: platelet; RDW: red cell distribution width; MPV: mean platelet volume; fL: femtoliter.
In our ROC curve analyses, we found a significant diagnostic performance for SII in discriminating between dippers and non-dippers (area under the ROC curve \[AUC = 0.610, p=0.031\]). The optimal cut-off point for non-dippers was \(>373.23\), corresponding to a 78.95% (95% confidence interval [CI]: 68.1–87.5) sensitivity and a 49.09% (95% CI: 35.4–62.9) specificity. AUCs for MHR \((p=0.932)\), PLR \((p=0.118)\), and NLR \((p=0.149)\) were not statistically significant (Figure-3).

**Discussion**

In this study, we found that among the studied parameters, only SII differed significantly between groups. Moreover, SII and PLR were negatively correlated with a nocturnal decline of SBP in non-dipper normotensives. MHR, NLR, and PLR values were similar between dipper and non-dipper normotensives.
Increased inflammation may increase neutrophil and platelet counts while decreasing lymphocyte count. Inflammatory cytokines are secreted by monocytes as a result of inflammatory reactions, whereas HDL has anti-inflammatory effects. MHR has been identified as an easy cardiovascular prognostic marker indicating the intensity of inflammation.

|                  | Dipper (n=55) | Non-dipper (n=76) | p-value |
|------------------|---------------|-------------------|---------|
| SII              | 391.4 (266.6) | 457.4 (233.5)     | 0.033   |
| MHR              | 1.18 (1.0)    | 1.21 (0.71)       | 0.929   |
| PLR              | 0.96 (0.44)   | 1.09 (0.34)       | 0.110   |
| NLR              | 1.68 (0.86)   | 1.89 (1.0)        | 0.152   |

Data presented as median (interquartile range [IQR]) values.
MHR: monocyte to high-density lipoprotein ratio; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune-inflammation index.

Figure 3 – Receiver operating characteristic curve for the systemic immune-inflammation index in predicting non-dippers. AUC: area under the receiver operating characteristic curve.

High levels of inflammatory markers were described in hypertensive patients with non-dipper BP. Inflammation may play a role in individuals being non-dipper, even if they are normotensive. Therefore, the patients’ inflammatory conditions should be considered. Due to expensive and time-consuming procedures, the measurement of cytokines, adhesion molecules, and chemokines to assess
inflammatory status is difficult. On the other hand, SII, MHR, PLR, and NLR are inflammation-based indexes that are cost-effective and can be easily obtained by routine blood tests. Based on this, we searched for an easy and accessible inflammation-based index to distinguish patients who may be non-dipper even if they are normotensive and who should be confirmed with an ABPM evaluation.

Previous studies have investigated the cardiovascular effects of a nocturnal decline in BP in normotensives, as well as in hypertensive patients. Cardiovascular mortality among dipper hypertensive patients and non-dipper normotensive patients is similar, and it is unknown if non dipper normotensives are candidates to being hypertensive. Therefore, diagnosing and managing non-dippers not only among hypertensives but also among normotensives is important. If their dipping status is not determined early enough, non-dipper normotensive individuals may not have the chance to receive an antihypertensive medication despite a higher cardiovascular risk. Hence, an SII cut-off may be useful to select patients who need to be evaluated with ABPM regarding their nocturnal BP pattern among those defined as normotensive according to office BP measurements.

Although in previous studies the association of inflammation with being non-dipper has been investigated in hypertensive patients, as far as we know, our study is the first to investigate the relationship between nocturnal BP pattern and inflammation-based indexes derived from complete blood count and biochemical test results in normotensive individuals.

Limitations

Firstly, we only searched for the relationship between dipping status and inflammation-based indexes derived from complete blood count and biochemical test results. Apart from these study parameters, we did not measure other inflammatory markers such as C-reactive protein or interleukin-6. Another limitation of our study is the lack of data on salt consumption on the day of measurement, the menopausal status of female participants, and sleep diaries including sleep-wake hours.

Conclusion

We observed a significant relationship between SII and a nocturnal decline of SBP in normotensives. SII may be a predictive parameter for non-dipper normotensive individuals and may be useful to distinguish those who should be confirmed with ABPM in terms of dipping status before target organ damage develops. Further studies are needed on how to distinguish non-dipper individuals among normotensives both correctly and easily in daily practice.

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Author contributions

Conception and design of the research: Gunay S, Caliskan S. Acquisition of data: Caliskan S, Gunay S. Analysis and interpretation of the data: Gunay S, Sigirli D. Statistical analysis : Sigirli D. Writing of the manuscript : Gunay S. Critical revision of the manuscript for intellectual content : Gunay S.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Istanbul Bakirkoy Dr Sadi Konuk Training and Research Hospital under the protocol number 2019-10-10. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.
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