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ORIGINAL ARTICLE

Comprehensive Analysis of Novel Inflammatory Biomarkers (dNLR, NHR, MHR, SIRI): Reference Intervals in Healthy Adults and Diagnostic Value in AMI and HF

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Abstract

Introduction: Inflammatory indices derived from routine blood tests, such as the systemic inflammatory response index (SIRI), the derived neutrophil-to-lymphocyte ratio (dNLR), the neutrophil-to-HDL ratio (NHR), and the monocyte-to-HDL ratio (MHR), have gained interest as potential cardiovascular biomarkers. This study aimed to establish reference intervals for these indices in healthy adults and assess their clinical relevance in acute myocardial infarction (AMI), heart failure (HF), and heart failure following AMI.

Methods: This retrospective study included adult patients from the Istanbul Faculty of Medicine Central Laboratory. Reference intervals were established using the Bhattacharya method, and odds ratios (ORs) were calculated to assess the association between elevated inflammatory indices and cardiovascular conditions.

Results: The upper reference limits (URLs) for the inflammatory indices were as follows: dNLR≤2.57, MHR≤0.49, NHR≤3.62, and SIRI≤1.24. Elevated levels of SIRI, MHR, and NHR were significantly associated with increased odds of AMI (ORs of 3.43, 3.44, and 2.93, respectively). In HF patients, all four indices were significantly elevated, with MHR (OR=7.82) and SIRI (OR=5.52) showing the strongest associations. In the AMI+HF group, SIRI (OR=2.38) and dNLR (OR=2.63) were significantly elevated.

Discussion and Conclusion: This study demonstrates the clinical relevance of CBC-derived inflammatory indices, particularly SIRI and MHR, in distinguishing patients with coexisting myocardial infarction and heart failure. Our robust approach, including healthy controls and precise determination of reference intervals, highlights the potential utility of these markers for enhanced risk stratification and management in cardiovascular disease.

Keywords: Acute Myocardial Infarction; Derived Neutrophil-to-Lymphocyte Ratio (dNLR); Heart Failure; Monocyte-to-HDL Ratio (MHR); Neutrophil-to-HDL Ratio (NHR); Systemic Inflammatory Response Index (SIRI).

Cardiovascular diseases (CVDs) remain a major public health concern across Europe, accounting for more than four million deaths annually. Acute myocardial infarction (AMI) and heart failure (HF) are common clinical manifestations of CVDs, frequently leading to serious health complications and increased risk of mortality[1–3]. Cardiac-specific biomarkers such as hs-cTnI and hs-cTnT are widely used for the diagnosis of myocardial infarction, while BNP and NT-proBNP are considered essential indicators for heart failure evaluation[4,5]. Systemic inflammation plays a central role in both conditions, contributing to atherosclerosis, plaque rupture, myocardial injury, and ventricular dysfunction. It is also a shared underlying mechanism in various pathological states, including infections, autoimmune diseases, cancers,

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and cardiovascular disorders. Several inflammation-based indices, including the systemic inflammatory response index (SIRI), neutrophil-to-lymphocyte ratio (dNLR), neutrophil-to-HDL ratio (NHR), and monocyte-to-HDL ratio (MHR), have recently been investigated for their potential to support diagnosis and follow-up in various conditions, particularly cardiovascular diseases[6–9]. The examination of the distribution of laboratory values in healthy individuals is of significant importance in the context of reference interval studies, as it contributes to the enhancement of the precision of diagnostic evaluations and clinical judgments[10]. According to the EP28-A3C guideline, population-based reference intervals can be determined either by directly recruiting healthy individuals or by applying indirect statistical techniques such as data mining[11].

Studies suggest that indirect methods often produce results comparable to those derived from direct sampling[12]. Bhattacharya analysis is a data mining technique that facilitates the evaluation of extensive laboratory databases. It enables the stratification of subjects according to age and sex without compromising statistical power, even after the application of stringent exclusion criteria[13,14]. The primary objective of this study was to establish reference intervals for four complete blood count (CBC)-derived inflammatory indices (dNLR, MHR, SIRI, and NHR) in a healthy adult population using indirect statistical methods (Bhattacharya analysis) and to evaluate their distribution in patients with AMI and HF, both separately and combined. Despite the investigation of these indices in various cardiovascular conditions, there is an absence of comprehensive reference interval data from healthy populations. The present study also examines their diagnostic performance in AMI and HF using high-sensitivity biomarkers (hs-Troponin, NT-proBNP), providing insight into their potential clinical utility.

Materials and Methods

Subjects

This study utilized retrospective data collected between 2019 and 2023 from the Central Laboratory of Istanbul University, Faculty of Medicine. To isolate a healthy population, we extracted records of individuals who had a complete blood count (CBC) test performed in conjunction with concurrent measurements of HDL, LDL, triglycerides (TG), total cholesterol, HbA1c, and CRP (n=155,901). We applied a comprehensive set of exclusion criteria to ensure the selection of a metabolically and hematologically healthy population. Patients with conditions that affect inflammatory or hematologic indices, such as hospitalization, intensive care unit (ICU) admission, hematologic or oncologic diseases, dialysis, active infections, rheumatologic conditions, and incomplete or repeated laboratory records, were excluded. Additionally, individuals under 18 and over 60 were excluded from the study. Only those whose results for these parameters fell within the reference ranges were included in the study, ensuring a more reliable dataset for calculating reference ranges (n=14,290). A visual representation of the data filtering and selection process, including all inclusion and exclusion steps, is provided in the Sankey diagram (Fig. 1). After this thorough data cleaning process, we applied the Bhattacharya method to determine the distribution of dNLR, MHR, SIRI, and NHR in the healthy population, ensuring the highest standards of accuracy and reliability in our results. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Istanbul University Faculty of Medicine Ethics Committee (Approval No. 3330770, Date: May 23, 2025). Since the study used anonymized retrospective data, the requirement for informed consent was waived.

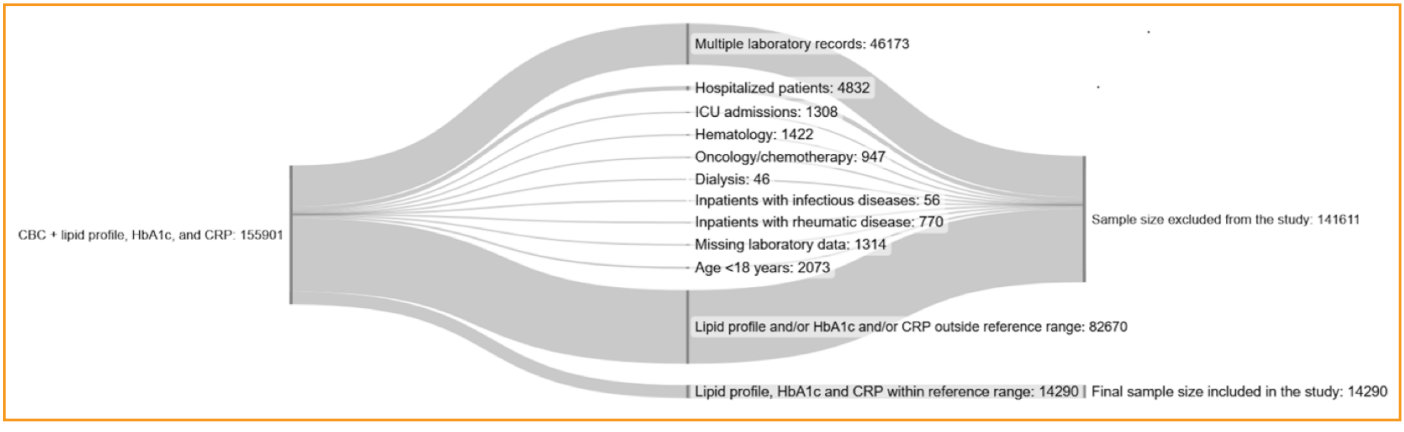

Figure 1. Sankey diagram illustrating the inclusion and exclusion criteria of the study population.

Methods

From 2019 to 2023, plasma levels of NT-proBNP and high-sensitivity troponin T (hs-TnT) were measured using the Roche Elecsys immunoassay platform. Complete blood count (CBC) analyses were conducted using the LH-780 hematology analyzer (Beckman Coulter), while biochemical parameters including total cholesterol, HDL, LDL, triglycerides, and CRP were assessed on the Roche C8000 automated platform. Measurement of HbA1c levels was performed using the Lifotronic H100 hemoglobin analyzer.

Patients with troponin T levels exceeding 14 ng/L were classified as having MI, based on the manufacturer's cut-off value, while those below this threshold were considered non-MI. Similarly, in accordance with the National Institute for Health and Care Excellence (NICE) guidelines, an NT-proBNP level≥300 pg/mL was considered indicative of heart failure (HF) [15]. Patients were stratified into MI, HF, and combined MI+HF groups according to whether their SIRI, MHR, NHR, and dNLR values fell within or above the reference intervals established from the healthy population. Risk associations (ORs) were calculated by comparing individuals with values above the reference range to those within it. This approach enabled evaluation of the clinical relevance of these indices not only for isolated MI or HF but also for their coexistence.

Statistical Analysis

1. Reference Interval Analysis

Data analysis was performed using SPSS version 26 (SPSS Inc., Chicago, IL), with a significance threshold set at $p<0.05$. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test, which revealed that none of the variables followed a normal distribution. Consequently, continuous data were reported as medians with interquartile ranges (IQRs) and compared using the Mann–Whitney U test. Categorical variables were analyzed using the Chi-square test. To assess whether reference interval partitioning by age or sex was required, the Lahti algorithm was applied (Tables 1 and 2)[16,17]. Reference ranges for dNLR, MHR, NHR, and SIRI were then calculated using the Bhattacharya statistical method[12]. In this approach, data were grouped into equal intervals and smoothed to minimize random variation. A weighting factor was applied to improve precision, facilitating the identification of the

Table 1. Partitioning of inflammatory indices by age was assessed using the Lahti criteria

Index	Age Group	LL	UL	Mean±SD	D(s) LL	Decision for LL	D(s) UL	Decision for UL	Final Decision
dNLR	20–29	0.79	4.25	1.92±1.25	0.02	NP	0.07	NP	NP
dNLR	30–39	0.87	4.33	2.0±1.0	0.02	NP	0.37	M	NP
dNLR	40–49	0.89	4.7	2.1±1.17	0.01	NP	0.4	NP	NP
dNLR	50–59	0.88	4.32	1.94±0.95	-		-	-	
MHR	20–29	0.16	0.71	0.37±0.17	0.08	NP	0.13	NP	NP
MHR	30–39	0.15	0.69	0.36±0.14	0.08	NP	0.13	NP	NP
MHR	40–49	0.16	0.71	0.37±0.17	0.0	NP	0.2	NP	NP
MHR	50–59	0.16	0.74	0.37±0.15	-		-	-	-
NHR	20–29	1.16	5.8	2.9±1.16	0.05	NP	0.14	NP	NP
NHR	30–39	1.1	5.65	2.8±1.2	0.03	NP	0.14	NP	NP
NHR	40–49	1.1	5.4	2.72±1.12	0.03	NP	0.36	M	NP
NHR	50–59	1.1	5.4	2.72±1.12	-		-	-	-
SIRI	20–29	0.32	2.7	1.04±0.98	0.015	NP	0.23	NP	NP
SIRI	30–39	0.33	2.56	1.0±0.65	0.015	NP	0.37	M	NP
SIRI	40–49	0.34	2.8	1.1±1.0	0.14	NP	0.28	M	NP
SIRI	50–59	0.33	2.6	1.1±1.0	-		-	-	-

LL: Lower limit; UL: Upper limit; Mean±SD: Mean (average) and standard deviation of the inflammatory index within the subgroup; D(s): Distance between subgroup reference limits (LL or UL), expressed in units of the smaller subgroup's standard deviation; P: Partitioning; M: Marginal; NP: Non-partitioning.

For partitioning decisions, the distance between subgroup reference limits (D(s) LL and D(s) UL) was calculated using the Lahti method, where the distance between the limits is measured in terms of the narrower subgroup's standard deviation. Partitioning was recommended if either D(s) LL or D(s) UL > 0.75, not recommended if both <0.25, and considered marginal if either value was between 0.25 and 0.75. The limits were based on the 2.5th and 97.5th percentiles within each subgroup.

Table 2. The partitioning of inflammatory indices by sex was assessed using the Lahti criteria

Index	Age group	Sex	LL	UL	Mean±SD	D(s) LL	D(s) UL	Final Decision
dNLR	20–29	Male	0.77	4.0	1.8±1.62	0.03	0.21	NP
		Female	0.81	4.3	1.98±1.37			
dNLR	30–39	Male	0.84	4.1	1.9±0.83	0.05	0.36	NP
		Female	0.88	4.4	2.0±1.0			
dNLR	40–49	Male	0.87	5.0	1.8±1.3	0.02	0.35	NP
		Female	0.89	4.6	2.1±1.12			
dNLR	50–59	Male	0.89	4.5	2.0±1.0	0.01	0.40	NP
		Female	0.88	4.1	1.9±0.9			
MHR	20–29	Male	0.19	0.77	0.43±0.15	0.30	0.08	NP
		Female	0.15	0.66	0.35±0.15			
MHR	30–39	Male	0.19	0.76	0.43±0.15	0.33	0.66	NP
		Female	0.15	0.68	0.33±0.12			
MHR	40–49	Male	0.20	0.80	0.43±0.16	0.25	0.62	NP
		Female	0.16	0.70	0.35±0.17			
MHR	50–59	Male	0.20	0.78	0.44±0.16	0.38	0.46	NP
		Female	0.15	0.72	0.35±0.13			
NHR	20–29	Male	1.30	5.65	3.0±1.13	0.18	0.13	NP
		Female	1.10	5.50	2.7±1.17			
NHR	30–39	Male	1.36	5.90	3.16±1.29	0.30	0.43	NP
		Female	1.02	5.40	2.7±1.17			
NHR	40–49	Male	1.40	5.90	3.2±1.29	0.26	0.52	NP
		Female	1.10	5.30	2.76±1.15			
NHR	50–59	Male	1.40	5.80	3.17±1.14	0.40	0.70	NP
		Female	1.00	5.10	2.5±1.0			
SIRI	20–29	Male	0.33	2.5	1.0±0.65	0.05	0.30	NP
		Female	0.30	2.7	1.1±1.1			
SIRI	30–39	Male	0.34	2.7	1.1±0.67	0.015	0.30	NP
		Female	0.33	2.5	1.0±0.65			
SIRI	40–49	Male	0.36	3.0	1.1±1.0	0.05	0.24	NP
		Female	0.34	2.76	1.1±1.03			
SIRI	50–59	Male	0.37	2.78	1.15±0.7	0.10	0.54	NP
		Female	0.30	2.4	0.95±0.72			

LL: Lower limit; UL: Upper limit; Mean±SD: Mean (average) and standard deviation within each subgroup; D(s): Distance between subgroup-specific limits, expressed in units of the smaller subgroup's standard deviation; NP: Non-partitioning. Partitioning decisions were made using the Lahti method described in Table 1.

Gaussian portion of the distribution. The relationship between frequency and concentration was examined with particular attention to the linear segment of the frequency curve, characterized by a high coefficient of determination (R^2>0.99). Where appropriate, a Box-Cox transformation was applied to enhance data normality, with the transformation parameter (λ) selected for optimal model fit (Fig. 2), following procedures outlined at https://www.statology.org/box-cox-transformation-excel/. Lower and upper reference limits (LRL and URL) were calculated as mean±1.96×SD from the Gaussian portion of the data. While the Bhattacharya method served as the primary tool for reference interval estimation, non-parametric methods were also employed due to the overall non-normality of the dataset, allowing for estimation of 95% confidence intervals (CI). Final graphical analyses and calculations were conducted using Microsoft Excel.

2. Odds Ratio Analysis Using Reference Interval Cut-offs

To evaluate the association between inflammatory indices and cardiovascular conditions, binary logistic regression was performed using upper reference limits (URLs) as cut-off values derived from the healthy population. The

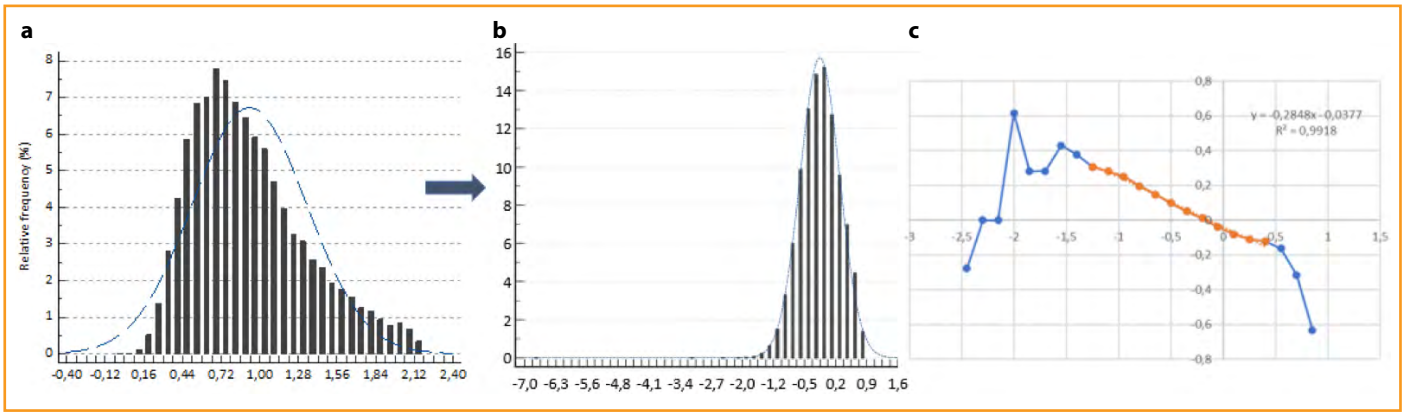

Figure 2. Reference range determination for SIRI using the Bhattacharya method.

(a) Distribution of raw SIRI data. **(b)** SIRI data after Box-Cox transformation (λ=0.15). **(c)** Linear segment of the frequency–concentration plot with a high coefficient of determination (R^2=0.99), used to calculate reference intervals.

independent predictive values of dNLR, MHR, SIRI, and NHR were assessed for AMI, HF, and the overlapping AMI+HF group. Odds ratios (ORs) with corresponding 95% confidence intervals were calculated, and a two-tailed p-value<0.05 was considered statistically significant. This analysis enabled the evaluation of both individual and combined diagnostic utility of these inflammatory markers based on elevated index levels.

Results

Inflammatory indices showed no requirement for age- or sex-based partitioning, and reference intervals were established for the 18–60-year age group (Table 3). As shown in Table 4, systemic inflammatory indices demonstrated significant associations with cardiovascular conditions when compared to healthy controls. Specifically, SIRI, MHR, and NHR were significantly elevated in patients with myocardial infarction (MI), with ORs of 3.43, 3.44, and 2.93, respectively (p<0.001). In contrast, dNLR did not show a significant association with MI (OR=1.04; 95% CI: 0.92–1.33; p=0.58).

When comparing patients with HF to healthy controls, all four indices were significantly elevated. Notably, MHR (OR=7.82) and SIRI (OR=5.52) showed the strongest associations, followed by dNLR (OR=4.84) and NHR (OR=2.79) (p<0.001 for all comparisons).

In subgroup analyses comparing patients with MI only versus those with both MI and HF, significant differences were observed for SIRI (OR=2.38; 95% CI: 1.84–3.08; p<0.001) and dNLR (OR=2.63; 95% CI: 2.00–3.48; p<0.001), suggesting their potential utility in identifying the presence of HF among MI patients. However, MHR and NHR did not differ significantly between these two groups (p>0.05).

These findings highlight SIRI and MHR as robust inflammatory markers across distinct cardiovascular conditions, with SIRI and dNLR also showing discriminatory potential in identifying combined disease states.

Table 3. Reference intervals of inflammatory indices

Indices	LL	LL (%95 CI)	UL	UL (%95 CI)
dNLR	1.02	1.0 – 1.02	2.57	2.56 – 2.58
MHR	0.17	0.17 – 0.18	0.49	0.49 – 0.49
NHR	1.47	1.47 – 1.48	3.62	3.60 – 3.63
SIRI	0.39	0.38 – 0.40	1.24	1.24 – 1.25

Reference intervals for inflammatory indices (dNLR, MHR, NHR, and SIRI) in adults aged 18–60 were calculated using the Bhattacharyya method. The 2.5th and 97.5th percentiles were used to define the reference limits. LL: Lower limit; UL: Upper limit; CI: 95% confidence interval.

Table 4. Odds Ratios of Inflammatory Indices

Index	Comparison	OR	95% CI	p
SIRI	HC vs. MI	3.43	3.03–3.68	<0.001*
MHR	HC vs. MI	3.44	3.11–3.81	<0.001*
dNLR	HC vs. MI	1.04	0.92–1.33	0.58
NHR	HC vs. MI	2.93	2.60–3.30	<0.001*
SIRI	HC vs. HF	5.52	5.30–5.80	<0.001*
MHR	HC vs. HF	7.82	7.30–8.40	<0.001*
dNLR	HC vs. HF	4.84	4.54–5.00	<0.001*
NHR	HC vs. HF	2.79	2.55–3.05	<0.001*
SIRI	MI vs. MI+HF	2.38	1.84–3.08	<0.001*
MHR	MI vs. MI+HF	1.06	0.81–1.39	0.68
dNLR	MI vs. MI+HF	2.63	2.00–3.48	<0.001*
NHR	MI vs. MI+HF	1.13	0.65–1.96	0.67

HC: Healthy Controls; MI: Myocardial Infarction Patients; HF: Heart Failure Patients; OR: Odds Ratio; CI: 95% Confidence Interval; *p<0.05 indicates statistical significance.

Discussion

This study examined systemic inflammatory indices—SIRI, MHR, dNLR, and NHR—across healthy individuals and patients with MI, HF, or both conditions. These indices, derived from CBC and lipid parameters, have emerged as cost-effective and easily accessible markers reflecting systemic immune and inflammatory responses. They integrate the relative proportions of leukocyte subtypes and lipid levels, offering insight into the balance between pro-inflammatory and anti-inflammatory mechanisms [18]. There has been growing interest in evaluating these markers across diverse pathological conditions, such as cardiovascular disorders[19,20], malignancies[21–23], infectious diseases[24], and autoimmune disorders[25–27]. Given the role of chronic low-grade inflammation in the development and progression of atherosclerosis, MI, and HF, these indices may offer additional clinical value in cardiovascular risk evaluation and patient monitoring[28,29].

All four inflammatory markers were significantly increased among patients compared to controls, indicating their possible involvement in cardiovascular pathophysiology. Among all groups, patients with coexisting MI and HF demonstrated the most pronounced elevations in inflammatory indices, implying a synergistic increase in systemic inflammation. Another central objective of the present work was to estimate normal reference limits for these markers among healthy adults, utilizing the Bhattacharya technique to ensure robust statistical validity. The analysis of our reference cohort revealed that the upper limits for these indices were 2.57 for dNLR, 0.49 for MHR, 3.62 for NHR, and 1.24 for SIRI.

Notably, several studies have reported that values exceeding these thresholds may already be associated with increased cardiovascular risk in specific patient populations. For instance, Jiang et al.[30] reported that MHR levels associated with elevated mortality in cardiovascular disease patients were higher than our upper reference limit of 0.49. Conversely, significantly elevated MHR and SIRI levels were observed in high-risk polycythaemia vera patients, with both indices demonstrating independent association with thrombotic progression[31]. Elevated dNLR-PNI scores have also been found to predict adverse outcomes in acute coronary syndrome (ACS) patients following percutaneous coronary intervention (PCI)[32]. Furthermore, elevated NHR levels have been identified as independent predictors of in-hospital major adverse cardiovascular events (MACE), severe coronary artery stenosis, and thrombosis in patients with ST-segment elevation myocardial infarction (STEMI), all of which were above our upper reference values[33].

The study demonstrates that not only are these novel indices clinically informative, but elevations beyond the reference ranges derived from healthy individuals may indicate a higher risk profile.

However, these studies do not define specific reference intervals for healthy individuals, limiting the possibility of direct comparison. These discrepancies likely reflect differences in study populations, disease states, or methodological approaches. Thus, our findings may provide valuable reference data for using these biomarkers in healthy populations. Among the indices, SIRI, a marker of systemic inflammation, has been widely studied in cardiovascular diseases. Due to its reflection of systemic inflammatory burden, SIRI has become a focus of many studies examining its importance in cardiovascular disease. For example, Qu et al.[34] reported that higher SIRI levels were linked to poorer outcomes in myocardial infarction. At the same time, Gao et al.[35] found similar links with hospitalization and death among heart failure patients.

Consistent with these findings, our study showed significantly higher SIRI values in all patient groups compared to healthy controls, with the highest values observed in patients with both MI and HF. This may reflect a greater inflammatory burden in patients with overlapping cardiac conditions. Previous research has primarily examined MI or HF separately, but our results indicate that SIRI might be helpful in detecting high-risk patients with both conditions.

Similarly, MHR has been linked to adverse cardiovascular outcomes[6,36,37]. In our study, MHR was significantly higher in MI and HF groups than in healthy individuals, with the highest values observed in patients with both conditions. The results demonstrate that inflammation levels are elevated in individuals suffering from both heart attack and heart failure. Although the prognostic value of MHR has been addressed in cardiovascular research, its capacity to distinguish overlapping disease states like MI+HF has not been thoroughly investigated. Our findings suggest that both MHR and SIRI may have the potential to identify patients with compounded disease burden.

In contrast, dNLR showed a more limited association with MI in our analysis, yet demonstrated stronger associations in HF and the MI+HF group. This pattern may indicate that dNLR is more relevant in chronic or advanced disease states. Supporting this, Li et al.[38] demonstrated that dNLR is associated with all-cause and cardiovascular mortality in patients with cardiovascular disease, emphasizing its potential as a prognostic tool, particularly in later stages of disease progression.

Our findings for NHR were also consistent with previous reports. NHR levels were notably higher in patients with MI and HF compared to healthy individuals, supporting its function as a reliable marker of cardiovascular inflammation[39]. However, among the studied indices, NHR was the only marker that did not show a significant increase in patients who developed HF after MI. This may be attributed to the complex, multifactorial nature of post-infarction HF. As emphasized by Jenča et al.,[40] factors such as infarct size, residual ventricular function, and comorbidities play critical roles in post-MI HF progression. These mechanisms may limit the sensitivity of specific inflammation-based markers such as NHR in this subgroup.

Conclusion

In summary, using a single dataset, this study evaluated multiple CBC-derived inflammatory indices (SIRI, MHR, dNLR, and NHR) across various cardiovascular conditions. Our study offers novel insights that may support clinical practice, achieved through the inclusion of healthy controls and the application of a robust method for determining reference ranges. Our findings suggest that SIRI and MHR may be particularly useful in identifying patients with concomitant MI and HF. This subgroup may otherwise be underrecognized despite their elevated inflammatory burden.

Ethics Committee Approval: The study was approved by Istanbul University Faculty of Medicine Ethics Committee (No: 3330770, Date: 23.05.2025).

Conflict of Interest: The authors declare that there is no conflict of interest.

Informed Consent: Written informed consent was obtained from all participants or their legal guardians.

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