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Low Aspartate Aminotransferase (AST)/Alanine Aminotransferase (ALT) Ratio Associated with Increased Cardiovascular Disease and its Risk Factors in Healthy Japanese Population

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ABSTRACT

Aims: This study aimed to evaluate the association between aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio and cardiovascular disease, and risk factors in a healthy Japanese population.
Methods: A retrospective cohort study was conducted at St. Luke's International Hospital, Tokyo, Japan, between 2005 and 2018. We included all participants who visited the hospital for voluntary health checkups. Our primary outcome was the development of cardiovascular disease, and the secondary outcomes were cardiovascular risk factors. We grouped the participants into quartiles (Qs) according to their baseline AST/ALT ratios and examined the outcomes of patients in each group.
Results: 87,740 participants were included in this study. The mean age of the participants was 44.9 years [standard deviation (SD): 12.1], and 43,191 (49.2%) were men. The mean AST and ALT levels were 21.7 IU/L (SD 10.0) and 22.4 IU/L (SD 16.5), respectively, resulting in a mean AST/ALT ratio of 1.1 (0.4). During the median follow-up of 1,829 days (interquartile range 756–3,470), 1,493 (1.7%) participants developed cardiovascular disease, 831 (1%) experienced ischemic heart disease, and 723 (0.8%) experienced strokes. Those in the Q1 AST/ALT ratio group had significantly higher hazard ratios compared to those in the Q3 AST/ALT ratio group [adjusted hazard ratio (HR)=1.32, 95% confidence interval (CI): 1.12-1.56 for cardiovascular disease; HR=1.36, 95%CI: 1.09-1.68 for ischemic heart disease; HR=1.28, 95%CI: 1.00-1.65 for stroke]. However, those belonging to the Q4 or Q5 AST/ALT ratio groups was not statistically different for primary outcomes compared to the Q3 AST/ALT ratio group. In contrast, the adjusted HRs for all secondary outcomes decreased in a dose-dependent manner as the AST/ALT ratio increased.
Conclusions: A Q1 AST/ALT ratio was associated with an increased risk of cardiovascular disease compared to the Q3 AST/ALT ratio in the Japanese population, which is in contrast with the Western population. In our study, Q4 or Q5 AST/ALT ratios were not associated with cardiovascular disease compared to the Q3 AST/ALT ratio. As for cardiovascular risk factors, the risk decreased as the AST/ALT ratio increased.

Key words: AST/ALT ratio – Japan – hypertension – diabetes – dyslipidemia.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CI: confidence interval; HR: hazard ratio; Q: quartile; SD: standard deviation.

INTRODUCTION

Liver enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), are well-known markers that indicate liver injury, and can be used to diagnose and evaluate the severity or prognosis of liver diseases [1]. However, liver enzymes can also be associated with other health conditions. A previous study reported a non-monotonic dose-response association between AST and ALT levels and all-cause mortality in the general population [2]. Similarly, elevated ALT, but not AST, may be associated with increased cardiovascular diseases and multiple metabolic disorders according to the Framingham Offspring Heart Study [3]. Therefore, liver enzymes may be able to predict other health conditions, including cardiovascular diseases.

In addition to AST and ALT separately, the AST/ALT ratio can be a potentially useful marker for several health conditions. The AST/ALT ratio has been used for liver injury, especially alcohol-related [4], diagnosis of cirrhosis among patients with primary biliary cirrhosis [5], and hepatocellular carcinoma in patients with chronic hepatitis [6]. Apart from liver disease, our previous study demonstrated a positive association between the AST/ALT ratio and any type of cancer in regular drinkers, and a negative association among abstainers [7]. A different study from the UK suggested that an elevated AST/ALT ratio was associated with an increased risk of cardiovascular disease in men, but not in women [8]. Another study from China reported that a high AST/ALT ratio was positively correlated with increased all-cause and cardiovascular mortality in the hypertensive population. Based on these previous studies, AST/ALT ratio could be an indicator of cardiovascular disease.

A previous review mentioned that ALT, but not AST, was associated with cardiovascular disease [9], assuming that it was mainly ALT affecting the AST/ALT ratio. However, evidence of this association is mixed. Studies from both the United States [3] and the Netherlands [10] reported that high ALT levels were associated with cardiovascular disease. Another study from Korea [11] reported a positive association between ALT and cardiovascular mortality, but other studies from the US [12] and Australia [13] did not find any evidence of the same association. A recent meta-analysis and systematic review revealed that elevated ALT levels were associated with increased coronary heart disease and decreased stroke [9, 14]. It also suggested potential racial differences: increased ALT was associated with increased cardiovascular disease in the Asian population but was associated with a decrease in the Western population. All taken together, further evidence is required.

The aims of this study were to evaluate the potential association between the AST/ALT ratio and cardiovascular disease and its risk factors in an otherwise healthy Japanese population.

METHODS

A retrospective cohort study was conducted at St. Luke's International Hospital, Tokyo, Japan, between 2005 and 2018. We included all participants who visited the Center for Preventive Medicine at the hospital for voluntary health checkups, and the data was collected from St. Luke's Health Checkup Database. Participants with a prior history of cardiovascular disease, hepatobiliary diseases such as common bile duct stone/gall stone, liver cirrhosis, or tumors at baseline were excluded. Our primary outcome was the development of cardiovascular disease, and the secondary outcomes were cardiovascular risk factors. We grouped the participants into quintiles based on the baseline AST/ALT ratios and examined the outcomes of the groups. The St. Luke's Ethics Committee Institutional Review Board approved this study (approval number: 18-R203, comprehensive approvals for studies on environmental risk factors or clinical information).

Cardiovascular Disease and its Risk Factors

Our primary outcome was the first development of any cardiovascular disease during follow-up. Cardiovascular disease in this study was defined as ischemic heart disease (angina or myocardial infarction) or stroke (cerebral infarction, cerebral bleeding, subarachnoid hemorrhage, or transient ischemic attack). Our secondary outcomes were newly diagnosed hypertension, diabetes, and dyslipidemia during the follow-up period. The data on outcomes were obtained from the participants' self-reports or electronic medical records. All participants were asked about their medical history and outcomes each time they underwent health check-ups. Since most participants underwent the next health check-up one year after the previous one, they often reported new outcomes at the same time at subsequent check-ups. We also obtained data on patient outcomes from electronic medical records. In each case, a physician made the outcome diagnosis.

AST, ALT, and AST/ALT Ratio

The absolute values of serum AST (IU/L) and ALT (IU/L) levels were measured during the health checkups for all participants. Based on the AST and ALT measurements, the AST/ALT ratio was calculated. We then divided the participants into five groups based on their AST/ALT ratio and compared their outcomes. The third quintile (Q) group was assigned as the reference group.

Covariates

For covariates, data on the participants' demographics, social histories, and cardiovascular risk factors were self-reported using questionnaires or examinations during the health checkup. Social histories included smoking status (never, former, or current smoker), alcohol consumption status (abstainer, occasional drinker, or regular drinker), and exercise habits (almost none, 1–2 times a week, 3–5 times a week, and almost every day). We also obtained data on cardiovascular risk factors including history of hypertension, diabetes, and dyslipidemia. Participants' height and body weight were measured to calculate body mass index (BMI) and categorized based on the World Health Organization's Asian criteria: underweight (< 18.5 kg/m^2), normal weight (> 18.5 to ≤ 24.9 kg/m^2), and overweight/obese (> 24.9 kg/m^2).

Statistical Analysis

We first summarized the summary statistics of participant characteristics by group based on the AST/ALT ratio. We then used the Cox proportional hazard model to compare the primary outcomes of the different AST/ALT ratio categories, adjusting for potential confounders. In terms of secondary outcomes, similar analyses were applied, but those who already had each secondary outcome at baseline were excluded from the analyses. The effect of gender or alcohol consumption on the association between the AST/ALT ratio and cardiovascular disease was examined, because it is reasonable to believe either of these factors would affect the association. If there was significant effect modification, stratified analyses were planned. We also conducted restricted cubic spline analyses with knots at the threshold values of quintile AST/ALT ratio groups [15]. In addition, we conducted sensitivity analyses with the data excluding those who had abnormally high liver enzymes (ALT > 33 IU/L for men or ALT > 25 IU/L for women based on the American College of Gastroenterology clinical guideline [16]; AST 50 IU/L or higher, or ALT 50 IU/L or higher). Another sensitivity analysis was also conducted using the log AST/log ALT ratio, because both AST and ALT were not normally distributed and right skewed.

All analyses were performed using Stata MP 16.1 in 2021 (STATA Corp., College Station, TX, USA).

RESULTS

87,740 participants were included in this study. The mean participant age was 44.9 years [standard deviation (SD): 12.1], and 43,191 (49.2%) were men. The mean AST and ALT levels were 21.7 IU/L (SD 10.0) and 22.4 IU/L (SD 16.5), respectively, resulting in an AST/ALT ratio of 1.1 (SD: 0.4). The participants were divided into different quintiles based on the baseline AST/ALT ratios (Q1: < 0.82, Q2: > 0.82 to < 1.00, Q3: > 1.00 to < 1.20, Q4: > 1.20 to < 1.40, and Q5: > 1.40).

Table I shows the comparison of baseline participant characteristics and subsequent outcomes by AST/ALT ratio groups. Participants who had a higher AST/ALT ratio were

Table I. Baseline participant characteristics and subsequent outcomes by aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio category

	AST/ALT ratio										
	First quintile <0.82 (n= 17,548)		Second quintile >0.82, <1.00 (n= 18,330)		Third quintile >1.00, <1.20 (n= 17,792)		Fourth quintile >1.20, <1.40 (n= 16,663)		Fifth quintile >1.40 (n= 17,407)		p
Age, years, mean (SD)	43.9	(10.4)	46.3	(11.8)	46.0	(12.3)	44.9	(12.5)	43.3	(13.0)	<0.01
Men, n (%)	14,871	(84.7)	11,697	(63.8)	7,933	(44.6)	5,024	(30.2)	3,666	(21.1)	<0.01
Alcohol consumption, n (%)											
Abstainer	5,987	(34.1)	6,627	(36.2)	7,151	(40.2)	7,067	(42.4)	7,444	(42.8)	<0.01
Occasional	3,336	(19.0)	3,045	(16.6)	3,060	(17.2)	2,910	(17.5)	2,916	(16.8)	
Regular	8,225	(46.9)	8,658	(47.2)	7,581	(42.6)	6,686	(40.1)	7,047	(40.5)	
Smoking status, n (%)											
Never smoker	8,217	(46.8)	10,223	(55.8)	11,501	(64.6)	11,584	(69.5)	12,613	(72.5)	<0.01
Former smoker	4,800	(27.4)	4,643	(25.3)	3,762	(21.1)	3,048	(18.3)	2,791	(16.0)	
Current smoker	4,531	(25.8)	3,464	(18.9)	2,529	(14.2)	2,031	(12.2)	2,003	(11.5)	
Exercise habits, n (%)											
Almost none	7,402	(42.2)	6,756	(36.9)	6,331	(35.6)	6,250	(37.5)	7,030	(40.4)	<0.01
1-2 times a week	6,728	(38.3)	7,028	(38.3)	6,752	(38.0)	6,047	(36.3)	6,068	(34.9)	
3-5 times a week	2,097	(12.0)	2,802	(15.3)	2,928	(16.5)	2,745	(16.5)	2,692	(15.5)	
Almost everyday	1,321	(7.5)	1,744	(9.5)	1,781	(10.0)	1,621	(9.7)	1,617	(9.3)	
Physical examination											
Blood pressure, mmHg, mean (SD)											
Systolic blood pressure	123.6	(15.8)	119.5	(16.6)	116.3	(16.4)	113.9	(16.0)	112.2	(15.8)	<0.01
Diastolic blood pressure	76.5	(11.1)	73.6	(11.4)	71.4	(11.2)	69.7	(10.8)	68.7	(10.5)	<0.01
Body mass index category, n (%)											
Underweight	278	(1.6)	1,066	(5.8)	1,828	(10.3)	2,345	(14.1)	3,245	(18.6)	<0.01
Normal weight	9,273	(52.9)	13,131	(71.6)	13,680	(76.9)	13,043	(78.3)	13,385	(76.9)	
Obesity/ overweight	7,996	(45.6)	4,133	(22.6)	2,284	(12.8)	1,275	(7.7)	776	(4.5)	
Laboratory measures, mean (SD)											
AST*, IU/L	26.7	(12.1)	21.5	(7.0)	20.5	(8.8)	19.6	(5.5)	19.9	(12.6)	<0.01
ALT†, IU/L	42.6	(24.5)	23.4	(8.0)	18.4	(8.0)	15.1	(4.3)	12.2	(6.1)	<0.01
AST/ALT ratio	0.7	(0.1)	0.9	(0.1)	1.1	(0.1)	1.3	(0.1)	1.7	(0.3)	<0.01
γ-glutamyl trans peptidase, IU/L	61.1	(59.7)	37.7	(37.5)	28.1	(32.0)	22.0	(23.9)	19.3	(31.7)	<0.01
Fasting blood glucose, g/dl	104.4	(19.2)	100.9	(15.8)	97.9	(12.2)	95.8	(10.4)	94.1	(9.7)	<0.01
Hemoglobin A1c, %	5.3	(0.7)	5.2	(0.6)	5.1	(0.5)	5.1	(0.4)	5.0	(0.4)	<0.01
Total cholesterol, mg/dl	206.7	(34.8)	201.6	(33.7)	199.5	(34.4)	196.6	(33.7)	193.6	(33.1)	<0.01
Low density lipoprotein (LDL) cholesterol, mg/dl	127.1	(30.6)	118.6	(29.5)	113.8	(29.9)	109.5	(28.9)	105.7	(28.1)	<0.01
High density lipoprotein (HDL) cholesterol, mg/dl	52.7	(12.7)	59.9	(14.4)	64.7	(14.9)	67.7	(14.8)	69.5	(14.7)	<0.01
Triglyceride, mg/dl	142.3	(97.4)	106.1	(80.1)	87.2	(65.1)	75.5	(51.7)	68.9	(45.6)	<0.01
Cardiovascular risk factors at baseline, n (%)											
Hypertension	1,403	(8.0)	1,385	(7.6)	1,063	(6.0)	794	(4.8)	665	(3.8)	<0.01
Diabetes	475	(2.7)	443	(2.4)	291	(1.6)	179	(1.1)	125	(0.7)	<0.01
Dyslipidemia	939	(5.4)	874	(4.8)	714	(4.0)	503	(3.0)	400	(2.3)	<0.01

Table I (continued)

Outcomes, n (%)											
Cardiovascular disease	370	(2.1)	388	(2.1)	288	(1.6)	241	(1.5)	206	(1.2)	<0.01
Ischemic heart disease	236	(1.3)	224	(1.2)	163	(0.9)	111	(0.7)	97	(0.6)	<0.01
Stroke	149	(0.9)	184	(1.0)	134	(0.8)	137	(0.8)	119	(0.7)	0.01
Newly diagnosed hypertension§	1,533/ 16,145	(9.5)	1,332/ 16,945	(7.9)	1,046/ 16,729	(6.3)	836/ 15,869	(5.3)	697/ 16,742	(4.2)	<0.01
Newly diagnosed diabetes§	854/ 17,073	(5.0)	497/ 17,887	(2.8)	309/ 17,501	(1.8)	196/ 16,484	(1.2)	154/ 17,282	(0.9)	<0.01
Newly diagnosed dyslipidemia§	1,674/ 16,609	(10.1)	1,468/ 17,456	(8.4)	1,179/ 17,078	(6.9)	891/ 16,160	(5.5)	718/ 17,007	(4.2)	<0.01

*AST: aspartate aminotransferase; †ALT: alanine aminotransferase; § Newly diagnosed hypertension, diabetes and dyslipidemia, denominator in each cell were composed from those who did not have consistent risk factor at baseline.

more likely to be women, abstainers, never smokers, and underweight. In terms of physical examination and laboratory measurements, those with a higher AST/ALT ratio tended to have more favorable results in terms of blood pressure, diabetes-related measures, and lipid profiles. As for primary outcomes, those in the Q1 or Q2 groups had a higher incidence of cardiovascular disease compared to those in the Q3 group. In contrast, the incidence in the Q4 or Q5 groups was similar to that in the Q3 group. In terms of secondary outcomes, incidences of hypertension, diabetes, and dyslipidemia decreased as the groups shifted to the right in a dose-dependent manner.

During the median follow-up of 1,829 days (interquartile range 756–3,470), 1,493 (1.7%) participants developed cardiovascular disease, 831 (1.0%) experienced ischemic heart disease, and 723 (0.8%) experienced strokes. There were no significant effects of gender (p=0.74) or alcohol consumption status (p=0.17) on the association between AST/ALT ratio and cardiovascular disease, suggesting no sex-related or alcohol consumption-related difference exists in the relation between AST/ALT ratios and cardiovascular diseases.

Table II compares outcomes to AST/ALT ratio groups using the multivariable Cox proportional hazard model. Regarding the primary outcome (cardiovascular disease), those in the Q1 AST/ALT group had significantly higher adjusted hazard ratios (HR) compared to those in the Q3 AST/ALT ratio group [HR=1.32, 95% confidence interval (CI): 1.12-1.56 for cardiovascular disease; HR=1.36, 95%CI: 1.09-1.68 for ischemic heart disease; HR=1.28, 95%CI: 1.00-1.65 for stroke]. However, those belonging to the Q4 or Q5 AST/ALT ratio groups had similar hazard ratios for primary outcomes compared to the Q3 AST/ALT ratio group. In contrast, the adjusted HRs for all secondary outcomes decreased in a dose-dependent manner as the AST/ALT ratio increased.

Fig. 1 shows the estimated restricted cubic splines of the associations between AST/ALT ratios and primary outcomes. The splines gradually decreased as the AST/ALT ratio increased

Table II. Adjusted hazard ratios for the development of cardiovascular diseases and its risk factors by AST/ALT ratio category

	Number of any type of cardiovascular disease. Adjusted hazard ratio (95% confidence interval)				
AST/ALT ratio	First quintile	Second quintile	Third quintile	Fourth quintile	Fifth quintile
Primary outcomes					
Cardiovascular disease	1.32	1.16	Reference	1.01	0.96
	(1.12–1.56)	(1.00–1.36)		(0.85–1.20)	(0.81–1.16)
Ischemic heart disease	1.36	1.13	Reference	0.84	0.84
	(1.09–1.68)	(0.92–1.39)		(0.66–1.08)	(0.65–1.09)
Stroke	1.28	1.24	Reference	1.20	1.13
	(1.00–1.65)	(0.99–1.56)		(0.94–1.52)	(0.88–1.45)
Cardiovascular risk factors					
Hypertension	**1.36**	**1.12**	Reference	1.00	**0.90**
	(1.25–1.48)	**(1.03–1.22)**		(0.91–1.09)	**(0.82–0.99)**
Diabetes	**2.28**	**1.35**	Reference	**0.77**	**0.68**
	(1.99–2.63)	**(1.17–1.55)**		**(0.65–0.93)**	**(0.56–0.83)**
Dyslipidemia	**1.60**	**1.19**	Reference	**0.84**	**0.71**
	(1.48–1.74)	**(1.10–1.29)**		**(0.77–0.92)**	**(0.65–0.78)**

Models for primary outcomes were adjusted for age; sex; body mass index; smoking status; alcohol consumption; exercise habits; medical histories of hypertension, diabetes, dyslipidemia, and γ-glutamyl trans peptidase (γ-GTP). Models for cardiovascular risk factors were adjusted for age; sex; body mass index; smoking status; alcohol consumption; exercise habits; other medical histories than itself. The numbers in bold represent that the p value is <0.05; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

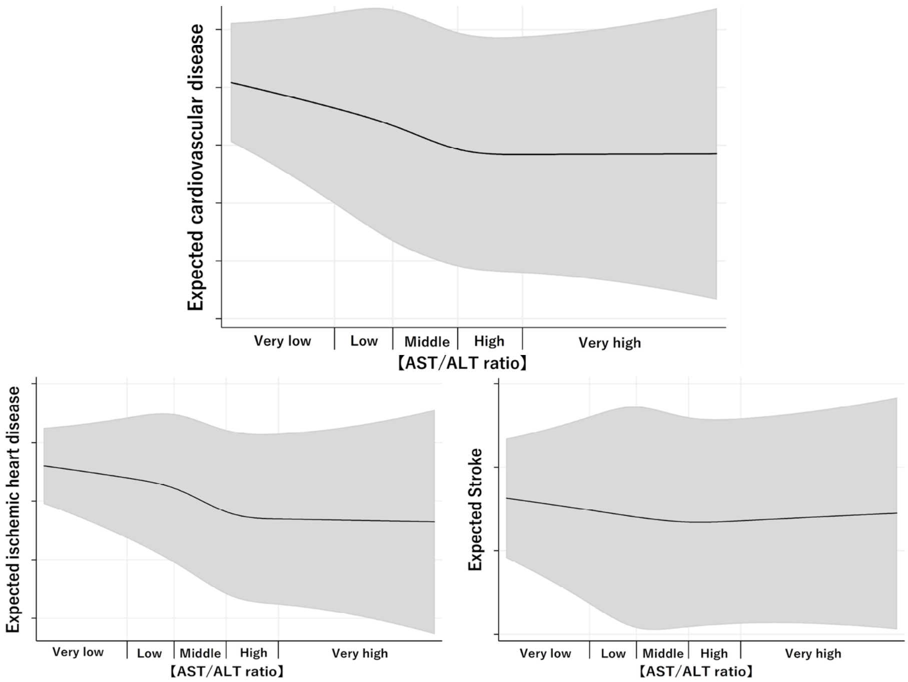

Fig. 1. Estimated restricted cubic splines of the associations between the aspartate aminotransaminase (AST)/alanine aminotransaminase (ALT) ratios and cardiovascular disease, ischemic heart disease, and stroke

but plateaued at the ratio of the Q3 group in all primary outcomes. In contrast, the splines for secondary outcomes gradually decreased as the AST/ALT ratio increased without reaching a plateau (Fig. 2).

Supplementary file shows the results of sensitivity analyses excluding those with abnormally high liver enzymes and those with the data categorized by log AST/log ALT ratio. The findings were almost consistent with those of the main analyses, except for stroke.

DISCUSSION

Our cohort study demonstrated that a Q1 AST/ALT ratio was associated with an increased risk of cardiovascular disease

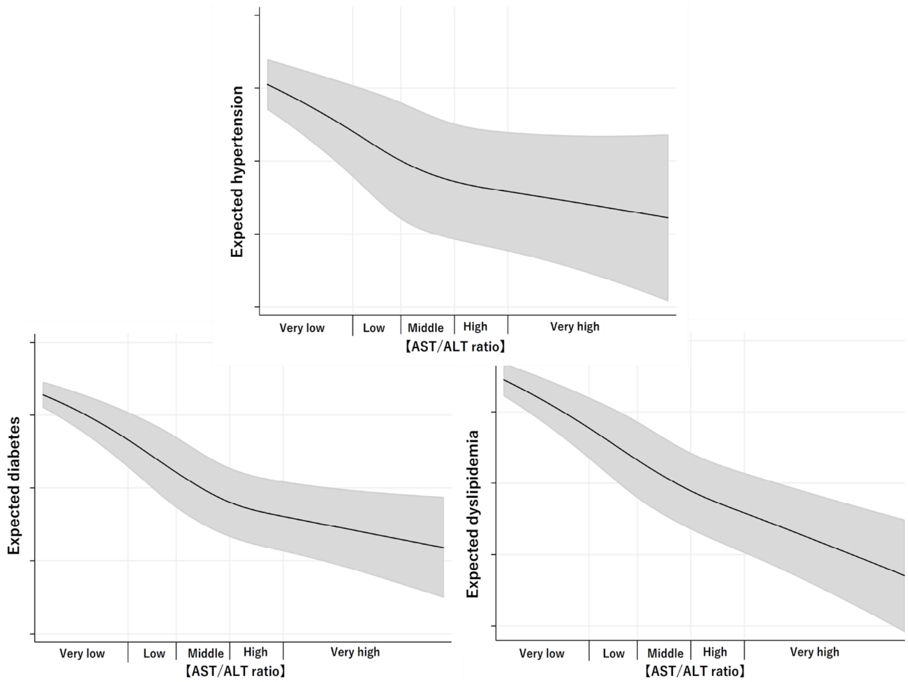

Fig. 2. Estimated restricted cubic splines of the associations between the aspartate aminotransaminase (AST)/alanine aminotransaminase (ALT) ratios and hypertension, diabetes, and dyslipidemia.

compared to a Q3 AST/ALT ratio, even when evaluated separately for ischemic heart disease or stroke. In contrast, Q4 or Q5 AST/ALT ratios were not statistically different in cardiovascular disease compared to the Q3 AST/ALT ratio. As for newly onset conventional cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia, the risks were negatively associated with AST/ALT ratio.

A Q1 AST/ALT ratio was associated with an increased risk of cardiovascular disease in our study, which is partially consistent with previous studies. A cross-sectional study in Japan concluded that the ALT/AST ratio (inverse ratio to our study) was the best surrogate marker for insulin resistance [17]. Another study from Thailand reported that an increased ALT/AST ratio was significantly associated with an increased incidence of metabolic syndrome [18]. If we focus on increased ALT levels alone, which may result in a decreased AST/ALT ratio, there is a wider selection of published research to reference. A cohort study in the Netherlands reported that elevated ALT levels were associated with increased ischemic heart disease, but not cardiovascular disease [10]. Another previous review found that people who were in the highest ALT group had an increased relative risk (approximately 1.4 to 2.1 times) of metabolic syndrome or type 2 diabetes compared to those in the lowest ALT group [19]. As introduced above, because previous studies mainly focused on ALT alone, ALT may be primarily responsible for the association to cardiovascular diseases. However, studies about the AST/ALT ratio, including our study, still have added evidence on the association between liver enzymes and cardiovascular diseases.

We hypothesized the potential underlying mechanism of the association between low AST/ALT ratio and cardiovascular diseases as the reflection of metabolic status. As discussed above, many previous studies mentioned that low AST/ALT ratio (or high ALT alone) associated with insulin resistance or metabolic syndrome. Although our analyses adjusted for potential confounders, including known metabolic syndrome associated factors, unaware metabolic syndrome associated factors may affect on the AST/ALT ratio, resulting in increased cardiovascular diseases.

We found that the risk of cardiovascular disease gradually decreased as the AST/ALT ratio increased but reached a plateau at an AST/ALT ratio of 1.2. In contrast, the AST/ALT ratio showed a positive linear association with the occurrence of new-onset conventional cardiovascular risk factors (hypertension, dyslipidemia, and diabetes). There are several explanations for this finding. First, in the Q4/Q5 AST/ALT ratio groups, other cardiovascular risk factors such as being underweight were frequently observed. The AST/ALT ratio was higher in people with a lower BMI, but low BMI can be a risk factor for cardiovascular disease [20, 21]. Cardiovascular risk factors other than hypertension, dyslipidemia, and diabetes could increase the risk of cardiovascular disease in the Q4 or Q5 AST/ALT groups, which could negate the lower rate of conventional cardiovascular risk factors. Second, a Q1 AST/ALT ratio itself could predict cardiovascular disease risk more specifically than conventional cardiovascular risk factors. In one study, some liver enzyme-increasing genetic variants were associated with a lower risk of cardiovascular disease, while others were associated with higher risk [22]. ALT-increasing allele such as rs1277930 associated with increased dyslipidemia and coronary artery disease, but an AST-increasing allele like rs1260326 could be associated with a lower risk of diabetes and not related to cardiovascular disease itself. Considering the relationships between genetic variants, risk factors, and cardiovascular disease occurrence, a Q1 AST/ALT ratio could be considered as a highly specific marker for ischemic heart disease regardless of the presence of conventional cardiovascular risk factors. Finally, AST levels also reached a plateau around the Q3 AST/ALT ratio group, which implied that in the Q4 and Q5 ratio groups, higher AST/ALT ratios were mainly due to lower ALT values. This plateau may be explained by the smaller number of events, as suggested in restricted cubic splines, which showed a wider 95% confidence interval in the Q4 or Q5 AST/ALT groups. Considering our population of AST range of 6 to 1,071 IU/L, the AST/ALT ratio could be a meaningful marker for the risk of cardiovascular disease only in patients whose ratios fall within the first to third quintiles. Therefore, further studies are warranted.

Weng et al. [8] reported that a high AST/ALT ratio was associated with an increased risk of developing cardiovascular disease in men by using UK primary care patients, which was not consistent with our study. The following reasons might explain these results. First, there may be population differences between that study and our study, including racial differences. The mean AST/ALT ratio was 0.8 for men and 1.0 for women in the UK study, whereas in our study the means were 0.97 for men and 1.28 for women. Interestingly, a previous systematic review and a meta-analysis suggested a potential association between increased ALT levels and increased cardiovascular disease in the Asian population. The same studies found an association between increased ALT levels and decreased cardiovascular diseases in North American and European populations [9, 14]. Moreover, our study excluded those who had hepatic disease by using ultrasound to mitigate the bias from hepatic disease, which would dramatically affect the AST/ALT ratio. Another reason was that our study adjusted for alcohol consumption, which would also greatly affect both the AST/ALT ratio and cardiovascular diseases. Furthermore, a previous study dealt with the AST/ALT ratio as a continuous variable, anticipating a linear association between the AST/ALT ratio and cardiovascular disease. Our study shows that the association may not be linear and could have other shapes, such as U or mirrored J. Considering these reasons, our study still provides valuable insight into the association.

Current guidelines on cardiovascular disease prevention advocated that potential risk modifiers are psychosocial factors, ethnicity, imaging, frailty, family history, genetics, socioeconomic determinants, environmental exposure, biomarkers in blood and body composition [23]. Our finding that the AST/ALT ratio may be associated with cardiovascular disease may be classified in the risk modifier of “biomarkers in blood”. Patients with non-alcoholic steatohepatitis (NASH), which is now known as an independent risk factor of cardiovascular disease [24, 25], may have abnormal AST/ALT ratio, resulting in the development of cardiovascular diseases.

Our study had some limitations. First, a median follow-up of 1,829 days (almost 5 years) may be a short period to evaluate cardiovascular disease. However, the approximately 1,500 cardiovascular events are still very useful for evaluating the association. Another limitation was that our study could not evaluate all-cause or cardiovascular mortality because we extracted our data from a relatively healthy population with a very limited number of deaths.

CONCLUSIONS

A Q1 AST/ALT ratio was associated with an increased risk of cardiovascular disease compared to a Q3 AST/ALT ratio in the Japanese population. This contrasts with the association of higher AST/ALT ratio with cardiovascular disease in the Western population. Q4 or Q5 AST/ALT ratios in our study were not associated with cardiovascular disease compared to the Q3 AST/ALT ratio. Cardiovascular risk factors also decreased as the AST/ALT ratio increased.

Conflicts of interest: None to declare.

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Authors' contribution: D.K. designed and conceived the study. D.K., M.H., A.M., T.K., K.Y., and T.S collected data. D.H. analysed the data and wrote the draft. M.H., A.M., T.K., K.Y., and T.S. contributed to the discussion and critically revised the manuscript. All authors approved the final version of the article.

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