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Neutrophil-to-lymphocyte ratio as a predictive marker of metabolic syndrome

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Abstract

Neutrophil-to-lymphocyte ratio (NLR) serves as a strong prognostic indicator for patients suffering from various diseases. Neutrophil activation promotes the recruitment of a number of different cell types that are involved in acute and chronic inflammation and are associated with cancer treatment outcome. Measurement of NLR, an established inflammation marker, is cost-effective, and it is likely that NLR can be used to predict the development of metabolic syndrome (MS) at an early stage. MS scores range from 1 to 5, and an elevated MS score indicates a greater risk for MS. Monitoring NLR can prevent the risk of MS.

A total of 34,013 subjects were enrolled in this study. The subjects (score 0–5) within the 6 groups were classified according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, and all anthropometrics, laboratory biomarkers, and hematological measurements were recorded. For the 6 groups, statistical analysis and receiver operating characteristic (ROC) curves were used to identify the development of MS.

Analysis of the ROC curve indicated that NLR served as a good predictor for MS. An MS score of 1 to 2 yielded an acceptable discrimination rate, and these rates were even higher for MS scores of 3 to 5 ($P < .001$), where the prevalence of MS was 30.8%.

NLR can be used as a prognostic marker for several diseases, including those associated with MS.

Abbreviations: CI = confidence intervals, CRP = C-reactive protein, DBP = diastolic blood pressure, DM = diabetes mellitus, Hb = hemoglobin, HbA1c = hemoglobin A1c, HDL-cholesterol = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, Hs-CRP = high-sensitivity CRP, Ht = hematocrit, IDF = International Diabetes Federation, LDL-cholesterol = low-density lipoprotein cholesterol, MS = metabolic syndrome, NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III, NLR = Neutrophil-to-lymphocyte ratio, OR = odds ratios, ROC = receiver operating characteristic, SBP = systolic blood pressure, WBC = white blood cells, WC = waist circumference.

Keywords: metabolic syndrome (MS), neutrophil-to-lymphocyte ratio (NLR)

1. Introduction

Neutrophils and lymphocytes constitute the first line of defense within the body against foreign invaders. Neutrophils and lymphocytes are the first inflammation and regulatory markers, respectively, found in injured areas. They activate major cell types involved in acute and chronic inflammation. The neutrophil-to-lymphocyte ratio (NLR), calculated by dividing the neutrophil count by the lymphocyte count, is used to determine the prognosis of an inflammatory reaction and is a component of routine blood count analyses performed in the clinic. Use of NLR as an inflammatory marker has been previously reported.[1–4] A recent study showed that NLR is a strong prognostic indicator for patients suffering from various diseases. Further, NLR has also been associated with poor clinical outcomes in a variety of diseases including myocardial infarction, coronary artery disease, atherosclerosis, chronic obstructive pulmonary disease, and high nuclear grade renal cell carcinoma in obese individuals.[5–11]

Earlier studies demonstrated an association between increased NLR and decreased overall survival and disease-free survival in melanoma, breast cancer, lung cancer, and gastrointestinal cancer.[12–15]

The association of metabolic syndrome (MS) with several biomarkers of inflammatory and chronic diseases is well documented. The reported prevalence of MS according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and International Diabetes Federation (IDF) criteria is 24% and 30%, respectively, and in mainland China, the reported prevalence of MS is 24.5%.[16–18] According to criteria of the American Heart Association, the prevalence of MS has recently risen to include 35% of adults in the US, and this increase is attributed to lifestyle changes. Nearly 50% of the individuals affected by MS are adults over the age of 60 years.[19–21] Obesity is

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also a major factor that contributes to the development of MS, and a study by Ryder et al indicated a high prevalence of MS in obese women.[22–25]

MS is not a disease, and instead refers to a cluster of individual risk factors. A number of prospective studies have identified elevated levels of circulating serum biomarkers or inflammatory markers such as white blood cells (WBC), C-reactive protein (CRP), and high-sensitivity CRP (Hs-CRP). These studies have also identified elevated hyperlipidemia markers such as total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-cholesterol), and high-density lipoprotein cholesterol (HDL-cholesterol). Additionally, studies have found elevated hyperglycemia markers, such as fasting blood glucose, hemoglobin A1c (HbA1c), insulin, and homeostasis model assessment of insulin resistance (HOMA-IR), in association with the kidney function marker uric acid. A combination of several factors characteristic of MS result in the development of various diseases.[23–29]

Recent studies indicated that MS is associated with many chronic inflammation risk factors, especially high levels of total leukocytes and NLR. NLR can be readily measured using a simple blood test to provide a convenient and cost-effective marker of systemic inflammation, and NLR measurements are used to identify the inflammatory state.[30–35] NLR can predict the prognosis of certain diseases and cancer treatment outcomes. We were interested in determining if NLR could be used as an indicator or predictor when an inflammatory reaction manifests as MS. The objective of this study was to identify inflammatory biomarkers that could help predict the risk of MS. Here, we used low-cost inflammatory indicators such as circulating leukocytes and NLR to predict the risk of MS and other diseases.

We propose that NLR, an inflammatory biomarker, may predict the development of MS at an early stage with MS scores 1 to 5, and we propose that a higher MS score may predict the risk for development of MS.

2. Materials and methods

2.1. Study population and design

This study included retrospectively collected patient data from 2006 to 2017. Adults (44,230) who underwent voluntary health evaluation at the Health Evaluation Center, Mackay Memorial Hospital, Taipei, Taiwan were included in the analysis. Subjects completed one health evaluation visit that included a complete physical examination. The exclusion criteria were:

(1) incomplete questionnaire or an incomplete drinking history questionnaire;
(2) incomplete anthropometric measurements;
(3) pregnant women;
(4) incomplete lab data;
(5) incomplete reports;
(6) subjects with self-reported diabetes mellitus (DM) or heart disease that were undergoing treatment.

Based on the above criteria, the final cohort study population consisted of 34,013 subjects. The flowchart of current study subjects and subjects excluded for final analysis design outlined in Figure 1. This study was approved by the local ethics committee of the Mackay Memorial Hospital (IRB No: 12MMHIS163).

All patient information was anonymized and de-identified prior to analysis. Approval to perform retrospective research using secondary data was granted by the Institutional Review Board (12MMHIS163), and our study was performed in accordance with the relevant guidelines and regulations.

2.2. Anthropometric measurements

Anthropometric measurements included those for height, weight, and BMI (calculated as weight [in kg] divided by the square of the height [in m]).

Blood pressure was recorded using a mercury sphygmomanometer (Diamond Deluxe BP apparatus, Industrial-Electronic and Allied Products, Pune, India) from the right arm when patients were in the sitting position, and the resulting values were rounded to the nearest 2 mm Hg.

Waist circumference (WC) was measured, using a measuring tape, at the umbilical level, and hip circumference was measured over non-restrictive underwear using a non-stretch fiber measuring tape.

MS score criteria According to the NCEP ATP III criteria, MS is defined according to the presence of at least 3 of the following 5 criteria: systolic blood pressure (SBP) $\geq$ 130 mm Hg or diastolic blood pressure (DBP) $\geq$ 85 mm Hg and/or use of anti-hypertensive medications; fasting glucose $\geq$ 100 mg/dL and/or use of anti-diabetic medications; hypertriglyceridemia $\geq$ 150 mg/dL, HDL-cholesterol levels $<$ 50 mg/dL for females and $<$ 40 mg/dL for males; WC: women $\geq$ 80 cm and men $\geq$ 90 cm.[16,17]

All subjects were classified into 6 groups. The subjects in the normal control group N (score of 0) had no history of smoking, drug use, or other high-risk habits, based on the questionnaire results. Groups 1 to 5 were sorted by MS scores of 1 to 5, based on responses to the questionnaires and MS score criteria.

2.3. Biochemical and hematological measurements

Laboratory analyses were performed at the hospital laboratories (TAF ISO-15189 accreditation). Blood samples were collected early in the morning after overnight (8–10 hours) fasting. Serum uric acid, cholesterol, triglycerides, HDL, LDL, glucose, CRP, and Hs-CRP levels were measured using a Hitachi-912 Autoanalyzer (Boehringer Mannheim/Hitachi, Mannheim, Germany). Plasma insulin levels were determined by a chemiluminescence immunoassay (IMMULITE 1000, Siemens Diagnostics, USA), and HOMA-IR was calculated using the method described by Mathews et al.[36] Serum insulin levels were analyzed using a human insulin-specific radioimmunoassay kit (Millipore, Billerica, MA). HbA1c levels were estimated using a Variant (Bio-Rad, Hercules, CA) high-pressure liquid chromatography machine.

Complete blood counts including WBC, red blood cell, hemoglobin (Hb), hematocrit (Ht), platelet, and leukocyte subtypes were determined using an autoanalyzer (Beckman Coulter Counter DXH series, Coulters Corporation, FL, USA). NLR was defined as the log e neutrophil count/log e lymphocyte count within the peripheral blood.

2.4. Statistical analysis

The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables are presented as mean $\pm$ standard deviation, while non-normally distributed variables are presented as median (range).

Categorical variables are presented as frequencies and percentages, and between-group differences were assessed using a Chi-square test.

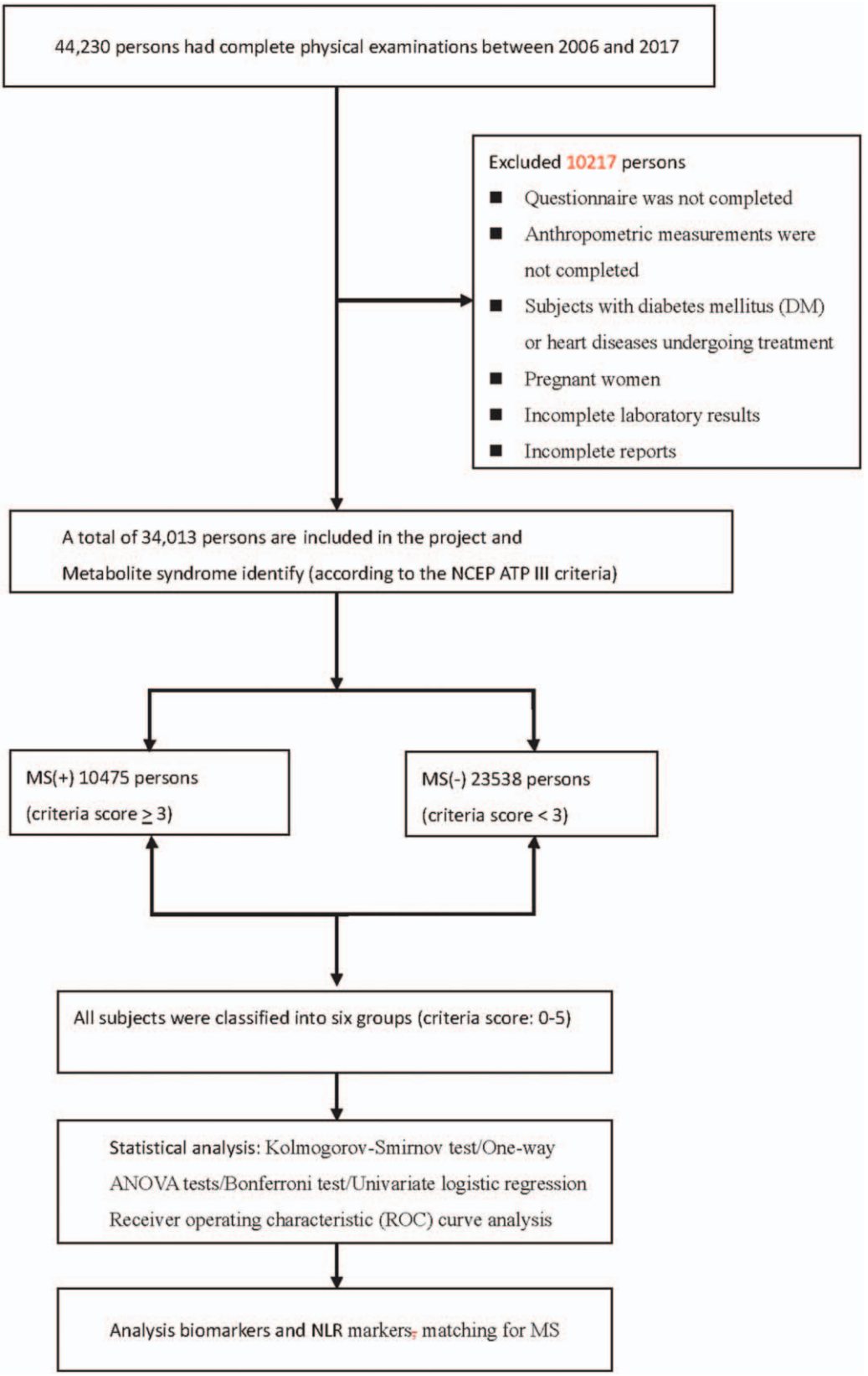

Figure 1. The flowchart of current study subjects and subjects excluded for final analysis design outlined.

Table 1

Baseline demographic and biochemical characteristics of the study population disaggregated by the presence or absence of MS.

Characteristic	MS Mean ± SD	95% CI	Non-MS Mean ± SD	95% CI	*P* value
Subjects, n (%)	10,475 (30.8%)		23,538 (69.2%)		
Age, years	50.46 ± 11.09	50.25–50.68	45.56 ± 11.08	45.42–45.7	<.001
Gender, male	7375 (70.2%)		11,681 (52.2%)		<.001
Smoking (%)	2955 (28.2%)		4104 (18.1%)		<.001
Anthropometric measurements					
Body mass index, kg/m^2	27.09 ± 3.46	27.02–27.15	23.29 ± 2.81	23.26–23.33	<.001
Waist circumference, cm	99.0 ± 6.9	98.9–99.1	80.3 ± 8.5	80.2–80.4	<.001
Systolic blood pressure, mm Hg	133.33 ± 16.3	133.01–133.64	117.15 ± 14.61	116.97–117.34	<.001
Diastolic blood pressure, mm Hg	82.02 ± 10.61	81.81–82.22	72.13 ± 9.95	72–72.26	<.001
Biochemical parameters					
Neutrophil-to-lymphocyte ratio	1.96 ± 0.77	1.95–1.98	1.84 ± 0.69	1.84–1.85	<.001
White blood cell, × 1,000/μL	6.83 ± 1.72	6.8–6.87	6.05 ± 1.45	6.03–6.07	<.001
Platelets, × 10^3/μL	254.62 ± 61.38	253.44–255.79	253.03 ± 57.26	252.29–253.76	.024
Cholesterol, mg/dL	205.63 ± 38.23	204.9–206.37	194.83 ± 34.69	194.39–195.28	<.001
Triglycerides, mg/dL	199.61 ± 102.06	197.65–201.56	110.02 ± 61.02	109.24–110.81	<.001
HDL, mg/dL	43.51 ± 10.85	43.29–43.72	56.45 ± 14.14	56.26–56.64	<.001
LDL, mg/dL	134.51 ± 34.78	133.83–135.19	125.08 ± 32.14	124.65–125.51	<.001
Fasting glucose, mg/dL	113.09 ± 30.6	112.5–113.68	96.41 ± 16.66	96.2–96.62	<.001
HbA1c, %	6.14 ± 1.14	6.11–6.17	5.57 ± 0.67	5.56–5.58	<.001
Insulin, μIU/mL	9.58 ± 7.83	9.27–9.89	5.59 ± 3.77	5.47–5.72	<.001
HOMO-IR	2.7 ± 2.38	2.6–2.79	1.32 ± 1.03	1.29–1.36	<.001
Uric acid, mg/dL	6.41 ± 1.49	6.38–6.44	5.4 ± 1.27	5.39–5.42	<.001
Hs-CRP, mg/dL	0.17 ± 0.61	0.15–0.19	0.11 ± 0.57	0.1–0.13	<.001
CRP, mg/dL	0.35 ± 0.55	0.33–0.37	0.25 ± 0.53	0.23–0.27	<.001

MS = metabolic syndrome.

Between-group differences with respect to continuous variables were assessed using Student *t* test or one-way ANOVA (with Tukey's HSD). Spearman correlation coefficient was determined to examine the association between MS and non-MS continuous variables, and post hoc sample size calculation was performed.

One-way ANOVA tests were used to compare the 6 groups, and 95% confidence intervals (CI) were obtained by Bonferroni test to avoid type I error. Univariate logistic regression was used to calculate the odds ratios (OR) and 95% CI for variables in the 6 groups, and these values were adjusted for BMI, smoking history, drinking history, CRP, age, and sex. Multivariate logistic regression incorporated intertwine to exclude confounders.

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value for biomarkers and NLR associated with maximum sensitivity and specificity for the development of MS.

3. Results

A total of 34,013 subjects were enrolled in this study. Of these, 10,475 (30.8%) subjects were categorized as positive for MS (score ≥ 3), while 23,538 (69.2%) were categorized as non-MS. Baseline demographic and biochemical characteristics included MS (score ≥ 3), age (mean ± SD, 50.46 ± 11.09), sex ratio (70.2% men), and active smokers (28.2%).

A significant between-group difference in NLR was observed (mean ± SD) in the MS compared to the non-MS groups (1.96 ± 0.77 vs 1.84 ± 0.69; $P < .001$) in regard to body mass index (BMI), WC, SBP, and DBP. All four parameters were significantly higher in the MS group ($P < .001$). Levels of inflammatory biomarkers (WBC, CRP, and Hs-CRP), hyperlipidemia markers (total cholesterol, triglycerides, and LDL-cholesterol), hyperglycemia markers, fasting blood glucose, HbA1c, insulin, HOMA-IR, and serum uric acid in the MS group were significantly higher than those observed in the non-MS group ($P < .001$ for all). The serum level of HDL-cholesterol in the MS group was significantly lower than that detected in the non-MS group (Table 1).

We categorized the study population into six groups based on the MS scores of the subjects. Study subjects possessing a 0 score were categorized as group N, while those with MS scores of 1 to 5 were categorized as groups 1 to 5, respectively (Table 2).

One-way analysis of variance (ANOVA) was used to compare the 6 groups and the 95% CI for NLR values (mean ± SD) among group N and groups 1 to 5. Statistical significance ($P < .001$) for all groups is shown in Table 2. The results of Bonferroni tests used to avoid type I error in multi-group comparisons are presented in Table 3.

The anthropometric measurements and the levels of WBC, triglycerides, fasting glucose, HbA1c, uric acid, and CRP exhibited a progressive increase from group N to groups 1 to 5. Insulin and HOMO-IR levels were normal in group N and groups 1 to 2; however, from group 3 to group 5, there was a significant increase in these levels. The HDL-cholesterol level exhibited a gradual decrease from group N to groups 1 to 5 ($P < .001$ for all). Box-and-whisker plots for all parameters are provided in Figures 2–4, and the results of univariate logistic regression are presented in Table 4. The OR for the development of MS in each of the five groups is shown using group N as the reference. Concerning the demographic characteristics, the overall range of OR associated with the respective variables was as follows: NLR, OR (95% CI) groups 1–5: 1.13 (1.08–1.18), 1.26 (1.2–1.32), 1.39 (1.32–1.45), 1.44 (1.36–1.52), and 1.45 (1.33–1.59), respectively. The between-group differences

Table 2

Baseline demographic and biochemical characteristics of the study population disaggregated by metabolic syndrome score.

Characteristic	Score 0		Score 1		Score 2		Score 3		Score 4		Score 5		*P* value
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
Subjects, n (%)	7177 (21.1%)		8429 (24.8%)		7932 (23.3%)		6363 (18.7%)		3192 (9.4%)		920 (2.7%)		
Age, years	40.17 ± 9.61	39.95–40.39	46.86 ± 10.56	46.63–47.08	49.1 ± 11	48.86–49.34	50.24 ± 11.19	49.97–50.52	50.74 ± 10.93	50.36–51.12	51.04 ± 10.87	50.34–51.74	<.001
Gender, male	2565 (42.6%)		3829 (45.4%)		5287 (66.7%)		4473 (70.3%)		2276 (71.3%)		608 (66.1%)		<.001
Smoking (%)	866 (12.4%)		1352 (16%)		1886 (23.8%)		1726 (27.1%)		979 (30.7%)		250 (27.2%)		<.001
Body mass index, kg/m^2	21.67 ± 2.06	21.63–21.72	23.19 ± 2.52	23.14–23.25	24.86 ± 2.83	24.8–24.92	26.54 ± 3.33	26.45–26.62	27.68 ± 3.39	27.56–27.79	28.87 ± 3.6	28.64–29.1	<.001
Waist Circumference, cm	74.5 ± 6.7	74.4–74.7	80.3 ± 7.5	80.1–80.4	85.6 ± 7.6	85.4–85.7	90.1 ± 8.3	89.9–90.3	93.1 ± 8.3	92.8–93.4	95.7 ± 8.6	95.2–96.3	<.001
Systolic blood pressure, mm Hg	109.37 ± 9.85	109.15–109.6	116.85 ± 13.52	116.56–117.14	124.59 ± 15.55	124.25–124.93	131.14 ± 16.46	130.74–131.55	135.46 ± 15.84	134.91–136.01	141 ± 13.21	140.15–141.86	<.001
Diastolic blood pressure, mm Hg	67.54 ± 7.92	67.36–67.73	71.81 ± 9.43	71.61–72.01	76.71 ± 10.14	76.49–76.93	80.61 ± 10.53	80.35–80.86	83.44 ± 10.43	83.07–83.8	86.84 ± 9.71	86.21–87.47	<.001
Biochemical parameters													
Neutrophil-to-lymphocyte ratio	1.79 ± 0.57	1.78–1.8	1.84 ± 0.71	1.83–1.86	1.9 ± 0.77	1.88–1.91	1.95 ± 0.77	1.93–1.97	1.97 ± 0.77	1.95–2	1.98 ± 0.73	1.93–2.03	<.001
White blood cell, ×1,000/μL	5.79 ± 1.16	5.77–5.82	5.97 ± 1.46	5.93–6	6.36 ± 1.62	6.33–6.4	6.7 ± 1.7	6.66–6.75	6.98 ± 1.74	6.92–7.04	7.21 ± 1.74	7.09–7.32	<.001
Platelets, × 10^3/μL	251.07 ± 53.17	249.84–252.3	253.52 ± 58.3	252.28–254.76	253.67 ± 59.66	252.36–254.97	253.87 ± 60.3	252.39–255.36	254.97 ± 61.81	252.83–257.12	258.53 ± 66.96	254.20–262.86	<.001
Cholesterol, mg/dL	173.96 ± 17.19	173.56–174.36	201.83 ± 35.9	201.06–202.6	206.65 ± 36.79	205.84–207.46	205.2 ± 38.38	204.26–206.15	206.63 ± 38.23	205.3–207.95	205.18 ± 37.12	202.77–207.58	<.001
Triglycerides, mg/dL	76.46 ± 25.75	75.86–77.06	104.04 ± 48.36	103–105.07	146.8 ± 74.66	145.16–148.44	177.85 ± 89.83	175.64–180.07	225.03 ± 104.96	221.39–228.67	260.92 ± 123.44	252.93–268.91	<.001
HDL, mg/dL	61.9 ± 12.28	61.6–62.2	58.04 ± 14.44	57.72–58.36	50.18 ± 12.9	49.89–50.47	45.88 ± 11.61	45.59–46.17	40.91 ± 8.91	40.6–41.23	36.67 ± 5.43	36.31–37.02	<.001
LDL, mg/dL	103.76 ± 18.35	103.31–104.21	131.22 ± 31.99	130.52–131.93	137.34 ± 32.6	136.61–138.07	135.38 ± 34.75	134.5–136.25	134 ± 34.84	132.77–135.22	130.48 ± 34.49	128.25–132.71	<.001
Fasting glucose, mg/dL	89.86 ± 5.74	89.73-90	95.93 ± 14.88	95.61–96.24	102.77 ± 21.7	102.3–103.25	109.28 ± 26.75	108.62–109.94	116.37 ± 32.39	115.24–117.49	128.05 ± 41.43	125.37–130.73	<.001
HbA1c, %	5.41 ± 0.31	5.4–5.42	5.57 ± 0.62	5.56–5.59	5.72 ± 0.9	5.69–5.74	6.01 ± 1.05	5.98–6.05	6.24 ± 1.17	6.19–6.29	6.62 ± 1.44	6.51–6.73	<.001
Insulin, μU/mL	5.38 ± 3.32	5.17–5.58	5.57 ± 3.77	5.36–5.78	5.8 ± 4.1	5.57–6.03	8.97 ± 8.93	8.51–9.44	10.18 ± 5.79	9.77–10.58	11.2 ± 6.15	10.42–11.98	<.001
HOMO-IR	1.21 ± 0.83	1.16–1.26	1.31 ± 1.02	1.26–1.37	1.43 ± 1.17	1.36–1.49	2.41 ± 2.51	2.28–2.54	2.94 ± 2.03	2.8–3.08	3.59 ± 2.34	3.3–3.89	<.001
Uric acid, mg/dL	5.03 ± 1.13	5.01–5.06	5.12 ± 0.98	5.1–5.14	6.03 ± 1.41	6–6.06	6.34 ± 1.48	6.3–6.38	6.49 ± 1.49	6.44–6.54	6.6 ± 1.57	6.49–6.7	<.001
Hs-CRP, mg/dL	0.1 ± 0.58	0.07–0.14	0.1 ± 0.53	0.07–0.13	0.14 ± 0.6	0.11–0.17	0.16 ± 0.65	0.13–0.19	0.15 ± 0.45	0.12–0.18	0.28 ± 0.72	0.19–0.37	<.001
CRP, mg/dL	0.25 ± 0.65	0.22–0.29	0.24 ± 0.52	0.21–0.27	0.26 ± 0.41	0.23–0.28	0.33 ± 0.62	0.3–0.37	0.35 ± 0.35	0.33–0.38	0.45 ± 0.62	0.37–0.53	<.001

with respect to OR (group 1–5) for all anthropometric parameters, age, BMI, WC, SBP, and DBP were all statistically significant ($P < .001$). For the biochemical parameters, the overall range of OR (groups 1–5) was determined for WBC, fasting glucose, HbA1c, insulin, HOMO-IR, uric acid, Hs-CRP, and CRP. OR increased for all parameters as MS score increased (Table 4).

Multivariate logistic regression after adjusting for BMI, smoking status, drinking history, CRP, age, and sex showed an increase in the OR for NLR and WC. In contrast to those of NLR and WC, OR of other markers decreased, with the exception of the MS score. Additionally, between-group differences (groups 1–5) were determined to be statistically significant ($P < .001$), with the exception of insulin levels. HOMO-IR markers from subjects with an MS score of 3 (group 3) were also statistically significant ($P < .001$) (Table 5).

To further support the utility of inflammatory biomarkers, hyperlipidemia markers, and hyperglycemia markers as useful predictors for MS, we performed Box-plot and ROC curve analyses to determine the diagnostic values of MS scores >3. The results for HbA1c, insulin, and HOMO-IR are presented in Figure 2, and those for CRP, uric acid, and WBC are shown in Figure 3. All markers allowed for acceptable discrimination.

Our premise that NLR can predict the development of MS at an early stage from MS groups 1 to 5 (scores 1–5) was tested by analyzing NLR Box-plots and ROC curves, as shown in Figure 4. These results allowed for acceptable discrimination for MS scores 1 to 2 and excellent discrimination for MS scores 3 to 5. These results confirmed that NLR is a good predictor for MS. Additionally, as MS score increases, NLR allows for a higher discrimination rate ($P < .001$).

4. Discussion

In our study population, the prevalence of MS was 30.8%, which is similar to the prevalence of 20.7% to 37.2% according to the ATP III definition and 29.6% to 36.2% according to the IDF definition. These figures are comparable to those reported in Asian populations where the prevalence of MS in men was 2.25 times higher than that in women.[16–19]

Compared to values from an earlier study, age distribution in our study showed a trend toward younger age in the 6 groups. Additionally, a higher percentage of subjects in our study were smokers (12.4% in group N and 30.7% in group 4). In our study, approximately 48.1% of the subjects were assigned MS scores of 1 to 2, demonstrating an increase in the prevalence of MS with age but not with smoking status.[20–22]

Baseline demographics of the MS and non-MS groups indicated NLR values (mean ± SD) of 1.96 ± 0.77 and 1.84 ± 0.69, respectively, and these values are similar to those published previously.[37] The normal range of NLR in this report was 1.76 ± 1.42. Two studies (Buyukkaya et al and Surendar et al) reported NLR values of 1.89 ± 0.72 and 2.92 ± 0.83 ($P < .001$) and 1.68 ± 0.63 and 2.10 ± 0.70 ($P < .001$) in the MS (negative) and MS (positive) subjects, respectively. In our study, NLR values in the MS-negative subjects were similar to the above results, but these values were lower in the MS-positive subjects. These results could be attributed to the fact that our study contained a smaller number of subjects (10,475 [30.8%]) with an MS score ≥ 3 compared to 23,538 (69.2%) non-MS subjects, and this discrepancy may contribute to lower NLR ratios.[33,35]

A significant between-group difference was observed between the MS and non-MS groups with respect to BMI, WC, SBP, and

Table 3

Bonferroni test comparison of *P* values among multiple groups.

	Score 1	Score 2		Score 3			Score 4				Score 5				
vs. Score	Score0	Score0	Score1	Score0	Score1	Score2	Score0	Score1	Score2	Score3	Score0	Score1	Score2	Score3	Score4
No. of subjects															
Age, y	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.439*	<0.001	<0.001	<0.001	0.501*	1*
Gender, male															
Smoking, (%)															
Body mass index, kg/m^2	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Waist Circumference, cm	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Systolic blood pressure, mm Hg	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Diastolic blood pressure, mm Hg	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Biochemical parameters															
Neutrophil-to-lymphocyte ratio	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	1*	<0.001	<0.001	0.01*	1*	1*
White blood cell, $\times$ 1,000/μL	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
Platelets, $\times 10^3/\mu$L	0.135*	0.094*	1*	0.081*	1*	1*	0.026*	1*	1*	1*	0.004*	0.206*	0.256*	0.364*	1*
Cholesterol, mg/dL	<0.001	<0.001	<0.001	<0.001	<0.001	0.166*	<0.001	<0.001	1*	0.795*	<0.001	0.068*	1*	1*	1*
Triglycerides, mg/dL	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HDL, mg/dL	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
LDL, mg/dL	<0.001	<0.001	<0.001	<0.001	<0.001	0.003*	<0.001	<0.001	<0.001	0.636*	<0.001	1*	<0.001	<0.001	0.036*
Fasting glucose, mg/dL	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HbA1c, %	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Insulin, μIU/mL	1*	1*	1*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	0.243*
HOMO-IR	1*	0.033*	1*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Uric acid, mg/dL	0.001*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.41*
Hs-CRP, mg/dL	1*	1*	1*	0.155*	0.093*	1*	0.781*	0.586*	1*	1*	<0.001	<0.001	0.003*	0.025*	0.027*
CRP, mg/dL	1*	1*	1*	0.005*	<0.001	0.003*	0.001*	<0.001	0.001*	1*	<0.001	<0.001	<0.001	0.04*	0.317*

* Bonferroni.

DBP. All four parameters were significantly higher in the MS group ($P < .001$).

Levels of inflammatory biomarkers (WBC, CRP, and Hs-CRP), hyperlipidemia markers (total cholesterol, triglycerides, and LDL-cholesterol), and hyperglycemia markers (fasting blood glucose, HbA1c, insulin, HOMA-IR, and serum uric acid) were significantly ($P < .001$) increased in subjects with MS compared to those in non-MS subjects whose mean ± SD values were within reference intervals. Biochemical analyses demonstrated increased levels of markers of chronic inflammation in subjects with MS, consistent with earlier studies. This observation is of clinical relevance, as these markers may help predict the development of MS. Additionally, earlier studies demonstrated an association of these markers with MS and other diseases.[23–25]

We performed ANOVA to compare the six groups, and the 95% CIs are shown in Table 2. To avoid type I error, we performed the Bonferroni post hoc test for correction of multi-group comparisons, and certain biomarkers did not exhibit significant between-group differences (Table 3).

NLR values (mean ± SD) in subjects with MS scores of 1 to 5 increased gradually. Similarly, increases were observed in BMI, WC, SBP, and DBP, with the exception of group N, where levels were within normal ranges. All tested parameters were increased in groups 1 to 5, and in particular, there was a greater difference between groups 2 and 3. With respect to all markers, a progressive increase in mean ± SD was observed in groups 1 to 5, with the exception of HDL levels that exhibited a gradual decrease that is consistent with earlier reports.

Similar studies Surendar et al. (subjects n = 754), and Ge Meng et al (subjects n = 6312), all inflammatory markers were shows associations with MS (all *P* values <.05). NLR value in MS scores of 1 to 5, 2 studies results are different and decreased then our study. It is interested that NLR has a significant association with MS (Surendar et al); and Meng et al demonstrated was not, even though necessitate further studies to suggest.[35,38]

Notably, univariate logistic regression results for the five groups demonstrated an increase in OR for all markers, with the exception of platelet, insulin, Hs-CRP, and CRP, in group 1 (MS score 1) to group 5 (MS score 5) with a *P* value <.001. An elevation in odds risk was observed as a function of increased MS score. In particular, ORs for BMI, WC, NLR, WBC, HbA1c, HOMA-IR, uric acid, and CRP markers were significantly higher in the MS group ($P < .001$) than those in the control group.

For multivariate logistic regression analysis after adjusting for BMI, smoking, drinking, CRP, age, and sex, however, OR for HbA1c increased in groups 1 to 5 from 2.18 to 6.56. Previous reports indicated that such an increase in OR for HbA1c was likely due to DM instead of MS. In this study, the OR for HbA1c in individual with MS scores of 1 to 5 was higher than those of other markers, and these values were high compared to those found in other diseases. These finding warrant further investigation.

In subjects with an increase in MS score, NLR, and WC, the ORs of HbA1c, insulin, HOMA-IR, uric acid, and WBC were decreased. Our results and the results of previous studies indicate that these markers, can be considered low-cost biomarkers to

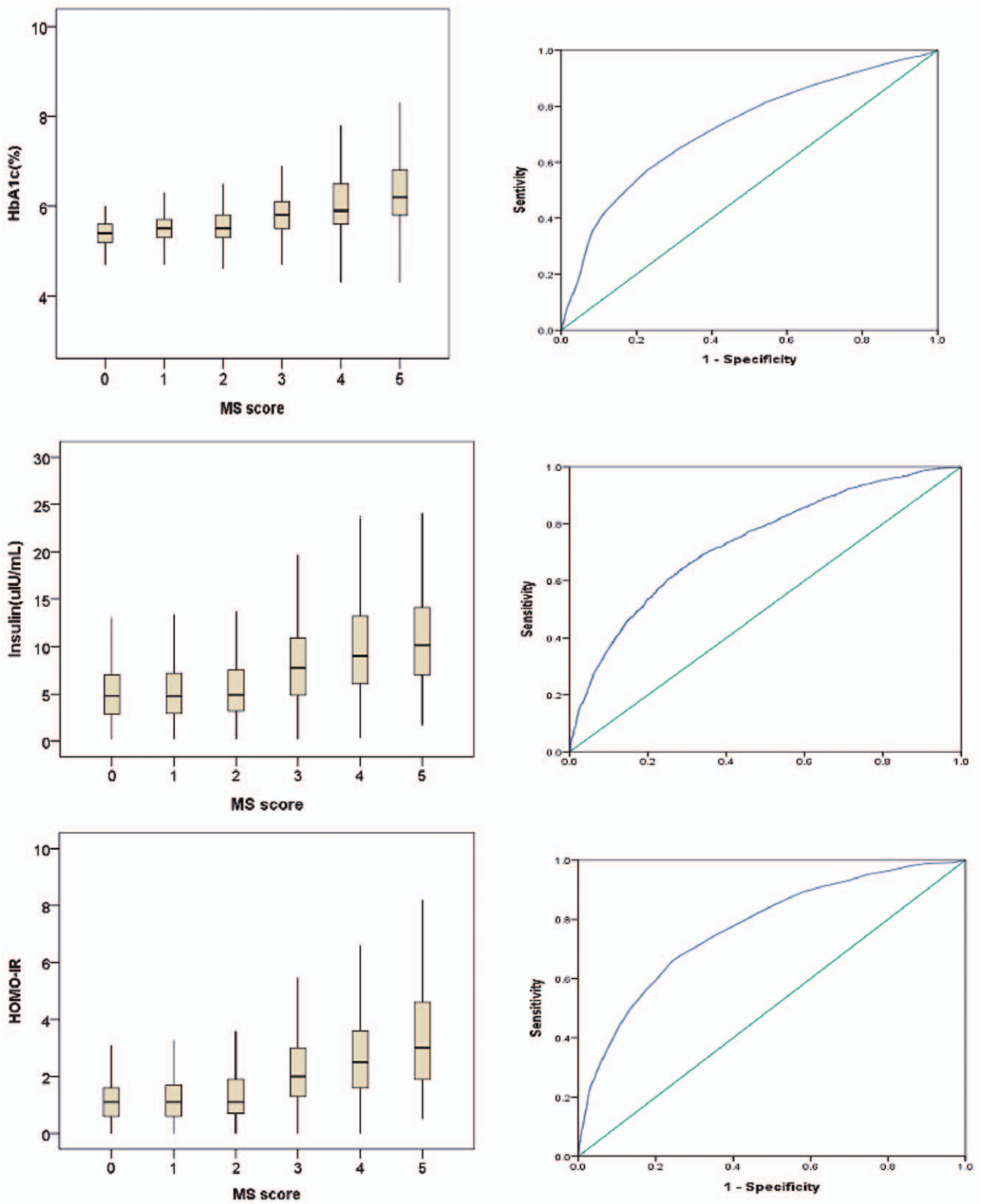

Figure 2. Box-plot and receiver operating characteristic curve for metabolic syndrome (+) representation of HbA1c, insulin, and HOMO-IR; HbA1c AUC = 0.72 ($P < .001$); Insulin AUC = 0.73 ($P < .001$); HOMO-IR AUC = 0.77 ($P < .001$). HOMA-IR = homeostasis model assessment of insulin resistance.

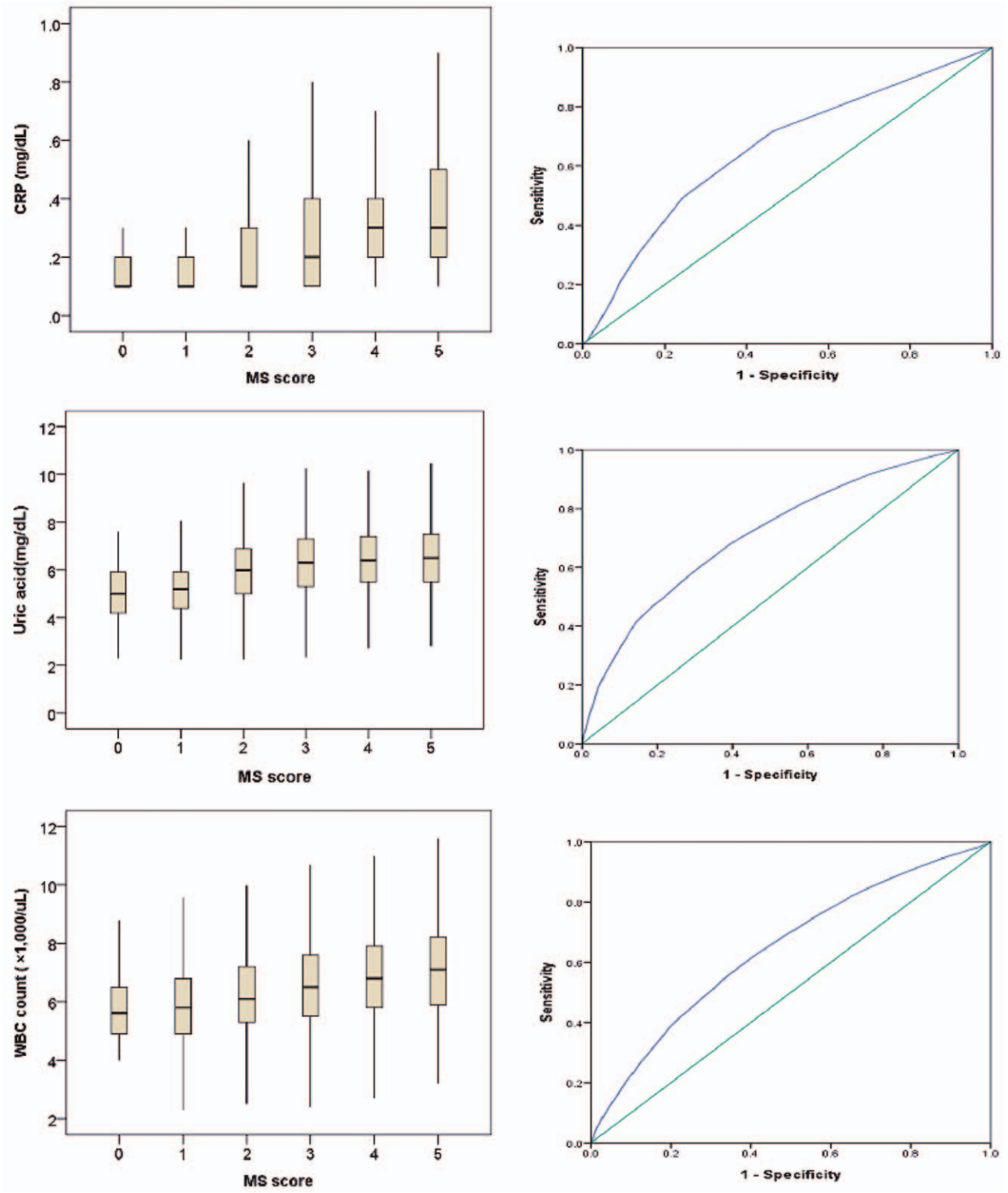

Figure 3. Box-plot and receiver operating characteristic curve for metabolic syndrome (+) representation of CRP, uric acid, and WBC; CRP AUC = 0.66 ($P < .001$); Uric acid AUC = 0.70 ($P < .001$); WBC AUC = 0.64 ($P < .001$). CRP = C-reactive protein, WBC = white blood cells.

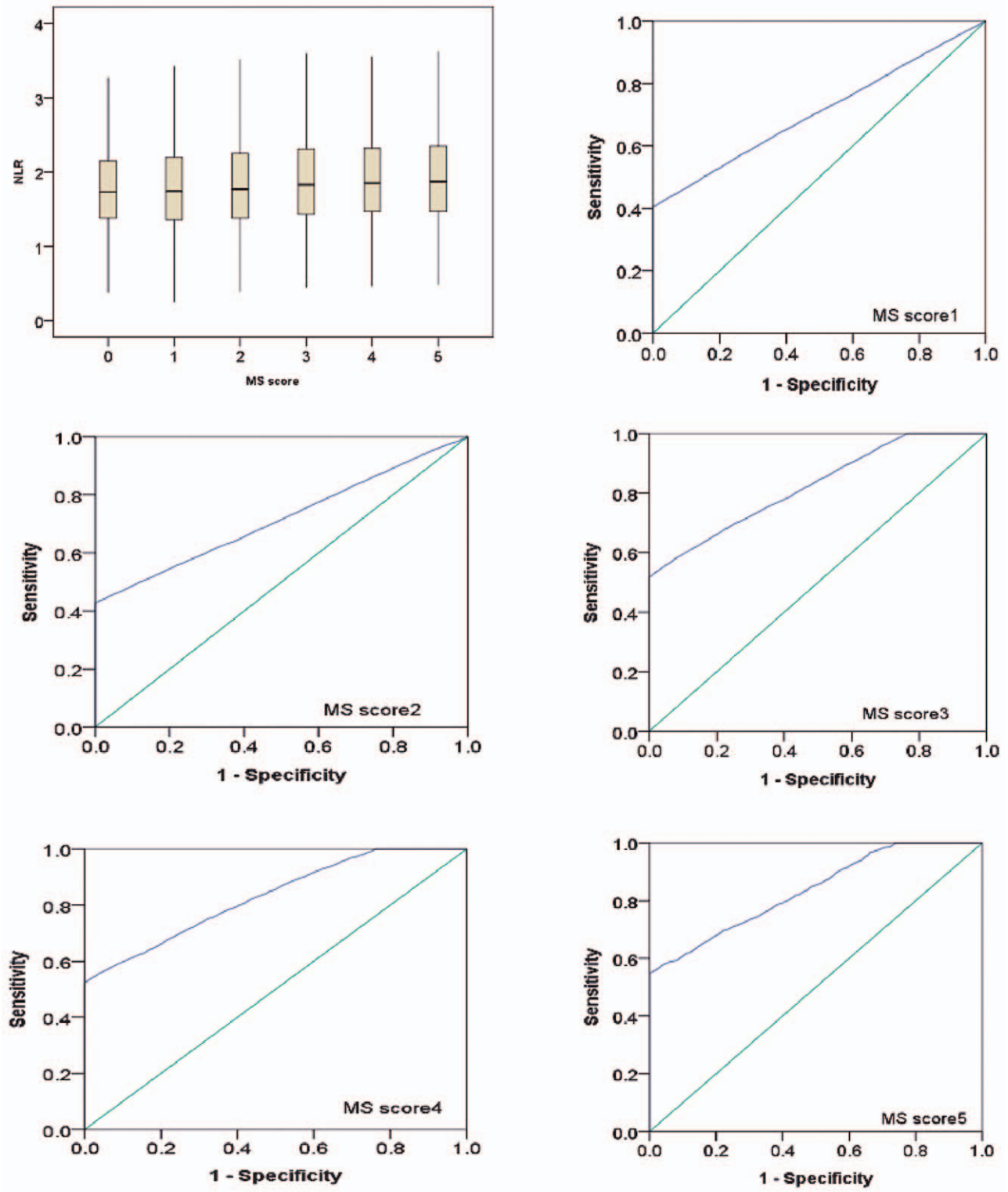

Figure 4. Box-plot and receiver operating characteristic curve for metabolic syndrome 1 to 5 representation of neutrophil-to-lymphocyte ratio. Group 1 AUC = 0.71 ($P < .001$); group 2 AUC = 0.72 ($P < .001$); group 3 AUC = 0.82 ($P < .001$), group 4 AUC = 0.83 ($P < .001$), group 5 AUC = 0.83 ($P < .001$). Positive predictive value was 70.7 (60.2–79.7), and negative predictive value was 89.8 (77.6–98.7).

Table 4

Results of univariate logistic regression indicating the odds ratios and 95% CI between variables in 5 groups.

	1			2			3			4			5		
	OR	*P* value	95% CI	OR	*P* value	95% CI	OR	*P* value	95% CI	OR	*P* value	95% CI	OR	*P* value	95% CI
Age	1.07	<.001	1.06–1.07	1.09	<.001	1.08–1.09	1.1	<.001	1.09–1.1	1.1	<.001	1.1–1.11	1.11	<.001	1.1–1.11
Body mass index	1.33	<.001	1.31–1.35	1.71	<.001	1.68–1.74	2.08	<.001	2.05–2.12	2.3	<.001	2.26–2.34	2.48	<.001	2.42–2.54
Waist Circumference	1.12	<.001	1.11–1.12	1.23	<.001	1.22–1.24	1.33	<.001	1.32–1.34	1.39	<.001	1.38–1.4	1.43	<.001	1.42–1.45
Systolic blood pressure	1.05	<.001	1.05–1.06	1.1	<.001	1.09–1.1	1.13	<.001	1.13–1.13	1.15	<.001	1.14–1.15	1.17	<.001	1.16–1.17
Diastolic blood pressure	1.05	<.001	1.05–1.06	1.11	<.001	1.11–1.12	1.16	<.001	1.15–1.16	1.19	<.001	1.18–1.2	1.22	<.001	1.21–1.23
Neutrophil-to-lymphocyte ratio	1.13	<.001	1.08–1.18	1.26	<.001	1.2–1.32	1.39	<.001	1.32–1.45	1.44	<.001	1.36–1.52	1.45	<.001	1.33–1.59
White blood cell	1.11	<.001	1.08–1.13	1.34	<.001	1.31–1.37	1.53	<.001	1.49–1.57	1.67	<.001	1.62–1.71	1.77	<.001	1.7–1.84
Platelets	1.001	.009	1–1.001	1.001	.006	1–1.001	1.001	.005	1–1.001	1.001	.002	1–1.002	1.002	<.001	1.001–1.003
Cholesterol	1.03	<.001	1.03–1.03	1.034	<.001	1.03–1.03	1.033	<.001	1.03–1.03	1.034	<.001	1.03–1.04	1.033	<.001	1.03–1.03
Triglycerides	1.023	<.001	1.02–1.02	1.04	<.001	1.04–1.04	1.046	<.001	1.04–1.05	1.051	<.001	1.05–1.05	1.053	<.001	1.05–1.05
HDL	0.98	<.001	0.98–0.98	0.94	<.001	0.93–0.94	0.9	<.001	0.9–0.91	0.85	<.001	0.85–0.86	0.79	<.001	0.78–0.8
LDL	1.035	<.001	1.03–1.04	1.041	<.001	1.04–1.04	1.039	<.001	1.04–1.04	1.038	<.001	1.04–1.04	1.034	<.001	1.03–1.04
Fasting glucose	1.11	<.001	1.1–1.11	1.17	<.001	1.16–1.17	1.18	<.001	1.18–1.19	1.19	<.001	1.19–1.2	1.2	<.001	1.19–1.2
HbA1c	2.37	<.001	2.14–2.61	3.77	<.001	3.43–4.15	5.81	<.001	5.29–6.39	6.75	<.001	6.12–7.44	7.87	<.001	7.1–8.73
Insulin	1.02	.17	0.99–1.04	1.04	<.001	1.01–1.06	1.23	<.001	1.2–1.26	1.26	0	1.23–1.29	1.27	<.001	1.24–1.31
HOMO-IR	1.15	<.001	1.05–1.27	1.33	<.001	1.21–1.46	2.52	<.001	2.3–2.75	2.9	<.001	2.64–3.18	3.08	<.001	2.79–3.4
Uric acid	1.07	<.001	1.04–1.1	1.93	<.001	1.87–1.98	2.27	<.001	2.2–2.34	2.44	<.001	2.36–2.53	2.56	<.001	2.44–2.7
Hs-CRP	0.99	.91	0.83–1.19	1.15	.09	0.98–1.35	1.22	.01	1.05–1.43	1.21	.03	1.02–1.43	1.43	<.001	1.2–1.71
CRP	0.83	.23	0.61–1.13	1.02	.9	0.77–1.35	1.59	<.001	1.25–2.02	1.65	<.001	1.29–2.12	1.81	<.001	1.4–2.35
Gender, male	1.15	0	1.08–1.23	2.75	0	2.58–2.94	3.25	0	3.03–3.49	3.41	0	3.12–3.73	2.68	0	2.32–3.09
Non-smoking	0.86	<.001	0.79–0.94	0.53	<.001	0.48–0.57	0.44	<.001	0.4–0.48	0.37	<.001	0.34–0.41	0.44	<.001	0.38–0.52

allow for the prediction of MS with an MS score cut-off value of 3 and an elevated OR.

To determine if the above marker/s are reliable for the prediction of MS, we performed Box-plot and ROC curve analysis. ROC AUC values for HbA1c 0.72 (95% CI:0.71–0.73, $P < .001$), insulin 0.73 (95% CI:0.72–0.75, $P < .001$), HOMO-IR 0.77 (95% CI:0.76–0.78, $P < .001$), CRP 0.66 (95% CI:0.64–0.67, $P < .001$), uric acid 0.70 (95% CI:0.69–0.71, $P < .001$), and WBC 0.64 (95% CI:0.63–0.65, $P < .001$) were between 0.64 and 0.77, the sensitivity was between 0.65 and 0.72, and the specificity values were between 0.53 and 0.69 ($P < .001$). All markers from ROC analysis allowed for acceptable discrimination as good predictive markers.

We analyzed the NLR Box-plot and ROC curve to verify our hypothesis and to determine the NLR cut-off level, AUC, 95% CI, *P* value, sensitivity, and specificity. ROC analysis of subjects with MS scores of 1 to 2 revealed acceptable discrimination and specificity (0.98), and ROC analysis of patients with MS scores of 3 to 5 revealed excellent discrimination and specificity (0.98, 0.96, 0.94, respectively). Therefore, NLR may serve as a useful predictor of MS and increases in MS score and NLR values allow for a higher discrimination rate ($P < .001$).

Table 5

Results of multivariate logistic regression indicating the odds ratios and 95% CI between variables in 5 groups.

	1			2			3			4			5		
	OR	*P* value	95% CI	OR	*P* value	95% CI	OR	*P* value	95% CI	OR	*P* value	95% CI	OR	*P* value	95% CI
Waist Circumference	1.14	<.001	1.14–1.15	1.25	<.001	1.24–1.26	1.37	<.001	1.36–1.38	1.43	<.001	1.42–1.45	1.49	<.001	1.47–1.50
Systolic blood pressure	1.04	<.001	1.04–1.05	1.09	<.001	1.08–1.09	1.11	<.001	1.11–1.12	1.13	<.001	1.12–1.14	1.15	<.001	1.14–1.16
Diastolic blood pressure	1.04	<.001	1.03–1.04	1.08	<.001	1.08–1.09	1.13	<.001	1.13–1.14	1.16	<.001	1.15–1.17	1.2	<.001	1.19–1.21
White blood cell	1.15	<.001	1.1–1.19	1.35	<.001	1.3–1.4	1.44	<.001	1.38–1.5	1.55	<.001	1.48–1.62	1.6	<.001	1.51–1.7
Platelets	1	<.001	1–1	1	<.001	1–1.01	1.01	<.001	1–1.01	1.01	<.001	1.01–1.01	1.01	<.001	1.01–1.01
Neutrophil-to-lymphocyte ratio	1.18	<.001	1.1–1.27	1.4	<.001	1.3–1.51	1.53	<.001	1.41–1.66	1.59	<.001	1.45–1.74	1.66	<.001	1.3–2.11
Cholesterol	1.03	<.001	1.03–1.03	1.03	<.001	1.03–1.03	1.03	<.001	1.03–1.03	1.03	<.001	1.03–1.03	1.03	<.001	1.03–1.03
Triglycerides	1.02	<.001	1.02–1.02	1.04	<.001	1.03–1.04	1.04	<.001	1.04–1.05	1.05	<.001	1.05–1.05	1.05	<.001	1.05–1.05
HDL	0.97	<.001	0.97–0.98	0.93	<.001	0.93–0.94	0.89	<.001	0.88–0.89	0.82	<.001	0.81–0.83	0.74	<.001	0.73–0.75
LDL	1.03	<.001	1.03–1.04	1.04	<.001	1.03–1.04	1.03	<.001	1.03–1.04	1.03	<.001	1.03–1.04	1.03	<.001	1.03–1.03
Fasting glucose	1.1	<.001	1.1–1.11	1.14	<.001	1.14–1.15	1.14	<.001	1.13–1.15	1.15	<.001	1.14–1.15	1.15	<.001	1.14–1.16
HbA1c	2.8	<.001	2.23–3.5	3.75	<.001	2.99–4.72	4.54	<.001	3.6–5.72	5.5	<.001	4.35–6.95	6.56	<.001	5.15–8.35
Hs-CRP	0.95	.58	0.81–1.13	1.03	.77	0.86–1.22	0.99	.94	0.83–1.19	0.89	.28	0.72–1.1	0.99	.91	0.78–1.25
Insulin	1	.81	0.97–1.02	0.99	.61	0.96–1.02	1.16	<.001	1.12–1.19	1.18	<.001	1.14–1.21	1.18	<.001	1.14–1.22
HOMO-IR	1.01	.9	0.9–1.12	1.03	.59	0.92–1.16	1.82	<.001	1.62–2.04	1.95	<.001	1.73–2.19	2	<.001	1.77–2.27
Uric acid	0.93	<.001	0.88–0.98	1.63	<.001	1.55–1.72	1.87	<.001	1.77–1.98	1.98	<.001	1.87–2.11	2.15	<.001	1.99–2.33

5. Conclusion

Risk of MS increases as NLR increases, and NLR values may provide a useful tool to predict the development of MS.

6. Limitations

One of the limitations of our study is that the study subjects underwent a health examination and may or may not have been diagnosed with a comorbidity. This was a retrospective observational study that only included patients from relatively high-income groups and health awareness, which may not represent the general population. Our results, however, showed a relationship between many of the biomarkers with respect to their role in MS, especially in subjects with MS scores between 1 and 2, who accounted for 48.1% of the study population. Early detection and early intervention are possible in subjects with these scores to prevent the onset of MS.

Although this study involved prospective patient enrollment and follow-up, the study design was observational in nature and subject to limitations, including selection bias and uncorrected confounding.

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References

[1] Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol 2013;13:159–75.
[2] Oncel RC, Ucar M, Karakas MS, et al. Relation of neutrophil-to-lymphocyte ratio with GRACE risk score to in-hospital cardiac events in patients with ST-segment elevated myocardial infarction. Clin Appl Thromb Hemost 2015;21:383–8.
[3] Horne BD, Anderson JL, John JM, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005;45: 1638–43.
[4] Karakas MS, Korucuk N, Tosun V, et al. Red cell distribution width and neutrophil-to-lymphocyte ratio predict left ventricular dysfunction in acute anterior ST-segment elevation myocardial infarction. J Saudi Heart Assoc 2016;28:152–8.
[5] Williams BA, Merhige ME. Association between neutrophil-lymphocyte ratio and impaired myocardial perfusion in patients with known or suspected coronary disease. Heart Lung 2013;42:436–41.
[6] Chen J, Chen MH, Li S, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting the severity of coronary artery disease: a Gensini score assessment. J Atheroscler Thromb 2014;21:1271–82.
[7] Verdoia M, Schaffer A, Barbieri L, et al. Impact of diabetes on neutrophil-to-lymphocyte ratio and its relationship to coronary artery disease. Diabetes Metab 2015;41:304–11.
[8] Balta S, Celik T, Mikhailidis DP, et al. The relation between atherosclerosis and the neutrophil-lymphocyte ratio. Clin Appl Thromb Hemost 2016;22:405–11.
[9] Kalay N, Dogdu O, Koc F. Hematologic parameters and angiographic progression of coronary atherosclerosis. Angiology 2012;63:213–7.
[10] de Martino M, Pantuck AJ, Hofbauer S, et al. Prognostic impact of preoperative neutrophil-to-lymphocyte ratio in localized nonclear cell renal cell carcinoma. J Urol 2013;190:1999–2004.
[11] Yasar Z, Buyuksirin M, Ucsular FD, et al. Is an elevated neutrophil-to-lymphocyte ratio a predictor of metabolic syndrome in patients with chronic obstructive pulmonary disease? Eur Rev Med Pharmacol Sci 2015;19:956–62.
[12] Azab B, Shah N, Radbel J, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol 2013;30:432.
[13] Junjie Ma , Kuzman J, Ray A, et al. Neutrophil-to-lymphocyte Ratio (NLR) as a predictor for recurrence in patients with stage III melanoma. Sci Rep 2018;8:4044.
[14] Bowen RC, Little NAB, Harmer JR, et al. Neutrophil-to-lymphocyte ratio as prognostic indicator in gastrointestinal cancers: a systematic review and meta-analysis. Oncotarget 2017;8:32171–89.
[15] Shimada H, Takiguchi N, Kainuma O, et al. High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer 2010;13:170–6.
[16] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[17] Grundy SM, Brewer HBJr, Cleeman JI, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/ American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–8.
[18] Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am 2014;43:1–23.
[19] Beltrán-Sánchez H, Harhay MO, Harhay MM, et al. Prevalence and trends of Metabolic Syndrome in the adult U.S. population, 1999-2010. J Am Coll Cardiol 2013;62:697–703.
[20] Aguilar M, Bhuket T, Torres S, et al. Prevalence of the metabolic syndrome in the United States, 2003-2012. JAMA 2015;313:1973–4.
[21] Li R, Li W, Lun Z, et al. Prevalence of metabolic syndrome in mainland china: a meta-analysis of published studies. BMC Public Health 2016;16:296.
[22] Otsuka R, Imai T, Kato Y, et al. Relationship between number of metabolic syndrome components and dietary factors in middle-aged and elderly Japanese subjects. Hypertens Res 2010;33:548–54.
[23] Esser N, Legrand-Poels S, Piette J, et al. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract 2014;105:141–50.
[24] Kelly AS, Jacobs DRJr, Sinaiko AR, et al. Relation of circulating oxidized LDL to obesity and insulin resistance in children. Pediatr Diabetes 2010;11:552–5.
[25] Oliver E, McGillicuddy F, Phillips C, et al. The role of inflammation and macrophage accumulation in the development of obesity-induced type 2 diabetes mellitus and the possible therapeutic effects of long-chain n-3 PUFA. Proc Nutr Soc 2010;69:232–43.
[26] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and (-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412–9.
[27] Rezaianzadeh A, Namayandeh SM, Sadr SM. National Cholesterol Education Program adult treatment Panel III Versus International Diabetic Federation Definition of Metabolic Syndrome, which one is associated with diabetes mellitus and coronary artery disease? Int J Prev Med 2012;3:552–8.
[28] Fagerberg B, Hultén LM, Hulthe J. Plasma ghrelin, body fat, insulin resistance, and smoking in clinically healthy men: the atherosclerosis and insulin resistance study. Metab Clin Exp 2003;52:1460–3.
[29] Lee JM, Kim JH, Son HS, et al. Valsartan increases circulating adiponectin levels without changing HOMA-IR in patients with type 2 diabetes mellitus and hypertension. J Int Med Res 2010;38:234–41.
[30] Gupta A, Gupta V. Metabolic syndrome: what are the risks for humans? Biosci Trends 2010;4:204–12.
[31] Welty FK, Alfaddagh A, Elajami TK. Targeting inflammation in metabolic syndrome. Transl Res 2016;167:257–80.
[32] Srikanthan K, Feyh A, Visweshwar H, et al. Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the west Virginian population. Int J Med Sci 2016;13:25–38.
[33] Buyukkaya E, Karakas MF, Karakas E, et al. Correlation of neutrophil to lymphocyte ratio with the presence and severity of metabolic syndrome. Clin Appl Thromb Hemost 2014;20:159–63.
[34] Bahadır A, Baltacı D, Türker Y, et al. Is the neutrophil-to-lymphocyte ratio indicative of inflammatory state in patients with obesity and metabolic syndrome? Anatol J Cardiol 2015;10:816–22.

[35] Surendar J, Indulekha K, Mohan V, et al. Association of neutrophil-lymphocyte ratio with metabolic syndrome and its components in Asian Indians (CURES-143). J Diabetes Complic 2016;30:1525–9.
[36] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
[37] Forget P, Khalifa C, Defour JP, et al. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes 2017; 10:12.
[38] Meng G, Zhu Q, Shao J, et al. Comparing the diagnostic ability of inflammatory markers in metabolic syndrome. Clinica Chimica Acta 2017;475:1–6.