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# Clinical Effect of Non-Dipper and Dipper Hypertension in Patients with Acute Coronary Syndrome

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ABSTRACT

**Objective:** During sleep, blood pressure (BP) is generally 10%–20% lower, and the risk of target organ damage in non-dipper hypertension (HT) is related to left ventricle hypertrophy, MI, and stroke. This study aimed to analyze the effect of non-dipper HT on the prevalence of coronary artery disease (CAD), time of symptom onset, and in-hospital MACE in patients with acute coronary syndrome (ACS).

**Materials and Methods:** We included 107 patients who were diagnosed with ACS and had angina pectoris lasting 12 h at most and no history of CAD in this study. Patients' ambulatory BP was monitored for 24 h. Patients were divided into the non-hipper and dipper groups according to the decrease in BP during nighttime. We compared the prevalence of CAD, time of symptom onset, and in-hospital MACE in both groups.

**Results:** We included 52 patients in the non-dipper group and 55 patients in the dipper group in this study. When we compared the Syntax and Gensini scores between the groups, statistical significance was determined (p=0.006). In terms of symptom onset hours, 32 (62%) and 19 (35%) patients were admitted with night angina pectoris in the non-dipper and dipper groups, respectively (p=0.007). In terms of in-hospital MACE ratios, we identified MACE in six patients in the non-dipper group and three patients in the dipper group (p=0.223).

**Conclusion:** In our study, we conclude that non-dipper HT increases the number of lesions, MI cases at night, and MACE ratios in CAD by causing endothelium dysfunction and stimulating thrombocyte activation.

**Keywords:** Acute coronary syndrome, dipper hypertension, non-dipper hypertension

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## INTRODUCTION

As with all around the globe, coronary artery disease (CAD) is the leading cause of mortality and morbidity in our country, and its prevalence is continuously increasing. While there is a decrease in the mortality rates due to the disease in Europe and the United States, no decrease was seen in the absolute numbers of the individuals who died from this disease (1). The physiopathology of atherosclerosis, which is the principal cause of CAD, includes the interaction of genetic and environmental factors on the coronary artery wall and the formation of plaque due to stimulation of endothelial cells, vascular smooth muscle cells, and other inflammatory cells. Atherosclerosis is a chronic progressive process that is closely associated with endothelial dysfunction (ED) (2). It causes a large range of clinical presentations, from stable angina pectoris to acute coronary syndrome (ACS), and results in myocardial ischemia or necrosis.

The management of risk factors in CAD is significant for the prevention of CAD in asymptomatic individuals (primary prevention) and recurrences in individuals with CAD (secondary prevention) (3).

Hypertension (HT) is responsible for approximately 35% of the atherosclerotic cardiovascular events. It is a crucial risk factor for not only CAD but also cardiac failure, peripheral arterial disease, stroke, and renal failure. CAD is seen two- to threefold more in hypertensive patients compared with that in normotensive individuals (4).

Cardiovascular parameters such as blood pressure (BP), heart rate, and coronary tonus change throughout the day due to circadian rhythm (5). The ambulatory blood pressure measurement (ABPM) data for normal individuals indicates that BP is at the highest level in the morning hours, tends to decrease throughout the day, and is at the lowest level at night. This is called dipper HT. If BP does not decrease more than 10% at night, it is called non-dipper HT (6). Cardiovascular risk is affected not only by BP elevation but also greatly from changes to circadian rhythm (7). Therefore, the occurrence rate of cerebrovascular disease, cardiovascular mortality and morbidity, and left ventricle hypertrophy is higher in patients with non-dipper HT (8).

This study examined the effect of non-dipper and dipper HT in patients who were admitted and followed up with the diagnosis of ACS.

## MATERIALS and METHODS

### Patient Population

This study was designed as a retrospective case-controlled study. We prospectively included patients without a history of CAG, those who had been admitted with the complaint of chest pain for a maximum of 12 h, and those diagnosed with ACS (non-STEMI and unstable angina). This study was approved by the local ethics committee (number 2013-326). A total of 156 patients were screened. After the exclusion criteria were applied, 107 patients (55 with dipper, 52 with non-dipper) were included in this study. The ACS diagnosis was made based on the international criteria.

Patients under 18 and over 85 years of age with acute and/or chronic renal failure, chronic and acute hepatic failure, malignancy, previous CAD, resistant HT, and cardiogenic shock history were excluded from this study. All patients chewed 300 mg of non-enteric-coated aspirin in the emergency room. Moreover, standard ACS treatment (beta-blocker, ACE inhibitor, ASA, clopidogrel, and statin) was initiated for all patients based on their hemodynamic status.

### Laboratory Assessments

At the time of admission, complete blood count samples in tripotassium ethylenediaminetetraacetic acid tubes and biochemistry parameters from blood samples in Isotherm-Gel Clot Activator based biochemistry tubes (fasting blood glucose, renal and liver function tests, total lipid profile) along with sedimentation were studied in all patients. To assess the inflammatory status of the participants, the C-reactive protein (CRP) levels were measured using a BN2 nephelometer (Dade Behring, Schwalbach, Germany).

### Echocardiography

All echocardiographic assessments were performed by an experienced cardiologist, based on the recommendations of the American Association of Echocardiography with a GE Vingmed Vivid 7 system echocardiography device using 2.5-MHz transducers. Left ventricular (LV) diastolic and systolic and LV diastolic septal and posterior wall thickness were measured by placing the M-mode cursor through the parasternal long axis window, vertical to the long axis of the LV, right in front of the mitral valve ends. Using 2D echocardiography, the left ventricle ejection fraction was measured on the apical four chambers using modified Simpson's method.

### Coronary Angiography

Selective coronary angiography was performed in all patients from the femoral approach using the standard Judkins technique. Coronary angiography analyses were performed by specialist cardiologists. The patients were evaluated to have normal coronary arteries if they had no angiographic plaque formation in all epicardial coronary arteries (including sub-branches), no irregular margins, no ectasia, and no slow flow. They were considered to have CAD if they had at least one of the aforementioned conditions. Patients diagnosed with CAD were considered to have obstructive CAD if they had ≥50% stenosis in at least one coronary artery. Patients who had <50% stenosis in at least one coronary artery were considered to have nonobstructive CAD. Gensini and Syntax scoring were used to evaluate the prevalence of CAD.

**Table 1.** Baseline demographical and biochemical features of the study population

| | Dipper group (n=55) | Non-dipper group (n=52) | p |
|---|---|---|---|
| Age | 58.2±10.9 | 60.5±10.7 | 0.349 |
| Diabetes mellitus | 10 (18%) | 7 (14%) | 0.791 |
| Hypertension | 9 (16%) | 15 (28%) | 0.104 |
| Smoking | 22 (40%) | 17 (34%) | 0.684 |
| Hyperlipidemia | 3 (5%) | 4 (7%) | 0.379 |
| Sex (M/F) | 42/13 | 37/15 | 0.408 |
| BMI (kg/m$^2$) | 27.3±5.1 | 28.2±2.5 | 0.537 |
| Hemoglobin (g/dL) | 14.0±1.6 | 13.7±1.7 | 0.386 |
| Hematocrit (%) | 42.3±5.2 | 41.8±5.9 | 0.431 |
| White shape (10$^3$ µL) | 9.1±3.5 | 8.7±3.8 | 0.267 |
| CRP | 17.8±4.3 | 16.7±4.9 | 0.286 |
| Platelet count (10$^3$ µL) | 264.5±70.6 | 275.3±83.7 | 0.525 |
| Creatinine (mg/dL) | 0.8±0.2 | 0.8±0.1 | 0.931 |
| Glucose (mg/dL) | 127±13 | 122±18 | 0.366 |
| Total cholesterol (mg/dL) | 173.2±42.6 | 183.1±39.7 | 0.358 |
| LDL (mg/dL) | 114.7±31.2 | 121.0±28.2 | 0.449 |
| HDL (mg/dL) | 37.7±8.2 | 36.0±8.3 | 0.563 |
| Triglycerides (mg/dL) | 155.9±71.4 | 165.8±77.6 | 0.441 |

BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

**Table 2.** Transthoracic echocardiography and hemodynamic parameters between groups

| | Dipper group (n=55) | Non-dipper group (n=52) | p |
|---|---|---|---|
| LVEF % | 47.3±7.8 | 45.3±7.4 | 0.149 |
| Systolic PAP (mmHg) | 30.9±9.9 | 32.1±10.7 | 0.167 |
| LVDD (cm) | 4.7±0.6 | 4.9±0.7 | 0.212 |
| LVSD (cm) | 3.1±0.5 | 3.0±0.4 | 0.101 |
| IVSD | 1.0±0.2 | 1.1±0.2 | 0.631 |
| Heart rate | 72±12 | 69±14 | 0.427 |
| Systolic blood pressure (mmHg) | 127±18 | 132±17 | 0.295 |
| Diastolic blood pressure (mmHg) | 77±8 | 81±7 | 0.164 |

LVEF: Left ventricular ejection fraction; PAB: Pulmonary artery pressure; LVDD: Left ventricular diastolic diameter; LVSD: Left ventricular systolic diameter; IVSD: Interventricular septal diameter

### ABPM

BP measurements in the clinic were performed using a sphygmomanometer and according to the European Society of Hypertension. ABPM was performed using a Microlife WatchBP device in the 24-h period after the patient was included in this study, based on the inclusion criteria, using the proper cuff size for the patient's arm diameter.

### Dipper and Non-Dipper Criteria

BP measurements were taken every 30 min during daytime (between 07:00 and 22:00) and every 60 min during nighttime (22:00 to 07:00). Nighttime and daytime measurements for 24 h were analyzed. The percentage of nighttime BP decrease was calculated using the following formula: nighttime BP decrease (%) = (daytime BP − night KB) × 100 / nighttime BP. If the patient's mean BP measured during nighttime was <10% lower than the mean daytime measurement, it was considered to be "non-dipper BP," and if the difference was 10% or more, it was considered to be "dipper BP." This procedure was performed at the patient's first admission and on day 3. Groups were formed based on the average of both measurements.

### Statistical Analysis

The distribution normality of the variables was determined using the Kolmogorov–Smirnov test. The baseline characteristics of the patients were assessed between the groups using Student's t-test for numerical variables and the chi-square test for categorical variables. Analysis results were assessed within a 95% confidence interval, and a P value of <0.05 was considered statistically significant. SPSS 15.0 software (version 15, SPSS Inc., Chicago, IL, USA) was used for basic statistical analysis.

## RESULTS

A total of 107 patients, 52 in the non-dipper group (mean age, 60.5±10.7 years) and 55 in the dipper group (mean age, 58.2±10.9 years), were included in this study. Moreover, 70% (n=37) of the patients in the non-dipper group and 76% (n=42) of those in the dipper group were men (p=0.408). No significant difference was observed between the groups for HT, diabetes mellitus (DM), smoking status, and hyperlipidemia history (p=0.104, p=0.791, p=0.684, and p=0.379, respectively) (Table 1).

No significant difference was noted between the two groups in terms of heart rate and systolic and diastolic BP at admission (p=0.427, p=0.295, and p=0.164, respectively).

No significant difference was shown between the two groups in terms of echocardiography parameters (Table 2). Moreover, no significant difference was noted between the two groups in terms of biochemical and hematological parameters (white blood cell count; platelet count; and hemoglobin, hematocrit, CRP, creatinine, glucose, and cholesterol values) (Table 1).

The Syntax and Gensini scores determined the prevalence of CAD. When the Syntax scores were compared between the two groups, the mean Syntax scores were 10.2±4.8 and 8.0±4.2 in the non-dipper and dipper groups, respectively, and the difference was statistically significant (p=0.011) (Fig. 1a). While the patients in the non-dipper group were mostly distributed at high Syntax scores, those in the dipper group were mostly distributed at low Syntax scores (Fig. 1b). When the Gensini scores were compared between the two groups, the mean Gensini scores were 29.5±13.3 and 22.2±13.2 in the non-dipper and dipper groups, respectively, and the difference was statistically significant (p=0.006) (Fig. 2a, b).

When the hours at which the pain started were compared between two groups, the number of patients who were admitted with chest

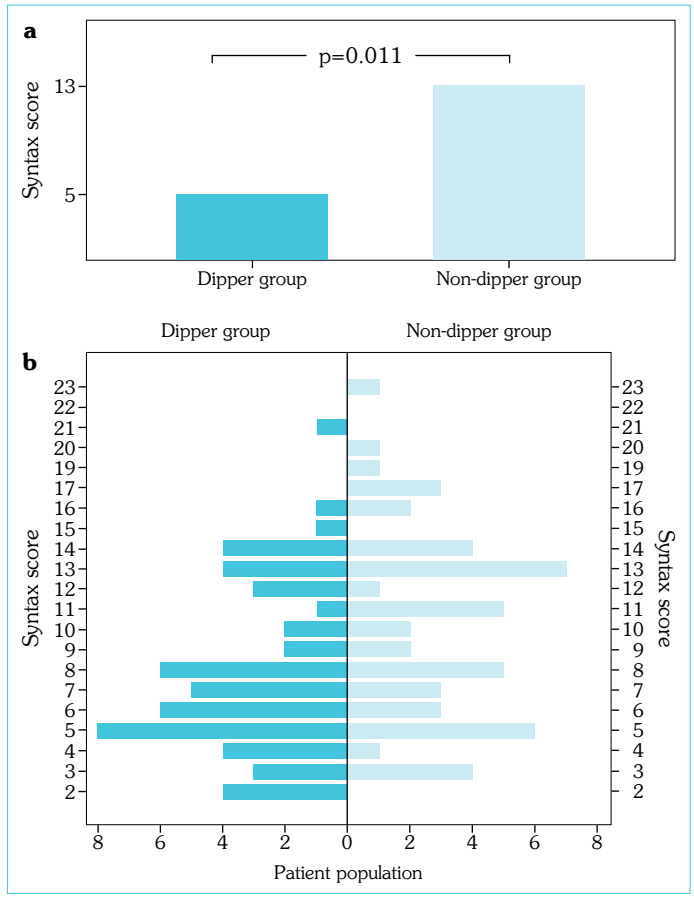


**Figure 1. Evaluation of the Syntax risk score among patient groups and Syntax risk score distribution. In Figure 1a, the mean Syntax scores are 10.2±4.8 and 8.0±4.2 in the non-dipper and dipper groups, respectively**

pain at night in the non-dipper group was 32 (62%), while that in the dipper groups was 19 (35%), and the difference was statistically significant (p=0.007) (Fig. 3).

When the in-hospital MACE rates were compared, MACE was found in six patients in the non-dipper group and three patients in the dipper group. This difference was not statistically significant (p=0.223).

## DISCUSSION

The association of HT and night to day change of HT with cardiovascular diseases (mortality, morbidity, and end-organ damage) has been demonstrated in several studies (8, 9). These studies have found an inadequate decrease in night cardiac index and sympathetic activity in patients with non-dipper HT. The cardiovascular system is exposed to higher pressure at night, and the structural and functional changes in the body developed to compensate this pressure are thought to cause irreversible damage in all vascular systems. The patients' prevalence of CAD, the hour of pain onset, and in-hospital MACE rates were assessed.

Atherosclerosis is a chronic progressive disease characterized by intimal smooth cell accumulation and proliferation, macrophage and T lymphocyte infiltration, and lipid deposition as free choles-

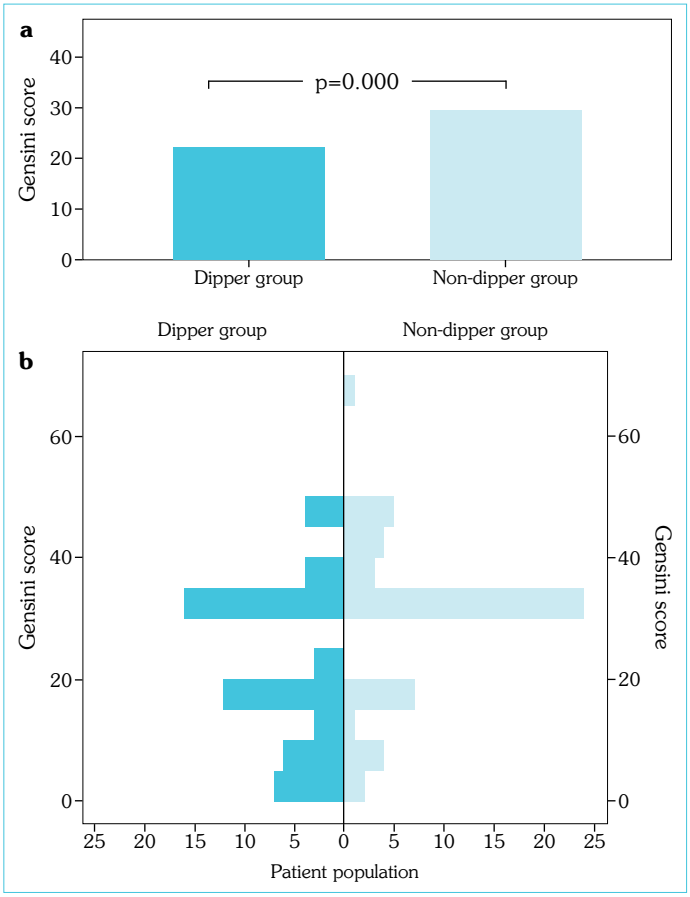


**Figure 2. Evaluation of the Gensini risk score among patient groups and Gensini risk score distribution. In Figure 2a, the mean Gensini scores are 29.5±13.3 and 22.2±13.2 in the non-dipper and dipper groups, respectively**

terol, and cholesterol esters in collagen-, elastin-, fibronectin-, and proteoglycan-rich connective tissue matrix, in the intra- and extracellular connective tissue, and is closely associated with ED (2). Clinical signs present by the stenosis caused by the atherosclerotic plaque developed over the years or by atherothrombosis developed due to the rupture, fissure, and erosion of this plaque. Vascular endothelial damage is the first and the most important step of this process. After endothelial damage, lipid deposition and platelet and leukocyte adhesion occur in the same area. Endothelial growth factors are released by the cells accumulated in this area causing proliferation of smooth muscle cells (10). In our study, we believe that the erosion caused by HT is the cause of this.

There is a strong connection between atherogenic risk factors and ED. With the downregulation of the endothelial nitric oxide (NO) synthase expression, oxidized low-density lipoprotein decreases receptor-mediated NO release and increases the production of superoxide anion and NO inactivation causing a strong impairment in endothelial function. Impairment of NO production or activity predisposes individuals to several diseases targeting the cardiovascular system, such as CAD, HT, cardiac failure, renal failure, DM, metabolic syndrome, and obesity, and accelerates atherosclerosis (11). Especially in patients with HT, impairment of NO bioavailability causes impairment of endothelium-mediated vasodilation, and this may be an indicator of early atherosclerosis. As in our study,

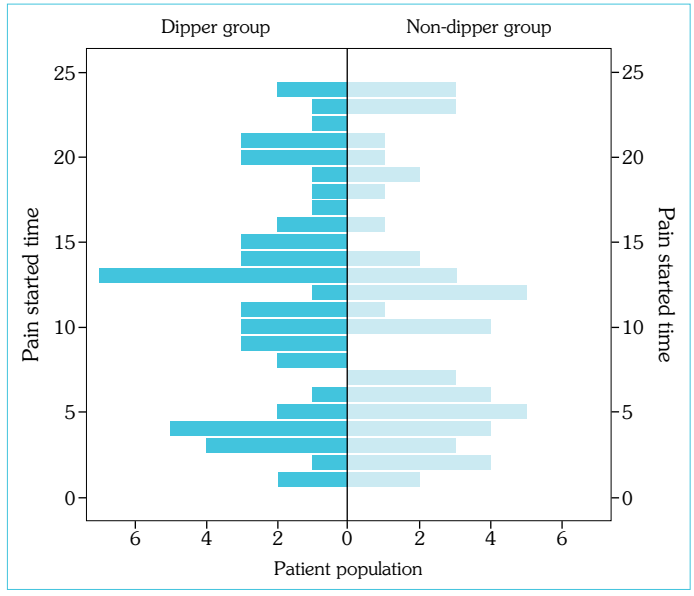


**Figure 3. Patients' pain start time distribution**

non-dipper HT also plays a significant role in atherosclerosis because it is a branch of HT. Treatment strategies applied to restore endothelial function may provide a decrease in atherosclerosis progression in patients with HT. As in our study, this progression helps to increase the severity of atherosclerosis and increases the Syntax and Gensini values.

Arterial BP physiologically changes throughout the day. Physiologically, BP at night should be >10% lower than the daytime BP, and this is called the dipper activity. If the night BP drops <10% from the daytime value, it is called the non-dipper activity (12). Individuals with non-dipper BP have been found to have more frequent end-organ damage (ventricular hypertrophy, microalbuminuria, decreased arterial compliance, etc.) and cardiovascular morbidity and mortality (13, 14). In our study, no difference was found in the LV walls of the patients. The probable cause is that we do not know the exact duration of non-dipper HT and therefore have not fully reached the required duration for hypertrophy. The possible mechanisms of HT causing coronary events include ED and the increases in the endothelial lipoprotein permeability; oxidative stress; hemodynamic stress, triggering acute plaque rupture; myocardial wall stress; and myocardial oxygen need (15). The loss of endothelial integrity is detected in the presence of atherosclerosis and the risk factors related with it such as HT, and an association of endothelial integrity loss with each risk factor for clinical events such as atherosclerosis development, myocardial infarction, and stroke has been shown (16). Because of this reason, in our study, with the effect of non-dipper HT, they presented with more nighttime complaints.

It is known that there is a direct proportion between BP levels, the grade of ED, vascular damage, and end-organ damage. Several studies have shown that ED is significant for the development and prevalence of CAD. Endothelium-dependent vasodilation impairment due to the decrease in NO release has been shown to be a risk factor in cardiovascular and cerebrovascular patients (17). In a study comparing non-dipper and dipper patient groups for ED, Higashi et al. (18) assessed the 24-h urinary excretion of the NO

final product nitrite/nitrate and cyclic guanosine monophosphate as a marker of ED. In conclusion, the 24-h urinary nitrite/nitrate and cyclic guanosine monophosphate levels were found to be significantly lower in the non-dipper patient group. Inadequate BP drop at night and exposure of the endothelium to higher pressure for a longer period may have caused more endothelial damage and vascular inflammation in the non-dipper group leading to a higher prevalence for CAD. Consistent with other studies, it can be concluded that the coronary prevalence scoring difference in our study may have been caused by ED.

Kaya et al. (19) demonstrated that non-dipper HT has adverse effects on MPV, which is a marker of platelet activity and an inflammatory mediator. It may be considered that in addition to the ED, atherosclerosis activated by platelets that are triggered by non-dipper HT had higher prevalence and contributed to the finding of significant difference in our study in the Syntax and Gensini scores, which determine the prevalence of CAD.

There are publications reporting that increased sympathetic nervous system activation plays a role in the pathophysiology of non-dipper BP (20). Because of the activation of the sympathetic nervous system, adrenergic mediators from the nerve ends bind to several mediator receptors in tissue and vessels and exert their activity. With the activation of the sympathetic nervous system, vasoconstriction and spasm occur in coronary arteries due to the stimulation of alpha-1 receptors by norepinephrine in both normal individuals and those with CAD (21, 22). The main cause of this activation is known to be the epinephrine and cortisol peak in morning hours. Similar to this mechanism, several studies have shown that the increase in sympathetic activation plays a role in the pathogenesis of non-dipper HT. In our study, it can be said that the time of onset of the symptoms and the fact that the symptoms onset in the night hours is caused by the aforementioned mechanisms.

Bahçıvan et al. (23) investigated the effect of preoperative circadian BP pattern on early postoperative course in patients who underwent coronary artery bypass graft surgery and showed that the need for inotropic medication, low cardiac output syndrome, postoperative myocardial infarction (28.6% vs. 71.4%), and malignant ventricular arrhythmias (27.8% vs. 72.2%) were found more in the non-dipper group compared with those in the dipper group ($p<0.05$). In our study, while there was no statistical significance, the MACE rates increased in patients in the non-dipper group.

In conclusion, our study showed that in patients admitted with ACS, the non-dipper activity causes more prevalence of CAD, symptoms that are present mostly in the night hours, and increase in the MACE rates compared with the dipper activity. In line with this data, with the diagnosis and treatment of non-dipper HT, we believe that these complications would decrease.

**Ethics Committee Approval:** The Erciyes University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 07.05.2013, number: 2013/326).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – DE, ŞK, BB, ZÇ; Design – DE, MTİ, AD, NK; Supervision – DE, AD, AO, RT; Materials – DE, AO, RT, NK, ŞK; Data Collection and/or Processing – DE, ZK, BB, ŞK; Analysis and/or Interpretation – DE, ZÇ, NK; Literature Search – DE, ZÇ, ŞK, BB; Writing – DE, ZÇ, ŞK; Critical Reviews – DE, ZÇ, ŞK.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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