

Association Between AST to ALT Ratio and Peripheral Artery Disease in Chinese Hypertensive Population: A Cross-Sectional Study

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Abstract

Background: Previous studies had shown the role of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AST/ALT) in cardiovascular disease . Peripheral artery disease(PAD) is an important risk factor for cardiovascular death. However, there are fewer investigations of the correlations between the AST/ALT ratio and Peripheral artery disease (PAD).

Methods: We analyzed data of 10,900 hypertensive patients from the Chinese Hypertension Registry Study. Using a multivariate logistic regression model, we examined the association between AST / ALT and peripheral arterial disease (PAD),which was defined as $ABI \leq 0.9$ in either leg.

Results A total of 350 patients had peripheral arterial disease and the prevalence of PAD was 3.21%. After adjusting for potential confounders, AST / ALT ratio was independently and positively associated with risk of PAD (OR: 1.31, 95% CI: 1.13 to 1.59), and a statistically significant increased risk of PAD for the third AST / ALT ratio tertile (T3) compared to the first tertile (T1) (OR:1.49, 95% CI: 1.09 to 2.04, P -trend= 0.005) was found. Moreover, when we combined T1-T2 into one group and used it as a reference group, the risk of PAD increased with the increase of AST/ALT and the risk ratio was 1.52 (95% CI :1.20 to 1.95).

Conclusion: A higher AST/ALT ratio (≥ 1.65) was associated with PAD risk in Chinese adults with hypertension. Our results suggested that AST / ALT maybe help us highlight patients who was at high risk of vascular endpoints.

Trial registration: CHICTR, CHICTR1800017274. Registered 20 July 2018.

Introduction

The burden of atherosclerotic cardiovascular disease is rapidly increasing as a result of the economic growth, urbanization, and aging of the population in China. Peripheral artery disease(PAD) is the third leading cause of atherosclerotic cardiovascular morbidity, following coronary artery disease and stroke^[1]. Smoking, diabetes mellitus (DM), obesity, hypertension, dyslipidemia, aging and a family history of peripheral artery disease, heart disease are the risk factors for developing PAD^[2]. Despite the control of these risk factors, the prevalence of PAD is still high, while the awareness rate,treatment rate and control rate are low. According to an epidemiological study in China, standardized prevalence rate of PAD was 6.6%, awareness rate was 4.9%, treatment rate was 1.9%, and control rate was 0.2%^[3]. Peripheral arterial disease has become a global health problem^[4], with high mortality and cardiovascular morbidity^[5]. Thence, in addition to traditional risk factors, it is critical to find new markers that can predict PAD more easily and prevent cardiovascular death earlier.

Aspartate aminotransferase (AST) is mainly distributed in the heart muscle, followed by tissues such as liver, skeletal muscle and kidney and Alanine aminotransferase (ALT) exists in various cells, especially liver cells. In the past, the AST/ALT ratio was often used to reflect a variety of chronic liver diseases,

including alcoholic and non-alcoholic liver diseases^[6], autoimmune liver diseases^[7], and hepatitis C^[8]. In particular, non-alcoholic fatty liver disease is associated with increased cardiovascular disease, all-cause mortality, and diabetes^[9]. Current findings emphasized that higher AST / ALT level can be bio-markers for cardiovascular diseases. For example, a prospective cohort of 29 316 UK primary care patients arrived at a conclusion that elevated AST / ALT ratio is significantly associated with increased risk of developing CVD in men but not women^[10]. Moreover, Miyuki Yokoyama et al. revealed that AST / ALT is a predictive of all-cause mortality and cardiovascular mortality in a general population^[11]. Considering that both the AST/ALT ratio and PAD are related to cardiovascular disease and data on the relationship between AST/ALT ratio and PAD was limited, the purpose of this study was to assess whether the AST / ALT ratio was associated with PAD.

Materials And Methods

Study design and participants

The present study population comes from the China Hypertension Registry Study whose main aim is to establish a national registry of hypertension patients, investigate the prevalence and treatment of hypertension in China. In addition, this observational study plans to evaluate the correlative factors that affect hypertension and its prognosis. Patients were eligible for enrollment if they were 18 years of age or older; had hypertension which defined based on the usual 140/90 mmHg threshold, self-report history of hypertension, or the use of anti-hypertensive drug(s) at baseline^[12]; signed informed consent. And if they had psychological or nervous system impairment resulting in an inability to demonstrate informed consent or unable to be followed-up according to the study protocol, or plans to relocate in the near future or those patients who were not suitable for inclusion or for long-term follow-up as assessed by study physicians, they would be excluded. We recruited a total of 14,268 study participants in Wuyuan, Jiangxi Province, China from March 2018 to August 2018. After excluding non-hypertensive, individuals with ABI date missing and AST/ALT date missing, 10,900 subjects included in the analysis finally.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Anhui Medical University Biomedical Institute. Informed written consent was obtained from all patients before their enrollment in this study.

Measurement of Ankle brachial index (ABI) and assessment of PAD

The resting ABI is the initial diagnostic test for PAD^[13]. Systolic blood pressure is measured by Doppler ultrasonography in each arm and in the dorsalis pedis (DP) and posterior tibial (PT) arteries in each ankle using the Omron Colin BP-203RPE III device (Omron Health Care, Kyoto, Japan). The right and left ankle-brachial index values are determined by dividing the higher ankle pressure in each leg by the higher arm pressure^[14]. In present study, patients with resting ABI ≤ 0.9 were defined as PAD.

Laboratory assays

All the study subjects were told one day in advance that fasting venous blood samples would be collected the next morning. After an overnight fast, venous blood samples were obtained from all study participants. Next, the blood samples of all the subjects were collected, frozen and transported to the Biaojia Biotechnology Laboratory for analysis in Shenzhen, China. Serum concentrations of fasting blood glucose (FBG), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TG), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), aspartate aminotransferases (AST) and alanine transaminase (ALT), total bilirubin (TBIL), direct bilirubin (DBIL), glutamyltransferase (GGT), albumin (ALB), uric acid (UA), homocysteine (Hcy), creatinine were measured using automatic clinical analyzers (Beckman Coulter, USA) and the laboratory staff were blind to the research protocol. estimated glomerular filtration rate (eGFR) was estimated using the newly developed CKD-EPI equation^[15].

Covariates

At this baseline assessment, age, smoking, alcohol consumption, medical history (any hypertension, stroke, diabetes, hyperlipidemia and chronic kidney disease) and medication intake (antihypertensive drugs, glucose-lowering drugs, lipid-lowering drugs, antiplatelet drugs) were queried by trained health professionals. Systolic diastolic pressures (SBP, mmHg) and diastolic blood pressure (DBP, mmHg), measured by electronic sphygmomanometers after the subjects had rested for 10 minutes. The anthropometric examinations included weight, height, waist circumference and hip circumference. Body mass index (BMI) was calculated as the body weight in kilograms divided by the square of the height in meters (kg/m²).

Statistical analysis

In order to investigate whether the AST / ALT ratio of the selected participants is related to PAD, the statistical analysis includes four main steps. First, baseline characteristics of participants according to tertiles of AST / ALT ratio were presented. Continuous variables were expressed as the means \pm standard deviations and categorical variables were expressed as a frequency (%). Second, crude and adjusted regression models were used to assess the association between AST/ALT ratio (as continuous variable and categorical variable, respectively) and PAD. Third, generalized additive model (GAM) and smooth curve fitting (penalized spline method) were conducted. Finally, we performed various subgroup analyses.

All data analysis used the statistical package R (<https://www.R-project.org>, The R Foundation) and Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA). Two-tailed $P < 0.05$ was defined as statistically significant.

Results

Baseline Characteristics of Study Participants

Table 1 listed the baseline characteristics of participants. In general, the average age of the participants was 63.86 ± 9.25 years old, and approximately 47.06% of them were male. In our study, a total of 350

patients had peripheral arterial disease and the prevalence of PAD was 3.21%. The prevalence of PAD increased with the increase of the AST/ALT ratio. Specifically, the prevalence rates in the first tertile, second tertile, and highest tertile were 2.36%, 2.51% and 4.76%, respectively. Except for drinking, taking antiplatelet drugs, the history of stroke and CKD, other variables were significantly different among the different AST/ALT groups. Compared with the lowest group (T1), patients in the highest group (T3) tended to have a higher age, systolic blood pressure and homocysteine, and had a lower BMI, diastolic blood pressure, fasting blood glucose, total cholesterol, triglyceride and eGFR. More subjects were current smoking and diabetes in the lowest group (T1). Moreover, the proportion of people who took antihypertensive drugs, lipid-lowering drugs, glucose-lowering drugs and antiplatelets drugs was lower in the highest group (T3). The baseline characteristics were displayed by the status of PAD (no, yes) in Table S1. Compared with those who without PAD, patients with PAD had a higher levels of age, systolic blood pressure, low-density lipoprotein, homocysteine, uric acid, AST/ALT ratio and smoking rates, while lower levels of BMI, glomerular filtration rate, diastolic blood pressure, fasting blood glucose and triglyceride.

Association between AST/ALT ratio and PAD

In our study, we made three models to evaluate the relationship between AST / ALT ratio and peripheral arterial disease (PAD). The odds ratios (ORs) and 95% confidence intervals (CIs) for these three equations are presented in Table 2. When AST / ALT ratio was analyzed as a continuous variable in the crude model (model 1), for every one increase in AST / ALT ratio, the risk of PAD increased by 63% (OR: 1.63, 95% CI: 1.42 to 1.88). After adjusting for gender, age, smoking, drinking, and BMI (Model 2), the risk of PAD increased by 41% as the AST / ALT ratio increased (OR: 1.41, 95% CI: 1.20 to 1.64). In the fully adjusted model (model 3), for every 1 increase in the AST / ALT ratio, the risk of PAD increased by 34% (OR: 1.34, 95% CI: 1.13, 1.59). We also converted AST / ALT ratio from a continuous variable to a categorical variable (tertiles). The relative risks (95% CI) for participants in the second (1.24 to 1.65) and third tertile (≥ 1.65) were 0.96 (95% CI: 0.70 to 1.32) and 1.49 (95% CI: 1.09 to 2.04) respectively, when compared with those in tertile 1. In view of the statistical significance of the P value of the tertile 2, we combined T1-T2 into a group and used as a reference. A significantly higher risk of PAD (OR: 1.53, 95% CI: 1.20, 1.95) was found in participants in tertile 3 (≥ 1.65) compared with participants in tertiles 1-2 (≈ 1.65). Figure 1 showed the relationship between AST/ALT and PAD with a curve clearly.

The results of subgroup analyses

We further explored the role of other covariables on the association between AST/ALT and PAD. As shown in Figure 2, the subgroup analysis revealed a highly consistent pattern in the following subgroups: sex (male, female), age (<60, ≥ 65 years), BMI (≤ 24 kg/m², ≥ 24 kg/m²), smoking (no, yes), drinking (no, yes), Hcy (<15, ≥ 15 μ mol/L) and eGFR (<90, ≥ 90 , ml/min/1.73m²) (all P for interaction > 0.05).

Discussion

In this cross-sectional study, we found that the prevalence of PAD was 3.21% and the higher AST / ALT ratio (≥ 1.65 , tertile 3) was associated with higher risk of PAD in comparison to lower AST/ALT ratio (< 1.65 , tertiles 1-2). These results remain stable after adjusting for other risk factors.

Previous studies have shown that AST/ALT was associated with cardiovascular disease. For instance, Mohammed Ewid et al. conducted a study which evaluated the functional severity of chronic heart failure with reduced left ventricular ejection (HFrEF), found that 0.9 was the best predictive cut-off value of the AST / ALT ratio^[16]. At the same time, a study demonstrated that the best cut-off value in predicting the cardiometabolic risk in the AST / ALT ratio was 1^[17]. As can be seen from the above studies, the AST / ALT ratio does help to detect cardiovascular diseases. We all know that atherosclerosis is the root cause of most cardiovascular diseases^[18], and peripheral arterial disease is one of the main manifestations of atherosclerosis^[19]. Since PAD was also related to cardiovascular morbidity and mortality and high AST/ALT ratio was associated with PAD in our study, which would help us to screen more patients with latent diseases. The potential clinical value of AST / ALT ratio might be used to assess arteriosclerosis in the future. Moreover, the AST / ALT ratio is available, simpler and inexpensive compared to other methods.

To explain the results of this study, we conducted a Pub-Med search using the keywords "peripheral arterial disease or lower extremity arterial disease or arteriosclerosis" and "AST / ALT". Fewer scientific papers were retrieved from the database as of the end of October 2020. A cross-sectional study based on the Japanese health check-up population analyzed the relationship between AST/ALT and baPWV which was employed to evaluate arterial stiffness^[20]. These people were between 24-84 years old and had no fatty liver. It reached a conclusion that the relationship between AST/ALT and baPWV was non-linear and AST/ALT was positively correlated with baPWV when AST/ALT (every 0.1 change) was greater than 13.1. Another cross-sectional study conducted by Peter Rief et al. included 1782 patients who had been diagnosed with peripheral occlusive arterial disease, and evaluated the correlation between the AST/ALT ratio and severe limb ischemia. As an optimal cut-off value was identified. After adjusting for other established vascular risk factors, a AST/ALT ratio > 1.67 had a high risk for critical limb ischemia (OR:2.0, 95% CI: 1.7-2.3)^[21]. Our study focused on the participants with hypertension and the sample size was larger.

In terms of the results of present study, the possible explanation was as follows. In the first place, high levels of AST/ALT were associated with an increase in non-alcoholic fatty liver disease (NAFLD) which could cause dyslipidemia. Secondly, we consulted the literature found that the AST / ALT ratio was an indicator of insulin resistance^[22, 23], and studies have shown that insulin resistance was closely related to PAD^[24, 25]. Therefore, we suspect that AST / ALT may cause PAD by forming insulin resistance and dyslipidemia. The exact mechanism responsible for the relationship between AST/ALT ratio elevation and PAD was still obscure and required further investigation.

There were some limitations that need to be noted. First, this study was an analytical cross-sectional study, it was difficult for us to make out the cause and effect. Second, the selection of AST and ALT was the result of baseline measurement, and no multiple measurements. Third, due to data limitations, we had not

adjusted the history of arteriosclerosis and liver disease, which may remain confounding factors. Last, as the study population contained only Chinese hypertensive participants, it might be not generalizable to other ethnic groups.

Conclusions

A higher AST/ALT ratio (≥ 1.65) was associated with PAD risk in Chinese adults with hypertension. Our results suggested that AST / ALT maybe help us highlight patients who was at high risk of vascular endpoints.

Abbreviations

BMI.body mass index; SUA serum uric acid; SBP systolic blood pressure; DBP diastolic blood pressure; FBG fasting blood glucose; TC total cholesterol; TG triglyceride; LDL-C low density lipoprotein; HDL-C high density lipoprotein cholesterol; TBIL total bilirubin; DBIL direc tbilirubin; GGT glutamyltransferase; ALB albumin; HCY homocysteine; eGFR estimated glomerular filtration rate; PAD peripheral artery disease; CKD chronic kidney disease ; ABI Ankle brachial index

Declarations

Authors' Note

HL wrote the manuscript and participated in the literature search, data analysis, and data interpretation. LHH extracted and collected data. XYZ,CCD, LHH, MHL, WZ, TW, LJZ conceived of the study and participated in its design and coordination. HHB and XSC participated in the study design and provided critical revision. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Anhui Medical University Biomedical Institute.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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Tables

Table 1 Baseline characteristics of participants stratified by tertiles of AST/ALT ratio.				
AST/ALT ratio	Total	T1 ≤1.23	T2 (1.24-1.65)	T3 (≥1.65)
N	10900	3595	3669	3636
Male	5129 (47.06%)	1955 (54.38%)	1591 (43.36%)	1583 (43.54%)
AGE (years)	63.86 ± 9.25	60.11 ± 8.67	63.87 ± 8.47	67.55 ± 9.08
Current smoking	2868 (26.31%)	1026 (28.55%)	868 (23.66%)	974 (26.79%)
Current drinking	2469 (22.66%)	820 (22.82%)	794 (21.64%)	855 (23.51%)
BMI (kg/m ²)	23.59 ± 3.81	25.34 ± 4.14	23.48 ± 3.24	21.96 ± 3.21
mean SBP (mmHg)	148.48 ± 17.79	147.37 ± 16.98	148.72 ± 17.76	149.33 ± 18.52
mean DBP (mmHg)	89.02 ± 10.74	91.00 ± 10.33	88.96 ± 10.54	87.12 ± 11.00
FBG,mmol/L	6.17 ± 1.60	6.62 ± 2.14	6.07 ± 1.30	5.82 ± 1.07
TC,mmol/L	5.14 ± 1.11	5.22 ± 1.17	5.18 ± 1.08	5.04 ± 1.08
TG,mmol/L	1.78 ± 1.25	2.17 ± 1.53	1.73 ± 1.07	1.45 ± 0.97
LDL-C,mmol/L	2.99 ± 0.81	3.13 ± 0.84	3.00 ± 0.78	2.84 ± 0.78
HDL-C,mmol/L	1.59 ± 0.44	1.48 ± 0.38	1.60 ± 0.43	1.69 ± 0.47
TBIL,μmol/L	14.66 ± 6.86	14.97 ± 6.57	14.47 ± 6.15	14.54 ± 7.75
DBIL,μmol/L	5.61 ± 2.66	5.60 ± 2.22	5.52 ± 2.07	5.71 ± 3.46
GGT,U/L	33.03 ± 42.61	44.48 ± 50.24	28.77 ± 34.43	26.02 ± 39.44
ALB,g/L	46.80 ± 4.16	47.38 ± 4.06	46.86 ± 3.99	46.18 ± 4.34
UA,mg/dL	6.98 ± 2.03	7.30 ± 2.08	6.86 ± 1.96	6.77 ± 2.01
Hcy,μmol/L	18.00 ± 11.04	17.33 ± 11.08	17.71 ± 10.73	18.95 ± 11.23
eGFR,ml/min/1.73m ²	88.67 ± 20.38	92.16 ± 20.26	89.13 ± 19.60	84.75 ± 20.58
PAD	350 (3.21%)	85 (2.36%)	92 (2.51%)	173 (4.76%)
Medical history(n,%)				
Diabetes	1978 (18.15%)	1002 (27.87%)	584 (15.92%)	392 (10.78%)
Stroke	708 (6.50%)	247 (6.87%)	239 (6.51%)	222 (6.11%)
CKD	538 (4.94%)	183 (5.09%)	177 (4.82%)	178 (4.90%)
Dyslipidemia	1536 (14.09%)	731 (20.33%)	481 (13.11%)	324 (8.91%)
Medication use,n(%)				

Antihypertensive drugs	7155 (65.65%)	2456 (68.34%)	2394 (65.25%)	2305 (63.39%)
Glucose-lowering drugs	572 (5.25%)	331 (9.21%)	158 (4.31%)	83 (2.28%)
Lipid-lowering drugs	381 (3.50%)	167 (4.65%)	127 (3.46%)	87 (2.39%)
Antiplatelet drugs	429 (3.94%)	162 (4.51%)	143 (3.90%)	124 (3.41%)

Values of continuous variables are presented as mean \pm SD, categorical variables are presented as n(%). Abbreviations: **BMI** body mass index, **SUA** serum uric acid, **SBP** systolic blood pressure, **DBP** diastolic blood pressure, **FBG** fasting blood glucose, **TC** total cholesterol, **TG** triglyceride, **LDL-C** low density lipoprotein, **HDL-C** high density lipoprotein cholesterol, **TBIL** total bilirubin, **DBIL** direct bilirubin, **GGT** glutamyltransferase, **ALB** albumin, **UA** uric acid, **Hcy** homocysteine; **eGFR**: estimated glomerular filtration rate, **PAD** peripheral artery disease, **CKD** chronic kidney disease

Table 2. Association between AST/ALT ratio and peripheral arterial disease (PAD)

	Model 1		Model 2		
AST/ALT ratio	OR(95% CI)	<i>P</i>	OR(95% CI)	<i>P</i>	<i>P</i>
Continuous	1.63 (1.42, 1.88)	<0.0001	1.41 (1.20, 1.65)	<0.0001	0.001
Tertiles					
T1(\leq 1.23)	Ref.		Ref.		
T2(1.24-1.65)	1.06 (0.79, 1.43)	0.693	0.92 (0.68, 1.26)	0.607	0.801
T3(\geq 1.65)	1.17 (0.84, 1.64)	0.350	1.52 (1.13, 2.04)	0.005	0.012
P for trend		<0.0001		0.001	0.005
Categories					
T1-T2(\leq 1.65)	Ref.		Ref.		
T3(\geq 1.65)	2.00 (1.62, 2.48)	<0.0001	1.60 (1.27, 2.01)	<0.0001	<0.0006
Model 1: adjusted for none.					
Model 2: adjusted for age, gender, smoking, drinking, BMI.					
Model 3: adjusted for age, gender, smoking, drinking, BMI; SBP; DBP; TC; TG;					
LDL-C; HDL-C; FBG; GGT; TBIL; DBIL; ALB; UA; Hcy; eGFR; diabetes; antihypertensive drugs; Glucose-lowering drugs; Lipid-lowering drugs.					

Figures

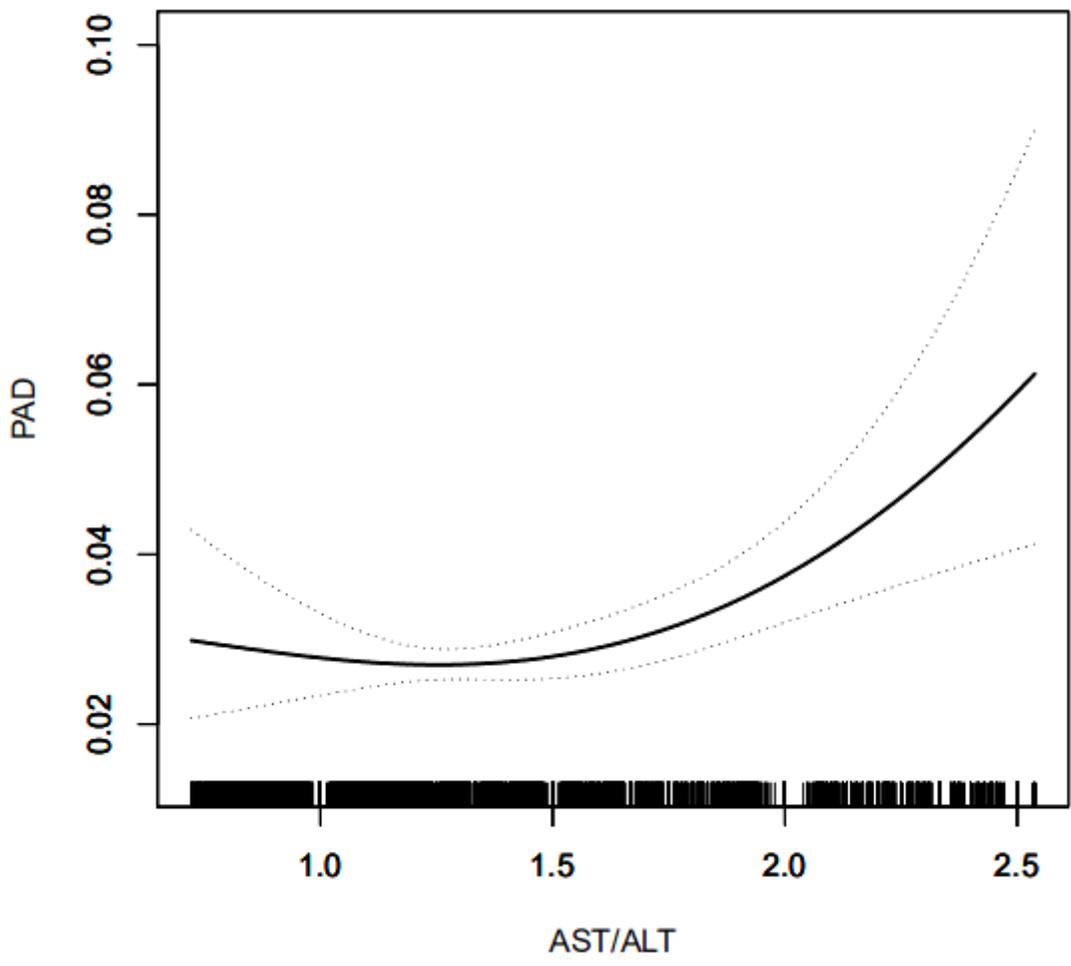


Figure 1

Association between AST/ALT ratio and peripheral arterial disease (PAD) adjusted for age, sex, smoking, drinking, BMI, SBP, DBP, TC, TG, LDL-C, HDL-C, FBG, GGT, TBIL, DBIL, ALB, UA, Hcy, eGFR, diabetes, anti-hypertensive drugs, glucose-lowering drugs and Lipid-lowering drugs.

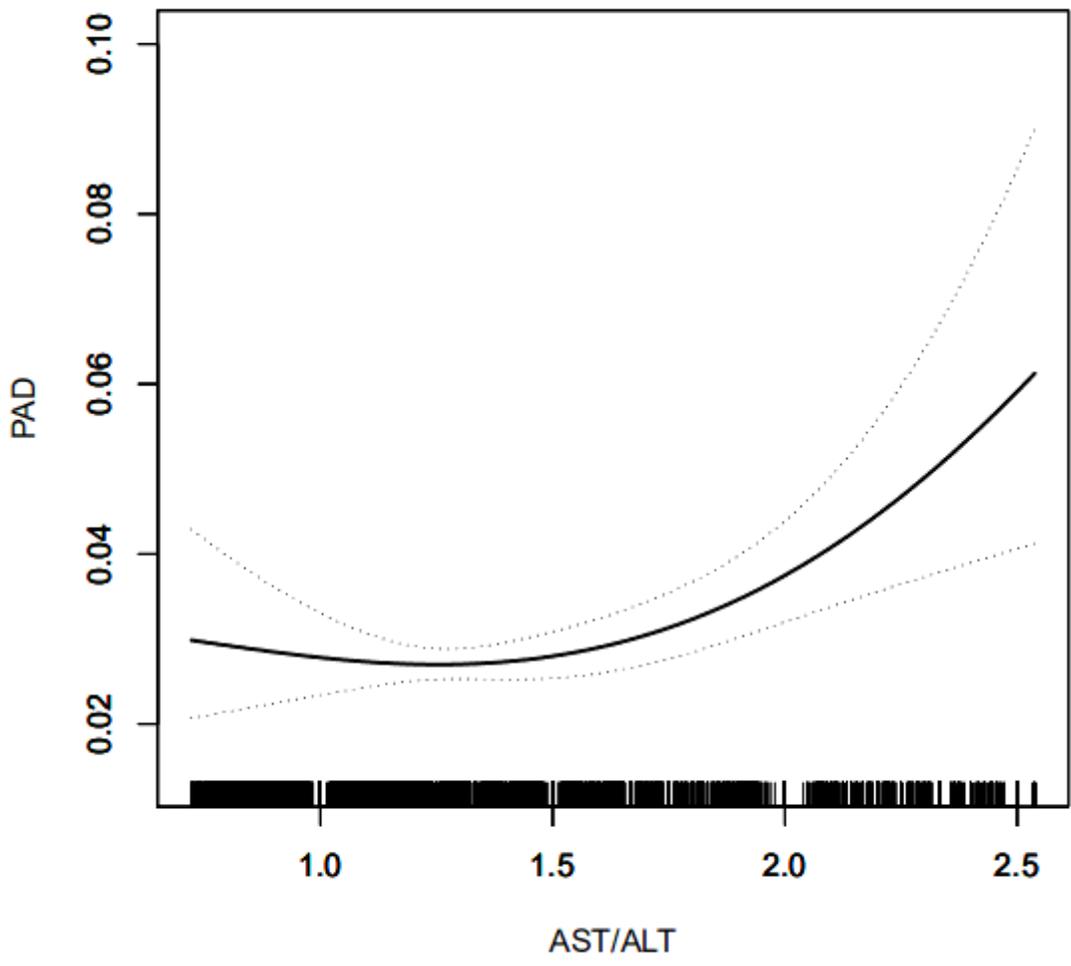


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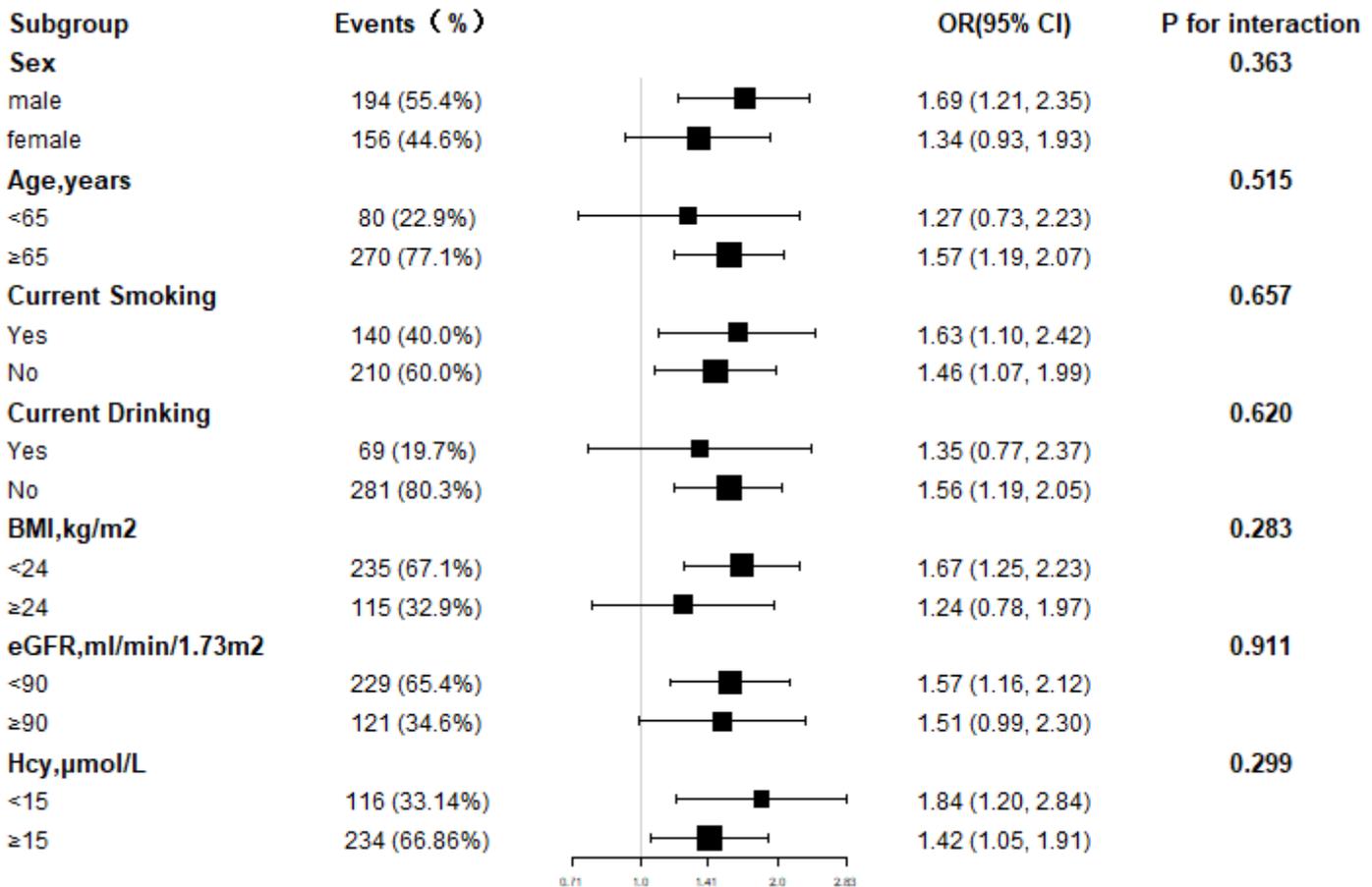


Figure 2

The association between AST/ALT (T3 vs. T1-T2) and PAD in various subgroups. The models adjusted for age, sex, smoking, drinking, BMI, SBP, DBP, TC, TG, LDL-C, HDL-C, FBG, GGT, TBIL, DBIL, ALB, UA, Hcy, eGFR, diabetes, anti-hypertensive drugs, glucose-lowering drugs and Lipid-lowering drugs, except for the stratify.

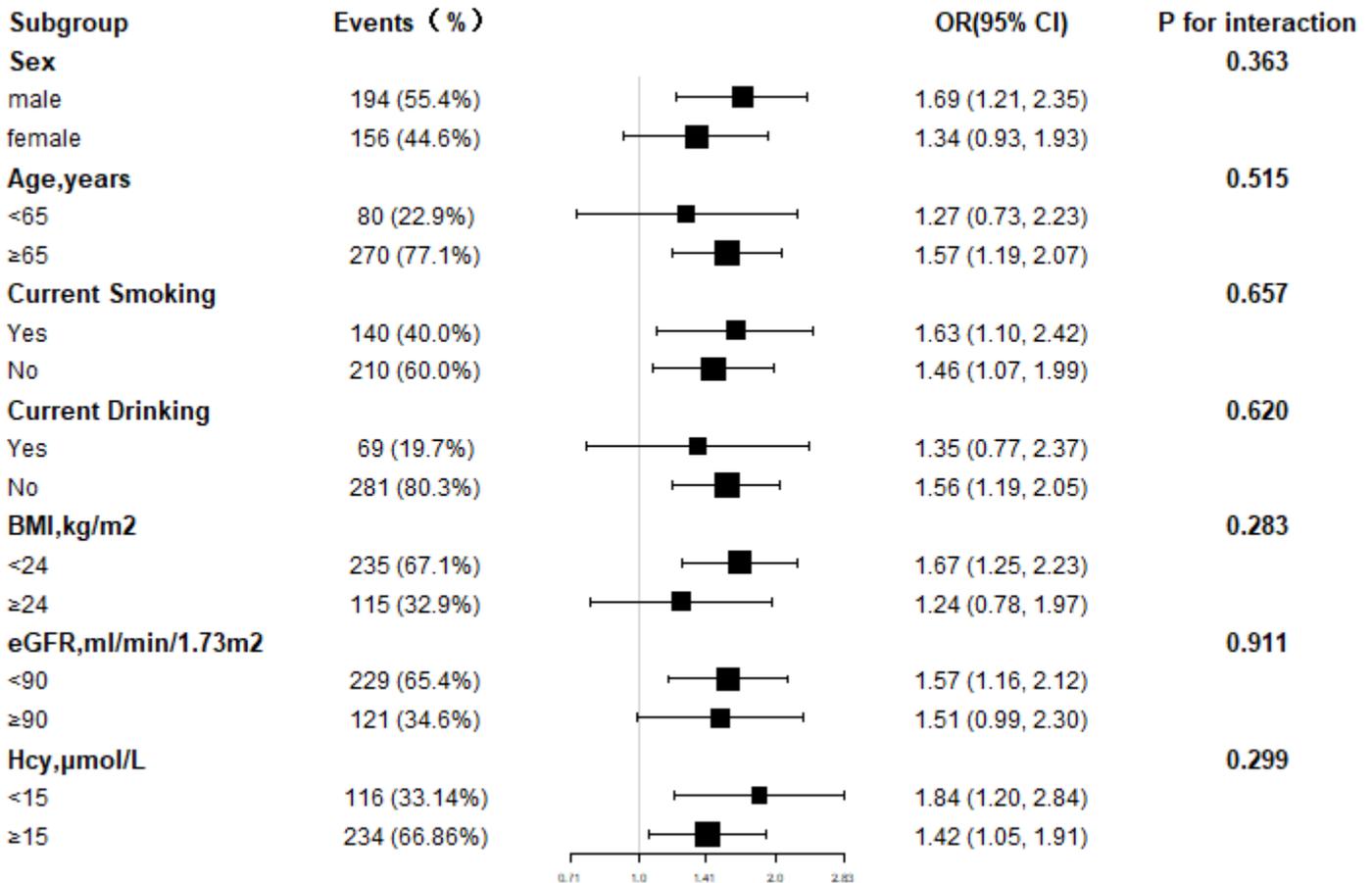


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Supplementary Files

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- [SupplementaryTable1.doc](#)
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