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ORIGINAL RESEARCH

Association of the Monocyte to High-Density Lipoprotein Cholesterol Ratio and Neutrophil to High-Density Lipoprotein Cholesterol Ratio With the Severity of New-Onset Coronary Artery Disease

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Background: The monocyte to high-density lipoprotein cholesterol (MHR) and neutrophil to high-density lipoprotein cholesterol ratio (NHR) are novel comprehensive indicators reflecting the body's inflammation and lipid metabolism. Previous studies have found that MHR and NHR are associated with the risk of cardiovascular and cerebrovascular events and death. However, the correlation between MHR, NHR, and the severity of newly diagnosed coronary artery disease (CAD) has not been thoroughly explored.

Methods: In this retrospective study, we enrolled 1489 patients who underwent coronary angiography for the first time between January 2022 and December 2023, of which 1143 were diagnosed with CAD. The severity of CAD was gauged by the Gensini score (GS). The relationship between MHR and NHR with CAD was validated through logistic regression analysis, adjusting for traditional cardiovascular risk factors and medication therapy. The nonlinear relationship between MHR and NHR with CAD and GS was assessed by using restricted cubic spline (RCS) models. Their independent and combined predictive effects on CAD were evaluated through receiver operating characteristic (ROC) curve analysis.

Results: MHR and NHR were independently associated with CAD (both $P<0.001$). In the fully adjusted model, an increase in MHR was significantly associated with an increased odds ratio (OR) for CAD (OR=4.29, 95% CI 2.72–6.78, $P<0.001$). Sensitivity analysis revealed a consistent trend (P for trend<0.05). RCS curve analysis indicated a nonlinear relationship between the two biomarkers and GS ($P<0.05$) and there were clear inflection points. The area under the curve for predicting CAD was 0.68 for MHR and 0.69 for NHR, with optimal cut-off values of 0.42 (Youden index:0.29) and 5.43 (Youden index:0.31) respectively. Combined MHR and NHR has higher predictive value.

Conclusion: MHR and NHR are independently associated with CAD, and there is a nonlinear correlation with the GS. Both have some predictive value for the severity of CAD.

Keywords: monocyte to high-density lipoprotein cholesterol ratio, neutrophil to high-density lipoprotein cholesterol, coronary artery disease, coronary artery disease severity, Gensini score

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Introduction

CAD is a prevalent cardiovascular condition characterized by myocardial ischemia and hypoxia resulting from the constriction or blockage of coronary arteries, and remains the main cause of death worldwide.[1,2] Atherosclerosis is considered to be the initiating factor in the development of CAD, which is a systemic, lipid-driven immune-inflammatory response.[3] Among the lipid markers, high-density lipoprotein cholesterol (HDL-C) has been considered in the past to have a significant negative correlation with CAD.[4] However, recent studies have found that as the levels of HDL-C increase excessively, its protective effect on the cardiovascular system is gradually diminished. Furthermore, larger HDL particles have been associated with an increased risk of CAD.[5,6] This indicates a gradual decline in the predictive ability of traditional lipid markers for CAD. Therefore, early identification of CAD risk factors and the establishment of a stable biomarker are crucial for enhancing the diagnostic capability of CAD.

Chronic inflammatory response has been identified as a major factor in the formation of atherosclerotic plaques, with various inflammatory cells and cytokines playing significant roles in the onset of CAD.[7] Neutrophils and monocytes are key cells in the initiation of the immune-inflammatory response, and activation of inflammatory pathways is often accompanied by lipid accumulation, which accelerates vascular stenosis.[8] Neutrophils and monocytes have been found to correlate with HDL-C, and there is an interaction between reduced HDL-C levels and increased neutrophil counts.[9–11] Therefore, the novel inflammation-lipid index created by combining Neutrophil or monocyte with HDL-C has attracted researchers' attention. Recent studies have revealed that MHR and NHR were associated with coronary artery plaque formation and adverse prognosis of CAD.[12,13] For the patients with CAD, novel inflammation-lipid index combination may offer a more comprehensive assessment of lipid status compared to a single lipid index. Furthermore, the linear relationship between these two biomarkers and the severity of CAD has not been further elucidated. However, it has come to our attention that the relationship between these two biomarkers and the severity of CAD has not been further elucidated.

Materials and Methods

Study Participants

The retrospective study included 2380 patients who underwent CAG at the Affiliated Qingyuan Hospital, Guangzhou Medical University (Qingyuan People's Hospital) between 2022 and 2023. Patients with a history of CAG or coronary artery bypass grafting, aged below 18 or above 75, malignancies, severe liver or kidney dysfunction, thyroid dysfunction, severe infections, autoimmune diseases, or incomplete medical records were excluded from the study. Ultimately, 1489 patients were recruited for this study, with 1143 patients diagnosed with CAD and 346 non-CAD patients (Figure 1).This study was conducted at the Qingyuan People's Hospital and the research was carried out following the Helsinki Declaration and was authorized by the Institutional Review Board (IRB-2024-092) of the Qingyuan People's Hospital. Due to its retrospective nature, the requirement for informed consent was waived by the committee.

Data Collection and Outcome

Data were collected by qualified research coordinators from electronic medical records at each participating center. Baseline demographic and clinical information including age, gender, height, weight, systolic blood pressure, diastolic blood pressure, smoking and drinking status, clinical history including hypertension, diabetes, and medication treatment (antihypertensive and antidiabetic medications). Blood samples were collected from all patients before undergoing coronary angiography, with fasting blood glucose specimens collected on the second day of hospitalization, calculating the MHR and NHR for all blood samples. Assessment of coronary artery stenosis by two independent senior cardiologists based on CAG results. The GS system was used to determine the coronary artery atherosclerotic lesions: luminal stenosis less than 25%, 25 to 50%, 51 to 75%, 76 to 90%, 91 to 99%, and 100%, and given 1, 2, 4, 8, 16, and 32 scores, respectively; and the resulting score was multiplied by the coefficients of the vessels in which the lesions were located: 5 for the left main coronary artery, 2.5 for proximal segment of the left anterior descending coronary artery and proximal segment of the circumflex artery, 1.5 for the mid-segment of the left anterior descending coronary artery, 1 for the the right coronary artery, the distal segment of the left anterior descending coronary artery, the posterolateral artery, and the obtuse marginal artery, and 0.5 for the rest of the branches; the total score of coronary artery lesions in each patient was

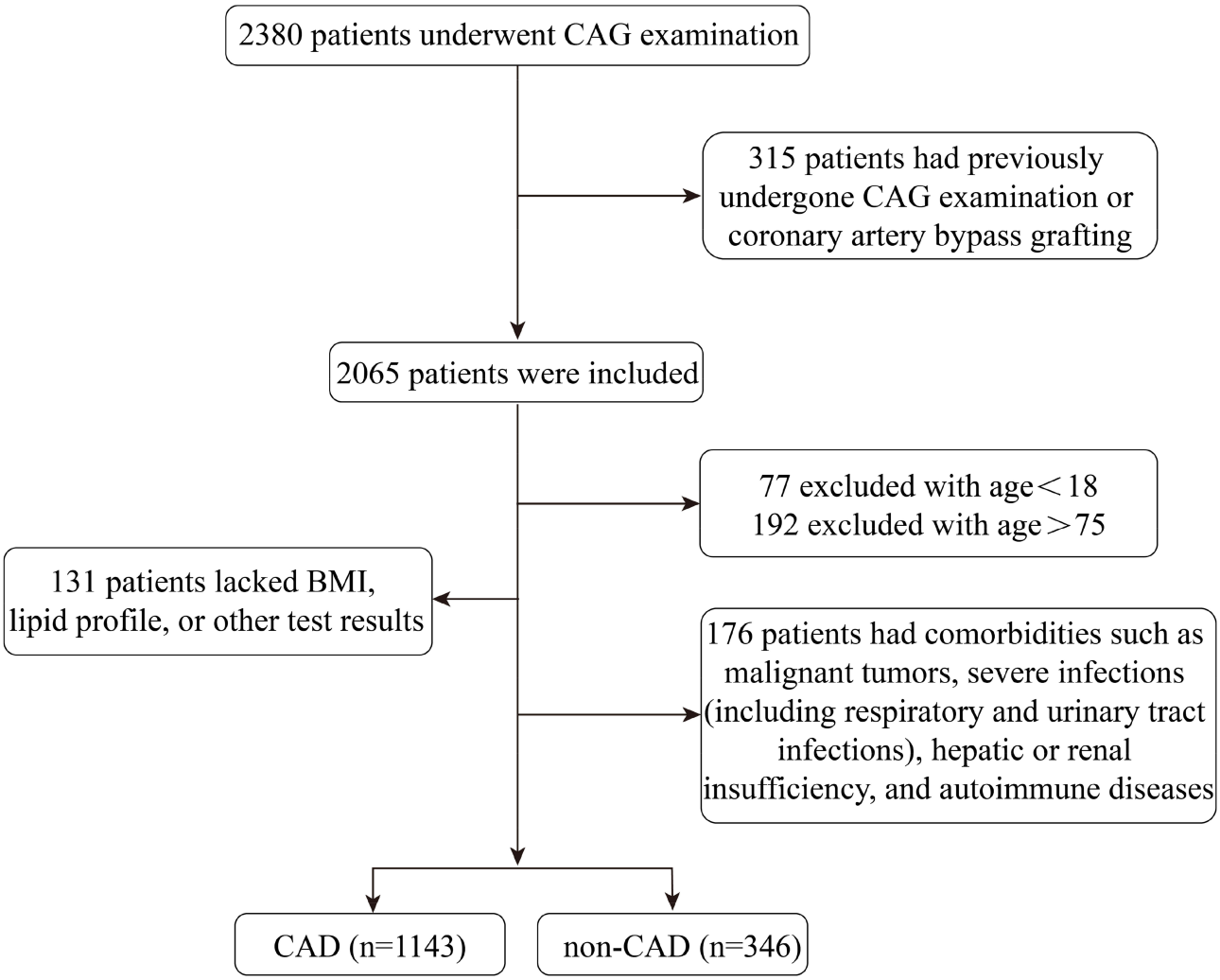

Figure 1 The flow chart of study population selection.
Abbreviations: CAG, coronary angiography; BMI, body mass index; CAD, coronary artery disease.

the sum of the scores of the various branches of the vessels, and the higher the score represents the more severe stenosis of the lesion.[14]

Definitions

According to the 2012 ACC/AHA guidelines, CAD is characterized by a ≥50% stenosis (diameter>2mm) in at least one epicardial coronary artery;[2] hypertension is defined as a condition in which blood pressure remains at 140/90mmHg or higher, or they were being given antihypertensive drugs.[15] Height and weight were measured to calculate body mass index (BMI), which was counted as weight divided by height squared (weight in kilograms and height in meters). The MHR and NHR were determined using the formulas: MHR=monocyte (10^9/L) to HDL-C (mmol/L); NHR=neutrophil (10^9/L) to HDL-C (mmol/L).

Statistical Analysis

All statistical analyses were performed using R software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria) and MSTATA software https://www.mstata.com/). All continuous variable data were tested for normality (Kolmogorov–Smirnov test) before being analyzed, presented as mean±standard deviation (SD) if normally distributed, with independent Student,s *t*-test or one-way ANOVA. Otherwise, it is represented as the median and interquartile range

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(IQR), using the Mann–Whitney *U*-test or the Kruskal–Wallis *H*-test. Categorical variables were shown as frequency and percentage, the Chi-squared test or Fisher's exact test was used to compare these variables.

We conducted univariate and multivariate logistic regression analyses for patients in the CAD and non-CAD groups, incorporating OR and corresponding 95% confidence intervals (CIs) to validate the relationships between MHR, NHR, and CAD. In the multivariate logistic regression analysis, we adjusted for potential confounders, primarily those with p-values <0.05 in baseline characteristics including age, sex, BMI, smoking status, hypertension, diabetes, antihypertensive drugs, and antidiabetic drugs. Three models were formulated within quartiles of MHR and NHR to scrutinize the interactions between MHR and NHR with CAD: Model 1(crude model) was analyzed with no covariate adjusted. Model 2 adjusted for age and sex. Model 3 was the fully adjusted model that improved on Model 2 by introducing BMI, smoking, hypertension, antihypertensive drugs, diabetic, and antidiabetic drugs. In addition, in order to explore the non-linear relationship between MHR, NHR, and the severity of new-onset CAD, RCS regression was performed based on Model 3.[16]

ROC were used to analyze the predictive value of MHR and NHR for CAD. The area under the curve (AUC) was compared using a Z-test, and the optimal cutoff value was determined by maximizing the Youden index. All reported p-values are 2-sided, and a $P<0.05$ was regarded as statistically significant.

Results

Baseline Characteristics of the non-CAD and CAD

The clinicodemographic feature analysis involved a total of 1143 newly diagnosed CAD patients and 346 non-CAD patients. Among the CAD patients, there were 890 males with a mean age of 59 years (IQR, 53–68). Patients in the CAD group had a higher percentage of age, male, and history of smoking, hypertension, diabetes, antihypertensive drugs, and antidiabetic drugs ($P<0.001$), respectively. The BMI, FPG, HbA1c, TG, HDL-C, LDL-C, CRP, WBC, MON, Neu, NHR, and MHR were observed between the CAD and non-CAD groups ($P<0.05$) (Table 1).

Associations of the MHR and NHR With CAD

The MHR was categorized into four groups based on quartiles: I ($0\leq MHR<0.35$), II ($0.35\leq MHR<0.57$), III ($0.57\leq MHR<0.71$), and IV ($0.71\leq MHR\leq 3.52$). After adjusting for traditional cardiovascular risk factors and medical treatments, the logistic regression model revealed a significant correlation between the MHR and CAD ($P<0.001$). A notable connection with CAD was demonstrated when MHR was considered as a continuous variable (OR=6.64, 95% CI 3.66–12.07; $P<0.001$). Furthermore, in fully adjusted analyses, the association between MHR as a categorical variable and CAD remained significant (OR=4.29, 95% CI 2.72–6.78, $P<0.001$) (Table 2). Based on Model 3, we employed the RCS model to assess the relationship between MHR and CAD. The findings indicated that there was no significant nonlinear relationship (P for nonlinear=0.154) (Figure 2), it seemed that the prevalence of CAD increased with increasing MHR.

Similarly, the NHR was categorized into four groups based on quartiles: I ($0.34\leq NHR<3.70$), II ($3.70\leq NHR<6.16$), III ($6.16\leq NHR<7.58$), and IV ($7.58\leq NHR\leq 37.8$). The fully adjusted logistic regression model revealed a stable and significant positive correlation between NHR and CAD ($P<0.001$). Furthermore, when NHR was a categorical variable, the fully adjusted model indicated that a significant correlation with CAD was firmly established (OR=4.69, 95% CI 3.04–7.23, $P<0.001$) (Table 3). The RCS model demonstrated a significant nonlinear relationship between NHR and CAD (P for nonlinear<0.001) (Figure 3). From Figure 3 we can detect that the ORs for the association between NHR and CAD were increased with elevated NHR levels. When NHR reached 10.8, the OR showed a declining trend.

To further explore the differences between MHR and NHR in predicting CAD in males and females, we stratified the population. As shown in Table 4 and Table 5, MHR was significantly correlated with new-onset CAD in the male population; however, the same result did not occur in females ($P=0.751$). In both males and females, NHR was significantly correlated with new-onset CAD, and trend analysis showed the same results (both $P<0.05$).

Table 1 Baseline Characteristics of the non-CAD and CAD

Variables	CAD		*P*
	Non-CAD (n = 346)	CAD (n = 1143)	
Age (year)	57 (49, 65)	59 (53, 68)	<0.001*
Male [n(%)]	177 (51.2%)	890 (77.9%)	<0.001*
BMI (kg/m^2)	24.4 (22.5, 27.2)	24.2 (22.1, 26.2)	0.045*
Smoking [n(%)]	113 (32.7%)	658 (57.6%)	<0.001*
Hypertension [n(%)]	146 (42.2%)	604 (52.8%)	<0.001*
Antihypertensive drugs [n(%)]	111 (32.1%)	484 (42.3%)	<0.001*
Diabetes [n(%)]	70 (20.2%)	407 (35.6%)	<0.001*
Antidiabetic drugs [n(%)]	46 (13.3%)	240 (21.0%)	0.001*
SBP (mmHg)	134 (120, 148)	132 (119, 147)	0.685
DBP (mmHg)	83 (75, 93)	82 (74, 92)	0.237
Fasting plasma glucose (mmol/L)	5.48 (5.01, 6.15)	6.00 (5.21, 7.41)	<0.001*
Hemoglobin A1c (%)	5.95 (5.60, 6.40)	6.10 (5.70, 6.90)	<0.001*
Total cholesterol (mmol/L)	4.37 (3.86, 5.12)	4.51 (3.80, 5.32)	0.065
Triglyceride (mmol/L)	1.36 (0.97, 1.89)	1.53 (1.08, 2.29)	<0.001*
HDL-C (mmol/L)	1.17 (0.98, 1.42)	1.02 (0.86, 1.22)	<0.001*
LDL-C (mmol/L)	2.86 (2.33, 3.50)	3.02 (2.40, 3.74)	0.011*
C-reactive protein (mg/L)	2 (1, 4)	3 (1, 11)	<0.001*
White blood cell (×10^9/L)	7.5 (6.0, 9.1)	8.7 (7.0, 11.1)	<0.001*
Monocyte (×10^9/L)	0.49 (0.40, 0.60)	0.51 (0.40, 0.70)	<0.001*
Neutrophil (×10^9/L)	4.67 (3.60, 6.24)	5.88 (4.40, 7.88)	<0.001*
Gensini score	0 (0, 2)	50 (28, 80)	<0.001*
MHR	0.38 (0.29, 0.53)	0.53 (0.38, 0.75)	<0.001*
NHR	4.0 (2.8, 5.4)	5.9 (4.1, 7.9)	<0.001*

Notes: Continuous variates were shown as median and interquartile range (IQR), encompassing the 25th (Q25) and 75th (Q75) percentiles. The Mann–Whitney *U*-test or Chi-squared test were used to compare these variables.*P<0.05.

Abbreviations: CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHR, neutrophil to HDL-C ratio; MHR, monocyte to HDL-C ratio.

Table 2 Association Between the MHR and CAD

Variables	CAD					
	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
MHR	11.30 (6.46,19.76)	<0.001*	8.04 (4.48,14.43)	<0.001*	6.64 (3.66,12.07)	<0.001*
I	1.0		1.0		1.0	
II	1.71 (1.25,2.33)	<0.001*	1.44 (1.04,2.01)	0.029*	1.29 (0.92,1.81)	0.144
III	2.76 (1.97,3.86)	<0.001*	2.22 (1.55,3.19)	<0.001*	1.98 (1.36,2.87)	<0.001*
IV	6.25 (4.14,9.41)	<0.001*	5.07 (3.26,7.88)	<0.001*	4.29 (2.72,6.78)	<0.001*
P for trend	<0.001*		<0.001*		<0.001*	

Notes: Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, BMI, smoking, hypertension, antihypertensive drugs, diabetic, and antidiabetic drugs.*P<0.05.

Abbreviations: OR, Odds ratio; CI, Confidence interval; CAD, coronary artery disease; MHR, Monocyte to HDL-C ratio.

Relationship Between MHR, NHR, and GS

In RCS, adjustments were made for covariates including age, gender, body mass index, smoking, hypertension, antihypertensive drug, diabetes, and antidiabetic drug. A significant nonlinear relationship between MHR and GS was

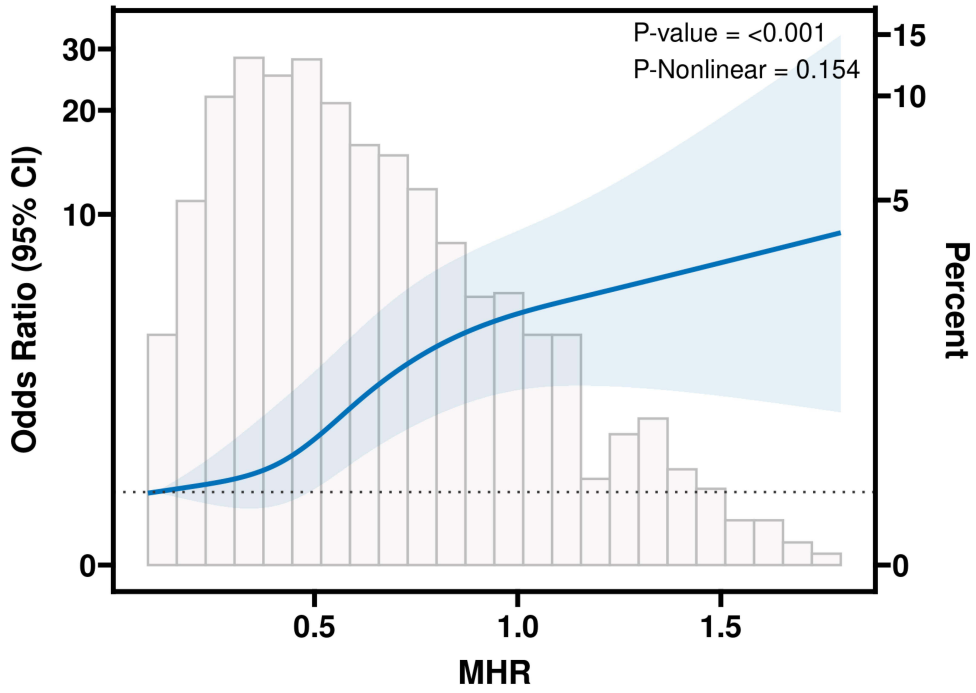

Figure 2 Association between MHR and CAD with the RCS function. The Y-axis represents the OR to present CAD for any value of MHR compared to individuals with the reference value (1st percentile) of MHR. The logistic regression was adjusted for Gender, Age, BMI, Hypertension, and antihypertensive drugs, Diabetes, antidiabetic drugs, and Smoking.
Abbreviations: MHR, Monocyte to HDL-C ratio; CI, Confidence interval.

observed (*P* for nonlinear<0.012) (Figure 4). It was observed that the prevalence of CAD with increasing MHR until it reached 0.65, after which the β value of CAD reached a plateau. Also, there is a nonlinear relationship between NHR and GS (*P* for nonlinear<0.001) (Figure 5). When the inflection point value of NHR is less than 10.3, the β-value of GS gradually increases with the increase in NHR, and then the β-value of the GS appeared to be decreasing.

Predictive Values of the MHR and NHR in CAD

The ROC curve analysis of CAD prediction by MHR and NHR is shown in Figure 6. The AUC for CAD prediction by MHR and NHR was 0.677 and 0.689 (both *P*<0.001), respectively, with the cut-off value of 0.420 (Youden's index:

Table 3 Association Between the NHR and CAD

Variables	CAD					
	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
NHR	11.30 (6.46,19.76)	<0.001*	8.04 (4.48,14.43)	<0.001*	1.21 (1.14,1.27)	<0.001*
I	1.0		1.0		1.0	
II	1.79 (1.31,2.43)	<0.001*	1.63 (1.17,2.26)	0.004*	1.57 (1.12,2.21)	0.009*
III	3.98 (2.79,5.68)	<0.001*	3.79 (2.60,5.54)	<0.001*	3.36 (2.27,4.96)	<0.001*
IV	5.62 (3.82,8.29)	<0.001*	5.41 (3.55,8.24)	<0.001*	4.69 (3.04,7.23)	<0.001*
P for trend	<0.001*		<0.001*		<0.001*	

Notes: Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, BMI, smoking, hypertension, antihypertensive drugs, diabetic, and antidiabetic drugs.**P*<0.05.
Abbreviations: OR, Odds ratio; CI, Confidence interval; CAD, coronary artery disease; NHR, neutrophil to HDL-C ratio.

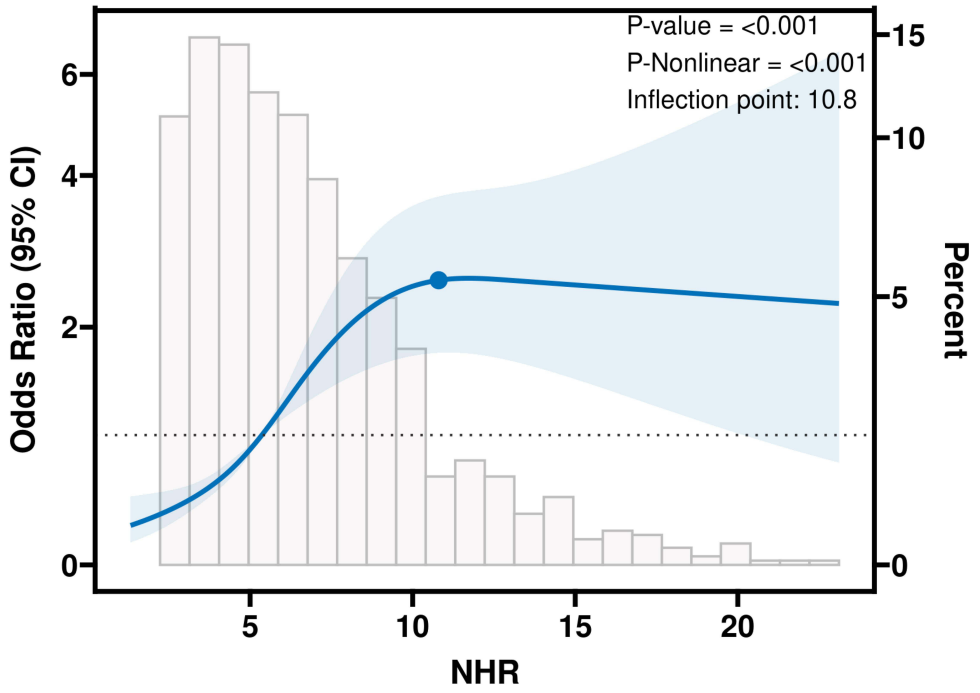

Figure 3 Association between NHR and CAD with the RCS function. The Y-axis represents the OR to present CAD for any value of NHR compared to individuals with a reference value (50th percentile) of NHR. The logistic regression was adjusted for Gender, Age, BMI, Hypertension, and antihypertensive drugs, Diabetes, antidiabetic drugs, and Smoking.
Abbreviations: NHR, Neutrophil to HDL-C ratio; CI, Confidence interval.

0.286) and 5.434 (Youden's index: 0.316). The AUC for the joint prediction of CAD by MHR and NHR was 0.705 (95% CI 0.673–0.737, P<0.001).

Discussion

The present study demonstrated that both MHR and NHR, as comprehensive assessment indicators of inflammation and lipids, were independently associated with new-onset CAD. Moreover, we utilized CAG results to calculate patients' GS for assessing the relationship between MHR, HNR, and the severity of coronary artery stenosis. The RCS curves revealed a non-linear correlation between the two biomarkers with distinct thresholds. Subsequently, MHR reached a plateau phase in its impact on the severity of coronary artery stenosis, whereas the influence of HNR gradually diminished

Table 4 Relationship Between MHR and New-Onset CAD in Different Gender Populations

	CAD					
	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Male						
MHR	8.75 (4.33,17.66)	<0.001*	12.46(5.97,26.00)	<0.001*	8.61 (3.82,19.39)	<0.001*
I	Reference		Reference		Reference	
II	1.40 (0.91,2.17)	0.130	1.51 (0.97,2.37)	0.070	1.40 (0.87,2.24)	0.162
III	2.33 (1.48,3.67)	<0.001*	2.73 (1.70,4.37)	<0.001*	2.20 (1.32,3.66)	0.002*
IV	5.80 (3.37,9.96)	<0.001*	7.42 (4.23,13.00)	<0.001*	5.50 (2.96,10.21)	<0.001*
P for trend	<0.001*		<0.001*		<0.001*	

(*Continued*)

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Table 4 (Continued).

	CAD					
	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Female						
MHR	3.49 (1.32,9.24)	0.012*	3.27 (1.17,9.08)	0.023*	1.19 (0.40,3.57)	0.751
I	Reference		Reference		Reference	
II	1.57 (0.98,2.52)	0.061	1.58 (0.96,2.58)	0.071	1.10 (0.61,1.97)	0.751
III	1.78 (1.01,3.14)	0.045*	1.78 (0.99,3.23)	0.056	1.26 (0.63,2.54)	0.509
IV	2.08 (1.01,4.33)	0.050	2.06 (0.94,4.53)	0.071	1.06 (0.41,2.71)	0.903
P for trend	0.009*		0.021*		0.762	

Notes: Model 1: unadjusted; Model 2: adjusted for age and BMI; Model 3: adjusted for age, BMI, smoking, hypertension, antihypertensive drugs, diabetic, and antidiabetic drugs.*P<0.05.
Abbreviations: OR, Odds ratio; CI, Confidence interval; CAD, coronary artery disease; MHR, Monocyte to HDL-C ratio.

Table 5 Relationship Between NHR and New-Onset CAD in Different Gender Populations

	CAD					
	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Male						
NHR	1.16 (1.09,1.23)	<0.001*	1.21 (1.13,1.29)	<0.001*	1.15 (1.07,1.23)	<0.001*
I	Reference		Reference		Reference	
II	1.32 (0.86, 2.02)	0.199	1.54 (0.99,2.39)	0.054	1.33 (0.84,2.09)	0.228
III	3.13 (1.93, 5.08)	<0.001*	4.07 (2.46,6.74)	<0.001*	3.16 (1.85,5.40)	<0.001*
IV	3.78 (2.32, 6.18)	<0.001*	5.43 (3.23,9.14)	<0.001*	3.73 (2.11,6.58)	<0.001*
P for trend	<0.001*		<0.001*		<0.001*	
Female						
NHR	1.29 (1.17, 1.43)	<0.001*	1.32 (1.18,1.47)	<0.001*	1.03 (1.06,1.10)	0.036*
I	Reference		Reference		Reference	
II	1.78 (1.09, 2.91)	0.020*	1.91 (1.14,3.21)	0.014*	1.48 (0.81, 2.70)	0.020*
III	3.22 (1.83, 5.68)	<0.001*	3.63 (1.99,6.61)	<0.001*	2.26 (1.14, 4.51)	0.010*
IV	4.91(2.33,10.38)	<0.001*	5.50 (2.46,12.31)	<0.001*	3.39 (1.34, 8.61)	<0.001*
P for trend	<0.001*		<0.001*		0.002*	

Notes: Model 1: unadjusted; Model 2: adjusted for age and BMI; Model 3: adjusted for age, BMI, smoking, hypertension, antihypertensive drugs, diabetic, and antidiabetic drugs.*P<0.05.
Abbreviations: OR, Odds ratio; CI, Confidence interval; CAD, coronary artery disease; NHR, neutrophil to HDL-C ratio.

beyond a certain point. Finally, the ROC curves revealed the optimal cutoff values of MHR and NHR for the diagnosis of new-onset CAD, and our study showed that MHR≧0.420 and NHR≧5.434 had a good discriminatory power in diagnosing patients with CAD.

There is substantial support from previous studies for the relationship between MHR, NHR, and CAD.[17–19] However, due to the sample size and design of the study, further confirmation is needed to establish the relationship between these biomarkers and the severity of CAD. We have the advantage of having a larger sample size to achieve robust results compared to previous studies. The current work complements existing knowledge by furthering the understanding of

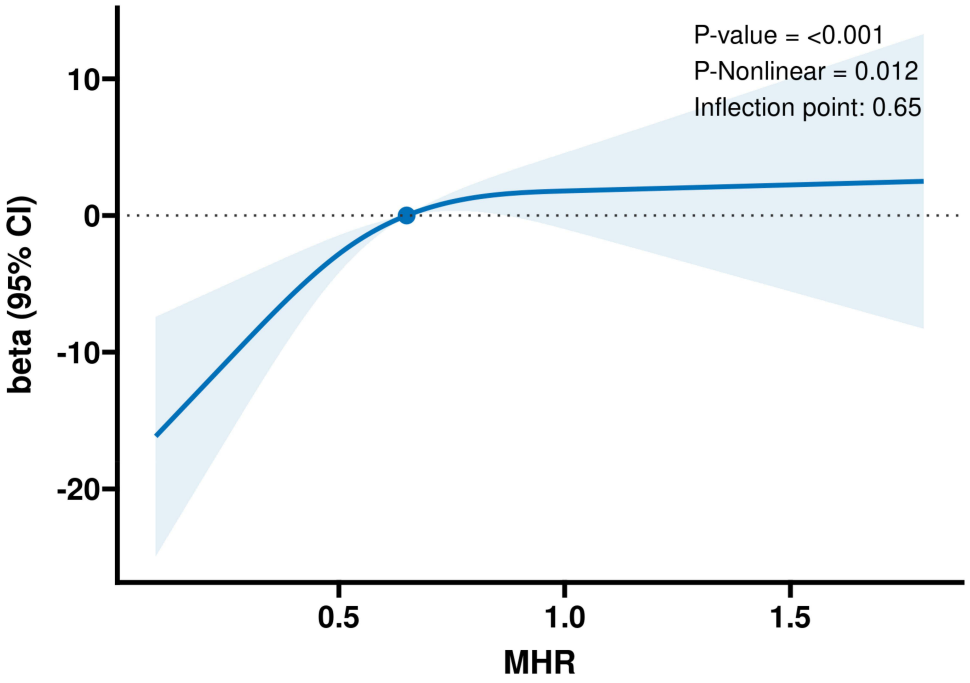

Figure 4 Association between MHR and GS with the RCS function. The Y-axis represents the beta to present GS for any value of MHR compared to individuals with a reference value (50th percentile) of MHR. The logistic regression was adjusted for Gender, Age, BMI, Hypertension, and antihypertensive drugs, Diabetes, antidiabetic drugs, and Smoking.
Abbreviations: MHR, Monocyte to HDL-C ratio; CI, Confidence interval.

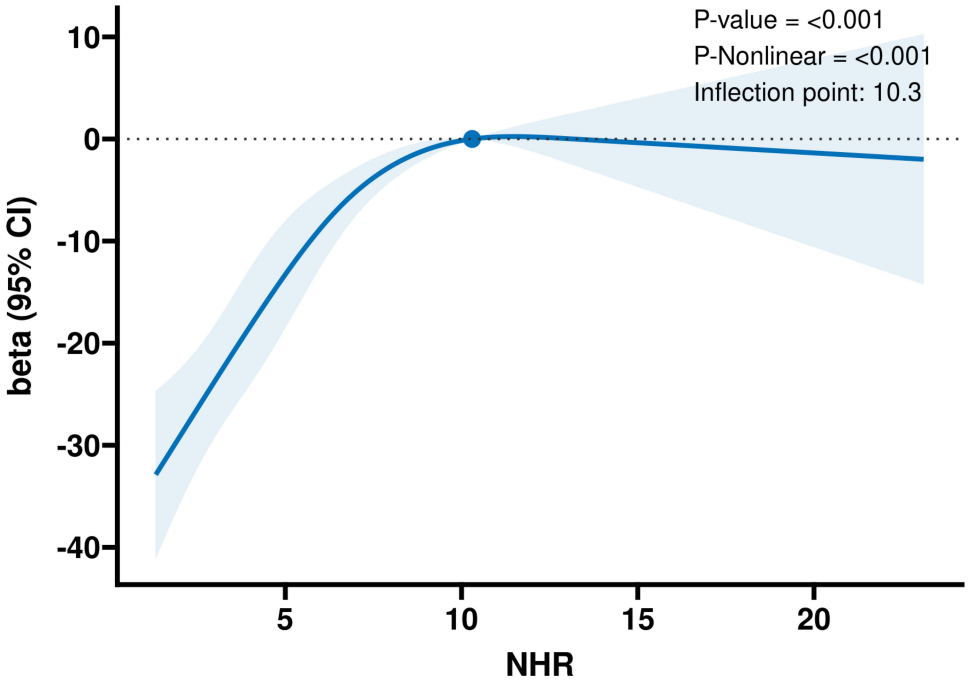

Figure 5 Association between NHR and GS with the RCS function. The Y-axis represents the beta to present GS for any value of NHR compared to individuals with a reference value (50th percentile) of NHR. The logistic regression was adjusted for Gender, Age, BMI, Hypertension, and antihypertensive drugs, Diabetes, antidiabetic drugs, and Smoking.
Abbreviations: NHR, Neutrophil to HDL-C ratio; CI, Confidence interval.

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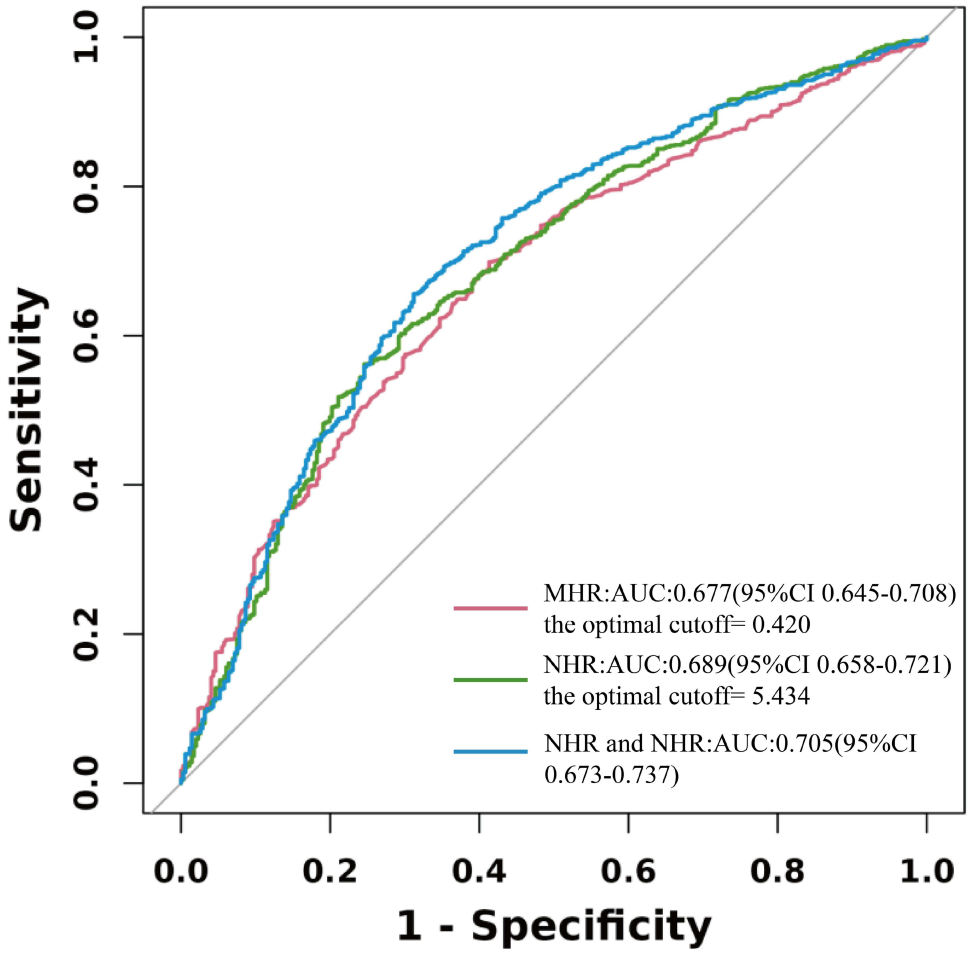

Figure 6 ROC curve analysis of the MHR and NHR for CAD prediction.
Abbreviations: ROC curve, receiver operator characteristic curve; AUC, area under the curve; NHR, Neutrophil to HDL-C ratio; MHR, Monocyte to HDL-C ratio; CI, Confidence interval.

inflammation cells like monocytes and neutrophils in atherosclerosis. These cells play a pivotal role in coordinating the inflammatory process, which is a fundamental component in the occurrence and progression of atherosclerosis. More critically, there appears to be a close interaction between circulating monocytes and HDL-C. Inflammatory monocytes adhere to the arterial wall, penetrate the intima, differentiate into macrophages, and subsequently ingest lipids to transform into foam cells, leading to local lipid metabolism imbalance. Importantly, they interact with platelets and endothelial cells, exacerbating inflammation, activating the thrombotic pathway, and ultimately culminating in the occurrence of cardiovascular diseases. Initially, monocytes serve as a diagnostic marker for cardiovascular diseases,[20,21] The HDL-C molecules can impede the differentiation of monocytes into macrophages, inhibit the migration of macrophages, and facilitate the clearance of cholesterol within these cells.[22] In addition, HDL-C exerts anti-inflammatory, antithrombotic, and antioxidant effects to a certain extent in CAD patients and attenuates and reverses monocyte activation through apoA-I-mediated CD11b inhibition.[23] MHR has been identified as a composite indicator of monocyte and HDL-C and has been reported as a novel predictive and prognostic marker for CAD and sepsis.[24] Our study confirmed that MHR was a risk factor for new-onset CAD. Furthermore, we found the nonlinear relationship between MHR and GS using RCS curves in this study. Notably, as MHR levels increase to 0.65, the risk of CAD occurrence will plateau. This supplements previous studies by highlighting that high HDL-C levels do not always confer protective effects, and under certain conditions, may even increase risk, emphasizing the critical role of HDL-C functionality.[6]

Neutrophils, the most abundant subtype of white blood cells, play a crucial role in inflammation within the body and can exacerbate vascular wall inflammation.[25] Neutrophils will activate macrophages, further promoting monocyte recruitment and cytotoxicity, thereby accelerating various stages of atherosclerosis.[26] Activated neutrophils can mediate HDL oxidation and impede cholesterol efflux by possessing oxidant-producing enzymes.[27] A significant presence of neutrophils is observed in advanced atherosclerotic plaques, with their count positively correlating with the histopathological features of vulnerable atherosclerotic lesions prone to rupture.[28] Current findings show a correlation between neutrophils and CAD.[29] Our data also indicates that the levels of inflammatory markers, including CRP, are higher in the CAD group compared to the non-CAD group ($P<0.001$). In recent years, with the emergence of some low-cost and scientifically proven markers for inflammation and blood lipids, NHR has been associated with the occurrence of CAD. In the diabetic population, elevated glucose levels can increase the expression of markers associated with chronic inflammation, leading to the accumulation of white blood cells, particularly neutrophils,[30] insulin resistance may also disrupt glucose metabolism, initiating oxidative stress and inflammatory responses that harm vascular endothelial cells.[31] In a retrospective study analysis, researchers found that patients with type 2 diabetes had higher levels of neutrophils and lower lymphocytes, and that the ratio correlated significantly with the development of acute coronary syndromes.[32] Apart from CAD, NHR can also be used to predict the incidence of peripheral arterial disease, ischemic stroke, and other vascular diseases in patients with type 2 diabetes.[33,34]

In our study, MHR and NHR demonstrated significant differences between CAD and non-CAD groups, and based on regression analysis, it remained a risk factor for CAD. The usefulness of traditional lipids including total cholesterol, HDL-C, low-density lipoprotein cholesterol, and triglyceride is mainly limited to predicting risk in populations at the low and high ends of the CVD risk spectrum. In contrast, MHR and NHR serve as composite measures that consider both inflammatory and lipid fractions. As such, they reflect bidirectional cholesterol transport (inward and outward) through the arterial intima and are more reliable than individual lipid fractions in predicting cardiovascular disease.[35]

In clinical practice, despite significant advances in percutaneous coronary intervention (PCI), the prediction of CAD occurrence remains challenging. In this context, the present study evaluated biomarkers (MHR and NHR) for predicting CVD events in search of a suitable tool for CAD (inexpensive, rapid, specific, and non-invasive). In recent years, in addition to blood parameters, innovative non-invasive imaging technologies have played a role in predicting CAD occurrence. The modified Haller index (MHI), calculated using transthoracic echocardiography and simple tools as the ratio of chest transverse diameter to the distance between the sternum and spine, indicates that a higher MHI ($MHI > 2.5$) signifies a lower risk of cardiovascular events, stable lipid levels, and lower inflammation indices.[36] Despite the different methods of obtaining these new indices, their application will reduce unnecessary examinations and further save medical resources. This information is invaluable for healthcare professionals, in addition, it is important to recognize that some patients may not be suitable for PCI due to hemodynamic instability, refusal of the procedure by a family member, time constraints for intervention, or limited resources in the hospital. In these cases, the MHR, or NHR can be used as an initial assessment tool to evaluate the degree of coronary stenosis. It is important to note that although MHR and HNR have some advantages in predicting new-onset CAD, gender differences may affect our identification of high-risk populations. As shown in our study, there was no significant correlation between MHR and CAD occurrence in the female population, the mechanisms need to be further explored. Nevertheless, these initial assessments have high application value and assist the clinician to take appropriate decisions.

Limitations

Our analysis had some potential limitations. Firstly, being a single-center retrospective study, we solely utilized data from a specific region in China. The patient information of all participants was sourced from the electronic medical record system of a tertiary hospital in that region, lacking in randomization and thus susceptible to bias. Second, the GS system used to assess the severity of coronary lesions neglected to assess the coronary vessel bifurcation sites, vessel calcification, and vessel alignment, which may have underestimated the extent of the lesions and may have affected our results, which could have well avoided by the SYNTAX scoring as opposed to the GS system, and which is what we further intend to study in the future to achieve a more accurate assessment of study outcomes. In addition to this, a certain degree of subjectivity exists even though the same imaging results were reviewed by two specialized physicians. Third, our study population included patients with stable angina and acute coronary syndromes, and we know that immunoinflammatory cells such as neutrophils, monocytes, lymphocytes, and

macrophages are elevated after an acute myocardial infarction to participate in the cardiac healing process.[37,38] Possessing measurements of dynamic inflammation and blood lipid levels could enhance the stability of our research endeavors. Additionally, despite adjusting for covariates, inherent individual differences may still present potential biases. Future studies should consider these factors and necessitate well-designed, larger-scale prospective research to further investigate the predictive value of NHR combined with MHR in patients with coronary artery disease.

Conclusion

MHR and NHR can be rapidly and conveniently obtained in laboratory tests upon admission, making them applicable in various clinical settings. This study has confirmed the correlation between MHR and NHR with new-onset CAD and GS, both have some predictive value, and the combination of the two indicators has higher predictive efficacy. In clinical practice, We can identify people at high risk for CAD by the results shown in the RCS and ROC.

Abbreviations

CAD, coronary artery disease; MHR, monocyte to high-density lipoprotein cholesterol ratio; NHR, neutrophil to high-density lipoprotein cholesterol ratio; CAG, coronary angiography; GS, Gensini score; RCS, restricted cubic spline; OR, the odds ratio; ROC curves, Receiver operating characteristic curves; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; BMI, body mass index; IQR, interquartile range; CIs, confidence intervals; AUC, area under the curve; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; WBC, white blood cell; Mon, monocyte; Neu, neutrophil; PCI, percutaneous coronary intervention.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to their containing information that could compromise the privacy of patients.

Ethics Approval and Consent to Participate

This study was conducted at the Qingyuan People's Hospital. The research was carried out following the Helsinki Declaration and was authorized by the Institutional Review Board (IRB-2024-092) of the Qingyuan People's Hospital. Due to its retrospective nature, the requirement for informed consent was waived by the committee. The study conducted was a retrospective analysis, only clinical data from participants/patients was collected for research purposes, with the study results intended solely for exploratory analysis. Furthermore, as there were no commercial interests involved, the ethics committee waived the requirement for patient informed consent. The results of the study will be stripped of any subject/patient identifying characters (such as name and address) to ensure that personal privacy is not compromised.

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Author Contributions

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

The author(s) report no conflicts of interest in this work.

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