Fatty Liver Index is Positively Associated with Arterial Stiffness in a Chinese Cohort Undergoing Health Assessment

Yueliang Hu[1†], Huijuan Chao[1†], Jiehui Zhao[2], Qian Wang[1], Biwen Tang[1] , Isabella Tan[3], Mark Butlin[3], Alberto Avolio[3], Peizhan Chen[4*] and Junli Zuo[1,3*]

Abstract

Objective: Nonalcoholic fatty fiver disease (NAFLD) is a metabolic liver injury closely related to insulin resistance. Fatty liver index (FLI) can be used as a surrogate marker and is a validated index for NAFLD. This study aimed to explore the relationship between FLI and arterial stiffness in a Chinese population.

Methods: From December 2017 to March 2019, 402 inpatients (mean age 51.12 ± 11.95 years) were recruited for cardiovascular disease screening at Ruijin Hospital North, Shanghai. Measurement of brachial systolic, diastolic, mean, and pulse pressure was done with cuff sphygmomanometry and carotid-femoral pulse wave velocity (cfPWV) was measured (SphygmoCor) to assess arterial stiffness.

Results: Subjects were divided into three groups according to their FLI < 30, normal; 30–59, intermediate fatty liver index; ≥ 60, NAFLD. The proportion of subjects with hepatic steatosis (FLI ≥ 60), intermediate FLI (30–59), and no steatosis (FLI < 30) was 34.4%, 31.8%, and 33.8%, respectively. The male population (53.9%) had significantly higher FLI levels ($p < 0.05$). Subjects with FLI ≥ 60 had higher cfPWV (8.41 ± 1.77 m/s) than those with FLI < 30 (7.81 ± 1.83 m/s; $p = 0.006$). cfPWV was positively correlated with logFLI ($r = 0.168$, $p = 0.001$). After adjusting for age, sex, body mass index, mean arterial blood pressure, glucose, cholesterol, heart rate, and glomerular filtration rate (eGFR), FLI remained positively associated with cfPWV ($\beta = 0.097$, $p = 0.024$).

Conclusion: cfPWV, as a measure of arterial stiffness, is higher in the NAFLD group when compared to that in normal groups. Fatty liver index is positively associated with arterial stiffness in a Chinese population.

Keywords: Nonalcoholic fatty liver disease, Fatty liver index, Arterial stiffness, Carotid-femoral pulse wave velocity

1 Introduction

Nonalcoholic fatty fiver disease (NAFLD) is a metabolic liver injury closely related to insulin resistance and genetic susceptibility [1]. NAFLD is the most common chronic liver disease in the world. The prevalence of NAFLD in most Asian countries (including China) is at the upper-middle level (14.76–43.91%, average 27.37%) [1, 2]. Based on China's large population, the number of patients may reach hundreds of millions.

Pathologically significant hepatic steatosis is an important feature of NAFLD. The degree of hepatic steatosis is closely related to hepatic inflammatory damage and fibrosis. For the diagnosis of NAFLD, conventional non-invasive diagnostic methods have their own advantages and disadvantages [1]. The accuracy of B-mode

*Correspondence: pzchen@me.com; zuo-junli@163.com
†Yueliang Hu and Huijuan Chao contributed equally to this study.
[1] Department of Geriatric Medicine, Ruijin Hospital, Shanghai Jiao Tong School of Medicine, No. 999, Xiwang Road, Shanghai, China
[4] Clinical Research Center, Ruijin Hospital, Shanghai Jiao Tong School of Medicine, No. 999, Xiwang Road, Shanghai, China
Full list of author information is available at the end of the article

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ultrasound, X-ray computed tomography (CT), and magnetic resonance imaging (MRI) is similar and slightly lower. Controlled attenuation parameter (CAP) can accurately distinguish mild, moderate, and severe hepatic steatosis, but it is easier to overestimate the degree of hepatic steatosis. Magnetic resonance spectroscopy (MRS) is highly accurate, but costly and difficult to popularize. Fatty liver index (FLI) uses a combination of body mass index (BMI), waist circumference, serum triglyceride, and γ-glutamyl transferase (GGT) levels and can be used as an alternative tool for imaging diagnosis of fatty liver. It has the advantage of being non-invasive and convenient. Studies have confirmed that FLI has an acceptable capability of predicting the occurrence of new cases of NAFLD [3].

Pulse wave velocity (PWV) has been widely used as a non-invasive measure of arterial stiffness to predict cardiovascular adverse events and all-cause mortality in unselected populations [4, 5]. This study used FLI to screen and diagnose NALFD in Chinese participants, as well as to examine the impact of NAFLD on early cardiovascular risk indicators such as PWV. We aimed to explore the relationship between FLI and arterial stiffness in a Chinese population. We hoped to provide new tools for screening cardiovascular risk in Chinese NAFLD patients.

2 Materials and Methods

2.1 Study Participants

From December 2017 to March 2019, a total of 402 undergoing health assessment (mean age 51.12 ± 11.95 years) were recruited from the Ruijin Hospital North Affiliated to Shanghai Jiaotong University School of Medicine. Inclusion criteria were subjects aged > 30 years and the absence of pregnancy. The exclusion criteria were (1) excessive alcohol intake (alcohol consumption > 14 g/week for men and > 7 g/week for women); (2) secondary causes of steatosis (e.g., corticosteroid use, gastric bypass surgery); (3) seropositive for hepatitis B surface antigen or anti-hepatitis C virus antibody; (4) underlying genetic or metabolic diseases influencing the liver, such as Wilson's disease, alpha 1-antitrypsin deficiency, genetic hemochromatosis, and autoimmune diseases; (5) missing data for tFLI; (6) use of medications associated with fatty liver within the past 3 months.

The study protocol was reviewed and approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. All subjects provided written informed consent.

2.2 Data Collection

All subjects participated in a demographic survey, physical examination, and blood tests. The demographic survey assessed the history of systemic or genetic diseases, medical history, family disease history, and alcohol intake. The physical examination evaluated and checked blood pressure, body weight, body height, and waist girth (circumference). BMI (kg/m^2) was calculated as weight (kg) divided by squared height (m). Body weight was measured on a calibrated balance to the nearest 0.1 kg while subjects wore minimum clothing and without shoes. Height was measured using a wall-mounted stadiometer to the nearest 0.5 cm without shoes. Waist circumference (WC) was measured at the midpoint between the lowest rib margin and the iliac crest with the subject standing and at the maximum point of normal expiration using an upstretched tape measure and recorded to the nearest 0.1 cm. Blood pressure measurements were obtained in 12-h fasting individuals in a seated position in the morning (7–9 a.m.) using a standard manual sphygmomanometer after a 10-min rest. The retained values were the average of the two readings (left and right arm). The mean arterial pressure (MAP) was calculated as $(PDP) + ((PSP - PDP)/3)$. Pulse pressure (PP) was calculated as the difference between PSP and PDP.

Blood samples were obtained from each participant during the study by the same team of trained nurses and using the same equipment after 12–14 h of overnight fasting using a Hitachi automatic analyzer 7600 (Hitachi Corp., Tokyo, Japan). Blood tests included complete blood cell count; liver biochemistry test, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and GGT; renal biochemistry test including serum creatinine (Cr) and serum uric acid (UA); fasting sugar (FBG); lipid profiles, including serum total cholesterol (TC), high-density lipoprotein cholesterol (LDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). The HBV antigens were determined using an E-170 assay (Roche, Mannheim, Germany).

The FLI was estimated using the algorithm which was reported by [6, 7]. The formula of FLI was as follows:

$$\text{FLI} = \left(e^{(0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745)} \right) / \left(1 + e^{(0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745)} \right) \times 100,$$

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where TG denotes TGs (mg/dL), GGT is γ-glutamyl transferase (U/L), and WC is the waist circumference (cm).

FLI was used for hepatic steatosis evaluation and was expressed as a value ranging from 0 to 100. FLI values were classified into three categories: < 30, 30–59, and ≥ 60 [6]. FLI values of < 30 and ≥ 60 would rule out and confirm the presence of hepatic steatosis, respectively.

Patients fasted overnight, and no caffeine beverage or smoking was allowed within 3 h of the measurement. cfPWV was measured using the delay between the ECG and the tonometric signal registered consecutively at the carotid and femoral arteries. (SphygmoCor, AtCor Medical, Sydney, Australia). cfPWV was calculated as the ratio of path length to transit time using the subtraction method between the carotid and femoral sites of measurements and pulse transit time was calculated as a direct delay between the two waves [6]. The subtraction method is associated with a cut-off threshold of 10 m/s. Following the measurement of office blood pressure, the carotid and femoral arterial waveforms at the patient's right side were recorded by applanation tonometry sequentially a short time apart by trained investigators.

2.3 Statistical Analysis

All analyses were performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant. Continuous variables are expressed as mean ± SD. One-way ANOVA analyses were used for comparisons across the three FLI groups. Pearson's coefficient correlation was used to assess the relations between logFLI and cfPWV, respectively. The relationships between the FLI and arterial stiffness values of the participants were evaluated using univariate linear models. The multiple linear regression model was applied to determine whether the FLI was independently associated with arterial stiffness in the participants adjusted for age, sex, body mass index, MAP, fasting blood glucose, total cholesterol, HR, and eGFR. Association between individual FLI with the presence of high cfPWV was assessed by means of logistic regression analysis with odds ratio (OR) calculation adjusted for confounding factors.

Table 1 Characteristics of the study subjects

Characteristics	Total (n = 402)	Men (n = 240)	Women (n = 162)	*p* value
Age, years	51.12 ± 11.95	49.86 ± 11.60	52.99 ± 12.26	0.010
BMI/(kg/m²)	25.50 ± 4.00	26.05 ± 3.74	24.69 ± 4.23	0.001
Waist (cm)	90.46 ± 10.67	93.69 ± 8.73	85.48 ± 11.32	< 0.001
Glucose (mmol/L)	5.76 ± 1.78	5.80 ± 1.76	5.68 ± 1.81	0.504
Triglycerides (mmol/L)	1.95 ± 1.30	2.15 ± 1.41	1.66 ± 1.05	< 0.001
Total cholesterol (mmol/L)	4.91 ± 1.04	4.80 ± 1.00	5.08 ± 1.10	0.007
LDL-C (mmol/L)	3.27 ± 0.80	3.20 ± 0.72	3.38 ± 0.88	0.036
HDL-C (mmol/L)	1.19 ± 0.44	1.09 ± 0.40	1.35 ± 0.45	< 0.001
ALT (IU/L)	24 (16–36)	28 (19–38)	18 (13–29)	*0.003*
AST (IU/L)	23 (19–29)	23 (20–29)	22 (18–28)	*0.876*
γ-GT (IU/L)	28 (18–46)	33 (22–51)	19 (13–33)	< 0.001
Creatinine (μmol/L)	77.11 ± 16.35	84.37 ± 16.42	66.42 ± 8.53	< 0.001
eGFR (mL/min·1.73 m²)	90.00 ± 15.76	91.32 ± 17.02	88.06 ± 13.50	0.043
PSP (mmHg)	132.59 ± 17.99	133.19 ± 15.90	131.70 ± 20.72	0.415
PDP (mmHg)	77.50 ± 12.33	78.64 ± 11.95	75.82 ± 12.72	0.024
PP (mmHg)	55.09 ± 13.07	54.55 ± 11.91	55.88 ± 14.64	0.320
MAP (mmHg)	95.86 ± 13.08	96.82 ± 12.16	94.45 ± 14.26	0.074
cfPWV	8.23 ± 1.86	8.33 ± 1.88	8.08 ± 1.82	0.187
HR	70.37 ± 10.56	69.72 ± 9.97	71.34 ± 11.33	0.132
FLI	45 (20–71)	57 (33–77)	36 (11–52)	< 0.001

Data are mean ± SD, median and interquartile range or percentage as marked. *P* value: independent *t* test analysis of variance for numeric variables and chi-squared test for categoric variables

Abbreviations: *FLI* fatty liver index, *ALT* alanine transaminase, *AST* aspartate transaminase, *γ-GT* gamma-glutamyl-transferase, *BMI* body mass index, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *PSP* peripheral systolic blood pressure, *PDP* peripheral diastolic blood pressure, *MAP* mean arterial pressure, *cfPWV* carotid-femoral pulse wave velocity, *eGFR* estimated glomerular filtration rate; *HR* heart rate, *PP* Pulse pressure

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3 Results

Baseline characteristics of participants are shown in Table 1. Among the 402 subjects, 240 were male (59.3%). Mean age for males and females was 49.86 ± 11.60 and 52.99 ± 12.26 years, respectively. The male population had a significantly larger waist circumference, greater BMI, higher triglycerides, a lower total cholesterol driven by lower HDL-cholesterol, higher uric acid, higher creatinine, higher diastolic blood pressure, higher liver enzymes (ALT, and GGT), and higher FLI levels ($p < 0.05$).

Table 2 shows the baseline characteristics according to FLI category. The proportion of subjects with hepatic steatosis (FLI $\geq$ 60), intermediate FLI (30–59), and no steatosis (FLI < 30) was 34.4%, 31.8%, and 33.8%, respectively. A total of 138 (34.4%) subjects had NAFLD as assessed by FLI ($\geq$ 60), and 136 (33.8%) subjects did not have NAFLD (FLI < 30). Subjects with FLI $\geq$ 60 were younger, they also had higher rates of unfavorable body composition (higher BMI and waist circumference; $p < 0.001$), higher fasting blood glucose ($p = 0.001$), higher uric acid ($p < 0.001$), higher

creatinine ($p < 0.001$), and their liver enzymes were more elevated than in the other groups (ALT, AST, and GGT; $p < 0.001$). Subjects with FLI $\geq$ 60 also had adverse lipid profile (higher levels of TG, higher levels of LDL cholesterol and lower values of HDL-cholesterol; $p < 0.001$, $p = 0.023$, and $p < 0.001$, respectively). Moreover, subjects with FLI $\geq$ 60 had higher systolic (PSP) and diastolic (PDP) blood pressure than those with FLI < 30 ($p = 0.001$ and $p < 0.001$, respectively). Finally, subjects with FLI $\geq$ 60 also had higher cfPWV than those with FLI < 30 ($p = 0.006$).

Pearson's correlation (Table 3) showed cfPWV and log-FLI were all positively correlated with BMI, waist, fasting blood glucose, triglycerides, creatinine, PSP, PDP, and MAP ($p < 0.05$). There was a positive correlation between cfPWV and logFLI ($r = 0.168$, $p = 0.001$). Using cfPWV as the independent continuous variable in multiple linear regression, age ($\beta = 0.505$, $p < 0.001$), FLI ($\beta = 0.126$, $p = 0.003$), and MAP ($\beta = 0.298$, $p < 0.001$) were all positively associated with cfPWV. After adjusting for confounding factors such as age, sex, body mass index, MAP, fasting blood glucose, total cholesterol, HR, and eGFR,

Table 2 Baseline characteristics of the subjects according to FLI categorical variables

Characteristics	Total ($n = 402$)	FLI categories			*p* value
		< 30 ($n = 136$)	30–59 ($n = 128$)	$\geq$ 60 ($n = 138$)	
Age, years	51.12 ± 11.95	51.27 ± 13.48	53.28 ± 11.51	48.98 ± 10.36	*0.013*
BMI/(kg/m^2)	25.50 ± 4.00	22.29 ± 2.52	25.52 ± 2.63	28.65 ± 3.73	*< 0.001*
Waist (cm)	90.46 ± 10.67	81.10 ± 8.47	90.75 ± 6.09	99.41 ± 7.78	*< 0.001*
Glucose (mmol/L)	5.76 ± 1.78	5.47 ± 1.61	5.68 ± 1.31	6.14 ± 2.21	0.002
Triglycerides (mmol/L)	1.95 ± 1.30	1.19 ± 0.45	1.76 ± 0.84	2.88 ± 1.60	*< 0.001*
Total cholesterol (mmol/L)	4.91 ± 1.04	4.80 ± 0.84	4.89 ± 1.09	5.05 ± 1.15	0.129
LDL-C (mmol/L)	3.27 ± 0.80	3.13 ± 0.78	3.29 ± 0.80	3.38 ± 0.77	0.043
HDL-C (mmol/L)	1.19 ± 0.44	1.33 ± 0.47	1.18 ± 0.43	1.07 ± 0.38	*< 0.001*
ALT (IU/L)	24 (16–36)	15 (12–21)	26 (19–35)	34.5 (24–47)	*< 0.001*
AST (IU/L)	23 (19–29)	20 (17–24)	24 (20–29)	25 (20–33)	*< 0.001*
γ-GT (IU/L)	28 (18–46)	16 (13–22)	27 (21–39)	47 (32–66)	*< 0.001*
Creatinine (µmol/L)	77.11 ± 16.35	71.93 ± 12.42	78.98 ± 14.22	80.56 ± 20.07	*< 0.001*
eGFR (mL/min·1.73 m^2)	90.00 ± 15.76	90.91 ± 13.31	86.99 ± 13.72	91.89 ± 19.12	*0.030*
PSP (mmHg)	132.59 ± 17.99	128.05 ± 19.40	135.05 ± 16.72	134.78 ± 16.92	*0.001*
PDP (mmHg)	77.50 ± 12.33	72.95 ± 11.78	79.22 ± 12.57	80.40 ± 11.39	*< 0.001*
PP (mmHg)	55.09 ± 13.07	55.10 ± 14.41	55.83 ± 12.84	54.38 ± 11.91	*0.668*
MAP (mmHg)	95.86 ± 13.08	91.32 ± 13.11	97.83 ± 12.72	98.53 ± 12.26	*< 0.001*
cfPWV (m/s)	8.23 ± 1.86	7.81 ± 1.83	8.49 ± 1.91	8.41 ± 1.77	*0.005*
HR (bpm)	70.37 ± 10.56	69.40 ± 11.21	70.25 ± 10.80	71.45 ± 9.60	*0.271*
FLI	45 (20–71)	14 (8–21)	44 (35–53)	79 (70–87)	*< 0.001*
logFLI	1.53 ± 0.38	1.08 ± 0.29	1.64 ± 0.09	1.89 ± 0.06	*< 0.001*

Data are mean $\pm$ SD or percentage or median and interquartile range as marked. *P* value: independent *t* test analysis of variance for numeric variables and chi-squared test for categoric variables

Abbreviations: *FLI* fatty liver index, *ALT* alanine transaminase, *AST* aspartate transaminase, *γ-GT* gamma-glutamyl-transferase, *BMI* body mass index, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *PSP* peripheral systolic blood pressure, *PDP* peripheral diastolic blood pressure, *MAP* mean arterial pressure, *cfPWV* carotid-femoral pulse wave velocity, *eGFR* estimated glomerular filtration rate, *HR* heart rate, *PP* Pulse pressure

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Table 3 Relationship between FLI and PWV

Variable	PWV		logFLI	
	r value	*p* value	*r* value	*p* value
Age, y	0.503	< 0.001	− 0.040	0.426
BMI/(kg/m²)	0.090	0.072	0.683	< 0.001
Waist (cm)	0.133	0.007	0.779	< 0.001
Glucose (mmol/L)	0.193	< 0.001	0.193	< 0.001
Triglyceride (mmol/L)	0.135	0.007	0.523	< 0.001
Total cholesterol (mmol/L)	− 0.051	0.307	0.122	0.015
LDL-C (mmol/L)	− 0.060	0.245	0.138	0.008
HDL-C (mmol/L)	− 0.049	0.343	− 0.351	< 0.001
ALT (IU/L)	0.010	0.847	0.454	< 0.001
AST (IU/L)	0.043	0.391	0.213	< 0.001
γ-GT (IU/L)	0.107	0.032	0.454	< 0.001
Creatinine (μmol/L)	0.154	0.002	0.237	< 0.001
eGFR	− 0.207	< 0.001	0.019	0.701
PSP (mmHg)	0.450	< 0.001	0.195	< 0.001
PDP (mmHg)	0.254	< 0.001	0.271	< 0.001
PP (mmHg)	0.379	< 0.001	0.013	0.794
MAP (mmHg)	0.402	< 0.001	0.260	< 0.001
logFLI	0.168	0.001		
PWV			0.168	0.001

FLI fatty liver index, *ALT* alanine transaminase, *AST* aspartate transaminase, *GGT* gamma-glutamyl-transferase, *BMI* body mass index, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *PSP* peripheral systolic blood pressure, *PDP* peripheral diastolic blood pressure, *MAP* mean arterial pressure, *cfPWV* carotid-femoral pulse wave velocity

Table 4 Linear regression analysis of associations between PWV and FLI

Variable	Standardized *β*-values	cfPWV (cm/s)		
		p value	95% CI	R^2
Model 1				0.379
Age, years	0.505	< 0.001	0.066–0.091	
FLI	0.126	0.003	0.003–0.014	
MAP (mmHg)	0.298	< 0.001	0.031–0.054	
Model 2				0.379
Age, years	0.502	< 0.001	0.066–0.091	
FLI	0.118	0.005	0.002–0.013	
MAP (mmHg)	0.301	< 0.001	0.031–0.054	
Model 3				0.380
Age, years	0.483	< 0.001	0.063–0.088	
FLI	0.097	0.024	0.001–0.012	
MAP (mmHg)	0.301	< 0.001	0.031–0.054	
Glucose (mmol/L)	0.092	0.026	0.012–0.180	

Model 1 adjusting for age, sex, body mass index, MAP, HR, and eGFR

Model 2 adjusting for age, sex, body mass index, MAP, total cholesterol, HR, and eGFR

Model 3 adjusting for age, sex, body mass index, MAP, total cholesterol, glucose, HR, and eGFR

Abbreviations: *FLI* fatty liver index, *MAP* mean artery blood pressure, *cfPWV* carotid-femoral pulse wave velocity

there was a positive association between FLI and cfPWV ($\beta = 0.097$, $p = 0.024$) (Table 4).

After adjusting for confounding variables, the OR of elevated cfPWV was not significantly higher with intermediate FLI or hepatic steatosis, compared those with FLI < 30 (Table 5).

In the comparison of males and females in the each FLI groups, the cfPWV for females is significantly higher with increasing FLI category (Fig. 1).

4 Discussion

Arterial stiffness, endothelial dysfunction and early atherosclerosis are markers and independent predictors of cardiovascular disease. Many studies have shown that FLI is associated with early atherosclerosis [8–10] and endothelial dysfunction [11–14]. Clarification of the association between NAFLD and arterial stiffness, with the involvement of NAFLD having an effect on cardiovascular disease will provide novel potentially different mechanisms for the prevention and treatment of NAFLD leading to cardiovascular events. NAFLD may cause cardiovascular disease in two ways [1]. First, NALFD is a systemic sub-inflammatory state. Acute or chronic

systemic inflammation may impair vascular endothelial function and worsen arterial function [15]. Hence, it is manifested as a significant correlation between FLI and PWV. Specifically, FLI is a manifestation of the severity of NAFLD, and the change of PWV is the result of systemic disease of NAFLD. Second, NAFLD may cause insulin resistance and atherogenic dyslipidemia which is associated with chronic hyperglycemia and hyperinsulinemia. And these changes may increase the local activity of the renin–angiotensin–aldosterone system and the expression of the angiotensin type I receptor, leading to hypertrophy of vascular wall and fibrosis [16].

The relationship between NAFLD and arterial stiffness may be mutually influenced [16]. NAFLD may accelerate the progression of arterial stiffness and increased arterial stiffness may result in a disruption of the hepatic artery buffer response that maintains metabolic homeostasis. This may lead NAFLD in the direction of advanced liver fibrosis [17].

This study found that subjects with NAFLD (FLI ≥ 60) had higher cfPWV than those with FLI < 30. In addition, we found that the intermediate fatty liver index group had higher age and blood pressure, which is the main dependency factor of cfPWV. Thus between groups 2 (FLI 30–60) and 3 (FLI ≥ 60), the relationship seems absent. However, the quadratic FLI term was not found

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Table 5 Odds ratios and 95% confidence intervals for increased PWV among subjects

	FLI categories	OR (95% CI)	*p* value
Age ≤ 50			
Model 1	< 30 (n = 70)	(Ref.)	
	30–59 (n = 57)	0.547 (0.042–7.136)	0.646
	≥ 60 (n = 78)	0.791 (0.249–2.519)	0.692
Model 2	< 30 (n = 70)	(Ref.)	
	30–59 (n = 57)	0.544 (0.045–6.529)	0.631
	≥ 60 (n = 78)	1.031 (0.290–3.665)	0.963
Model 3	< 30 (n = 70)	(Ref.)	
	30–59 (n = 57)	0.570 (0.046–7.085)	0.662
	≥ 60 (n = 78)	1.012 (0.278–3.676)	0.986
Age > 50			
Model 1	< 30 (n = 66)	(Ref.)	
	30–59 (n = 71)	2.176 (0.755–6.271)	0.150
	≥ 60 (n = 60)	1.482 (0.757–2.901)	0.251
Model 2	< 30 (n = 66)	(Ref.)	
	30–59 (n = 71)	2.182 (0.749–6.352)	0.153
	≥ 60 (n = 60)	1.401 (0.712–2.757)	0.329
Model 3	< 30 (n = 66)	(Ref.)	
	30–59 (n = 71)	2.133 (0.730–6.231)	0.166
	≥ 60 (n = 60)	1.440 (0.746–1.930)	0.309

Model 1 adjusting for age, sex, body mass index, MAP, HR, and eGFR

Model 2 adjusting for age, sex, body mass index, MAP, total cholesterol, HR, and eGFR

Model 3 adjusting for age, sex, body mass index, MAP, total cholesterol, glucose, HR, and eGFR

Abbreviations: *FLI* fatty liver index, *LDL-C* low-density lipoprotein cholesterol, *MAP* mean artery blood pressure, *cfPWV* carotid-femoral pulse wave velocity, *Ref* reference

Fig. 1 cfPWV for comparison of male and females in the each FLI groups
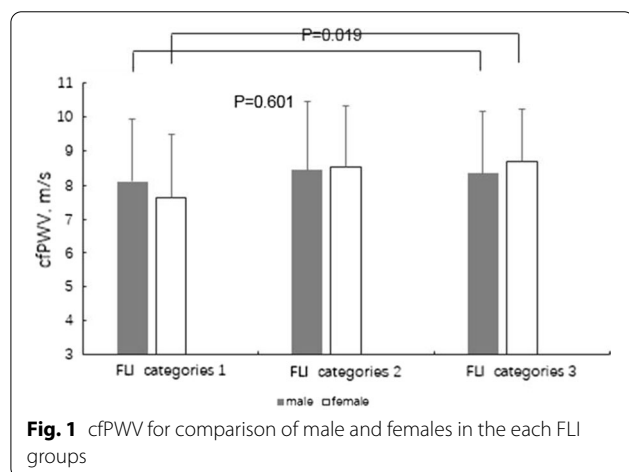
to be significant with cfPWV in our multivariable regression models ($\beta = 0.148$, $p = 0.382$).

We found that FLI > 60 is significantly associated with significantly lower HDL-C and higher triglyceride [18],

suggesting that elevated FLI (which means increased hepatic steatosis) can increase atherogenic protein levels and promote the development of atherosclerosis. In addition, NAFLD may represent liver manifestations of the metabolic syndrome. The liver's own fatty lesions and inflammatory lesions may promote systemic inflammatory levels and increased transcription of pro-inflammatory genes [10]. Elevated levels of pro-inflammatory cytokines lead to atherosclerosis. Therefore, cfPWV, as a measure of arterial stiffness, may also increase.

Adiponectin is a peptide substance secreted by adipose tissue and has anti-oxidant and anti-atherosclerotic effects. Studies have confirmed that adiponectin levels are significantly associated with PWV [19]. Patients with NALFD have a significant lower level of plasma adiponectin concentrations [20] and are closely related to the severity of liver disease. Leptin is also one of the peptides secreted by adipose tissue, which has the effect of reducing liver fat accumulation and is an independent predictor of aortic function [21]. Changes in adiponectin and leptin concentrations may be one of the reasons for the significant correlation between FLI and PWV, but the specific mechanism remains to be studied. Since both PWV and FLI are non-invasive and more operative in the field of screening, more relevant research may be considered in the future.

The most noteworthy result of our study is that FLI remained positively associated with cfPWV after adjusting for several confounding factors, suggesting that liver fat lesions aggravate arterial stiffness. Some studies have reported the correlation between NAFLD and PWV. Vlachopoulos et al. [22] reported that PWV was significantly higher in patients with NAFLD than in the control group. Salvi et al. [23] reported that PWV values were significantly lower in control group compared with NAFLD group. Sunbul et al. [24] reported that the liver fibrosis score was an independent predictor of both PWV and AIx values in NAFLD. However, little research has been done on the relevance of atraumatic FLI and PWV. Cicero et al. [25] confirmed that FLI and PWV were significantly associated in moderate to high risk (BMI ≥ 28 and/or type 2 diabetes) patients. Our study confirmed the correlation between FLI and PWV in the Chinese. NAFLD can develop into non-alcoholic steatohepatitis (NASH), which is characterized by liver fibrosis and closely related to cirrhosis [24]. Therefore, NALFD patients should be referred to in time for an accurate, non-invasive assessment of vascular risk. Conversely, cardiovascular physicians should also refer NAFLD patients with increased arterial stiffness to liver specialists for early diagnosis and treatment of liver fibrosis [24]. However, after adjustment for mean arterial

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blood pressure and other confounding factors, cfPWV in all of the models was not significantly associated with intermediate fatty liver index or hepatic steatosis group compared to those with FLI < 30. In interpreting the results, it is important to note that the relationship between cfPWV and blood pressure can be due to the dependency of cfPWV on blood pressure at the time of measurement or pressure-related remodeling of the arterial wall. The finding of a higher correlation for cfPWV with SBP than for DBP suggests that the possibility of remodeling effects of blood pressure on arterial stiffness. These two effects are not easily separated statistically. We calculated the CAVI0 according to the published formula [26, 27] to analyse the correlation between FLI and CAVI0; however, we did not find any significant correlation between FLI and CAVI0. The measurement of a pressure-independent stiffness index or the computation of a PWV ratio/"gradient" [28] would be an important intermediate marker in future studies.

This study showed that the effect of increased FLI on PWV changes by gender, which may be due to confounding factors such as gender-specific effects on hemodynamics. Women have more hemodynamic influence factors, such as estrogen-mediated vascular relaxation, shorter length of the arterial tree, difference of fat distribution and heart rate [29]. The presence of adipose tissue is more likely to act as a cushion, affecting the final PWV measurement. Therefore, it is necessary that gender grouping studies be conducted.

Our study also suggests that in Chinese males FLI is significantly higher than in females. This was similar to other studies [30] that showed that when using FLI to diagnose NAFLD, the incidence in males was higher than in females. This may be due to the fact that FLI is based on a combination of BMI, waist circumference, serum triglycerides and GGT levels, and differences in fat distribution and BMI between male and female can affect the outcome. In addition, the prevalence of NAFLD in Chinese males before the age of 50–55 is higher than that in females, and the prevalence in females increases rapidly and is even higher than that of males [1]. Failure of age-standardization may also be one of the causes of gender differences in FLI.

In addition to FLI, this study also suggested a significant correlation between age, blood pressure, and PWV, similar to other studies [31]. With age, there are many changes in blood vessels, such as decreased elastin content, increased collagen content, change in type of collagen, and collagen cross-links from advanced glycation end products. These changes will reduce the elasticity of the vessel wall and ultimately lead to an increase in PWV [31]. The mechanical stretching force of the arterial wall determines the stiffness of the artery, so PWV is related to the physical expansion of blood pressure on the arterial wall.

There are several limitations in the current study. First, the study was performed by cross-sectional design, and so it cannot provide predictive values of FLI on the progression of arterial stiffness. Second, due to the type of cardiovascular assessment conducted, there is lack of data on antihypertensive medication and smoking status.

5 Conclusion

cfPWV, as a measure of arterial stiffness, is higher in the NAFLD group when compared to that in normal groups. Fatty liver index is positively associated with arterial stiffness in a Chinese population.

Author Contributions
AA and J. Zuo contributed in study conceptualization and writing (review and editing) the manuscript. J. Zuo, YH, HC, QW, BT and J. Zhao contributed in data curation, formal analysis. J. Zuo contributed in funding acquisition and project administration. AA, J. Zuo, IT, MB and PC contributed in supervised the project. J. Zuo, YH and HC contributed in writing (original draft) the manuscript.

Declarations

Conflict of Interest
The authors declare there is no conflict of interest in the current study.

Author details
[1]Department of Geriatric Medicine, Ruijin Hospital, Shanghai Jiao Tong School of Medicine, No. 999, Xiwang Road, Shanghai, China. [2]Daning Community Health Service Center, Shanghai, China. [3]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia. [4]Clinical Research Center, Ruijin Hospital, Shanghai Jiao Tong School of Medicine, No. 999, Xiwang Road, Shanghai, China.

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