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Nonalcoholic Fatty Liver Disease as a Risk Factor of Arterial Stiffness Measured by the Cardioankle Vascular Index

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is associated with risk factors for cardiovascular disease. The cardioankle vascular index (CAVI), a new measure of arterial stiffness, was recently developed and is independent of blood pressure. We investigated whether NAFLD is associated with arterial stiffness as measured using the CAVI in an apparently healthy population.

A total of 2954 subjects without any known liver diseases were enrolled. NAFLD was diagnosed via typical ultrasonography. The clinical characteristics examined included age, sex, body mass index (BMI), waist circumference (WC), and the levels of aspartate aminotransferase, alanine aminotransferase, total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol triglycerides, and glucose. Arterial stiffness was defined using an age- and sex-specific threshold of the upper quartile of the CAVI.

NAFLD was found in 1249 (42.3%) of the analyzed subjects. Using an age-, sex-, and BMI-adjusted model, NAFLD was associated with a 42% increase in the risk for arterial stiffness (highest quartile of the CAVI). The risk for arterial stiffness increased according to the severity of NAFLD (adjusted odds ratio [95% confidence interval], 1.27 [1.02 – 1.57] vs 1.78 [1.37 – 2.31], mild vs moderate-to-severe, respectively). When adjusted for other risk factors, including BMI, WC, smoking status, diabetes, and hypertension, these relationships remained statistically significant.

Patients with NAFLD are at a high risk for arterial stiffness regardless of classical risk factors. The presence of cardiometabolic risk factors may attenuate the prediction of arterial stiffness by means of NAFLD presence. Thus, physicians should carefully assess subjects with NAFLD for atherosclerosis and associated comorbidities.

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Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CAVI = cardioankle vascular index, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, PWV = pulse wave velocity, WC = waist circumference.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease with an estimated prevalence of 20% to 30% in the West and 16% to 33% in Korea.[1–3] Because the development of NAFLD has been linked to insulin resistance and metabolic syndrome,[4–6] NAFLD is closely associated with obesity, dyslipidemia, type II diabetes, and cardiovascular disease.[7–9] Evidences suggest that the severity of NAFLD is associated with the extent of increased cardiovascular risk, independent of conventional risk factors.[10,11]

Arterial stiffness has been established as a surrogate marker for the prognosis of cardiovascular disease.[12] Arterial stiffness is a strong predictor of future cardiovascular events and all-cause mortality, and is among the earliest detectable manifestations of adverse structural and functional changes to blood vessel walls. Increased arterial stiffness is found in patients with cardiometabolic risk factors including hypertension[13] and metabolic syndrome.[14] The association between arterial stiffness and NAFLD has been reported.[15–17] Many methods such as pulse wave velocity (PWV), the augmentation index, and the β-stiffness index have been designed to assess arterial stiffness.[18] However, most of these approaches have the drawback of affecting blood pressure during measurement. Additionally, β-stiffness is limited in that it is applicable to only a local segment of the artery.

The cardioankle vascular index (CAVI) is a new index representing the stiffness of entire arterial segments from the aorta to the ankle; it is independent of the blood pressure at the time of the measurement.[19] The CAVI is highly reproducible and easy to measure.[20,21] The CAVI has been demonstrated as a superior index of arterial stiffness compared with previously established parameters, such as brachial-ankle PWV, and displays good correlations with left ventricular diastolic indices and lipid profiles in patients with angina pectoris.[22] Associations between CAVI and coronary atherosclerosis,[23] cardiac function,[24,25] hypertension,[26] and stroke[27] have been shown. However, no data regarding the association between CAVI and NAFLD have been reported. In this study, we aimed to evaluate

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the association between NAFLD and arterial stiffness using the CAVI in the apparently healthy general population.

PATIENTS AND METHODS

Study Population

A cross-sectional study was conducted to evaluate the association between NAFLD and the CAVI. The participants who underwent abdominal ultrasonography and the CAVI on the same day at the Seoul National University Hospital's Gangnam Healthcare Center in Seoul, Korea, for routine health checkups from 2010 to 2013 were recruited. Most of the study population voluntarily paid for their health checkups, whereas others were supported by their company. Patients with previous peripheral artery disease, an ankle–brachial index <0.9, or a history of clinically significant valvular heart disease were excluded from CAVI analysis.

Of a total of 119 subjects who were positive for hepatitis B virus, 36 subjects who were positive for hepatitis C virus and 448 subjects with a history of alcohol consumption (>30 g/d for males and >20 g/d for females) or had a history of other types of hepatitis were excluded. Finally, 2954 subjects were enrolled in this study. Ethical approval for this study was obtained from the institutional review board of the Seoul National University Hospital with an informed consent waiver prior to the study.

Clinical and Laboratory Assessments

Each subject completed a questionnaire on past medical history and lifestyle. Current smokers were defined as having smoked at least 1 cigarette per day during the previous year. Former smokers were defined as prior regular cigarette smokers.[28] All subjects received an anthropometric assessment and the laboratory and radiologic tests on the same day. Body weight and height were measured using a digital scale, and body mass index (BMI) was calculated as the weight (kilogram) divided by the height (meter) squared. Waist circumference (WC) was measured at the midpoint between the lower costal margin and the anterior superior iliac crest by a well-trained individual using a tape measure. Systolic and diastolic blood pressures were measured twice, and the average values were recorded. Hypertension was defined as treatment with an antihypertensive drug, a systolic blood pressure >140 mm Hg, or a diastolic blood pressure >90 mm Hg.

Blood samples were collected before 10:00 AM after a 12-hour overnight fast. All laboratory tests were performed using standard laboratory methods. Laboratory tests included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, fasting glucose, hepatitis B surface antigen, and hepatitis C virus antibody levels. Diabetes mellitus was defined as either a fasting serum glucose level ≥126 mg/dL or the use of blood glucose-lowering agents.

Assessment of NAFLD

NAFLD was defined as the presence of fatty liver disease as determined via ultrasonography in the absence of the following: a positive serologic marker for hepatitis B surface antigen or hepatitis C virus serological marker, excessive alcohol intake (>30 g/d for males and >20 g/d for females), medications known to produce fatty liver disease, and other specific hepatic disease. Ultrasonographic examination of the liver was performed by experienced radiologists blinded to the patients' clinical characteristics. The diagnosis of fatty liver was performed via ultrasonography (Acuson, Sequoia 512; Siemens, Mountain View, CA) using previously described standardized categories as follows[29]: normal, normal echogenicity; mild, slight diffuse increase in bright homogenous echoes in the liver parenchyma, with normal visualization of the diaphragm and the portal and hepatic vein borders, and normal hepatorenal contrast if echogenic; moderate, diffuse increase in bright echoes in the liver parenchyma, with slightly impaired visualization of the peripheral portal and hepatic vein borders; severe, marked increase in bright echoes at a shallow depth, with deep attenuation and impaired visualization of the diaphragm and marked vascular blurring.

The CAVI Measurement

The CAVI was measured using a VaSera VS-1000 (Fukuda Denshi Co Ltd, Tokyo, Japan) according to previous descriptions.[20,30] Briefly, the brachial pulse pressure was measured with an automated cuff oscillometer on seated individuals following a 5-minute rest. The average value of 2 measurements was obtained to determine the systolic and diastolic pressures and pulse pressure. Next, the cuffs were applied to ankles and both upper arms with the individuals in a resting lying position. After 10 minutes of rest, the measurement was performed. A phonocardiogram used for the detection of heart sounds was placed over the right sternum between the second intercostal spaces, and electrocardiogram electrodes were applied on both wrists. The PWV was calculated as the vascular length (L) by the time (T) required for the pulse wave to propagate from the aortic valve to the ankle. Because the initiation of blood release from the aortic valve is difficult to identify based on the opening sound of the valve, T is difficult to determine; thus, T value was defined as summing the interval between the initiation of the brachial pulse waveform and the initiation of the ankle pulse waveform, and the interval between the closing sound of the aortic valve and the notch of the brachial pulse waveform. Measurements were performed by a well-trained staff member. The CAVI was determined using the following equation:

$$\mathrm{CAVI} = \mathrm{a}([2\rho/\Delta \mathrm{P}] \times \ln[\mathrm{Ps}/\mathrm{Pd}] \times \mathrm{PWW}^2) + \mathrm{b}$$

where Ps and Pd are the systolic and diastolic blood pressures, respectively, ΔP is Ps−Pd, ρ is the blood density, and a and b are constants. The mean values of the left and right CAVI were used. Given the lack of data regarding an appropriate reference of "arterial stiffness," we selected the age- (10-year interval) and sex-specific highest quartile of the CAVI as the arterial stiffness group.

Statistical Analysis

Comparisons of continuous variables between the 2 groups were performed using Student *t* test, and categorical variables were compared using a χ^2 test or Fisher exact test. Analysis of variance and analysis of covariance (ANCOVA) were used to compare dependent variables. Logistic regression analysis was used to analyze the association between NAFLD and arterial stiffness while controlling for potential confounders. All statistical analyses were performed using SPSS 19.0 software (SPSS Inc, Chicago, IL). *P* values <0.05 were considered to be statistically significant.

RESULTS

A total of 2954 subjects (mean age 55.5 ± 9.6, male 64.7%) were analyzed. The characteristics of the study subjects

TABLE 1. Comparison of Baseline Characteristics Between Subjects With and Without Arterial Stiffness

	No Arterial Stiffness (n = 2258)	Arterial Stiffness (n = 696)	*P* Value
Age, y	55.4 ± 9.9	57.3 ± 9.3	<0.001
Male, n (%)	1466 (64.9)	446 (64.1)	0.684
Smoking, n (%)			0.029
Never	1783 (79.0)	519 (74.6)	
Former	137 (6.1)	44 (6.3)	
Current	338 (15.0)	133 (19.1)	
DM, n (%)	175 (7.8)	116 (16.7)	<0.001
Hypertension, n (%)	600 (26.6)	226 (32.5)	0.002
Systolic BP, mm Hg	120.4 ± 13.1	123.7 ± 15.3	<0.001
Diastolic BP, mm Hg	77.9 ± 10.1	79.5 ± 11.2	0.001
BMI, kg/m^2	24.27 ± 2.97	23.61 ± 2.89	<0.001
WC, cm	86.38 ± 8.75	85.81 ± 8.97	0.141
AST, IU/L	24.7 ± 12.3	25.9 ± 13.4	0.043
ALT, IU/L	26.7 ± 18.5	28.0 ± 21.0	0.142
Total cholesterol, mg/dL	195.7 ± 35.9	194.1 ± 38.2	0.345
Triglycerides, mg/dL	118.3 ± 73.9	125.9 ± 86.9	0.039
HDL-cholesterol, mg/dL	52.8 ± 13.5	54.7 ± 34.1	0.168
LDL-cholesterol, mg/dL	123.0 ± 33.9	120.7 ± 36.5	0.144
FBS, mg/dL	101.1 ± 20.7	108.4 ± 29.4	<0.001
NAFLD, n (%)	941 (41.7)	308 (44.3)	0.229

Data are shown as the mean ± SD. BMI = body mass index, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = blood pressure, DM = diabetes mellitus, FBS = fasting blood sugar, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, WC = waist circumference.

are shown in Table 1. Older age, currently smoking, increased prevalence of diabetes mellitus, hypertension, higher blood pressure, and levels of triglycerides and fasting glucose were found in the arterial stiffness group (highest age- and sex-specific quartile of the CAVI) compared with the nonarterial stiffness group. However, BMI was lower in the arterial stiffness group than in the nonarterial stiffness group. There were no differences in the rates of NAFLD depending on the presence of arterial stiffness.

Of the 2954 subjects, 1249 (42.3%) had ultrasonographically diagnosed NAFLD. Table 2 compares the subjects with and without NAFLD. The individuals with NAFLD had a higher prevalence of diabetes mellitus and hypertension, higher blood pressure, BMI, WC, and serum levels of AST, ALT, total cholesterol, triglycerides, LDL-cholesterol, fasting glucose, hemoglobin A1c (HbA1c) and lower levels of HDL-cholesterol than those without NAFLD. Individuals with moderate-to-severe NAFLD had a higher prevalence of diabetes mellitus and hypertension, higher blood pressure, BMI, WC, and serum levels of AST, ALT, total cholesterol, triglycerides, LDL-cholesterol, fasting glucose, and HbA1c, and lower levels of HDL-cholesterol than those with mild NAFLD.

The mean values of the CAVI for the subjects with and without NAFLD are shown in Table 3 and Supplementary Figure 1, http://links.lww.com/MD/A231. The mean value of the CAVI was significantly higher in the individuals with NAFLD than in those without NAFLD (7.80 ± 1.05 vs 7.67 ± 1.02, respectively, $P < 0.001$), and this difference remained significant after adjusting for multiple metabolic variables such as age, sex, BMI, WC, smoking status, diabetes, and hypertension (7.81 ± 0.02 vs 7.66 ± 0.02, respectively, $P < 0.001$).

Next, we analyzed the association between NAFLD and the presence of arterial stiffness (highest quartile of the CAVI). The associations between NAFLD and arterial stiffness, as measured using the CAVI, appeared to be robust to the influences of age, sex, and BMI. Based on an age-, sex-, and BMI-adjusted model, NAFLD was associated with a 42% increase in the risk for arterial stiffness. The risk for arterial stiffness increased according to the severity of NAFLD (adjusted odds ratio [OR] [95% confidence interval, CI], 1.27 [1.02 − 1.57] vs 1.78 [1.37 − 2.31], mild vs moderate-to-severe NAFLD, respectively, as shown in Table 4 and Supplementary Table 1, http://links.lww.com/MD/A231). This effect of NAFLD was attenuated, but remained significant based on multivariable analyses in which other well-identified risk factors for arterial stiffness were considered. When adjusted for age, sex, BMI, WC, smoking status, diabetes, and hypertension, NAFLD was associated with a 32% increase in the risk for arterial stiffness compared with the control. The risk for arterial stiffness increased according to the severity of NAFLD (adjusted OR [95% CI], 1.20 [0.96 − 1.50] vs 1.59 [1.21 − 2.08], mild vs moderate to severe NAFLD, respectively).

We also analyzed the association between NAFLD and arterial stiffness according to age and obesity (Table 5). Multivariate analyses showed an independent (OR 1.54, 95% CI 1.11–2.12) and dose-dependent relationship (moderate–severe NAFLD: OR 1.97, 95% CI 1.28–3.01, P for trend = 0.002) between NAFLD and arterial stiffness in the younger group (age < 55). In contrast, subjects over 55 years showed an insignificant association with the presence of NAFLD and the degree of NAFLD. Likewise, the presence and degree of NAFLD was associated with arterial stiffness in a dose-dependent manner, especially in the nonobese group (OR 1.35, 95% CI 1.05–1.73; moderate–severe NAFLD: OR 1.80, 95% CI 1.19–2.71, P for trend = 0.004).

DISCUSSION

In this study, we identified a strong relationship between NAFLD and arterial stiffness, a surrogate marker of cardiovascular disease. This association was independent of various

TABLE 2. Comparison of Baseline Characteristics Between Subjects With and Without NAFLD

	No NAFLD (n = 1705)	NAFLD (n = 1249)	*P* Value	Mild (n = 749)	Moderate–Severe (n = 500)	*P* Value (ANOVA)
Age, y	55.8 ± 10.2	55.9 ± 9.2	0.819	56.5 ± 9.0	55.0 ± 9.4	0.020
Male, %	961 (56.4)	951 (76.1)	<0.001	543 (72.5)	408 (81.6)	<0.001
Smoking, %			<0.001			<0.001
Never	1382 (81.1)	920 (73.7)		574 (76.6)	346 (69.2)	
Former	88 (5.2)	93 (7.4)		44 (5.9)	49 (9.8)	
Current	235 (13.8)	236 (18.9)		131 (17.5)	105 (21.0)	
DM, %	119 (7.0)	172 (13.8)	<0.001	83 (11.1)	89 (17.8)	<0.001
HT, %	396 (23.2)	430 (34.4)	<0.001	264 (35.2)	166 (33.2)	0.002
Systolic BP, mm Hg	119.7 ± 13.8	123.3 ± 13.3	<0.001	122.5 ± 12.9	124.4 ± 13.7	<0.001
Diastolic BP, mm Hg	77.0 ± 10.5	80.0 ± 10.0	<0.001	79.4 ± 10.0	80.9 ± 9.9	<0.001
BMI, kg/m^2	23.07 ± 2.59	25.54 ± 2.84	<0.001	24.86 ± 2.63	26.57 ± 2.83	<0.001
WC, cm	83.08 ± 8.17	90.54 ± 7.75	<0.001	88.76 ± 7.46	93.19 ± 7.41	<0.001
AST, IU/L	22.8 ± 10.9	28.0 ± 14.0	<0.001	26.1 ± 13.0	30.8 ± 15.0	<0.001
ALT, IU/L	21.8 ± 12.7	34.1 ± 23.5	<0.001	30.0 ± 20.8	40.3 ± 26.0	<0.001
Total cholesterol, mg/dL	192.9 ± 34.8	198.6 ± 38.4	<0.001	198.8 ± 37.4	198.3 ± 39.9	<0.001
Triglycerides, mg/dL	98.7 ± 52.9	149.1 ± 93.7	<0.001	138.4 ± 75.6	165.0 ± 113.8	<0.001
HDL-C, mg/dL	56.1 ± 24.2	49.4 ± 12.5	<0.001	50.9 ± 13.3	47.2 ± 10.9	<0.001
LDL-C, mg/dL	119.4 ± 33.3	126.6 ± 35.7	<0.001	127.0 ± 33.7	126.0 ± 38.6	<0.001
FBS, mg/dL	98.0 ± 17.9	109.4 ± 27.6	<0.001	106.8 ± 25.1	113.2 ± 30.7	<0.001
HbA1c	98.0 ± 17.9	109.4 ± 27.6	<0.001	106.8 ± 25.1	113.2 ± 30.7	<0.001
Arterial stiffness, %	388 (22.8)	308 (24.7)	0.229	178 (23.8)	130 (26.0)	0.320

Data are shown as the mean ± SD. ALT = alanine aminotransferase, ANOVA = analysis of variance, AST = aspartate aminotransferase, BMI = body mass index, BP = blood pressure, DM = diabetes mellitus, FBS = fasting blood sugar, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HT = hypertension, LDL-C = low-density lipoprotein-cholesterol, NAFLD = nonalcoholic fatty liver disease, WC = waist circumference.

well-identified risk factors for arterial stiffness, and canonical risk factors may attenuate the prediction of arterial stiffness by means of the NAFLD presence. Moreover, the risk for arterial stiffness increased with the severity of NAFLD, suggesting an important role for NAFLD in the pathogenesis of arterial stiffness.

Several studies have suggested NAFLD as an independent risk factor of arterial stiffness.[31,32] A population-based cohort study of Italian adults showed that arterial stiffness measured using the carotid-femoral PWV was significantly lower in controls than in subjects with NAFLD.[31] NAFLD was an independent risk factor of increased PWV in patients with biopsy-proven NAFLD.[32] A population-based cohort study of adolescents in Australia showed that NAFLD is only associated with increased arterial stiffness in subjects with adverse metabolic profiles.[17] Because subjects with severe fatty liver may have additional risk factors for metabolic syndrome, the findings of our study are in accordance with this previous result. However, it is a novel method of evaluating arterial stiffness, as it is not affected by blood pressure. In addition, our results expand upon the current knowledge by indicating that arterial stiffness increases in accordance with the severity of NAFLD. Consistent with our results, a recent study showed that increased arterial stiffness in patients with NAFLD was related to the histological severity of hepatic fibrosis.[33] Although these results were based on histological phenotypes, the previous study was limited by its small sample size. In contrast to our findings, VanWagner et al[34] demonstrated that NAFLD was not associated with subclinical atherosclerosis as measured by coronary artery calcification, and Tarantino et al[35] also indicated that the severity of hepatic steatosis was not associated with carotid intima media thickness in obese patients. These differences in these results may have been caused by different definitions of NAFLD or heterogeneous study populations.

TABLE 3. CAVI Between Control and NAFLD

	Control	NAFLD	*P* Value
CAVI	7.67 ± 1.02	7.80 ± 1.05	<0.001
CAVI, adjusted age, sex, and BMI	7.64 ± 0.02	7.84 ± 0.02	<0.001
CAVI, adjusted for the model	7.66 ± 0.02	7.81 ± 0.02	<0.001

Data are presented as mean ± standard error. The multivariable model was adjusted for age, sex, BMI, WC, smoking status, diabetes, and hypertension. BMI = body mass index, CAVI = cardiovascular ankle index, NAFLD = nonalcoholic fatty liver disease, WC = waist circumference.

In previous studies,[36,37] smoking has been reported to have a significant effect on arterial stiffness. However, when we analyzed our data, the effect of smoking was more significant in subjects without NAFLD than those with NAFLD. Another interesting finding in our study was that the association between NAFLD and arterial stiffness was significant in the younger and nonobese group. This finding might suggest that NAFLD may affect the earlier stages of arterial stiffness. Consistent with our results, a recent study in China showed a significant association between NAFLD and arterial stiffness in nonobese, nonhypertensive, and nondiabetic young individuals.[38]

Although the mechanism by which NAFLD is associated with arterial stiffness is yet to be determined, several plausible explanations have been introduced. Excessive fat accumulation in the liver is closely associated with insulin resistance, which correlates to arterial stiffness.[39,40] In addition to hepatic fat accumulation, epicardial adipose tissue, which reflects metabolic risk, displays a significant association with arterial stiffness.[30] Moreover, an excess of reactive oxygen species may induce the production of cytokines, such as tumor necrosis

TABLE 4. Univariable and Multivariable Binary and Ordinal Analyses of the Risk for Arterial Stiffness in Subjects With Versus Without NAFLD

	Age, Sex, and BMI Adjusted		Multivariable Model	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
No NAFLD	1 (reference)		1 (reference)	
NAFLD	1.42 (1.17–1.72)	<0.001	1.32 (1.08–1.61)	0.007
NAFLD grade				
No NAFLD	1 (reference)	<0.001*	1 (reference)	0.001*
Mild NAFLD	1.27 (1.02–1.57)	0.032	1.20 (0.96–1.50)	0.104
Moderate–severe NAFLD	1.78 (1.37–2.31)	<0.001	1.59 (1.21–2.08)	0.001

The multivariable model was adjusted for age, sex, BMI, WC, smoking status, diabetes, and hypertension. BMI = body mass index, CI = confidence interval, NAFLD = nonalcoholic fatty liver disease, OR = odds ratio, WC = waist circumference.
* *P* value for the test of trend of odds.

factor-α and interleukin-6, leading to lipid peroxidation in hepatocytes and resulting in hepatic inflammation in NAFLD.[41,42] Furthermore, NAFLD was associated with increased circulating levels and hepatic expression of molecular mediators of atherosclerosis, such as intracellular adhesion molecule and plasminogen activator inhibitor-1, which may exert a direct effect on arterial stiffness.[43]

A strength of this study is the first use of the CAVI, a reliable marker of arterial stiffness on a large number of subjects considered to be representative of the general population due to the nature of a health checkup. However, there are several limitations to this study. First, the cross-sectional design of the study made it difficult to evaluate the temporal association between NAFLD and arterial stiffness. Second, we were unable to obtain liver histology, the gold standard for diagnosis of NAFLD. Ultrasonography can lead to false-negative results when fatty infiltration of the liver falls below 30%.[44] Additionally, there is inter- and intraobserver diagnostic variability in hepatic ultrasonography. However, it is impossible to perform invasive tests in apparently healthy subjects; therefore, ultrasonography is used as a first-line method to detect NAFLD according to clinical practical guidelines.[45,46] Third, this study was performed at a single health screening center in Korea, which may result in selection bias.

In conclusion, our findings show an association between NAFLD and arterial stiffness in NAFLD severity-dependent manner. This finding suggests that canonical risk factors for cardiovascular disease may reduce the prediction of arterial stiffness by means of the NAFLD presence. Thus, physicians should carefully assess subjects with NAFLD for atherosclerosis and its associated comorbidities.

TABLE 5. Multivariate Analysis of the Association Between NAFLD and Risk Factors According to Age and Obesity

	OR (95% CI)	***P* Value**
Age <55 (n = 1343)		
No NAFLD	1 (reference)	
NAFLD	1.54 (1.11–2.12)	0.009
NAFLD grade		
No NAFLD	1 (reference)	0.002*
Mild NAFLD	1.34 (0.92–1.93)	0.122
Moderate–severe NAFLD	1.97 (1.28–3.01)	0.002
Age ≥55 (n = 1611)		
No NAFLD	1 (reference)	
NAFLD	1.16 (0.90–1.49)	0.257
NAFLD grade		
No NAFLD	1 (reference)	0.104*
Mild NAFLD	1.07 (0.81–1.42)	0.623
Moderate–severe NAFLD	1.37 (0.96–1.96)	0.081
BMI<25 (n = 1875)		
No NAFLD	1 (reference)	
NAFLD	1.35 (1.05–1.73)	0.018
NAFLD grade		
No NAFLD	1 (reference)	0.004*
Mild NAFLD	1.23 (0.94–1.62)	0.134
Moderate–severe NAFLD	1.80 (1.19–2.71)	0.005
BMI ≥25 (n = 1079)		
No NAFLD	1 (reference)	
NAFLD	1.24 (0.89–1.74)	0.205
NAFLD grade		
No NAFLD	1 (reference)	0.128*
Mild NAFLD	1.15 (0.78–1.69)	0.490
Moderate–severe NAFLD	1.35 (0.92–1.98)	0.128

The multivariable model was adjusted for age, sex, BMI, WC, diabetes, hypertension, smoking, and NAFLD. BMI = body mass index, CI = confidence interval, NAFLD = nonalcoholic fatty liver disease, OR = odds ratio, WC = waist circumference.
* *P* value for the test of trend of odds.

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