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ORIGINAL RESEARCH

Association of the Monocyte-to-High Density Lipoprotein Ratio with the FRS and as a Predictor of Cardiovascular Risk in Individuals with Psoriasis Vulgaris

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Objective: The monocyte-to-high-density lipoprotein ratio (MHR) has emerged as a novel inflammatory biomarker associated with cardiovascular diseases (CVDs). This retrospective study aimed to investigate the relationship between MHR and the Framingham risk score (FRS) and assess the prognostic significance of this relationship for mid- to high-risk CVD in individuals with psoriasis vulgaris (PsV).

Methods: A total of 128 PsV patients and 120 healthy controls were included. The neutrophil-to-high-density lipoprotein ratio (NHR), MHR, and neutrophil-to-lymphocyte ratio (NLR) were assessed and compared between the two groups. Correlations between MHR and FRS were evaluated.

Results: PsV patients with intermediate to high cardiovascular risk exhibited significantly higher NHR, MHR, and NLR compared to controls ($p = 0.018$, $p = 0.002$, $p < 0.001$, respectively). Furthermore, FRS was positively correlated with MHR, NHR, and NLR in the PsV patients ($r=0.27$, $p = 0.002$; $r=0.21$, $p = 0.017$ and $r=0.33$, $p < 0.001$, respectively). Logistic regression analysis identified age, sex, and the MHR as influencing factors for the FRS ($p < 0.05$). Receiver operating characteristic (ROC) curve analysis revealed that the highest Youden's index (0.316) was obtained at an MHR of 0.24, with sensitivity, specificity, and area under the ROC curve of 0.729, 0.587, and 0.662 (95% CI of 0.565, 0.758), respectively.

Conclusion: MHR was significantly associated with FRS, which may serve as a valuable predictor of medium to high risk of CVDs in patients with PsV.

Keywords: psoriasis vulgaris, cardiovascular diseases, monocyte, high-density lipoprotein cholesterol, Framingham risk score

Introduction

Psoriasis vulgaris (PsV) is a frequently observed immune-regulated and chronic inflammatory skin disorder with an approximate prevalence of 2–3% worldwide.[1] This disorder is considered a systemic disease related to cardiovascular diseases (CVDs).[2–4] Patients with PsV have a greater risk of CVD, which may be an independent risk factor for CVD.[4] Moreover, some experts have suggested that cardiovascular events are the main cause of death in PsV patients.[3]

Inflammation and the environment have significant effects on the pathogenesis of PsV. Increased oxidative stress (OS) and angiogenesis are critical contributors to CVD progression, and PsV promotes CVD development through both mechanisms. Therefore, the pathogenesis of PsV is similar to that of CVDs, such as OS, metabolic syndrome, systemic inflammation, and vascular endothelial cell dysfunction.[5]

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The monocyte-to-high-density lipoprotein ratio (MHR), neutrophil-to-high-density lipoprotein ratio (NHR), and neutrophil-to-lymphocyte ratio (NLR), which are related to systemic inflammation, have attracted increasing interest in recent years due to their wide availability and low costs.[6–9] Inflammation is usually linked to proinflammatory cytokine-mediated activation of circulating monocytes and neutrophils.[6] Circulating monocyte levels have been shown to predict extensive coronary plaque.[10] In endothelial cells, high-density lipoprotein (HDL) directly inhibits macrophage transmigration and the expression of adhesion molecules.[11] Some scholars have noted that the MHR is related to systemic inflammation in European and American PsV cohorts.[7] The NLR, which originates from the ratio of neutrophils to lymphocytes in peripheral blood, may reflect the balance between innate and adaptive immune responses.[8] Abnormal NLR values represent different inflammatory states. Neutrophils play a crucial role in the initial inflammatory response by producing cytokines that impact lymphocytes and monocytes. Conversely, HDL suppresses inflammation, as illustrated by its ability to reduce neutrophil activation and migration.[9] Therefore, the NHR can also be considered a valid biomarker for assessing oxidative stress in systemic inflammation.

The MHR, NHR, and NLR are novel inflammatory biomarkers that have been newly identified as predictors and prognostic factors for CVDs.[7,12–16] The NLR has potentially been a predictor of subclinical atherosclerosis or non-calcified coronary artery burden (NCB) among patients with PsV.[13,14] Moreover, a countrywide cohort study in the USA revealed that the MHR was significantly associated with cardiovascular and all-cause mortality among the general population.[15] A recently published paper in 2024 showed that the MHR was associated with NCB and significant coronary stenosis in 2 cohorts of patients with PsV.[7] Because the MHR, NHR, and NLR are predictive factors for CVD prognosis, a higher MHR can be a warning for detecting and preventing CVD. Nonetheless, such new inflammatory markers have not been extensively analyzed in PsV patients with medium- to high-risk CVD.

This study measured the following clinical blood markers in patients with PsV and healthy controls: the MHR, NHR, and NLR. We hypothesized that PsV patients would show higher levels of new inflammatory markers than healthy control individuals who were matched for age, sex, and body mass index (BMI) and that a specific marker would predict a medium to high risk of CVDs in PsV patients.

Materials and Methods

Participants

Participants, including 128 outpatients and inpatients (aged 20–78 years) with PsV confirmed by clinical or histopathological examination, were recruited from the Second People's Hospital of Nantong between January 2018 and December 2022. A total of 120 patients in the Physical Examination Department of Nantong Second People's Hospital composed the control group. The diagnosis was based on the Guidelines for the Diagnosis and Treatment of Psoriasis in China.[17] The following patients were excluded: 1) who developed severe liver/kidney disease; 2) who developed an autoimmune disease, including systemic lupus erythematosus, Hashimoto's thyroiditis, or rheumatoid arthritis; 3) who developed severe CVDs (coronary heart disease, cerebrovascular events, peripheral artery disease, and heart failure); 4) who developed malignant diseases; 5) who showed pregnancy or lactation; 6) who showed any evidence of concomitant inflammatory disease, acute infection, or chronic inflammation status; 7) who took lipid-lowering drugs within 3 m to eliminate factors affecting lipid levels; and 8) who had a history of systemic PsV treatment.

Treatment Status Assessment

To determine the impact of biologic and immunomodulatory treatments on inflammatory markers, we collected detailed treatment history from the medical records of all participants. This included current and past use of biologics and other immunomodulatory therapies. We categorized participants into groups based on their treatment regimen to analyze the differential effects of these therapies on the outcomes of our study.

Sample Collection and Processing

Blood samples were collected from all participants via venipuncture using EDTA tubes to prevent coagulation. A total of 10 mL of whole blood was drawn from each participant and then centrifuged at 1500 g for 15 minutes to separate plasma. The plasma was used for the subsequent biochemical assays.

Lipid Profile Measurement

Lipid profiles, including HDL levels, were measured using the AccuLipid BioKit obtained from BioMetrics Health, Inc., New Jersey, USA (Catalog No. BK-202-HD). Measurements were carried out according to the manufacturer's instructions on the BioMetrics BXL-100, an automated biochemistry analyzer.

Data Extraction

The current study was approved by the ethics committee of the Second People's Hospital of Nantong (Reference No.2022–072) and was carried out following the Declaration of Helsinki. All patients and their families signed the informed consent form prior to the beginning of the treatment.

Clinical Data

Clinical characteristics, including gender, age, PsV duration, smoking history, personal history, and comorbidities (hypertension, diabetes, coronary artery disease, hyperlipidemia, inflammatory bowel disease, and Hashimoto's thyroiditis), were considered. BMI was calculated as weight divided by height squared (kg/m2).

Laboratory Data

Fasting venous blood was sampled for routine blood data (white blood cell (WBC), platelet (PLT), neutrophil, lymphocyte, and monocyte cell counts; CRP, triglyceride (TG), total cholesterol (TC), high/low-density lipoprotein cholesterol (HDL-c/LDL-c), and albumin (Alb) levels; and blood glucose levels). The MHR, NHR, and NLR were measured in the participants. The NLR was estimated as the neutrophil-to-lymphocyte ratio. The MHR and NHR were calculated as the absolute monocyte count (10^9/L) and neutrophil count (10^9/L) divided by the HDL-c concentration (mmol/L) and are reported as 10^9/mmol.

PsV Area Severity Index (PASI) and Framingham Risk Score (FRS)

In the present study, PsV intensity/severity was determined based on baseline disease status features (desquamation, skin infiltration, and erythema) and represented by the PASI score. The PASI scores were determined by two dermatological physicians, and their mean values were calculated. PsV severity was evaluated as mild-to-intermediate (PASI < 10) or severe (PASI ≥ 10).[18] The FRS, developed as a parameter to assess CVD risk, estimates the 10-year risk of heart disease. It is calculated from the following indicators: patient age, sex, smoking history, HDL-c, TC, systolic blood pressure, and antihypertensive drug use. Blood pressure was measured using an upper-arm electronic sphygmomanometer, ensuring that the patient remained seated in a quiet environment for at least 5 minutes to reduce measurement errors. During measurement, the patient's upper arm should be maintained at heart level to ensure accuracy. For patients with an arm circumference greater than 32 cm, a large cuff should be used; for those with an arm circumference smaller than 24 cm, a small cuff should be used to ensure that the cuff fits tightly to the upper arm, preventing measurement inaccuracies. Blood pressure of both arms was measured. The side with the higher reading was used as a fixed arm for subsequent measurements in order to more accurately assess the patient's blood pressure status. A second measurement was taken after a 60-second interval, and the average of the two measurements was recorded. If the systolic or diastolic pressure difference between the two measurements exceeded 10 mmHg, an additional measurement was required, and the average of the three measurements was calculated. The risk is classified as low (<10%), intermediate (10%–20%), or high (>20%).[19]

Statistical Analysis

The data were analyzed with SPSS, version 27. Based on the Kolmogorov–Smirnov test, continuous data were first tested for their normal distribution. Normally distributed data were shown as the mean ± standard deviation, while categorical data were summarized as absolute numbers or percentages. Intergroup differences were assessed using the Student's *t* test or the Mann–Whitney *U*-test. The differences among the three groups were investigated with one-way ANOVA or the Kruskal–Wallis test. Spearman correlation coefficients were computed to determine the associations between the MHR and clinical hematological variables. The cardiovascular risk categorical variables based on the FRS and clinical quantitative variables were subjected to Spearman correlation analysis. Kendall's tau correlation coefficient was

computed to study FRS classification and clinical categorical variables (sex, smoking status, diabetes mellitus status, and severity of PsV. We conducted a multicollinearity test on potential risk factors determined by univariate analysis and selected variables with a variance expansion factor (VIF)<2 to determine risk factors related to cardiovascular risk level. Additionally, we used a binary logistic regression model to analyze influencing factors for mid- to high-risk CVD risk in patients with PsV. Furthermore, the ROC curve was plotted to assess the prognostic significance of the MHR in individuals with PsV who had mid- to high-risk CVD. The optimal cutoff value for the MHR for identifying the FRS in patients with PsV was determined using the Youden index. P<0.05 indicated a statistically significant difference.

Results

Basic Features

The current study involved 128 cases (PsV) and 120 controls. The study included 92 male patients with PsV and 85 healthy male controls. There were no significant differences between the two groups in terms of sex or age (p = 0.856, p = 0.183). The former group included 22 smokers, and the latter included 15 (p = 0.3). The range of PASI values was 1.3–28.3 for PsV patients. Forty-five patients had moderate to severe PsV, as measured by the PASI (median and interquartile interval: 8.1 [4.93–11.79]).

The differences in the WBC, neutrophil, monocyte, PLT, LDL, and NLR were statistically significant when the laboratory data were compared (p = 0.034, p = 0.021, p = 0.002, p < 0.001, p < 0.001, p = 0.036, Table 1).

Table 1 Demographic Features and Laboratory Parameter Values for the Psoriasis Vulgaris and Control Groups

	Psoriasis (n=128)	Controls (n=120)	Z(t) value	p-value
Demographic characteristics				
Age (years)	52(40.25,62)	54.5(45,66.75)	−1.332	0.183
Gender (M/F)	92(71.9)/36(28.1)	85(70.8)/35(29.2)	0.033	0.856
BMI (kg/m2)	23.57±2.35	23.13±2.28	1.488	0.138
Smoker, n (%)	22(17.19)	15(12.5)	1.072	0.3
Diabetes mellitus, n (%)	25(19.53)	15(12.5)	2.264	0.132
Disease duration (month)	96(48,213)			
PASI	8.1(4.93,11.79)			
Laboratory parameters				
WBC (10^9/L)	6.0(5.1,7.6)	5.75(4.83,6.7)	−2.124	0.034
Neu (10^9/L)	3.7(3.3,4.4)	3.4(2.8,4.28)	−2.304	0.021
Lym (10^9/L)	1.8(1.5,2.2)	1.8(1.4,2.3)	−0.09	0.929
Mon (10^9/L)	0.3(0.3,0.4)	0.3(0.2,0.4)	−3.093	0.002
PLT (10^9/L)	217.5(181.3,267.5)	153(141,168)	−8.332	<0.001
TG (mmol/L)	1.50(0.99,2.28)	1.42(0.94,2.21)	−0.599	0.549
TC (mmol/L)	4.69±0.81	4.68±0.78	0.066	0.948
HDL (mmol/L)	1.26(1.09,1.42)	1.21(1.02,1.51)	−1.124	0.261
LDL (mmol/L)	3.18±0.74	2.72±0.71	4.989	<0.001
Novel Ratio				
TC/HDL	3.60(3.07,4.2)	3.89(3.05,4.49)	−1.014	0.311
NHR (10^9 /mmol)	2.89(2.33,3.95)	2.70(2.04,3.94)	−1.646	0.1
MHR (10^9 /mmol)	0.25(0.20,0.36)	0.24(0.17,0.32)	−1.918	0.055
NLR	2.16(1.65,2.72)	1.94(1.43,2.44)	−2.094	0.036

Notes: The means ± SDs were analyzed by Student's *t*-test for independent samples. The median (median and interquartile interval) was obtained from the Mann–Whitney *U*-test.

Abbreviations: M, male; F, female; BMI, body mass index; WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; Mon, monocyte; PLT, platelet; TG, triglyceride; TC, total cholesterol; HDL/LDL, high/low-density lipoprotein; NHR, neutrophil to high-density lipoprotein ratio; MHR, monocyte to high-density lipoprotein ratio; NLR, neutrophil to lymphocyte ratio.

The MHR, NHR, and NLR of Patients with PsV Showing an Elevated Intermediate-High Cardiovascular Risk

Patients with PsV were categorized into two subgroups based on the FRS: mild and intermediate-high cardiovascular risk (mild: FRS<10% or intermediate and high: FRS ≥ 10%).

The intermediate and high cardiovascular risk groups included 48 patients, whereas the mild group included 80 patients.

Differences in age, BMI, lymphocyte count, monocyte count, PLT, HDL level, and LDL level were significantly different among the three groups ($p < 0.001$, $p = 0.045$, $p = 0.005$, $p = 0.002$, $p < 0.001$, $p = 0.007$, and $p < 0.001$, respectively) (Table 2).

Moreover, post hoc Bonferroni analysis (Table 3) revealed that compared with controls, PsV patients with intermediate and high cardiovascular risk had significantly greater monocyte (p=0.002), PLT (p=0.000), LDL (p=0.000), NHR ($p = 0.018$), MHR ($p = 0.002$), and NLR (p=0.000) values. Notably, PsV patients with mid-to-high cardiovascular risk had a greater MHR and NLR ($p = 0.01$ and $p = 0.001$, respectively) and significantly lower HDL levels (p=0.010) than those with low-risk CVD risk (Table 3).

Correlation of the FRS and MHR with Clinical Indicators in Patients with PsV

The FRS was positively correlated with the MHR, NHR, and NLR in patients with PsV (r=0.27, $p = 0.002$; r=0.21, $p = 0.017$ and r=0.33, $p < 0.001$, respectively) (Figure 1), whereas it was negatively related to lymphocyte count ($r = -0.293$, $p<0.001$). Furthermore, the FRS was related to traditional inflammatory factors such as CRP (r=0.196, $p = 0.027$) and the ESR (r=0.179, $p = 0.043$) (Table 4). Moreover, MHR exhibited positive relation to gender ($r = 0.293$, $p<0.001$), PASI level ($r = 0.241$, $p = 0.006$), CRP ($r = 0.245$, $p = 0.005$), WBC counts ($r = 0.545$, $p<0.001$), neutrophil counts ($r = 0.497$, $p<0.001$), lymphocyte counts ($r = 0.267$, $p = 0.002$), PLT ($r = 0.189$, $p = 0.033$) and TG ($r = 0.337$, $p<0.001$) (Table 4).

Table 2 Laboratory Data in Patients with Psoriasis Vulgaris and Controls Based on CVD Risk

	Mild FRS<10% (n=80)	Intermediate and High FRS≥10%(n=48)	Controls (n=120)	H (F) value	p-value
Age (years)	46(33.25,52.75)	63(54.25,68.75)	54.5(45,66.75)	39.259	<0.001
BMI (kg/m²)	23.21(21.63,24.96)	23.88(22.36,25.61)	23.12(21.57,24.40)	6.224	0.045
Smoker, n (%)	10(12.5)	12(25)	15(12.5)	4.765	0.092
WBC (10^9/L)	6.05(5.1,7.6)	6(4.85,8.28)	5.75(4.83,6.7)	4.641	0.098
Neu (10^9/L)	3.7(3.03,4.4)	3.75(3.03,5.18)	3.4(2.8,4.28)	5.993	0.05
Lym (10^9/L)	1.9(1.6,2.28)	1.6(1.3,2)	1.8(1.4,2.3)	10.666	0.005
Mon (10^9/L)	0.3(0.3,0.4)	0.4(0.3,0.5)	0.3(0.2,0.4)	12.668	0.002
PLT (10^9/L)	223.5(194.5,272.75)	212.5(164.25,258.5)	153(141,168)	74.816	<0.001
TG (mmol/L)	1.52(0.93,2.02)	1.48(1.09,2.62)	1.42(0.94,2.21)	1.669	0.434
TC (mmol/L)	4.67±0.80	4.71±0.83	4.68±0.78	0.044	0.957
HDL (mmol/L)	1.30(1.2,1.52)	1.21(1.03,1.39)	1.21(1.02,1.51)	9.899	0.007
LDL (mmol/L)	3.07(2.5,3.58)	3.31(2.68,3.76)	2.72(2.25,3.15)	22.694	<0.001
NHR (10^9 /mmol)	2.76(2.13,3.8)	3.26(2.49,4.28)	2.70(2.04,3.94)	7.962	0.019
MHR (10^9/mmol)	0.23(0.18,0.32)	0.31(0.23, 0.40)	0.24(0.17,0.32)	12.372	0.002
NLR	1.95(1.51,2.47)	2.45(2.01,3.06)	1.94(1.43,2.44)	17.821	<0.001
PASI	6.18(3.88,11.66)	9.53(7.54,12.64)	–	2.973	0.003

Notes: The results of one-way ANOVA for normally distributed continuous variables are reported as the means ± SDs. The Kruskal–Wallis test for nonnormally distributed variables is reported as the median (interquartile interval).

Abbreviations: BMI, body mass index; WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; Mon, monocyte; PLT, platelet; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NHR, neutrophil to high-density lipoprotein cholesterol ratio; MHR, monocyte to high-density lipoprotein cholesterol ratio; NLR, neutrophil to lymphocyte ratio; PASI, Psoriasis area and severity index; FRS, Framingham risk score.

Table 3 Pairwise Comparison of Blood Count-Derived Markers

Parameter	Psoriasis with Mild FRS		Psoriasis with Intermediate and High FRS		Controls	
	vs Psoriasis with Intermediate and High FRS	vs Controls	vs Psoriasis with Mild FRS	vs Controls	vs Psoriasis with Mild FRS	vs Psoriasis with Intermediate and High FRS
WBC (10^9/L)	1	0.306	1	0.070	0.306	0.070
Lym (10^9/L)	0.003	0.425	0.003	0.074	0.425	0.074
Mon (10^9/L)	0.234	0.178	0.234	0.002	0.178	0.002
PLT (10^9/L)	0.060	0.000	0.060	0.000	0.000	0.000
HDL (mmol/L)	0.010	0.051	0.010	0.779	0.051	0.779
LDL (mmol/L)	0.582	0.002	0.582	0.000	0.002	0.000
NHR (10^9 /mmol)	0.066	1	0.066	0.018	1	0.018
MHR (10^9/mmol)	0.010	1	0.010	0.002	1	0.002
NLR	0.001	1	0.001	0.000	1	0.000

Notes: Post hoc pairwise comparisons were made by Bonferroni correction.
Abbreviations: BMI, body mass index; WBC, white blood cell; Lym, lymphocyte; Mon, monocyte; PLT, platelet; HDL, high density lipoprotein; LDL, low density lipoprotein; NHR, neutrophil to high-density lipoprotein ratio; MHR, monocyte to high-density lipoprotein ratio; NLR, neutrophil to lymphocyte ratio.

Results of Logistic Regression in Patients with PsV Showing Intermediate and High CVD Risk Within 10 y

CVD risk can be categorized as <10% for low risk and ≥10% for medium-high risk. The FRS in the PsV group served as the dependent variable (FRS <10% = 0, FRS ≥ 10% = 1). We conducted a multicollinearity test on potential risk factors

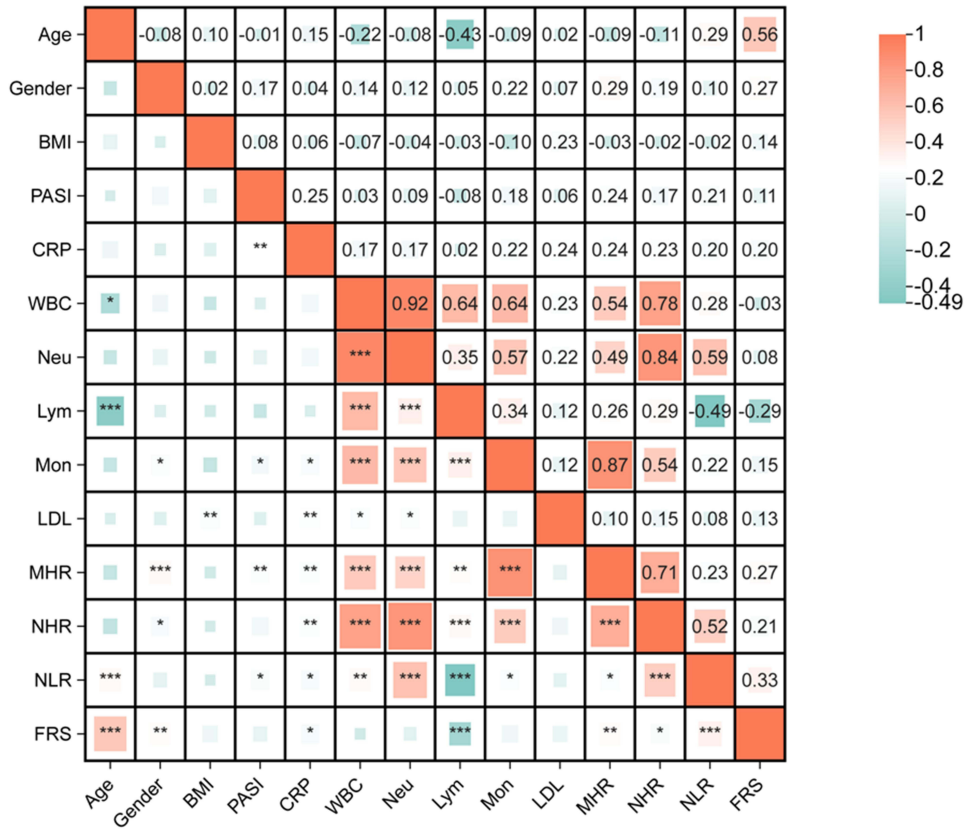

Figure 1 Heatmap showing the relationships between the different variables in patients with PsV stratified by the FRS. *p<0.05, ** p<0.01, *** p<0.001.

Table 4 Correlations Between the FRS and MHR and Clinical Data in Patients with Psoriasis Vulgaris

	FRS Level		MHR	
	Rho (tau—b)	**p-value**	**Rho**	**p-value**
Age (years)	0.561	<0.001	−0.089	0.319
Gender (M/F)	0.269	0.002	0.293	<0.001
BMI (kg/m^2)	0.14	0.114	−0.035	0.693
Smoking	0.16	0.071	0.031	0.73
Diabetes mellitus	0.148	0.096	0.094	0.291
PASI level	0.106	0.234	0.241	0.006
CRP (mg/L)	0.196	0.027	0.245	0.005
ESR (mm/h)	0.179	0.043	0.016	0.858
WBC (×10^9/L)	−0.028	0.752	0.545	<0.001
Neu (×10^9/L)	0.076	0.396	0.497	<0.001
Lym (×10^9/L)	−0.293	<0.001	0.267	0.002
Mon (×10^9/L)	0.154	0.082	0.870	<0.001
PLT (×10^9/L)	−0.177	0.046	0.189	0.033
TG (mmol/L)	0.095	0.286	0.337	<0.001
TC (mmol/L)	0.045	0.616	−0.107	0.23
HDL (mmol/L)	−0.278	0.002	−0.574	<0.001
LDL (mmol/L)	0.127	0.153	0.098	0.272
NHR	0.211	0.017	0.712	<0.001
MHR	0.271	0.002	——	——
NLR	0.333	<0.001	0.228	0.01

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; Mon, monocyte; PLT, platelet; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; NHR, neutrophil to high-density lipoprotein ratio; MHR, monocyte to high-density lipoprotein ratio; NLR, neutrophil to lymphocyte ratio; PASI, Psoriasis area severity index; FRS, Framingham risk score.

determined by univariate analysis and selected variables to determine risk factors (gender, age, CRP, ESR, PLT, NLR, and MHR) related to cardiovascular risk level. The p-value of the Hosmer and Lemeshow test for logistic regression was 0.383, which illustrated a good model fit. Based on the results, sex, age, and the MHR were the influencing factors for CVD risk according to the Framingham Scale in patients with PsV ($p < 0.05$, Table 5).

Table 5 Medium-High CVD risk Among Patients with Psoriasis Determined Using Binary Logistic Regression Analysis

Variable	SE	p-value	OR	95% CI
Gender(M)	1.027	<0.001	0.018	(0.002,0.133)
Age(years)	0.046	<0.001	1.249	(1.141,1.366)
ESR	0.035	0.068	1.066	(0.995,1.143)
CRP	0.022	0.196	0.972	(0.931,1.015)
PLT	0.006	0.095	1.010	(0.998,1.022)
MHR	0.115	0.003	1.411	(1.126,1.767)
NLR	0.375	0.089	1.893	(0.908,3.946)

Notes: Because the MHR is small, the HDL unit, mmol/L, is converted to mg/dL in the regression.

Abbreviations: ESR, erythrocyte sedimentation rate; NHR, neutrophil to high-density lipoprotein ratio; MHR, monocyte to high-density lipoprotein ratio; NLR, neutrophil to lymphocyte ratio.

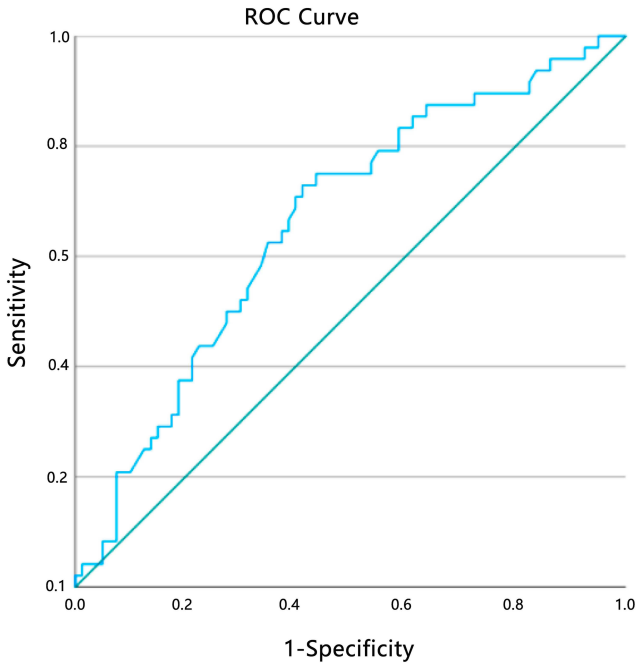

Figure 2 ROC curve of the MHR for identifying patients at medium-high risk of CVD in patients with PsV.

ROC Curve of the MHR for the Identification of the FRS in Patients with PsV

The ROC curve of the MHR in relation to the FRS is shown in Figure 2. The threshold for the MHR in predicting medium-high risk of CVDs in patients with PsV according to the ROC curve was 0.24, and the sensitivity and specificity were 72.9% and 58.7%, respectively (Figure 2). In line with the ROC curve, the area under the curve (AUC) was 0.662 (95% CI of 0.565, 0.758).

Discussion

The present study showed that patients with PsV with intermediate and high CVD risk had significantly greater MHR and NLR values than patients with mild CVD risk and controls. We revealed the relationship between the FRS and MHR in patients with PsV. Moreover, the present study is the first to show increased NHR value among patients with PsV (FRS ≥ 10%) relative to healthy controls ($p = 0.018$). As expected, the WBC, neutrophil, monocyte, platelet, and LDL-c counts and the NLR of the PsV group were greater than those of the healthy group. Our findings conformed to those in previous reports,[8,20–22] which suggested that patients had significantly greater levels of the aforementioned experimental indicators.

The FRS is supported by a wealth of scientific evidence and is widely used around the world. It is controversial whether the FRS can predict the risk of CVDs in PsV patients. The frequency of major adverse cardiac events was greater in patients with severe PsV than in patients in the unexposed group, according to the General Practice Research Database in the UK.[23] Two observational cohort studies confirmed that lifetime, short-term, and 'PsV-modified' risk scores did not accurately reflect PsV patients at high CVD risk.[24] However, Myasoedova, Elena et al compared the predicted 10-year risk of cardiovascular events using the FRS to the observed risk of CVDs in a population-based cohort of patients with PsV. The FRS reasonably estimated cardiovascular risk in PsV patients, suggesting that the FRS can be used in risk stratification in PsV patients without further adjustment.[25] In addition, according to a clinical practice research datalink conducted in the UK, CVD risk prediction using the FRS was accurate for PsV patients. The time-dependent AUC for the FRS was 0.840 for PsV, indicating reasonably good predictive performance.[26]

Atherosclerosis is a pathological process related to PsV and CVDs, and the latter two have similar pathogenic characteristics. They all include systemic and local immune progression and the involvement of inflammatory cytokines or markers.[27] Increased neutrophil, monocyte, and lymphocyte counts but decreased HDL-c levels are linked to inflammation.[21]

Monocytes are a unique type of leukocyte whose activation can be observed in the arterial wall and blood circulation. The intermediate subset of monocytes ($CD14^{+}CD16^{+}$; IM), as well as nonclassical monocytes ($CD14^{dim}CD16^{+}$; NCM), represent proinflammatory cells, and they can be cellular markers for atherosclerosis and are related to PsV pathogenesis.[28] Classic monocytes positively associated with coronary plaque were assessed by coronary computed tomography angiography in 81 PsV patients not currently receiving biologic treatment with moderate to severe disease severity.[29] HDL-c exhibits anti-inflammatory effects and immunomodulatory functions by regulating monocytes, macrophages, lymphocytes, and dendritic cells. According to the proinflammatory effects of monocytes, together with the anti-inflammatory effects of HDL-c, the MHR is a new inflammatory biomarker indicating systemic inflammation and OS.[15] Two Turkish studies[6,21] reported that the MHR was significantly greater in the PsV group than in the control group in 2019 and 2020. However, in accordance with our findings, the MHR of the PsV group increased but not significantly. Notably, the MHR of PsV patients with an FRS ≥ 10% increased relative to those with low cardiovascular risk (FRS<10%) and controls ($p = 0.01$; $p=0.002$). This may be due to the large proportion of patients with mild disease in our PsV group.

Further analysis was performed to determine the correlation of the MHR with inflammatory and blood lipid markers in the PsV population. The MHR seemed to adequately capture the systemic inflammatory nature of PsV. First, it was correlated with CRP and the PASI ($r = 0.245$, $p = 0.005$; $r = 0.241$, $p = 0.006$). Second, significantly positive WBC, neutrophil, lymphocyte, platelet, and TG counts were detected ($r = 0.545$, $p<0.001$; $r = 0.497$, $p<0.001$; $r = 0.267$, $p = 0.002$; $r = 0.189$, $p = 0.033$; $r = 0.337$, $p<0.001$), which are indicators of angiocardiopathy. These results were similar to those in recently published literature. The MHR was related to systemic inflammatory and metabolic parameters previously involved in atherosclerosis development in European and American PsV cohorts.[7] The MHR is related to inflammatory diseases such as CVDs, hypertension, and diabetes.[7,15,30,31] High MHR and NLR are currently associated with a dismal prognosis in CVD patients.[6,15,30,32,33] Funda Tamer et al reported that the MHR in patients with PsV markedly decreased following ixekizumab treatment and suggested that ixekizumab might positively affect treatment in patients with PsV who develop CVDs.[31] The finding that the MHR was independently associated with increased coronary subclinical atherosclerosis in PsV patients was validated in two international cohorts.[7] According to our findings, the MHR was associated with the FRS in PsV patients ($r = 0.271$, $p = 0.002$). Unfortunately, the correlation appears to be weak, although significant. This could be because the MHR is more strongly associated with systemic inflammation than with traditional cardiovascular risk factors, which are the variables included in the FRS.

Neutrophil frequency is a predictor of coronary events and is involved in early atherosclerotic plaque development.[34] Moreover, in vitro studies of neutrophils have shown that PsV is associated with non-calcified coronary plaques. Low-density granulocytes-platelet interactions may play a potential role in early atherogenesis.[35] Neutrophils can promote inflammatory cell infiltration and aggregation and platelet aggregation and cause vascular blockage and stenosis.[36] Nina Vorobjeva and colleagues demonstrated that mitochondria-derived reactive oxygen species induced neutrophil activation, which was implicated in the oxidative burst as well as specific granules in vitro.[37] Their role in the immunopathogenesis of PsV and atherosclerosis has been described.[38,39] During the early stage, adhesion and extravasation to the arterial wall by neutrophils can promote LDL-c accumulation and infiltration. In later stages, it leads to plaque instability and eventually results in atherothrombotic events.[40] The NLR is a valuable indicator for predicting subclinical systemic inflammation and cardiovascular risk. The index is an important inflammatory biomarker that is predictive of CVD and CVD-associated mortality.[32] Analyses from five contemporary randomized trials revealed that the NLR independently predicts CV risk and all-cause mortality.[33] An earlier study revealed that the NLR increased among patients with PsV who developed CVD relative to patients with no CVD, and this increase was related to hs-CRP, carotid intimal media thickness, and carotid vascular inflammation. Furthermore, the NLR was associated with mRNAs and proteins in circulation linked with neutrophil degranulation. In our study, the NLR was associated with the CRP level, WBC count, monocyte count, and PASI ($r=0.2$, $p<0.05$; $r=0.28$, $p<0.05$; $r=0.22$, $p<0.05$; and $r=0.21$, $p<0.05$, respectively) (Figure 1). Similarly, an observational cohort study showed that the NLR was associated with PsV severity, hs-CRP, and NCB at baseline in 2021.[14] The findings from all these experiments indicated that the NLR may be a biomarker for subclinical CVD among patients with PsV.[41] We observed a significant association between the NLR and FRS ($r = 0.333$, $p < 0.001$). In our regression analysis, we did not find that the NLR was a factor affecting the risk of CVD in patients with PsV. We noticed that the NLR was calculated for only neutrophils and lymphocytes, unlike the MHR, which

contains monocytes and lipoproteins. Thus, we believe that neutrophil counting alone does not provide a good evaluation of the immune state represented by monocytes, which seems to play an important role in PsV.

As a novel inflammatory marker, the NHR is associated with poor clinical prognosis. As discovered by some scholars, the NHR is a novel factor that independently predicts the all-cause mortality risk of patients receiving peritoneal dialysis and is significantly related to new cardiovascular events.[42] As shown in a study including 211 hospitalized patients with acute coronary syndrome complicated by type 2 diabetes (T2D), the NHR independently predicted acute coronary syndrome risk in T2D patients.[43] According to another study conducted in China,[44] a high NHR independently predicted a high Gensini score. No study assessing the NHR in PsV patients has been reported to date; nonetheless, based on our findings, the NHR notably increased among patients with PsV (FRS $\geq$ 10%) relative to that in healthy controls ($p = 0.018$). It was positively related to the FRS ($r = 0.211$, $p = 0.017$). To the best of our knowledge, this is the first paper to analyze NHR expression and the relationship between the NHR and FRS in PsV patients.

In addition, the MHR was an influencing factor for patients with PsV at medium-high cardiovascular risk, as revealed by binary regression. Among the factors analyzed, the MHR showed greater reliability in predicting CVD risk in patients with PsV. To evaluate the prognostic significance of the MHR for patients with a medium-high risk of CVD in PsV, ROC analysis was carried out to determine the threshold, sensitivity, specificity, and AUC of the MHR. Based on the ROC curve, we found that an MHR cutoff value of 0.24 could be used as a predictive marker in PsV patients at intermediate- to high-risk for CVD, with an AUC of 0.662, a sensitivity of 72.9% and a specificity of 58.7%. According to our findings, the MHR is a novel complementary biomarker that can be used as a potential complementary assessment for the prediction of medium- to high-risk CVDs among PsV patients.

Chronic inflammation is one of the major components of many autoimmune diseases, including PsV. The MHR and NLR may reflect the severity of these autoimmune diseases and reflect systemic inflammation.[6–8,12] Moreover, systemic inflammation and metabolic abnormalities are closely interrelated and may influence atherosclerosis development synergistically.[45]

Consequently, The estimation of patients with increased systemic inflammation would be useful for predicting PsV patients who have more intermediate and high CVD risk. In clinical practice, we can monitor the MHR and NLR to assess systemic inflammation in PsV patients. PsV patients who have a high inflammatory state may have a greater cardiovascular risk.

Despite providing some valuable insights, the present study still has certain limitations. First, this was a uni-center and retrospective study. As an exploratory study, the findings should be interpreted cautiously and require further validation in larger, multi-center prospective cohorts to establish their generalizability. Second, we used FRS outcomes instead of hard cardiovascular endpoints or a direct assessment of subclinical atherosclerosis, which may limit the ability to derive definite conclusions. Third, the FRS may have a subjective bias due to collective uncertainty related to smoking and blood pressure. Therefore, the results require further confirmation from extensive evidence-based clinical and large-scale prospective studies.

While our study provides important insights into the inflammatory markers associated with PsV, it is essential to consider the role of lifestyle factors such as diet, exercise, and general living habits, which were not directly assessed in our analysis. These factors could potentially influence both the severity of PsV and the levels of inflammatory markers. For instance, diet and exercise are known to affect systemic inflammation and may thus modulate disease manifestations in PsV patients. Future studies should aim to incorporate a holistic approach that includes these lifestyle variables to provide a more comprehensive understanding of their impacts on PsV and its biological markers.

Conclusions

Our study demonstrates that the MHR is elevated in patients with PsV who are at a medium to high cardiovascular risk. Additionally, we observed a positive correlation between the MHR and the FRS. Based on these findings, the MHR could serve as a valuable inflammatory biomarker for identifying PsV patients at an increased risk of cardiovascular events. This underscores the importance of considering MHR in the cardiovascular risk assessment of PsV patients.

Ethics Approval and Informed Consent

The current study was approved by the ethics committee of the Second People's Hospital of Nantong (Reference No.2022-072) and was carried out following the Declaration of Helsinki. All patients and their families signed the informed consent form prior to the beginning of the treatment.

Author Contributions

Xueqin Gu, Hongmei Shen, Jiafeng Jiang and Ping Gu contributed equally to this work and should be considered co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

This paper has been released as a pre-print at [https://www.researchsquare.com/article/rs-3326829/v1], (Xueqin Guet al).

The authors declare that they have no competing interests.

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