

Monocyte-to-high-density lipoprotein ratio: an independent predictor of reverse dipper pattern in hypertensive patients

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Abstract. – OBJECTIVE: In healthy individuals, blood pressure (BP) levels are expected to decrease by 10-20% during sleep hours, which is defined as the dipping pattern. On the other hand, the presence of a BP rise at night in hypertensive patients is defined as a reverse dipper hypertensive pattern (RDHT). RDHT has been associated with stroke and cardiovascular mortality. Similarly, the monocyte-to-high-density lipoprotein cholesterol ratio (MHR) has been associated with the prognosis of cardiovascular disease. We, therefore, aimed to assess the relationship between MHR and RDHT in patients with hypertension.

PATIENTS AND METHODS: A total of 363 patients were enrolled in the study, all of whom had undergone 24-hour ambulatory BP monitoring. The patients were analyzed in three groups: RDHT (n: 92), dipper hypertensive (DHT) (n: 124), and normotensive controls (n: 147). Univariable and multivariable analyses were performed to identify factors that could be used to predict RDHT presence.

RESULTS: The RDHT group was compared with the DHT and normotensive groups. A high MHR ($p = 0.014$, OR: 1.110, CIs: 1.021-1.206) and low daytime diastolic BP ($p = 0.026$, OR: 0.951, CIs: 0.910-0.994) were found to be independent factors that differentiated RDHT from DHT. Additionally, high MHR ($p < 0.001$, OR: 1.244, CIs: 1.140-1.357), body mass index ($p = 0.005$, OR: 1.143, CIs: 1.042-1.255), and C-reactive protein ($p = 0.009$, OR: 1.166, CIs: 1.039-1.308) were found to be independent factors that could differentiate patients with RDHT from controls.

CONCLUSIONS: We demonstrated that MHR, a novel inflammatory marker, independently predicts RDHT. This easily applicable and inexpensive marker can be used to predict RDHT in patients with hypertension.

Key Words:

Hypertension, Monocytes, High density lipoprotein cholesterol, Reverse dipper, Monocyte to high-density lipoprotein cholesterol ratio.

Introduction

Cardiovascular diseases and related complications are the leading cause of death worldwide¹. Hypertension (HT), which is estimated to be responsible for around 6% of adult deaths globally, is an important cardiovascular risk factor². The gold standard test for HT diagnosis is 24-hour ambulatory blood pressure (BP) monitoring (ABPM), and the utilization of this method has brought further opportunities to examine nighttime changes in BP among hypertensive and normotensive patients³.

It is now well established that BP shows a circadian pattern, with lower (10-20%) physiological levels during sleep – defined as “dipping”. Even in the presence of HT, this “dipping pattern” can be observed in many patients, described as the “dipping hypertensive pattern” (DHT), in which patients have 10-20% lower BP during sleep. When this decrease is less than 10%, it is referred to as a “non-dipping hypertensive pattern” (NDHT), whereas an increase is referred to as a “reverse-dipping hypertensive pattern” (RDHT)⁴. RDHT has been associated with increased end-organ damage, stroke, and cardiovascular mortality⁵.

Monocyte-to-high-density lipoprotein ratio (MHR) has recently gained recognition as a novel marker of inflammation. This is because monocytes and high-density lipoprotein cholesterol (HDL-C) particles have opposing effects: while monocytes contribute to inflammation by secreting cytokines⁶, HDL-C has antioxidant and anti-inflammatory properties⁷. Therefore, higher MHR is suggested to show greater inflammatory activity^{8,9}, and changes in MHR have been associated with prognosis¹⁰, mortality¹¹ in cardiovascular disease, acute ischemic stroke¹², and acute pulmonary embolism¹³. More specifically, a previous study examining HT patients with NDHT reported significant relationships with MHR¹⁴.

However, despite the demonstration of the impact of different dipping patterns (DHT, NDHT, and RDHT) on cardiovascular prognosis¹⁵⁻¹⁸ and the indisputable relationships between inflammation and cardiovascular disease¹⁹⁻²¹, there are very few studies that have examined whether new biomarkers of inflammation (e.g., MHR or other similar indices) can be utilized to distinguish dipping patterns among patients with HT. Therefore, we aimed to ascertain the potential relationships between MHR and two characteristic dipping patterns (DHT & RDHT) and to determine whether MHR could be used to predict the presence of RDHT –since this pattern is associated with poor prognosis in various cardiovascular diseases.

We hypothesized that inflammation was associated with the pathogenesis of RDHT, and that MHR could be used to predict the presence of this dipping pattern.

Patients and Methods

This study was designed as a single-center observational study, including two cohorts of patients with HT (DHT and RDHT) and normotensive con-

trols. Patients who presented to the cardiology clinic of Çankırı State Hospital between 2019 and 2021 were retrospectively evaluated. Our study started on October 25, 2022, with the permission of the Karatekin University Ethics Committee. A total of 363 patients between the ages of 18 and 90 were included in the study (Figure 1). Data were gathered from hospital records, encompassing 24-hour ABPM findings, demographic data, body mass index (BMI), laboratory test outcomes, medical history (including diabetes mellitus; DM), and echocardiographic measurements. Patients with a history of heart failure, coronary artery disease (CAD), history of HT, use of antihypertensive drugs, drug use due to a history of dyslipidemia, secondary HT, renal failure, liver failure, active infections, autoimmune diseases, hematologic diseases, cancer, respiratory diseases, and hypo- or hyperthyroidism were excluded from the study. BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m²). Low-density lipoprotein cholesterol (LDL-K) was calculated using the Friedewald formula. MHR was calculated by dividing monocyte count (x10³/μL) by the value of HDL-K (mg/dl) detected in blood samples obtained at admission.

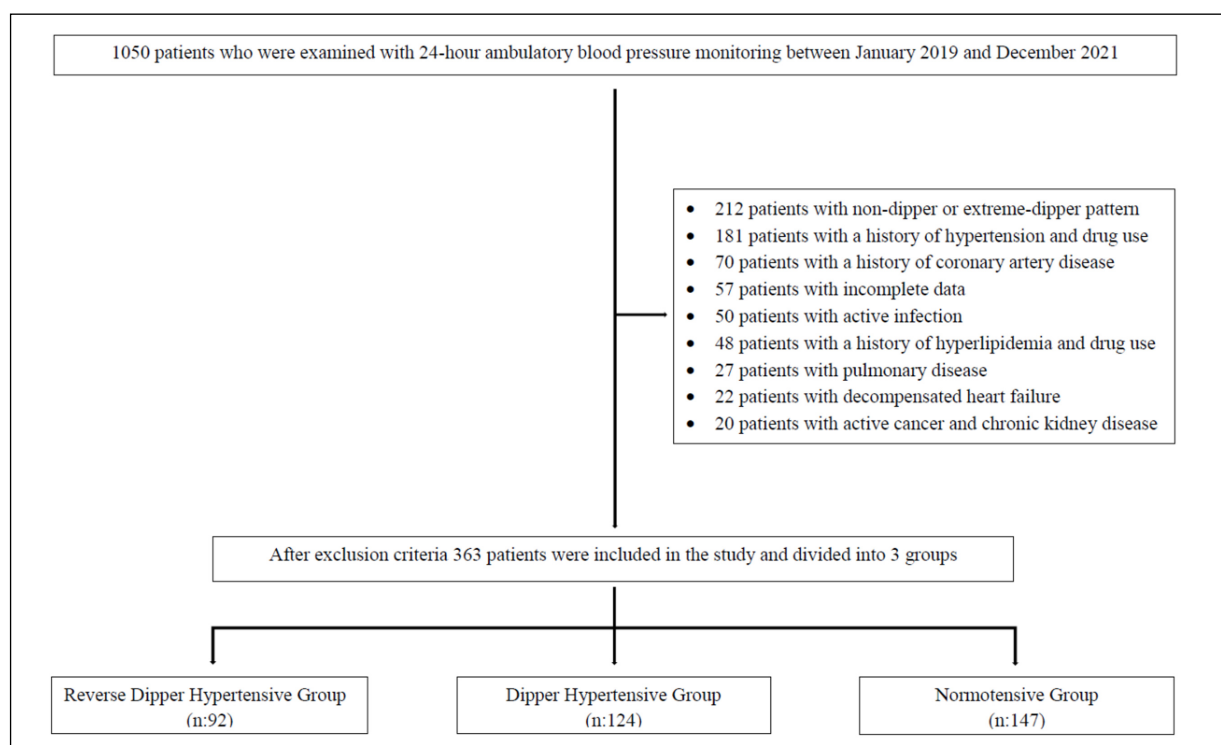


Figure 1. A flowchart showing the number of included and excluded patients.

The Schiller MT-300 (Schiller AG, Baar, Switzerland) device was used for ABPM measurement. The device was configured to perform 'awake' measurements between 07:00-22:00 and 'asleep' measurements between 22:00-07:00. Measurements were performed every 30 minutes during the awake phase and once per hour during the sleep phase. HT was diagnosed according to the 2018 guideline ESC/ESH Arterial HT²². The diagnosis of HT was determined according to Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) values. HT cutoff values: SBP \geq 135 mmHg or DBP \geq 85 mmHg for the daytime mean (or awake mean), SBP \geq 120 mmHg or DBP \geq 70 mmHg for the nighttime mean (or sleep mean), and SBP \geq 130 mmHg or DBP \geq 80 mmHg for the 24-hour mean. A BP decrease of less than 10% during sleep (from awake BP) was defined as non-dipper pattern, a decrease of more than 10% as dipper pattern, and an increase as reverse dipper pattern. The left ventricular ejection fraction (LVEF) was calculated by the Simpson method, and interventricular septum (IVS) thickness was also recorded. The patients were analyzed in three groups: RDHT (n: 92), DHT (n: 124), and normotensive (n: 147).

Statistical Analysis

Statistical analyses were performed in Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA) for Windows. Numerical variables with normal distribution are given as mean \pm standard deviation, and those with non-normal distribution are presented as median and interquartile range (25th-75th). Categorical variables were presented as frequency (n) and percentage. Before comparing groups for numerical variables, parametric test assumptions (normality and homogeneity of variances) were checked. The Shapiro-Wilk test was used to evaluate the distribution of numerical variables. The homogeneity of variances was tested using the Levene's test. In the comparison of numerical variables between groups, an independent sample *t*-test was used if parametric test conditions were met, while the Mann-Whitney U test was used for non-parametric variables. For the comparison of more than two groups in terms of numerical variables, one-way analysis of variance (ANOVA) was used when variances were homogeneous, and the Welch ANOVA test was used when they were heterogeneous. Pairwise post-hoc comparisons were performed with the Bonferroni test. For post-hoc comparisons, the Bonferroni correction was calculated and applied.

When parametric test assumptions were not met, 3-group comparisons were performed with the Kruskal-Wallis test, and two-group comparisons were made with the Dunn test. Differences in the distribution of categorical variables were examined with the Pearson chi-square test or Fisher exact test. Multivariable logistic regression analysis was applied to predictive factors related to RDHT. In model 1, the RDHT and DHT groups were compared. In model 2, the RHT and normotensive groups were compared. All variables that showed statistical significance in univariable analyses were included in each of the models. Receiver operating characteristic curve (ROC) analysis was used to determine the optimal cut-off value for MHR that predicted the presence of the RDHT pattern. The area under the curves (AUCs) and *p*-values were calculated. A *p*-value lower than 0.05 was considered statistically significant.

Results

According to the exclusion criteria, 363 patients were included in the study. In the RDHT group, the mean age was 58.6 ± 13.5 years, and 54.3% of patients were female. The age was significantly higher in the RDHT group than in the DHT group. The proportion of patients with DM was 21.7% in the RDHT group, which was higher than in the other groups. Other baseline characteristics and laboratory parameters are shown in Table I.

In post-hoc analyses, MHR was significantly higher in the RDHT group than in the normotensive and DHT groups (Figure 2).

In terms of echocardiography results, we found that the IVS was thinner in the normotensive group than in the other groups. Other echocardiographic and ABPM parameters are shown in Table II.

Univariable and multivariable analyzes were performed to determine factors predicting the presence of RDHT. In model 1, the RDHT group was compared with the DHT group, and in model 2, the RDHT group was compared with the normotensive group. In model 1, high MHR [*p* = 0.014, Odds ratio (OR): 1.110, Confidence intervals (CIs): 1.021-1.206] and low daytime DBP (*p* = 0.026, OR: 0.951, CIs: 0.910-0.994) were found to be independent predictors of RDHT. In model 2, we discovered that high MHR (*p* < 0.001, OR: 1.244, CIs: 1.140-1.357), BMI (*p* = 0.005, OR: 1.143, CIs: 1.042-1.255), and C-reactive protein (CRP) (*p* = 0.009, OR: 1.166, CIs: 1.039-1.308) were independent predictors of RDHT. Univari-

Table I. Baseline characteristics and laboratory parameters of the study population.

Variables	RDHT group (n: 92)	DHT group (n: 124)	Normotensive group (n: 147)	p
Baseline characteristics				
Age, years	58.6 ± 13.5	52.4 ± 13.0	53.4 ± 15.7	0.004
Gender, female, n (%)	50 (54.3%)	62 (50.0%)	87 (59.2%)	0.316
Diabetes Mellitus, n (%)	20 (21.7%)	15 (12.1%)	12 (8.2%)	0.009
Body mass index, kg/m ²	27.2 ± 3.2	27.0 ± 3.2	25.5 ± 3.2	<0.001
Laboratory parameters				
Serum glucose, mg/dl	106.5 (95.2-110.7)	98.0 (89.0-110.7)	97.0 (88.0-107.0)	<0.001
Creatinine, mg/dl	0.81 (0.66-0.97)	0.75 (0.66-0.89)	0.73 (0.61-0.87)	0.031
Sodium, mmol/L	140.0 (138.0-142.0)	140.0 (139.0-141.0)	140.0 (139.0-141.0)	0.522
Potassium, mmol/L	4.3 ± 0.4	4.3 ± 0.3	4.3 ± 0.4	0.111
HDL cholesterol, mg/dl	46.4 ± 10.7	48.5 ± 10.4	52.5 ± 10.8	<0.001
LDL cholesterol, mg/dl	121.8 ± 39.3	127.0 ± 34.4	125.9 ± 41.5	0.596
Triglyceride, mg/dl	138.5 (98.0-186.2)	142.0 (100.0-216.7)	123.0 (88.0-185.0)	0.107
Total cholesterol, mg/dl	198.4 ± 44.2	208.4 ± 42.7	208.6 ± 54.2	0.223
C Reactive Protein, mg/L	4.6 (2.4-5.0)	4.9 (2.7-6)	2.0 (1.0-5.0)	<0.001
TSH, mIU/L	1.6 (0.9-2.4)	1.5 (1.0-2.3)	1.7 (1.1-2.5)	0.534
WBC count, ×10 ³ /μL	7.93 ± 2.07	7.38 ± 1.68	7.31 ± 1.88	0.034
Monocytes, ×10 ³ /μL	0.62 ± 0.18	0.54 ± 0.15	0.52 ± 0.14	<0.001
Platelet count, ×10 ³ /μL	279.8 ± 79.5	281.2 ± 60.8	275.9 ± 66.0	0.799
MHR	12.94 (10.23-16.95)	11.39 (8.47-14.39)	10.21 (7.54-12.82)	<0.001

HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; MHR, Monocytes to High-Density Lipoprotein Ratio; TSH, Thyroid Stimulating Hormone; WBC, White blood cell.

able and multivariable logistic regression analyses showing independent predictors of the presence of RDHT are shown in Table III.

In the ROC analysis performed according to model 1, MHR >12.23 cut-off was found to predict RDHT with a sensitivity of 59.8% and

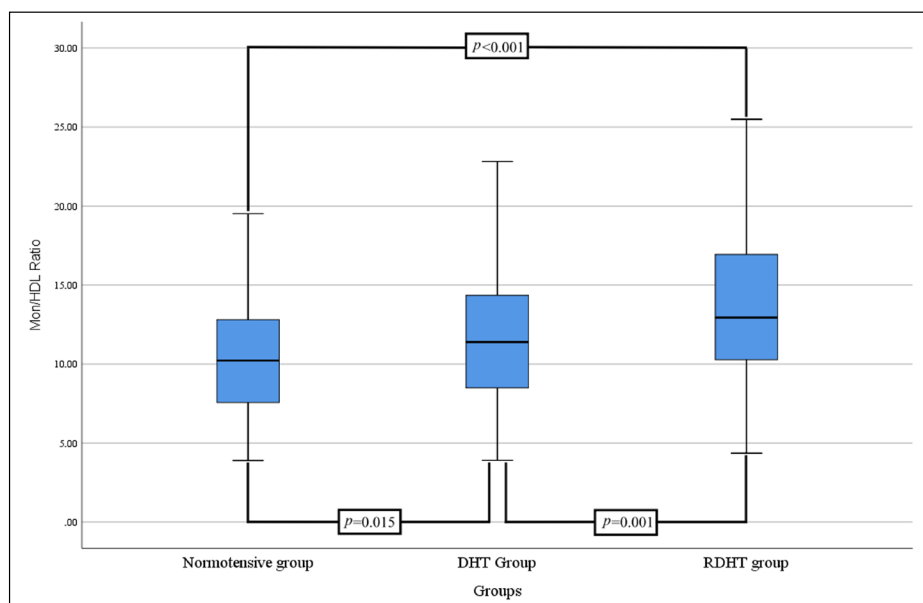


Figure 2. Comparison of monocyte-high density lipoprotein cholesterol ratio in the study groups.

Table II. Comparison of echocardiographic and ambulatory blood pressure parameters of the study population.

Variables	RDHT group (n: 92)	DHT group (n: 124)	Normotensive group (n: 147)	p
Echocardiographic parameters				
LVEF, %	58 (55-60)	60 (55-62)	60 (55-62)	0.181
IVS, mm	1.0 (0.9-1.2)	1.0 (0.9-1.1)	1.0 (0.9-1.0)	0.002
Ambulatory blood pressure parameters				
24-h SBP, mmHg	131.5 (125.0-141.7)	133.0 (126.0-142.0)	117.0 (110.0-122.0)	<0.001
Daytime SBP, mmHg	130.5 (124.2-141.0)	138.0 (132.2-147.7)	119.0 (111.0-125.0)	<0.001
Nighttime SBP, mmHg	136.0 (129.2-148.0)	118.5 (113.0-127.0)	108.0 (102.0-113.0)	<0.001
24-h DBP, mmHg	81.6 ± 10.2	84.7 ± 8.9	70.6 ± 5.2	<0.001
Daytime DBP, mmHg	81.4 ± 10.4	88.3 ± 9.6	73.3 ± 5.7	<0.001
Nighttime DBP, mmHg	82.3 ± 11.1	74.1 ± 8.8	63.0 ± 5.0	<0.001

DBP, Diastolic Blood Pressure; LVEF, Left ventricular ejection fraction; IVS, Interventricular septum; SBP, Systolic Blood Pressure.

a specificity of 61.3% (AUC: 0.637, CIs: 0.563-0.711, $p = 0.001$; Figure 3). In the ROC analysis performed according to model 2, MHR >12.59 cut-off was found to predict RDHT with a sensitivity of 57.6% and a specificity of 72.8% (AUC: 0.714, CIs: 0.648-0.781, $p < 0.001$; Figure 4).

Discussion

Our study investigated the relationship between MHR values and two critical dipper patterns (DHT and RDHT). The main finding of our study was that MHR was significantly higher in RDHT

Table III. Univariable and multivariable logistic regression analysis showing the independent predictors for the presence of reverse BP pattern.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Model 1 (RDHT group vs. DHT group)				
Age	1.037 (1.015-1.059)	0.001	1.022 (0.996-1.049)	0.104
Creatinine	3.914 (1.235-12.404)	0.020	1.633 (0.388-6.881)	0.504
WBC	1.171 (1.011-1.357)	0.035	1.011 (0.835-1.223)	0.914
MHR	1.112 (1.047-1.182)	0.001	1.110 (1.021-1.206)	0.014
LVEF	0.918 (0.856-0.985)	0.017	0.962 (0.884-1.048)	0.378
Daytime SBP	0.962 (0.941-0.984)	0.001	0.979 (0.948-1.012)	0.217
Daytime DBP	0.931 (0.902-0.960)	<0.001	0.951 (0.910-0.994)	0.026
Model 2 (RDHT group vs. Normotensive group)				
Age	1.024 (1.006-1.043)	0.010	1.008 (0.985-1.031)	0.514
DM	0.320 (0.148-0.692)	0.004	0.493 (0.183-1.328)	0.162
BMI	1.169 (1.075-1.272)	<0.001	1.143 (1.042-1.255)	0.005
Serum glucose	1.013 (1.003-1.024)	0.010	1.003 (0.992-1.015)	0.562
Creatinine	5.001 (1.664-15.029)	0.004	0.837 (0.209-3.345)	0.801
CRP	1.167 (1.055-1.293)	0.003	1.166 (1.039-1.308)	0.009
WBC	1.173 (1.025-1.342)	0.020	0.901 (0.751-1.082)	0.266
MHR	1.230 (1.141-1.325)	<0.001	1.244 (1.140-1.357)	<0.001
IVS	17.792 (3.235-97.847)	0.001	6.885 (0.951-49.855)	0.056

BMI, body mass index; CI, confidence interval; CRP, C reactive protein; DM, Diabetes mellitus; DBP, Diastolic blood pressure; IVS, Interventricular septum; LVEF, Left ventricular ejection fraction; MHR, Monocytes HDL ratio; OR, Odds ratio; SBP, Systolic blood pressure; WBC, White blood cell.

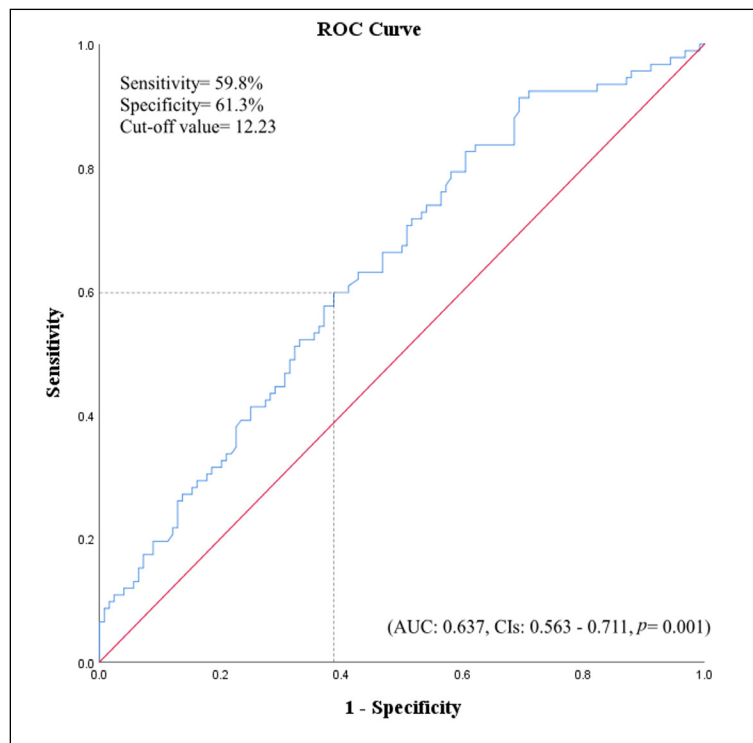


Figure 3. Receiver operating characteristics (ROC) curves of monocyte-high density lipoprotein cholesterol ratio associated with RDHT vs. DHT group (Model 1).

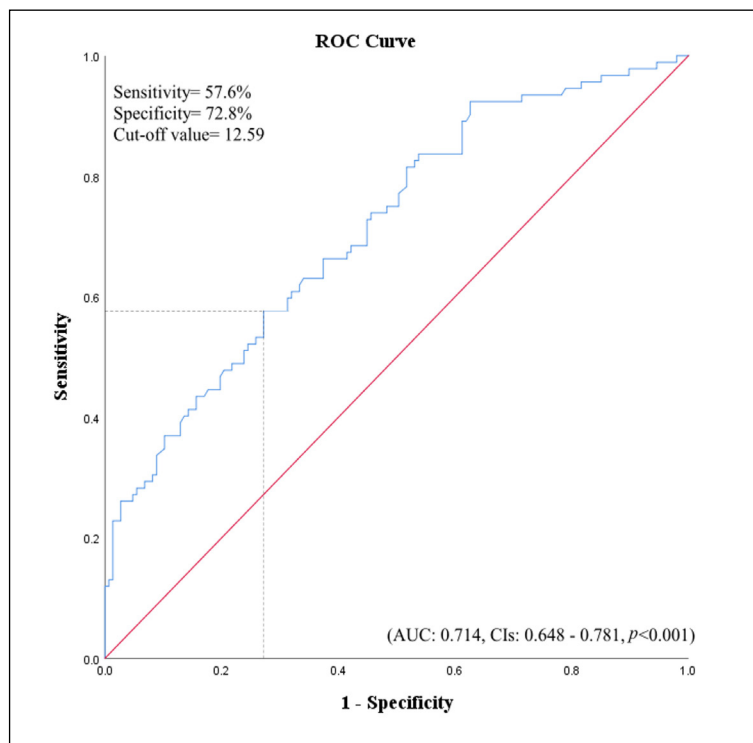


Figure 4. Receiver operating characteristics (ROC) curves of monocyte-high density lipoprotein cholesterol ratio associated with RDHT vs. normotensive group (Model 2).

patients compared to DHT patients and normotensive subjects. We found that high MHR and low daytime DBP levels were independent predictors of RDHT (*vs.* DHT). We also found that high MHR, high BMI, and high CRP levels were independent predictors of RDHT compared (*vs.* normotensive).

The incidence of cardiovascular events is higher among patients with RDHT, most likely due to greater levels of end-organ damage in this population. This is exemplified by various studies in the literature, which have shown worse prognosis for a number of diseases in the presence of RDHT. Yan et al²³ demonstrated the association between RDHT and lacunar infarction. Park et al²⁴ found that RDHT was associated with mortality in patients with acute cerebral infarction. In addition, stable CAD was found to be associated with RDHT in patients with essential HT²⁵. High average 24-hour SBP and average nocturnal SBP increased cardiovascular events and mortality. Even slight deviations have been associated with worse outcomes; for instance, one study found that a 5% increase in mean nocturnal SBP and DBP was associated with a 20% increase in cardiovascular mortality²⁶. When compared to other dipping patterns, RDHT has the worst prognosis²⁷. When patients are asked for a home blood pressure follow-up chart for diagnosis, it can sometimes be difficult to detect the reverse dipper pattern and, therefore, hypertension, as they usually perform daytime measurements. Therefore, biomarkers predicting the reverse dipper pattern and guiding the ABPM examination may be valuable. MHR is an important marker of inflammation. It is an easily accessible, calculable, and inexpensive parameter. Selçuk et al¹⁴ found that MHR was associated with a non-dipper pattern in hypertensive patients. Zhou et al²⁸ found a continuous positive linear relationship between MHR and HT in their study. In addition, MHR has been investigated in previous studies and reported to be associated with cardiovascular diseases such as acute ischemic stroke¹², prognosis in pulmonary embolism¹³, and resistant HT in chronic kidney patients²⁹.

Comorbidities may also play a role in dipper patterns among patients with HT. For instance, a history of DM has been associated with RDHT as detected by ABPM³⁰. Similarly, our study showed that DM frequency and serum glucose levels were significantly higher in the RDHT group. The reason for the significantly higher serum glucose level is highly likely to be a direct result of DM prevalence in the RDHT group; however, this cannot be definitively confirmed by our results due to the lack of data concerning glucose control in DM pa-

tients. Increased BMI and obesity are associated with HT³¹. In our results, higher BMI proved to be an independent predictor of RDHT in the model, performing comparisons with the normotensive subgroup of patients, thereby demonstrating similarities with previous studies.

RDHT is also associated with increasing age. Autonomic dysfunction, which worsens with increasing age, may be the cause³². This is in agreement with our results, which showed that age was significantly higher in the RDHT group.

Inflammation has an indisputable place in the etiology of HT. Previous scholars³³ have shown an association between CRP levels and HT. We found that inflammatory markers such as CRP, white blood cell count, and monocyte count were higher in the RDHT group. Furthermore, high CRP (as well as high MHR) was an independent predictor of RDHT.

Inflammation is also a critical contributor to the pathogenesis and prognosis of various other cardiovascular diseases. The most widely recognized cellular-level phenomenon in this relationship is the migration of monocytes into tissues and their transformation into macrophages, and the downstream activation of inflammation followed by atherosclerosis and other forms of tissue injury¹⁰. HDL-C protects the endothelium from the deleterious effects of LDL-C, inhibits LDL-C oxidation, and thus has anti-inflammatory and antioxidant effects³⁴.

We observed the daytime DBP average lower in the RDHT group than in the DHT group. The same difference was not observed in daytime SBP. In patients with low daytime DBP, it will be helpful to be examined with ABPM for reverse dipper pattern.

The pathogenesis of the reverse pattern in HT patients, associated with a poor prognosis in cardiovascular diseases, is not fully understood. Inflammation may play a role in pathogenesis and has never been investigated before. According to the results of our study, MHR, a new inflammatory marker, appears to be associated with RDHT. Our study revealed the need for more comprehensive studies in the future to show the relationship between RDHT and inflammation.

Limitations

This study has some limitations. First, this was a retrospective study performed at a single center. We could not examine other, more detailed inflammatory markers because our center did not analyze cytokines. Third, we only calculated MHR on admission and did not evaluate follow-up

values. However, we believe that the results of our study may be valuable for future studies, and the relationships revealed herein could provide a basis for research focusing on the detection of dipping patterns among patients with HT.

Conclusions

In addition to comparing various characteristics of HT patients with two characteristic dipper patterns (DHT vs. RDHT), our findings indicate that MHR, a novel inflammatory marker, was a factor that was independently associated with RDH – both vs. normotensive subjects and patients with DHT. This easily applicable and inexpensive marker can be used as a supportive data point to assess the likelihood of RDHT in patients with HT. Individuals suspected of having RDHT as a result of MHR calculation could be referred for ABPM, especially in the presence of other independent risk factors that were identified in this study.

Conflict of Interest

The Authors declare no conflict of interest.

Funding

The authors did not receive support or funding from any organization for the submitted work.

Informed Consent

Not applicable due to the retrospective nature of the study.

Ethics Approval

This study was conducted following the Declaration of Helsinki and was initiated with the approval of the Karatekin University Ethics Committee (Date: 25.10.2022, Decision No.: 28/3ed2e30b500a4838).

Authors' Contributions

Bekir Demirtaş is the principal author of this study and designed the study with resource acquisition, data collection and processing data, data analysis and interpretation, writing- original draft preparation, and editing. All the authors conceived the idea for the article, framing the hypothesis, designed the methods to generate results, data collection and processing data, data analysis and interpretation, writing- original draft preparation, critical review, and edited together. All authors have read and approved the paper.

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Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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