The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2021; 28: 524-534. http://doi.org/10.5551/jat.56945

Correlation of the Fatty Liver Index with the Pathophysiological Abnormalities Associated with Cardiovascular Risk Markers in Japanese Men without any History of Cardiovascular Disease: Comparison with the Fibrosis-4 Score

Yoichi Iwasaki, Kazuki Shiina, Chisa Matsumoto, Hiroki Nakano, Masatsune Fujii, Akira Yamashina, Taishiro Chikamori and Hirofumi Tomiyama

Department of Cardiology, Tokyo Medical University, Tokyo, Japan

Aim: Fatty liver and the liver fibrosis are known risk factors for cardiovascular disease (CVD). The severity of fatty liver can be assessed by determining the fatty liver index (FLI), and the severity of liver fibrosis can be assessed by determining the fibrosis-4 (FIB-4) score. We examined the differences in the associations of these two liver scoring systems with the pathophysiological abnormalities associated with the risk of development of CVD.

Methods: The FLI and FIB-4 score were calculated in 2,437 Japanese men without any history of CVD. The serum NT-pro-BNP levels and brachial-ankle pulse wave velocity (baPWV) were also measured at the start of the study and the end of three years' follow-up.

Results: The FLI was significantly correlated with the baPWV ($p<0.01$) and the FIB-4 score was significantly correlated with the serum NT-pro-BNP level ($p<0.01$). Furthermore, the delta change of the FLI was significantly correlated with the delta change of the baPWV during the study period ($p=0.01$), and the delta change of the FIB-4 score was significantly correlated with the delta change of the serum NT-pro-BNP level during the study period ($p<0.01$).

Conclusions: While the FIB-4 score may serve as a marker of the risk of development of heart failure, the FLI may be a marker of arterial stiffness in Japanese men without any history of CVD.

Key words: Arterial stiffness, Heart failure, Fatty liver, Liver fibrosis

Introduction

Fatty liver disease is the most frequently encountered chronic liver disease in the world[1, 2], and fatty liver can progress from simple steatosis to steatohepatitis and liver fibrosis[3]. Simple liver scoring systems have been proposed to assess the severity of fatty liver and also of the related liver fibrosis, because of the high prevalence rates of fatty liver. Non-alcoholic fatty liver disease (NAFLD), in addition to hepatocellular carcinoma, is known as a risk factor for cardiovascular diseases (CVD) including heart failure (HF)[4, 5]. Reported to be associated with the severity of atherosclerotic vascular damage, the fatty liver index (FLI) is a simply-measured marker to assess the severity of fatty liver[6, 7]. On the other hand, we reported previously that the fibrosis-4 (FIB-4) score, a simply-measured marker of liver fibrosis, may be a marker of the risk of development of HF because it was associated with the serum NT-pro-BNP levels[8]. However, it has not clearly been determined whether the FLI and FIB-4 score reflect different facets of the pathophysiological abnormalities associated with the risk of development of CVD.

The present cross-sectional and longitudinal studies were conducted to examine whether the FLI and FIB-4 score are individually associated with different facets of the pathophysiological abnormalities

Address for correspondence: Hirofumi Tomiyama, Department of Cardiology and Division of Preemptive Medicine for Vascular Damage, Tokyo Medical University 6-7-1 Nishi-Shinjuku, Tokyo, Japan 160-0023 E-mail: tomiyama@tokyo-med.ac.jp

Received: April 10, 2020 Accepted for publication: June 4, 2020

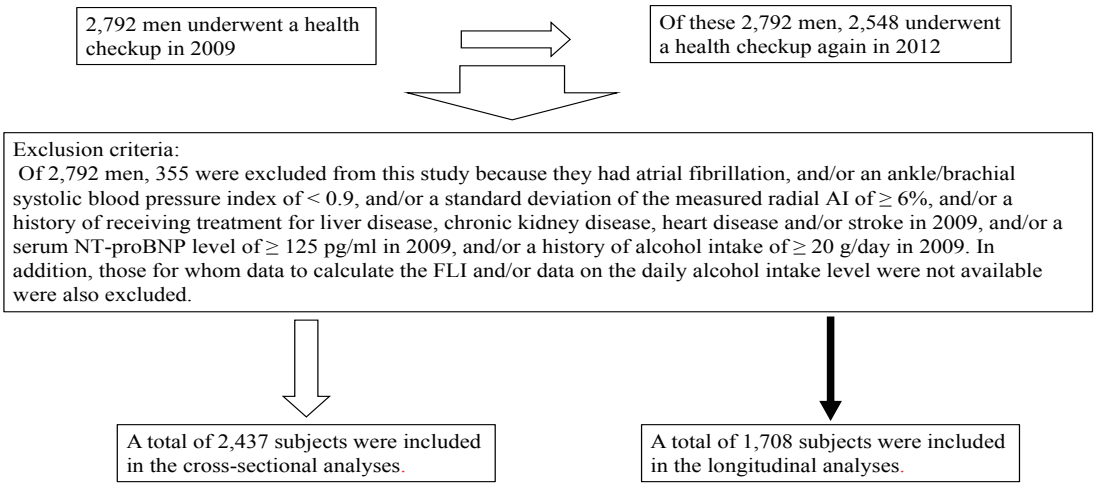

Fig. 1. Patients selection process

associated with the risk of development of CVD.

Methods

2-1. Study Subjects

Fig. 1 shows a flow-chart of the patient selection procedure in the present cross-sectional and longitudinal study. The participants in this study were all employees of a single construction company. In Japan, all company employees are mandated to undergo annual health checkups, and so we used the data from the annual health checkup records of 2009 and 2012. The health checkups, including the history taking and physical examination, blood and urine examinations, blood pressure measurement (two times), and measurements of the baPWV and r-AI, were conducted in the mornings, after the patients had fasted overnight.

In 2009, 2,792 male employees had undergone health checkups. From this cohort, we excluded 355 patients, as they had atrial fibrillation, suspected peripheral arterial disease, an r-AI value of ≥ 6%, a serum NT-pro-BNP level of ≥ 125 pg/ml, history of alcohol intake of ≥ 20 g/day, or history of treatment for liver disease, chronic kidney disease, heart disease, or stroke; in other words, we excluded patients who already might have had HF and/or a history of heavy drinking. Finally, a total of 2,437 patients were included in this cross-sectional study. Of the 2,437 patients, 1,708 patients were successfully followed up for three years. The present study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Guidelines Committee of Tokyo Medical University (SH3718).

2-2. Measurements

2-2-1. Pulse Wave Velocity

The brachial-ankle PWV was measured using a volume-plethysmographic apparatus (Form/ABI, Colin Co. Ltd., Komaki, Japan), in accordance with a previously described method[9]. In brief, occlusion cuffs, which were connected to both plethysmographic and oscillometric sensors, were tied around both the upper arms and ankles of the patients lying in the supine position. The brachial and post-tibial arterial pressures were measured using the oscillometric sensor. The measurements were conducted after the patients had rested for at least 5 min in the supine position, in a temperature-controlled room (24℃–26℃) designed exclusively for this purpose.

2-2-2. Augmentation Index

Measurements of blood pressure and r-AI were performed after the participants had rested in the sitting position for at least 5 min. Blood pressure was measured in the right upper arm using the oscillometric method (HEM-907; Omron Healthcare, Kyoto, Japan). Immediately after this measurement, the left radial arterial waveform was recorded using an arterial applanation tonometry probe equipped with 40 micropiezo-resistive transducers (HEM-9010 AI; Omron Healthcare). The HEM-9010 AI device is programmed to automatically determine the pressure of the radial artery and yield the optimal radial arterial pressure waveform[10]. Then, the first and second peaks of the peripheral systolic blood pressure (SBP1, a marker of the brachial blood pressure, and SBP2, a marker of the central systolic blood pressure) and peripheral diastolic blood pressure (DBP) were automatically detected using the fourth derivatives of each

radial arterial waveform, and were averaged. The r-AI, a marker of the central AI, was calculated as follows: (SBP2 - DBP)/(SBP1 - DBP) × 100 (%). Pulse pressure 1 (PP1) and PP2, as a marker of the CPP, were also calculated as follows: PP1 = SBP1 - DBP; PP2 = SBP2 – DBP[10].

2-2-3. Laboratory Measurements

Fasting serum concentrations of triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, creatinine (Cr), AST, ALT, and gamma-glutamyl-transferase (GGT), and the fasting plasma glucose (FPG) concentrations were measured using enzymatic methods. PLT was measured using the sheath flow method (Falco Biosystems Co., Ltd., Tokyo, Japan). Serum NT-pro-BNP levels were determined using blood samples obtained in the morning after the participants had fasted overnight. The FIB-4 score was calculated using the following formula: (age [yr] × AST [U/L])/(PLT [10^9/L] × (ALT [U/L])$^{1/2}$), and the cutoff values were as follows (high-progression liver fibrosis: ≥ 2.67; mid-progression liver fibrosis: 1.30–2.67; low-progression liver fibrosis: < 1.30)[11]. The FLI was calculated as follows: ($e^{0.953}$ × loge [TG] + 0.139 × BMI + 0.718 × loge [GGT] + 0.053 × waist circumference - 15.745)/(1 + $e^{0.953}$ × loge [TG] + 0.139 × BMI + 0.718 × loge [GGT] + 0.053 × waist circumference - 15.745) × 100, and the cutoff value was 60[12].

2-3. Statistical Analysis

Data are expressed as the means ± standard deviation (SD). Differences in the variables between the first examination and the second examination were analyzed by–a paired *t*-test or the McNemar test. The delta changes of the variables during the study period were assessed as the values recorded at the second examination minus those recorded at the first examination. In the plotting of the distributions of the variables, the distribution of the serum NT-pro-BNP levels was skewed leftward, whereas the distributions of the other variables were not skewed. Therefore, the serum NT-pro-BNP levels are expressed as the mean ± SD and median values (interquartile range: IQR). In addition, the serum NT-pro-BNP levels were log-transformed (log BNP) for the analyses conducted to examine the relationships. The relationships between the liver scoring systems and the cardiovascular variables/log BNP were assessed using Pearson's correlation analysis and multivariate linear regression analysis with adjustments for covariates, including the age, body mass index, daily alcohol intake, heart rate, systolic blood pressure, serum creatinine, history of medications for hypertension, diabetes mellitus, and/or dyslipidemia (receiving medication = 1; not receiving medication = 0). All of the analyses were performed using the IBM/SPSS software, version 26.0 (IBM/SPSS, Chicago, IL, USA) The statistical significance level was set at $p < 0.05$.

Results

Table 1 shows the clinical characteristics of the study participants at the first examination. Because the distribution of the serum NT-pro-BNP levels was skewed leftward, the mean ± SD and median (IQR) values are shown in **Table 1**. **Table 2** shows the results of Pearson's correlation analysis. FLI showed a negative correlation with the log BNP. Obesity was related to increase in the FLI (i.e., in the present study, FLI showed a significant correlation with the BMI [R = 0.79, $P < 0.01$]); therefore, obesity might act to decrease the serum NT-pro-BNP levels[13]. The results of Pearson's correlation analysis also revealed that the FLI was significantly positively correlated with both the baPWV and r-AI **(Table 2)**. Moreover, multivariate linear regression analysis with adjustments also revealed a significant positive association of the FLI with both the baPWV and the r-AI **(Table 2)**. In addition, at the start of the study period, we divided the patients into two groups according to the value of the FLI (FLI < 60 vs. FLI ≥ 60)[12], i.e., into the non-NAFLD and NAFLD groups. The clinical characteristics of both groups are shown in **Supplementary Table 1**. The adjusted value of the baPWV, but not that of the r-AI, and also that of the serum NT-proBNP level, was higher in the NAFLD group than in the non-NAFLD group **(Fig. 2)**.

As shown in **Table 2**, while Pearson's correlation analysis showed significant positive correlations of the FIB-4 score with the baPWV, r-AI, and log BNP, the results of multivariate analysis with adjustments showed a significant positive relationship of the FIB-4 score only with the log BNP value **(Table 2)**. On the other hand, after the adjustments, the FIB-4 score showed a significant negative relationship with the r-AI **(Table 2)**. The cutoff values of the FIB-4 score were as follows: high-progression liver fibrosis: FIB-4 score ≥ 2.67; mid-progression liver fibrosis: 1.30–2.67; and low progression liver fibrosis: < 1.30[11]. The numbers of patients in the high, mid, and low progression groups were 18, 429, and 1990, respectively. For the purpose of this study, the patients were dichotomized into two groups by the FIB-4 score at the start of the study period, using the cutoff value of 1.30, as follows: high-mid progression group ($n = 447$); low progression group ($n = 1{,}990$). The adjusted value of the serum NT-pro-BNP level in the high-mid progression group was higher than that in the low progression

Table 1. Clinical characteristics of the study subjects at the first examination

Parameter	
Number	2437
Age (y.o.)	46 ± 9
BMI (kg/m^2)	24.0 ± 3
Alcohol intake, ethanol g/day	9.4 ± 6.0
SBP (mm Hg)	123 ± 15
DBP (mm Hg)	76 ± 11
Pulse rate (bpm)	69 ± 10
Hb (g/L)	149 ± 10
PLT (10^9/L)	230 ± 48
AST (U/L)	23 ± 9
ALT (U/L)	27 ± 17
GGT (U/L)	52 ± 46
TC (mmol/L)	5.4 ± 0.9
HDL (mmol/L)	1.6 ± 0.4
TG (mmol/L)	1.4 ± 1.2
FPG (mmol/L)	5.1 ± 0.7
Serum creatinine (μmol/L)	76 ± 10
Serum NT- pro BNP (pg/ml)	24 ± 20
median (IQR)	18 (8-31)
baPWV (cm/sec)	1305 ± 195
r-AI (%)	70 ± 13
FIB-4	1.0 ± 0.5
FLI	35 ± 25
Medication history	
Hypertension: number of subjects (%)	263 (11)
Dyslipidemia: number of subjects (%)	98 (4)
Diabetes mellitus: number of subjects (%)	67 (3)

Abbreviations: BMI: Body mass index; Alcohol intake, ethanol g/day: Alcohol intake per day converted into ethanol equivalent; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb: Hemoglobin; PLT: Platelet count; AST: Serum aspartate aminotransferase; ALT: Serum alanine aminotransferase; GGT: Serum gamma-glutamyl-transferase; TC: Serum total cholesterol; HDL: Serum high-density lipoprotein cholesterol; TG: Serum triglycerides; FPG: Fasting plasma glucose; NT-proBNP: Serum N-terminal of B-type natriuretic peptide; baPWV: brachial-ankle pulse wave velocity; r-AI : Radial augmentation index; FIB-4: Fibrosis 4 score; FLI: Fatty liver index;

Table 2. Pearson's correlation analysis and multivariate linear regression analysis conducted to assess the associations of the FLI and FIB-4 score with the cardiovascular risk markers?

Pearson's correlation analysis			Multivariate linear regression analysis			
Associations of the FLI						
Outcome variables	Correlation coefficient	*p*	Total R-square	Standardized coefficient	Non-standardized coefficient (95% CI)	*p*
baPWV	0.24	< 0.01	0.54	0.16	1.25 (0.89 – 1.61)	< 0.01
r-AI	0.04	0.04	0.43	0.11	0.06 (0.03 – 0.08)	< 0.01
Log BNP	-0.10	< 0.01	-	-	-	-
Associations of the FIB-4 score						
baPWV	0.27	< 0.01	0.53	-0.03×10^{-1}	-1.32 (-15.3 – 12.6)	0.85
r-AI	0.26	< 0.01	0.43	-0.09	-2.42 (-3.45 – -1.39)	< 0.01
Log BNP	0.28	< 0.01	0.15	0.10	0.17 (0.09 – 0.25)	< 0.01

Abbreviations are as described in the footnote for Table 1.

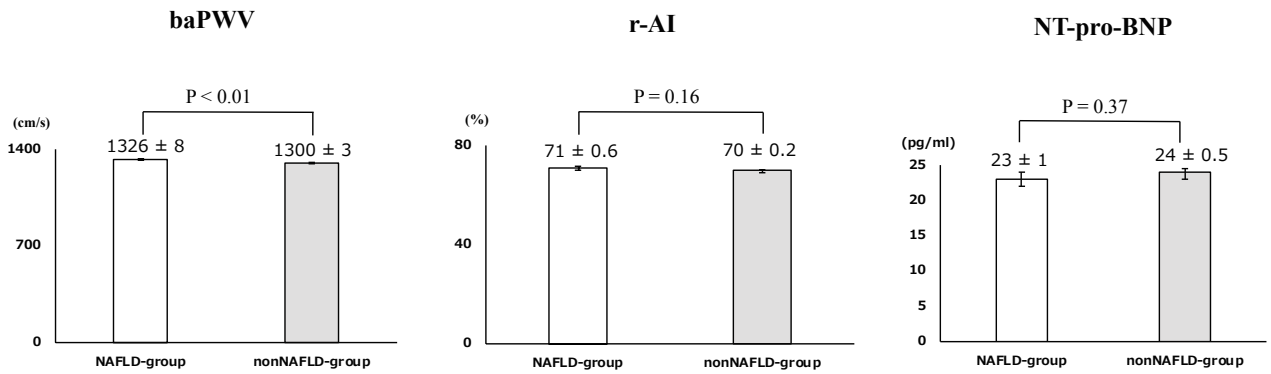

Fig. 2. Comparison of the brachial-ankle pulse wave velocity, radial augmentation index, and serum NT-proBNP level between patients with and without non-alcoholic fatty liver disease

Abbreviations: baPWV = brachial-ankle pulse wave velocity; r-AI = radial augmentation index; NT-pro-BNP = the serum levels of NT-pro-BNP

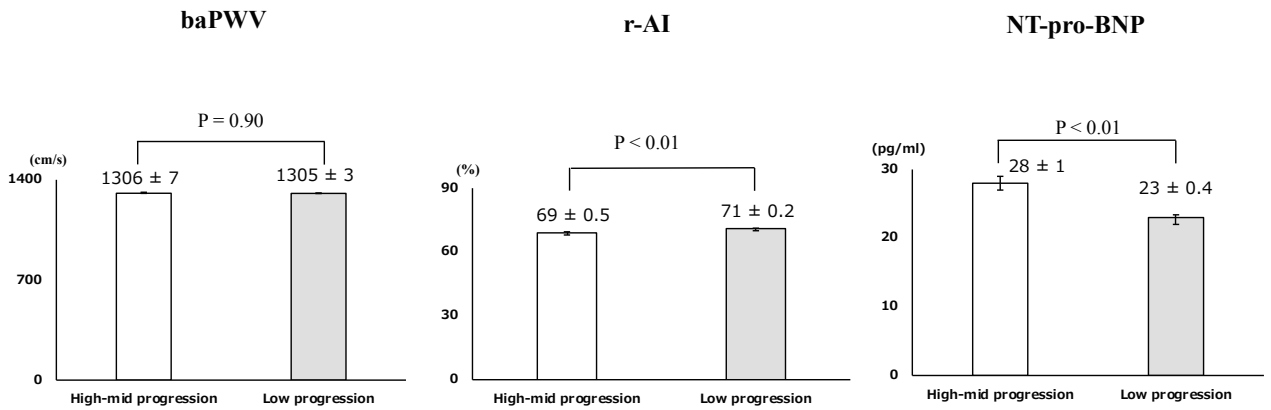

Fig. 3. Comparison of the brachial-ankle pulse wave velocity, radial augmentation index, and serum NT-pro-BNP level between patients with high-mid progression of liver fibrosis and those with low progression of liver fibrosis

group, and the adjusted value of the r-AI in the high-mid progression group was lower than that in the low progression group **(Fig. 3)** The clinical characteristics of the two groups are shown in **Supplementary Table 2**.

Of the patients enrolled in the study, 1,708 patients were followed up successfully until three years later. The values of all of the baPWV, r-AI, FIB-4 score and serum NT-pro-BNP levels recorded at the second examination were higher than those recorded at the first examination **(Table 3)**. The delta change of the FLI during the study period was significantly associated with that of the baPWV **(Table 4)**, according to the multivariate analyses performed with adjustments for changes in the values of the covariates during the study period. On the other hand, the delta change of the FIB-4 score was significantly associated with that of the serum NT-pro-BNP level **(Table 4)**.

Discussion

The present study is the first prospective observational study performed to assess the difference in the association of the FLI, as compared to that of the FIB-4 score, with the pathophysiological abnormalities associated with the risk of development of CVD in Japanese men without any prior history of CVD. The results revealed that, while the FIB-4 score was associated with the serum NT-pro-BNP levels, the FLI was associated with the baPWV.

Fatty liver is the most prevalent chronic liver disease in the world[1, 2], and NAFLD is also known as a risk factor for CVD, including HF[4, 5]. Some liver scoring systems are available to assess the grades of fatty liver and liver fibrosis. However, the individual relationships of the two liver scoring systems with the pathophysiological abnormalities associated with the risk of development of CVD, including HF, have not yet been fully clarified. The FLI, a surrogate marker of

Table 3. Clinical characteristics of the study subjects in the longitudinal study

Parameter	First examination	Second examination
Number	1708	1708
Age (y.o.)	45 ± 9	48 ± 9*
BMI (kg/m^2)	24.0 ± 3	24.1 ± 3*
Alcohol intake, ethanol g/day	9.4 ± 6.0	17.2 ± 16*
SBP (mm Hg)	122 ± 14	121 ± 14*
DBP (mm Hg)	76 ± 11	73 ± 11*
Pulse rate (bpm)	68 ± 9	68 ± 10*
Hb (g/L)	149 ± 10	147 ± 9*
PLT (10^9/L)	230 ± 48	228 ± 47*
AST (U/L)	26 ± 17	24 ± 10
ALT (U/L)	26 ± 17	27 ± 19
GGT (U/L)	51 ± 44	50 ± 48
TC (mmol/L)	5.4 ± 0.9	5.4 ± 0.8
HDL (mmol/L)	1.6 ± 0.4	1.7 ± 0.4*
TG (mmol/L)	1.4 ± 1.3	1.4 ± 1.0
FPG (mmol/L)	5.1 ± 0.6	5.1 ± 0.7
Serum creatinine (μmol/L)	76 ± 9	74 ± 10*
Serum NT- pro-BNP (pg/ml)	23 ± 20	30 ± 28*
median (IQR)	17 (8 - 30)	23 (14-38)
baPWV (cm/sec)	1288 ± 181	1315 ± 197*
r-AI (%)	70 ± 13	72 ± 13*
FIB-4	1.0 ± 0.4	1.1 ± 0.5*
FLI	35 ± 25	34 ± 25
Medication history		
Hypertension: number of subjects (%)	157 (9)	233 (14)*
Dyslipidemia: number of subjects (%)	61 (4)	108 (6)*
Diabetes mellitus: number of subjects (%)	43 (3)	64 (4)*

*$p < 0.01$ vs. First examination
Abbreviations are as described in the footnote for Table 1.

Table 4. Associations of the changes in the FLI and FIB-4 score with the changes in the values of the cardiovascular risk markers during the study period

	Pearson's correlation analysis		Multivariate linear regression analysis			
Outcome variables	Correlation coefficient	p	Total R-square	Standardized coefficient	Non-standardized coefficient (95% CI)	p
of ΔFLI						
ΔbaPWV	0.11	< 0.01	0.23	0.08	0.62 (0.13 – 1.11)	0.01
Δr-AI	0.01	0.83	-	-	-	-
ΔBNP	-0.05	0.04	-	-	-	-
of ΔFIB-4						
ΔbaPWV	0.01	0.71	-	-	-	-
Δr-AI	0.01	0.69	-	-	-	-
ΔBNP	0.10	< 0.01	0.02	0.09	0.91 (0.43 – 1.40)	< 0.01

Abbreviations are as described in the footnote for Table 1.

fatty liver[12], has been reported to be associated with the incidence of coronary heart disease and early atherosclerosis in patients without prior history of CVD[7, 14]. While the present study demonstrated a significant association of the FLI with the baPWV, a recent individual-participants data meta-analysis reported that the baPWV is an independent risk factor for the development of CVD[15]. Further studies are needed to clarify whether the FLI is a useful marker for cardiovascular risk screening in the general population because the estimated prevalence of NAFLD in the general population is as high as 20%–30%[16].

NAFLD refers to a spectrum of entities ranging from fatty liver, which is considered as a benign disease, to steatohepatitis, which indicates ongoing injury to the liver, to cirrhosis of the liver. Thus, fatty liver, reflected by FLI, and liver fibrosis, reflected by the FIB-4 score, might reflect different facets of the pathophysiological abnormalities associated with chronic liver disease[17]. However, whether FLI and FIB-4 score indeed reflect difference facets of the pathophysiological abnormalities associated with the development of CVD has not yet been fully clarified. The serum NT-pro-BNP levels are a useful marker to predict the development of HF, and arterial stiffness, which was associated with the FLI in the present study, is a known risk factor for the development of HF[18, 19]. Based on these findings, it is possible that FLI, via its association with the arterial stiffness, reflects the risk of development of HF associated with fatty liver. However, it was the FIB-4 score, rather than the FLI, that was significantly associated with the serum NT-pro-BNP levels and the changes of these levels during the study period. Thus, in healthy patients, the FLI and FIB-4 score may reflect different facets of the pathophysiological abnormalities associated with the development of CVD.

Consistent with our present findings, Cicero AFG *et al.* have already reported the existence of a significant association of the FLI with the arterial stiffness[6]. In this study, we could not clarify the mechanisms underlying the significant association of the arterial stiffness with the FLI. Fatty liver may not only be a marker of the insulin resistance, but also may be involved in its pathogenesis[20]. This pathogenetic process may be mediated by systemic release of pro-atherogenic factors from the inflamed liver[20]. In addition to explaining the significant association of the FLI with the arterial stiffness, this could be the reason why NAFLD is associated with the mortality from CVD.

As described above, we found that the FIB-4 score was significantly associated with the log BNP, but not with the baPWV. Plausible explanations for these findings are as follows: 1) The FIB-4 score is a marker of liver fibrosis. Proliferation of collagen fibers is a key element in liver fibrosis, and it is possible that similar proliferation in the arterial wall could be expected to increase the arterial stiffness. However, in the present study, we found no significant association of the FIB-4 score with the baPWV. Therefore, the FIB-4 score might be a marker of the extent of fibrosis in the liver alone, and not a systemic fibrosis marker; 2) in addition to cardiac afterload, increased cardiac preload is also thought to affect the serum NT-pro-BNP levels[21]. One of the key contributors to venous capacitance function, liver fibrosis causes compromised capacitance of the splanchnic vasculature[22], and could increase the cardiac filling pressure and increase the serum NT- pro-BNP levels.

Study Limitations

The present study had several limitations. Firstly, the patients were all men; whether the associations observed in the present study may also be applicable to females needs to be clarified. Studies are therefore needed to examine the associations in female patients, as well as in other races. Secondly, we used FLI as a marker of fatty liver and FIB-4 score as a marker of liver fibrosis, but did not evaluate fatty liver or liver fibrosis by liver biopsy or imaging examinations (e.g., elastography, CT, MRI, etc.). Thirdly, in the present study, we excluded patients with liver disease, chronic kidney disease, heart disease, and stroke, but only a questionnaire survey and not qualitative/quantitative examinations were used to assess the patients for the presence/absence of these diseases. Fourthly, of the 2,437 patients enrolled in this cross-sectional study, data of only 1,708 patients were available for the longitudinal study, as before the follow-up could be completed the remaining patients were transferred from the head office to branch offices or were retired. Fifthly, the FLI was associated with the r-AI in the present cross-sectional analysis, but not in the longitudinal analysis. Further study is needed to clarify whether the FLI may also reflect the pathophysiological abnormalities reflected by abnormal pressure wave reflection. Sixth, unexpectedly, the FIB4 score showed a negative relationship with the r-AI; we could not clarify any such confounding variables in the present study, while some confounding variables could have led to this negative relationship.

Conclusion

Liver scoring systems may individually reflect the pathophysiological abnormalities associated with the risk of development of CVD. Our results suggested that while the FIB-4 score may serve as a marker of

the risk of development of heart failure, the FLI may be a marker of the increased arterial stiffness in middle-aged Japanese men without prior history of CVD.

Acknowledgement

This work was supported by Omron Health Care Company (Kyoto, Japan).

Disclosure

Omron Health Care Company assisted in the data formatting, (i.e., the data on the baPWV stored in the equipment used for measurement of the baPWV were transferred to an Excel sheet). However, this company was not involved in the planning of or analysis in the present study, or in the preparation of this manuscript. The authors have no other conflicts of interests to declare.

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Supplementary Table 1. Clinical characteristics of the study subjects in the NAFLD and Non-NAFLD groups at the first examination

Parameter	NAFLD	Non-NAFLD
Number	470	1967
Age (y.o.)	47 ± 9	45 ± 10*
BMI (kg/m^2)	27.7 ± 3	23.1 ± 2*
Alcohol intake, ethanol g/day	10.8 ± 6.2	9.0 ± 6*
SBP (mm Hg)	123 ± 15	121 ± 14*
DBP (mm Hg)	82 ± 11	75 ± 11*
Pulse rate (bpm)	70 ± 10	68 ± 10*
Hb (g/L)	153 ± 10	148 ± 9*
PLT (10^9/L)	238 ± 51	228 ± 48*
AST (U/L)	30 ± 13	22 ± 7*
ALT (U/L)	42 ± 25	23 ± 12*
GGT (U/L)	96 ± 70	41 ± 29*
TC (mmol/L)	5.7 ± 0.9	5.3 ± 0.8*
HDL (mmol/L)	1.4 ± 0.3	1.7 ± 0.4*
TG (mmol/L)	2.5 ± 2.0	1.2 ± 0.6*
FPG (mmol/L)	5.3 ± 0.9	5.0 ± 0.6*
Serum creatinine (μmol/L)	77 ± 10	76 ± 9
Serum NT- pro-BNP (pg/ml)	21 ± 18	25 ± 21*
median (IQR)	16 (6-27)	19 (9-32)
baPWV (cm/sec)	1368 ± 210	1291 ± 188*
r-AI (%)	70 ± 12	70 ± 13
FIB-4	1.0 ± 0.5	1.0 ± 0.5
FLI	76 ± 11	26 ± 16*
Medication history		
Hypertension: number of subjects (%)	96 (20)	167 (8)*
Dyslipidemia: number of subjects (%)	41 (9)	57 (3)*
Diabetes mellitus: number of subjects (%)	32 (7)	35 (2)*

*$p < 0.01$ vs. NAFLD
Abbreviations are as described in the footnote for Table1.

Supplementary Table 2. Clinical characteristics of the study subjects in the High-mid progression group and Low progression group at the fist examination

Parameter	High-mid progression	Low progression
Number	447	1990
Age (y.o.)	56 ± 6	43 ± 8*
BMI (kg/m^2)	23.7 ± 3	24.0 ± 3
Alcohol intake, ethanol g/day	9.3 ± 5	9.4 ± 6
SBP (mm Hg)	127 ± 17	122 ± 14*
DBP (mm Hg)	79 ± 12	76 ± 11*
Pulse rate (bpm)	68 ± 10	69 ± 10
Hb (g/L)	147 ± 11	149 ± 9*
PLT (10^9/L)	186 ± 34	240 ± 46*
AST (U/L)	28 ± 14	22 ± 7*
ALT (U/L)	26 ± 19	27 ± 17
GGT (U/L)	58 ± 54	50 ± 43
TC (mmol/L)	5.5 ± 0.9	5.4 ± 0.9
HDL (mmol/L)	1.8 ± 0.5	1.6 ± 0.4*
TG (mmol/L)	1.4 ± 1.0	1.4 ± 1.2
FPG (mmol/L)	5.3 ± 0.8	5.0 ± 0.7*
Serum creatinine (μmol/L)	77 ± 11	76 ± 9
Serum NT- pro-BNP (pg/ml)	34 ± 25	22 ± 18*
median (IQR)	27 (16-46)	16 (7-28)
baPWV (cm/sec)	1404 ± 225	1283 ± 180*
r-AI (%)	77 ± 12	69 ± 13*
FIB-4	1.7 ± 0.6	0.8 ± 0.2*
FLI	36 ± 25	35 ± 25
Medication history		
Hypertension: number of subjects (%)	92 (21)	171 (9)*
Dyslipidemia: number of subjects (%)	29 (6)	69 (3)
Diabetes mellitus: number of subjects (%)	25 (6)	42 (2)*

*$p < 0.01$ vs. High-mid progression
Abbreviations are as described in the footnote for Table1.