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The association between neutrophil and lymphocyte to high-density lipoprotein cholesterol ratio and metabolic syndrome among Iranian population, finding from Bandare Kong cohort study

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Abstract

Background Metabolic Syndrome (MetS) is characterized by the co-occurrence of various metabolic risk factors, significantly increasing the risk of cardiovascular diseases (CVD) and type 2 diabetes (T2DM). This study investigates the potential of hematological indices, specifically the neutrophil to high-density lipoprotein cholesterol ratio (NHR) and lymphocyte to high-density lipoprotein cholesterol ratio (LHR), as predictors of MetS in a population from southern Iran.

Methods Utilizing baseline data from the Bandare-Kong Non-Communicable Diseases (BKNCD) Cohort, part of the Prospective Epidemiological Research Studies in IrAN (PERSIAN), A total of 2,684 participants aged 35–70 years were analyzed. Participants were evaluated using the Iranian National Cholesterol Education Program (NCEP) criteria to diagnose MetS. Receiver operating characteristic (ROC) analysis was conducted to assess the predictive validity of NHR and LHR across different demographic categories.

Results The mean LHR and NHR values were significantly higher in individuals diagnosed with MetS ($P < 0.001$). Specifically, the LHR was 0.85 ± 0.26 in MetS patients compared to 0.76 ± 0.23 in those without MetS, while the NHR was 1.33 ± 0.35 in MetS patients compared to 1.20 ± 0.32 in those without MetS. After adjusting for confounding factors, both LHR and NHR remained significantly associated with MetS, with odds ratios (OR) of 6.61 (95% CI: 4.43–9.83) for LHR and 4.76 (95% CI: 3.51–6.45) for NHR. Among MetS components, LHR was associated with low HDL cholesterol and elevated triglycerides, while NHR showed significant associations with central obesity, low HDL cholesterol, and elevated triglycerides. ROC analysis revealed moderate predictive capabilities for both indices, with areas under the curve of 0.60 for LHR and 0.61 for NHR.

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Conclusion The findings suggest that NHR and LHR are promising, easily obtainable hematological markers for predicting MetS. These indices could serve as valuable tools for early detection and ongoing monitoring in clinical settings, aiding in the prevention and management of MetS.

Keywords Metabolic syndrome, Neutrophil to high-density lipoprotein cholesterol ratio, Lymphocyte to high-density lipoprotein cholesterol ratio, Prospective epidemiological research studies in IrAN (PERSIAN)

Introduction

MetS presents a significant global health challenge, encompassing a range of interrelated metabolic disorders including systemic hypertension, insulin resistance, central obesity, non-alcoholic fatty liver disease, and atherogenic dyslipidemia [1–3]. Epidemiological data consistently demonstrate that individuals with MetS face substantially higher risks of serious health conditions, including a five-fold increase in the likelihood of developing T2DM and a two-fold higher risk of CVD [4–6]. Prevalence rates of MetS are strikingly high, with national studies reporting rates between 32% and 47.6%, while systematic reviews estimate that approximately 30.4% of the Iranian population is affected [7, 8]. Additionally, data from the BKNCD cohort study in southern Iran indicate that 34.5% of individuals in this region are living with MetS [9].

The pathophysiology of MetS is complex, involving genetic, environmental, and metabolic factors [10–12]. Central to MetS is insulin resistance, often driven by visceral obesity, which promotes a pro-inflammatory state and endothelial dysfunction [13–17]. Dyslipidemia, characterized by high triglyceride (TG) and low HDL-C levels, further contributes to MetS. Chronic inflammation and oxidative stress are also key players [18–21]. Emerging evidence highlights the role of gut microbiota in MetS, with alterations in microbial composition influencing energy metabolism, fat storage, and inflammation, thereby contributing to the development of MetS and related metabolic disorders [22–26].

Research into the inflammatory processes associated with MetS has produced a wide range of findings, particularly concerning hematological parameters such as red blood cells, platelets, white blood cells, and various inflammatory markers [27–29]. These variations underscore the complexity of MetS and the difficulty in pinpointing consistent biomarkers.

For instance, some studies have documented a decrease in lymphocyte count among MetS patients [30, 31], suggesting a potential immune suppression aspect. In contrast, other research indicates a possible connection between lymphocyte proliferation and the onset of MetS [32, 33]. Additionally, under normal physiological conditions, HDL-C plays a protective role by inhibiting macrophage migration and fat deposition in blood vessel walls [31]. However, in the context of MetS, the reduction in HDL-C levels may accelerate the development

of atherosclerosis, thereby worsening cardiovascular outcomes.

Numerous studies have established correlations between peripheral blood counts and metabolic components of MetS [34–36]. However, the limitations of using individual hematological parameters as reliable predictors for MetS have prompted the exploration of such indices, such as NHR and LHR, which may offer more accurate assessments. This study hypothesizes that NHR and LHR, as composite hematological indices, provide a more robust predictive and diagnostic approach for MetS than individual blood parameters due to their combined reflection of inflammatory and lipid profiles. By examining these associations, this research seeks to contribute valuable insights to the existing knowledge on MetS biomarkers, supporting the development of enhanced diagnostic methods and therapeutic strategies. Such advancements are crucial to meeting the increasing demand for early detection and effective management of MetS, both within Iran and on a global scale.

Method

Study design and sampling

A cross-sectional population-based study was conducted using baseline data from the BKNCD Cohort Study, a segment of the PERSIAN. The PERSIAN cohort study enrolled individuals aged 35–70 from 18 distinct geographical regions across Iran, with detailed information available [37]. Initially, the study encompassed 4,063 participants aged 35–70, recruited between November 2016 and November 2018 from Bandare-Kong, Hormozgan Province, in southern Iran.

Exclusion criteria were applied to pregnant women, incomplete or insufficient data, and patients with conditions capable of impacting the blood system, including acute or ongoing infections, end-stage renal or liver diseases, cancers, hematologic malignancies, CVD, and those on antihyperlipidemic or corticosteroid treatment. By refining the study sample through these exclusions, potential confounding variables were minimized, enhancing the validity of the results. Following these exclusions, the final analysis included a total of 2,684 participants (1,328 males and 1,356 females), ensuring a balanced representation. The study sample was further divided into 802 cases and 1,882 controls.

Data collection

Key demographic information, such as age, gender, educational background, marital status, occupation, and social factors like smoking habits, dietary patterns, and levels of physical activity, was collected. Participants' daily food consumption was documented using a food frequency questionnaire (FFQ), and daily calorie intake was calculated based on the caloric content of the consumed items. Trained personnel conducted face-to-face interviews using validated and reliable questionnaires, specifically designed for consistent data collection across all sites in the PERSIAN cohort.

Anthropometric and biochemical measurements

A digital scale was carefully calibrated and used to measure the weight of each participant, ensuring precision by instructing participants to wear only light clothing and no shoes. This method minimizes measurement variability and helps standardize weight data across the study. Each weight was rounded to the nearest 0.5 kg to maintain uniformity in data recording and analysis. Height was measured using a stadiometer, a precise instrument specifically designed for height assessment. Participants were instructed to stand straight with their feet flat on the ground, shoulders relaxed, and head positioned in the Frankfort horizontal plane to ensure accuracy. By removing shoes, any discrepancies due to footwear were eliminated, thereby enhancing the reliability of the height data.

Waist circumference (WC) measurements were obtained following specific anatomical landmarks to ensure consistency. The measurement site was set at the midpoint between the top of the iliac crest and the lower edge of the last palpable rib along the mid-axillary line. This location provides an accurate representation of central adiposity. Each WC measurement was performed twice by trained professionals using a non-stretch tape, and the average of these readings, rounded to the nearest 0.5 cm, was recorded to ensure accuracy and reduce potential measurement error. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. This index serves as an indicator of overall body fat distribution and is a commonly used metric for categorizing weight status.

Blood pressure (BP) assessments included both systolic (SBP) and diastolic (DBP) readings using a standard mercury sphygmomanometer. Participants were instructed to sit comfortably with their arms at heart level, and they were given a 15-minute rest period prior to measurement to eliminate any temporary influence of stress or physical exertion. Each participant's SBP and DBP were measured twice, and the mean of these measurements was recorded for precision.

For biochemical analysis, fasting blood samples were collected after participants had fasted for at least 12 h overnight. Fasting plasma glucose (FPG) levels were determined using the glucose oxidase method, which is known for its high specificity in glucose detection. Lipid profile measurements—including total cholesterol (TC), TG, low-density lipoprotein (LDL), and high-density lipoprotein cholesterol (HDL-C)—were conducted using the enzymatic method, which provides reliable and reproducible results for lipid quantification, essential for assessing cardiovascular risk factors.

The criteria established by the Iranian National Committee of Obesity were utilized to identify MetS, with any three out of five criteria met indicating a person's qualification for MetS [38]:

1. **WC:** A waist measurement of 95 cm or more. This threshold indicates central obesity, which is a significant risk factor for MetS.
2. **FPG:** A blood glucose level of 100 mg/dL or higher, or the individual is currently receiving medical treatment to control elevated blood sugar. High fasting glucose can be an indicator of insulin resistance, a key component of MetS.
3. **HDL Cholesterol Levels:** For men, HDL levels should be below 40 mg/dL, while for women, they should be below 50 mg/dL. Alternatively, if the individual is undergoing treatment for low HDL levels, they also meet this criterion. Low HDL is considered a risk factor because HDL helps remove cholesterol from the bloodstream.
4. **TG Levels:** Triglyceride levels of 150 mg/dL or higher, or current treatment for elevated triglycerides, also indicate a risk. Elevated triglycerides are associated with a higher likelihood of heart disease and other MetS-related conditions.
5. **BP:** BP readings of 130/85 mmHg or higher, or ongoing treatment for hypertension, are also a marker. High BP places additional strain on the heart and blood vessels, increasing the risk of cardiovascular issues.

Meeting any three of these five criteria is typically considered enough to diagnose MetS. Each of these factors contributes to an increased risk of developing CVD, diabetes, and other health complications, highlighting the importance of regular health screenings and preventive measures.

Data analysis

This research constitutes a descriptive, cross-sectional analysis of data obtained from the Bandar Kong cohort study, aimed at identifying patterns and relationships related to MetS among participants. In this analysis,

categorical variables were represented using frequencies and percentages (%), enabling an overview of the distribution of these variables within the sample population. Continuous variables were summarized through mean values and standard deviations (SD) to illustrate central tendencies and the variability within the data. To assess differences in the average values of continuous variables between two groups, the t-test was employed, providing insight into statistically significant mean differences. For categorical data, the chi-square test was used to evaluate the association between two categorical variables, offering a measure of whether relationships observed within the data were likely to have occurred by chance.

Further analysis involved logistic regression to explore the potential relationship between two critical ratios—NHR and LHR—and their association with MetS. This method helped quantify the likelihood of MetS in relation to changes in these ratios. To determine the predictive power of NHR and LHR ratios in identifying MetS and its components, the ROC curve and the Area Under the Curve (AUC) were employed. These metrics provide an assessment of how well the NHR and LHR ratios can differentiate between individuals with and without MetS, with the AUC offering a numerical measure of predictive accuracy. To enhance the precision of the diagnostic tool, Youden's J statistic was applied to calculate the optimal cut-off values for NHR and LHR. This statistic was used to maximize the combined sensitivity and specificity (sensitivity+specificity – 1) for detecting MetS, ultimately improving the practical utility of these ratios as screening markers.

The ROC curve analysis was conducted using MedCalc Version 20, a software known for its robust tools in medical statistics, while all other statistical procedures, including general data analysis and validation, were performed using IBM SPSS Version 25 to ensure consistency and accuracy across different analytical methods. A two-sided *P*-value of less than 0.05 was considered indicative of statistical significance, ensuring that findings were robust and unlikely to be due to random variation alone.

Results

Among the 2684 participants, 29.9% (802 individuals) were afflicted by MetS. Results revealed significant association between various demographic factors—such as age, gender, marital status, place of residence, education, employment status, and physical activity—and the presence of MetS ($P < 0.05$). As age advanced, there was a corresponding escalation in the prevalence of MetS, with women exhibiting a higher prevalence (33.7%) compared to men (26.0%). Those who were divorced or widowed presented a notably higher prevalence of MetS (40.4%) compared to their single or married counterparts. Moreover, individuals residing in urban areas, possessing lower

educational attainment, experiencing unemployment, and engaging in minimal physical activity demonstrated the highest prevalence of MetS. These baseline demographic characteristics of the population are presented in Table 1.

The results revealed significant differences between individuals with MetS and those without it in various variables (Table 2). Participants with MetS had an average age of 50.35 ± 9.23 years, which was significantly higher than the 46.11 ± 8.73 years observed in those without MetS ($P < 0.01$). MetS group exhibited a significantly higher BMI, with a mean of 29.16 ± 4.23 , compared to a mean of 25.16 ± 4.43 in the non-MetS group ($P < 0.01$). Regarding hematological indices, the NHR and the LHR were both elevated in the MetS group. The NHR was 1.33 ± 0.35 in MetS patients, compared to 1.20 ± 0.32 in those without MetS ($P < 0.01$). Similarly, the LHR was higher in the MetS group, with a mean of 0.85 ± 0.26 versus 0.76 ± 0.23 in the non-MetS group ($P < 0.01$).

The results of the binary logistic regression models indicated that both NHR and LHR are significant risk factors for MetS, after adjusting for other variables such as age, BMI, gender, and physical activity.

For NHR, the adjusted odds ratio (OR) for MetS was 4.76 (95% CI: 3.51, 6.45) (Table 3). Similarly, for LHR, the adjusted OR was 6.61 (95% CI: 4.43, 9.83) (Table 4).

Additionally, age was found to be a significant predictor in both models, with each year increase in age associated with an adjusted OR of 1.08 (95% CI: 1.07, 1.09) in the NHR model and 1.07 (95% CI: 1.06, 1.09) in the LHR model (Tables 3 and 4).

BMI also demonstrated a significant association with MetS, with an adjusted OR of 1.25 (95% CI: 1.22, 1.28) in the NHR model and 1.26 (95% CI: 1.23, 1.29) in the LHR model (Tables 3 and 4).

Gender differences were noted, with females having a higher risk of MetS compared to males, as reflected by an adjusted OR of 1.24 (95% CI: 1.01, 1.52) in the NHR model and 1.20 (95% CI: 0.98, 1.47) in the LHR model (Tables 3 and 4).

Physical activity was inversely related to MetS, with moderate levels of physical activity (36.6–44.9 METS/week) showing a protective effect against MetS, as indicated by an adjusted OR of 1.46 (95% CI: 1.08, 1.98) in the NHR model and 1.37 (95% CI: 1.02, 1.84) in the LHR model (Tables 3 and 4).

Based on the findings presented in Table 5, significant differences in the NHR were observed in relation to central (abdominal) obesity, triglyceride levels, and HDL cholesterol levels. Specifically, individuals with high abdominal obesity had a significantly higher NHR (1.27 ± 0.33) compared to those with normal abdominal measurements (1.22 ± 0.33 , $P < 0.01$). Additionally, those with elevated triglycerides and low HDL cholesterol

Table 1 Base line Characteristics of the study population

Variables		MetS				P-value*
		Yes (n = 802)		No (n = 1882)		
		Frequency	percentage	Frequency	percentage	
Age	35–44	251	20.7	960	79.3	< 0.01
	45–54	259	31.7	559	68.3	
	55–70	292	44.6	363	55.4	
Gender	Male	345	26.0	983	74.0	< 0.01
	Female	457	33.7	899	66.3	
marital status	Single	15	20.5	58	79.5	< 0.01
	Married	711	29.3	1712	70.7	
	Widowed or divorced	76	40.4	112	59.6	
place of residence	City	657	29.0	1609	71.0	0.02
	Suburbs	145	34.7	273	65.3	
Education	< 6	526	34.7	991	65.3	< 0.01
	6–12	223	24.2	697	75.8	
	> 12	53	21.5	194	78.5	
Employment status	Employed	335	24.3	1041	75.7	< 0.01
	Unemployed	467	35.7	841	64.3	
Smoking	Yes	116	27.4	307	72.6	0.23
	No	686	30.3	1575	69.7	
Physical activity	24–36.5	209	33.6	413	66.4	< 0.01
	36.6–44.9	497	31.1	1102	68.9	
	≥45	86	20.1	341	79.9	
Economic Status	Poor	314	30.0	733	70.0	0.90
	Medium	156	30.5	355	69.5	
	Rich	330	29.4	791	70.6	

Mets: Metabolic Syndrome

Chi-Square test was used in the analysis of contingency tables

Table 2 Comparison of quantitative variables between participants with and without MetS

Variables	MetS				P-value*
	Yes (n = 802)		No (n = 1882)		
	Mean	standard deviation	Mean	standard deviation	
Age	50.35	9.23	46.11	8.73	< 0.01
BMI	29.16	4.23	25.16	4.43	< 0.01
Daily Energy intake	2954.48	932.91	2975.96	947.28	0.59
NHR	1.33	0.35	1.20	0.32	< 0.01
LHR	0.85	0.26	0.76	0.23	< 0.01

BMI: Body mass index

NHR: Neutrophil to High-Density Lipoprotein cholesterol Ratio

LHR: Lymphocyte High-Density Lipoprotein Cholesterol Ratio

*Independent Samples T test was used to compare the means of two groups

levels also exhibited significantly higher NHR values (1.31 ± 0.35 vs. 1.20 ± 0.32 , $P < 0.01$; and 1.47 ± 0.32 vs. 1.09 ± 0.25 , $P < 0.01$, respectively). Similarly, LHR showed significant associations with triglyceride levels and HDL cholesterol levels. Participants with high triglyceride levels had a higher LHR (0.86 ± 0.26) compared to those with normal levels (0.76 ± 0.23). Furthermore, those with low HDL cholesterol had a higher LHR

(0.93 ± 0.26) compared to individuals with normal HDL levels (0.70 ± 0.19). No significant differences in NHR or LHR were found in relation to hypertension or impaired fasting glucose (IFG).

According to the ROC analysis, as illustrated in Fig. 1 and summarized in Table 6, the results indicated that both NHR and LHR performed similarly in predicting diagnosed MetS for both sexes, with AUC values slightly above 0.6. These findings suggested that both NHR and LHR could be considered moderate predictors for identifying MetS in both men and women. The optimal cut-off points for NHR and LHR were determined using Youden's J statistic. For NHR, the optimal cut-off values for screening MetS were identified as 1.29 for men and 1.13 for women. In the case of LHR, the optimal cut-off values were 0.91 for men and 0.68 for women (Table 6). Table 7 presented the association between actual MetS and MetS predicted by logistic regression models, which were adjusted for age, BMI, and physical activity for both sexes. The analysis showed that when NHR was used as a predictor, the association between MetS and predicted MetS was statistically significant for both men and women ($P < 0.05$). However, when LHR was used as a predictor, the association was statistically significant only in men ($P < 0.05$), and not in women. The strength of

Table 3 Logistic regression analysis for predicting MetS based on NHR

Variables		Crude				Adjusted			
		B	OR*	confidence interval %95	P-value	B	OR*	confidence interval %95	P-value
NHR		1.19	3.29	2.56–4.24	< 0.01	56.1	76.4	3.51–6.45	< 0.01
Age		05.0	05.1	1.04,106	< 0.01	08.0	08.1	1.07–109	01.0>
BMI		20.0	22.1	1.19,1.25	< 0.01	22.0	25.1	1.22–1.28	01.0>
Gender	Female	37.0	45.1	1.22–1.71	< 0.01	22.0	24.1	1.01–1.52	03.0
	Male	Reference Category				Reference Category			
Smoking	Yes	14.0	87.0	0.68–1.09	23.0	-	-	-	-
	No	Reference Category				Reference Category			
Economic Status	Poor	02.0	02.1	0.85–1.23	78.0	-	-	-	-
	Medium	05.0	05.1	0.84–1.32	65.0	-	-	-	-
	Rich	Reference Category				Reference Category			
Physical activity METS/ week	24–36.5	69.0	00.2	1.50–2.68	< 0.001	23.0	25.1	0.89–1.75	18.0
	36.6–44.9	58.0	79.1	1.38–2.32	< 0.001	38.0	46.1	1.08–1.98	01.0
	>=45	Reference Category				Reference Category			

BMI: Body mass index

NHR: Neutrophil to High-Density Lipoprotein cholesterol Ratio

LHR: Lymphocyte High-Density Lipoprotein Cholesterol Ratio

OR: Odds Ratio

*Independent variables with *P* value less than 0.2 were included in multivariable logistic regression to estimate the adjusted ORs**Table 4** Logistic regression analysis for predicting MetS based on LHR

Variables		Crude				Adjusted			
		B	OR	Confidence interval %95	P-value	B	OR	Confidence interval %95	P-value
LHR		19.1	29.3	2.56–4.24	01.0>	88.1	61.6	4.43–9.84	01.0>
Age		05.0	05.1	1.04–1.06	01.0>	07.0	07.1	1.06–1.09	01.0>
BMI		20.0	22.1	1.19–1.25	01.0>	23.0	26.1	1.23–1.29	01.0>
Gender	Female	37.0	45.1	1.22–1.71	01.0>	19.0	20.1	0.98–1.47	07.0
	Male	Reference Category				Reference Category			
Smoking	Yes	14.0	87.0	0.68–1.09	23.0	-	-	-	-
	No	Reference Category				Reference Category			
Economic Status	Poor	02.0	02.1	0.85–1.23	78.0	-	-	-	-
	Moderate	05.0	05.1	0.84–1.32	65.0	-	-	-	-
	Rich	Reference Category				Reference Category			
Physical activity METS/ week	24–36.5	69.0	00.2	1.50–2.68	01.0>	16.0	18.1	0.85–1.65	32.0
	36.6–44.9	58.0	79.1	1.38–2.32	01.0>	31.0	37.1	1.02–1.84	04.0
	>=45	Reference Category				Reference Category			

BMI: Body mass index

NHR: Neutrophil to High-Density Lipoprotein cholesterol Ratio

LHR: Lymphocyte High-Density Lipoprotein Cholesterol Ratio

OR: Odds Ratio

*Independent variables with *P* value less than 0.2 were included in multivariable logistic regression to estimate the adjusted ORs

the association between actual and predicted MetS was assessed using Somers' *d*, Kendall's tau, and Goodman and Kruskal's gamma indices.

Discussion

In this cross-sectional study, the neutrophil and lymphocyte to HDL cholesterol ratios were evaluated to assess their potential contribution to the diagnosis and prediction of MetS occurrence in a large population in southern Iran. MetS is identified by a set of risk factors, including

insulin resistance, which is associated with subclinical chronic inflammation [39]. Blood parameters can be used as indirect predictors of this inflammation. Therefore, changes in blood parameters have important prognostic implications for chronic inflammation and the progression of MetS.

Many investigations have shown changes in hematological parameters in high-risk patients for MetS. Wang et al. discovered that individuals in the highest quartile of WBC counts had three times the risk of MetS compared

Table 5 Comparison of NHR and LHR across different MetS components

Variables	NHR		LHR
Hypertension	Yes	1.23 ± 0.33	0.79 ± 0.25
	No	1.24 ± 0.33	0.79 ± 0.24
P-value	0.27		0.81
Central obesity (Abdominal)	Normal	1.22 ± 0.33	0.79 ± 0.25
	High	1.27 ± 0.33	0.79 ± 0.24
P-value	< 0.01		0.70
IFG	Normal	1.24 ± 0.33	0.79 ± 0.24
	High	1.23 ± 0.34	0.79 ± 0.25
P-value	0.81		0.58
TG	Normal	1.20 ± 0.32	0.76 ± 0.23
	High	1.31 ± 0.35	0.86 ± 0.26
P-value	< 0.01		< 0.01
HDL	Normal	1.09 ± 0.25	0.70 ± 0.19
	Low	1.47 ± 0.32	0.93 ± 0.26
P-value	< 0.01		< 0.01

NHR: Neutrophil to High-Density Lipoprotein cholesterol Ratio

LHR: Lymphocyte High-Density Lipoprotein Cholesterol Ratio

IFG: Impaired Fasting Glucose

TG: Triglyceride

HDL: High Density Lipoprotein

P values refer to Independent Samples T Test

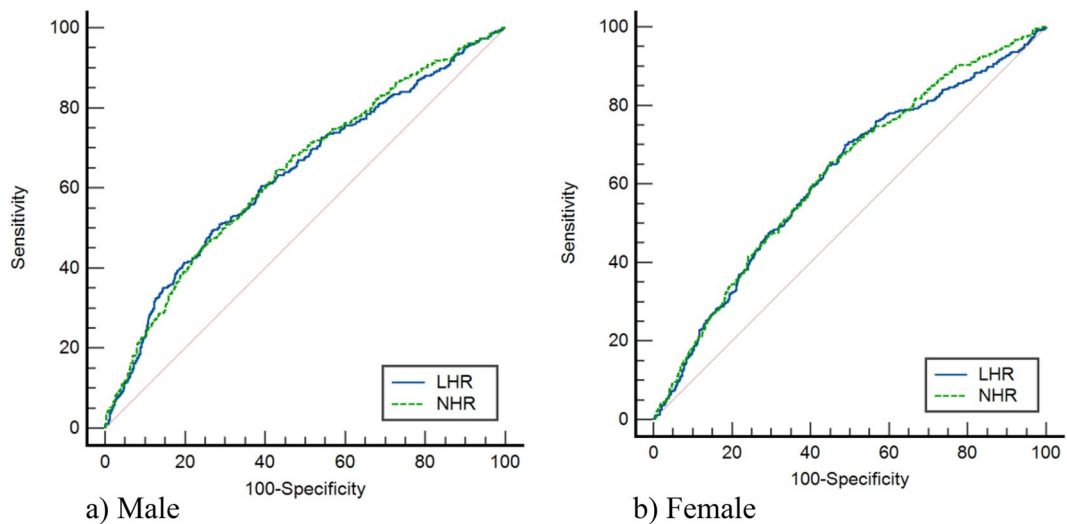


Fig. 1 ROC curve displaying the ability of NHR and LHR to predict MetS according to sex

Table 6 Area under the curve and optimal cut-of points demonstrating the ability of NHR and LHR to predict MetS according to sex

Measures	Male					Female				
	AUC (95% CI)	P value*	Cut-off-value	Sensitivity	Specificity	AUC (95% CI)	P value*	Cut-off-value	Sensitivity	Specificity
NHR	0.64 (0.61–0.66)	< 0.001	1.29	64.35%	57.27%	0.62 (0.60–0.65)	< 0.001	1.13	65.43%	55.06%
LHR	0.63 (0.60–0.67)	< 0.001	0.91	49.28%	73.35%	0.61 (0.59–0.64)	< 0.001	0.68	70.02%	51.06%

NHR: Neutrophil to High-Density Lipoprotein cholesterol Ratio

LHR: Lymphocyte High-Density Lipoprotein Cholesterol Ratio

AUC: Area Under Curve

CI: confidence interval

Null hypothesis: True area=0.5

Table 7 Association between predicted MetS and actual MetS according to logistic regression models by sex

Measures	Male				Female			
	Association	Value	Standard Error	P value	Association	Value	Standard Error	P value
NHR	Somers' d	0.314	0.091	0.003	Somers' d	0.150	0.061	0.017
	Kendall's tau	0.106	0.032	0.003	Kendall's tau	0.071	0.029	0.017
	Goodman and Kruskal's gamma	0.589	0.122	0.003	Goodman and Kruskal's gamma	0.304	0.111	0.017
LHR	Somers' d	0.231	0.088	0.016	Somers' d	0.089	0.070	0.206
	Kendall's tau	0.082	0.032	0.016	Kendall's tau	0.036	0.028	0.206
	Goodman and Kruskal's gamma	0.469	0.138	0.016	Goodman and Kruskal's gamma	0.189	0.138	0.206

to those in the lowest quartile [40]. Nagasawa et al. conducted research including 3,594 Japanese males between the ages of 34 and 69. They discovered that there was a positive correlation between WBC count and BMI, BP, triglycerides, glucose, and insulin levels. Conversely, there was a negative correlation between WBC count and HDL cholesterol. Individuals diagnosed with MetS had elevated WBC counts and insulin levels [41]. Consistent with this study, a cross-sectional survey among 1,401 adults in China demonstrated that LHR and NHR are strong predictors of MetS in females, independent of other factors. In males, while LHR and NHR were initially significant predictors, their significance diminished after adjusting for fasting glucose levels [27]. ROC analysis indicated that LHR is the best predictor for MetS in females and NHR in males. In the present study, LHR and NHR were significantly higher in MetS patients (<0.001). In addition, there was a significant association between LHR and NHR and the incidence of MetS after adjusting for age, gender, BMI, smoking, economic state, and activity.

In line with this study, an investigation in China revealed a positive correlation between MetS and blood parameters. ROC analysis showed that LHR is an independent predictor of MetS with a cut-off value of 1.657, sensitivity of 65%, and specificity of 64% [42]. Assessing the accuracy of LHR and NHR with ROC curve analysis in this study indicated that NHR and LHR had the same acceptable value for MetS (AUC; LHR: %60, NHR: %61).

In another study conducted by Najafzadeh et al. [43] on a southeastern Iranian population, it was found that the NHR was significantly associated with the severity of MetS. These findings align with these results, further highlighting the utility of NHR as a predictive marker for MetS across different Iranian populations.

Another study in rural China found that the LHR can effectively predict newly diagnosed MetS. The study also discovered that individuals with higher LHR values tended to be younger, male, and smokers. Additionally, they had a higher WC, higher levels of triglycerides, and lower levels of HDL. The study concluded that LHR could be useful for identifying rural individuals at risk of MetS as a new inflammatory marker. However, the platelet-to-lymphocyte ratio (PLR) was insignificant in predicting

MetS [28]. The associations between the NHR and LHR with various components of MetS were investigated. The comprehensive study included both urban and rural populations, and the findings were closely aligned with previous research. Analysis indicated that NHR and LHR had the strongest correlations with elevated TG levels and reduced HDL cholesterol levels. Moreover, NHR demonstrated a significant association with central obesity, underscoring its relevance as an indicator of this particular aspect of MetS. These results suggest that NHR and LHR are valuable markers for identifying specific metabolic abnormalities across diverse population settings.

In another study, researchers found that in patients with early-stage MetS, the ratios of leukocytes (specifically PMNs and monocytes) to HDL-C and adiponectin were significantly higher [44]. Additionally, they discovered that the ratios of PMN to HDL-C and monocyte to HDL-C were better indicators of MetS compared to high-sensitivity C-reactive protein (hs-CRP). WBC count is a commonly used marker for mild systemic inflammation. However, high-sensitivity hs-CRP has been identified as a superior marker for evaluating the inflammatory aspects of MetS. Numerous studies have linked hs-CRP with diabetes, CVD, and MetS [34–36, 45]. Despite this, WBC counts may be more advantageous in clinical settings due to their affordability and ease of access, simplifying diagnosis and treatment while reducing costs [46, 47].

Furthermore, in various studies where CRP has been utilized as an inflammatory marker for diagnosing MetS in comparison to NHR and LHR, its application has often been accompanied by notable limitations. For instance, according to Chen et al., [27] CRP is a less effective predictor of MetS due to its susceptibility to confounding factors such as infections and tissue injuries, which can lead to elevated levels that are unrelated to the syndrome. In contrast, NHR and LHR are more closely linked to chronic inflammation, a key driver of MetS, and maintain their predictive accuracy even after adjusting for factors like fasting glucose. Moreover, CRP is a general inflammatory marker, while NHR and LHR are more specifically associated with inflammation linked to MetS, making them more reliable indicators [27].

Additionally, the latest systematic review by Podeanu et al. [48] underscores several limitations in using CRP as

a marker for MetS. One major limitation is its inability to distinguish between patients with MetS and those who are simply obese, as elevated CRP levels may be a result of obesity-related inflammation rather than the syndrome itself. Moreover, variability in measurement methods, such as standard CRP versus hsCRP, can influence diagnostic accuracy. CRP levels are also influenced by various confounding factors, such as infections and tissue damage, further complicating the diagnosis of MetS [48].

Also, Marra et al. [49] demonstrated that the NHR and LHR showed clear superiority over other examined inflammatory markers in individuals with MetS. These two ratios outperformed other CBC-derived indices, such as monocyte-to-HDL-C ratio, platelet-to-HDL-C ratio, SIRI (Systemic Inflammation Response Index), SII (Systemic Immune-Inflammation Index), and AISI (Aggregate Index of Systemic Inflammation), in predicting the severity of MetS. Moreover, NHR and LHR were significantly more associated with cardiometabolic risk factors such as HOMA-IR and the TG/HDL-C ratio, further highlighting their stronger predictive power. While SIRI also showed some correlation with these factors, SII and AISI demonstrated weaker associations and lower predictive value [49].

The mechanisms underlying this association are not yet fully understood, though several plausible hypotheses have been proposed [50]. MetS is characterized by a combination of factors that are closely linked to chronic low-grade inflammation. Elevated neutrophil levels in individuals with MetS serve as markers of increased systemic inflammation, driven in part by pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α). These cytokines induce oxidative stress, which in turn worsens insulin resistance—one of the key hallmarks of MetS. Neutrophils, as part of the innate immune system, proliferate in response to these cytokines, indicating ongoing inflammation. Likewise, lymphocytes, crucial to the adaptive immune system, are also elevated in MetS. This rise reflects a prolonged immune response to chronic low-grade inflammation, often associated with obesity and insulin resistance. Persistent inflammation in obese individuals disrupts normal immune function, resulting in continuous lymphocyte activation, which exacerbates insulin resistance, contributes to endothelial dysfunction, and accelerates atherosclerosis—all key factors in the progression of MetS [42, 43, 50].

Insulin resistance, a condition that hampers insulin's effectiveness in promoting glucose uptake in adipose and muscle tissues and reducing glucose production in the liver, can lead to the accumulation of inflammatory markers, including total leukocytes [51–54]. This inflammation can also reduce the production of prostacyclin and nitric oxide, compromising endothelial integrity

and function and leading to increased WBC counts and their subtypes, such as neutrophils and lymphocytes. Additionally, adipose tissue consistently expresses TNF- α , contributing to elevated leukocyte levels due to these proinflammatory cytokines [55].

On the other hand, the reduction of HDL-C in individuals with MetS is also attributed to several known factors. Chronic inflammation, characterized by increased pro-inflammatory cytokines such as TNF- α and IL-6, impairs HDL-C production and function, reducing its anti-inflammatory and antioxidant properties. Insulin resistance further contributes to dyslipidemia, decreasing HDL-C production and raising triglyceride levels. Moreover, adipose tissue dysfunction, particularly in visceral fat, leads to higher secretion of inflammatory cytokines, which not only increase systemic inflammation but also reduce HDL-C synthesis and accelerate its clearance from circulation [56–58].

The clinical significance of NHR and LHR lies in their potential as accessible and cost-effective biomarkers for predicting MetS. These ratios, derived from routine blood tests, provide a practical and reliable approach for early diagnosis and risk stratification, particularly given gender-specific differences. Their integration into clinical practice facilitates the early identification of individuals at elevated risk, allowing for preventing complications such as CVD and diabetes. Additionally, NHR and LHR are valuable for monitoring the effectiveness of therapeutic interventions, reinforcing their role in both the prevention and management of MetS. Their ease of measurement, affordability, and applicability across diverse healthcare settings make them vital tools for improving patient outcomes through early detection and tailored treatment strategies, ultimately contributing to enhanced population health [42, 43].

Strengths and limitations

The research's strengths include its use of a large, population-based cohort from the Bandar-Kong Non-Communicable Diseases study, which provides robust data on a broad demographic within southern Iran. This strengthens the reliability of the findings and makes them more representative of the local population. Additionally, the study's focus on simple, accessible hematological markers (NHR and LHR) for predicting MetS is a practical contribution, as these markers are easily measured in routine blood tests, making the findings potentially useful in standard clinical practice for early identification and monitoring of MetS risk. Moreover, the study's design allowed for a comprehensive analysis of associations between NHR and LHR and various MetS components, further supporting the value of these markers as diagnostic tools. The careful adjustment for potential confounders like age, gender, BMI, and physical activity levels adds

to the study's rigor, helping isolate the specific impact of these hematological indices on MetS.

This study has several limitations that should be acknowledged. First, the cross-sectional design restricts the ability to establish causality between the hematological indices (NHR and LHR) and the development of MetS. Although associations were identified, causal relationships cannot be inferred from this type of study. Second, the study was conducted within a specific geographic region of southern Iran, which may limit the generalizability of the findings to other populations or ethnic groups. Differences in genetic, environmental, and lifestyle factors could influence the applicability of these results to broader or more diverse populations.

Third, while the study adjusted for several confounding factors such as age, gender, BMI, and smoking status, there may still be unmeasured confounders that could affect the associations observed. Furthermore, there was not information regarding lactating. Fourth, the study did not include other potential inflammatory biomarkers or cytokines that could provide a more comprehensive understanding of the inflammatory processes involved in MetS. Inclusion of markers such as high-sensitivity hs-CRP or IL-6 could have enriched the analysis. Lastly, the reliance on self-reported data for some variables, such as alcohol consumption, physical activity and smoking status, may introduce bias due to inaccurate or incomplete reporting. Objective measurements or longitudinal data could help mitigate this issue in future research.

Conclusion

In conclusion, the study's findings underscore the value of LHR and NHR as effective tools for identifying individuals at risk for MetS, particularly in resource-limited clinical settings where cost and accessibility are critical factors. The strong correlations between these hematological indices and key components of MetS highlight their potential as practical, cost-effective markers for early detection and intervention. This could play a significant role in managing and preventing MetS-related complications. The clinical relevance of this study lies in the practical application of LHR and NHR as accessible and affordable markers that can be integrated into routine patient care. By using these indices for regular assessments, especially in low-resource environments, healthcare providers can identify at-risk individuals early, allowing for timely interventions to prevent severe complications, such as CVD and T2DM. Implementing LHR and NHR as part of standard MetS screening protocols would thus enhance proactive management and contribute to better patient outcomes.

However, it is important to recognize that baseline differences and varied responses among different populations may influence the strength and nature of

these associations. Therefore, future research, including meta-analyses, should aim to encompass a broader range of populations and include subgroup analyses and meta-regression. Such studies would enhance the understanding of how individual characteristics affect the relationship between LHR, NHR, and MetS, thereby refining the applicability and limitations of these markers in diverse clinical settings worldwide. These advancements could further support the development of targeted intervention thresholds, enhancing the effectiveness of MetS management in diverse patient populations.

Abbreviations

PERSIAN	Prospective Epidemiological Research Studies in Iran
BKNCD	Bandare-Kong Non-Communicable Diseases
MetS	Metabolic Syndrome
NCEP	National Cholesterol Education Program
BMI	Body Mass Index
CVD	Cardiovascular Disease
T2DM	Type 2 Diabetes Mellitus
BP	Blood Pressure
DBP	Diastolic Blood Pressure
SBP	Systolic Blood Pressure
FPG	Fasting Plasma Glucose
TG	Triglyceride
HDL	High-Density Lipoprotein
SIRI	Systemic Inflammation Response Index
SII	Systemic Immune-Inflammation Index
AISI	Aggregate Index of Systemic Inflammation
IL-6	Interleukin-6
TNF- α	Tumor necrosis factor- α
hs-CRP	high-sensitivity C-reactive protein

Supplementary Information

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Supplementary Material 1

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Author contributions

AR designed and supervised the study. SMH and PS wrote the manuscript. EAS and MHK consulted on the possible associated factors to be taken into account. SR analyzed and interpreted the data. MK performed the technical revision of the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study obtained informed consent from all subjects. For the vulnerable population, informed consent was obtained from parents or legal guardians.

The study protocol underwent thorough evaluation and received approval from the Ethics Committee of Hormozgan University of Medical Sciences (Ethics Code: IRC.HUMS.REC.1401.320), aligning with the ethical principles outlined in the Declaration of Helsinki.

Competing interests

The authors declare no competing interests.

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