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ORIGINAL RESEARCH

Correlation of White Blood Cell, Neutrophils, and Hemoglobin with Metabolic Syndrome and Its Components

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Background: Metabolic syndrome (MetS) is a global health problem. White blood cell (WBC), neutrophils and neutrophil-to-lymphocyte ratio (NLR) are valid indicators involved in acute and chronic inflammation. The aims of our study were to analyze the correlation and severity of these indicators with MetS and its components, and explore the diagnostic value of their combined tests for MetS.

Methods: A total of 7726 subjects were recruited, and laboratory biomarkers were collected. The differences of indicators between MetS group and non-MetS group were analyzed. The linear trend between each indicator and the increasing number of metabolic disorders was analyzed using trend variance test. The correlation between each indicator and MetS with its components was analyzed by logistic regression.

Results: The levels of WBC, neutrophil, and hemoglobin grew significantly in the MetS group compared to non-MetS group, and gradually increased with the increased number of MetS disorders. Logistic regression analysis indicated significant correlations between WBC, neutrophils, and hemoglobin with MetS and its components. ROC curve analysis showed WBC, neutrophils, and hemoglobin served as good predictors for MetS, especially in adults aged under 40.

Conclusion: Our study indicated that WBC, neutrophils, and hemoglobin are efficient indicators for predicting MetS and evaluate its severity.

Keywords: white blood cell, neutrophils, hemoglobin, neutrophil-to-lymphocyte ratio, metabolic syndrome

Introduction

Metabolic syndrome (MetS), characterized by a series of metabolic disorders, such as abdominal obesity, hypertension, insulin resistance, and hyperlipidemia, is not a single disease, but a set of risk factors for cardiovascular disease.[1] Furthermore, cancer, subclinical hypothyroidism, diseases of renal system are also associated with MetS.[2–5] The International Diabetes Federation (IDF) estimates that about one-fourth of the world population diagnosed MetS.[6] Based on data from China Nutrition and Health Surveillance (2015–2017), the standardized prevalence of MetS was 31.1% among Chinese residents aged over 20.[7] At present, the prevalence of MetS increases dramatically, and become one of the major health hazard of the modern world. Therefore, it is urgent to improve the prognosis of MetS patients by early diagnosis and treatment.

Previous studies confirmed that insulin resistance, endothelial dysfunction, chronic oxidative stress, and systemic inflammation contribute to tissue fibrosis, atherogenesis, and subsequently MetS.[8,9] WBC, neutrophils, hemoglobin, platelet, and NLR were considered to be simple makers of systemic inflammatory responses. Nevertheless, the relationship between those hematological parameters and MetS is controversial. A comprehensive literature review about complete blood counts and metabolic disease and cardiovascular disease suggested that WBC and NLR could improve the sensitivity and specificity of detecting and predicting metabolic disease as early as possible.[10] A large-scale study of

Received: 10 February 2023
Accepted: 29 April 2023
Published: 10 May 2023

5278 Chinese people found that the total WBC counts was significantly and positively correlated with MetS in both sexes.[11] Another research suggested that there was a positive relationship between NLR with the incidence of diabetes and its severity. Also, studies indicated that central obesity, hypertension and hyperlipidemia were related to the NLR.[12] However, Adams-Huet[13] reported that the NLR did not increase with the increasing severity of MetS, and the absolute value of neutrophils seemed to be superior to NLR as a biomarker of inflammation in nascent MetS. Another cohort study indicated significant association was not observed between total leukocytes, lymphocytes, NLR with MetS development over a 5-year period.[14] He et al[15] proved that hemoglobin was closely related to low-density lipoprotein cholesterol (LDL-C) and high triglycerides, so hemoglobin may play an important role in predicting nascent MetS. A study based on Weitang Geriatric Diseases Study stated the level of platelet increased with the risk of MetS in population aged 60 years or above, which may be a useful maker for MetS,[16] while Jialal et al[17] found the platelet count was not significantly correlated with nascent MetS.

Therefore, it is merited to assess the relationship between these indicators and MetS. Our retrospective study is to analysis the correlation and change of hematological parameters (such as WBC, neutrophils, hemoglobin, platelet, and NLR) with MetS and its components, and to evaluate the diagnostic value for MetS at different ages.

Materials and Methods

Study Population

This study recruited subjects over 18 years old who underwent physical examination in the Health Management Center, the First Affiliated Hospital of Zhejiang University School of Medicine from January 2021 to December 2021. The exclusion criteria were

(1) incomplete anthropometric measurements or lab data;
(2) clinical atherosclerosis (coronary artery disease, peripheral artery disease, CVD, etc.) or other severe liver and kidney diseases or other autoimmune diseases or malignancy;
(3) acute or chronic inflammatory diseases or taking anti-inflammatory drugs;
(4) taking steroids, anti-coagulants drugs, oral contraceptive, antioxidant supplements within the past 6 months;
(5) pregnant women.

Individuals who met the inclusion and exclusion criteria were all included. Finally, the study consisted of 7726 subjects, including 4379 males and 3347 females. This study is retrospective, and all participants were anonymous. It passed the ethical approval of the First Affiliated Hospital of Zhejiang University School of Medicine and was exempt from informed consent. This study was completed in accordance with the Declaration of Helsinki.

Data Collection

Demographic data including sex, age, medical history were collected by the questionnaire. Physical examinations, including waist circumference and blood pressure, were conducted by medical professionals in accordance with the operating manual. Waist circumference was measured by a type, at the umbilical level, with the subject standing and wearing only underwear. Blood pressure was recorded using an electronic sphygmomanometer (HBP-9020, OMRON, Kyoto, Japan) after 10 minutes of rest in the seated position, and the right arm was used.

Blood samples were collected early in the morning after overnight (about 8 hours) fasting by professional medical staff. Venous blood samples (2mL) were collected into tubes (containing K2-ethylenediaminetetraacetic acid) and used to detect compete blood cells including WBC, neutrophils, lymphocyte, hemoglobin, platelet by a biochemical autoanalyzer (Sysmex XN-20, Kobe, Japan). Cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG) were collected using a 3mL venous blood tube without anticoagulant or procoagulant ingredients and tested by a biochemical autoanalyzer (Roche Cobas c702, Mannheim, Germany). Fasting insulin (3mL venous blood tube containing coagulant) was tested using a biochemical autoanalyzer (Abbott Architect i2000, Chicago, USA). Glycosylated hemoglobin (HbA1c) was collected by a 2mL

venous blood tube (containing NaF and heparin sodium), and was detected by a biochemical autoanalyzer (Tosoh HLC-723 G8, Tokyo, Japan). NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Insulin resistance index (HOMA-IR) was calculated by multiplying FPG (mmol/L) by fasting insulin level (μIU/mL), then divided by 22.5.[18]

Diagnosis of MetS

According to the Chinese Diabetes Society criteria,[19] MetS was defined for those individuals with at least three types of the following five criteria: (1) central obesity: WC ≥ 90 cm in men and ≥85 cm in women; (2) hypertension: systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg or use of anti-hypertensive medications; (3) hyperglycemia: FPG ≥6.1 mmol/L or 2-hour postprandial blood glucose ≥7.8 mmol/L or use of anti-diabetic medications; (4) triglycerides ≥1.70 mmol/L or using anti-triglyceride medications; (5) HDL-C <1.04 mmol/L. Since the data of 2-hour postprandial blood glucose are not available in population underwent a physical examination, according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),[20] the diagnostic criterion for hyperglycemia was as follows: FPG≥ 5.6 mmol/L or using anti-triglyceride medications.

Statistical Analysis

Continuous variables were represented as means ± standard deviation (SD) if they conformed to a normal distribution, and Student's *t*-test was used between groups; non-normal distributed data were presented as median (P25, P75) and the Mann–Whitney *U*-test was used to compare between groups. Categorical variables were represented as the number of subjects (%), and chi-square test was used between-group comparisons. One-way ANOVA tests were used to determine the association between WBC, neutrophils, hemoglobin, platelet and NLR and increasing number of features of MetS. The correlation between WBC, neutrophils, and hemoglobin with MetS and its components are analyzed by logistic regression analyses adjusting gender, age, smoking and drinking. Each odds ratio (OR) is presented with a 95% confidence interval (CI). Data were analyzed using IBM SPSS version 23.0 (IBM Co., Armonk, NY). Significance was defined as a p-value <0.05.

Results

In this cross-sectional study, the detection rate of MetS was 25.98%. The MetS subjects were predominantly male and elderly people. All five features (central obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low HDL-C) of MetS were significantly different between the two groups. In addition, the MetS subjects had significantly increased levels of HbAlc, fasting insulin, HOMA-IR, and total cholesterol compared to the non-MetS subjects. The levels of WBC, neutrophils, hemoglobin and NLR in the MetS group were significantly higher than those observed in the non-MetS group. However, we did not find a statistically significant difference in LDL-C and platelet between two groups (Table 1).

We divided all subjects into six groups based on the MetS scores. One-way ANOVA was used to compare the values of WBC, neutrophils, hemoglobin, platelet, and NLR among the six groups. Table 2 indicates statistically significant differences in WBC, neutrophils, hemoglobin, platelet among all groups. The levels of WBC, neutrophils, hemoglobin increased gradually with increasing numbers of features of MetS (P<0.05). With the increased numbers of MetS disorders, the level of NLR also increased, but no statistical difference was observed. We further found different value of platelet between subjects was associated with different numbers of MetS disorders (Table 2).

The association between each marker and MetS with its components was evaluated by multivariate logistic regression analysis (Table 3), which revealed WBC, neutrophils, and hemoglobin were risk factors for MetS and all its components after adjusting age, gender, current smoking and drinking status. Platelet was positively associated with MetS and its components except for hyperglycemia. NLR had positive associations with hypertension, hyperglycemia, and low HDL-C separately.

We used ROC curves to analyze the ability of WBC, neutrophils and hemoglobin to define clinical features of MetS (Figure 1), and calculate the AUC (95% confidence interval), optimal cut-off value, the sensitivity, specificity and

Table 1 Baseline Characteristics of MetS Group and Non-MetS Group

	Total (n=7726)	Non-MetS Group (n=5719)	MetS Group (n=2007)	*P*-value
Male (%)	4379 (56.7)	2766 (48.4)	1613 (80.4)	<0.001
Age (years)	48.40±10.73	47.41±10.73	51.23±10.21	<0.001
Current smoking (%)	1644 (21.3)	958 (16.8)	686 (34.2)	<0.001
Current drinking (%)	1166 (15.1)	647 (11.8)	492 (24.5)	<0.001
Waist circumference (cm)	84.21±9.75	81.07±8.49	93.17±7.23	<0.001
SBP (mmHg)	122.39±16.93	118.79±15.73	132.65±16.01	<0.001
DBP (mmHg)	73.22±11.62	70.81±10.84	80.07±11.02	<0.001
FPG (mmol/L)	5.05±1.17	4.80±0.71	5.76±1.76	<0.001
HbAlc (%)	5.76±0.77	5.61±0.52	6.20±1.12	<0.001
Fasting insulin (μIU/mL)	6.60(4.80,9.30)	5.90(4.40,8.00)	9.40(6.90,12.70)	<0.001
HOMA-IR	1.43(1.01,2.09)	1.25(0.92,1.72)	2.30(1.64,3.22)	<0.001
TC (mmol/L)	4.84±0.92	4.81±0.88	4.93±1.00	<0.001
TG (mmol/L)	1.30(0.91,1.94)	1.11(0.82,1.49)	2.21(1.74,3.04)	<0.001
LDL-C (mmol/L)	2.73±0.74	2.74±0.72	2.73±0.80	0.564
HDL-C (mmol/L)	1.25±0.34	1.34±0.32	1.01±0.25	<0.001
WBC ($\times 10^9$/L)	5.80±1.53	5.60±1.44	6.36±1.62	<0.001
Neutrophils ($\times 10^9$/L)	3.31±1.12	3.20±1.10	3.64±1.13	<0.001
Hemoglobin (g/L)	144.70±16.41	141.94±16.30	152.56±13.99	<0.001
Platelet ($\times 10^9$/L)	229.39±56.10	229.66±56.38	228.61±55.32	0.470
NLR	1.86±0.82	1.85±0.81	1.89±0.84	<0.05

Abbreviations: MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbAlc, glycosylated hemoglobin; HOMA-IR, insulin resistance index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio.

Table 2 WBC, Neutrophils, Hemoglobin and the Increasing Numbers of Metabolic Disorders

Score	WBC ($\times 10^9$/L)	Neutrophils ($\times 10^9$/L)	Hemoglobin (g/L)	Platelet ($\times 10^9$/L)	NLR
0 (n=2442)	5.33±1.38	3.04±1.08	136.40±15.88	228.33±53.94	1.82±0.81
1 (n=1792)	5.63±1.39	3.23±1.06	144.12±15.47	229.49±59.19	1.86±0.82
2 (n=1485)	5.99±1.51	3.42±1.13	148.44±14.89	232.04±56.78	1.87±0.80
3 (n=1169)	6.24±1.47	3.57±1.10	151.94±14.24	229.18±54.60	1.87±0.83
4 (n=652)	6.53±1.64	3.75±1.16	153.22±13.60	229.75±56.36	1.92±0.89
5 (n=186)	6.54±2.21	3.73±1.19	154.12±13.66	221.08±55.86	1.94±0.77
F-value	120.564	73.301	275.484	1.666	2.175
P-value	<0.001	<0.001	<0.001	0.021	0.767

Abbreviations: MetS, metabolic syndrome; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio.

Table 3 Logistic Regression Analysis Showing the Association Between Hematological Parameters and MetS with Its Components

	WBC *OR (95% CI)*	Neutrophils *OR (95% CI)*	Hemoglobin *OR (95% CI)*	Platelet *OR (95% CI)*	NLR *OR (95% CI)*
MetS	1.342 (1.291, 1.394)**	1.355 (1.290, 1.423)**	1.033 (1.028, 1.039)**	1.002 (1.001, 1.003)**	1.036 (0.971, 1.105)
Central obesity	1.252 (1.209, 1.297)**	1.229 (1.175, 1.286)**	1.026 (1.021, 1.031)**	1.003 (1.002, 1.003)**	0.963 (0.906, 1.023)
Hypertension	1.229 (1.186, 1.274)**	1.254 (1.197, 1.314)**	1.024 (1.019, 1.029)**	1.003 (1.002, 1.004)**	1.089 (1.023, 1.158)**
Hyperglycemia	1.165 (1.118, 1.214)**	1.223 (1.159, 1.291)**	1.019 (1.013, 1.026)**	1.001 (1.000, 1.002)	1.117 (1.040, 1.200)**
Hypertriglyceridemia	1.292 (1.246, 1.339)**	1.286 (1.229, 1.346) **	1.029 (1.024, 1.034)**	1.003 (1.002, 1.004)**	0.969 (0.912, 1.030)
Low HDL-C	1.253 (1.208, 1.300)**	1.282 (1.222, 1.345) **	1.015 (1.009, 1.020)**	1.001 (1.000, 1.002)*	1.074 (1.008, 1.144)*

Notes: **P<0.01; *P<0.05.
Abbreviations: MetS, metabolic syndrome; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval.

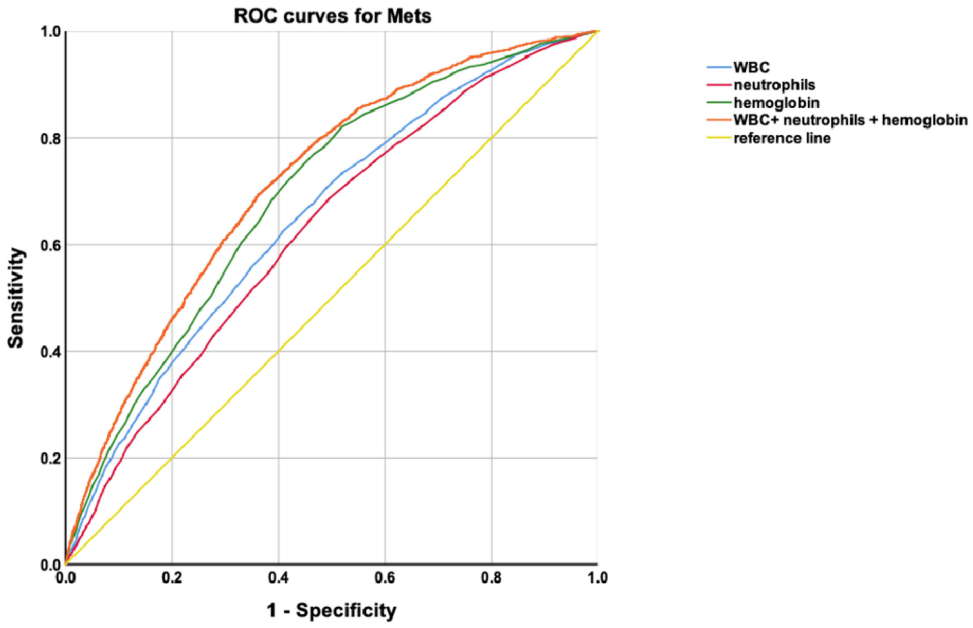

Figure 1 Receiver operating characteristic (ROC) curve analysis of WBC, neutrophils and hemoglobin for MetS.

Youden's index (Table 4). In all subgroups, the AUC of combining WBC, neutrophils, and hemoglobin was higher than WBC, neutrophils and hemoglobin alone, except in subjects aged ≥60 (Figures 2-4 and Table 4).

Discussion

In our present study, the number (the detection rate) of MetS was 2007 (25.98%), including 1613 males and 394 females. Similarly, previous studies reported that the prevalence of MetS ranged from 16.2% to 37.1% worldwide.[21] A systematic review for the Middle East suggested the prevalence of MetS was 20.7–37.2% in men and 32.1–42.7% in women (using

Table 4 Predictive Value of WBC, Neutrophils and Hemoglobin for MetS

	AUC (95% CI)	Optimal Cut-Off Value	Sensitivity (%)	Specificity (%)	Youden's Index
All subjects					
WBC	0.650 (0.637, 0.664)**	5.48×10^9/L	70.5	51.2	0.217
Neutrophils	0.625 (0.611, 0.639)**	3.05×10^9/L	68.6	50.6	0.192
Hemoglobin	0.691 (0.678, 0.704)**	144.5g/L	75.1	55.2	0.303
WBC+ neutrophils + hemoglobin	0.717 (0.704,0.729)**	—	69.0	64.2	0.332
Aged <40					
WBC	0.720 (0.690, 0.750)**	6.35×10^9/L	63.1	69.1	0.322
Neutrophils	0.670 (0.638, 0.702)**	3.77×10^9/L	53.2	70.8	0.240
Hemoglobin	0.781 (0.755, 0.807)**	146.5g/L	88.5	58.0	0.465
WBC+ neutrophils + hemoglobin	0.819 (0.795, 0.842)**	—	81.4	68.7	0.501
Aged 40–60					
WBC	0.660 (0.643, 0.677)**	5.72×10^9/L	61.7	62.1	0.238
Neutrophils	0.631 (0.614, 0.648)**	3.04×10^9/L	68.1	52.5	0.206
Hemoglobin	0.705 (0.689, 0.720)**	143.5g/L	80.0	53.5	0.335
WBC+ neutrophils + hemoglobin	0.731 (0.716, 0.746)**	—	71.5	64.9	0.364
Aged ≥60					
WBC	0.606 (0.571, 0.641)**	5.35×10^9/L	66.4	51.8	0.182
Neutrophils	0.597 (0.561, 0.632)**	2.85×10^9/L	73.6	44.0	0.176
Hemoglobin	0.570 (0.534, 0.607)**	146.5g/L	48.5	63.1	0.116
WBC+ neutrophils + hemoglobin	0.604 (0.568, 0.640)**	—	54.3	62.9	0.172

Note: **P<0.01.
Abbreviations: AUC, area under curve; MetS, metabolic syndrome; WBC, white blood cell.

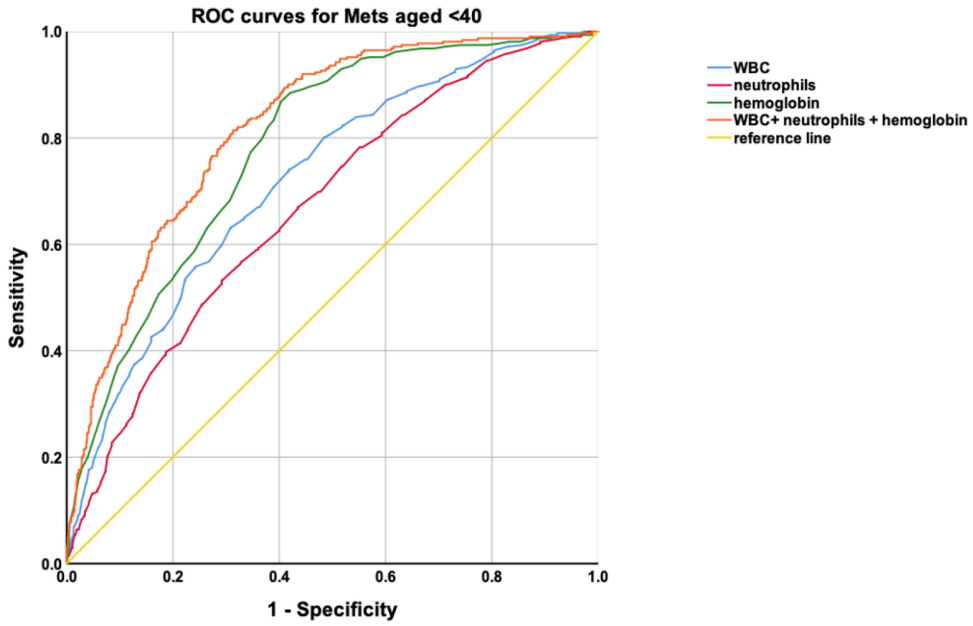

Figure 2 Receiver operating characteristic (ROC) curve analysis of WBC, neutrophils and hemoglobin for MetS in subjects aged <40.

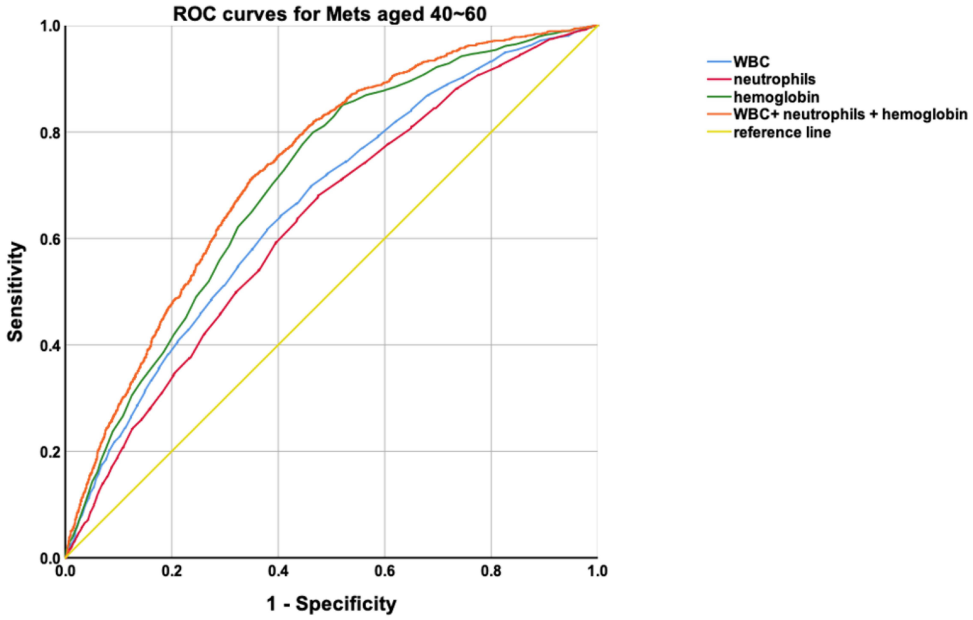

Figure 3 Receiver operating characteristic (ROC) curve analysis of WBC, neutrophils and hemoglobin for MetS in subjects aged 40–60.

ATP III criteria).[22] According to a large cross-sectional study for Chinese population, a total of 10,475 (30.8%) subjects were diagnosed with MetS, while another study for Chinese adults found about 27.9% of the male population and 26.8% of the female population suffered from MetS.[23]

Previous studies indicated MetS was related to inflammation responses.[24,25] In terms of WBC, neutrophils, and NLR as hematological indicators for MetS, the results were not consistent. The present study revealed that the MetS individuals had high level of WBC and neutrophils than non-MetS individuals. Moreover, there was a hierarchical relationship between increased number of metabolic disorders and the value of WBC and neutrophils. Multivariate Logistic regression showed that WBC and neutrophils were risk factors for MetS and all metabolic disorders after

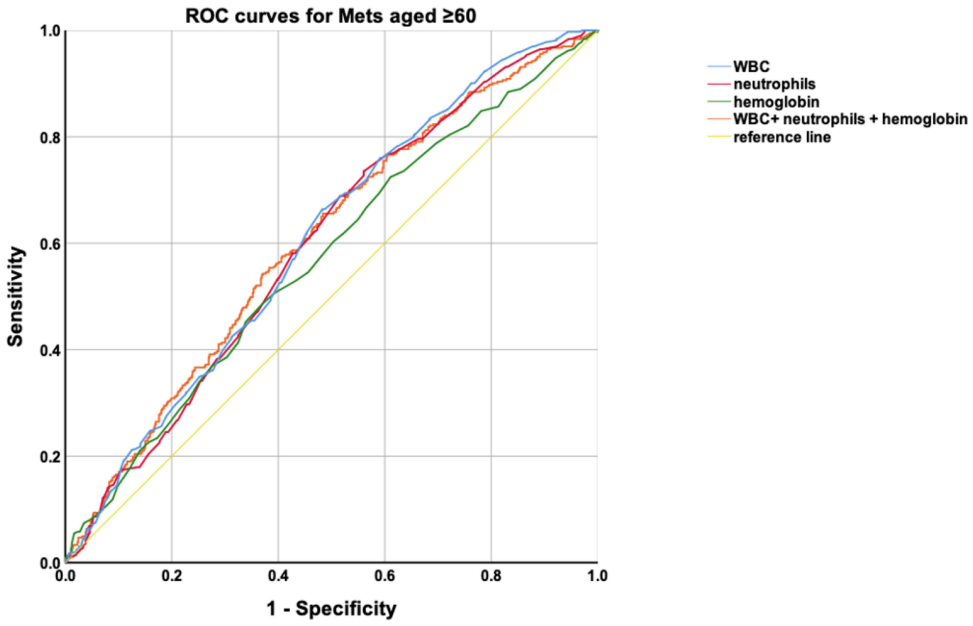

Figure 4 Receiver operating characteristic (ROC) curve analysis of WBC, neutrophils and hemoglobin for MetS in subjects aged ≥60.

adjusting for gender, age, smoking, and drinking status. NLR had significantly positive relationship with hypertension, hyperglycemia and low HDL-C after adjusting the related confounding factors. The pathogenetic mechanism may be that WBCs and neutrophils can infiltrate adipose tissue and product cytokines and other inflammatory productions, which contribute to insulin resistance and visceral fat denaturation.[26] Further, insulin resistance lead to metabolic disturbances and intracellular adhesion molecule-1, resulting in higher gathering of WBC, neutrophils and other inflammatory factors.[27] The findings were consistent with previous studies that WBC and neutrophils were good biomarkers for MetS patients with inflammation.[14,28,29] However, data in our present study suggested that the level of NLR did not increase with the increased number of features of MetS and NLR had no significant association with MetS after adjusting for the related confounding factors, which was consistent with part of previous findings.[13,30] Similarly, a cross-sectional study based on the population of Kerman in southeast Iran also confirmed a positive correlation between WBC and its subcomponent cells counts such as neutrophil, lymphocyte and monocyte and the severity of MetS, especially in females, but NLR was not recognized as a predictor for MetS.[31] Hence, the relationship and mechanism between NLR and MetS needed to be further studied.

Hemoglobin is a special protein that carries oxygen within red blood cells and is composed of globin and heme. Hashimoto et al confirmed that high level of hemoglobin was associated with the risk of nascent MetS after 8-year follow-up period in men.[32] Another study also demonstrated serum hemoglobin may be a predictor of MetS.[33] Similarly, our study showed that the mean concentration of hemoglobin had significant association with MetS or with any of the components of MetS in Chinese adults. The possible mechanism between hemoglobin and MetS is elevated hemoglobin level contributes to high blood viscosity and reduces the delivery of oxygen, glucose and insulin resulting in decreased blood flow and insulin resistance.[34] Consistent with previous studies,[35,36] our study found that high level of platelet counts was correlated with higher risk of MetS. Previous studies reported that CXXR6 expression on platelet-bound monocytes and CD8+ lymphocytes might be associated with metabolic disorders, and endothelial microparticles can promote the activation of platelet in MetS.[37,38] Those inflammatory responses could contribute to platelet aggregation in MetS subjects.

We found that the AUC of combining WBC, neutrophils, and hemoglobin was higher than WBC, neutrophils and hemoglobin alone, except in subjects aged ≥60. These findings are new approaches for the hematological parameters in the pathogenesis of MetS, and the early diagnosis of MetS. However, there were some limitations in our study. First, the study was cross-sectional, so the causal relationship could not be determined. Second, some potential confounding effects

such as dietary habits, exercise were not analyzed, which might weaken the effect of WBC, neutrophils, and hemoglobin for MetS.

Conclusion

In conclusion, WBC, neutrophils, and hemoglobin were clearly correlated with MetS and its components, and those indicators were proportional to the severity of MetS. The combination of WBC, neutrophils, and hemoglobin had certain diagnostic value for MetS. Thus, WBC, neutrophils, and hemoglobin are useful and promising markers for early diagnosis of MetS.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The study protocol was ethically approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (2022-454).

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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