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Aspartate Aminotransferase to Alanine Aminotransferase Ratio and Arterial Stiffness in Persian Cohort Study

*Sahar Sobhani[1], Sara Raji[1], Fatemeh Roudi[2], Mohamad Amin Bakhshali [3], Dina Javidjam[4], Effat Saghi [2], Zahra Ataee[5], Saeid Eslami[6]

1.Persian Cohort Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
2.Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3.Postdoc Researcher, Department of Medical Informatics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
4.Department of Clinical Biochemistry, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
5.Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
6.Department of Medical Informatics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

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ABSTRACT

Introduction
Liver function tests such as AST/ALT ratio may play an important role in the progression of nonalcoholic fatty liver disease (NAFLD) and its related cardiovascular dysfunctions. The study aims to assess whether AST/ALT was associated with arterial stiffness in a large population-based cohort of apparently healthy Persian women and men.

Material and Methods:
To evaluate arterial stiffness non-invasively, Pulse Wave Velocity (PWV) and Augmentation Index (AI) were measured in 5031 healthy adults. Laboratory parameters, including AST and ALT, were measured after all subject's blood samples were collected. The one-way-ANOVA, the Kruskal-Wallis, and chi-square tests were used to compare the AST/ALT ratio among groups with baseline characteristics of participants following the calculation of AST: ALT through the division of AST levels by ALT levels. The univariate linear regression model was used to assess the association between mean pulse wave velocity (PWV) and AST/ALT ratio quartiles.

Results:
The results showed no statically significant difference in Age, HR, and MET among the different AST/ALT groups. Univariate analysis displayed that age, SBP, DBP, FBS, TG, MET, Fatty liver status, and hypertension status were positively correlated with Mean PWV. Evaluation of univariate linear regression models presented that AST/ALT has a significant correlation with Mean PWV (β = -0.139, 95% confidence interval (CI): -0.032 to -0.021, P-value < 0.001). We found that there was no linear relationship.

Conclusions:
According to the present study results, there was a significant negative correlation between AST/ALT with PWV. Moreover, a non-linear relationship between AST/ALT and PWV was observed as well.

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Persian Cohort Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: sobhanis3@mums.ac.ir

Introduction

Arterial stiffness is a growing epidemic associated with a higher risk of cardiovascular disease. (CVD), which is evaluated by broadly mainstream Pulse Wave Velocity (PWV) (1). This non-invasive and reproducible tool has been accounted to be an independent factor of cardiovascular diseases (CVDs) and mortality (2). CVDs, as the foremost non-communicable diseases, are responsible for 31% of all global mortality (3). The prevalence of total cardiovascular disease in Iran was reported about 1027 in 100, 000 person-years (4). As shown by prior studies, liver function tests, such as serum concentration of aspartate transaminase (AST), alanine transaminase (ALT), are pivotal measurements in liver disease and CVD risk stratification (5,6). Moreover, previous researchers have demonstrated that CVD extremely brought about fatality in non-alcoholic fatty liver disease (NAFLD) (7,8).

Inevitably, applying the enzymes in a basic ratio (AST/ALT) has been introduced to possess diagnostic accuracy in several chronic liver diseases, including hepatitis C (9), alcoholic, and non-alcoholic liver disease (10,11). In addition, it has been shown that these substitutes of liver injury enhance the prediction of future clinical outcomes, with cardiovascular outcomes in patients suffering from liver diseases (12,13). Meanwhile, it is still unidentified whether the AST/ALT ratio can project cardiovascular events in a general population or not. The recent British study schowed that AST/ALT ratios were independently associated with an increased risk of developing CVD among males but not among females (6). Hence, we hypothesize that AST/ALT ratios might associate with PWV. As such, and given the high mortality and morbidity of CVDs in the world (4,6,14), we used data from a large population-based cohort of apparently healthy Persian women and men to investigate whether the association between AST/ALT ratios and pulse wave velocity parameters is established or not.

Materials and Methods

Setting and Participants

This study was a retrospective cross-sectional study founded on the PERSIAN Cohort study data, comprised about 5031 healthy adult Iranian population in Mashhad, the large northeast city in Iran. The national protocol and previous studies have been reported concisely (5,15,16).

The participants were Mashhad University of Medical sciences' employees aged 30-70 years old who voluntarily took part in the study. National and Local Ethics Committee of MUMS (IR.MUMS.REC.1395.526) approved the project protocol, which was in agreement with the Helsinki declaration. The subjects have been informed regarding the study process, and they signed the written consent prior to their enrollment in the study. Also, they were assured to present their clinical information anonymously.

Cardiovascular evaluation

In order to evaluate arterial stiffness non-invasively, Pulse Wave Velocity (PWV) and Augmentation Index (AI) were measured using the SphygmoCor XCEL system (AtCor Medical Incorporation, Sydney, Australia) by a trained medical doctor.

The subjects were requested to be fast for at least six hours and not consume alcohol, tobacco, and caffeine for at least 12 hours before the test. The test was directed in two phases in the supine position following about 15 min rest:

(1) The central aortic pressure waveform at the brachial artery was recorded via cuff pulsations through three continuous inflation and deflation cycles.

(2) An ultrasound tonometer was placed on the patient's carotid pulse to capture pulse wave velocity between descending aorta to the femoral artery while a cuff was set around the thigh.

The percentage of central pulse pressure, called AIx, was measured simultaneously during the test. Blood pressure was also measured on both arms in the sitting position after 3 mins rest using the mercury sphygmomanometer (Sanaphon, Rudolf Riester GmbH, Brückstr, Germany). BP measurements were conducted using a proper-sized cuff through the standardized auscultatory method protocol.

The pulse rate, systolic blood pressure, and diastolic pressure were measured twice at 10-min intervals.

Laboratory Measurement

Twenty-five ml of blood was collected from every subject after fasting for 12-10 hours to measure laboratory parameters, including gamma-glutamyl transferase (GGT), fasting

blood sugar (FBS), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDLC), and Alkaline phosphatase (ALP) usingBT1500 auto analyzer (Biotechnical Instruments, Rome, Italy). Abnormal levels of FBS, TG, TC, LDL and HDLC were considered as amounts higher than 125 mg/dl, 240 mg/dl, 150 mg/dl, 130 mg/dl and 40 mg/dl, respectively.

AST: ALT ratio was assessed as AST level divided by ALT level, and the AST/ALT ratio elevation was considered as >90 percentile of the study population. Meanwhile, the participants recorded history of hypertension and fatty liver, diagnosed by a physician at PERSIAN Cohort Center or elsewhere. MET or one metabolic equivalent is described as the standard quantity of oxygen consumed by the body while seated at rest from inspired air, which is defined as 3.5 mL of oxygen per kg body per minute. (3.5 mL O2/kg × min)

Statistical Analysis

First, we categorized AST/ALT into quartiles (Q1-Q4). All continuous variables with normal distribution were presented as the mean ± standard deviation, and others with skewed distribution were expressed as quartiles (Q1-Q4), while categorical variables were presented as frequencies and percentages. Quartile deviation is a better measure of variation for highly skewed distribution or distribution with extreme values. This deviation is an effective way to compare different parts of the data such as maximum, minimum, median and outlier values. These statistical values are essential for comparing groups.

The one-way-ANOVA, the Kruskal-Wallis, and chi-square tests were used to compare the AST/ALT ratio among groups with baseline characteristics of participants. To expand the value of AST/ALT, we increased it ten times and characterized it per 0.1 change. Next, the univariate linear regression model was utilized to assess the association among mean pulse wave velocity (PWV) and other mentioned factors and AST/ALT ratio quartiles. Linear and non-linear relationships between AST/ALT and mean PWV was illustrated as a plot. Moreover, a two-piecewise linear regression model was performed to determine the threshold effect of the AST/ALT on the mean PWV if a non-linear relationship was noticed. A value of $P < 0.05$ was considered statistically significant. The Statistical Package for the Social Sciences (SPSS version 20, SPSS, Inc., Chicago, IL, USA) was used to achieve all statistical analyses.

Results

We excluded 135 participants of the 5166 from this study. Of the 135 excluded participants, 90 subjects did not have blood pressure recording properly, and 45 subjects did not have pulse wave velocity recording. The average age of the subjects was 45.41±8.96 years old, and almost 52.8 of them were female.

Baseline characteristics are reported in Table 1**.** There was no statically significant difference in age, HR and MET among the different AST/ALT groups. Compared with the Q1 group with more fatty liver patients, participants had a significantly higher mean BP, GGT, TG, and ALT than in the other three groups (Q2-Q4).

In the group with higher AST/ALT (Q1, Q2), more than half (73.7%) were males, and more participants had fatty liver than the other groups (Q3, Q4). Also, the Q1 group has more hypertension than the other groups, and the Q4 group has more MET than other groups.

The univariate analysis between mean PWV and other variables are demonstrated in Table 2**.**

The results of the univariate analysis showed that age, SBP, DBP, FBS, TG, MET, Fatty liver status, and hypertension status were positively correlated with Mean PWV. We also found that Mean BP, HR, GGT, TC, LDL, C_AI, and ALP were not related with Mean PWV, whereas HDLC and female gender were negatively associated with higher Mean PWV.

Table 1: Baseline Characteristics of participants

AST/ALT	Q1	Q2	Q3	Q4	*P*-value
N	**1306**	**1211**	**1289**	**1225**	
Age (years, mean ± sd)	44.85±8.24	46.22±8.99	45.86±9.40	44.75±9.10	0.291
SBP (mmHg, mean ± sd)	121.96±13.38	119.90±13.21	117.50±13.79	115.28±13.25	<0.001
DBP (mmHg, mean ± sd)	75.53±9.04	74.09±8.66	72.31±8.95	70.95±8.66	<0.001
Mean BP (mmHg, mean ± sd)	98.74±11.21	96.99±10.93	94.90±11.37	93.11±10.95	<0.001
HR (BPM, mean ± sd)	68.33±9.50	67.99±9.55	67.60±9.56	66.95±9.34	0.750
GGT (IU/L, mean ± sd)	36.92±26.09	28.04±21.63	22.67±12.86	19.38±14.69	<0.001
FBS (mg/dL, mean ± sd)	103.14±31.61	99.01±27.09	94.66±18.06	92.38±18.65	<0.001
TC (mg/dL, mean ± sd)	181.69±37.69	183.81±37.88	178.57±36.27	175.58±35.38	<0.001
TG (mg/dL, mean ± sd)	148.17±87.55	136.38±87.45	110.341±58.72	97.85±54.77	<0.001
LDL (mg/dL, mean ± sd)	101.19±32.26	102.21±30.96	99.19±30.28	96.20±29.76	<0.001
HDLC (mg/dL, mean ± sd)	51.58±11.89	54.75±12.90	57.44±13.03	59.94±13.37	<0.001
Mean PWV (m/s, mean ± sd)	7.46±1.61	7.36±1.61	7.04±1.63	6.82±1.51	<0.001
C_AI (%)	13.35±3.48	13.55±3.36	12.94±3.21	13.28±3.24	<0.001
AST (IU/L, mean ± sd)	23.74±8.30	22.00±7.94	20.615±6.58	20.89±8.61	<0.001
ALT (IU/L, mean ± sd)	38.22±16.10	26.46±9.77	20.50±6.69	15.71±6.40	<0.001
ALP (IU/L, mean ± sd)	183.27±52.32	176.60±69.05	169.86±49.41	165.06±54.07	<0.001
MET (ml O2/kg/min, ± sd)	34.08±12.98	34.01±13.36	34.52±13.79	35.92±12.65	0.839
Sex (n, %)					<0.001
Male	962 (73.7%)	642 (53.0%)	464 (36.0%)	307 (25.1%)	
Female	344 (26.3%)	569 (47.0%)	825 (64.0%)	918 (74.9%)	
Has Fatty Liver (n, %)					<0.001
Yes	308 (23.6%)	210 (17.3%)	167 (13.0%)	90 (7.3%)	
No	998 (76.4%)	1001 (82.7%)	1122 (87.0%)	1135 (92.7%)	
Has Hypertension (n, %)					0.017
Yes	180 (13.8%)	163 (13.5%)	153 (11.9%)	92 (7.5%)	
No	1126 (86.2%)	1048 (86.5)	1136 (88.1%)	1133 (92.5%)	

SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, Mean BP=Mean Blood Pressure, HR=Heart Rate, GGT= Gamma-glutamyl Transferase, FBS=Fasting Blood Sugar, TC=Total Cholesterol, TG= Triglycerides, LDL=low-density lipoprotein, HDLC= High-Density Lipoprotein Cholesterol, Mean PWV=Mean Pulse Wave Velocity, C_AI=Cavity Augmentation Index, AST= Aspartate Amino Transferase, ALT=Alanine Amino Transferase, ALP=Alkaline Phosphatase, MET=Metabolic measurement.

Table 2: The results of univariate analysis

Mean PWV	Statistics	*β*(95%CI), *P*-value
Sex		
Male	2375 (47.2%)	ref
Female	2656 (52.8%)	-0.272(-0.967, -0.795) <0.001
Age	45.41±8.96	0.250(0.040, 0.050) <0.001
SBP	118.69±13.64	0.216(0.021, 0.030) <0.001
DBP	73.24±9.00	0.200(0.029, 0.043) <0.001
Mean BP	88.35±9.97	0.018(0.00, 0.00) 0.115
HR	67.72±9.50	0.014(-0.002, 0.007) 0.261
GGT	26.86±20.71	0.002(-0.002, 0.002) 0.895
FBS	97.35±24.92	0.69(0.003, 0.006) <0.001
TC	179.91±36.94	0.252(0.00, 0.00)0.841
TG	123.39±76.44	0.45(0.001, 0.002) 0.001
LDL	99.70±30.92	-0.002(-0.001, 0.001) 0.877
HDLC	55.88±13.17	-0.045(-0.009, -0.003) <0.001
C_AI	13.40±3.08	0.014(0.00, 0.00) 0.204
ALP	173.80±56.93	-0.019(-0.001, 0.00) 0.132
MET	34.63±13.22	0.189(0.020, 0.026) <0.001
Has Fatty Liver		
Yes	775 (15.4%)	0.102 (0.333, 0.579) <0.001
No	4256 (84.6%)	0
Has Hypertension		
Yes	588 (11.7%)	0.271 (1.229, 1.497) <0.001
No	4443(88.3%)	0

The associations between AST/ALT and mean PWV were evaluated through univariate linear regression. Meanwhile, we show the results of the model in Table 3**.** In this table, AST/ALT presented significant correlation with Mean PWV (β=-0.139, 95% confidence interval (CI): -0.032 to -0.021, *P*-value<0.001).

Also, we can see the significant negative correlation between AST/ALT with Mean PWV in groups of AST/ALT.

Table 3: Relationship between AST/ALT and Mean PWV

Variable	β(95%CI), *P*-value
AST/ALT (per 0.1 change)	-0.139 (-0.032, -0.021) <0.001
AST/ALT (quartile)	
Q1	Ref
Q2	-0.115 (-0.898, -0.309) <0.001
Q3	-0.142 (-0.975, -0.436) <0.001
Q4	-0.142 (-0.975, -0.436) <0.001

As AST/ALT is a continuous variable, we conducted the non-linear analysis between AST/ALT and Mean PWV. Figure 1 demonstrates linear and non-linear relationships between AST/ALT and Mean PWV with solid and dashed lines, respectively. We found that this relationship was non-linear. The inflection point of 9.36 was calculated among two-piecewise linear regression model. On the left side of the inflection point, the effect size, 95% CI and *P* value were -0.062, -0.076 to -0.018 and 0.002, respectively. However, we also observed a negative relationship (β=-0.061, 95% confidence interval (CI): -0.176 to -0.036, *P*-value=0.003) between AST/ALT and Mean PWV on the right side of the inflection point (Table 4).

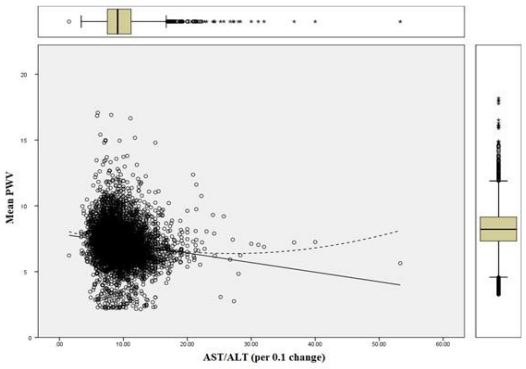

Fig 1: The linear (solid line) and non-linear (dashed line) relationship between AST/ALT and Mean PWV.

Table 4: The results of two-piecewise linear regression model

Inflection Point AST/ALT (Per 0.1 change)	Effect Size (β)	95%CI	*P*-value
< 9.36	-0.062	-0.076 to -0.018	0.002
> 9.36	-0.061	-0.176 to -0.036	0.003

Discussion

In the current study, the probable relations between AST/ALT and PWV values were evaluated using the univariate linear regression models. According to the current study results, while there was a significant relationship between AST/ALT and mean value of PWV; there was a significant negative correlation between AST/ALT with the mean value of PWV among the different study groups. Moreover, a non-linear relationship between AST/ALT and PWV was observed as well. To the best of our knowledge, this was the only study examining the relationship between AST to ALT ratio and arterial stiffness using PWV until February 2022 through PubMed search (17). Therefore, the present study is one of the few studies to identify and assess the association

between the AST to ALT ratio and arterial stiffness.

Cardiovascular diseases (CVDs) are the paramount explanation of global mortality, affecting the lives of millions of people around the world (3). Arterial stiffness as alterations in the structural and functional arterial properties is an independent predictor of future cardiovascular events, specifically, among asymptomatic individuals and disease burden (2,18). Increased arterial stiffness can cause pulse pressure (PP) and PWV enhancement (19).

Increased PP by isolated systolic hypertension is associated with multiple adverse consequences, including CVDs among the general population (20, 21). Increased PWV resulting from arteries wall changes is used as a reliable factor to measure arterial stiffness (19-22).

In addition to the beneficial aspect of being a non-invasive technique, PWV is the gold standard for assessing arterial stiffness (23)

The AST/ALT ratio or the *De Ritis ratio* is typically used to evaluate liver function and severity of liver disease (24). However, prior studies have shown that the AST/ALT ratio was associated with cardiovascular diseases. A study in Saudi Arabia used the AST/ALT ratio to predict the functional severity of chronic heart disease (25). Notably, *Long et al.* showed the best cutoff value of the AST/ALT ratio to predict the cardio-metabolic risk (26).

Also, it is determined that elevated AST/ALT can be an independent risk factor for morbidity and mortality among patients with cardiovascular events (24, 27). In our study, the decreased AST/ALT ratio was related to the stiffness of the vessel, which is in contrast to previous studies, but in a study by *Wang et al.,* Which looked at the relationship between AST/ALT ratio and coronary artery disease in children with Kawasaki disease in 2020, concluded that the ratio was inversely related to coronary artery disease (28). We must note that the place of synthesis of these two factors is different. ALT is produced in the cytoplasm of liver cells and AST in the mitochondria of the heart, brain, liver, kidney, and muscle cells (28,29). A 2012 study made by *Sungha Park et al.* on the effect of inflammation in the pathogenesis of vascular stiffness concluded that inflammation directly affects vascular stiffness and that this stiffness can be reduced by reducing inflammation (30).

Nevertheless, a study by *Wang et al.* found that the AST/ALT ratio could be used to assess inflammation because white blood cell levels, ESR, CRP, BNP were higher in the lower ratio group. Finally, they concluded that a lower AST/ALT ratio would be associated with a more severe inflammatory response and a higher risk of coronary artery injury (28).

Despite the studies that have been done so far and in which the increase in the AST/ALT ratio has been associated with an increased risk of metabolic syndrome, a Korean study by *Dhananjay Yadav et al.* conducted in 2016, concluded that this ratio should be checked in the future for cardiac metabolic risks and should be considered important (31).

As long as the ratio of the serum activities of AST and ALT was known as an independent risk factor for cardiovascular diseases and considering the association between PWV and cardiovascular morbidities and mortality; it is likely to use AST/ALT ratio to assess arterial stiffness in the future. Due to the fact that a group of studies has mentioned the increase of AST/ALT ratio as a risk factor for metabolic syndrome and its components, and some studies have mentioned the decrease of AST/ALT ratio as a risk factor, additional studies in the future of the population of more patients are needed.

Also, due to the simplicity and inexpensiveness of the aforementioned test compared to other methods, AST/ALT ratio is widely used and requested by clinicians in practice. Therefore, the potential clinical value of our study is placed on it.

Additional huge population-based prospective studies are mandated to study the exact relationship between AST/ALT ratio and arterial stiffness. Eventually, our study was not without limitations. First, this article is an analytical cross-sectional study and could not provide strong evidence connecting exposure and outcome. Second, the target population includes only Iranian participants, so it may not generalize to other ethnic groups.

Conclusion

To the best of our knowledge, our study is the first study in Iran and other Middle East countries to investigate the AST/ALT ratio

with arterial stiffness. The association between AST/ALT and PWV is non-linear, also we found a negative correlation between AST/ALT and PWV. Also According to the results obtained in the study of the AST/ALT ratio of metabolic syndrome and its various complications, studies with a larger sample size are needed in the future

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