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THE ROLE OF THE NEUTROPHIL-TO-LYMPHOCYTE RATIO IN THE DEVELOPMENT OF HEART FAILURE IN PATIENTS WITH CONCOMITANT HYPERTENSION, TYPE 2 DIABETES, AND OBESITY

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УЛОГА ОДНОСА НЕУТРОФИЛА И ЛИМФОЦИТА У РАЗВОЈУ СРЧАНЕ ИНСУФИЦИЈЕНЦИЈЕ КОД ПАЦИЈЕНАТА СА ПРИДРУЖЕНОМ ХИПЕРТЕНЗИЈОМ, ДИЈАБЕТЕСОМ ТИПА 2 И ГОЈАЗНОШЋУ

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ABSTRACTS

Objective. Arterial hypertension, type 2 diabetes mellitus (T2DM), and obesity increase cardiovascular risk, including heart failure (HF). The neutrophil-to-lymphocyte ratio (NLR), a systemic inflammation marker, has been linked to adverse cardiovascular outcomes, but its role in HF development remains unclear. This study evaluated NLR as a predictor of HF in these patients.

Methods. A total of 293 patients with essential hypertension, T2DM, and obesity were enrolled in a prospective study. They were categorized into two groups: HF group (n=85) and non-HF group (n=208). NLR was calculated from complete blood count results. HF was diagnosed based on the 2023 ESC guidelines and confirmed via biomarkers (NT-proBNP) or echocardiography. Patients were followed for 24 months.

Results. Patients who developed HF had significantly higher NLR (3.39 ± 1.23 vs. 2.66 ± 1.14, p<0.001), longer durations of type 2 diabetes mellitus (12.75 ± 5.86 vs. 10.25 ± 4.39 years, p<0.001) and hypertension (18.87 ± 8.54 vs. 16.05 ± 7.14 years, p=0.004), and a more frequent non-dipper blood pressure profile (36.5% vs. 20.7%, p=0.005), compared to patients who did not develop HF. In multivariate regression, NLR (OR 1.383; 95% CI 1.073–2.222; p=0.037), non-dipper BP profile (OR 2.193; 95% CI 1.181–5.502; p=0.021), hypertension duration (OR 1.052; 95% CI 1.005–3.190; p=0.032), and diabetes duration (OR 1.040; 95% CI 1.007–1.215; p=0.044) remained independent HF predictors.

Conclusion. NLR is independently associated with HF onset in patients with hypertension, T2DM, and obesity. It may serve as a simple, cost-effective biomarker for HF risk stratification, facilitating early intervention and improved outcomes.

Key words: *heart failure; hypertension; diabetes mellitus, type 2; obesity.*

САЖЕТАК

Циљ. Артеријска хипертензија, дијабетес типа 2 (T2DM) и гојазност повећавају кардиоваскуларни ризик, укључујући и срчану инсуфицијенцију (HF). Однос неутрофила и лимфоцита (NLR), маркер системске инфламације, повезан је с неповољним кардиоваскуларним исходом, али његова улога у развоју HF остаје нејасна. Ова студија је процењивала NLR као предиктор HF код ових пацијената.

Методе. У проспективну студију укључена су укупно 293 пацијента са есенцијалном хипертензијом, T2DM и гојазношћу. Подељени су у две групе: група са HF (n = 85) и група без HF (n = 208). NLR је израчунат из резултата комплетне крвне слике. Дијагноза HF постављена је на основу ESC смерница из 2023. и потврђена биомаркерима (NT-proBNP) или ехокардиографијом. Пацијенти су праћени 24 месеца.

Резултати. Пацијенти који су развили HF имали су значајно виши NLR (3,39 ± 1,23 vs 2,66 ± 1,14, p < 0,001), дуже трајање дијабетеса типа 2 (12,75 ± 5,86 vs 10,25 ± 4,39 године, p < 0,001) и хипертензије (18,87 ± 8,54 vs 16,05 ± 7,14 година, p = 0,004), и чешћи non-dipper профил крвног притиска (36,5% vs 20,7%, p = 0,005) у поређењу с пацијентима који нису развили HF. У мултиваријантној регресији, NLR (OR 1,383; 95% CI 1,073–2,222; p = 0,037), non-dipper BP профил (OR 2,193; 95% CI 1,181–5,502; p = 0,021), трајање хипертензије (OR 1,052; 95% CI 1,005–3,190; p = 0,032) и трајање дијабетеса (OR 1,040; 95% CI 1,007–1,215; p = 0,044) остали су независни предиктори HF.

Закључак. NLR је независно повезан са настанком HF код пацијената с хипертензијом, T2DM и гојазношћу. Може послужити као једноставан, исплатив биомаркер за стратификацију ризика од HF, олакшавајући рану интервенцију и побољшање исхода.

Кључне речи: *срчана инсуфицијенција; хипертензија; дијабетес типа 2; гојазност.*

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INTRODUCTION

Heart failure (HF) remains one of the leading causes of morbidity and mortality worldwide, particularly among patients with multiple cardiometabolic risk factors such as hypertension (HTN), type 2 diabetes mellitus (T2DM), and obesity (1).

These conditions contribute to the development of chronic inflammation, endothelial dysfunction, and myocardial remodeling, thereby increasing the risk of HF even in individuals with a preserved left ventricular ejection fraction (2). In recent years, increasing attention has been directed towards systemic inflammation markers that may play a crucial role in the pathogenesis of HF.

One such biomarker is the neutrophil-to-lymphocyte ratio (NLR), which reflects the balance between pro-inflammatory (neutrophils) and immunoregulatory (lymphocytes) processes in the body. Elevated NLR levels have been associated with adverse cardiometabolic outcomes, including left ventricular hypertrophy, atherosclerosis (3, 4). Notably, recent studies have demonstrated that in patients with obesity, hypertension, and T2DM, high NLR values correlate with an increased risk of cardiovascular complications, making this parameter a promising candidate as a prognostic marker for HF (5).

Despite the growing body of research on NLR, its clinical significance in the context of HF development in patients with concurrent HTN, T2DM, and obesity remains insufficiently explored. Most studies either focus on individual components of the metabolic syndrome or on populations with established HF, while the role of NLR in the early identification of patients at high risk for HF requires further investigation (6). Specifically, it remains unclear whether increased NLR serves as an independent predictor of HF development and what threshold values could be utilized for clinical risk stratification.

An additional factor that underscores the relevance of this topic is the alteration of circadian blood pressure (BP) profiles. It is well established that patients with a "non-dipper" BP profile — characterized by the absence of a normal nocturnal BP decline — have a higher risk of cardiovascular complications, including HF. Studies suggest that such patients also exhibit elevated levels of inflammatory biomarkers, including NLR, indicating a possible link between chronic inflammation and disruptions in circadian BP rhythms (7).

Thus, the present study aims to assess the role of NLR as a predictor of HF development in patients with concomitant HTN, T2DM, and obesity. We hypothesize that elevated NLR levels will be associated with an increased risk of HF over a 24-month follow-up period and that this marker could be utilized for the early identification of patients requiring intensive cardiac monitoring and timely intervention.

PATIENTS AND METHODS

This study was designed as a prospective cohort study and conducted in accordance with the international STROBE reporting guidelines to ensure high methodological quality and reproducibility of results. Patients with HTN, T2DM, and obesity were recruited from the cardiology department of a multidisciplinary medical center, with a follow-up period of 24 months. Throughout the study, patients attended regular clinical visits and underwent additional assessments at baseline, 12 months, and 24 months, as well as in cases where the symptoms of heart failure emerged. In addition to these visits, telephone follow-ups were conducted every three months to assess participants' well-being and promptly detect complications. All procedures were carried out in compliance with the principles of the 2013 Declaration of Helsinki and were approved by the institutional review board. Each participant provided written informed consent for voluntary participation.

Inclusion criteria required patients to be over 40 years old, have a confirmed diagnosis of hypertension for at least five years, a documented history of T2DM for a minimum of three years, and obesity classified as grade I–III. Participants were excluded if they had acute inflammatory conditions or active chronic infections, malignancies (including those in remission for less than five years), severe renal insufficiency (defined per KDIGO 2024 as eGFR < 30 mL/min/1.73 m² (CKD stage 4–5) or the need for chronic renal replacement therapy), severe hepatic insufficiency (defined per EASL 2023 as Child–Pugh class C or clinical decompensation including ascites, variceal bleeding, hepatic encephalopathy, or total bilirubin > 3 mg/dL), ongoing immunomodulatory therapy, or a history of myocardial infarction or stroke. Additionally, patients with heart failure at baseline, defined according to ESC 2023 and ACC/AHA 2022 criteria, were excluded from enrollment in order to evaluate the development of incident HF during follow-up. The study cohort comprised 293 individuals who met the diagnostic criteria established by leading professional associations: the European Society of Cardiology/ European Society of Hypertension (ESC/ESH) 2023 guidelines for arterial hypertension, the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) 2022 guidelines for type 2 diabetes mellitus, and the World Health Organization (WHO) classification for obesity (body mass index (BMI) ≥ 30 kg/m²).

The diagnosis of HF was established based on current guidelines from the ESC (2023) and the American College of Cardiology/American Heart Association (ACC/AHA) (2022). Clinical manifestations such as dyspnea, fatigue, and peripheral edema were considered, alongside objective assessments of cardiac structure and function.

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HF classification included reduced ejection fraction HF (HFrEF; left ventricular ejection fraction (LVEF) <0 40%), mildly reduced ejection fraction HF (HFmrEF; LVEF 40–50%), and preserved ejection fraction HF (HFpEF; LVEF >50% with diastolic dysfunction). Diastolic function was assessed according to the 2025 ASE/EACVI recommendations, with diastolic dysfunction defined as ≥2 abnormal parameters among: average E/e' ratio > 14, septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s, tricuspid regurgitation peak velocity > 2.8 m/s, left atrial volume index > 34 mL/m², or left atrial reservoir strain < 23%. Additional diagnostic criteria included elevated NT-proBNP (>125 pg/mL in the absence of atrial fibrillation), electrocardiographic findings, and chest radiography. The final HF diagnosis was confirmed independently by two cardiologists. The participants were divided into two groups based on whether they developed HF during the two-year follow-up period. The first group included 85 individuals who developed HF (New York Heart Association (NYHA) class II–IV), with diagnosis confirmed through clinical and instrumental methods. The second group consisted of 208 individuals who did not develop HF.

A comprehensive set of laboratory and instrumental investigations was employed in the study. NLR was calculated as the ratio of absolute neutrophil count to absolute lymphocyte count. Other inflammatory markers, including C-reactive protein (CRP), fibrinogen, and erythrocyte sedimentation rate (ESR), were measured, along with standard metabolic profile parameters such as glycated hemoglobin (HbA1c), total cholesterol and its fractions, triglycerides, and renal function markers. Echocardiography was performed using a modern system with 2D/3D imaging capabilities, measuring LVEF using Simpson's method, left ventricular mass using the Devereux formula, and diastolic function parameters (E/A and E/e' ratios).

According to standard definitions based on 24-hour ambulatory blood pressure monitoring (ABPM), patients with a 10–20% nocturnal systolic BP drop were classified as "dippers". Those with <10% reduction ("non-dippers"), >20% reduction ("overdippers"), or a rise in nocturnal BP ("reverse dippers") were collectively categorized as having an abnormal BP dipping pattern ("non-dippers") for the purposes of this analysis.

All collected data were subjected to statistical analysis using MedCalc 23.1.7 and SPSS 27.0 software. The Shapiro–Wilk test was applied to assess the normality of data distribution. Depending on the results, continuous variables were expressed as means with standard deviations or medians with interquartile ranges. Categorical variables were analyzed using the chi-square (χ^2) test. Comparisons between groups were performed using either the independent t-test (for normally distributed data) or the Mann–Whitney U test (for non-normally distributed data). The association of risk factors with HF was assessed using univariate and multivariate logistic regression, calculating odds ratios (ORs) with 95% confidence intervals (CIs). The diagnostic and prognostic value of NLR was evaluated through receiver operating characteristic (ROC) curve analysis. To reduce confounding, the final multivariate model was adjusted for clinically relevant variables, including age, sex, BMI, glycemic status, blood pressure profile, and NLR. A backward elimination approach was applied, incorporating all variables with a p-value < 0.1 from the univariate analysis.

RESULTS

By the end of the observation period, 85 patients (29.0%) had developed HF, while the remaining 208 served as the non HF comparison group. Among the HF group, 77 (90.6%) were classified as HFpEF and 8 (9.4%) as HFmrEF. No cases of HFrEF were observed, which is consistent with the study design excluding patients with baseline heart failure.

In the Table 1 we presented the baseline clinical and anthropometric measures for the observed groups of patients (Table 1).

We noted that most participants, regardless of their final HF status, exhibited a body mass index (BMI) in the Class I–II obesity range (30.0–39.9 kg/m²). Although individuals who ultimately developed HF had a slightly higher BMI on average (34.11 ± 4.85 vs. 32.89 ± 5.22 kg/m² in the non HF group), this difference did not achieve statistical significance (p=0.065). Similarly, the mean age trended older among HF patients (62.12 ± 11.48 vs. 59.83 ± 10.21 years) but again did not reach significance (p=0.094). Males comprised approximately half of each subgroup (52.9% vs. 51.4%, p=0.816). In both groups' population these demographic findings were statistically equal.

In contrast, two parameters were clearly distinguished in the HF cohort: their history of hypertension extended an average of 18.87 ± 8.54 years, significantly longer than in patients who did not develop HF (16.05 ± 7.14 years, p=0.004), and same statistical significance was observed for diabetes duration (12.75 ± 5.86 vs. 10.25 ± 4.39 years, p<0.001). This suggests that the cumulative burden of elevated blood pressure and prolonged hyperglycemia may be crucial to precipitating overt HF.

Although the mean systolic and diastolic pressures were statistically similar between HF and non HF groups—152.11 ± 14.03 vs. 149.22 ± 13.64 mmHg (p=0.104) and 92.32 ± 9.88 vs. 94.56 ± 9.14 mmHg (p=0.064), respectively — 24-hour blood pressure profile differed significantly. We found that a significantly larger

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Table 1. Baseline characteristics of the participants.

Characteristics	All patients (n = 293)	HF (n = 85)	Non-HF (n = 208)	p-value
Age, years (mean ± SD)	61 ±12	62 ± 11	60 ± 10	0.094
Males, n (%)*	152 (52%)	45 (53%)	107 (51%)	0.816
Body mass index, kg/m² (mean ± SD)	33.2 ± 5.5	34.1 ± 4.9	32.9 ± 5.2	0.065
Hypertension duration, years (mean ± SD)	17 ± 8	19 ± 9	16 ± 7	0.004
Diabetes duration, years (mean ± SD)	11 ± 5	13 ± 6	10 ± 4	<0.001
History of smoking, n (%)*	88 (30%)	28 (33%)	60 (29%)	0.488
Systolic BP, mmHg (mean ± SD)	150 ± 14	152 ± 14	149 ± 14	0.104
Diastolic BP, mmHg (mean ± SD)	94 ± 9	92 ± 10	95 ± 9	0.064
Non-dipper BP profile, n (%)*	74 (25%)	31 (37%)	43 (21%)	0.005
Serum glucose, mg/dL (mean ± SD)	140.06 ± 29.30	146.8 ± 31.2	137.3 ± 28.1	0.012
HbA1c, % (mean ± SD)	7.52 ± 1.55	7.78 ± 1.61	7.42 ± 1.52	0.072
Serum creatinine, mg/dL (mean ± SD)	0.90 ± 0.27	0.95 ± 0.25	0.88 ± 0.27	0.040
Total cholesterol, mg/dL (mean ± SD)	203.16 ± 35.17	207.55 ± 39.11	201.37 ± 34.22	0.180
Triglycerides, mg/dL (mean ± SD)	138.09 ± 25.9	142.36 ± 28.3	136.22 ± 24.7	0.065
HDL-C, mg/dL (mean ± SD)	48.76 ± 8.94	48.11 ± 8.54	49.02 ± 9.11	0.430
LDL-C, mg/dL (mean ± SD)	121.68 ± 31.14	128.05 ± 31.77	119.08 ± 30.57	0.025
Left ventricular ejection fraction, % (mean ± SD)	56.36 ± 4.82	55.71 ± 4.12	57.05 ± 5.03	0.030
NLR (neutrophil-to-lymphocyte ratio) (mean ± SD)	2.87 ± 1.21	3.39 ± 1.23	2.66 ± 1.14	<0.001

*categorical variables (used a two-proportion test / chi-square); HF – heart failure; BP – blood pressure; HbA1c – glycated hemoglobin; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; NLR – neutrophil-to-lymphocyte ratio.

Table 2. Univariate and multivariate logistic regression analysis of factors associated with heart failure.

Variable	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
NLR	1.450 (1.090–2.110)	0.018	1.383 (1.073–2.222)	0.037
Systolic BP (mmHg)	1.020 (0.989–1.045)	0.140	–	–
Diastolic BP (mmHg)	1.021 (0.995–1.067)	0.091	–	–
Non-dipper BP profile (yes/no)	2.561 (1.324–5.665)	0.004	2.193 (1.181–5.502)	0.021
Gender (M/F)	1.020 (0.661–1.829)	0.711	–	–
Age (years)	1.027 (0.975–1.049)	0.067	–	–
Body mass index (kg/m²)	1.068 (1.013–1.211)	0.059	–	–
History of smoking (yes/no)	1.211 (0.785–2.554)	0.301	–	–
Duration of hypertension	1.067 (1.012–3.310)	0.037	1.052 (1.005-3.190)	0.032
Duration of diabetes	1.052 (1.014–1.210)	0.049	1.040 (1.007–1.215)	0.044
Serum glucose (mg/dL)	1.021 (1.002–1.043)	0.032	–	–
HbA1c (%)	1.325 (1.042–1.821)	0.028	–	–
Serum creatinine (mg/dL)	3.112 (0.990–9.880)	0.052	–	–
LVEF (%)	0.945 (0.889–0.992)	0.044	–	–

variables with p<0.1 in univariate analysis were included in the multivariate model; NLR – neutrophil-to-lymphocyte ratio; BP – blood pressure; HbA1c – glycated hemoglobin; LVEF – left ventricular ejection fraction; OR – odds ratio; CI – confidence interval.

part of HF patients displayed a “non dipper” BP profile (36.5% vs. 20.7%, p=0.005).

Regarding glycemic control, fasting serum glucose was notably higher among those who progressed to HF (146.8 ± 31.2 vs. 137.3 ± 28.1 mg/dL, p=0.012). The difference in HbA1c approached but did not reach significance (7.78 ± 1.61% vs. 7.42 ± 1.52%, p=0.072), possibly reflecting partial glycemic control in both cohorts. Serum creatinine, on the other hand, emerged as significantly higher in the HF group (0.95 ± 0.25 vs. 0.88 ± 0.27 mg/dL, p=0.040), suggesting a subtle degree of renal function compromise or increased systemic congestion in those developing HF.

Lipid profiles revealed a higher mean LDL C level among HF patients (128.05 ± 31.77 vs. 119.08 ± 30.57 mg/dL, p=0.025), whereas total cholesterol, triglyceride, and HDL C measurements did not differ significantly (p=0.180, p=0.065, and p=0.430, respectively).

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Collectively, these data highlight the multifactorial background against which HF emerges: longer disease durations, slightly worse glycemic metrics, and particular lipid abnormalities.

Left ventricular ejection fraction (LVEF) was modestly but significantly lower in individuals who advanced to HF (55.71 ± 4.12% vs. 57.05 ± 5.03%, p=0.030). Although an absolute difference of approximately 1.3% may seem small, a trend toward decreased systolic performance is evident.

It is of particular importance to note that we observed a significantly elevated NLR in patients developing HF compared to their counterparts (3.39 ± 1.23 vs. 2.66 ± 1.14, p<0.001). Because NLR captures an imbalance favoring pro inflammatory neutrophils over protective or regulatory lymphocytes, this result strongly implicates systemic inflammation in the pathophysiology of HF.

To clarify the influence of NLR and other baseline features on HF incidence, we conducted a univariate logistic regression (Table 2).

Notably, an increased NLR emerged as a significant predictor (odds ratio (OR) 1.450, 95% confidence interval (CI) 1.090–2.110, p=0.018), consistent with the premise that inflamed states promote adverse cardiac remodeling. A non dipper BP profile was likewise influential (OR 2.561, 95% CI 1.324–5.665, p=0.004), reflecting the detrimental impact of persistently elevated BP through the night. Longer durations of both hypertension and diabetes were also linked to greater HF risk, as was lower LVEF (OR 0.945, 95% CI 0.889–0.992, p=0.044). Variables such as age, BMI, and serum glucose exhibited borderline or modest associations (p > 0.05) but did not meet the conventional threshold for strong significance in the univariate model.

We entered all factors meeting p<0.1 into a stepwise multivariate logistic regression to identify independent risk determinants. Our analysis confirmed that NLR (OR 1.383, 95% CI 1.073–2.222, p=0.037) maintained its predictive power. Meanwhile, a non dipper BP profile (OR 2.193, 95% CI 1.181–5.502, p=0.021), longer diabetes duration (OR 1.040, 95% CI 1.007–1.215, p=0.044), and prolonged hypertension (OR 1.052, 95% CI 1.005–3.190, p=0.032) also emerged as independent contributors to HF onset. Although LVEF did not appear in the final multivariate column, it remained significant in univariate analysis (p=0.044), indicating that even mild systolic compromise can predispose patients to future HF in this complex, high-risk cohort.

DISCUSSION

Our study demonstrates that an elevated NLR is a significant predictor of HF development in patients with HTN, T2DM, and obesity. Our data suggest that NLR may be a valuable surrogate marker for heightened cardiovascular risk, warranting closer scrutiny in the clinical setting. We found that patients who developed HF over the 24-month follow-up period had significantly higher NLR values compared to those who did not (3.19 ± 1.23 vs. 2.57 ± 1.31; p = 0.0002). Furthermore, the presence of a “non-dipper” blood pressure (BP) profile and the duration of HTN and T2DM were also independent predictors of HF development, as confirmed by multivariate logistic regression analysis.

These findings underscore the critical role of chronic inflammation and circadian BP dysregulation in HF pathogenesis. The results indicate the need for further investigation into NLR as a potential biomarker for HF risk stratification in patients with cardiometabolic comorbidities.

The General Role of NLR as an Inflammatory Marker. Numerous studies highlight that neutrophils act as mediators of acute inflammation, whereas lymphocytes regulate immune function. Therefore, an increased NLR, reflecting a relative rise in neutrophils and a decline in lymphocytes, signifies an imbalance in the inflammatory response. Bhat et al. demonstrated that NLR is a valuable addition to conventional cardiovascular risk markers, being associated with arterial stiffness, increased coronary calcium burden, and poor prognosis in various clinical settings (8). Similarly, Balta et al. emphasized that NLR is a cost-effective, easily calculable parameter that may serve as an extended risk stratification tool alongside other inflammatory indices (9).

A recent review by Gosav et al. reinforced the importance of NLR as a readily available and reliable marker in various cardiovascular pathologies, ranging from atherosclerosis to chronic HF, highlighting its prognostic value (5).

NLR in Hypertension. A landmark study by Liu et al. was among the first to establish that increased NLR correlates with a heightened risk of developing HTN and target organ damage (10). Our observation that elevated NLR is frequently associated with a “non-dipper” BP profile, a known HF risk factor, aligns with these findings. Similar conclusions were drawn by Yang et al., who also demonstrated that high NLR levels in hypertensive patients were linked to increased all-cause mortality and cardiovascular complications (11).

Additionally, Wang et al. highlighted that in patients with HTN combined with obesity and inflammation, elevated NLR further contributes to cardiovascular risk (7). In patients with hypertension, elevated systemic immune inflammatory index (SII) was found to be an independent predictor of increased carotid intima-medial thickness, suggesting its potential role in early assessment of atherosclerotic event risk. These findings may inform preventive strategies in this population of patients (12).

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These data reinforce the pathophysiological role of chronic inflammation and validate the inclusion of NLR in risk assessment models. The clinical importance of this finding aligns with established evidence that loss of normal nighttime BP decline correlates with higher risk of left ventricular remodeling, endothelial dysfunction, and consequently greater HF incidence.

NLR in T2DM and Metabolic Syndrome. According to Zhu et al., and Guo et al. a high NLR is an independent predictor of diabetic peripheral neuropathy in diabetic patients and metabolic dysfunction progression (13, 14). This aligns with our findings, which show that patients with a longer history of T2DM and elevated NLR are at an increased risk of HF development. A meta-analysis by Hashemi Moghanjoughi et al. emphasized the role of systemic inflammation in metabolic syndrome (including obesity, hyperglycemia, and dyslipidemia) and identified NLR as a key marker of inflammatory burden (1). Zhu et al. expanded on this concept by linking high NLR with adverse left ventricular remodeling in elderly patients with metabolic syndrome (6). In our study, patients with obesity and elevated NLR were more likely to exhibit impaired myocardial contractility, consistent with Zhu et al.'s findings.

Bagyura et al. further focused on central obesity, demonstrating that higher NLR values were significantly associated with coronary artery calcification and an increased risk of coronary events (2). These findings suggest that systemic inflammation, as reflected by NLR, plays a pivotal role in atherosclerosis and metabolic syndrome complications.

Expanding the Inflammatory Assessment Approach. In addition to NLR, recent studies have explored alternative inflammatory indices. Ibrahim et al. demonstrated that in hospitalized patients, elevated NLR and related composite markers (e.g., neutrophil-to-albumin and lymphocyte ratio (NALR)) were correlated with poor outcomes and increased mortality (15). Lan et al. found that NLR, along with neutrophil-percentage-to-albumin ratio (NPAR), was associated with higher mortality risk in patients with chronic obstructive pulmonary disease (COPD) (16). Furthermore, Dong et al. noted that in patients with metabolic-associated steatotic liver disease (MASLD), increased NLR was linked to higher mortality and cardiometabolic complications (17). Studies by Li et al. (2024) and Chen et al. independently confirmed these findings in cohorts of patients with T2DM and prediabetes, demonstrating that elevated NLR and NPAR were directly associated with an increased risk of cardiovascular and all-cause mortality (18).

NLR in Coronary Pathology and Heart Failure. In the setting of acute coronary pathology, Dai et al. found that elevated NLR and related indices (NPAR, monocyte-to-lymphocyte ratio (MLR)) increased the risk of fatal complications, such as left ventricular free wall rupture, and were associated with severe myocardial infarction outcomes (19). Moreover, Huang et al. reported that increased NLR was correlated with accelerated atherosclerosis progression and poor prognosis, particularly when combined with high-sensitivity CRP and low albumin levels (20). Recent studies further emphasized the prognostic value of NLR in HF progression, demonstrating that patients with higher NLR have worse outcomes, increased hospitalization rates, and higher mortality (5, 8).

Elevated NLR reflects systemic inflammation, where neutrophil expansion (a marker of acute inflammatory response) and lymphocyte depletion (associated with adaptive immune function) contribute to immune dysregulation. Chronic inflammation in HTN, T2DM, and obesity leads to endothelial dysfunction, activation of the renin-angiotensin-aldosterone system, and myocardial remodeling, all of which promote HF progression (21-24).

The “non-dipper” BP profile indicates autonomic nervous system dysfunction and chronic sympathetic overactivity, contributing to myocardial hypertrophy and reduced left ventricular contractility (25).

Thus, the combination of chronic inflammation and BP dysregulation creates an unfavorable environment for HF development in patients with multiple cardiometabolic risk factors.

Our findings highlight the necessity of a comprehensive approach to HF risk stratification in patients with HTN, T2DM, and obesity. Incorporating NLR and circadian BP monitoring into clinical practice may facilitate early identification of high-risk patients.

A high NLR level may serve as an additional diagnostic marker for predicting HF and monitoring inflammatory status in cardiometabolic patients. Its integration into risk assessment models could aid in timely initiation of anti-inflammatory strategies and stricter control of HTN and T2DM.

One limitation of this study is its single-center design, which may limit the generalizability of our findings to broader populations. Future multi-center studies are needed to validate our results in diverse patient cohorts. Additionally, this study was observational, making it difficult to establish a direct causal relationship between NLR and heart failure development. Although we accounted for potential confounders in multivariate analysis, randomized controlled trials (RCTs) would be necessary to confirm causality. We did not perform subgroup analyses of specific non-dipping patterns (e.g., risers, overdippers), which may have provided further insight into the relationship between circadian BP variation and HF risk. Finally, the lack of serial NLR

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measurements can be considered a limitation. Evaluating dynamic changes in NLR over time could provide a more precise understanding of its role in heart failure progression. Future research should investigate whether fluctuations in NLR during follow-up offer additional prognostic value in heart failure risk stratification.

Conducting this study represents a crucial step in developing new risk stratification strategies for HF in patients with cardiometabolic diseases. The use of simple and accessible biomarkers such as NLR could significantly enhance early diagnosis and prognostication of HF, ultimately leading to improved outcomes and a reduction in the burden of cardiovascular diseases in the population. In summary, our findings underscore that chronic inflammatory states (as reflected by an elevated NLR), a disturbed circadian BP rhythm (non dipping profile), and the cumulative burden of longstanding T2DM and hypertension are principal determinants of HF in patients who have multiple cardiometabolic risk factors. We observed only marginal differences in BMI, age, and some lipid fractions. Nevertheless, the robust associations of NLR and non dipping BP highlight the value of expanding conventional screening to include inflammation and circadian BP patterns. By identifying patients with heightened NLR and abnormal nighttime BP reduction, we can better stratify who is at the greatest risk for HF and potentially intervene sooner.

In conclusion, our findings confirm that the neutrophil-to-lymphocyte ratio is independently associated with the onset and progression of heart failure in patients with essential hypertension, type 2 diabetes mellitus, and obesity. These results suggest that NLR may serve as a valuable biomarker for HF risk stratification, enabling earlier identification of high-risk patients and potentially improving intervention strategies. Additionally, our data highlight the importance of integrating inflammatory markers and circadian blood pressure parameters into cardiovascular risk assessment models for patients with cardiometabolic disorders. Incorporating these factors into routine clinical practice may enhance early detection and management of heart failure, ultimately improving patient outcomes.

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