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ORIGINAL RESEARCH

The Association Between Neutrophil/High-Density Lipoprotein Cholesterol Ratio and Non-Alcoholic Fatty Liver Disease in a Healthy Population

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Objective: Non-alcoholic fatty liver disease (NAFLD) is characterized by abnormal lipid metabolism and inflammation. This study aimed to investigate the relationship between neutrophil-HDL cholesterol ratio (NHR) and NAFLD in a healthy population.

Methods: 1881 healthy people who underwent a physical examination from August to December 2023 at the Hebei General Hospital were chosen for this cross-sectional study. 936 individuals were ultimately included thanks to propensity matching and exclusion criteria. Ultrasound was used to diagnose fatty liver and a *t*-test or Mann–Whitney test was used to compare the clinical characteristics of participants between groups with and without fatty liver. Logistic regression was used to construct a new model that included NHR. The predictive value of NHR as well as the new model for NAFLD in a healthy population was assessed using logistic regression and subject work characteristic curves.

Results: NHR levels were higher among participants in the NAFLD group than those without NAFLD($P<0.05$). NHR is a risk factor for NAFLD in a healthy population($P<0.05$). The odds ratios (ORs) of NHR for predicting NAFLD in Model I (adjusted for sex, age, and BMI) and Model II (adjusted for sex, age, BMI, HbA1c, TC, TG, and ALT) were 1.166 (1.022, 1.331) and 1.248 (1.110, 1.402) ($P<0.05$). The new model created by logistic regression predicted NAFLD with an area under the curve of 0.676 (0.645, 0.706). Compared to participants in the low NHR group, the high NHR group exhibited a higher prevalence of NAFLD($p<0.05$).

Conclusion: NHR is associated with NAFLD, which is a good predictor of NAFLD in a healthy population.

Keywords: neutrophil/high-density lipoprotein cholesterol ratio, nonalcoholic fatty liver disease

Introduction

Due to the epidemic of obesity and contemporary lifestyle modifications, Non-alcoholic fatty liver disease (NAFLD) has become one of the most common chronic liver metabolic disorders around the world. NAFLD could primarily contribute to liver-related morbidity and mortality. It affects approximately 30% to 32% of the population worldwide nowadays.[1] The persistent accumulation of excessive lipids within the liver results in progressive cellular damage, potentially leading to liver irreversible fibrosis and cirrhosis, and in some cases, even the onset of liver cancer.

Lipid accumulation in the hepatocyte is an initiating factor in the onset of NAFLD. Liver damage can occur during the development of fatty liver disease. In the early stages of liver injury, macrophages are activated and release chemokines and pro-inflammatory cytokines, including C-C motif chemokine ligand 2, TNF-A, (IL)-1β, and IL-6, which lead to the recruitment of monocytes and neutrophils into the injured liver, thereby promoting the progression of NAFLD.[2] In previous studies, the application of the neutrophil-depleting antibody 1A8 has been shown to prevent liver dysfunction in vivo experiments.[3] HDL cholesterol transports excessive cholesterol to the liver, while also reducing neutrophil activation, adhesion, and migration, inhibiting inflammation.[4] The intricate interactions between neutrophils

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and HDL-C give rise to NHR, defined as neutrophil/HDL cholesterol, as a novel index for assessing inflammation and lipids.[5] Previous studies have revealed a robust correlation between NHR and several illnesses, such as liver cancer, cardiovascular disease, and Parkinson's.[6–8] Studies of the association between NHR and NAFLD have rarely been systematically reported.

About 20–30% of hepatocellular steatosis is detected by ultrasound, which is the most commonly used tool to detect fatty liver in clinical practice and is difficult to use for mass screening. Liver steatosis can be detected by magnetic resonance imaging (MRI), which is expensive and difficult to generalize. Liver biopsy, an invasive test, is usually not accepted by patients.[9] To fill these gaps, we explored the relationship between NHR and NAFLD in a healthy population and constructed a new model to predict NAFLD.

Materials and Methods

Research Objectives

This cross-sectional study was conducted in the Medical Examination Center of the Hebei General Hospital from August to December 2023. A total of 2230 subjects were recruited. They completed questionnaires, anthropometric measurements, laboratory tests, and liver ultrasound. Those with high blood pressure, diabetes, severe heart and kidney disease, and missing data were excluded. Viruses, alcohol, drugs, and other diseases that can cause fatty liver were also excluded. 936 people were finally included in the study. All participants voluntarily agreed to participate in the study (Figure 1).

Information Collection

Physical exams, blood testing, and ultrasounds were conducted while participants fasted in the morning. The participants' basic data, such as gender, age, and smoking habits, were gathered. Waist circumference (WC), height, and weight were measured. Blood biomarkers including glycated hemoglobin (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), glomerular filtration rate (eGFR), total cholesterol (TC), triglycerides (TG), HDL-C, and low-density lipoprotein cholesterol (LDL-C) were examined. An abdominal ultrasound was performed on each subject to determine the presence of NAFLD. Weight (kg)/height (m^2) equals body mass index (BMI). NHR = NE × 10^9/HDL-C.

Statistical Analysis

Continuous variables having normal distribution reflected mean ± standard deviation, while data without normal distribution reflected medians (interquartile range), with categorical parameters reflected as percentages. Comparative

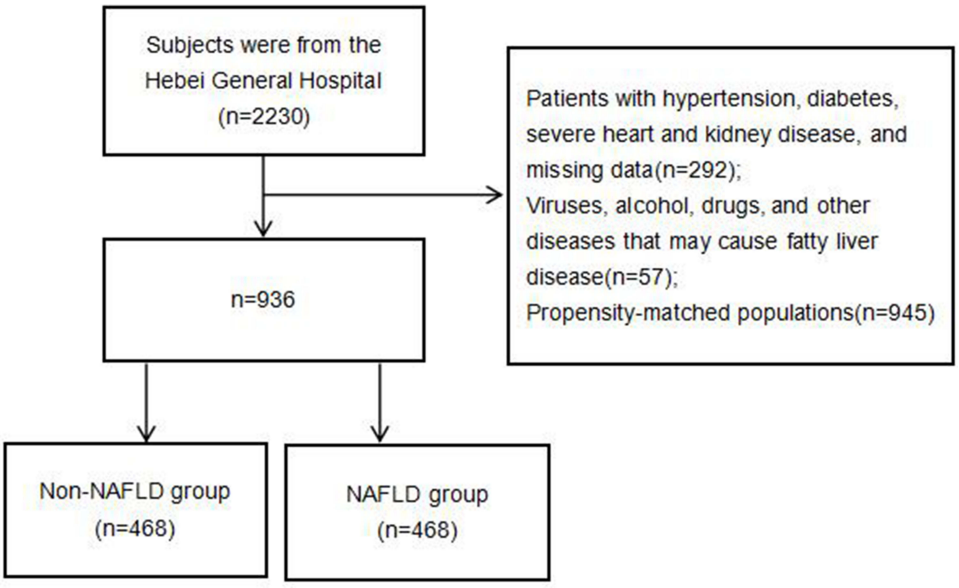

Figure 1 Flowchart for inclusion of populations.

analyses across both cohorts employed a *t*-test or Mann–Whitney test. χ^2 test comparatively analyzed categorical variables. Univariate or multivariate logistic regression analyses were performed to assess the predictive value of NHR for NAFLD. Logistic regression constructs a new model for predicting NAFLD. ROC curves further validate the predictive value of NHR and the new model for NAFLD. Clinical characteristics were analyzed by dividing the cut-off value of NHR into high and low groups. The significance level was P<0.05. Statistical analyses were performed using SPSS27 statistical software, and graphs were generated using GraphPad Prism 8.0 graphing software.

Result

Clinical Characteristics of the Population with and without NAFLD

BMI and age were matched between NAFLD and non-NAFLD controls. At last, 936 individuals were finally included in the study. The mean age of all participants in the study was 52.99 years, and their BMI was 24.58 kg/m². HbA1c, TC, TG, LDL-C, ALT, and SUA were higher in the NAFLD group compared to the non-NAFLD group, and HDL-C was reduced (all P < 0.05) (Table 1). The comparison of the NHR between the two groups is shown in Figure 2.

NHR Was an Independent Risk Factor for NAFLD

The presence of NHR was associated with the presence of NAFLD with an OR (95% CI) of 1.229 (1.099, 1.375) (Table 2).

The multivariate logistic regression analysis of NHR for predicting NAFLD in a healthy population is shown in Table 3. In model I (adjusted for sex, age, and BMI), the prevalence of NAFLD was increased in cases with elevated NHR with an OR of 1.248 (1.110, 1.402) (P<0.05). In model II (adjusted for sex, age, BMI, HbA1c, TC, TG, and ALT), NHR was found to have an equally good predictive value for NAFLD in a healthy population, with an OR of 1.166 (1.022, 1.331) (P<0.05).

Table 1 Clinical Characteristics of the Population in the NAFLD and Non-NAFLD Groups

Variable	Non-NAFLD (n=468)	NAFLD (n= 468)	P value
Male (%)	282 (60.3%)	272 (58.1%)	0.506
Age (yr)	51.50 (44, 61.75)	52 (45, 59)	0.876
Smoking history (%)	87 (18.60%)	88 (18.80%)	0.933
WC (cm)	84.45±8.10	85.17±7.80	0.164
BMI (kg/m^2)	24.45 (22.89, 25.90)	24.44 (23.18, 25.97)	0.576
HbA1c (%)	5.70 (5.50, 5.85)	5.70 (5.50, 5.90)	<0.001*
TC (mmol/L)	4.98 (4.35, 5.57)	5.04 (4.54, 5.73)	0.005*
TG (mmol/L)	1.18 (0.88, 1.58)	1.48 (1.07, 2.11)	<0.001*
HDL-C (mmol/L)	1.38 (1.20, 1.57)	1.28 (1.11, 1.49)	<0.001*
LDL-C (mmol/L)	3.12±0.69	3.30±0.68	<0.001*
ALT (U/L)	15.30 (12.32, 20.1)	18.15 (14.10, 25.78)	<0.001*
AST (U/L)	20 (17.63, 24.38)	20.75 (17.83, 24.90)	0.124
SUA (μmol/L)	347.40 (291.78, 410.82)	373.35 (315.75, 429.23)	<0.001*
eGFR (mL/min)	97.85 (88.75, 105.97)	99.67 (90.31, 106.90)	0.068
NHR	2.49 (1.80, 3.16)	2.66 (1.98, 3.48)	<0.001*

Note: *P <0.05.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; WC, waist circumference; BMI, body mass index; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SUA, serum uric acid; eGFR, glomerular filtration rate; NHR, neutrophil/HDL cholesterol.

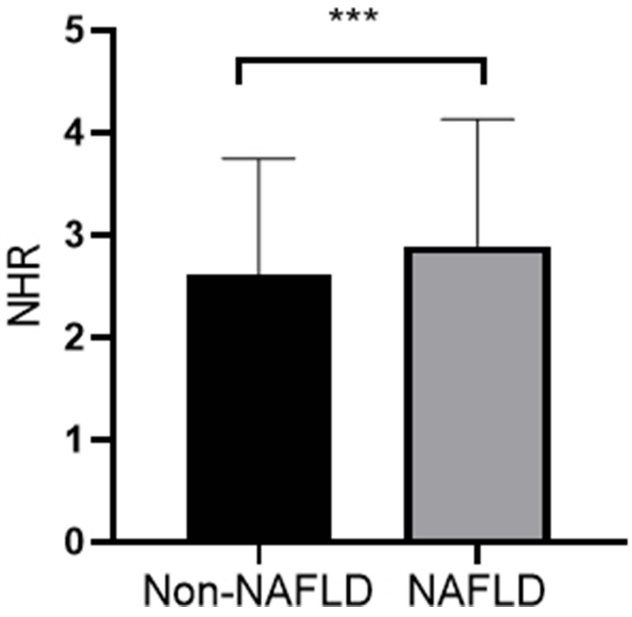

Figure 2 Comparison of NHR between groups with and without NAFLD.
Note: ***P < 0.001.

Construction of a New Model for Predicting NAFLD

To better predict the incidence of NAFLD in a healthy population, we included sex, age, BMI, HbA1c, TC, TG, and ALT in the logistic regression analysis to construct a new prediction model (Table 4). The new model was calculated as logit (the new model) = =−5.665+0.624*HbA1c+0.131*TC+0.445*TG+0.02*ALT+0.141*NHR.

NHR and the New Model to Predict ROC Curves in NAFLD

Table 2 Univariate Logistic Regression Analysis of Risk Factors for NAFLD

Variable	β	SE	Wald χ2	P value	OR (95% CI)
HbA1c (%)	0.810	0.227	12.747	<0.001*	2.248 (1.441, 3.508)
TC (mmol/L)	0.226	0.070	10.312	<0.001*	1.253 (1.092, 1.438)
TG (mmol/L)	0.610	0.095	41.282	<0.001*	1.840 (1.528, 2.217)
LDL-C (mmol/L)	0.382	0.098	15.336	<0.001*	1.466 (1.210, 1.775)
ALT (U/L)	0.030	0.007	18.178	<0.001*	1.031 (1.017, 1.046)
SUA (μmol/L)	0.003	0.001	18.731	<0.001*	1.003 (1.002, 1.005)
NHR	0.206	0.057	13.016	<0.001*	1.229 (1.099, 1.375)

Note: *P <0.05.
Abbreviations: HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; SUA, serum uric acid; NHR, neutrophil/HDL cholesterol.

Table 3 Multivariate Logistic Regression Analysis of the Relationship Between NHR and NAFLD

	β	SE	Wald χ2	P value	OR (95% CI)
Model I	0.221	0.059	13.857	<0.001*	1.248(1.110, 1.402)
Model II	0.154	0.067	5.231	0.022*	1.166(1.022, 1.331)

Note: *P < 0.05.
Model I: Adjusted for sex, age, and BMI; Model II: Adjusted for sex, age, BMI, HbA1c, TC, TG, and ALT.

Table 4 Logistic Regression Constructs a New Model for Predicting NAFLD

Variable	β	SE	Wald χ 2	P value	OR (95% CI)
HbA1c	0.624	0.237	6.94	0.008*	1.867(1.173, 2.969)
TC	0.131	0.081	2.621	0.105	1.14(0.973, 1.336)
TG	0.445	0.103	18.701	<0.001*	1.561(1.276, 1.91)
ALT	0.02	0.008	7.234	0.007*	1.02(1.005, 1.036)
NHR	0.141	0.066	4.636	0.031*	1.152(1.013, 1.31)
Constants	−5.665	1.38	16.85		

Note: *P <0.05.
Abbreviations: HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; ALT, alanine aminotransferase; NHR, neutrophil/HDL cholesterol.

Table 5 NHR and New Models Predict the Area Under the AUC Curve in NAFLD

Variable	AUC (95% CI)	P value	Sensitivity (%)	Specificity (%)	Youden index	Cutoff value
NHR	0.568 (0.536, 0.6)	<0.001*	52.56	58.33	0.109	2.62
The new model	0.676 (0.645, 0.706)	<0.001*	49.15	80.56	0.297	>0.54

Note: *P < 0.05.
Abbreviations: AUC, area under the curve; NHR, neutrophil/HDL cholesterol.

The area under the ROC curve for NAFLD in a healthy population predicted by NHR was 0.568 (0.536, 0.6), with a sensitivity of 52.56% and a specificity of 58.33% (P < 0.05). Its cut-off value for the prediction of NAFLD was 2.62. The area under the ROC curve for NAFLD in a healthy population predicted by the new model was 0.676(0.645, 0.706), with a sensitivity of 49.15% and a specificity of 80.56%. (Table 5 and Figure 3).

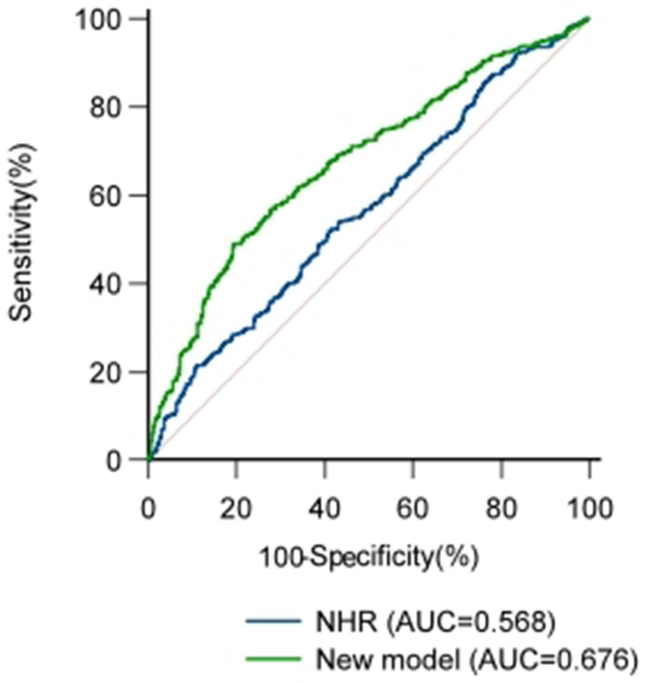

Figure 3 NHR and new models to predict ROC curves in NAFLD.

Table 6 Clinical Characteristics of the Population in the High and Low NHR Groups

Variable	Low-NHR (n=484)	High-NHR (n=452)	P value
Male (%)	243 (50.2%)	311 (68.8)	<0.001*
Age (yr)	52 (45.25, 59)	51 (43, 60.75)	0.064
Smoking history (%)	66 (13.60%)	109 (24.10%)	<0.001 *
NAFLD (%)	218 (45%)	250 (55.30%)	0.002*
WC (cm)	83.11±7.72	86 (81.25, 92)	<0.001*
BMI (kg/m^2)	24.22 (22.68, 25.59)	24.67 (23.46, 26.40)	<0.001*
HbA1c (%)	5.7 (5.5, 5.9)	5.7 (5.5, 5.9)	0.725
TC (mmol/L)	5.18 (4.66, 5.88)	4.87±0.92	<0.001*
TG (mmol/L)	1.19 (0.85, 1.63)	1.47 (1.08, 2.13)	<0.001*
HDL-C (mmol/L)	1.48 (1.31, 1.68)	1.19 (1.07, 1.34)	<0.001*
LDL-C (mmol/L)	3.30±0.70	3.11±0.67	<0.001*
ALT (U/L)	15.95 (12.80, 22.55)	17.50 (13.50, 23.78)	<0.001*
AST (U/L)	20.75 (17.90, 25)	20 (17.50, 23.80)	0.020*
SUA (μmol/L)	344.60 (292.90, 405.68)	377.50 (318.03, 438.85)	<0.001*
eGFR (mL/min)	98.39 (89.37, 105.05)	99.54 (89.67, 107.43)	0.093

Note: *P < 0.05.
Abbreviations: WC, waist circumference; BMI, body mass index; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. ALT, alanine aminotransferase; AST, aspartate aminotransferase; SUA, serum uric acid; eGFR, glomerular filtration rate.

The Participant Population Was Divided into Two Groups Using the NHR Cutoff

The participant population was divided into two groups of high and low NHR based on the NHR cutoff of 2.62 for predicting NAFLD. The clinical characteristics of those enrolled in the two groups are shown in Table 6. Age, HbA1c, and eGFR were not significantly different between groups (P>0.05). Compared with the low NHR group, the male ratio, smoking ratio, NAFLD prevalence, WC, BMI, TG, ALT, and SUA were increased in the high NHR group population (P < 0.05). The levels of TC, HDL-C, LDL-C, and AST were reduced in the group with the lower NHR (P < 0.05). The prevalence of NAFLD between the two groups is shown in Figure 4.

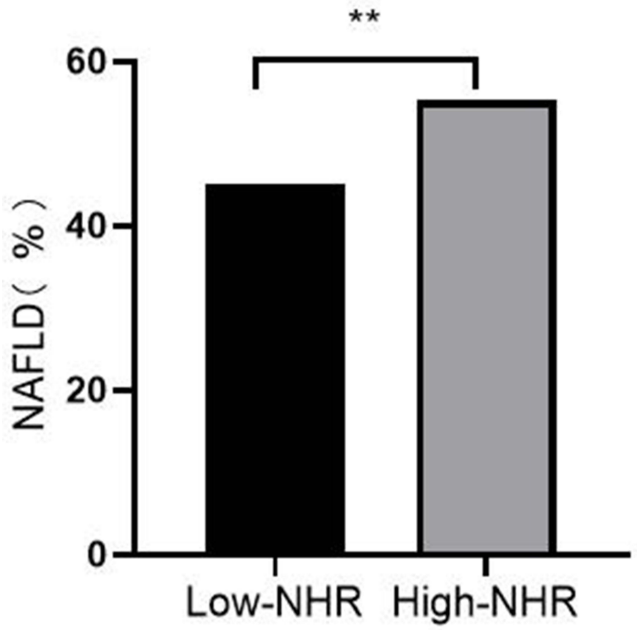

Figure 4 Comparison of NAFLD incidence in high and low NHR groups.
Note: **P < 0.01.

Discussion

In our study, NHR was associated with NAFLD. In a healthy population, NHR was a risk factor for the emergence of NAFLD. Furthermore, we constructed a new model with high predictive efficacy to predict NAFLD.

Neutrophils are thought to mediate the early stages of the inflammatory response and are involved in the activation of monocytes and lymphocytes.[2] HDL-C, a typical lipid-related biomarker, transports excess cholesterol from peripheral tissues back to the liver. In addition, HDL-C reduces neutrophil activation, adhesion, and migration to exert an inhibitory effect on inflammation.[7] Given the complex interactions between neutrophils and HDL-C, NHR, a comprehensive index, may be more effective and reliable than a single index in responding to abnormal lipid metabolism and inflammation. Research suggests that NHR and inflammation-related diseases may be closely related. A retrospective study of 1639 patients with hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) found that NHR, either as a continuous or categorical variable, was independently associated with 3-year mortality and was validated in a cohort study of 373 individuals.[6] Retrospective studies have found higher levels of NHR in patients with schizophrenia (SCZ), manic episodes of bipolar disorder (BD-M), and depressive episodes of bipolar disorder (BD-D) compared to healthy populations.[10] Ninety-eight Parkinson's disease (PD) patients were divided into three groups according to disease duration: <6 years, 6–10 years, and >10 years, and were classified into early disease (grade 1 ~ 2.5) and advanced disease (grade 3 ~ 5) according to the Hoehn and Yahr classification system. The cross-sectional study found that NHR was significantly negatively correlated with PD disease duration and positively correlated with disease severity.[8] In conclusion, NHR is strongly associated with inflammation-related diseases such as HCC, SCZ, BD, and PD.

A cross-sectional study of 404 patients with typical symptoms of coronary artery disease, such as chest pain, who underwent coronary angiography to determine the severity of coronary artery disease found that NHR was not only closely related to coronary artery stenosis but also an independent predictor of severe coronary artery stenosis.[7] In a follow-up study of 528 elderly (65–85 years) patients with myocardial infarction (AMI), NHR was found to be a potential predictor of their long-term mortality and recurrent myocardial infarction (RMI).[11] The retrospective study found that NHR was not only an independent risk factor for acute ischemic stroke (AIS) but also positively correlated with the National Institutes of Health Stroke Scale (NIHSS) severity score.[12] In addition, in a cross-sectional study of 1033 adults from southeastern Iran, NHR was found to be a valuable biomarker for assessing the risk of metabolic syndrome.[13] Taken together, NHR, a novel indicator of inflammatory cells and cholesterol, may comprehensively reflect the inflammatory state and dyslipidemia in diseases such as coronary heart disease, stroke, and metabolic syndrome. The relationship between NHR and NAFLD has not been extensively studied. Therefore, this study is focused on investigating the relationship between NHR and NAFLD in a healthy population.

Neutrophils are present in various stages of NAFLD, and several rodent studies have suggested that neutrophils may contribute to disease progression. More and more studies have shown that the immune system plays a critical role in all stages of NAFLD development.[14] It is known that the induction of inflammation and inflammatory cytokines such as TNF and IL-1 plays a critical role in the disease process.[15] Previous studies have shown that patients with NAFLD have elevated circulating levels of inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and c-C chemokine ligand 2 (CCL2).[16] Previous studies have found significantly elevated levels of pro-inflammatory markers such as IL-1β and iNOS in high-fat diet (HFD)-fed NAFLD rats compared to normal chow-fed rats. IL-1β has been suggested to play an important role in hepatic steatosis, inflammation, and fibrosis.[17] NHR evaluates the body's inflammatory response and plays an important role in lipid metabolism. NHR may directly influence the body's inflammatory response and thereby mediate NAFLD development. It may also influence the body's lipid metabolism, which is also involved in the development of NAFLD.

The current study offers various advantages over previous research. First, NHR was found to be an independent risk factor for NAFLD in a healthy population. In addition, this study identified a critical value of NHR for predicting NAFLD, which may help improve timely attention to NAFLD among healthcare professionals. Furthermore, these markers are economical, non-invasive, effortless to administer, and widely

accessible, facilitating their clinical utility in predicting and epidemiological research of NAFLD. Nevertheless, this study exhibits few limitations. First, this cross-sectional study is limited in its ability to examine the causal relationship between this indicator and NAFLD. Additionally, potential confounders, such as dietary patterns and physical activity, were not assessed within the population. Finally, the study was conducted solely at a single medical center. Therefore, more multicenter prospective cohort studies are needed in the future to investigate and validate the relationship between NHR and NAFLD.

Conclusion

In this study, NHR was an independent risk factor for NAFLD in a healthy population.

Ethics Approval and Informed Consent

This study was conducted by the principles of the Declaration of Helsinki. Approved by the Ethics Committee of the Hebei General Hospital (Ethics Committee No. 2023104). Informed consent was obtained from all individuals participating in the study.

Disclosure

The authors declare no competing conflicts of interest in this work.

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