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Relationship of monocyte to high-density lipoprotein ratio (MHR) and other inflammatory biomarkers with sarcopenia: a population-based study

Zhiwei Xue[1], Jian Cao[1], Jianhui Mou[1], Rui Wang[1] and Peng Liu[1*]

Abstract

Objectives In previous studies, several inflammatory biomarkers derived from complete blood cell counts (CBC), such as systemic immune inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) have been identified as predictors of sarcopenia. However, whether Monocyte to High-Density Lipoprotein Cholesterol Ratio (MHR) can predict the development of sarcopenia has not yet been established. The research first attempts to investigate the association between MHR and low muscle mass and to compare the predictive abilities of MHR, SII, NLR, and NHHR for low muscle mass risk.

Methods The study comprised 10,321 participants aged 20 years and above from the United States. Multiple logistic regression was performed to explore the association between ln-transformed MHR, SII, NLR, NHHR and low muscle mass. Additionally, AUC values and ROC curves were used to assess the predictive effectiveness of ln MHR and other markers (ln SII, ln NLR, ln NHHR, ln MHR + ln SII, ln MHR + ln NHHR, and ln MHR + ln NLR). The bootstrap estimated 95% CI was shown with the AUC.

Results In the fully adjusted model, ln SII, ln NLR, ln NHHR, ln MHR, ln MHR + ln SII, ln MHR + ln NHHR, and ln MHR + ln NLR were positively associated with low muscle mass (ln SII: OR = 1.59 [1.37–1.84]; ln NLR: OR = 1.35 [1.13–1.60]; ln NHHR: OR = 1.49[1.27–1.75]; ln MHR: OR = 1.98 [1.68–2.33]; ln MHR + ln SII: OR = 1.61 [1.46–1.79]; ln MHR + ln NHHR: OR = 1.42 [1.29–1.56]; ln MHR + ln NLR: OR = 1.58 [1.41–1.78]). Compared to the lowest quartile of ln MHR, higher quartiles were significantly associated with increased odds of low muscle mass (*P* for trend < 0.0001). In ROC analysis, ln MHR + ln SII had a higher AUC value than other indicators (AUC = 0.608).

Conclusion Ln-transformed MHR, SII, NLR, and NHHR were positively associated with low muscle mass. MHR outperforms SII, NLR, and NHHR in predicting sarcopenia.

Keywords Monocyte to high-density lipoprotein cholesterol ratio, Sarcopenia, Low muscle mass, NHANES

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Introduction

Sarcopenia is a systemic condition associated with the aging process, clinically characterized by a reduction in skeletal muscle mass and impaired functional capacity [1–3]. Sarcopenia can cause weakness, falls, and physical disability [4], with a significant impact on well-being and standard of living [5]. The prevalence is increasing with the development of an aging population [6]. Sarcopenia is primarily caused by natural aging but can also be influenced by additional factors [7]. It is reported to occur not solely among the elderly [8]. Oxidative stress is the primary pathogenesis of sarcopenia [9], but the degree of obesity [10], sex hormone levels [11], amount of exercise [12], and protein intake [13] may also affect its development. Prevalence estimates vary depending on the definition of sarcopenia; however, even with conservative methodologies, the prevalence in the general population ranges from 5–10% [14]. Sarcopenia requires increased attention in clinical practice.

In previous studies, several inflammatory biomarkers derived from CBC, including systemic immune inflammation index (SII) [15], and non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) [16] have been shown to act as predictors of sarcopenia. Increased neutrophil-to-lymphocyte ratio (NLR) levels are significantly correlated with a higher incidence of sarcopenia [17]. Monocytes can maintain homeostasis through recruitment but can also promote inflammation [18]. In contrast, HDL-c has strong antioxidant and anti-inflammatory capacity [19]. T-cell immunomodulation mitigates chronic inflammation, thereby alleviating sarcopenia [20]. Reduced muscle mass may be prevalent in an aged Chinese demographic with HDL-C levels exceeding 70 mg/dl [21]. The monocyte to high-density lipoprotein cholesterol ratio (MHR), a new biomarker associated with oxidative stress and inflammation, has been derived from monocytes and HDL-c [22]. Whether MHR can predict the development of sarcopenia has yet to be demonstrated. The research first attempts to investigate the association between MHR and low muscle mass and to compare the predictive abilities of MHR, SII, NLR, and NHHR for low muscle mass risk.

Methods

Study participants

The NHANES survey, a nationally representative assessment of the health and nutritional status of the U.S. population, is conducted every two years by the National Center for Health Statistics (NCHS) in the United States. Comprehensive information is available at http://www.cdc.gov/nchs/nhanes/. The study initially comprised 39,156 participants from the United States. Following the exclusion of adults aged under 20 years, as well as cases with unclear information regarding ALM, MHR, SII, NLR, and NHHR, the remaining 10,321 individuals were recruited for this research (Fig. 1).

Definition of MHR and ALM_{BMI}

$$MHR = \frac{\text{monocyte}(10^3 cells/\mu L)}{HDL-c(mg/dL)}$$

$$ALM_{BMI} = \frac{appendicular\ lean\ mass(kg)}{BMI(kg/m^2)}$$

MHR was used as the exposure variable in this study, and the formula was provided above. The monocyte count was obtained using the Beckman Coulter MAXM automated analytical instrument. More than 9 h of fasting is required before morning measurements. HDL-c measurement is performed using the Roche Cobas 6000. Ln logarithmic function treatment was applied to MHR in the research. Appendicular lean mass (ALM), measured by dual-energy X-ray absorptiometry (DXA), refers to the total mass of lean soft tissue in the extremities. Following the FNIH's previously published criteria [23], participants with ALM_{BMI} levels below 0.789 in males and 0.512 in females were classified as having low muscle mass. Additionally, the following formulas were used to calculate the NLR, SII, and NHHR: NLR = neutrophil counts/lymphocyte counts, SII = platelet counts × neutrophil counts/lymphocyte counts, NHHR = non-HDL-c/HDL-c.

Selection of covariates

The multivariable-adjusted models were constructed using the variables including age, sex, race, educational level, smoking, congestive heart failure, coronary artery, stroke, arthritis, diabetes, and cancer. Reducing confounding effects between MHR and ALM_{BMI} by adjusting for these variables. The educational level was categorized into three segments based on whether participants had completed upper secondary education or higher. Smoking status was dichotomized as yes or no, according to whether participants had smoked at least 100 cigarettes in their lifetime. Data on congestive heart failure, coronary heart disease, stroke, arthritis, diabetes, and cancer were obtained from the questionnaire module of the NHANES database.

Statistical analysis

Since MHR showed a skewed distribution in the analyses, the natural logarithmic function was used for transformation and divided the ln transformed MHR into quartiles. Continuous variables were expressed as

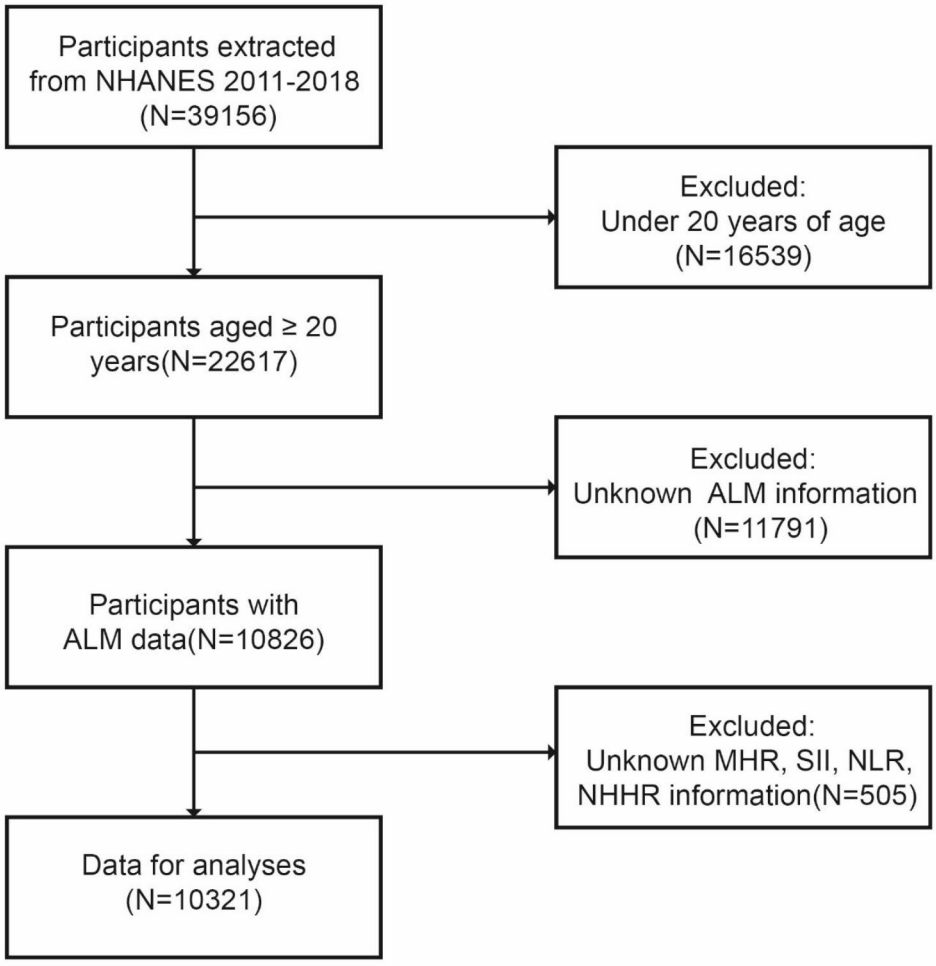

Fig. 1 Flow chart of participants selection

mean ± standard deviation in the descriptive analyses, and the Student's t-test was employed to evaluate the differences between groups. Categorical variables were indicated as percentages in the descriptive analyses, and the chi-squared test was used in assessing differences among groups. Multiple logistic regression analysis was employed to analyze the association between inflammatory indicators and the odds of low muscle mass. Three models were developed to calculate odds ratios (OR) and 95% confidence intervals (CI). Model 1 included no adjusted variables. Model 2 was adjusted for the four variables: gender, age [years], race, and educational level; and Model 3 adjusted for the four variables in Model 2, as well as congestive heart failure [No or Yes], coronary artery [No or Yes], stroke [No or Yes], arthritis [No or Yes], diabetes [No or Yes], cancer [No or Yes]. Furthermore, area under the curve (AUC) values and receiver operating characteristic (ROC) curves were used to assess the predictive effectiveness of ln-transformed MHR and other inflammatory markers (SII, NLR, and NHHR). Considering that AUC values below 0.6 are generally regarded as poor [24], this study sought to combine various inflammatory indicators. The R packages "pROC" was performed to assess the diagnostic ability of the combination (ln MHR + ln SII, ln MHR + ln NHHR, ln MHR + ln NLR) for low muscle mass. The bootstrap estimated 95% CI was shown with the AUC. Additionally, subgroup analyses and interaction tests were performed to further validate the findings.

Data for this study were analyzed using R software and EmpowerStats. $P < 0.05$ was considered statistically significant.

Results

Study population

In this study, participants were 50.77% female and 49.23% male, with a mean age of 39.32 ± 11.49 years and a mean ln transformed MHR of -2.72 ± 0.99. The prevalence rates of cancer, stroke, coronary heart disease, congestive heart failure, arthritis, diabetes mellitus, and low muscle mass were 3.68%, 1.46%, 0.97%,

1.02%, 13.93%, 7.36%, and 8.79%, respectively. All other variable subgroup associations were significant except for age, stroke, and cancer subgroups. Compared with the lowest MHR quartile, the highest MHR quartile was often Men and Non-Hispanic White (Table 1).

These inflammatory markers were transformed by the ln log function to give the data a positive distribution for more accurate results. Three regression models were constructed to explore the association of ln SII, ln NLR, ln NHHR, ln MHR, ln MHR + ln SII, ln MHR + ln NHHR, ln MHR + ln NLR, ln MHR (quartile) and low muscle mass (Table 2). In model 1 and model 2, each indicator exhibited a significant positive association with low muscle mass ($P < 0.05$). In model 3, ln SII, ln NLR, ln NHHR, ln MHR, ln MHR + ln SII, ln MHR + ln NHHR, and ln MHR + ln NLR were positively associated with low muscle mass (ln SII: OR = 1.59 [1.37–1.84]; ln NLR: OR = 1.35 [1.13–1.60]; ln NHHR: OR = 1.49[1.27–1.75]; ln MHR: OR = 1.98 [1.68–2.33]; ln MHR + ln SII: OR = 1.61 [1.46–1.79]; ln MHR + ln NHHR: OR = 1.42 [1.29–1.56]; ln MHR + ln NLR: OR = 1.58 [1.41–1.78]). This means that the odds of the disease increase by 59%, 35%, 49%, and 98% for each unit increase in ln SII, ln NLR, ln NHHR, or ln MHR.

Table 1 Baseline characteristics of participants

Ln MHR	Q1 (*n* = 2547)	Q2 (*n* = 2596)	Q3 (*n* = 2576)	Q4 (*n* = 2602)	*P*-value
ln NHHR	-2.94 ± 0.94	-2.77 ± 0.96	-2.63 ± 0.93	-2.44 ± 0.90	< 0.001
ln SII	-2.88 ± 0.96	-2.76 ± 1.00	-2.65 ± 0.96	-2.52 ± 0.93	< 0.001
ln NLR	-2.83 ± 0.93	-2.73 ± 0.97	-2.64 ± 0.93	-2.53 ± 0.90	< 0.001
ln MHR	-3.22 ± 0.93	-2.85 ± 0.95	-2.59 ± 0.92	-2.23 ± 0.90	< 0.001
Age (years)	40.28 ± 11.65	38.79 ± 11.58	39.10 ± 11.53	39.12 ± 11.16	< 0.001
Sex (%)					< 0.001
Men	30.90%	43.62%	54.62%	67.45%	
Women	69.10%	56.38%	45.38%	32.55%	
Race (%)					< 0.001
Mexican American	11.39%	15.68%	15.99%	17.45%	
Other Hispanic	9.03%	9.56%	11.76%	11.64%	
Non-Hispanic White	29.25%	34.37%	36.10%	39.78%	
Non-Hispanic Black	26.50%	21.70%	19.18%	14.95%	
Other Races	23.83%	18.69%	16.96%	16.18%	
Educational level (%)					< 0.001
Less than high school	13.98%	17.96%	18.87%	21.64%	
High school or GED	17.94%	20.27%	23.37%	25.29%	
Above high school	68.08%	61.77%	57.76%	53.07%	
Smoking (%)					< 0.001
No	68.55%	64.51%	58.70%	52.04%	
Yes	31.45%	35.49%	41.30%	47.96%	
Diabetes (%)					< 0.001
No	95.52%	93.72%	92.00%	89.35%	
Yes	4.48%	6.28%	8.00%	10.65%	
Coronary artery disease (%)					< 0.001
No	99.49%	99.34%	98.95%	98.35%	
Yes	0.51%	0.66%	1.05%	1.65%	
Congestive heart failure (%)					0.030
No	99.37%	99.04%	98.99%	98.54%	
Yes	0.63%	0.96%	1.01%	1.46%	
Cancer (%)					0.919
No	96.23%	96.22%	96.27%	96.54%	
Yes	3.77%	3.78%	3.73%	3.46%	
Arthritis (%)					0.025
No	87.39%	86.71%	85.48%	84.70%	
Yes	12.61%	13.29%	14.52%	15.30%	
Stroke (%)					0.113
No	98.51%	98.77%	98.80%	98.08%	
Yes	1.49%	1.23%	1.20%	1.92%	

Table 2 Indicates the association between biomarkers and low muscle mass

	Model 1 OR (95% CI) *P* value	Model 2 OR (95% CI) *P* value	Model 3 OR (95% CI) *P* value
ln SII	1.68 (1.47, 1.92) < 0.0001	1.61 (1.39, 1.86) < 0.0001	1.59 (1.37, 1.84) < 0.0001
ln NLR	1.57 (1.34, 1.84) < 0.0001	1.39 (1.17, 1.65) 0.0001	1.35 (1.13, 1.60) 0.0008
ln NHHR	1.98 (1.70, 2.29) < 0.0001	1.53 (1.30, 1.80) < 0.0001	1.49 (1.27, 1.75) < 0.0001
ln MHR	2.05 (1.77, 2.37) < 0.0001	2.04 (1.73, 2.39) < 0.0001	1.98 (1.68, 2.33) < 0.0001
ln MHR + ln SII	1.69 (1.54, 1.86) < 0.0001	1.64 (1.48, 1.81) < 0.0001	1.61 (1.46, 1.79) < 0.0001
ln MHR + ln NHHR	1.56 (1.43, 1.69) < 0.0001	1.44 (1.32, 1.58) < 0.0001	1.42 (1.29, 1.56) < 0.0001
ln MHR + ln NLR	1.70 (1.54, 1.89) < 0.0001	1.62 (1.45, 1.82) < 0.0001	1.58 (1.41, 1.78) < 0.0001
ln MHR (quartile)			
Quartile 1	Reference	Reference	Reference
Quartile 2	1.54 (1.23, 1.92) 0.0001	1.50 (1.19, 1.89) 0.0006	1.47 (1.17, 1.85) 0.0011
Quartile 3	1.85 (1.49, 2.30) < 0.0001	1.79 (1.42, 2.25) < 0.0001	1.73 (1.38, 2.17) < 0.0001
Quartile 4	2.43 (1.97, 3.00) < 0.0001	2.33 (1.86, 2.92) < 0.0001	2.22 (1.77, 2.78) < 0.0001
P for trend	0.0011	< 0.0001	< 0.0001

Compared to the lowest quartile of ln MHR, higher quartiles were significantly associated with increased OR for low muscle mass (*P* for trend < 0.0001).

Subgroup analysis

The analysis of the interaction test demonstrated that sex, race, educational level, smoking, congestive heart failure, arthritis, stroke, and cancer subgroups did not have a significant effect on the association between MHR and low muscle mass (*P* for interaction > 0.05). However, significant differences were observed in the subgroups of diabetes, coronary heart disease, and age. Stronger association between MHR and the occurrence of low muscle mass in age < 50, diabetic, and coronary heart disease participants compared with those aged ≥ 50, non-diabetic, and coronary heart disease participants (Fig. 2).

ROC analysis

ROC analyses were conducted to explore the predictive capacity of all indicators for low muscle mass. As shown in Fig. 3, ln MHR + ln SII has higher AUC values than other markers (AUC = 0.608). The result suggests that the predictive value of MHR for low muscle mass was higher compared to NLR, SII, NHHR in this study. Additionally, red shading shows the bootstrap estimated 95% Cl with the AUC (Fig. 4).

Discussion

This is the first cross-sectional study to demonstrate a positive association between MHR and low muscle mass. Ln transformation was applied to MHR and other systemic immune indices derived from CBC. The ln-transformed MHR, SII, NLR, and NHHR all showed a significantly positive association with low muscle mass. In ROC analysis, ln MHR exhibited higher AUC values than other inflammatory markers. Moreover, in subgroup analysis, age, coronary heart disease, and diabetes mellitus modified the association between MHR and low muscle mass.

Kanat et al. conducted a cross-sectional retrospective study in Turkey that included 262 sarcopenia patients and found that sarcopenic patients had a higher MHR than non-sarcopenic participants. The results are consistent with the findings in the U.S. population [25]. Guo et al. investigated the U.S. NHANES database and found an association between higher NLR, SII, and a higher prevalence of low muscle mass [17]. Hao et al. found that NHHR can serve as a novel predictor of low muscle mass and has a negative association with muscle mass [16]. These conclusions align with the results of the data analyses performed in this study. In addition, a ROC analysis was performed to assess the predictive capacity of these indicators in detecting low muscle mass. ln MHR + ln SII has a higher AUC value than other indicators (AUC = 0.608).

The mechanisms of sarcopenia are associated with a number of factors, including oxidative stress, inflammation, and insulin resistance [26]. Furthermore, these factors can interact with one another, resulting in a vicious cycle [27]. Oxidative stress caused by cellular senescence after aging promotes inflammation [28]. Some studies have indicated an association between chronic inflammation and low muscle mass [29]. Moreover, patients with sarcopenia have elevated levels of the cytokines IL-6 and TNF-α [30]. Cytokines regulate inflammation; however, prolonged elevations are deleterious to muscle mass [31]. Inflammation-induced lipolysis and redistribution can lead to ectopic fat infiltration in multiple organs [32], especially in the vicinity of skeletal muscle [33], resulting in loss of muscle mass [34]. Lipids enter skeletal muscle and are metabolized to generate substantial energy, with lipid oxidation accounting for nearly two-thirds of

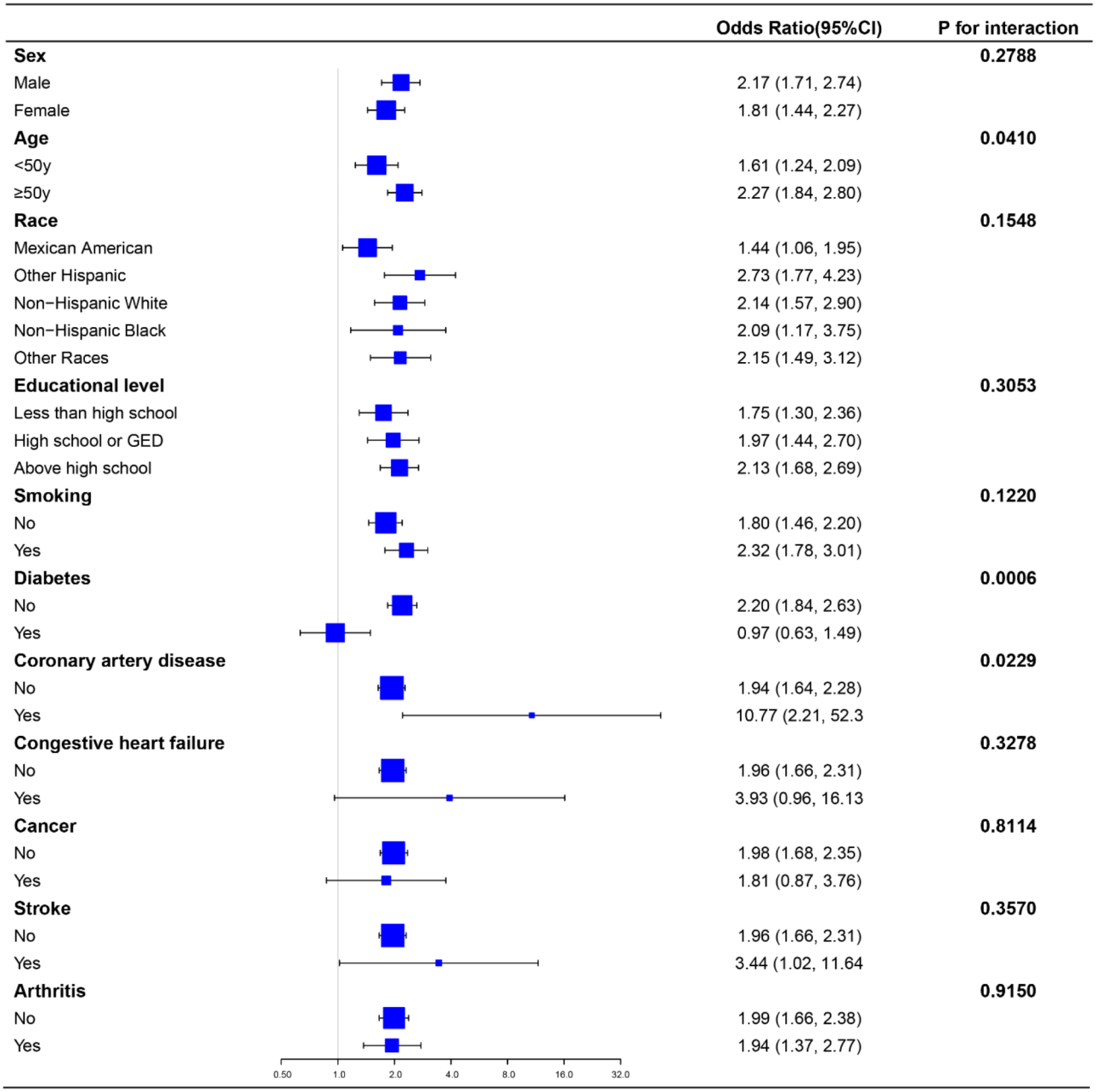

Fig. 2 Subgroup analysis of the association between MHR and low muscle mass

the energy in resting skeletal muscle. Lipid accumulation and metabolism in muscle cells is a method for acquiring energy sources [35]. MHR is an indicator of lipid metabolism and systemic inflammation [36] that has been shown to be associated with a variety of diseases. The NHANES database revealed that MHR was associated with hypertension, chronic kidney disease (CKD) [37], abdominal aortic calcification (AAC) [38], and coronary heart disease (CHD) [39]. Monocytes and HDL-C are involved in the processes of oxidative stress, inflammation, and lipid metabolism [40]. Both are strongly correlated with the development of sarcopenia. Moreover, subgroup analyses and interaction test results demonstrated that age, diabetes, and coronary heart disease significantly influenced the association between MHR and sarcopenia. Individuals with coronary artery disease exhibited a significantly increased odds ratio compared to those without coronary artery disease. The underlying mechanism may be linked to an increased predisposition to dyslipidemia in individuals with a low skeletal muscle mass index [41]. In general, diabetes accelerates sarcopenia

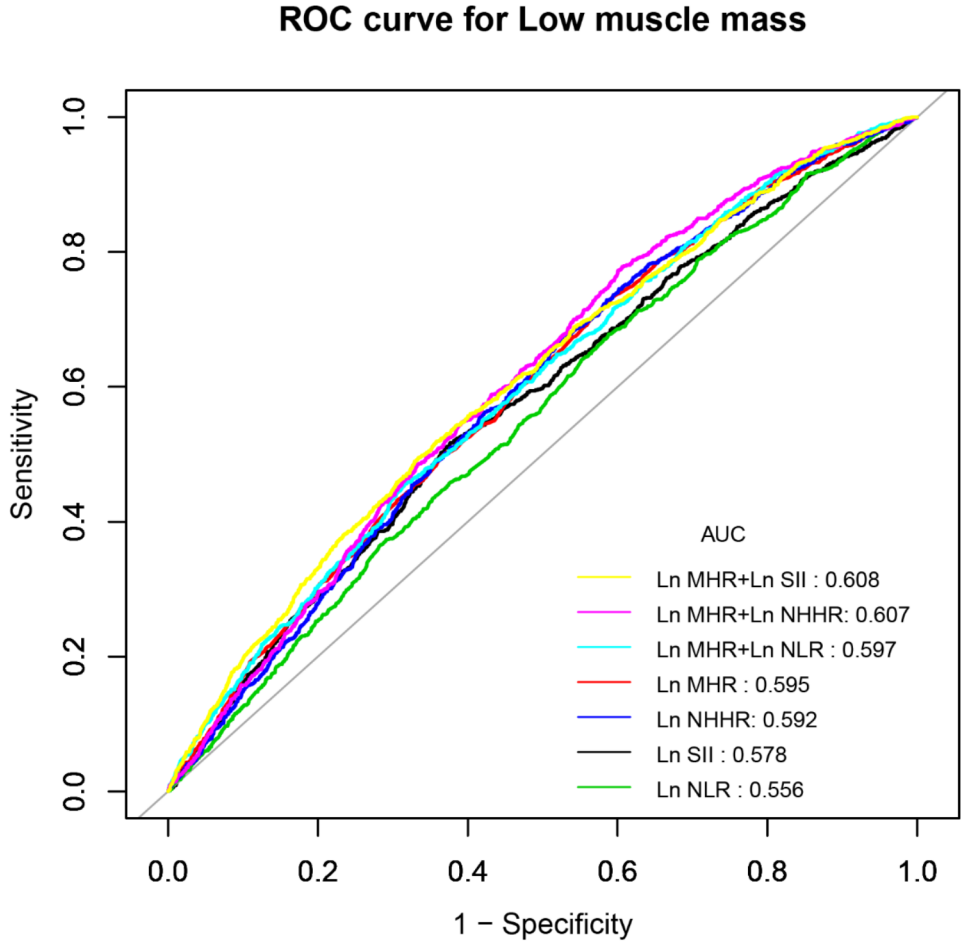

Fig. 3 Receiver operating characteristic (ROC) curves for low muscle mass

via processes including hyperglycemia, chronic inflammation, and oxidative stress [42]. However, the study revealed that the association between MHR and the incidence of low muscle mass was reduced in individuals with diabetes. This may be attributed to the fact that this population has adopted a healthier lifestyle of exercise and diet after the disease, leading to biased results. In addition, MHR was more strongly correlated with low muscle mass in the < 50 years group compared to the older age group. It is possible that the presence of other potential confounders in the upper age groups influenced the results. These findings require further research. Additionally, given the established associations between multiple inflammatory indicators and sarcopenia, future research should focus on therapeutic strategies targeting oxidative stress and inflammation. Potential approaches could involve pharmacological interventions to inhibit inflammation and oxidative stress, thereby preventing muscle loss and avoiding associated injuries such as falls, weakness, and difficulties in mobility. The results of the ROC analysis suggest that MHR, SII, NLR, and NHHR do not perform optimally in predicting sarcopenia.

Study strengths and limitations

This research has several strengths. First, the sample size is huge and nationally representative. Second, numerous confounders were adjusted to make the results more reliable. Third, the predictive value of multiple inflammatory indicators in association with outcome variables was evaluated through the use of ROC analysis. There are some limitations to this research. Firstly, it was not possible to take into account the effects of all potential confounders on this study, which could have introduced bias into the results. Secondly, multiple testing in multiple logistic regression analyses presents several limitations, including inflated type I error rates, decreased statistical power, interpretation complexity, computational burdens, and practical constraints. Thirdly, the study was unable to fully elucidate certain mechanisms and causal relationships, thus indicating the necessity for further in-depth research.

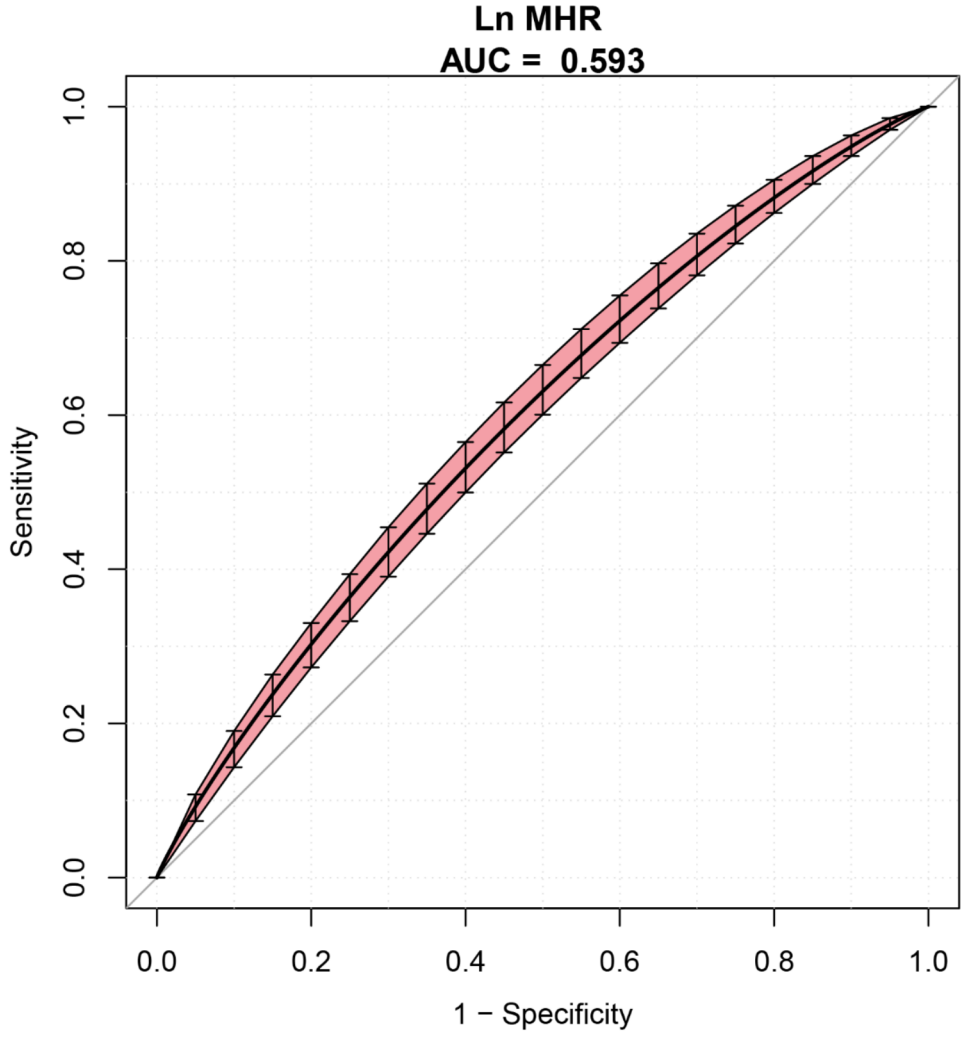

Fig. 4 Receiver operating characteristic curves. Red shading shows the bootstrap estimated 95% CI with the AUC

Conclusion

ln-transformed MHR, SII, NLR, and NHHR were positively associated with low muscle mass. MHR performs better in predicting sarcopenia compared to SII, NLR, and NHHR.

Author contributions

ZWX: Methodology, Writing– original draft, Data curation. JC, JHM, RW: Validation, Visualization. PL: Supervision, Writing– review & editing.

Funding

None.

Data availability

This study examined datasets that are accessible to the public. The data can be accessed at: https://www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate

The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and were approved by the NCHS Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

Competing interests

The authors declare no competing interests.

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