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A J-shaped relationship between the atherogenic index of plasma and new-onset myocardial infarction in hypertensive patients with obstructive sleep apnea: a cohort study

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Abstract. – OBJECTIVE: This study aimed to investigate the relationship between baseline atherogenic index of plasma (AIP) and new-onset myocardial infarction (MI) in hypertensive patients with obstructive sleep apnoea (OSA).

PATIENTS AND METHODS: 2,281 participants were included in this analysis after strict adherence to the inclusion and exclusion criteria. Hazard ratio (HR) and 95% confidence interval (CI) were estimated using multivariable Cox regression models. A generalized additive model was employed to determine nonlinear relationships.

RESULTS: In multivariate-adjusted models, there was a positive association between AIP and new-onset MI (per SD increase; HR=1.42, 95% CI: 1.22-1.65). Smoothing curve fitting revealed a J-shaped association between AIP and new-onset MI, with a turning point of approximately -0.08. The addition of AIP to a model with established risk factors improved the C-index (p=0.007), integrated discrimination improvement (p=0.007), and continuous net reclassification improvement (p=0.027) for the new-onset MI.

CONCLUSIONS: A J-shaped relationship was observed between AIP and new-onset MI.

Key Words:
Atherogenic index of plasma, Myocardial infarction, J-shaped relationship, Cohort study.

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide[1]. Myocardial infarction (MI) is a key component of the CVD burden. Previous investigations have shown that dyslipidemia plays an essential causal role in the development of MI and has been widely demonstrated to be a significant risk factor for CVD[2,3]. Additionally, dyslipidemia coexists with hypertension, obstructive sleep apnea (OSA), diabetes mellitus, and obesity, all of which are known risk factors for CVD[4]. The prevalence of dyslipidemia has been shown to be high in hypertensive patients with OSA[5]. Several mechanisms involving chronic intermittent hypoxia, sympathetic activation, insulin resistance (IR), oxidative stress, and activation of the systemic inflammatory response may explain dyslipidemia in patients with hypertension combined with OSA[6]. The frequent coincidence of hypertension, OSA, and dyslipidemia may increase the risk of CVD in hypertensive patients with OSA[4]. The atherogenic index of plasma (AIP) from fasting triglycerides (TG) and fasting high-density lipoprotein cholesterol (HDL-c) has been suggested as a reliable surrogate for dyslipidemia. In recent years, AIP has been recognized as a better indicator of lipid metabolism and a sensitive indicator of CVD risk than lipid parameters alone[7]. Several investigations have found a significant positive association between AIP and cardiovascular risk, including symptomatic coronary artery disease, coronary artery calcification, carotid atherosclerosis, systemic arterial stiffness, hypertension, and metabolic syndrome[8-10]. However, although a positive association between AIP and CVD prevalence has been observed in previous cross-sectional studies, data from longitudinal investigations on the association between AIP and MI incidence are inconclusive and limited.

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Therefore, this study aimed to investigate the relationship between AIP levels and new-onset MI in hypertensive patients with OSA.

Patients and Methods

Study Design and Participants

All data were obtained from the Urumqi Research on Sleep Apnea and Hypertension (UROSAH) study, and a detailed description of the study has been reported elsewhere[11]. The inclusion and exclusion criteria for this study are detailed in the flow chart (Figure 1). Overall, 2281 participants were ultimately included in this analysis after strict adherence to the inclusion and exclusion criteria.

Covariables

Baseline data were collected by trained healthcare professionals following standard operating procedures, as detailed in previously published studies[11-13]. The AIP was calculated using the following formula: AIP = log (TG (mmol/L) / HDL-c (mmol/L))[7]. Regular continuous positive airway pressure (CPAP) treatment was defined as the use of CPAP therapy for more than 70% of nights throughout the follow-up period and no less than 4 hours per night, or an average of ≥4 hours per night (CPAP devices only provide cumulative hours of use). Diagnosis of OSA was defined as a minimum of 5 events per hour of AHI[11]. The details of the polysomnography (PSG) and scoring criteria used in this study are provided in the **Supplementary information**. Definitions of respiratory events are shown in **Supplementary Table I**. The criteria for defining hypertension and diabetes were in agreement with previous studies[11]. Based on the frequency of smoking and drinking, we classified them as never, former, and current.

Clinical End Points

The primary outcome was defined as new-onset MI (fatal and non-fatal). Outcome events were obtained by inpatient medical records, telephone follow-up, and outpatient review. Death certificates and hospital records confirmed fatal MI. For out-of-hospital deaths, follow-up data were obtained by contacting family members by telephone. All events were adjudicated by an independent and blinded clinical events committee. The follow-up period was from the date of enrollment to the end of January 2021.

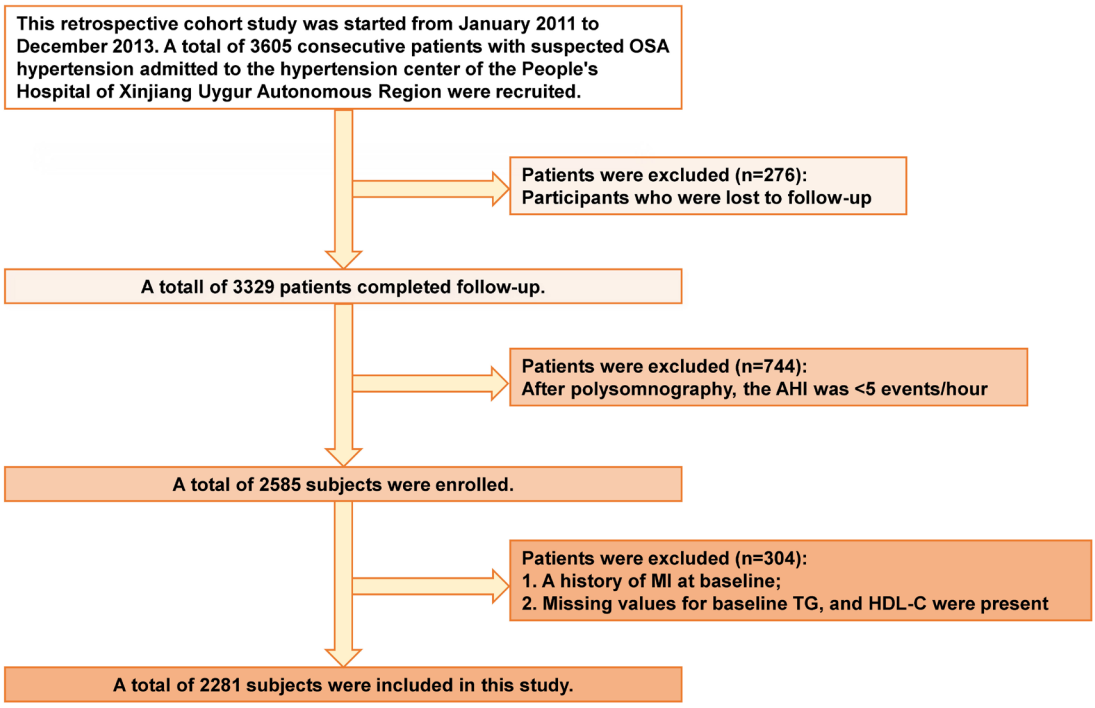

Figure 1. Flow diagram for study selection.

Statistical Analysis

Baseline characteristics of participants were calculated based on the AIP quartiles. Collinearity was tested using the variance inflation factor (**Supplementary Table II**). Four multivariate Cox regression models were established to estimate the association between AIP and new-onset MI, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A generalized additive model was used to assess the nonlinear relationship between AIP and new-onset MI. C-index, integrated discrimination improvement (IDI), and net reclassification improvement (NRI) were measured to evaluate whether the accuracy of predicting new-onset MI would improve with the addition of AIP to the established model of risk factors. Statistical analysis was performed using software R, version 3.6.1, and 2-sided *p*-values less than .05.

Results

Baseline Characteristics

The overall features of the study subjects by AIP quartiles are shown in Table I. Individuals in the highest AIP group (quartile 4) were usually younger and had higher BMI, DBP, TC, TG,

Table I. Baseline characteristics.

Variable	AIP				
	Quartile 1 (<0.04)	Quartile 2 (≥0.04 to <0.22)	Quartile 3 (≥0.22 to <0.41)	Quartile 4 (≥0.41)	*p*-value
Participants	570	570	570	571	
Age, years	53.24 ± 11.39	49.60 ± 10.83	48.52 ± 10.15	46.53 ± 8.97	<0.01
Gender, N (%)					<0.01
Female	271 (47.5%)	198 (34.7%)	150 (26.3%)	100 (17.5%)	
Male	299 (52.5%)	372 (65.3%)	420 (73.7%)	471 (82.5%)	
BMI, kg/m²	27.51 ± 3.94	28.61 ± 4.13	28.72 ± 3.76	28.98 ± 3.26	<0.01
DBP, mmHg	90.41 ± 13.92	91.95 ± 14.26	91.73 ± 14.20	93.63 ± 13.93	<0.01
SBP, mmHg	141.47 ± 19.96	140.33 ± 19.93	139.21 ± 19.40	139.48 ± 19.40	0.21
Smoking status, N (%)					<0.01
Never	417 (73.2%)	349 (61.2%)	296 (51.9%)	250 (43.8%)	
Former	56 (9.8%)	60 (10.5%)	62 (10.9%)	67 (11.7%)	
Current	97 (17.0%)	161 (28.3%)	212 (37.2%)	254 (44.5%)	
Drinking status, N (%)					<0.01
Never	455 (79.8%)	404 (70.9%)	338 (59.30%)	323 (56.6%)	
Former	21 (3.7%)	35 (6.1%)	55 (9.65%)	42 (7.4%)	
Current	94 (16.5%)	131 (23.0%)	177 (31.1%)	206 (36.1%)	
Diabetes, N (%)	74 (13.0%)	91 (16.0%)	105 (18.4%)	129 (22.6%)	<0.01
Laboratory examinations					
TG, mmol/L	1.06 ± 0.27	1.54 ± 0.33	2.09 ± 0.44	4.06 ± 2.46	<0.01
TC, mmol/L	4.41 ± 1.44	4.55 ± 1.23	4.55 ± 1.02	4.76 ± 1.06	<0.01
LDL-c, mmol/L	2.55 ± 0.75	2.80 ± 0.82	2.75 ± 0.83	2.49 ± 0.78	<0.01
HDL-c, mmol/L	1.37 ± 0.31	1.12 ± 0.21	1.02 ± 0.20	0.90 ± 0.20	<0.01
FPG, mmol/L	5.08 ± 1.16	5.19 ± 1.29	5.25 ± 1.29	5.62 ± 1.96	<0.01
hs-CRP, mg/L	1.94 (0.83-3.63)	2.21 (1.00-4.13)	2.46 (1.05-4.24)	2.02 (0.95-4.17)	0.09
eGFR, ml/min/1.73 m2	94.50 ± 21.74	96.77 ± 21.43	95.29 ± 19.89	97.65 ± 22.82	0.06
Hcy, μmol/L	14.29 (10.09-19.77)	14.93 (10.12-21.68)	14.19 (10.04-22.23)	15.08 (10.12-22.02)	0.32
Cr, μmol/L	74.23 ± 21.83	76.22 ± 27.67	78.60 ± 22.96	79.98 ± 23.59	<0.01
Polysomnography examinations					
AHI, events/h	16.20 (9.60-29.40)	19.00 (9.90-33.30)	18.60 (10.90-35.20)	21.50 (11.50-37.40)	<0.01
Mean SaO2, %	91.47 ± 5.96	90.57 ± 10.13	91.40 ± 6.97	91.01 ± 9.09	0.94
Medication use					
Lipid-lowering drugs, N (%)	278 (48.8%)	298 (52.3%)	437 (76.7%)	471 (82.5%)	<0.01
Antihypertensive drugs, N (%)	479 (84.0%)	520 (91.2%)	548 (96.1%)	531 (93.0%)	<0.01
Antiplatelet drugs, N (%)	339 (59.5%)	386 (67.7%)	412 (72.3%)	483 (84.6%)	<0.01
Regularly CPAP treatment, N (%)	11 (1.9%)	21 (3.7%)	30 (5.3%)	34 (6.0%)	<0.01

Values are N (%), mean ± SD or median (IQR).

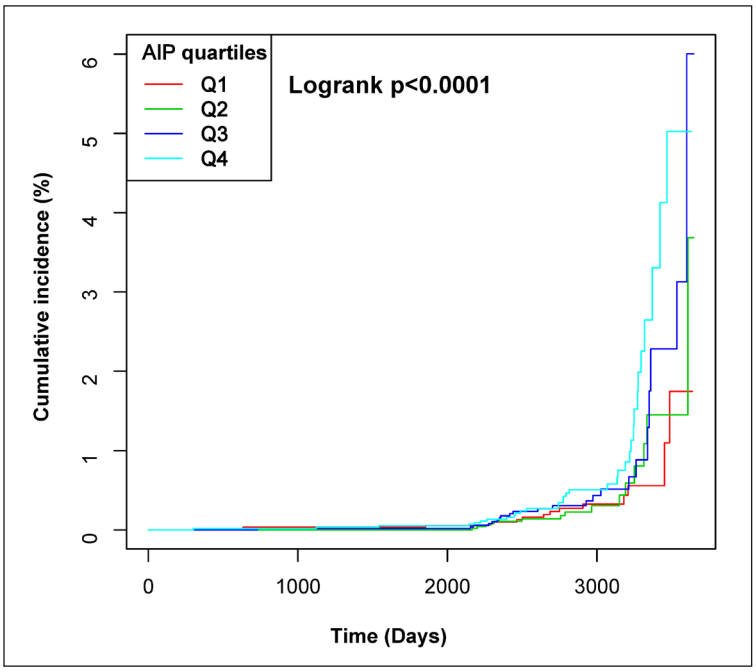

Figure 2. Kaplan-Meier curves compared cumulative incidence of first MI after grouping by the AIP quartile.

HDL-c, LDL-c, FPG, Cr, and eGFR than individuals in the lowest AIP group (quartile 1). Over a median of 7.15 years (IQR, 6.27-8.18 years) of follow-up, 85 (3.62%) incident MI cases were documented. The cumulative incidence of new-onset MI increased progressively with increasing AIP (Figure 2).

Association Between the AIP and New-Onset MI

Table II shows the association between the AIP and new-onset MI in hypertensive patients with OSA. The fully adjusted HR for the incidence of new-onset MI was 1.42 (95% CI: 1.22-1.65, p<0.01) for every 1-SD increase in the AIP. Adjusting for all non-collinear covariates (Model 4), AIP remained positively correlated with new-onset MI. HRs corresponding to the quartiles of the AIP were 1, 0.80, 1.57, and 2.25, respectively, (p for trend< 0.01).

Nonlinearity and Threshold Effect Between the AIP and New-Onset MI

In Figure 3, a J-shape relationship was observed between the AIP and new-onset MI. Using a two-piecewise linear regression model, we computed the inflection point for AIP to be -0.08 (log-likelihood ratio test p=0.046). On the right

Table II. Association between AIP and incident first MI in different models.

Exposure	HR (95%CI) *p*-value			
	Model 1	Model 2	Model 3	Model 4
AIP (per SD increase)	1.42 (1.23, 1.63) <0.01	1.39 (1.20, 1.62) <0.01	1.40 (1.21, 1.63) <0.01	1.42 (1.22, 1.65) <0.01
AIP (quartile)				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.01 (0.60, 1.68) 0.98	0.89 (0.53, 1.49) 0.65	0.85 (0.51, 1.43) 0.55	0.80 (0.48, 1.35) 0.41
Quartile 3	1.60 (1.00, 2.57) 0.05	1.51 (0.94, 2.44) 0.09	1.46 (0.90, 2.35) 0.12	1.57 (0.97, 2.53) 0.07
Quartile 4	2.67 (1.70, 4.19) <0.01	2.37 (1.49, 3.77) <0.01	2.26 (1.42, 3.61) <0.01	2.25 (1.40, 3.61) <0.01
P for trend	<0.01	<0.01	<0.01	<0.01

Model 1 adjusted for age and gender at baseline; Model 2 adjusted for model 1 plus drinking status, SBP, smoking status, DBP, diabetes, and BMI at baseline; Model 3 adjusted for model 2 plus lipid-lowering drugs, antiplatelet drugs, regularly CPAP treatment, and antihypertensive drugs; Model 4 adjusted all non-colinear variables.

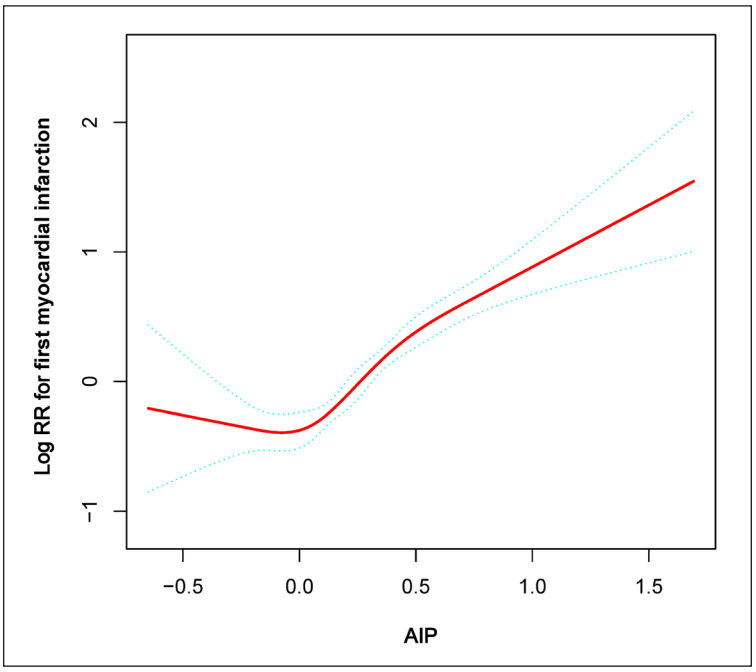

Figure 3. Association between the AIP and first MI

side of the inflection point, we identified a positive association between AIP and new-onset MI (per SD increase; HR=1.46, 95% CI: 1.35-1.58, $p<0.01$) (Table III).

Discrimination and Reclassification of AIP

The C-index of new-onset MI was greater in the model with the addition of AIP compared to the established risk factors ($p=0.007$). The continuous NRI and IDI for new-onset MI were also dramatically increased with the addition of AIP to the established risk factors (Table IV).

Discussion

Over the past few years, researchers have focused on a new composite lipid index, AIP[9]. As an alternative to small-density LDL particle size with little additional cost, AIP is considered an economical and reliable predictor of CAD in clinical practice[14]. Furthermore, a few investigations have employed AIP for CVD prognosis as a biomarker[15,16]. For example, a prospective study of 2676 Turkish adults (median follow-up 7.8 years) by Onat et al[14] evaluated the relationship between AIP and cardiovascular disease. The results showed that high AIP was an important factor in the risk of cardiovascular events when adjusted for confounding variables[15]. Also, a study conducted in the United States to evaluate women with ischemic syndromes showed that AIP was an extremely important indicator of new malignant CVD events, especially in women with no previous history of MI or coronary revascularization[17]. However, some studies have yielded inconsistent results. A study by Nansseu et al[18] found that AIP was not an independent determinant of the impact of CVD risk in postmenopausal women in Cameroon. In another prospective cohort study, Hartopo et al[19] investigated the relationship between AIP and CVD events during hospitalization in

Table III. The result of the two-piecewise linear regression model.

	HR (95% CI)	*p*-value
The inflection point of AIP	-0.08	
≤-0.08 (per SD increase)	0.90 (0.59, 1.37)	0.61
>-0.08 (per SD increase)	1.46 (1.35, 1.58)	<0.01
Log-likelihood ratio test		0.046

The model adjusted all non-colinear variables.

Table IV. Discrimination of predictive models for outcome using C-index, continuous-NRI, and IDI.

	C-index (95% CI)	*p*-value	Continuous-NRI (95% CI)	*p*-value	IDI (95% CI)	*p*-value
Established risk factors	0.659 (0.619, 0.698)	—	Ref.	—	Ref.	—
Established risk factors+AIP	0.690 (0.651, 0.729)	0.007	0.099 (0.010, 0.187)	0.027	0.008 (0.002, 0.019)	0.007

Established risk factors included age, gender, smoking status, drinking status, diabetes, BMI, TC, TG, HDL-C, LDL-C, and FPG levels. NRI, net reclassification index; IDI, integrated discrimination improvement.

patients with MI. They found that the low AIP segment (AIP < 0.24) was an additional predictive factor for all-cause mortality in patients with MI receiving intensive hospitalization compared to a high AIP segment (AIP ≥ 0.24). Although the potential mechanisms by AIP are associated with MI risk and have not been illuminated, there are a few potential explanations summarized below. First, IR could be an essential factor. Numerous presentations in the literature discuss how AIP may be a useful surrogate for estimating IR[20,21]. In addition, IR may also be strongly associated with an elevated risk of metabolic abnormalities, including abnormal glucose metabolism, hypertension, and dyslipidemia, all of which are associated with an increased risk of MI[22,23]. Notably, Reardon et al[24] revealed that IR may promote atherosclerosis through the IFN γ-macrophage pathway. Second, a higher AIP represents an elevated TG or reduced HDL-c. Presently, there is evidence that increased TG may serve an important role in increased atherosclerosis[25]. However, HDL-c is heterogeneous, with non-vascular effects and anti-atherogenic properties[26]. Thus, AIP reflects the balance between protective lipoproteins and atherogenic. Furthermore, dyslipidemia, characterized by low levels of HDL-c or high levels of TG, is a common risk factor for atherogenesis[27]. Finally, the inflammatory response and oxidative stress may also be another important cause. A prior investigation demonstrated that the TG/HDL-c ratio was substantially associated with the presence of small, small dense LDL cholesterol particles that are proactively absorbed by arterial tissue and induce oxidative damage to vascular tissue[28]. The accumulation of oxidized LDL cholesterol spurs the secretion of pro-inflammatory cytokines and chemokines by monocytes and macrophages[29]. Thus, further research is warranted to find the definitive mechanism. Several limitations should be considered in interpreting these findings. First, because this was an observational study, we were incapable to determine a causal relationship between AIP and new-onset MI. Second, data on other confounding factors were not included in the analysis because of missing information. Finally, in our current study, AIP was measured only at baseline. More frequent measurements of AIP could provide more valuable information. Because of these limitations, our study only generated hypotheses. These results do warrant further examination and validation in other studies.

Conclusions

A J-shaped relationship was observed between AIP and new-onset MI. The AIP is an independent predictor of new-onset MI in hypertensive patients with OSA.

Conflict of Interests

The authors report no conflicts of interest in this work.

Funding

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Ethical Committee Approval

The study was approved by the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (2019030662).

Informed Consent

Informed consent was given by all patients in accordance with the Declaration of Helsinki.

Data Availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contribution

XC and JG conceived and designed the study; JH and MW participated in the literature search and data collection; SL, JH, and NL reviewed and edited the manuscript. All authors read and approved the final manuscript.

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