METABOLIC DISEASES

The biomarkers associated with non-dipper pattern in patients with type 2 diabetes with hypertension

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Abstract

Background and aims. The non-dipper pattern is present in about 50 percent of patients with type 2 diabetes (T2D) and hypertension, a status associated with more frequent cardiovascular complications and restrained prognosis. This study aimed to identify simple biomarkers that can be used for the classification of dipper and non-dipper individuals with type 2 diabetes and hypertension.

Method. 138 consecutive patients with type 2 diabetes mellitus (DM) and hypertension underwent 24-hour ambulatory blood pressure monitoring (ABPM), 54 (39.1%) dippers and 84 (60.9%) non-dippers; CBC and determinations of different biomarkers, as well as their ratio was also performed, for comparing the two dipper profiles. The different dipper profiles were established by ABPM, which highlights the mean arterial pressure (MAP), the mean heart rate (MHR), and the mean pulse pressure (MPP). The area under the receiver operating characteristic curve (AUC) was used to evaluate the ability of biomarkers to differentiate dippers from non-dippers.

Results. The study included 54 dipper and 84 non-dipper patients. The median age was 64 years (interquartile range 58-74), ranging from 24 to 85 years. The comparison between dipper and non-dipper in patients with type 2 diabetes and hypertension concerning different biomarkers found only two that were statistically significant: triglycerides to hemoglobin A1c (HbA1c) ratio and triglycerides to glucose ratio. For both biomarkers, the dippers had higher values than non-dippers. The best AUCs were found for triglycerides (Trig) to glucose ratio of 0.774 (95% confidence interval 0.601 - 0.92), statistically significant, followed at a distance by lymphocytes, platelets-lymphocytes ratio (PLR), platelet distribution width (PDW-SD), mean platelet volume (MPV) /Lymphocytes, and others, none of them being statistically significant.

Conclusions. This study offers valuable insights into the classification of dipper and non-dipper individuals with type 2 diabetes and hypertension using several biomarkers. Notably, the triglyceride-to-glucose ratio appeared as a significant marker with considerable discriminative capacity, indicating its potential therapeutic value in risk stratification and personalized treatment strategies.

Keywords: non-dipper, biomarkers, platelet-lymphocytes ratio, triglycerides-glucose ratio

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Introduction

Hypertension is a pervasive global health issue, affecting over 1.3 billion people worldwide and representing a leading cause of cardiovascular morbidity and mortality. In the United States, nearly half of the adult population is affected by hypertension, contributing to substantial healthcare costs and increased risk for stroke, heart attack, and kidney disease [1].

Similarly, in Europe, hypertension prevalence ranges from 30% to 45%, with significant variations across countries and ethnicities [2].

Diabetes mellitus, particularly type 2 diabetes (T2DM), is another major chronic disease with a significant global burden, affecting over 463 million people worldwide. In the United States, approximately 34.2 million people, or 10.5% of the population, are diagnosed with diabetes, with an even higher prevalence among older adults [3].

Europe also faces a significant diabetes burden, with around 60 million people affected. Diabetes significantly increases the risk of cardiovascular diseases, kidney failure, and neuropathy, making it a critical public health globally concern [4].

Ambulatory blood pressure monitoring (ABPM) is essential in evaluating and managing arterial blood pressure in patients with type 2 diabetes. ABPM is the gold standard for detecting non-dipper patterns and for determining associated cardiovascular comorbidities and risk factors [5].

In the non-dipper profile, the nocturnal drop in blood pressure is less than 10 percent; instead, in the dipper (normal profile) is between 10 and 20 percent. In the context of high blood pressure (HBP), the term "dipper" refers to a normal pattern of variation in blood pressure over the course of a day. Normally, in a healthy person, blood pressure drops during sleep, and this phenomenon of nocturnal decrease is called "dipping".

Within the hypertensive and diabetic populations, a significant subset of individuals, known as non-dippers, exhibit a lack of the typical nocturnal decline in blood pressure. Non-dippers are at a heightened risk for adverse cardiovascular outcomes, including left ventricular hypertrophy, stroke, and chronic kidney disease, due to their persistent elevated nighttime blood pressure. This non-dipping pattern is a crucial indicator of increased cardiovascular risk, making it essential to identify and manage effectively these patients [6].

On a global scale, non-dippers contribute significantly to the burden of cardiovascular diseases, exacerbating the risks associated with hypertension and diabetes and leading to increased rates of stroke, myocardial infarction, and kidney disease [7].

Biomarkers are biological indicators that can be measured to assess physiological or pathological processes or responses to treatment. In the case of the non-dippers profile, biomarkers can be used to evaluate cardiovascular risk and to identify the mechanisms involved in this condition [8].

The complete blood count (CBC), through its complexity, offers many biomarkers that can predict and diagnose diseases and monitor therapeutic efficiency.

Chronic inflammation plays an essential role in the pathophysiology of arterial hypertension (HTN) and is more pronounced in individuals with a non-dipper circadian blood pressure (BP) pattern. A non-dipping BP pattern is, in turn, associated with increased cardiovascular morbidity and mortality and a higher risk of atherosclerotic events. The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) are readily available predictors of systemic inflammation and cardiovascular risk [9].

Increasing research has shown that changes in hemogram parameters are also associated with hypertension (HT), including white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (HCT), platelet count (PLT), mean platelet volume (MPV), and platelet distribution width (PDW). In addition, some studies of the predictive ability of hematological factors for the risk of HT have reported a significant predictive effect, but others have suggested a weak association [10].

Identifying biomarkers that can reliably differentiate between these two dipper groups is of significant clinical importance. Several studies have proposed various hematological and biochemical markers as potential tools for this classification. Among these, the triglyceride-to-glucose ratio (TGR) has shown promise, demonstrating a significant ability to distinguish between dipper and non-dipper patients with T2DM and hypertension. Other markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the mean platelet volume-to-lymphocyte ratio (MPV/L), have also been explored for their predictive value in this context.

The evidence supporting the use of these biomarkers is growing. For example, the NLR has been linked to increased cardiovascular risk and has been proposed as a marker of systemic inflammation in T2DM patients [11].

Similarly, the PLR has been associated with microvascular complications in diabetes, making it a potential marker for distinguishing dipper from non-dipper patients [12]. Furthermore, the triglyceride-to-glucose ratio has been shown to predict cardiovascular events and mortality in patients with T2DM [13].

These findings are supported by studies that have highlighted the significance of other markers, such as the lymphocyte-to-monocyte ratio (LMR) [14], systemic immune-inflammation index (SII) [15].

Moreover, the red cell distribution width-coefficient of variation (RDW-CV) and the platelet distribution width-standard deviation (PDW-SD) have also been investigated for their roles in predicting cardiovascular risk in T2DM patients [16].

Additionally, the triglyceride-to-HbA1c ratio has been proposed as a marker for insulin resistance and cardiovascular risk [17].

The systemic inflammation response index (SIRI) [18] and the prognostic index value (PIV) [19] are among other indices that have been evaluated for their predictive value in this patient population.

Additionally, the monocyte-to-HDL ratio (MHR) has been associated with increased cardiovascular risk in non-dipper patients [20].

The FIB-4 score, traditionally used for liver fibrosis assessment, has also been linked to cardiovascular events in diabetic patients [21].

Other studies have focused on the predictive value of aspartate aminotransferase-to-alanine aminotransferase ratio (ASAT/ALAT) and aspartate aminotransferase-to-platelet ratio (ASAT/Platelets) in identifying cardiovascular risk [22].

Finally, the total cholesterol-to-HDL ratio (TC/HDL) has been extensively studied for its association with atherosclerotic cardiovascular disease in diabetic patients [23].

The current literature is lacking in studies assessing biomarkers to identify dippers from non-dippers hypertensive patients.

Therefore, the present study aimed to identify simple biomarkers that can be used for the classification of dipper and non-dipper individuals with type 2 diabetes and hypertension.

Methods

Ethics statement

The Ethics Committee of the Emergency County Hospital Baia Mare, Romania, gave its approval to this study (Decision Nr 3034/ 21.11.2019). All of the recruited patients signed a written informed permission form in order to participate and publish the data. Prior to analysis, patient records and data were de-identified and anonymized.

Study design and setting

Our research was a prospective cohort study that enrolled between February 2020 and May 2021 consecutive hypertensive patients with type 2 DM and ambulatory follow-up at the Diabetes, Metabolic, and Nutrition and Cardiology Department of Emergency County Hospital Baia Mare, Romania.

Population

Patients with type 2 diabetes mellitus who were hypertensive and had a complete blood count (CBC) were included. Individuals with acute heart failure, acute coronary disease, secondary hypertension, endocrine or oncologic disorders, and acute heart failure were not included.

Variables and measurement

The European Society of Cardiology's Hypertension Guidelines (2018) were used to diagnose hypertension status, and the European Society of Cardiology's Diabetes Guidelines (2019) were used to diagnosis diabetes [4].

According to the 2018 ESC Hypertension recommendations, blood pressure (BP) was measured using a validated BTL-08 ABPM II machine; BP measurements were taken prior to installing the ABPM [2].

A valid ABPM measuring session necessitates at least 70% of acceptable blood pressure measurements.

Details on the body mass index (BMI), height, weight, and belly circumference were recorded along with general data. Every patient's medical history was documented, with particular attention paid to hypertension, other cardiovascular disorders, dyslipidemia, the type of diabetes mellitus (DM), and its complications, such as peripheral chronic arterial disease (PAD), retinopathy, polyneuropathy, and nephropathy. Every patient had electrocardiography (ECG) to reveal any potential rhythm or ischemia abnormalities, as well as left ventricular hypertrophy (LVH).

The following current sanguine test results were noted: total cholesterol, LDL and HDL cholesterol, triglycerides, glucose, glycated hemoglobin (HbA1C), urea, creatinine, and uric acid. Urinary albumin/creatinine ratio (ACR) and albuminuria were assessed in a spot sample of urine taken in the morning. ACR for microalbuminuria was found to range from 30 to 299 mg/g.

We collected the following biomarkers: platelet, neutrophil, lymphocyte and monocyte count, low-density lipoprotein (LDL), high-density lipoprotein (HDL), HbA1c, and C-reactive protein (CRP). We calculated NLR using the absolute neutrophil (N) and lymphocyte (L) values by the following formula: NLR = N/L. We calculated PLR using the absolute platelets (P) and lymphocyte (L) values, by the following formula: PLR = P/L. We calculated MLR using the absolute monocyte (M) and lymphocyte (L) values using the following formula: MLR = M/L [10-12].

ABPM

A validated BTL-08 ABPM II machine (BTL Industries, UK) was employed in this investigation. The average heart rate (HR) during a 24-hour period, morning, day, and night, as well as the average systolic and diastolic blood pressure readings with the variations determined by circadian cycles, were noted and examined.

We measured and examined the mean arterial pressure (MAP) and pulse pressure (PP) for every patient throughout the course of 24 hours, day and night. Throughout the course of the 24-hour wear period of the BTL-08 monitor, blood pressure readings were taken every 30 minutes between 06:00 and 22:00 and every hour between 22:00 and 06:00.

Dippers were identified persons whose 24-hour mean ambulatory blood pressure dropped by more than 10%. Those with a 0–9% reduction in blood pressure are considered non-dippers. Individuals classified as extreme dippers have a blood pressure decrease of more than 20%,

whereas reverse dippers have a decline of less than 0%. The relative nighttime fall in blood pressure, or the percentage decrease of the average nocturnal blood pressure value over the average diurnal blood pressure value, was used to calculate the dipping index [2].

A 24-hour average of less than 130/80 mmHg is typical for ambulatory blood pressure during the day, which is <135/~85 mmHg (BP threshold: 135/85 mmHg) and <120/~70 mmHg at night (BP threshold: 120/70 mmHg). The diagnostic criterion for hypertension is ≥130/80 mmHg over 24 hours, ≥135/85 mmHg for the daytime average, and ≥120/70 for the nighttime average (all comparable to office BP ≥140/90 mmHg). ABPM measurements are, on average, lower than office BP values [24].

Statistical analysis

Qualitative data were presented as frequencies and percentages. Quantitative data were reported as medians and interquartile ranges (IQR) due to their non-normal distribution. The chi-squared test was used to compare the qualitative variables between the dipper and non-dipper groups. However, when the expected frequency in any cell of a contingency table was less than five, Fisher's exact test was employed. For the comparison of quantitative variables, the Mann-Whitney U test was applied, given the non-normal distribution of the data. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the biomarkers' discriminative ability to distinguish between dipper and non-dipper participants. The area under the ROC curve (AUC) was calculated for each biomarker. To identify the optimal cutoff points for the biomarkers, the Youden index was utilized, which maximizes the sum of sensitivity and specificity. For each cut-off point, the sensitivity and specificity were computed. In all statistical analyses, a two-tailed p-value of less than 0.05 was considered to indicate statistical significance. The statistical analysis was conducted using R environment for statistical computing and graphics (R Foundation for Statistical Computing, Vienna, Austria), version 4.3.2.

Results

The study consisted of 54 (39.1%) dipper participants and 84 (60.9%) non-dipper participants. The median age was 64 years (IQR of 58-74), ranging from 24 to 85 years. The participants' characteristics are presented in table I. There were no statistically significant differences between the dipper and non-dipper participants regarding age, sex, comorbidities, diabetes complications, and serum lipid levels.

The comparison between dipper and non-dipper in patients with type 2 diabetes and hypertension concerning different biomarkers found only two that were statistically significant: triglycerides to HbA1c ratio and triglycerides to glucose ratio (Table II). For both biomarkers, the dippers had higher values than non-dippers.

Next, we proceeded to assess the classifying ability of the biomarkers to differentiate dippers from nondippers using the area under the receiver operating characteristic curve (AUC) (Table III). The best AUCs were found for triglycerides to glucose ratio of 0.774 (95% CI 0.601 - 0.92), statistically significant, followed at a distance by Lymphocytes, PLR, PDW-SD, MPV/Lymphocytes (Figure 1), and others, none of them being statistically significant.

Table I. Patients characteristics.

Characteristics	Dipper (n=54)	Non-dipper (n=84)	P-value
Age (years), median (IQR)	62 (56.25 - 71)	64 (59 - 69.5)	0.563
Sex (F), no. (%)	30 (55.56)	41 (48.81)	0.439
BMI (kg/m^2), median (IQR)	33.03 (29.38 - 37.92)	33.28 (27.77 - 38.99)	0.938
Stroke, no. (%)	8 (14.81)	9 (10.71)	0.474
CIHD, no. (%)	24 (44.44)	43 (51.19)	0.439
Type 1 diabetes, no. (%)	1 (1.85)	4 (4.76)	0.648
Type 2 diabetes, no. (%)	53 (98.15)	80 (95.24)	0.648
Atrial fibrillation, no. (%)	3 (5.56)	8 (9.52)	0.528
Heart failure, no.(%)	13 (24.07)	22 (26.19)	0.78
Myocardial infarction, no. (%)	5 (9.26)	16 (19.05)	0.118
Diabetic nephropathy, no. (%)	26 (48.15)	38 (45.24)	0.738
Diabetic polyneuropathy, no. (%)	48 (88.89)	67 (79.76)	0.16
Diabetic retinopathy, no. (%)	14 (25.93)	20 (23.81)	0.778
Total cholesterol (mg/dL), median (IQR)	197 (159 - 231)	192.5 (154 - 218.25)	0.184
Triglycerides (mg/dL), median (IQR)	182 (159.5 - 263.75)	166 (116.55 - 272)	0.113

BMI, body mass index; IQR, interquartile range; CIHD: chronic ischemic heart disease.

Table II. Comparison of biomarkers between dipper and non-dipper with hypertension and diabetes.

Group	Dipper (n=54)	Non-dipper (n=84)	P
Leukocytes (10^3/uL), median (IQR)	7.19 (6.08 - 8.71)	7.83 (6.26 - 9.91)	0.231
Neutrophils (10^3/uL), median (IQR)	4.16 (3.5 - 5.34)	4.46 (3.3 - 6.2)	0.348
Lymphocytes (10^3/uL), median (IQR)	2.15 (1.88 - 2.78)	2.24 (1.67 - 2.87)	0.965
Monocytes (10^3/uL), median (IQR)	0.48 (0.38 - 0.58)	0.51 (0.39 - 0.6)	0.182
Eosinophils (10^3/uL), median (IQR)	0.2 (0.13 - 0.26)	0.18 (0.13 - 0.32)	0.93
Basophils (10^3/uL), median (IQR)	0.03 (0.02 - 0.05)	0.03 (0.03 - 0.05)	0.648
Platelets (10^3/uL), median (IQR)	250.5 (199.75 - 289.5)	244.5 (199.75 - 291.75)	0.865
NLR, median (IQR)	1.89 (1.55 - 2.39)	2.26 (1.41 - 2.9)	0.152
dNLR, median (IQR)	1.43 (1.19 - 1.73)	1.68 (1.08 - 2.12)	0.213
PLR, median (IQR)	107.31 (80.97 - 152.8)	110.33 (81.71 - 150.26)	0.901
NPR, median (IQR)	0.02 (0.01 - 0.02)	0.02 (0.02 - 0.02)	0.276
LMR, median (IQR)	4.85 (4.07 - 5.75)	4.33 (3.39 - 5.34)	0.057
SII, median (IQR)	478.49 (344.45 - 641.49)	516.94 (368.02 - 713.13)	0.431
SIRI, median (IQR)	0.88 (0.65 - 1.26)	1.04 (0.7 - 1.57)	0.113
PIV, median (IQR)	223.98 (144.8 - 301.3)	244.6 (156.95 - 467.5)	0.284
Monocytes/HDL, median (IQR)	0.01 (0.01 - 0.01)	0.01 (0.01 - 0.02)	0.203
MPV/Lymphocytes, median (IQR)	4.78 (3.99 - 5.6)	4.62 (3.67 - 6.11)	0.846
PCT, median (IQR)	0.26 (0.22 - 0.32)	0.25 (0.22 - 0.3)	0.588
MPV, median (IQR)	10.45 (9.53 - 11.6)	10.35 (9.7 - 11.33)	0.748
PDW-SD, median (IQR)	12.9 (11.1 - 15.67)	12.8 (11.7 - 15.3)	0.692
RDW-CV, median (IQR)	13.45 (13 - 14.1)	13.3 (12.8 - 14.22)	0.403
ASAT/ALAT, median (IQR)	0.95 (0.79 - 1.17)	0.93 (0.8 - 1.19)	0.733
ASAT/Platelets, median (IQR)	0.08 (0.06 - 0.13)	0.07 (0.06 - 0.11)	0.534
FIB-4, median (IQR)	1.08 (0.85 - 1.54)	1.03 (0.8 - 1.9)	0.806
TC/HDL, median (IQR)	4.17 (3.4 - 5.1)	4.06 (3.46 - 5.52)	0.836
TG/HDL, median (IQR)	3.68 (2.82 - 5.9)	3.9 (2.29 - 6.41)	0.319
Triglycerides/HbA1c, median (IQR)	19.26 (15.52 - 25.38)	15.92 (11.71 - 23.62)	0.043
Triglycerides, median (IQR)	0.99 (0.65 - 1.22)	0.66 (0.43 - 1.11)	0.002

IQR, interquartile range; NLR, Neutrophil-to-Lymphocyte Ratio; dNLR, Derived Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; NPR, Neutrophil-to-Platelet Ratio; LMR, Lymphocyte-to-Monocyte Ratio; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammation Response Index; PIV, Prognostic Index Value; Monocytes/HDL, Monocyte-to-High-Density Lipoprotein Ratio; MPV/Lymphocytes, Mean Platelet Volume-to-Lymphocyte Ratio; PCT, Plateletcrit ; MPV, Mean Platelet Volume; PDW-SD, Platelet Distribution Width-Standard Deviation; RDW-CV, Red Cell Distribution Width-Coefficient of Variation; ASAT/ALAT, Aspartate Aminotransferase-to-Alanine Aminotransferase Ratio; ASAT/Platelets, Aspartate Aminotransferase-to-Platelet Ratio; FIB-4, Fibrosis-4 Score; TC/HDL, Total Cholesterol-to-High-Density Lipoprotein Ratio; TG/HDL, Triglyceride-to-High-Density Lipoprotein Ratio; Triglyceride/HbA1c, Triglyceride-to-Hemoglobin A1c Ratio; The formula for FIB-4 is: Age ([yr] x AST [U/L]) / ((PLT [10(9)/L]) x (ALT [U/L])(1/2)).

Table III. Area under the receiver operating characteristic curve for classifying dipper and non-dipper patients with hypertension and diabetes using different biomarkers.

Variable	AUC (95% CI)	p	Se	Sp	Cut-off
Triglycerides to glucose ratio	0.774 (0.601 - 0.92)	<0.000	83.33	66.67	1.11706
Lymphocytes (10^3/uL)	0.668 (0.491 - 0.826)	0.049	100	10.42	1.51
PLR	0.646 (0.448 - 0.816)	0.120	83.33	56.25	109.406
PDW-SD	0.63 (0.388 - 0.837)	0.256	100	8.7	9.9
MPV/Lymphocytes	0.625 (0.441 - 0.806)	0.179	100	39.58	4.19355
Leukocytes (10^3/uL)	0.623 (0.378 - 0.852)	0.309	50	64.58	8.07
MPV	0.622 (0.368 - 0.842)	0.313	100	8.33	8.8
Monocytes/HDL	0.618 (0.362 - 0.829)	0.322	100	17.07	0.00644
LMR	0.601 (0.375 - 0.83)	0.384	100	6.25	2.56
TC/HDL	0.599 (0.323 - 0.83)	0.444	66.67	68.09	4.72414
FIB-4	0.583 (0.333 - 0.848)	0.528	75	45.45	0.98727
ASAT/Platelets	0.568 (0.235 - 0.879)	0.679	25	87.88	0.14552
Triglyceride/HbA1c	0.562 (0.229 - 0.833)	0.687	75	61.11	19.6875
Monocytes (10^3/uL)	0.561 (0.323 - 0.773)	0.595	100	12.5	0.3
TG/HDL	0.557 (0.281 - 0.826)	0.682	60	65.96	5.27941
Basophils (10^3/uL)	0.553 (0.293 - 0.803)	0.684	16.67	93.62	0.06
NLR	0.545 (0.25 - 0.819)	0.757	50	81.25	2.4557
Platelets (10^3/uL)	0.543 (0.273 - 0.802)	0.750	50	77.08	288
ASAT/ALAT	0.54 (0.255 - 0.81)	0.777	80	45	0.87097
SII	0.538 (0.24 - 0.809)	0.793	33.33	89.58	844.472
PIV	0.535 (0.208 - 0.854)	0.832	50	83.33	322.227
Eosinophils (10^3/uL)	0.532 (0.321 - 0.732)	0.760	100	21.28	0.1
dNLR	0.528 (0.233 - 0.802)	0.847	33.33	89.58	1.94
PCT	0.514 (0.299 - 0.712)	0.894	100	18.75	0.19
RDW-CV	0.512 (0.312 - 0.707)	0.905	100	18.75	12.7
SIRI	0.5 (0.191 - 0.813)	1	33.33	93.75	1.55081
Neutrophils (10^3/uL)	0.417 (0.139 - 0.722)	0.577	50	77.08	5.2
NPR	0.396 (0.174 - 0.625)	0.366	66.67	47.92	0.01647

AUC, area under the curve; CI, confidence interval; Se, sensitivity; Sp, Specificity; PLR, Platelet-to-Lymphocyte Ratio; PDW-SD, Platelet Distribution Width-Standard Deviation; MPV/Lymphocytes, Mean Platelet Volume-to-Lymphocyte Ratio; Leukocytes, White Blood Cell Count; MPV, Mean Platelet Volume; Monocytes/HDL, Monocyte-to-High-Density Lipoprotein Ratio; LMR, Lymphocyte-to-Monocyte Ratio; TC/HDL, Total Cholesterol-to-High-Density Lipoprotein Ratio; FIB-4, Fibrosis-4 Score; ASAT/Platelets, Aspartate Aminotransferase-to-Platelet Ratio; Triglyceride/HbA1c, Triglyceride-to-Hemoglobin A1c Ratio; Monocytes, Monocyte Count; TG/HDL, Triglyceride-to-High-Density Lipoprotein Ratio; Basophils, Basophil Count; NLR, Neutrophil-to-Lymphocyte Ratio; Platelets, Platelet Count; ASAT/ALAT, Aspartate Aminotransferase-to-Alanine Aminotransferase Ratio; SII, Systemic Immune-Inflammation Index; PIV, Prognostic Index Value; Eosinophils, Eosinophil Count; dNLR, Derived Neutrophil-to-Lymphocyte Ratio; PCT, Plachetocrit; RDW-CV, Red Cell Distribution Width-Coefficient of Variation; SIRI, Systemic Inflammation Response Index; Neutrophils, Neutrophil Count; NPR, Neutrophil-to-Platelet Ratio.

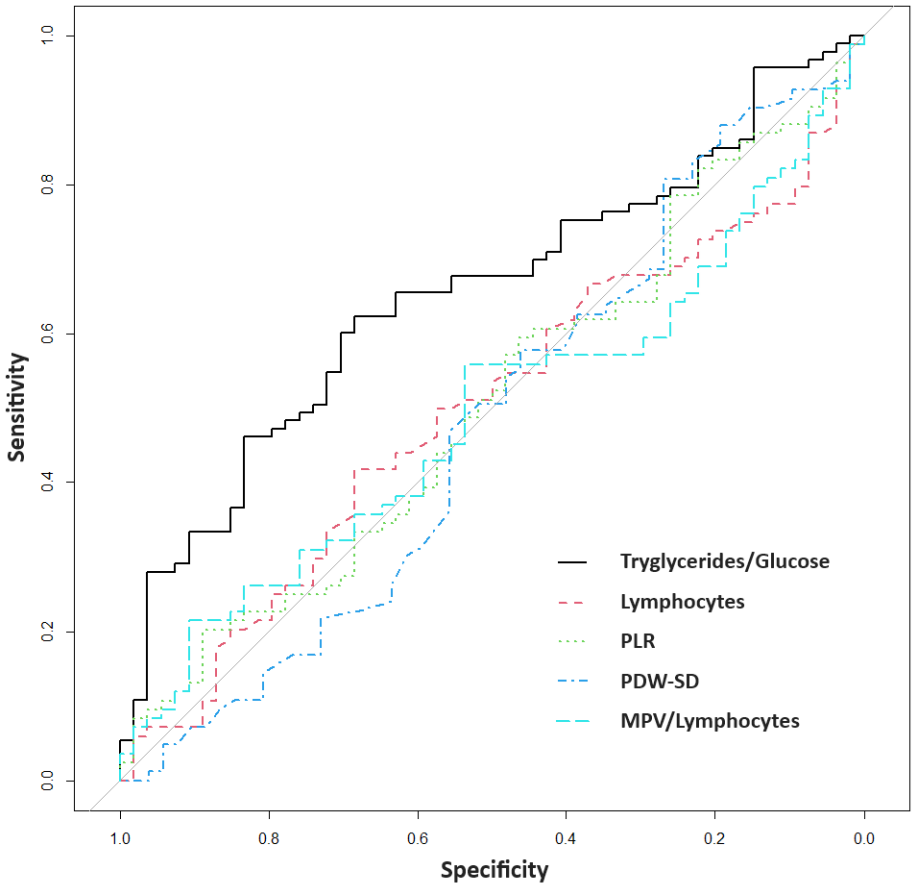

Figure 1. Receiver operating characteristic curve for classifying dipper and non-dipper patients with type 2 diabetes and hypertension using different biomarkers.
PLR, Platelet-to-Lymphocyte Ratio; Platelet Distribution Width-Standard Deviation; MPV, Mean Platelet Volume.

Discussion

The present study successfully managed to identify and evaluate potential biomarkers for the classification of dipper and non-dipper individuals among patients with type 2 diabetes and hypertension. Our findings revealed that the triglycerides to HbA1c ratio and triglycerides to glucose ratio were significantly different between dipper and non-dipper groups, with higher values observed in the dipper population. Notably, the triglycerides to glucose ratio demonstrated the strongest classifying ability, as evidenced by an area under the receiver operating characteristic curve (AUC) of 0.774, suggesting its potential utility as a reliable biomarker for distinguishing between these two groups. Other biomarkers assessed, including lymphocytes, PLR, PDW-SD, and MPV/lymphocytes, did not achieve statistical significance.

The characteristics of patients who exhibit a "dipper" or "non-dipper" blood pressure (BP) pattern can differ significantly. These characteristics are often associated with varying levels of cardiovascular risk and the presence of comorbidities. Dippers are often younger than non-dippers. Non-dippers are often older, as the ability to maintain a normal BP dip during sleep tends to decline with age. There may be a slight predominance of the dipper pattern in women, though this can vary based on the population studied. Non-dipping patterns may be more common in men, though this is influenced by other risk factors and comorbidities [24].

Patients with diabetes and hypertension are at an increased risk of macrovascular and microvascular complications. Targeting multiple risk factors is essential in preventing and slowing the progression of these complications. Optimization of glycemic, lipid, and BP control has been demonstrated to improve patient outcomes [25].

A majority of patients with diabetes were found to have an abnormal pattern of blood pressure that included non-dipping and reverse dipping patterns. Duration of

diabetes and severity of Hba1C had a direct correlation with abnormal pattern of blood pressure variability that included non-dippers and reverse dippers [26].

Dippers often have lower levels of LDL cholesterol and higher HDL cholesterol levels compared to non-dippers. Non-dippers often have higher levels of LDL cholesterol, triglycerides, and lower levels of HDL cholesterol.

The current study looked at the differences between dippers and non-dippers in a group of participants with type 2 diabetes and hypertension. Age, sex, comorbidities, diabetic complications, and blood cholesterol levels did not differ significantly among participants. (Table I)

An elevated circulating white blood cell (WBC) count, a well-known independent marker of systemic inflammation, has been associated with cardiovascular disease (CVD) and death. However, nearly all elements of the complete blood count (CBC), including WBCs, red blood cells (RBCs), and platelets, are also involved in the underlying pathogenesis of atherosclerosis. Platelet activity is an important contributor to atherothrombosis, which is the primary risk factor of most CVD. Platelet indices include platelet count, mean MPV, and PDW. Platelet count has also been associated with death and future CVD [10].

Red blood cell distribution width (RDW), mean platelet volume (MPV) and neutrophil to lymphocyte ratio (NLR) levels, which are indicators of platelet activation and inflammatory response are significantly higher in non-dippler hypertensive patients compared to dipper hyperensives [27]. The correlation between RDW and hypertension, especially the non-dipper pattern of hypertension, has been demonstrated in many studies [28].

Creatinine clearance and high-density lipoprotein (HDL) concentrations were significantly lower and NLR and HBA1c levels higher amongst the reverse dippers versus the normal and non-dippers. Conversely, the NLR, monocyte to lymphocyte ratio (MLR) and HBA1c levels were progressively higher among the non-dippers and reverse-dippers respectively. Major adverse cardiovascular events (MACE) were more common among the reverse-dippers [29].

NLR and PLR values were shown to have significant association with the nondipper pattern in a retrospectively study, which is a significant cardiovascular risk factor; this association was found to be particularly prominent in prehypertensive and hypertensive patients. These easily available and inexpensive parameters may, along with the conventional risk factors, guide us in the future for the detection of nondipper hypertension and the identification of the patients at high risk for the target organ damage [30].

The higher MPV and neutrophil count may be potential indicators of increased risk for the development of hypertension in children. In addition, MPV and platelet count may help to determine the presence of non-dipper status in children with hypertension.

Higher platelet count, MPV and plateletcrit (PCT) may help determine the presence of non-dipper status in children with hypertension [31].

Leukocytes and monocytes counts were higher in patients with non-dipper hypertension. These results suggest that higher NLR, an emerging marker of inflammation, has a positive correlation with blood pressure and is elevated in non-dippers compared with dippers [32]. The patients with non-dipper hypertension had significantly higher NLR and PLR compared to dipper hypertension [33]. Current evidence shows that a high PLR reflects inflammation,atherosclerosis and platelet activation. The PLR can be easily calculated and is widely available. More research is needed to determine how the PLR may be used in clinical practice [34].

The non-dipper hypertension (HT) pattern is associated with more end-organ damage and cardiovascular events than is dipper HT. Systemic immune-inflammation index (SII) was calculated according to neutrophil, platelet, and lymphocyte counts. SII was calculated using the formula SII = (neutrophil count x platelet count)/lymphocyte count. The SII level was higher in the non-dipper HT patient group than in the dipper HT group. Furthermore, SII was an independent predictor of non-dipper HT. The high SII value in hypertension patients can be used as an early warning parameter to identify non-dipper HT patients [35]. SII levels are higher in patients with reverse-dipper patterns than the dipper and non-dipper group in newly diagnosed hypertensive patients. Because the SII is a simple and easy-to-calculate parameter, it may be utilized as an additional diagnostic test to determine reverse-dipper BP patterns in newly diagnosed hypertensive patients [36].

In our study we did not find significant differences of SII level between the dipper and non-dipper groups. (Table II).

To estimate hepatic fibrosis using non-imaging modalities, noninvasive biomarker models such as fibrosis-4 (FIB-4) is well-validated and widely used for screening high-risk patients with non-alcoholic fatty liver disease (NAFLD). The formula for FIB-4 is: Age ([yr] x ASAT [U/L]) / ((PLT [10(9)/L]) x (ALAT [U/L])(1/2))', PLT-platelets [21].

In our study the comparison between dipper and non-dipper in patients with type 2 diabetes and hypertension concerning different FIB-4 does not found a statistically significant difference (Table II and III).

In our study dippers had significantly greater levels of two biomarkers: the triglyceride to HbA1c ratio (Table II) and the triglyceride to glucose ratio (Table III). The triglyceride to glucose ratio showed the largest area under the receiver operating characteristic curve (AUC) of 0.774 (95% CI 0.601 - 0.92), showing that it could successfully distinguish between dippers and non-dippers, as opposed to other biomarkers that were not statistically significant.

Limitations

It is necessary to acknowledge the limitations of this

research. First, complete blood count data were gathered retrospectively, but many other parameters were obtained prospectively through the use of a cross-sectional approach. Biases may arise from this dual approach, particularly with regard to the accuracy of historical data. It's possible that the retrospective component left some blood count records with insufficient information. However, when blood counts are measured accurately, the correctness is unquestionable. Moreover, the cross-sectional nature of the study limits the ability to show causal relationships between dipping status and biomarkers. Furthermore, it is unable to control confounding factors including lifestyle choices, medication adherence, and clinical treatment impacts, which may have an impact on biomarker levels and dipping status.

Strengths

This study has a number of noteworthy advantages. A prospective cross-sectional design is used to evaluate a number of criteria, making it possible to examine participant characteristics and biomarkers with more accuracy. The results are more easily generalized to similar cohorts when a somewhat high sample size is used. Moreover, a comprehensive analysis of several biomarkers, such as a novel evaluation of the triglyceride to glucose ratio, provides valuable information on potential distinguishing factors between individuals with and without diabetes.

The results of the study have significant therapeutic implications, particularly for the management of diabetes and hypertension in patients. The triglyceride to glucose ratio has been identified as a potential biomarker. Its high area under the receiver operating characteristic curve (0.774) suggests that it could be a valuable tool for differentiating between dippers and non-dippers. Given that non-dippers are known to have a higher risk of cardiovascular events, this distinction is quite important. By incorporating this biomarker into standard clinical tests, medical professionals can more effectively assess risk and adjust treatment plans accordingly.

Expanding the sample size and conducting long term studies that confirm the study's conclusions and demonstrate causal relationships between biomarkers and dipping status should be the main goals of future research.

Future perspectives

In future studies, several strategies could address the limitations of biomarker research in non-dipper patients with type 2 diabetes. Firstly, larger and more diverse patient populations are essential to improve the generalizability of findings. Multicenter studies with participants from various demographic and ethnic backgrounds would provide a more comprehensive understanding of biomarker variations in different populations. Additionally, longitudinal studies that monitor patients over extended periods could provide insights into the dynamic changes in biomarker levels and their association with disease progression and therapeutic response. By addressing these limitations, future research could pave the way for improved clinical management of non-dipper patients with type 2 diabetes.

Conclusion

In conclusion, this study offers valuable insights into the classification of dipper and non-dipper individuals with type 2 diabetes and hypertension using several biomarkers. Notably, the triglyceride-to-glucose ratio appeared as a significant marker with considerable discriminative capacity, indicating its potential therapeutic value in risk stratification and personalized treatment strategies.

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