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Non-linear Association between Atherogenic Index of Plasma and Disease Activity in Rheumatoid Arthritis: A Cross-sectional Study

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Article

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Abstract

Objective: To explore the relationship between plasma atherogenic index (AIP) and disease activity of rheumatoid arthritis (RA).

Method: This cross-sectional study included a total of 1088 RA patients. According to the third quartile of AIP, patients were divided into three groups (T1, T2, T3), and a multiple linear regression model was used to analyze the association between AIP and 28 joint disease range of motion scores (DAS28-ESR). In addition, a two-stage linear regression model is used to explore potential nonlinear relationships.

Result: After adjusting for confounding factors, multiple linear regression showed that, with T1 group as a reference, the DAS28-ESR scores of T2 group (β=0.159, 95% CI: 0.041~0.277) and T3 group (β=0.192, 95% CI: 0.071~0.314) were significantly higher (trend P-value=0.002). The analysis of AIP as a continuous variable also yielded consistent conclusions (β=0.312, 95% CI: 0.080~0.545). However, the two-segment linear regression revealed a significant nonlinear relationship (log likelihood ratio P□0.001), with an inflection point of AIP=0.175. Before the inflection point (AIP<0.175), AIP was positively correlated with DAS28-ESR (β=0.927, 95% CI: 0.543-1.311); After the inflection point (AIP>0.175), AIP showed a negative correlation with DAS28-ESR (β=-1.010, 95% CI: -1.682~-0.339).

Conclusion: There is a significant nonlinear correlation between AIP and RA disease activity. When AIP is lower than 0.175, it is positively correlated with disease activity; But when AIP exceeds this critical value, the correlation reverses. This result suggests that lipid metabolism may play a complex role in RA inflammation.

Introduction

Rheumatoid arthritis (RA) is a common systemic autoimmune disease characterized by chronic synovitis and progressive joint destruction, causing significant disability burden and decreased quality of life worldwide[1]. In addition to the limitation of musculoskeletal system, RA is clearly considered as an independent risk factor for accelerating atherosclerosis and premature cardiovascular disease (CVD), which is the main cause of death in this patient group[2,3]. This complex connection is largely coordinated by a sustained systemic inflammatory state, in which circulating pro-inflammatory cytokines, especially tumor necrosis factor alpha (TNF - α) and interleukin-6 (IL-6), not only cause joint damage, but also trigger endothelial dysfunction, promote plaque instability, and disrupt metabolic homeostasis[4,5].

Evaluating the cardiovascular risk of RA requires a multifaceted approach that combines traditional risk factors with disease-specific parameters. Among them, dyslipidemia plays a crucial but contradictory and complex role. The classic lipid mass spectrum of active RA usually shows a "lipid paradox", characterized by low levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), which is in sharp contrast to the typical atherogenic lipid model common in the general population[6,7]. This phenomenon is attributed to the increased inflammatory cascade reaction leading to lipid consumption, which complicates the interpretation of traditional lipid parameters and may

underestimate the real risk of atherosclerosis[8]. Therefore, there is an urgent need for a more robust and anti-inflammatory lipid index in clinical practice to accurately reflect cardiovascular risk under autoimmune background.

The plasma atherosclerosis index (AIP) is calculated by the base logarithm of 10 of the molar ratio of triglyceride to high-density lipoprotein cholesterol (log (TG/HDL-C)), which has become an effective and comprehensive biomarker of atherosclerotic dyslipidemia[9]. Unlike individual lipid measurements, AIP is closely associated with the presence of small and dense LDL particles, which are a subtype highly sensitive to oxidation and have good arterial intima permeability. They are also closely related to insulin resistance and systemic inflammation[10,11]. Its prognostic value for cardiovascular events has been verified in metabolic syndrome, diabetes and the general population[12,13]. Given that the TG/HDL-C ratio reflects pro-inflammatory and pro thrombotic states, AIP can serve as a mirror to capture the interaction between lipid metabolism and inflammatory burden in RA. Therefore, this study utilized data from 1088 RA patients to comprehensively elucidate the association between AIP and RA disease activity, provide a more complex and detailed understanding of the lipid inflammatory axis of RA, and provide information for future targeted therapy strategies.

Method

Research Design and Participants

This study is a cross-sectional study that included 1088 consecutive RA patients who visited Xingtai People's Hospital. All patients met the RA classification criteria proposed by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) in 2010[14]. Exclusion criteria include: severe liver and kidney dysfunction, malignant tumors, and incomplete data. The screening process for research participants is shown in Figure 1. This study was approved by the Ethics Committee of our hospital (batch number: 2025 [031]), and all patients signed informed consent forms.

Data Collection

Collect demographic data, clinical characteristics, and laboratory indicators of patients through an electronic medical record system. Including: gender, age, course of disease (MH), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking history, drinking history, hypertension history, diabetes mellitus (DM) history, coronary heart disease (CHD) history, and use of lipid-lowering drugs. Laboratory indicators include: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), uric acid (UA), fasting blood glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C). AIP is calculated using the formula: AIP=log (TG/HDL-C). Disease activity was evaluated using the 28 joint disease activity score DAS28-ESR score.

Statistical analysis

According to the third quartile of AIP, all patients were divided into three groups: T1, T2, and T3. If the measurement data conforms to a normal distribution, it is expressed as mean ± standard deviation, and analysis of variance is used for inter group comparison; If it does not follow a normal distribution, it is represented by the median (interquartile range), and the Kruskal Wallis H test is used for inter group comparison. Count data is presented in terms of examples (percentage), and comparison between groups is conducted using chi square test. Preliminary screening of variables related to DAS28-ESR using single factor linear regression. Subsequently, a multiple linear regression model was constructed to analyze the association between AIP and DAS28-ESR. We established three models: crude model (unadjusted variables), adjusted model I (adjusted for gender, age, BMI) and adjusted model II (further adjusted for hypertension, DM, CHD, use of lipid-lowering drugs, UA, and FPG). To explore nonlinear relationships, we use a two-stage linear regression model and calculate the inflection point. Compare the goodness of fit between the piecewise linear model and the standard linear model using a log likelihood ratio test. All statistical analyses were conducted using R software (version 4.0.3) and SPSS (version 26.0). P<0.05 indicates that the difference is statistically significant.

Results

Baseline Characteristics

A total of 1088 RA patients were included in this study, and their baseline characteristics were grouped according to AIP quartiles as shown in Table 1. There were significant differences in BMI, DBP, diabetes history, ESR, CRP, UA, FPG, TC, TG, HDL-C, LDL-C and DAS28-ESR among the three groups (P<0.05). As AIP levels increase (from T1 to T3), TG, FPG, TC, LDL-C, UA levels, and DAS28-ESR scores show an upward trend, while HDL-C levels significantly decrease.

Single factor analysis affecting DAS28-ESR

The results of single factor linear regression analysis (Table 2) showed that age (β=0.012, P<0.001), hypertension (β=0.109, P=0.039), diabetes (β=0.170, P=0.047), ESR (β=0.019, P<0.001), CRP (β=0.009, P<0.001), FPG (β=0.061, P=0.005) were positively correlated with DAS28-ESR. But TC（β=-0.083, P=0.001）、TG（β=-0.121, P=0.001）、HDL-C（β=-0.804, P<0.001） It is negatively correlated with DAS28-ESR. It is worth noting that AIP is significantly positively correlated with DAS28-ESR (β=0.262, P=0.022).

Multivariate linear regression analysis of AIP and DAS28-ESR

As shown in Table 3, in the unadjusted coarse model, for every unit increase in AIP, the DAS28-ESR score significantly increased by 0.262 units (95% CI: 0.039~0.486). After gradually adjusting for gender, age, BMI (Model I), and other metabolic confounding factors (Model II), this positive correlation remained significant, and the effect value even slightly increased (adjusted Model II: β=0.312, 95% CI: 0.080-0.545). After analyzing AIP as a categorical variable (triplet array), the results showed that compared with the T1 group, the DAS28-ESR scores of patients in the T2 and T3 groups were significantly higher, and there was a significant dose-response trend (trend P-value=0.002).

Nonlinear Relationship Analysis

Given the complexity of lipid metabolism, we further investigated whether there is a nonlinear correlation between AIP and DAS28-ESR. The two-stage linear regression model (Table 4) revealed a significant nonlinear relationship (log likelihood ratio test P<0.001), with an inflection point of AIP=0.175. Within the range of AIP<0.175, there is a strong positive correlation between AIP and DAS28-ESR (β=0.927, 95% CI: 0.543-1.311); However, when AIP>0.175, the relationship between the two reverses and shows a negative correlation (β=-1.010, 95% CI: -1.682~-0.339). See Figure 2.

Discussion

We confirmed that among 1088 RA patients, higher AIP was associated with increased disease activity, and this association still existed after strict adjustment for confounding factors. Secondly, and most interestingly, our analysis using a two-stage linear regression model revealed a significant nonlinear relationship characterized by a critical inflection point at AIP=0.175. Below this threshold, AIP is strongly positively correlated with DAS28-ESR; Surprisingly, beyond this point, this relationship reversed and showed a negative correlation. These findings deepen our understanding of the complex interactions between lipid metabolism and disease activity in RA.

AIP is widely considered as a reliable marker of dyslipidemia and atherosclerosis. Multiple studies have shown that both baseline and cumulative AIP exposure are associated with cardiovascular disease, particularly coronary artery disease[15,16]. In addition, studies have found that higher levels of AIP are positively correlated with the risk of hypertension and non-alcoholic fatty liver disease[17,18]. A cross-sectional study shows that there is a close relationship between the increased AIP level, the increased risk of insulin resistance and the onset of type 2 diabetes[19]. Recent studies have explored the relationship between AIP and cerebrovascular diseases, indicating that a higher level of AIP is associated with a higher incidence of carotid and intracranial atherosclerotic stenosis[20,21]. In terms of RA disease, more research has focused on the relationship between AIP and the risk of developing cardiovascular disease, indicating that AIP can serve as an independent indicator of long-term CVD risk in RA patients[22]. Further investigation is needed to determine whether AIP levels can serve as a biomarker for disease activity in RA patients. To our knowledge, this study provides the first evidence of a non-linear correlation between baseline AIP levels and disease activity in RA patients.

Our initial linear model is consistent with an increasing number of literature indicating that dyslipidemia is associated with the inflammatory pathogenesis of RA[23,24]. The positive correlation between AIP and DAS28-ESR, even after adjusting the confounding factors, also strengthens the concept that atherosclerotic dyslipidemia is not only a complication, but also may have an internal relationship with disease activity. Mechanistically, this relationship can be conceptualized through several pathways. Research has shown that the levels of small and dense low-density lipoprotein (sdLDL) are significantly elevated in RA patients, and the ability of LDL to specifically bind to chondroitin sulfate proteoglycans on the surface of macrophages is enhanced[25,26]. In addition, sdLDL can promote the growth of

atherosclerosis by regulating lipid metabolism, inducing inflammation and enhancing endothelial damage[27]. It is worth noting that smaller sdLDL particles are more likely to form oxidized LDL, penetrate target cells, and are not easily cleared[28]. Because of this, the LDL receptor is unable to recognize sdLDL, making it easier to be absorbed by macrophages and become foam cells, thus promoting the development and occurrence of atherosclerosis[29]. Simultaneously oxidized LDL can also activate synovial fibroblasts and innate immune cells through scavenger receptors, making pro-inflammatory cytokine cascades (such as IL-1 β, IL-6, TNF - α) permanent, thereby exacerbating systemic inflammation and joint damage[30]. In addition, insulin resistance (AIP is a recognized alternative biomarker) can lead to a pro-inflammatory state characterized by elevated levels of free fatty acids and adipokines, further exacerbating the progression of RA disease[31].

However, the most provocative finding in our study was that the inversion of the AIP-DAS28 relationship exceeded the threshold of 0.175. This phenomenon can be explained by the well described 'lipid paradox' in RA and other chronic inflammatory states. We hypothesize a biphasic model of lipid inflammation interaction: in the mild to moderate inflammatory stage (usually corresponding to low to moderate AIP levels), positive correlation dominates. Here, metabolic abnormalities drive inflammation through the aforementioned mechanisms. On the contrary, in severe and uncontrolled inflammatory states (which may occur simultaneously with very high AIP levels), the classic lipid paradox becomes apparent. High levels of systemic cytokines can significantly inhibit lipoprotein lipase activity, leading to hypertriglyceridemia, while inhibiting lecithin cholesterol acyltransferase (LCAT) enzyme, reducing the maturity and function of HDL-C[32]. More importantly, rampant inflammatory reactions may lead to the depletion of lipid components, which are used as energy substrates by overactive immune cells or incorporated into cell membranes during rapid immune cell proliferation[33]. This consumption effect may paradoxically lead to a relative decrease in measured disease activity, which explains the negative slope observed at very high AIP levels. Therefore, this inflection point (AIP=0.175) may represent a critical metabolic inflammatory threshold.

Our research must be explained within the context of its limitations. The cross-sectional design excludes any inference of causal relationships; We cannot determine whether AIP triggers inflammation, whether inflammation alters lipid metabolism, or whether both processes are influenced by a third unmeasured factor. Although we have adjusted for various confounding factors, residual confounding factors are still a possibility. For example, there is no detailed data available for adjusting dietary habits and physical activity levels. Finally, as a single center study, the generalizability of our findings, including specific inflection point values, needs to be validated in larger multicenter prospective cohorts.

Conclusion

In summary, our research indicates that the relationship between AIP and RA disease activity is not linear, but rather has a significant threshold effect. Future prospective research is crucial for verifying this turning point and exploring the potential mechanisms driving this biphasic relationship. Ultimately,

understanding this complex interaction can provide a basis for more personalized management strategies targeting both inflammation and lipid metabolism in RA patients.

Declarations

Data availability

The data will be shared on reasonable request to the corresponding or the senior author.

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Competing interests

The authors declare no competing interests.

Author contributions

LL and XL proposed the strategy, LL conducted the data extraction and organization as well as the final draft, QT provided statistical methodological guidance, LL, YL, JZ and YH analyzed and validated the data, and QT and YL produced the charts. All authors conducted the review and approved the final manuscript. LL and XL are the guarantors of this work and are responsible for the completeness and accuracy of the work.

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Ethics approval and consent to participate

This study received approval from the Research Ethics Committee of Xingtai People’s Hospital (approval number: 2025[031]). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

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Tables

Table 1. General feature description according to tertiles of AIP.

Characteristics	Total	Tertiles of AIP			
		T1(-0.53, -0.07)	T2(-0.07, 0.11)	T3(0.11, 1.03)	*P* value
N	1088	364	364	360	
Sex, %					0.306
Female	856 (78.70%)	295 (81.04%)	278 (76.37%)	283 (78.61%)	
Male	232 (21.30%)	69 (18.96%)	86 (23.63%)	77 (21.39%)	
Age (year)	59.00 (51.00-68.00)	60.00 (49.00-68.00)	59.00 (51.00-69.00)	58.00 (51.00-66.00)	0.490
MH (month)	72.00 (12.00-132.00)	72.00 (21.00-144.00)	60.00 (12.00-120.00)	72.00 (12.00-130.75)	0.249
BMI (kg/m^2)	23.81±3.55	22.89 (20.70-24.97)	23.96±3.55	24.57±3.72	<0.001
SBP (mmHg)	132.00 (120.00-145.00)	130.00 (120.00-142.75)	132.00 (120.00-145.00)	133.13±15.97	0.236
DBP (mmHg)	80.00 (73.00-86.00)	80.00 (71.00-85.00)	80.00 (72.00-86.00)	80.00 (74.00-89.00)	0.007
Smoking, N (%)					0.185
No	1030 (94.70%)	351 (96.43%)	341 (93.68%)	338 (93.89%)	
Yes	58 (5.30%)	13 (3.57%)	23 (6.32%)	22 (6.11%)	
Alcohol use, N (%)					0.194
No	1069 (98.30%)	360 (98.90%)	354 (97.25%)	355 (98.61%)	
Yes	19 (1.70%)	4 (1.09%)	10 (2.75%)	5 (1.39%)	
Hypertension, N (%)					0.085
No	734 (67.50%)	261 (71.70%)	242 (66.48%)	231 (64.17%)	
Yes	354 (32.50%)	103 (28.30%)	122 (33.52%)	129 (35.83%)	
DM, N (%)					0.018
No	987 (90.70%)	343 (94.23%)	324 (89.01%)	320 (88.89%)	
Yes	101 (9.30%)	21 (5.77%)	40 (10.99%)	40 (11.11%)	
CHD, N (%)					0.157

No	1014 (93.20%)	343 (94.23%)	343 (94.23%)	328 (91.11%)	
Yes	74 (6.80%)	21 (94.23%)	21 (94.23%)	32 (8.89%)	
Antihyperlipidemic, N (%)					0.624
No	972 (89.3%)	327 (89.84%)	328 (90.11%)	317 (88.06%)	
Yes	116 (10.70%)	37 (10.16%)	36 (9.89%)	43 (11.94%)	
ESR (mm/H)	60.00 (35.00-88.00)	51.00 (30.00-86.00)	65.00 (39.00-90.00)	59.00 (37.00-87.00)	0.007
CRP (mg/L)	28.53 (7.45-48.97)	25.97 (6.06-47.81)	33.01 (10.62-53.09)	22.72 (6.60-45.88)	0.018
UA (umol/L)	249.00 (195.00-296.00)	224.50 (179.00-275.75)	248.18±73.86	264.00 (216.25-319.88)	0.001
FPG (mmol/L)	4.88 (4.52-5.35)	4.77 (4.45-5.15)	4.89 (4.53-5.45)	4.98 (4.60-5.45)	0.001
TC (mmol/L)	4.08 (3.48-4.69)	4.01 (3.45-4.57)	4.04 (3.46-4.67)	4.27±0.99	0.013
TG (mmol/L)	1.05 (0.83-1.41)	0.78 (0.67-0.91)	1.05 (0.92-1.20)	1.58 (1.31-1.97)	<0.001
HDL-C (mmol/L)	1.02 (0.86-1.19)	1.19 (1.03-1.36)	1.01 (0.87-1.14)	0.87 (0.76-1.01)	<0.001
LDL-C (mmol/L)	2.38 (1.95-2.90)	2.19 (1.80-2.65)	2.43 (1.97-2.90)	2.60±0.75	<0.001
DAS28-ESR	4.53 (3.92-5.06)	4.45 (3.72-4.94)	4.62 (4.01-5.10)	4.54 (3.98-5.08)	0.007

Abbreviations: *AIP* atherogenic index of plasma, *MH* medical history, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *CHD* coronary heart disease, *ESR* erythrocyte sedimentation rate, *CRP* high-sensitivity C-reactive protein, *UA* uric acid, *FPG* fasting plasma glucose, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol.

Table 2. The results of univariate analysis.

Characteristics	Statistics	DAS28-ESR β (95% CI)	P value
Sex, N (%)			
Female	856 (78.70%)	Ref	
Male	232 (21.30%)	-0.111 (-0.229, 0.008)	0.067
Age (year)	59.00 (51.00, 68.00)	0.012 (0.008, 0.016)	<0.001
MH (month)	72.00 (12.00, 132.00)	0.000 (0.000, 0.001)	0.582
BMI (kg/m^2)	23.81±3.55	-0.005 (-0.018, 0.009)	0.502
SBP (mmHg)	132.00 (120.00, 145.00)	-0.001 (-0.004, 0.002)	0.548
DBP (mmHg)	80.00 (73.00, 86.00)	-0.004 (-0.009, 0.001)	0.089
Smoking, N (%)			
No	1030 (94.70%)	Ref	
Yes	58 (5.30%)	0.104 (-0.113, 0.320)	0.348
Alcohol use, N (%)			
No	1069 (98.30%)	Ref	
Yes	19 (1.70%)	-0.037 (-0.408, 0.335)	0.847
Hypertension, N (%)			
No	734 (67.50%)	Ref	
Yes	354 (32.50%)	0.109 (0.006, 0.213)	0.039
DM, N (%)			
No	987 (90.70%)	Ref	
Yes	101 (9.30%)	0.170 (0.003, 0.337)	0.047
CHD, N (%)			
No	1014 (93.20%)	Ref	
Yes	74 (6.80%)	0.014 (-0.180, 0.207)	0.891
Antihyperlipidemic, N (%)			
No	972 (89.3%)	Ref	
Yes	116 (10.70%)	0.054 (-0.103, 0.212)	0.498
ESR (mm/H)	60.00 (35.00, 88.00)	0.019 (0.018, 0.020)	<0.001
CRP (mg/L)	28.53 (7.45, 48.97)	0.009 (0.008, 0.010)	<0.001

UA (umol/L)	249.00 (195.00, 296.00)	0.000 (0.000, 0.001)	0.535
FPG (mmol/L)	4.88 (4.52, 5.35)	0.061 (0.019, 0.102)	0.005
TC (mmol/L)	4.08 (3.48, 4.69)	-0.083 (-0.134, -0.032)	0.001
TG (mmol/L)	1.05 (0.83, 1.41)	-0.121 (-0.196, -0.047)	0.001
HDL-C (mmol/L)	1.02 (0.86, 1.19)	-0.804 (-0.984, -0.623)	<0.001
LDL-C (mmol/L)	2.38 (1.95, 2.90)	0.008(-0.059, 0.075)	0.812
AIP	0.02 (-0.12, 0.16)	0.262 (0.039, 0.486)	0.022

Abbreviations: *MH* medical history, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *CHD* coronary heart disease, *ESR* erythrocyte sedimentation rate, *CRP* high-sensitivity C-reactive protein, *UA* uric acid, *FPG* fasting plasma glucose, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *AIP* atherogenic index of plasma.

Table 3. Multivariate linear regression results of association between AIP and DAS28-ESR.

Exposure	Crude model β (95% CI)	Adjust I β (95% CI)	Adjust II β (95% CI)
DAS28-ESR			
AIP	0.262 (0.039, 0.486)	0.320 (0.095, 0.546)	0.312 (0.080, 0.545)
AIP (Tertiles)			
T1	Ref	Ref	Ref
T2	0.166 (0.047, 0.284)	0.163 (0.045, 0.280)	0.159 (0.041, 0.277)
T3	0.178 (0.059, 0.297)	0.192 (0.073, 0.311)	0.192 (0.071, 0.314)
P for trend	0.003	0.002	0.002

Crude model adjust for: None.

Adjust I model adjust for: sex; age; BMI.

Adjust II model adjust for: sex; age; BMI; hypertension; diabetes mellitus; coronary heart disease; antihyperlipidemic; uric acid; fasting plasma glucose.

Abbreviations: *AIP* atherogenic index of plasma.

Table 4. The result of two-piecewise linear regression model of AIP with DAS28-ESR.

	DAS28-ESR β (95% CI)
Fitting model by standard linear regression	4.434 (4.386, 4.482)
Fitting model by two-piecewise linear regression	
Inflection points of AIP	0.175
<Inflection point	0.927 (0.543, 1.311)
>Inflection point	-1.010 (-1.682, -0.339)
P for log likelihood ratio test	<0.001

Note: The models were adjusted for: sex; age; BMI; hypertension; diabetes mellitus; coronary heart disease; antihyperlipidemic; uric acid; fasting plasma glucose.

Abbreviations: *AIP* atherogenic index of plasma.

Figures

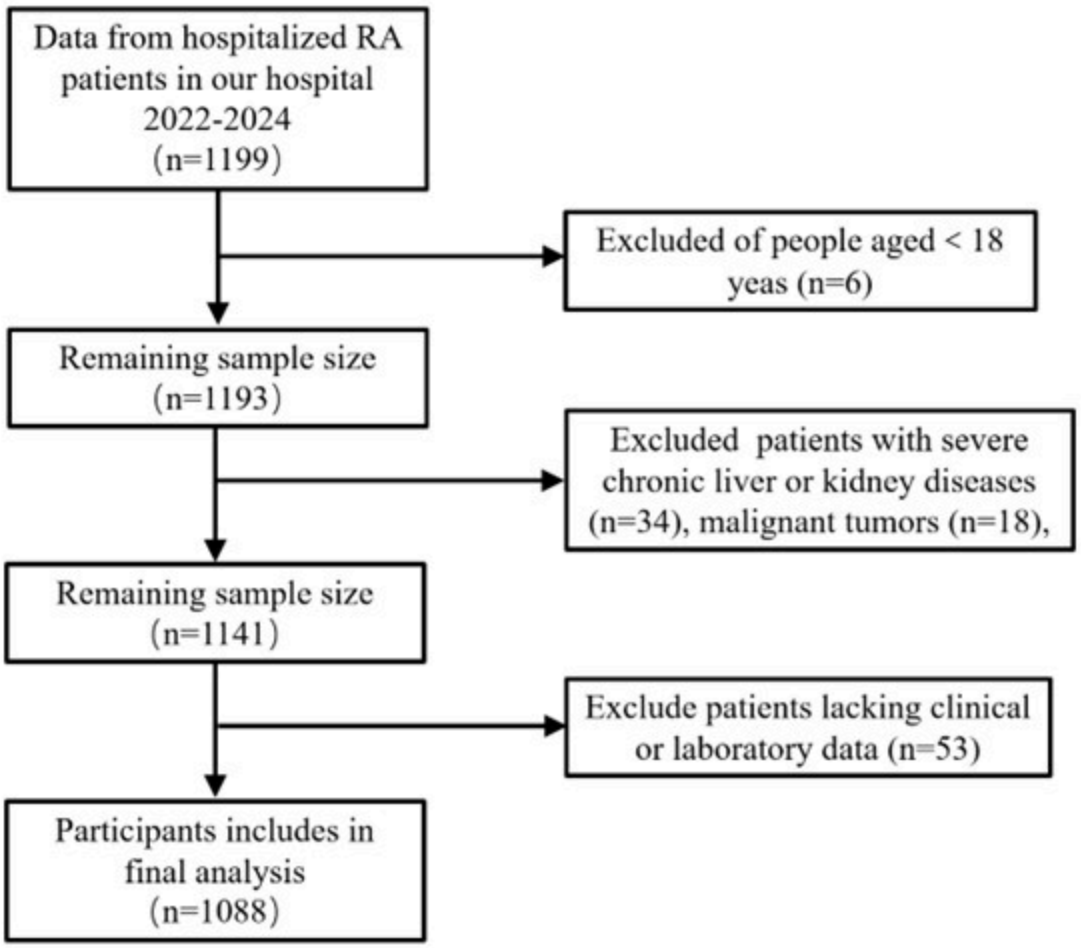


Figure 1

Flowchart of participant selection.

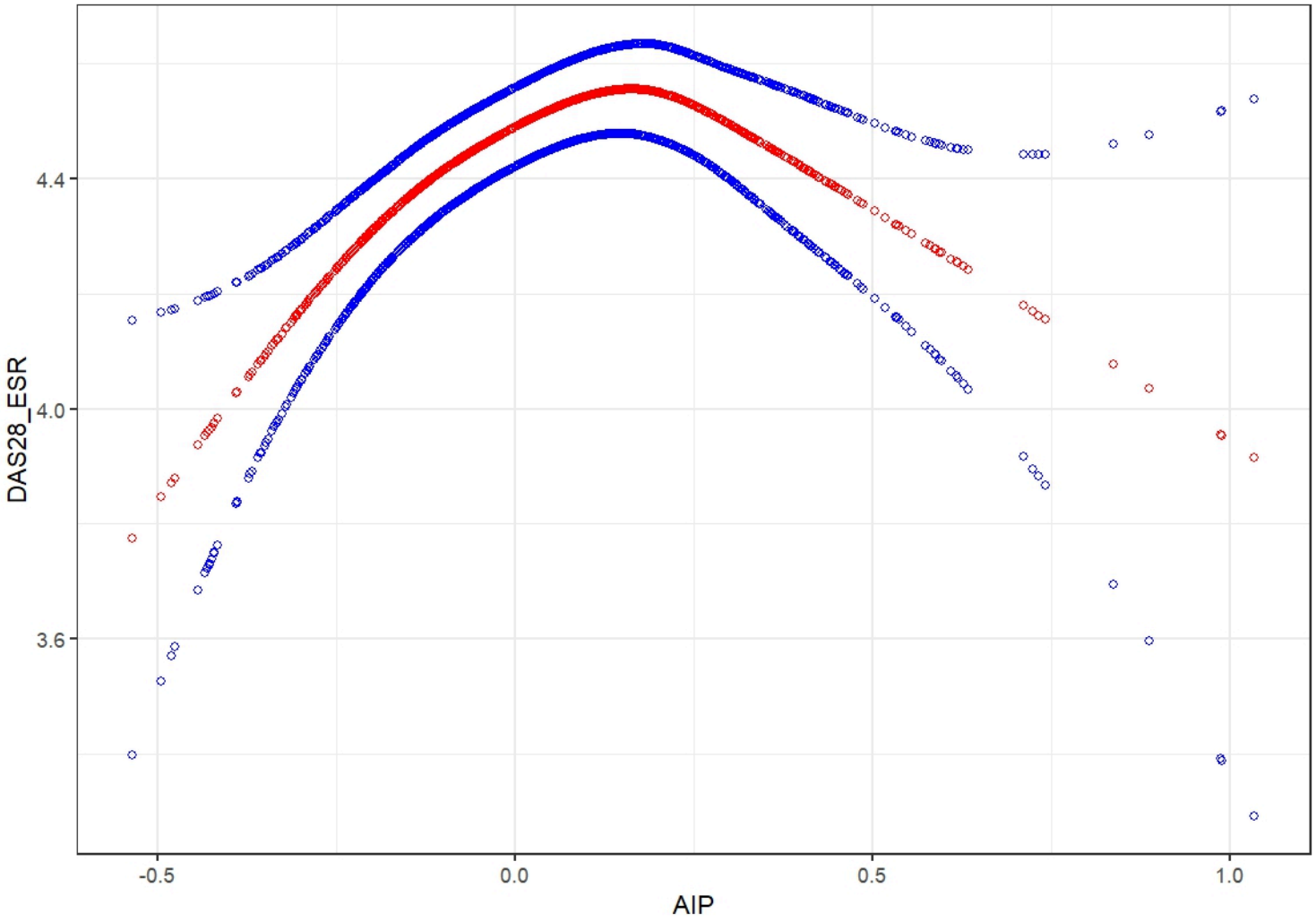


Figure 2

A nonlinear relationship of plasma atherogenic index with DAS28-ESR. Note: The model was adjusted for sex; age; BMI; hypertension; diabetes mellitus; coronary heart disease; antihyperlipidemic; uric acid; fasting plasma glucose.