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Association between systemic inflammation markers and abdominal aortic calcification: a cross-sectional study

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Abstract

Background: Systemic inflammatory markers are associated with cardiovascular disease. This study aimed to assess the relationship between systemic inflammatory markers and abdominal aortic calcification (AAC).

Methods: Data were collected from the 2013 to 2014 cycle of the National Health and Nutrition Examination Survey (NHANES). AAC was quantified using the Kauppila scoring system, which is based on dual-energy X-ray absorptiometry. Severe abdominal aortic calcification (sAAC) was defined as a total AAC score ≥6. Multivariate regression models were used to determine the relationships between systemic inflammation indicators, AAC scores, and sAAC.

Results: Data from 3047 participants were analyzed. After adjusting for multiple covariates, AAC scores increased slightly for every one-unit increase in standardized systemic immune-inflammation index (SII; β = 0.13; 95% confidence interval [CI]: 0.01–0.25, *P*=0.030). Neutrophil-to-lymphocyte ratio (NLR) was positively correlated with higher AAC scores (β = 0.15; 95% CI: 0.06–0.24, *P*=0.001) and sAAC (odds ratio [OR]: 1.10; 95% CI: 1.01–1.19, *P*=0.025). There was no significant correlation between platelet-to-lymphocyte ratio (PLR) and AAC scores (β = –0.0006; 95% CI: –0.0018 to 0.0030). Conversely, lymphocyte-to-monocyte ratio (LMR) was positively associated with lower AAC scores (β = –0.14; 95% CI: –0.22 to –0.05, *P*=0.001), with a 12% decrease in the odds of sAAC for every one-unit increase in LMR (OR: 0.88; 95% CI: 0.79–0.97, *P*=0.013).

Conclusion: Correlations between different systemic inflammation markers and AAC varied among the adult population of the United States. NLR was associated with higher AAC scores and an increased incidence of sAAC, whereas LMR had the opposite effect. NLR and LMR have emerged as potential biomarkers for AAC risk, highlighting their importance in understanding the inflammatory processes associated with AAC.

Keywords: Abdominal aortic calcification, Cross-sectional study, Systemic inflammation markers

Introduction

Vascular calcification (VC) is a pathological process closely associated with vascular aging and is characterized by the abnormal deposition of calcium salts in the intima and media of blood vessels, leading to the development of atherosclerosis and arterial stiffening.[1] Abdominal aortic calcification (AAC) is a common manifestation of VC, associated with the severity of coronary artery disease, heart failure, and stroke,[2–4] and serves as a marker of atherosclerotic vascular disease.[5] It is also an independent predictor of cardiovascular events in the general population.[6,7] Recent studies have demonstrated that the AAC is more effective than the Framingham risk score in predicting cardiovascular events.[8]

Recently, accumulating evidence has suggested a correlation between VC and elevated levels of inflammatory markers including interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α.[9] Pro-inflammatory immune cells, particularly macrophages, promote VC by releasing inflammatory cytokines and extracellular vesicles.[10] Inflammation and immunity are considered to be important pathogenic mechanisms underlying AAC.[11,12]

Systemic inflammatory markers are novel indicators used to characterize the severity of systemic inflammation. Unlike many other inflammatory markers detected using unconventional methods, systemic inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), and platelet-to-lymphocyte ratio (PLR), can be calculated using data obtained in routine laboratory investigations. Their widespread application and cost effectiveness in

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The datasets generated during and/or analyzed during the current study are publicly available.

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clinical practice have attracted attention.[13] Multiple studies have demonstrated the significant roles of NLR, LMR, SII, and PLR in predicting cardiovascular and cerebrovascular diseases.[14–17] Although associations between the SII, NLR, and AAC have been observed,[9,18] most studies have been conducted in specific disease populations, and there has been no research examining these ratios at the population level.

As such, this large-scale epidemiological cross-sectional investigation used data from the 2013 to 2014 cycle of the National Health and Nutrition Examination Survey (NHANES) to gain a better understanding of the correlations between the 4 blood cell ratios and AAC, with the aim of providing potential biomarker evidence for the early identification of the disease.

Materials and methods

Study population

The participants in this study were selected from the 2013 to 2014 cycle of the NHANES, a set of population-based national surveys undertaken by the National Center for Health Statistics (NCHS), intended to evaluate the health and nutritional conditions of United States citizens.[19] The study protocol was approved by the NCHS Research Ethics Review Board, and informed consent was obtained from each participant. Initially, data from 10,175 participants were included in the study. However, after excluding participants <40 years of age who did not undergo dual-energy X-ray absorptiometry (DXA) (n = 6360), those with missing AAC score data (n = 675), and those with missing information regarding systemic inflammatory markers (n = 95), data from 3047 participants were included in the final analysis (Fig. 1). Detailed information regarding the NHANES data is publicly accessible on the Centers for Disease Control and Prevention website (https://www.cdc.gov/nchs/nhanes/index.htm).

Exposure and outcomes

Blood samples were subjected to a complete blood count, and the distribution of blood cells of all participants was determined using a hematology analyzer (DxH 800, Beckman Coulter, Brea, CA, USA) in the NHANES mobile examination center. Platelet, neutrophil, monocyte, and lymphocyte counts are expressed as $\times 10^3$ cells/μL. Four systemic inflammatory markers (NLR, LMR, SII, and PLR) were calculated based on peripheral blood cell counts as follows:

NLR= neutrophils/lymphocytes;
LMR = lymphocytes/monocytes;
SII = (neutrophils × platelets)/lymphocytes;
PLR = platelets/lymphocytes.

The primary outcomes of this study were AAC scores and severe AAC (sAAC), which were only measured during the 2013 to 2014 NHANES cycle. AAC severity was evaluated using the Kauppila scoring system, which entails analysis of lumbar (L) spine (vertebrae L1–L4) images obtained using DXA.[20] In the current study, Kauppila scores ranged from 0 to 24. A score of 0 denoted the absence of AAC, scores ≥1 indicated the presence of AAC, and scores >5 indicated significant calcification and categorized as sAAC. Thus, this study examined 2 key outcome variables: AAC score, a continuous measure reflecting the degree of calcification, and sAAC, a categorical variable denoting the presence of severe calcification.

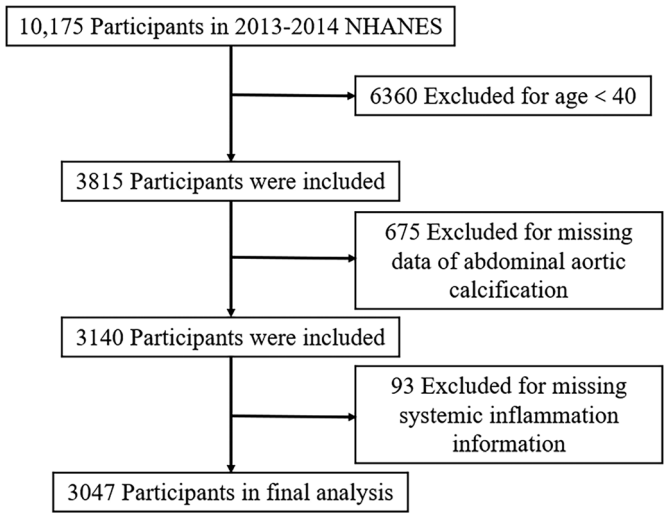

Figure 1. Flow-diagram illustrating the study process. Of 10,175 participants in the 2013 to 2014 cycle of the National Health and Nutrition Examination Survey (NHANES), data from 3047 were included in the final analysis.

Covariates

The following covariates were included in the study: age, sex (male, female), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), body mass index (BMI), education level (<9th grade, 9th–11th grade, high school graduate, some college or associate degree, college graduate or above), smoking status (participants who had smoked ≥100 cigarettes in their lifetime were defined as smokers), and drinking habits (participants who consumed ≥12 alcoholic drinks per year were defined as drinkers). Comorbidities included hypertension (based on physician diagnosis, blood pressure >140/90 mm Hg, or a history of taking antihypertensive medications) and diabetes (based on physician diagnosis, glycated hemoglobin A1C concentration ≥6.5%, fasting plasma glucose level ≥126 mg/dL, or currently taking insulin).

Statistical analysis

Participant characteristics are expressed as mean with standard deviation (SD) for continuous variables that adhered to a normal distribution and percentage for categorical variables. Nonnormally distributed continuous variables are expressed as median (interquartile range [IQR]). Participants were categorized based on the presence or absence of AAC and further subclassified into those with mild-to-moderate AAC (non-sAAC) and those with sAAC. Differences in the clinical characteristics between the groups were evaluated using the t test and χ^2 test. Multivariate linear regression models were used to assess the association between systemic inflammatory markers and AAC scores, whereas multivariate logistic regression models were used to evaluate the risk for sAAC associated with these markers. Model 1 was not adjusted; model 2 was adjusted for age, sex, and race; and model 3 was adjusted for age, sex, race, BMI, education level, smoking status, drinking status, hypertension, and diabetes. Each model provided β values or odds ratio (OR) and corresponding 95% confidence interval (CI) to comprehensively evaluate the associations. In addition, after converting systemic inflammatory markers from a continuous variable to a categorical variable (tertile), a trend test that entered the median value of each category of systemic inflammatory markers as a continuous variable in the models was used to examine the trends in the linear association between systemic inflammatory markers and AAC. Subgroup analyses and interaction tests were performed for age, sex,

BMI, hypertension, and diabetes among the covariates to explore whether the associations remained consistent across the various subgroups. To assess these interactions, likelihood ratio tests were performed to compare the models with and without the interaction terms for these variables. All models were adjusted for the same potential confounders as described above. Empower(R) version 4.2.0 (X&Y Solutions, Inc., Boston, MA, USA) and R version 4.3.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses. Differences with $P < 0.05$ were considered to be statistically significant.

Results

Baseline characteristics

The baseline characteristics of the 3047 participants enrolled in the study, including 916 with AAC, 329 with sAAC, and 2131 without AAC, are summarized in Table 1. Among the participants, 48.21% were male and 44.27% were Caucasian, and the mean ± SD age at enrollment was 58.63 ± 12.00 years. In general, apart from SII, PLR, sex, education level, and alcohol consumption, marked differences in baseline characteristics emerged between the control and AAC groups. Compared to participants without AAC, those with AAC were older, were more likely to be a smoker, and had a greater number of comorbidities, such as hypertension and diabetes. Additionally, systemic inflammatory markers, SII, and NLR levels were higher, whereas LMR levels were lower in patients with AAC. Similar trends were observed in the non-sAAC and sAAC groups. Furthermore, when NLR, LMR, SII, and PLR were divided into tertiles according to AAC status, the highest proportion of patients with AAC with higher NLR and SII was found in the respective tertiles (Table 1 and Supplementary Table 1, http://links.lww.com/ECCM/A95).

Systemic inflammation markers and AAC

In the initial risk analysis, significant associations were found between NLR, LMR, SII, and AAC scores (Table 2). When treated as categorical variables, the associations between NLR, LMR, SII and sAAC were consistent with the trends observed in the continuous analysis (Table 3).

After adjusting for age, sex, and race, NLR exhibited a positive effect on increasing AAC scores ($\beta = 0.17$; 95% CI: 0.08–0.25), indicating that a one-unit increase in NLR was associated with a 0.17 increase in AAC score. Compared with the lowest tertile, participants in the highest NLR tertile exhibited an increase of 0.31 in AAC score. Conversely, LMR was negatively associated with AAC scores ($\beta = -0.13$; 95% CI: −0.21 to −0.05), with each unit increase in LMR corresponding to a 0.13 decrease in AAC score. After fully adjusting for all covariates, NLR exhibited a positive effect on increasing AAC scores ($\beta = 0.15$; 95% CI: 0.06–0.24), suggesting that a one-unit increment increase in NLR was associated with a 0.15 increase in AAC score. Simultaneously, a negative correlation between LMR and AAC scores was observed in the continuous

Table 1

Demographics and Comparisons between AAC Status and Severity

Characteristics	All (n = 3047)	AAC Scores = 0 (n = 2131)	AAC Scores ≥1 (n = 916) (% of All)	Non-sAAC (n = 587) (% of All Yes)	sAAC (n = 329) (% of all Yes)	*P* Value*	*P* Valve†
Age (y)	58.63 ± 12.00	55.92 ± 11.00	64.93 ± 11.89	61.59 ± 11.67	70.91 ± 9.74	<0.001	<0.001
Sex (%)						0.195	0.371
Male	1469 (48.21)	1011 (47.44)	458 (50.00)	300 (51.11)	158 (48.02)		
Female	1578 (51.79)	1120 (52.56)	458 (50.00)	287 (48.89)	171 (51.98)		
Race (%)						<0.001	0.005
Mexican American	402 (13.19)	309 (14.50)	93 (10.15)	64 (10.90)	29 (8.81)		
Other Hispanic	289 (9.48)	218 (10.23)	71 (7.75)	55 (9.37)	16 (4.86)		
Non-Hispanic White	1349 (44.27)	853 (40.03)	496 (54.15)	290 (49.40)	206 (62.61)		
Non-Hispanic Black	586 (19.23)	443 (20.79)	143 (15.61)	98 (16.70)	45 (13.68)		
Non-Hispanic Asian	359 (11.78)	264 (12.39)	95 (10.37)	67 (11.41)	28 (8.51)		
Other race	62 (2.03)	44 (2.06)	18 (1.97)	13 (2.21)	5 (1.52)		
BMI (kg/m^2)	28.45 ± 5.58	28.80 ± 5.84	27.65 ± 4.81	27.97 ± 5.01	27.09 ± 4.39	<0.001	0.009
Education level (%)						0.212	0.652
Less than 9th grade	286 (9.39)	201 (9.43)	85 (9.28)	54 (9.20)	31 (9.42)		
9–11th Grade	414 (13.59)	286 (13.42)	128 (13.97)	74 (12.61)	54 (16.41)		
High school	688 (22.58)	458 (21.49)	230 (25.11)	148 (25.21)	82 (24.92)		
College	857 (28.13)	604 (28.34)	253 (27.62)	167 (28.45)	86 (26.14)		
College graduate or above	800 (26.26)	581 (27.26)	219 (23.91)	143 (24.36)	76 (23.10)		
Smoking (%)	1406 (46.14)	910 (42.70)	496 (54.15)	299 (50.94)	197 (60.06)	<0.001	0.008
Alcohol (%)	2042 (71.10)	1415 (70.96)	627 (71.41)	398 (71.33)	229 (72.24)	0.692	0.773
Hypertension (%)	1551 (52.77)	943 (44.25)	608 (66.38)	355 (60.48)	253 (76.90)	<0.001	<0.001
Diabetes (%)	506 (16.6)	313 (14.69)	193 (21.07)	97 (16.52)	96 (29.18)	<0.001	<0.001
SII	444.00 (316.88–622.20)	442.17 (317.43–610.84)	445.57 (315.68–647.76)	426.00 (299.57–602.16)	492.77 (347.14–734.34)	0.289	<0.001
NLR	2.00 (1.48–2.64)	1.95 (1.46–2.55)	2.02 (1.53–2.88)	1.93 (1.48–2.54)	2.33 (1.68–3.25)	<0.001	<0.001
PLR	113.81 (89.26–143.08)	114.44 (90.56–144.42)	112.50 (86.55–140.57)	108.64 (85.34–136.25)	115.88 (89.00–147.00)	0.079	0.013
LMR	3.60 (2.83–4.67)	3.75 (3.00–4.75)	3.44 (2.62–4.33)	3.60 (2.82–4.60)	3.00 (2.33–3.89)	<0.001	<0.001

Data are mean ± SD, median (interquartile range), or percentage.

*Participants without AAC vs. participants with AAC.

†Participants without sAAC vs. participants with sAAC.

AAC, abdominal aortic calcification; BMI, body mass index; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; sAAC, severe abdominal aortic calcification; SII, systemic immune-inflammation index.

Table 2

Adjusted βs for Associations of Systemic Inflammation Markers with AAC Scores

	Crude Model		Model I		Model II	
Outcome	**β (95% CI)**	***P* Value**	**β (95% CI)**	***P* Value**	**β (95% CI)**	***P* Value**
Standardized SII	0.25 (0.13–0.38)	<0.001	0.15 (0.04–0.27)	0.010	0.13 (0.01–0.25)	0.030
SII (tertile)						
T1	Reference		Reference		Reference	
T2	0.10 (–0.20 to 0.41)	0.500	0.10 (–0.18 to 0.38)	0.486	0.12 (–0.17 to 0.41)	0.408
T3	0.52 (0.21–0.82)	0.001	0.34 (0.06–0.63)	0.019	0.32 (0.02–0.61)	0.035
P for trend	<0.001		0.019		0.035	
NLR	0.35 (0.25–0.44)	<0.001	0.17 (0.08–0.25)	<0.001	0.15 (0.06–0.24)	0.001
NLR (tertile)						
T1	Reference		Reference		Reference	
T2	0.00 (–0.30 to 0.31)	0.983	–0.05 (–0.34 to 0.23)	0.707	–0.07 (–0.36 to 0.22)	0.624
T3	0.81 (0.51–1.11)	<0.001	0.31 (0.02–0.59)	0.037	0.24 (–0.06 to 0.54)	0.114
P for trend	<0.001		0.037		0.113	
PLR	0.00 (0.00–0.00)	0.090	0.00 (0.00–0.00)	0.813	0.00 (0.00–0.00)	0.644
PLR (tertile)						
T1	Reference		Reference		Reference	
T2	–0.07 (–0.37 to 0.24)	0.654	–0.08 (–0.36 to 0.20)	0.596	–0.07 (–0.36 to 0.22)	0.643
T3	0.09 (–0.21 to 0.40)	0.551	–0.09 (–0.37 to 0.19)	0.539	–0.07 (–0.36 to 0.22)	0.637
P for trend	0.551	0.539	0.637			
LMR	–0.34 (–0.42 to –0.26)	<0.001	–0.13 (–0.21 to –0.05)	0.001	–0.14 (–0.22 to –0.05)	0.001
LMR (tertile)						
T1	Reference		Reference		Reference	
T2	–0.86 (–1.16 to –0.56)	<0.001	–0.32 (–0.60 to –0.03)	0.030	–0.28 (–0.57 to 0.01)	0.060
T3	–1.36 (–1.67 to –1.06)	<0.001	–0.54 (–0.84 to –0.24)	<0.001	–0.52 (–0.82 to –0.21)	0.001
P for trend	<0.001		<0.001		0.001	

Model I adjusted for age, sex, and race. Model II adjusted for age, sex, race, education level, smoking status, drinking user, BMI, diabetes, and hypertension.

AAC, abdominal aortic calcification; BMI, body mass index; CI, confidence interval; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

analysis (β = –0.14; 95% CI: –0.22 to –0.05). Similar outcomes were found among participants in the highest LMR tertile (β = –0.52; 95% CI: –0.82 to –0.21) (Table 2).

Similar to the results of the analysis for systemic inflammatory indicators with AAC scores, following adjustment for age, sex, and race, with every one-unit increase in NLR, the risk for sAAC increased by 12% (OR: 1.12; 95% CI: 1.03–1.21). Additionally, for every one-unit increase in LMR, the risk for sAAC decreased by 13% (OR: 0.87; 95% CI: 0.79–0.96). For every one-unit increase in NLR, the risk for sAAC increased by 10% (OR: 1.10; 95% CI: 1.01–1.19) after fully adjusting for all covariates. Compared with the lowest tertile, participants in the highest NLR tertile had a 36% increased risk for sAAC (OR: 1.36; 95% CI: 0.97–1.90). Conversely, for every one-unit increase in LMR, the risk for sAAC decreased by 12% (OR: 0.88; 95% CI: 0.79–0.97). In contrast to the lowest tertile, participants in the highest LMR tertile had a 40% lower risk for sAAC (OR: 0.60; 95% CI: 0.41–0.87) (Table 3).

Subgroup analyses

Subgroup analysis and interaction tests were performed to evaluate whether the relationship between systemic inflammatory markers and AAC scores was consistent across different strata of age, sex, race, BMI, diabetes, and hypertension.

As shown in Table 4, significant age-related heterogeneity was observed (*P* for interaction <0.001). Specifically, a positive association between NLR and AAC score was found in individuals aged ≥60 years (β = 0.26; 95% CI: 0.12–0.41), whereas no significant association was observed in those aged <60 years (β = –0.06; 95% CI: –0.14 to 0.03). Sex differences were not statistically significant (*P* = 0.998 for interaction), although males exhibited a slightly higher β coefficient (β = 0.17; 95% CI: 0.05–0.29) compared with females (β = 0.13; 95% CI: –0.01–0.26). Notably, racial groups also exhibited significant heterogeneity (*P* < 0.001 for interaction), with non-Hispanic Asians exhibiting the strongest positive association (β = 0.75; 95% CI: 0.50–1.00). BMI demonstrated a significant interaction (*P* = 0.004), with a positive association observed in individuals with BMI ≥ 24 kg/m^2. No significant associations were observed between hypertension and diabetes.

In the LMR analysis (Table 5), significant age-related heterogeneity was observed (*P* < 0.001 for interaction). A negative association was found among individuals aged ≥60 years (β = –0.38; 95% CI: –0.54 to –0.22), whereas the association was not significant among those aged <60 years (β = –0.01; 95% CI: –0.07 to 0.05). Sex did not significantly affect this association (*P* = 0.890 for interaction). Similarly, racial groups did not exhibit significant heterogeneity (*P* = 0.866 for interaction). BMI demonstrated a borderline significant interaction (*P* = 0.057), with a negative trend across increasing BMI categories; however, the result for BMI ≥28 kg/m^2 was significant. Notably, both hypertension (*P* < 0.001 for interaction) and diabetes status (*P* = 0.007 for interaction) significantly modified the association, with stronger negative associations observed in individuals with hypertension (β = –0.22; 95% CI: –0.36 to –0.09) and diabetes (β = –0.41; 95% CI: –0.68 to –0.14) compared with their counterparts.

Discussion

The primary findings of this cross-sectional study involving 3047 participants were as follows. First, NLR was positively correlated

Table 3

Adjusted ORs for Associations of Systemic Inflammation Markers with the Risk of sAAC

	Crude Model		Model I		Model II	
Outcome	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Standardized SII	1.22 (1.11–1.34)	<0.001	1.14 (1.03–1.27)	0.015	1.11 (0.99–1.24)	0.075
SII (tertile)						
T1	Reference		Reference		Reference	
T2	1.13 (0.83–1.52)	0.440	1.11 (0.80–1.53)	0.546	1.07 (0.76–1.51)	0.688
T3	1.68 (1.27–2.22)	<0.001	1.42 (1.04–1.94)	0.026	1.29 (0.93–1.80)	0.131
P for trend	<0.001		0.024		0.123	
NLR	1.26 (1.17–1.36)	<0.001	1.12 (1.03–1.21)	0.005	1.10 (1.01–1.19)	0.025
NLR (tertile)						
T1	Reference		Reference		Reference	
T2	1.11 (0.81–1.52)	0.528	1.03 (0.73–1.46)	0.850	1.01 (0.70–1.44)	0.975
T3	2.26 (1.70–3.00)	<0.001	1.49 (1.09–2.05)	0.013	1.36 (0.97–1.90)	0.073
P for trend	<0.001		0.008		0.054	
PLR	1.00 (1.00–1.01)	0.005	1.00 (1.00–1.00)	0.327	1.00 (1.00–1.00)	0.444
PLR (tertile)						
T1	Reference		Reference		Reference	
T2	0.99 (0.74–1.32)	0.953	0.98 (0.72–1.34)	0.905	0.94 (0.67–1.31)	0.705
T3	1.20 (0.91–1.58)	0.207	0.99 (0.73–1.35)	0.974	0.97 (0.70–1.34)	0.832
P for trend	0.201		0.9775		0.838	
LMR	0.69 (0.62–0.76)	<0.001	0.87 (0.79–0.96)	0.007	0.88 (0.79–0.97)	0.013
LMR (tertile)						
T1	Reference		Reference		Reference	
T2	0.56 (0.43–0.73)	<0.001	0.90 (0.67–1.20)	0.459	0.95 (0.70–1.30)	0.755
T3	0.28 (0.21–0.39)	<0.001	0.57 (0.40–0.82)	0.002	0.60 (0.41–0.87)	0.008
P for trend	<0.001		0.003		0.013	

Model I adjusted for age, sex and race. Model II adjusted for age, sex, race, education level, smoking status, drinking user, BMI, diabetes, and hypertension.

BMI, body mass index; CI, confidence interval; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; sAAC, severe abdominal aortic calcification; SII, systemic immune-inflammation index.

with AAC scores and sAAC, whereas LMR was negatively correlated with AAC scores and sAAC. Second, there was no significant correlation between PLR and AAC, and these associations were independent of demographic characteristics and comorbidities. When NLR and LMR were analyzed as categorical variables, participants in the highest three quartiles had AAC scores increased by 0.24 and decreased by 0.60, respectively, compared with those in the lowest 3 quartiles.

VC is a pathological vascular condition that results from an imbalance in the vascular microenvironment. It is associated with various diseases including hypertension, atherosclerosis, aortic valve stenosis, coronary heart disease, diabetes, and chronic kidney disease.[21] VC has previously been regarded to be a passive and degenerative process. However, it is now recognized to be an active and tightly regulated biological process similar to bone formation.[22,23] Currently, no therapeutic strategies have proven to be effective in reversing VC progression. Therefore, early prevention, timely identification, and improvement of prognosis are crucial.[21] Inflammation not only plays a crucial role in the development of atherosclerosis but also serves as a significant trigger for VC, occurring before arterial calcification.[24] A prospective observational study involving patients undergoing hemodialysis demonstrated a significant correlation between inflammation and AAC.[25] Similar to previous study results, we found a positive correlation between NLR and AAC, indicating that participants with higher systemic inflammation levels may have an increased AAC risk and severity. Conversely, LMR exhibited a more pronounced negative correlation with AAC.

To the best of our knowledge, this is the first large-scale study to evaluate the association between various systemic inflammatory markers and AAC. Importantly, we identified, for the first time, associations between NLR and LMR and AAC in a large-sample study. Moreover, to enhance the reliability of our results, we meticulously adjusted for confounding factors whenever possible. Furthermore, we concurrently analyzed the specific influence of 4 systemic inflammation markers on AAC scores and the occurrence of sAAC in the same population, with consistent adjustments made, potentially averting instability in the results due to heterogeneity among studies. One of our primary findings is that NLR emerged as a meaningful biomarker of AAC severity, with its predictive significance increasing as AAC severity worsened. Conversely, the LMR served as a significant negative factor for the severity of AAC. Because the cell counts required for calculating the NLR and LMR can be obtained through economical and convenient routine laboratory investigations, their application in routine clinical practice is feasible. The combined consideration of both markers may facilitate swift clinical assessment of AAC severity over existing clinical methods for assessing cardiovascular risk. However, the SII and PLR demonstrated limited diagnostic predictive utility for the occurrence and progression of AAC.

NLR serves as a biomarker that encompasses both the innate immune response initiated by neutrophils and the adaptive immune response supported by lymphocytes.[26] Several studies have indicated a positive correlation between NLR and cardiovascular disease (s).[27–29] In a prospective cohort study by Fries et al.,[27] elevated NLR was identified as an adverse prognostic indicator in cats with hypertrophic cardiomyopathy. Mirna et al.[28] reported a significant association between NLR and length of hospital stay in patients diagnosed with myocarditis, suggesting that NLR is a promising parameter for risk stratification in that patient population. Hong et al.[29] found that an elevated NLR was correlated with an increased risk for cardiovascular disease and all-cause mortality, independently predicting the prognosis of patients with hypertension.

Table 4

Subgroup Analysis for the Association between NLR and AAC Score

Characteristics	No. of Participants	β (95% CI)	*P* for Interaction
Age			<0.001
<60	1626	−0.06 (−0.14 to 0.03)	
≥60	1421	0.26 (0.12–0.41)	
Sex			0.998
Male	1469	0.17 (0.05–0.29)	
Female	1578	0.13 (−0.01 to 0.26)	
Race			<0.001
Mexican American	402	0.14 (−0.17 to 0.46)	
Other Hispanic	289	−0.04 (−0.41 to 0.34)	
Non-Hispanic White	1349	−0.03 (−0.15 to 0.09)	
Non-Hispanic Black	586	0.18 (−0.03 to 0.40)	
Non-Hispanic Asian	359	0.75 (0.50–1.00)	
Other race	62	0.28 (−0.64 to 1.19)	
BMI			0.004
<24	657	−0.02 (−0.20 to 0.16)	
≥24, <28	900	0.32 (0.14–0.49)	
≥28	1468	0.09 (−0.03 to 0.22)	
Hypertension			0.397
No	1496	0.15 (0.05–0.26)	
Yes	1551	0.13 (−0.00 to 0.26)	
Diabetes			0.069
No	2541	0.12 (0.02–0.21)	
Yes	506	0.25 (0.01–0.49)	

Data are adjusted for age, sex, race, education level, smoking status, drinking user, BMI, diabetes, and hypertension.

AAC,abdominal aorticcalcification; BMI, body mass index; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio.

The present study is the first to demonstrate a positive correlation between the NLR and AAC, consistent with previously reported significant adverse effects of the NLR on cardiovascular health. This suggests that greater levels of systemic inflammation may enhance the risk for and severity of AAC, particularly among individuals >60 years of age. Our findings imply that NLR has potential clinical significance in diagnosing the risk for and severity of AAC, potentially serving as the optimal marker among the 4 systemic inflammation markers for assessing AAC risk and severity. LMR has been reported to be associated with poor survival rates in various cancers.[30]

The detailed mechanism by which the NLR mirrors the equilibrium between systemic inflammation and immunity remains unclear in the context of AAC. An increased NLR results from the augmentation of neutrophils and/or a decrease in lymphocytes. Neutrophils are the predominant type of leukocytes in human blood and constitute the first wave of cells to be recruited to sites of inflammation.[31] They play a role in acute injury and repair, cancer, autoimmunity, and chronic inflammation and exerting pro-inflammatory effects.[32] Lymphocytes comprise T, B, and natural-killer cells, which typically increase in number during viral infections and constitute the core of the adaptive immune system.[33] Commonly, both chronic and acute inflammation lead to an elevated NLR by increasing the neutrophil count and decreasing the lymphocyte count. One likely explanation for our findings is that the stimulation of the release of inflammatory mediators by neutrophils leads to endothelial dysfunction, vascular wall degeneration, and increased chances of AAC occurrence.[34] The exact mechanism underlying the correlation between a low LMR and increased AAC severity, however, remains unclear. Monocytes regulate innate and adaptive immunity through phagocytosis, reactive oxygen species, cytokine and chemokine release, neutrophil recruitment, antigen presentation, and lymphocyte activation,[35] serving as a link between innate and adaptive immunity.[36] Monocytes play a crucial role in regulating inflammation, actively participating in all stages of the immune response, initiating inflammation, triggering adaptive immune responses to clear cellular debris, and resolving inflammation.[37] One possible explanation is that low lymphocyte counts may result in inadequate immune responses, thereby increasing the severity of AAC (Supplementary Tables 2 and 3, http://links.lww.com/ECCM/A95).

This study had several strengths. First, the large sample size enabled a more comprehensive and reliable analysis. Second, adjustment for confounding covariates ensured the robustness and credibility of the findings. Third, the robustness of the observed associations between various systemic inflammatory markers and AAC was thoroughly examined through subgroup analyses across diverse populations. Finally, this study was the first large-scale exploration to assess the intricate relationship between multiple systemic inflammatory markers and AAC, providing valuable insights into this area of study.

Limitations

Our study, however, also had several limitations, the first of which was its cross-sectional design, which precluded us from inferring causality between these markers and AAC. Second, despite adjusting for covariates, potential confounding factors may have influenced our results. Finally, because only a single blood cell count measurement was available, we were unable to assess the influence of changes in blood cell counts on AAC. Nevertheless, further research is required to validate these conclusions.

Table 5

Subgroup Analysis for the Association between LMR and AAC Score

Characteristics	No. of Participants	β (95% CI)	*P* for Interaction
Age			<0.001
<60	1626	−0.01 (−0.07 to 0.05)	
≥60	1421	−0.38 (−0.54 to −0.22)	
Sex			0.890
Male	1469	−0.16 (−0.29 to −0.02)	
Female	1578	−0.12 (−0.23 to −0.02)	
Race			0.866
Mexican American	402	−0.05 (−0.27 to 0.16)	
Other Hispanic	289	−0.05 (−0.30 to 0.21)	
Non-Hispanic White	1349	−0.10 (−0.24 to 0.04)	
Non-Hispanic Black	586	−0.20 (−0.36 to −0.04)	
Non-Hispanic Asian	359	−0.15 (−0.37 to 0.08)	
Other race	62	−0.05 (−0.79 to 0.69)	
BMI			0.057
<24	657	−0.01 (−0.17 to 0.14)	
≥24, <28	900	−0.23 (−0.40 to −0.06)	
≥28	1468	−0.13 (−0.25 to −0.02)	
Hypertension			<0.001
No	1496	−0.03 (−0.12 to 0.05)	
Yes	1551	−0.22 (−0.36 to −0.09)	
Diabetes			0.007
No	2541	−0.09 (−0.17 to −0.00)	
Yes	506	−0.41 (−0.68 to −0.14)	

Data are adjusted for age, sex, race, education level, smoking status, drinking user, BMI, diabetes, and hypertension.

AAC, abdominal aortic calcification; BMI, body mass index; CI, confidence interval; LMR, lymphocyte-to-monocyte ratio.

Conclusion

In summary, results of the present study suggest that elevated NLR is associated with increased AAC scores among adults aged 40 years and above in the United States, whereas higher LMR is linked to decreased AAC scores and reduced risk for the occurrence of sAAC. The NLR and LMR have emerged as potential biomarkers for AAC risk, highlighting their importance in understanding the inflammatory processes underlying AAC. However, further studies are required to validate these findings.

Conflict of interest statement

Feng Xu is an editorial board member of *Emergency and Critical Care Medicine*. The article was subject to the journal's standard procedures, with peer review handled independently of the Editorial Board member and their research groups. The authors declare no conflicts of interest.

Author contributions

Liu Y and Liu X designed this study and analyzed the data. Liu X collected the data. Liu Y completed the organization and writing of this article. Pan C, Yue H, Zhang X, and Xu F revised the manuscript. All authors approved the final manuscript.

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Ethical approval of studies and informed consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. The NHANES study was reviewed and approved by the NCHS Research Ethics Review Board, and all participants provided written informed consent. This research used deidentified data from NHANES, in accordance with the data release and use agreement.

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